Urinary peptidomics and *in-silico* analysis for the molecular characterisation of the cardiorenal syndrome (CRS) and chronic kidney disease (CKD)

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This thesis is dedicated to my family

For their endless love, support and encouragement

1. List of Publications

Publications for the thesis

1. **Petra E**, He T, Lygirou V, Latosinska A, Mischak H, Vlahou A, Jankowski J (2021). Urine peptidome analysis in cardiorenal syndrome reflects molecular processes. *Sci Rep*.;11(1):16219. doi:10.1038/s41598-021-95695-z.

2. **Petra E**, Siwy J, Vlahou A, Jankowski J (2022). Urine peptidome in combination with transcriptomics analysis highlights MMP7, MMP14 and PCSK5 for further investigation in chronic kidney disease. *PLoS One*;17(1):e0262667. doi:10.1371/journal.pone.0262667.

Other Publications

1. Makridakis M, Kontostathi G, **Petra E**, Stroggilos R, Lygirou V, Filip S, Duranton F, Mischak H, Argiles A, Zoidakis J, Vlahou A (2020). Multiplexed MRM-based protein quantification of putative prognostic biomarkers for chronic kidney disease progression in plasma. *Sci Rep*.;10(1):4815. doi:10.1038/s41598-020-61496-z.

2. **Petra E**, Zoidakis J, Vlahou A (2019). Protein biomarkers for cardiorenal syndrome. *Expert Rev Proteomics*;16(4):325-336. doi:10.1080/14789450.2019.1592682.

3. Shangaris P, Loukogeorgakis SP, Blundell MP, **Petra E**, Shaw SW, Ramachandra DL, Maghsoudlou P, Urbani L, Thrasher AJ, De Coppi P, David AL (2018). Long-term hematopoietic engraftment of congenic amniotic fluid stem cells after in utero intraperitoneal transplantation to immune competent mice. *Stem Cells Dev*.;27(8):515-523. doi:10.1089/scd.2017.0116.

4. McLaggan D, Amezaga MR, **Petra E**, Frost A, Duff EI, Rhind SM, Fowler PA, Glover LA, Lagido C (2012). Impact of sublethal levels of environmental pollutants found in sewage sludge on a novel *Caenorhabditis elegans* model biosensor. *PLoS One*;7 (10): e46503. doi:10.1371/ journal.pone.0046503.

2. English summary

Urinary peptidomics and *in-silico* analysis for the molecular characterisation of the cardiorenal syndrome (CRS) and chronic kidney disease (CKD)

The Cardiorenal Syndrome (CRS) manifests as concurrent bidirectional dysfunction of the kidneys and heart. Chronic Kidney Disease (CKD) is characterised by kidney impairment, indicated by either kidney damage or an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 sustained for at least three months. Given the incomplete comprehension of the underlying molecular mechanisms in both conditions, the present thesis endeavors to examine disparities in the urinary peptidome between patients afflicted with CRS and CKD, along with their respective matched controls. The primary objectives are to deepen the understanding at the molecular level and to prognosticate the involvement of proteases in the generation of peptides associated with these diseases.

The 'Human Urinary Proteome' database supplied mass spectrometry data from a cohort comprising 3,463 individuals. Peptidomic profiles of participants diagnosed with CRS, characterised by both heart failure (HF) and an eGFR <60 ml/min/1.73 m^2, or CKD, without concurrent HF and with eGFR <60 ml/min/1.73 m^2, were compared against controls. These controls, devoid of HF and exhibiting eGFR >60 ml/min/1.73 m^2, were matched for sex, age, and eGFR. Statistical analysis employed the Mann-Whitney test, followed by correction for multiple comparisons. Furthermore, the Proteasix tool predicted proteases generating urinary peptides.

Case-control matching yielded 353 CRS patients and 356 controls. Similarly, 241 CKD peptidome profiles were matched with 240 non-CKD individuals. Overall, 559 and 303 urinary peptides were significantly associated with CRS and CKD, respectively, with over half (55.9% for CRS and 60.4% for CKD) being fibril-forming collagen fragments (i.e. collagen types I, II and III). The *in-silico* protease analysis of the identified peptides revealed the potential involvement of 18 proteases in the context of CRS and 16 proteases in the scenario of CKD. The former 18 proteases were members of three protein families, including metalloproteinases (MMPs, n=11), proprotein convertases (PCSKs, n=4), cathepsins (n=2), as well as the kallikrein 4 (KLK4) protein. All proteases, except the two cathepsins, were also predicted to be involved in generating the CKD-associated peptides. Further cross-correlation of the CKD-associated proteases to transcriptomics datasets from the Nephroseq database highlighted and shortlisted MMP7, PCSK5 and MMP14.

Statistically robust distinctions were observed across multiple urinary peptides among patients with CRS, CKD and their corresponding control groups. Major alterations identified are associated with the extracellular matrix (ECM)-related pathways and the collagen turnover reflected in specific affected collagen peptides in both diseases. Furthermore, pathways associated with immune response, mostly inflammation and degranulation, were represented by the deregulated peptides which, among others, were sequenced fragments of clusterin and thymosin beta-4 (TMSB4X) (for CRS) as well as beta-2-microglobulin (B2M), alpha-2-HS-glycoprotein (AHSG) and complement C3 (for CKD) along with the proteases (MMP8 and MMP9) underscore the inflammatory involvement in these fibrotic diseases.

In conclusion, CRS and CKD exhibit numerous differentially excreted peptides, reflecting ECM-related pathways and immune response alterations. These peptides should be analysed more closely in the context of CRS and CKD in future studies. Furthermore, shortlisting MEP1B, MMP26 and KLK4 (for CRS) and MMP7, MMP14 and PCSK5 (for CKD) are the basis for the investigation of proteolytic events associated with both diseases, paving the way for future studies.

3. Zusammenfassung

Molekulare Charakterisierung des kardiorenalen Syndroms (CRS) und der chronischen Nierenerkrankung (CKD) mittels Peptidom- und in-silico Analysen

Das kardiorenale Syndrom (CRS) ist durch simultane bidirektionale Dysfunktionen der Nieren und des Herzens gekennzeichnet. Eine chronische Nierenerkrankung (CKD) wird durch eine Nierenschädigung oder eine geschätzte glomeruläre Filtrationsrate (eGFR) von weniger als 60 ml/min/1,73m^2 über einen Zeitraum von mindestens drei Monaten definiert. Da die zugrundeliegenden molekularen Mechanismen bislang nur ansatzweise bekannt sind, ist das Ziel der vorliegenden Dissertation, einen Beitrag zu einem besseren Verständnis der molekularen Mechanismen zu leisten und einen neuen prognostischen Ansatz zu etablieren, der auf die Bestimmung spezifischer Peptide fußt.

Über die 'Human Urinary Proteome'-Datenbank sind Massenspektrometrie Daten von 3.463 Teilnehmern zugänglich. Der Mann-Whitney-Test mit nachfolgender Korrektur für multiple Tests wurde verwendet, um die peptidomischen Profile von Patienten mit CRS (bei denen eine Herzinsuffizienz (HF) und eine eGFR <60 ml/min/1,73m^2 vorlagen) oder mit CKD (ohne HF und eGFR <60 ml/min/1,73m^2) im Vergleich zu entsprechenden Kontrollgruppen (ohne HF und mit eGFR >60 ml/min/1,73m^2) zu analysieren. Die Kontrollgruppen wurden hinsichtlich ihres Geschlechts, Alter und eGFR abgeglichen. Desweiteren wurden mithilfe des Proteasix-Tools Proteasen prognostiziert, die für die Generierung der identifizierten Peptide ursächlich sein könnten.

Der Fall-Kontroll-Abgleich ergab einen Vergleich von 353 CRS-Patienten mit 356 Kontrollproben, sowie von 241 CKD-Patienten mit 240 Nicht-CKD-Personen. Insgesamt wurden 559 bzw. 303 Urinpeptide signifikant mit CRS bzw. CKD in Verbindung gebracht, wobei 55,9% bei CRS und 60,4% bei CKD Fibrillen-bildende Kollagenfragmente des Typs I, II und III waren. Bei der *in-silico*-Protease-Analyse der Peptide wurden 18 für CRS und 16 für CKD Proteasen identifiziert, die an der Peptidspaltung aus den zugrunde liegenden Proteinen ursächlich sind. Die Proteasen der CRS-Gruppe gehörten zu Metalloproteinasen (n=11), Proprotein-Konvertasen (n=4), Cathepsine (n=2) sowie das Protein Kallikrein 4 (KLK4). Mit Ausnahme der beiden Cathepsine wird für alle Proteasen vorhergesagt, dass sie CKD-assoziierte Peptide erzeugen. Eine zusätzliche Kreuzkorrelation der mit CKD assoziierten Proteasen mit Transkriptomik-Datensätzen aus der Nephroseq-Datenbank identifizierte MMP7, PCSK5 und MMP14 als potenzielle Kandidaten.

Es wurden hochsignifikante Unterschiede bei mehreren Urinpeptiden zwischen Patienten mit CRS, CKD und der Kontrollgruppe festgestellt. Es wurden deregulierte Peptide identifiziert, die mit Immunreaktionen, insbesondere Entzündungen und Degranulation, in Verbindung gebracht werden können. Darunter sind Clusterin und Thymosin beta-4 (TMSB4X) (für CRS) sowie beta-2-Mikroglobulin (B2M), alpha-2-HS-Glykoprotein (AHSG) und Komplement C3 (für CKD), als auch die Proteasen (MMP8 und MMP9). Dies weist auf eine Beteiligung von Entzündungsprozessen an diesen fibrotischen Erkrankungen hin.

Insgesamt weisen das CRS und die CKD unterschiedliche Peptidprofile auf, die auf extrazelluläre Matrix-bezogene Signalwege und Veränderungen im Immunsystem hinweisen. Die Identifizierung von MEP1B, MMP26 und KLK4 für das CRS bzw. MMP7, MMP14 und PCSK5 für die CKD stellt einen wichtigen Schritt für die vertiefte Untersuchung proteolytischer Prozesse im Kontext beider Krankheitsbilder dar. Diese Erkenntnisse legen die Grundlage für zukünftige Studien auf dem Gebiet der CKD und des CRS.

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Urine peptidome analysis in cardiorenal syndrome reflects molecular processes

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The cardiorenal syndrome (CRS) is defined as the confluence of heart-kidney dysfunction. This study investigates the molecular differences at the level of the urinary peptidome between CRS patients and controls and their association to disease pathophysiology. The urinary peptidome of CRS patients (n = 353) was matched for age and sex with controls (n = 356) at a 1:1 ratio. Changes in the CRS peptidome versus controls were identified after applying the Mann–Whitney test, followed by correction for multiple testing. Proteasix tool was applied to investigate predicted proteases involved in CRS-associated peptide generation. Overall, 559 differentially excreted urinary peptides were associated with CRS patients. Of these, 193 peptides were specifically found in CRS when comparing with heart failure and chronic kidney disease urinary peptide profiles. Proteasix predicted 18 proteases involved in > 1% of proteolytic cleavage events including multiple forms of MMPs, proprotein convertases, cathepsins and kallikrein 4. Forty-four percent of the cleavage events were produced by 3 proteases including MMP13, MMP9 and MMP2. Pathway enrichment analysis supported that ECM-related pathways, fibrosis and inflammation were represented. Collectively, our study describes the changes in urinary peptides of CRS patients and potential proteases involved in their generation, laying the basis for further validation.

The cardiorenal syndrome (CRS) is a complex pathological disorder, which reflects the interplay between heart and chronic kidney diseases[1]. Epidemiologic data reveal that about 45–63% of chronic heart failure (HF) patients developed chronic kidney disease (CKD)[2]. CRS is classified into five subtypes, referring to primary organ dysfunction, each with different underlying pathological mechanisms[3]. The term "CRS" has been applied to the relation of these two diseases, but the definition and classification have not been clearly established on a molecular pathophysiologic level until now[4]. However, multi-factorial mechanisms including hemodynamic changes, fibrosis, vascular calcification, neurohormonal activity, immunologic imbalance, inflammation, apoptosis, endothelial injury, thrombosis, and oxidative stress have been proposed to explain the general pathophysiology of CRS[5].

In parallel to the efforts towards understanding disease pathophysiology, a number of biomarkers for heart and kidney disease have been studied in the context of CRS. These include changes in the levels of heart-specific biomarkers such as cardiac troponin T (cTnT) and B-type natriuretic peptide (BNP)[6,7], but also kidney-specific biomarkers including albumin (ALB), kidney injury molecule-1 (KIM-1)[8], liver-type fatty acid binding protein (L-FABP)[9], neutrophil gelatinase-associated lipocalin (NGAL)[10], β-2 microglobulin (B2M)[11], n-acetyl-beta-D-glucosaminidase (NAG)[12] and cystatin C[13], (reviewed in[14]).

Urinary peptidomics focuses on the analysis of naturally occurring peptides and small proteins in urine. Application of the approach enabled identification of biomarkers associated with kidney and heart diseases including, among others, CKD[15], kidney fibrosis[16], diabetic kidney disease (DKD)[17], acute kidney injury (AKI)[18] as well as HF[19], asymptomatic LV diastolic dysfunction (LVDD)[20], and ischemic and dilated cardiomyopathy[21]; with a biomarker panel for CKD also having reached the level of clinical implementation for patient stratification in large clinical trials[22].

Due to the lack of specific CRS biomarkers on a molecular level, we designed the current study to identify molecular differences at the level of the urinary peptidome between CRS and matched controls, prompted by the

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	Control	CRS
Number	356	353
Sex, male (%)	67	68
Age (years)	70 ± 7	72 ± 8
BMI	26.75 ± 4.00	29.19 ± 5.29*
Smoking status (yes, %)	9.5	5.3*
eGFR (CKD-EPI) (ml/min/1.73 m^2)	79.2 ± 18.8	43.1 ± 11.5*
CKD Stage 5 (%)	N/A	1
CKD Stage 4 (%)	N/A	14
CKD Stage 3 (%)	N/A	85
NT-proBNP (pg/mL)	195.16 ± 195.49	1587.48 ± 2111.07*
Serum creatinine (μmol/L)	79.20 ± 12.81	138.04 ± 47.15*
Ejection fraction	N/A	40.10 ± 11.92
Systolic BP (mmHg)	141.66 ± 18.13	126.91 ± 24.57*
Diastolic BP (mmHg)	79.75 ± 8.99	67.44 ± 13.16*
Diagnosis (%) HF/HFrEF/HFpEF/HFmrEF	N/A	15/60/20/5

Table 1. Demographics and clinicopathological features characterizing the CRS cohort under investigation. Differences between controls and CRS have been evaluated by the Mann–Whitney U test (for continuous variables) or Chi-Square test (for categorical variables) and are marked with * when $P < 0.05$. Data are presented as mean ± standard deviation (s.d.) or number (%). BMI: body mass index; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD Stage 5: 0–15 ml/min/1.73 m^2; CKD Stage 4: 15–29 ml/min/1.73 m^2; CKD Stage 3: 30–60 ml/min/1.73 m^2; NT-proBNP: N-terminal pro b-type natriuretic peptide; BP: blood pressure; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; N/A: not applicable.

availability of high resolution-large sized datasets. In addition, we targeted to investigate if the observed urinary changes reflect molecular processes associated with CRS and its underlying pathologies.

Results

Cohort characteristics. The urine peptidomics datasets were screened for the availability of clinical information on both kidney and heart failure. Based on these criteria, 3463 urinary peptidomics datasets were retained for investigation. Matching resulted in the inclusion of a total of 709 datasets (CRS; n = 353, controls; n = 356) in the study, which comprised the main groups under comparison (CRS versus the respective matched controls). The CRS patients had an estimated glomerular filtration rate (eGFR) mean value of 43.1 ml/min/1.73 m^2 whereas controls had 79.2 ml/min/1.73 m^2. A number of the clinicopathological characteristics including the NT-proBNP levels, the serum creatinine levels, the systolic blood pressure, the diastolic blood pressure were statistically significant different between the two groups. The characteristics of the matched cases-controls are presented in Table 1.

Urine peptidome analysis. A total of 3184 peptides were detected and considered when comparing CRS patients with controls. After applying the Benjamini-Hochberg (BH) adjustment, 1480 differentially excreted peptides (BH, $P < 0.05$) were identified when comparing cases with controls. To shortlist the more representative features, a 30% frequency threshold, frequently used in such analyses[23,24] was applied, which resulted in a final list of 559 differentially excreted peptides (see Fig. 1a and Supplementary Table S1). These peptides derived from 110 unique protein precursors, which based on functional annotation, reflected largely extracellular matrix (ECM) changes, cell-ECM interactions, collagen formation/degradation, metabolic and inflammatory processes. The top 15 most frequently observed protein precursors, associated with at least 400 differentially excreted peptides are presented in Fig. 1b. Of these 559 differentially excreted peptides, 313 (55.9%) originated from fibril-forming collagens and were fragments of collagen type I alpha 1 chain (COL1A1), collagen type I alpha 2 chain (COL1A2), and collagen type III alpha 1 chain (COL3A1). Together the collagens accounted for 72% of the quantified peptidome. The 20 most significant differentially excreted peptides included fragments of additional collagen types (COL4A1, COL4A3, COL9A3, COL5A1, COL5A2, COL5A3 and COL19A1) and other peptides originating from plasma proteins (such as apolipoprotein A1 (APOA1) and B2M) (see Table 2). Among the peptides showing the most prominent increase in abundance in patients versus controls were fragments of B2M, albumin, and alpha-1-antitrypsin (A1AT), whereas fragments of collagen types (IV, V and VI), clusterin (CLU) and ubiquitin-associated protein 1-like (UBAP1L) were the peptides with the most decreased abundance levels in CRS (see Fig. 1c).

Urinary peptide differences in CRS, CKD and HF. We further investigated if common peptides were identified between patients with HF and CRS as well as between CKD and CRS. We compared the 559 peptides

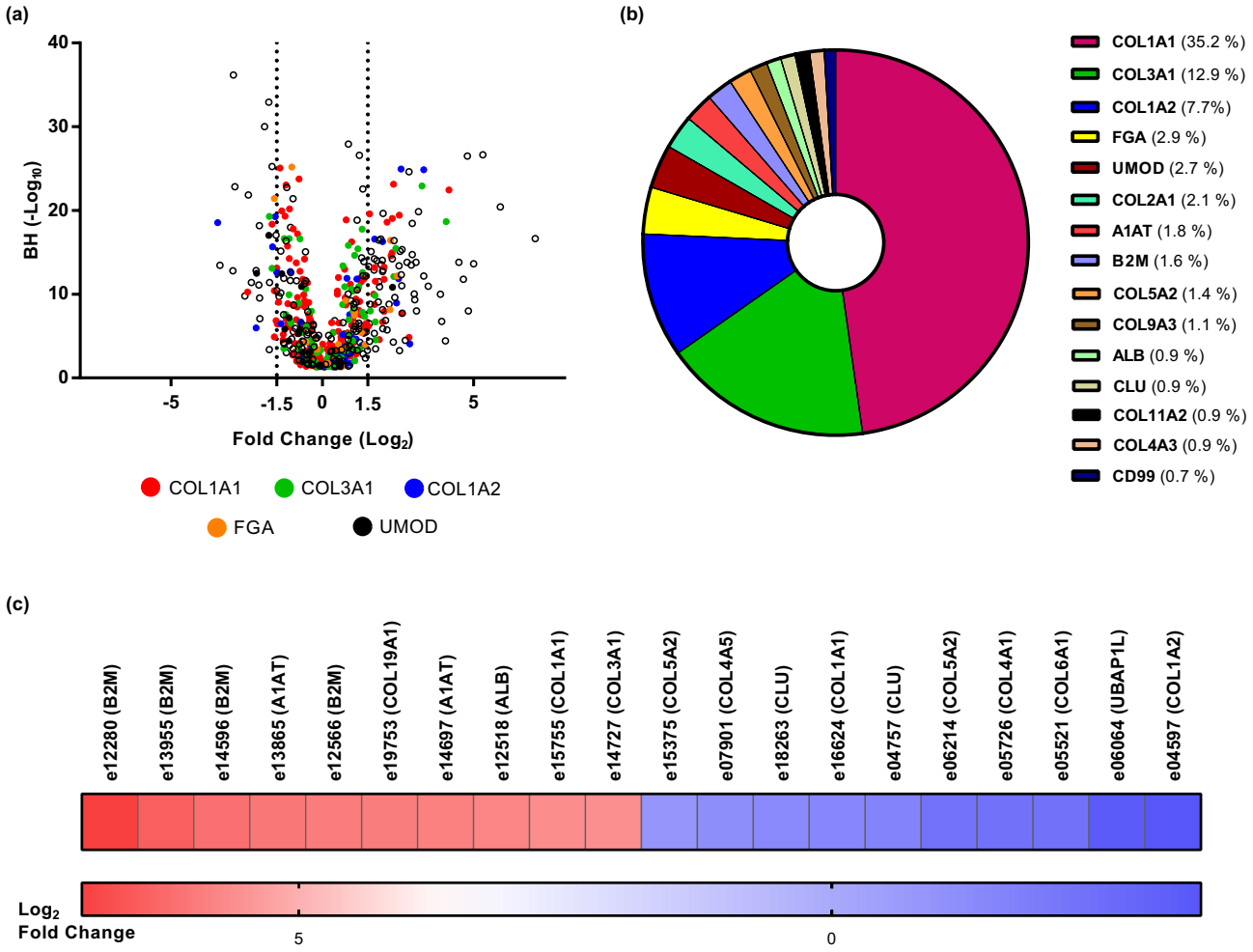


Figure 1. Urinary peptides in CRS. (**a**) Volcano plot showing the fold change (log_2 CRS/Control) plotted against the BH P-value ($-log_{10}$) of the 559 differentially excreted peptides between CRS and controls. The top five most representative protein precursors including COL1A1, COL3A1, COL1A2, FGA and UMOD are highlighted in different colors. (**b**) Pie chart of the top 15 most frequently observed protein precursors, associated with at least 400 differentially excreted CRS-associated peptides. The percentage of the differentially excreted peptides per protein precursor is presented. 55.9% of CRS-associated peptides originated from fibril-forming collagens and were fragments of COL1A1, COL1A2, and COL3A1. (**c**) Heatmap of the log_2 transformed fold change of the top 10 most increased and decreased peptides in the CRS cohort. In each case, the peptide codes are provided in Supplementary Table S1.

of our study with the 218 and 577 differentially excreted peptides which were associated with CKD and HF, respectively, and described in previous studies[15,19]. Of these 218 CKD-associated peptides, 31 (14.2%) were commonly identified in our study as well. These common 31 peptides were sequenced fragments of albumin, B2M, A1AT, APOA1, alpha-1B-glycoprotein (A1BG), alpha-2-HS-glycoprotein (AHSG), sodium/potassium–transporting ATPase subunit γ (FXYD2), osteopontin (SPP1), collagen types I and III and other proteins (see Supplementary Table S2). In addition, 341 out of 577 (59%) of the HF-specific peptides were commonly identified in CRS patients (see Supplementary Table S3). These shared peptides showed the same directionality of difference and originated mostly from collagen types (I, II, III, IV, V, IX, XI), B2M, A1AT and uromodulin (UMOD).

Overall, 193 of 559 (34.5%) CRS-associated peptides were not among those identified in the HF and CKD studies (see Supplementary Table S4). Most of these 193 peptides, which were found in the CRS cohort only, were collagen fragments (n = 134, 69.4%), with collagen types I, II, III, IV and V represented by the largest number of collagen fragments (n = 117, 60.6%). The top most represented protein precursors were collagen types I (40.9%) and III (9.3%), UMOD (4.1%) fibrinogen alpha chain (FGA, 2.6%), COL5A2 (2.1%), CD99 (1.6%), CLU (1.6%), FXYD2 (1.6%) and polymeric immunoglobulin receptor (PIGR, 1.6%).

On a protein level, we further investigated if any of the protein precursors represented by 193 CRS-associated peptides was not identified in the CKD and HF urinary profiles. Totally, 30 protein precursors were detected only in CRS cohort but not in HF and CKD. These protein precursors included several collagen types (COL4A2, COL4A4, COL6A5, COL7A1, COL8A1 and COL13A1), PIGR, secreted and transmembrane protein 1 (SECTM1), ankyrin repeat domain-containing protein 17 (ANR17), ubiquitin-like protein ATG12 (ATG12),

Sequence	Protein symbol	Start AA	Stop AA	p-value (BH)	Fold change
GPpGFTGppGPPGPPGP	COL4A1	197	213	6.99E−37	*0.13*
GppGFTGPpGpPGPPGP	COL4A1	197	213	1.14E−33	*0.29*
mPGFKGpTGYKGEQGEVGKDGEKGDpGpPG	COL9A3	151	180	9.57E−31	*0.27*
PGMPGADGpPGHPGKEGppGEKGGQGpPG	COL5A1	753	781	1.24E−28	**1.81**
LLKNGERIEKVEHSDLSFSKDWS	B2M	59	81	2.21E−27	**39.40**
cDDYRLcE	MGP	73	90	2.66E−27	**2.33**
GPEGPSGKpGINGKDGIPGAQGImGKpGDRGpKGERG-DQGIP	COL19A1	917	958	3.26E−27	**27.61**
GpKGDpGIpGLDRSGFpGETGSPGIPGHQ	COL4A3	836	864	5.66E−26	*0.32*
DEAGSEADHEGTHSTK	FGA	605	620	6.70E−26	*0.50*
DDGEAGKpGRpG	COL1A1	231	242	8.94E−26	*0.38*
LkGQpGApGVkGEpGApGENGTpGQTGARG	COL1A2	188	217	1.12E−25	**6.06**
GpAGPpGKAGEDGHPGKpGRpGERG	COL1A2	133	157	1.42E−25	**10.23**
VDVLKDSGRDYVSQFEGSALGKQLN	APOA1	43	67	2.32E−25	**7.26**
ApGDRGEpGPpGPAG	COL1A1	798	812	1.84E−24	*0.58*
SpGRDGSpGAKGDRGETGP	COL1A1	1023	1041	7.20E−24	**5.09**
AEGSpGRDGSpGAKGDRGETGPA	COL1A1	1020	1042	9.09E−24	*0.44*
GLAGTAGEpGRDGNPGSDGLPGRDGSpGGKGDRGENGSp-GAPGAPGHPGPPGp	COL3A1	1002	1054	1.20E−23	**9.81**
GSPGTSGppGSAGpPGSpG	COL5A2	435	453	1.53E−23	*0.14*
GPpGPpGFpGDPGPPG	COL5A3	407	422	1.85E−23	*0.44*
cDDYRLc	MGP	73	79	2.75E−23	**2.54**

Table 2. List of the 20 top most significant differentially excreted CRS peptides. Peptides increased in CRS are labelled in bold, decreased in italics. AA: amino acid; BH: Benjamin–Hochberg.

zinc-alpha-2-glycoprotein (AZGP1) and monocyte differentiation antigen CD14 (CD14) (and other proteins listed in Supplementary Table S5).

Protease prediction analysis. Proteases possibly implicated in the endogenous cleavage of the differentially excreted peptides were predicted by Proteasix tool (http://www.proteasix.org). The in silico analysis revealed that 117 of the 559 differentially excreted peptides were known substrates of 27 reported in the literature proteases. Of these 27, 18 shortlisted proteases had a percentage of cleavage events above 1% and are presented in Fig. 2a. Among the shortlisted proteases were multiple metalloproteinases (see Fig. 2a-in red), 4 proprotein convertases (see Fig. 2a-in blue), 2 cathepsins (see Fig. 2a-in green) and kallikrein 4 (KLK4). The 44% of the cleavage events were produced by 3 metalloproteinases (i.e. MMP13, MMP9 and MMP2). However, the most abundant diffrentially excreted peptides were putatively cleaved by the four proprotein convertases, KLK4 and MMP26, as shown in the heatmap (see Fig. 2b). For comparison, when analyzing the CRS-specific peptides (n = 193), similarly, 11 metalloproteinases and 4 cathepsins were predicted (see Fig. 2a marked with an asterisk), all included in the predictions from the 559 differentially excreted peptides.

Gene Ontology (Go) enrichment analysis of the 18 shortlisted proteases showed the over-representation of metalloproteinases (i.e. MMP3, MMP12, MMP14, MMP20, MMP26, MMP1, MMP2, MMP13, MMP9, MMP20, MEP1B, MMP8) in zinc ion binding and transition metal ion binding molecular functions. Together, metalloproteinases (i.e. MMP12, MMP13, MMP9) along with 2 cathepsins (i.e. CTSK, CTSS) displayed collagen-binding activity.

Pathway enrichment analysis of the shortlisted proteases along with the protein precursors of the differentially excreted peptides was performed by Metascape. The analysis revealed that ECM-related pathways (i.e. ECM organization and degradation) were significantly affected. Together, cathepsins K and S along with various metalloproteinases (i.e. MMP1, MMP2, MMP3, MMP8, MMP9, MMP12, MMP13, MMP14, MMP20 and MMP26) and KLK4 were mostly involved in the structure, organization and degradation of ECM. Additionally, pathway analysis highlighted that the predicted proteases along with the protein precursors were also inolved in collagen formation, protein processing, regulation of inflammatory response and neutrophil mediated immunity (see Fig. 3).

Discussion

In the present case–control matching study, a large-scale urine peptidome analysis of patients with CRS and matched controls was performed, targeting to identify the disease-specific urine peptidome profile and its potential links to pathophysiology. Importantly, our study identifies a high number of differentially excreted urine peptides between CRS patients and matched controls.

The results of the current study suggest that the urine peptidome of CRS patients integrates changes of 559 peptides originated from various protein precursors. These peptides originate to a large extent from proteins involved in ECM, collagen formation/degradation, inflammation, metabolism but also transcriptional regulation

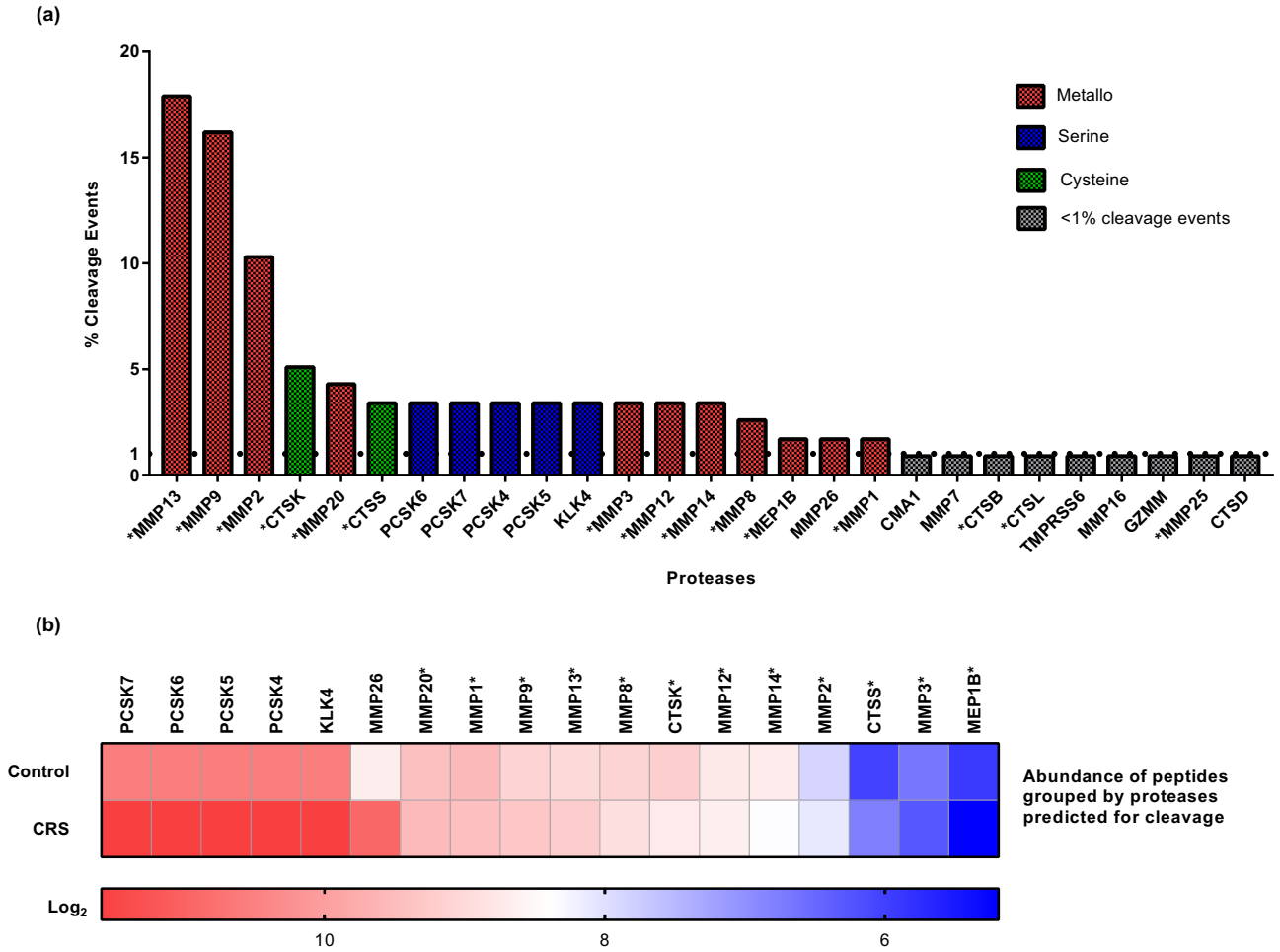
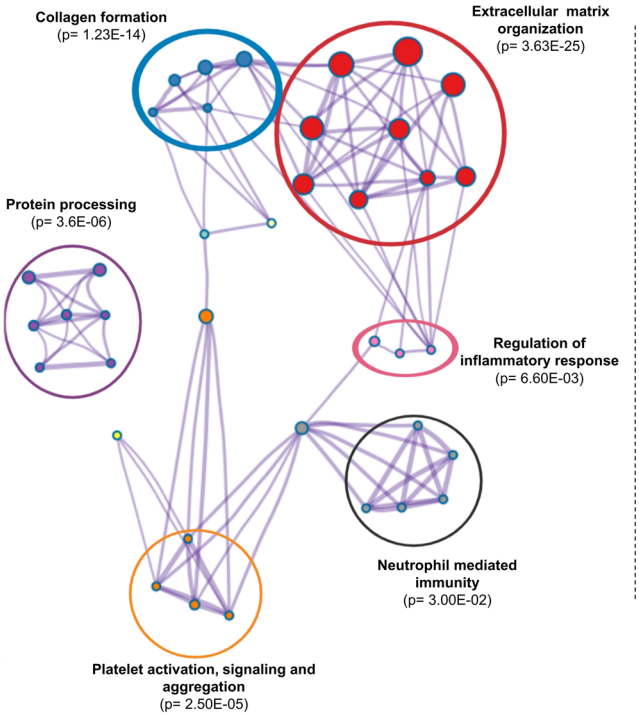


Figure 2. In silico predicted proteases. (**a**) The 27 predicted proteases are presented. Of these, 18 were linked to ≥ 1% of cleavage events and are highlighted in red, blue and green whereas 9 had < 1% of cleavage events (highlighted in grey). The 15 predicted proteases which were involved in the generation of the 193 CRS-specific peptides are marked with an asterisk. The catalytic mechanism of the shortlisted proteases is also depicted. (**b**) Heat map of the $\log_2$ transformed abundance of the differentially excreted peptides predicted as substrates of 18 shortlisted proteases by the Proteasix. The predicted proteases which were associated with the 193 CRS-specific peptides are marked with an asterisk.

reflecting the underlying associated mechanisms[25]. A large number of overlapping urine peptides between CRS and HF as well as CRS and CKD patients were expected, as the examined patients of our study have combined both pathologies. These overlapping peptides derived, among others, from plasma proteins which are well-known renal and heart failure biomarkers including albumin, B2M, SPP1, AHSG, but also uromodulin and collagens[26]. In addition, to the above overlapping protein precursors, two proteins including, APOA1 (a protein which is associated with renal dysfunction in HF patients[27]) and FXYD2 (a protein which mediates the function of the Na, K-ATPase in mammalian kidney epithelial cells[28]) are commonly identified in CRS and CKD, similarly reflecting the common underlying molecular profiles of these diseases.

The highly abundant COL1A1, COL1A2, and COL3A1 proteins were represented by multiple urinary fragments, reflecting most likely fibrosis and changes in the ECM in both organs. In a healthy heart, the ECM is more than 95% composed of the fibrillar profibrotic collagens, including collagen types I and III[29], important for maintaining the tensile strength, elasticity and extensibility of the myocardium[29]. Alterations of collagen type I and III expressions have been associated with myocardial fibrosis in HF patients[30] and vascular calcification in the heart[31] in animal studies. Similarly, collagen types I and III are the most abundant collagen types in the renal ECM[32] linked to ECM dysregulation and CKD progression[33]. In addition, the activity of proteases may also be linked with the high number of the detected collagen-related peptides as it is well reported that metalloproteinases regulate cardiac and renal remodeling as well as fibrosis by facilitating ECM turnover and inflammatory cells[34,35].

Further expected changes based on current knowledge were consistently detected. Among the most pronounced was the selective enrichment of increased albumin peptides in CRS, as expected for renal dysfunction and consequently albuminuria. Similarly, we observed an enrichment of peptides derived from COL9A3 and COL5A3, which are selectively highly expressed at the protein level in the heart and not detected in the kidneys



Pathways	Associated Genes
Extracellular matrix organization (p= 3.63E-25)	ALB|COL1A1|COL1A2|COL2A1| COL3A1|CTSK |CTSS|GSN|MMP1|MMP2| MMP3|MMP8 |MMP9|MMP12|MMP13| MMP14|SPP1|MMP20 |KLK4|MMP26|COL22A1
Collagen formation (p= 1.23E-14)	COL1A1|COL1A2|COL2A1 |COL3A1|CTSS|MMP3|MMP9 |MMP13|MMP20|COL22A1
Protein processing (p= 3.6E-06)	CLU|CTSS|GSN|MMP14 |PCSK6|PCSK5|PCSK7|PCSK4
Platelet activation, signaling and aggregation (p= 2.50E-05)	ALB|CLU|COL1A1|COL1A2 |A1AT|TMSB4X
Regulation of inflammatory response (p= 6.60E-03)	CLU|MMP3|MMP8|MMP9 |TMSB4X|MMP26
Neutrophil mediated immunity (p= 3.00E-02)	CTSS|GSN|MMP8 |MMP9|A1AT

Figure 3. Pathway enrichment analysis. Pathway enrichment analysis of the 18 shortlisted proteases along with the 110 protein precursors of the differentially excreted peptides. The six most significant clusters are presented in different colours and the most significant term of each cluster was selected as label. For each term the corrected P-value along with the associated gene names are presented. The associated proteases are highlited in red colour.

based on proteomics databases (ProteomicsDB). Along the same lines, the abundance of a matrix GLA peptide (MGP) was strongly increased in CRS patients. MGP was already described as a calcification inhibitor protein with a strong association to HF indices and mortality[36].

Similarly, in line with the literature, among protein precursors represented by decreased fragments in CRS patients were COL4A1 and COL4A3, collagens which are associated with nephropathy[37]. Furthermore, circulating proteins portrayed by increased fragments in CRS included AHSG (a protein which is associated with vascular calcification, cardiovascular mortality and kidney dysfunction[38]), APOA1 (a protein which is associated with HF and kidney dysfunction[27]), B2M (a protein which is associated with cardio-renal remodeling[11] and inflammation[39]), COL18A1 (endostatin, generated from COL18A1, is associated with the development of cardiovascular events in CKD patients[40]), MGP and thymosin beta-4 (TMSB4X, a protein which is associated with renal fibrosis[41]).

Protein precursors detected only in CRS cohort but not in HF and CKD were also investigated. These included several collagen types, including COL4A2, COL4A4, COL6A5. Although few studies have aimed to investigate the role of collagen type IV and VI in cardio and renal failure, recently, it was suggested that COL4A2 is associated with cardiac fibrosis phenotype[42], as well as with glomerular basement membrane alterations[43], suggesting that COL4A2 may play an important role in CRS. In addition, COL4A4 and COL6A5 are associated with CKD[44,45] but no evidence was found to link COL4A4 and COL6A5 with HF. Interestingly, two additional proteins, ROBO1 and HUWE1 are linked with cardiac and renal fibrosis[46,47] whereas ANR17 protein may play a key role in the formation and maintenance of the blood vessels[48]. Moreover, several proteins associated with the immune system were uniquely found in the CRS cohort. These proteins were CD14 (a protein which is associated with heart and renal dysfunction[49]), CD99 and IRF6, suggesting the importance of the immune response in CRS. In addition, urinary PIGR peptides have been previously associated with cardiorenal dysfunction[50], nevertheless, the exact role of the protein in the disease pathology remains unknown.

Our protease prediction analysis suggested the activity of 18 proteases responsible for more than 1% of the cleavage events. These predictions can be mostly supported by the existing bibliography on cardiovascular and renal pathologies. Notably, 9 out of the 11 predicted metalloproteases (MMP13, MMP9, MMP2, MMP20, MMP3, MMP12, MMP14, MMP8 and MMP1) were previously positively correlated with HF and were increased after myocardial infarction[34,51]. Interestingly, the transcriptional activation of MMP13 induces the vascular smooth muscle cell (VSMC) apoptosis and ECM breakdown via the FOXO3a activation[52]. These observations can be reflected by the contribution of these metalloproteases to vascular and kidney damage. Specifically, MMP2, MMP3, MMP8, MMP9 and MMP12 are involved in the ECM deposition in the glomeruli; MMP2, MMP3, MMP9, MMP13 and MMP14 induce epithelial-to-mesenchymal transition that leads to kidney fibrosis; and MMP2, MMP3 and MMP9 are correlated with vascular calcification, arterial stiffening and atherogenesis[53]. As reflected also by the cleavage events in our results, MMP2 and MMP9 have a prominent role in these processes

and their levels have been associated with cardiovascular events and HF in various studies[54,55]. The role of MEP1B and MMP26 predicted by our analysis to mediate a large number of cleavage events, yet not previously linked to renal or heart dysfunction, apparently merits further investigation in the context of CRS.

From the 4 predicted proprotein convertases, three PCSK6 PSCK5 and PCSK7, have been previously associated with heart failure, to our knowledge. PCSK6 converts procorin to corin which in turn can activate natriuretic peptides, regulating cardiovascular and renal function[56]. Interestingly, PCSK6 is a key regulator of smooth muscle cell function (SMCs) in vascular remodeling and a novel player in cardiac remodeling after myocardial infraction[57,58]. Additionally, the inactivation of PCSK6 along with PCSK5 in endothelial cells leads to decreased collagen deposition and cardiovascular hypotrophy via IGF-1/Akt/mTOR signaling[59]. Moreover, PCSK7 is associated with both cardiovascular disease (CVD)[60] and end-stage kidney disease[61]. However, the role of PCSK4 and KLK4 has not yet been linked to HF or CKD and would merit further investigation in the context of CRS based on our results.

Regarding cathepsins, elevated levels of CTSK were correlated with the presence of chronic HF[62] and with major adverse cardiac and cerebrovascular events in CKD patients[63], while circulating CTSS levels increase with CKD progression and GFR decline[64]. Levels of the mRNA, protein and activity of CTSS were found increased in the left ventricular myocardium of humans and rats with HF compared with controls, suggesting its participation in cardiac remodeling[65]. CTSS was also shown to affect epithelial-to-mesenchymal transition and ECM deposition in mouse models of mild and severe hydronephrosis, indicating its role in the regulation of renal fibrosis[66].

Collectively, the pathology of CRS is complex and a number of pathways including ECM-related, fibrosis and inflammation are involved. Urinary peptidomics analysis reflects such CRS-associated changes, occasionally overlapping, as expected, with changes earlier observed in HF and CKD; but also alterations such as collagen type IV (COL4A2 and COL4A4), type VI (COL6A5), HUWE1, CD14, ANR17, PIGR and ROBO1 as well as a number of predicted proteases including MEP1B, MMP26, PCSK4 and KLK4, meriting further investigation in the context of CRS.

Among the strengths of our study was the large sample size allowing for meaningful patient matching. Based on this large sample size as well as on the case–control matching, we are confident in data validity and reliability. Additionally, all urinary peptides were analyzed using the same analytical platform and protocols (CE-MS). In contrast to any MS/MS approach, (CE-)MS does not provide sequence information. However, also as a result of the excellent reproducibility, the dataspace can be well defined, which results in the identification of over 4000 urine peptides and assignment of sequence based on mass and migration time with very high confidence[67], which would not be possible based on LC–MS/MS. A detailed comparison of LC–MS/MS and CE-MS/MS is presented in Klein et al.[68]. In consequence, the approach combining highly reproducible CE-MS analysis with a large database on CE- and LC–MS/MS analyses, results in a much higher number of peptide identifications and in higher confidence in the results in comparison to LC–MS/MS only.

The study has some limitations: these include that it is retrospective, based on already available published data. However, the sample size, the multicenter design and the very high consistency and significance of the observed changes reduce the risk of this bias. Further, we limited our study to a subgroup of CRS: to subjects with CKD and HF. This is owed to the fact that we aimed towards depicting molecular changes. Such an approach requires homogeneity in molecular pathophysiology. In addition, a number of known kidney-specific and heart-specific protein biomarkers (such as KIM-1, L-FABP, NGAL, and NAG)[14] could not be detected in our study; this is in fact expected as the applied technique (CE-MS) resolves the peptidome (< 10 kDa molecular mass peptides). Finally, the analysis is descriptive which, however, still opens multiple research avenues towards understanding the functional impact from the generation of the presented significant fragments.

In conclusion, this study reports the detection of a high number of urinary CRS-associated peptides when compared with controls. The underlying molecular mechanisms for the CRS pathology, as reflected by these peptides, represent fibrosis, ECM-related pathways, collagens formation/degradation and inflammation, in line with the existent knowledge. However, a number of peptides/protein precursors, not highlighted previously in association to HF or CKD, such as peptides of PIGR, CD14, ANR17, COL4A2 COL4A4, COL6A5, ROBO1 and HUWE1 may be important players in the mechanisms of CRS. As the present work is the first attempt to explore the urine peptidome profile of CRS patients, the findings of our study require further validation.

Methods

Study design: patient data and selection. Urinary peptidomics datasets from patients with CRS (in this study, CRS patients simultaneously combine both pathologies; HF and CKD), as well as individuals with no signs of diseases (controls) at urine sampling were used. These datasets corresponded to urine samples from cohorts described in several published studies investigating mainly renal failure (including Syskid[15], FSGS-Aachen[24]), or heart and cardiovascular failure (including NTCVD-Urin[69], FROG-ICU[70], PCHF-Urin[71] and HOMAGE[72]). The data were investigated for the availability of information on both kidney (i.e. CKD) and heart (i.e. HF) disease. The kidney function was assessed via the eGFR assessed based on ´Chronic Kidney Disease Epidemiology Collaboration´ (CKD-EPI). The ´European Society of Cardiology´ guidelines were used for the HF diagnosis and subtyping[73]. Clinical, pathophysiological, and molecular variables such as ejection fraction, systolic blood pressure, diastolic blood pressure, serum creatinine, hypertension, NT-proBNP levels, left ventricular ejection fraction (LVEF) as well as information on the age and sex, were retrieved (see Table 1). These datasets (corresponding to 3463 individuals) were then separated into the CRS cohort consisting of patients with both pathologies; HF and CKD with an eGFR < 60 ml/min/1.73 m^2. The control group with no signs of heart disease and preserved kidney function (eGFR > 60 ml/min/1.73 m^2) was selected (see Table 1). The study had received ethics approval (EK163/19 Ethik-Commission of the medical faculty of the RWTH Aachen), fulfilling all the requirements on the protection of the individuals participating in medical research and in accord-

ance with the principles of the Declaration of Helsinki[74]. All data sets received were anonymized. All experiments were performed in accordance with relevant named guidelines and regulations. Each patient has written informed consent to use part of the tissue for scientific research.

Case–control matching. CRS patients were matched on age and sex with controls at a 1:1 ratio. Following the case–control matching procedure, the final groups consisted of 353 patients with CRS compared with 356 individuals with no signs of either disease as listed in Table 1.

CE-MS. The urine samples have been prepared and measured by CE-MS as stated before[75]. The P/ACE MDQ capillary electrophoresis system (Beckman Coulter, USA) connected to a micro-TOF–MS (Bruker Daltonic, Germany) was used for the CE-MS analysis. The probabilistic clustering algorithm along with isotopic distribution and conjugated masses for charge have been used for RAW MS data evaluation as described previously[67]. Totally, twenty-nine fragments of collagens that were not affected by disease were used for the normalization of the CE-MS data.

Peptide sequencing. Urinary peptides were fragmented using Orbitrap MS coupled to CE (CE-MS/MS) or liquid chromatography (LC–MS/MS)[68]. The fragmentation spectra were matched to the protein sequences from up-to-date databases (International Protein Index[76], Reference sequence database at NCBI[77] and UniProt Knowledgebase[78]) using Proteome Discoverer 1.4 (Thermo Scientific, Bremen, Germany) with an integrated Sequest search engine[79]). The following search parameters were applied: (1) precursor mass tolerance: 5 ppm, (2) fragment mass tolerance: 50 mDa and (3) variable post-translational modifications: hydroxylation of lysine and proline, and oxidation of methionine, and (4) Enzyme name: No enzyme (Unspecific). Identified biomarkers were also assigned in silico to sequenced peptides from the Human Urinary Proteome database.

Bioinformatic analysis. Information on the function and expression of the parental proteins was extracted from Gene Cards (http://www.genecards.org) and linked databases ProteomicsDB (http://www.proteomicsdb.org), Uniprot (http://www.uniprot.org), and Human Protein Atlas (http://www.proteinatlas.org). Pathway enrichment analysis and visualization of data were performed by the Metascape[80]. Gene Ontology (GO) annotation of molecular functions was performed by the Gene Ontology resource (GO; http://geneontology.org).

Proteases analysis. The Proteasix (http://www.proteasix.org), an open-source tool was used for the protease prediction analysis[81]. As such, the potentially involved proteases were linked with the generation of the identified CRS-associated peptides. In brief, Proteasix uses information about the protease/cleavage site associations from a number of protease databases including the MEROPS, the CutDB, the UniProt Knowledgebase and the literature. The generated list of proteases is divided into two types; (a) "predicted" and (b) "observed". For the "observed" proteases the protease/cleavage site association is collected from the literature, whereas for the "predicted" proteases the predicted proteolysis is determined by the MEROPS database. To improve the reliability of the proteolytic data, we decided to focus only on the "observed" proteases.

Statistical analysis. The Kolmogorov–Smirnov normality test was used to determine the distribution of the urine peptidome data. Statistical analysis of the abundance of urinary peptides was performed using the non-parametric Mann–Whitney U test, followed by correction for multiple testing using the Benjamini-Hochberg (BH) method. Statistical analysis was performed using SPSS software version 20.0 (SPSS, Inc., Chicago, Illinois). A BH-adjusted P-value < 0.05 was considered to be statistically significant. The abundance of urinary peptides was analyzed and plotted using GraphPad Prism 7 (GraphPad Software, La Jolla, California, USA). Data are presented as mean ± standard deviation (s.d.) (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$).

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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Author contributions

E.P., H.M., A.V., and J.J. designed the study; E.P., wrote the manuscript text, performed data analysis and interpretation; T.H., A.L., and H.M. compiled peptidomics datasets; V.L. contributed to the pathway enrichment analysis; all authors revised the manuscript; all authors read and approved the final manuscript.

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H.M. is the co-founder and co-owner of Mosaiques Diagnostics GmbH. T.H. and A.L. are employed by Mosaiques Diagnostics GmbH. E.P, V.L, A.V, J.J: The authors declare no competing interests.

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Supplementary Table S1. List of the 559 Cardiorenal Syndrome (CRS) differentially excreted peptides (Sci Rep. 2021 Aug 10;11(1):16219. doi: 10.1038/s41598-021-95695-z).

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e07000	FSNGADL	A1AT	Alpha-1-antitrypsin	336	342	66.29	57.79	4.69E-06	3.96E-05	2740.37	3648.07	1737.93	3075.63	0.63
e12741	MIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	398	418	15.73	44.76	2.89E-17	1.89E-15	697.93	4430.52	5451.53	23981.72	7.81
e18378	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAE	A1AT	Alpha-1-antitrypsin	25	56	31.18	58.36	8.06E-16	4.15E-14	654.42	3243.33	3777.57	11531.19	5.77
e13340	LMIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	397	418	11.24	32.01	1.91E-11	4.61E-10	420.52	2617.34	3494.64	15759.84	8.31
e12271	EDPQGDAAQKTDTSHHDQDHP	A1AT	Alpha-1-antitrypsin	25	45	67.98	55.81	2.69E-07	2.96E-06	167.29	225.94	86.25	132.49	0.52
e05929	TIDEKGTEAAGAMFL	A1AT	Alpha-1-antitrypsin	363	377	43.82	62.61	2.45E-08	3.35E-07	147.26	456.98	430.69	1307.44	2.92
e14697	FLPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	277	299	8.71	31.16	4.23E-14	1.61E-12	140.49	907.79	3546.50	25865.35	25.24
e11895	FFLPDEGKLQHLENELTHD	A1AT	Alpha-1-antitrypsin	276	294	54.21	75.07	6.14E-16	3.24E-14	86.37	141.77	664.51	3480.70	7.69
e11793	FKGKWERPFEVKDTEEED	A1AT	Alpha-1-antitrypsin	214	231	10.96	32.01	3.85E-12	1.03E-10	55.64	396.93	829.94	5210.61	14.92
e13865	LPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	278	299	14.61	41.64	4.20E-16	2.28E-14	47.40	262.25	1516.74	11854.83	32.00
e12950	LREGETKAVKTVRTPGAAANLEL	A1BG	Alpha-1B-glycoprotein	435	457	16.85	46.18	7.75E-17	4.73E-15	218.31	1179.12	538.23	1496.53	2.47
e12127	LREGETKAVKTVRTPGAAANLE	A1BG	Alpha-1B-glycoprotein	435	456	12.36	38.24	2.76E-16	1.54E-14	59.29	373.82	413.65	1910.86	6.98
e07656	VVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	324	340	24.44	50.42	3.15E-13	9.94E-12	244.01	1010.61	1500.29	5746.39	6.15
e09323	MGVVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	322	340	16.01	38.81	3.60E-12	9.73E-11	78.89	431.45	648.50	2100.08	8.22
e05548	VVSLGSPSGEVSHPR	AHSG	Alpha-2-HS-glycoprotein	324	338	22.19	34.84	8.53E-05	5.23E-04	66.96	252.32	188.37	788.27	2.81
e14790	DAHKSEVAHRFKDLGEENFKALVL	ALB	Albumin	25	48	32.30	48.73	8.52E-05	5.23E-04	5523.74	75796.51	8484.56	58573.44	1.54
e13562	DAHKSEVAHRFKDLGEENFKAL	ALB	Albumin	25	46	18.82	48.73	1.11E-17	7.65E-16	350.37	2780.00	2083.08	8375.65	5.95
e14191	DAHKSEVAHRFKDLGEENFKALV	ALB	Albumin	27	49	13.20	31.16	2.22E-08	3.05E-07	290.48	2664.32	619.46	3581.92	2.13
e12970	DAHKSEVAHRFKDLGEENFKA	ALB	Albumin	25	45	12.92	38.81	2.81E-16	1.56E-14	84.86	760.93	723.31	2776.86	8.52
e12518	DAHKSEVAHRFKDLGEENFK	ALB	Albumin	25	44	11.80	37.39	2.83E-16	1.57E-14	45.40	244.03	1035.29	5293.87	22.80
e05113	EAGSPPVVE	ANR17	Ankyrin repeat domain-containing protein 17	2,078	2,086	12.36	39.38	2.28E-16	1.29E-14	19.39	142.56	50.22	127.12	2.59
e04435	AILDETKGDYEK	ANXA1	Annexin	326	337	44.10	69.69	2.82E-15	1.33E-13	139.45	325.41	456.15	1042.74	3.27
e06716	LSALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	254	267	11.52	30.03	5.19E-10	9.85E-09	222.57	1311.10	1926.69	12480.98	8.66
e14633	VDVLKDSGRDYVSQFEGSALGKQLN	APOA1	Apolipoprotein A-I	43	67	28.65	65.16	6.36E-28	2.32E-25	135.50	1040.88	984.09	5138.49	7.26
e05683	SALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	233	245	38.48	60.06	7.28E-11	1.62E-09	91.44	268.38	420.46	1442.43	4.60
e03546	LGPHAGDVEGHLS	APOA4	Apolipoprotein A-IV	329	341	88.20	69.97	9.88E-21	1.07E-18	511.18	463.66	247.18	339.46	0.48
e10106	SNNAKEAVEHLQKSELTQ	APOA4	Apolipoprotein A-IV	39	56	21.63	37.96	1.15E-07	1.36E-06	44.21	146.39	176.61	537.48	3.99
e11210	FWDLDPEVRPTSA	APOC3	Apolipoprotein C-III	84	96	42.98	60.34	2.20E-04	1.19E-03	69.55	118.94	92.39	142.11	1.33
e04609	SIAAGGEGLTDVSPE	ATG12	Ubiquitin-like protein ATG12	14	28	30.90	23.23	2.31E-03	8.98E-03	115.63	283.23	64.52	507.76	0.56
e03035	WKYYYDGKD	AZGP1	Zinc-alpha-2-glycoprotein	135	143	35.39	22.38	1.72E-05	1.28E-04	42.89	99.64	20.33	68.89	0.47
e14596	LLKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	59	81	15.45	54.11	3.42E-30	2.21E-27	1855.36	23966.95	73093.64	476756.18	39.40
e13955	LKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	60	81	8.99	40.51	2.34E-23	3.88E-21	211.73	2111.69	12469.22	66859.69	58.89
e12566	NGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	62	81	21.07	40.23	5.19E-10	9.85E-09	29.50	181.50	831.63	4420.10	28.19
e12280	LLKNGERIEKVEHSDLSFSK	B2M	Beta-2-microglobulin	59	78	5.34	31.16	2.56E-19	2.28E-17	29.39	190.62	3853.53	19673.07	131.10
e00152	VSGFHPSD	B2M	Beta-2-microglobulin	47	54	18.54	52.97	1.50E-22	2.33E-20	25.46	126.19	102.72	270.50	4.03
e00153	NGERIEK	B2M	Beta-2-microglobulin	62	68	15.73	42.21	2.71E-15	1.28E-13	24.79	102.07	99.64	335.79	4.02
e01453	FHPSDIEVD	B2M	Beta-2-microglobulin	50	58	27.53	51.27	9.23E-14	3.25E-12	14.31	34.44	52.42	97.67	3.66
e00957	SGFHPSDIE	B2M	Beta-2-microglobulin	48	56	13.76	41.64	1.01E-16	6.02E-15	13.13	48.83	43.12	95.00	3.29
e00145	FHPSDIE	B2M	Beta-2-microglobulin	50	56	7.30	32.01	1.63E-16	9.38E-15	3.66	23.43	14.42	48.63	3.94
e00402	LDLSHNSL	CD14	Monocyte differentiation antigen CD14	254	261	26.40	45.04	4.53E-07	4.74E-06	12.92	36.31	42.46	327.65	3.29
e09580	NPPKPMPNPNPNHPSSSGS	CD99	CD99 antigen	71	89	32.02	43.63	1.67E-02	4.67E-02	125.46	282.34	132.06	250.88	1.05
e16206	DGVSGGEGKGGSDGGGSHRKEGEEADAPGVIPG	CD99	CD99 antigen	140	172	42.42	18.98	7.30E-12	1.88E-10	103.10	171.56	38.24	101.35	0.37
e10450	VSGGEGKGGSDGGGSHRKEGEE	CD99	CD99 antigen	99	120	63.48	54.67	1.26E-04	7.28E-04	82.09	110.23	49.67	71.56	0.61
e14231	DDPRPPNPPKPmPNPNPNHPSSSGS	CD99	CD99 antigen	65	89	32.87	42.78	1.52E-02	4.31E-02	31.92	63.22	44.05	97.35	1.38
e10043	FSHAVSSNGNAVEDPMEIL	CDH1	Cadherin 1	179	197	60.96	71.67	4.70E-03	1.63E-02	159.17	235.56	231.18	362.96	1.45

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e09883	ETLAEPEISGLWNEDYK	CFAP74	Cilia- and flagella-associated protein 74	448	464	44.38	61.47	5.01E-05	3.31E-04	59.71	100.21	202.67	1028.19	3.39
e12606	LSSLTETIEGVDAEDGHGPGEQQ	CFB	Complement factor B	236	257	27.53	43.63	4.47E-06	3.81E-05	71.67	177.56	1202.61	6258.45	16.78
e17006	SSQGGSLPSEEKGHPQEESEESNVSMASLGE	CHGB	Secretogranin-1	293	323	30.62	41.36	1.01E-02	3.10E-02	49.50	106.72	66.69	128.93	1.35
e18263	ASHTSDSDVPSGVTEVVVKLFDSDPITVTVPVEV	CLU	Clusterin	390	423	54.78	18.70	6.39E-25	1.43E-22	598.55	1178.38	109.99	447.37	0.18
e05622	FDSDPITVTVPVEV	CLU	Clusterin	410	423	28.37	41.36	4.05E-04	2.02E-03	309.09	695.83	465.02	823.04	1.50
e04757	SHTSDSDVPSGVTE	CLU	Clusterin	391	404	30.90	11.05	6.45E-12	1.68E-10	127.71	290.23	21.71	88.37	0.17
e06239	VASHTSDSDVPSGVTE	CLU	Clusterin	389	404	19.94	30.31	5.72E-03	1.94E-02	65.46	255.49	77.96	259.82	1.19
e14337	IHEAQQAMDIHFHSPAFQHPPTE	CLU	Clusterin	251	273	21.91	35.98	6.71E-06	5.49E-05	17.16	54.97	86.90	364.56	5.07
e02160	DKGDTGPPGPQG	COL3A1	Collagen alpha-1(III) chain	628	639	97.75	94.05	9.96E-09	1.48E-07	1953.80	1328.92	2594.94	1763.98	1.33
e04847	GGDkGEDGDPGQPGp	COL11A1	Collagen alpha-1(XI) chain	1,332	1,346	96.91	88.95	9.78E-09	1.46E-07	2931.61	1970.58	2219.83	1755.28	0.76
e05574	GpKGTSGGDGpPGpPGE	COL11A1	Collagen alpha-1(XI) chain	901	917	31.74	15.86	5.55E-09	8.72E-08	124.63	225.60	29.88	88.15	0.24
e12945	DGpQGPpGSVGSVGGVGEKGEPGEAGN	COL11A1	Collagen alpha-1(XI) chain	1,236	1,262	35.67	20.40	2.41E-06	2.18E-05	62.69	121.28	31.03	95.81	0.50
e11726	pGVVGPQGAAGETGPmGERGHpGP	COL11A2	Collagen alpha-2(XI) chain	924	947	95.22	85.84	1.72E-08	2.43E-07	1600.31	1218.23	1233.18	1309.86	0.77
e07199	pGPpGQQGTPGTQGLpGP	COL11A2	Collagen alpha-2(XI) chain	645	662	64.89	64.87	7.47E-03	2.40E-02	1086.62	1227.45	882.27	1360.08	0.81
e11542	pGpSGEKGETGDVGPMGpPGPpGP	COL11A2	Collagen alpha-2(XI) chain	1,161	1,184	83.99	71.67	6.82E-14	2.48E-12	429.64	452.93	237.91	500.19	0.55
e14204	GNEGpSGPPGpAGSPGERGAAGSGGPIGpPG	COL11A2	Collagen alpha-2(XI) chain	1,003	1,033	84.27	84.70	1.95E-03	7.78E-03	262.47	230.95	351.75	335.05	1.34
e09631	EPGppGQQGTpGTQGLpGPQ	COL11A2	Collagen alpha-2(XI) chain	644	663	7.30	35.98	3.21E-21	3.66E-19	33.89	185.11	265.92	508.94	7.85
e07106	EAGEKGNPGAEGLQGVpG	COL13A1	Collagen alpha-1(XIII) chain	555	572	37.36	47.88	1.14E-03	4.94E-03	301.97	625.48	404.00	556.39	1.34
e09468	GDKGAIGMpGRVGVKGQpGE	COL13A1	Collagen alpha-1(XIII) chain	134	153	12.64	30.88	1.72E-09	2.93E-08	105.20	926.28	265.76	1131.88	2.53
e17751	pPGPQGPSGLSIQGMpGmpGEKGEKGDTGLPGPQG	COL14A1	Collagen alpha-1(XIV) chain	1,502	1,536	92.98	82.15	1.55E-10	3.25E-09	782.98	677.77	532.67	612.88	0.68
e15200	GIpGGVGSpGRDGSpGQRGLPGKDGSSGPpG	COL14A1	Collagen alpha-1(XIV) chain	1,536	1,566	37.92	66.86	9.85E-16	5.01E-14	47.99	85.67	139.28	276.86	2.90
e02352	GDpGPpGPpGPpG	COL15A1	Collagen alpha-1(XV) chain	1,093	1,105	20.51	44.48	4.13E-13	1.27E-11	30.45	85.03	112.67	222.12	3.70
e17903	AGERGHPGApGPSGSPGLpGVPGSMGDMVNYDEIK	COL16A1	Collagen alpha-1(XVI) chain	1,406	1,440	76.97	89.80	1.13E-21	1.41E-19	571.25	621.57	1269.25	1115.67	2.22
e11495	GNSGEKGDQGFQGQPGFPGPpGP	COL16A1	Collagen alpha-1(XVI) chain	1,144	1,166	50.56	65.16	5.60E-07	5.75E-06	94.70	142.97	155.62	189.15	1.64
e10985	NSGEKGDQGFQGQPGFPGPPGP	COL16A1	Collagen alpha-1(XVI) chain	1,145	1,166	32.87	45.33	2.48E-03	9.49E-03	47.90	92.68	74.21	160.91	1.55
e05351	DKGEpGPPGQPGYpG	COL16A1	Collagen alpha-1(XVI) chain	1,079	1,093	40.73	28.90	1.78E-04	9.87E-04	43.92	200.82	19.24	66.34	0.44
e12384	EGpmGQRGREGPMGpRGEAGPpG	COL17A1	Collagen alpha-1(XVII) chain	617	639	34.55	59.21	5.37E-16	2.88E-14	41.12	92.14	157.53	375.55	3.83
e04863	SVPGPpGPpGPpGPpG	COL18A1	Collagen alpha-1(XVIII) chain	1,422	1,437	18.26	35.41	4.63E-08	5.97E-07	92.67	300.07	224.15	465.77	2.42
e11015	PKGDKGDPGVGERGppGpQGpP	COL18A1	Collagen alpha-1(XVIII) chain	848	869	32.30	40.51	9.27E-03	2.87E-02	33.30	65.10	62.26	144.61	1.87
e04820	GVNVpSYPGpPGPPG	COL19A1	Collagen alpha-1(XIX) chain	834	848	83.15	66.29	1.78E-06	1.65E-05	553.64	561.84	489.96	1195.12	0.88
e19753	GPEGPSGKpGINGKDGIPGAQGImGKpGDRGpKGERGDQGIP	COL19A1	Collagen alpha-1(XIX) chain	917	958	3.37	37.96	5.68E-30	3.26E-27	57.46	465.52	1586.34	4207.51	27.61
e03180	ApGDRGEpGPPGp	COL1A1	Collagen alpha-1(I) chain	798	810	95.79	96.88	3.93E-03	1.41E-02	22016.84	11295.74	24404.06	11092.84	1.11
e10266	NGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	229	249	100.00	97.45	2.99E-04	1.55E-03	8395.82	4567.06	9731.95	5570.24	1.16
e11498	GNSGEpGApGSKGDTGAKGEPGpVG	COL1A1	Collagen alpha-1(I) chain	431	455	99.16	96.88	8.51E-08	1.04E-06	7836.38	4794.73	6138.81	4422.11	0.78
e03890	ApGDRGEpGPpGPA	COL1A1	Collagen alpha-1(I) chain	798	811	92.98	88.10	1.54E-20	1.63E-18	7413.62	5699.83	3816.64	3653.42	0.51
e10554	EGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,021	1,042	99.72	95.75	1.06E-16	6.26E-15	7055.34	4079.57	4677.20	3175.67	0.66
e05682	VGPpGPpGPpGPpGPPS	COL1A1	Collagen alpha-1(I) chain	1,177	1,193	86.80	79.04	1.80E-05	1.33E-04	6390.34	5001.70	4837.82	4283.53	0.76
e11325	ADGQPGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843	91.85	91.22	9.90E-03	3.04E-02	5968.32	3474.36	6685.77	3883.04	1.12
e11452	ADGQpGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843	96.91	96.32	1.01E-05	7.92E-05	4769.53	2430.42	5675.13	2723.89	1.19
e16177	ESGREGApGAEGSPGRDGSpGAKGDRGETGpA	COL1A1	Collagen alpha-1(I) chain	1,011	1,042	94.66	81.87	2.52E-11	6.01E-10	4629.27	3943.26	3081.05	3405.67	0.67
e10395	NGDDGEAGKpGRPGERGpPGp	COL1A1	Collagen alpha-1(I) chain	229	249	99.72	98.30	1.75E-08	2.45E-07	4444.63	2319.24	5499.28	2801.07	1.24
e11375	NGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	700	725	91.85	90.65	1.34E-02	3.88E-02	3364.33	2385.49	3780.70	2535.85	1.12
e03322	SpGPDGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	546	559	99.16	92.07	6.29E-20	6.19E-18	3286.92	2772.28	1866.93	2306.69	0.57
e01758	ApGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	798	808	87.08	70.82	3.16E-16	1.74E-14	3166.42	2836.89	1739.14	2557.25	0.55
e10032	EGSpGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,021	1,041	99.44	94.33	3.29E-07	3.54E-06	2930.46	2176.41	3753.61	2468.25	1.28

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e10863	DGQPGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	820	843	99.16	98.58	3.86E-12	1.03E-10	2778.33	1491.51	3916.34	2410.46	1.41
e11613	GNSGEpGApGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	431	455	93.54	86.69	4.51E-14	1.70E-12	2738.82	1883.24	1751.23	1713.01	0.64
e11972	ADGQpGAKGEPGDAGAKGDAGppGPA	COL1A1	Collagen alpha-1(I) chain	819	844	97.75	94.33	8.93E-06	7.13E-05	2603.83	2054.76	2053.92	1946.11	0.79
e07132	EpGSpGENGAPGQmGPR	COL1A1	Collagen alpha-1(I) chain	288	304	60.39	65.16	9.98E-03	3.06E-02	2555.18	2554.09	1982.48	2130.91	0.78
e17288	GPpGESGREGAPGAEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,007	1,041	98.88	95.75	1.37E-04	7.88E-04	2300.28	1877.93	3088.88	2672.70	1.34
e05259	DGQPGAKGEpGDAGAK	COL1A1	Collagen alpha-1(I) chain	820	835	99.72	95.47	3.49E-03	1.28E-02	2115.56	1120.22	1817.41	918.23	0.86
e06709	GSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	542	560	96.07	95.18	1.17E-05	9.08E-05	2059.76	1086.96	2080.98	2581.90	1.01
e04419	ApGDRGEpGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812	97.75	93.20	5.67E-27	1.84E-24	2040.41	1124.31	1192.68	968.39	0.58
e05551	VGPpGPPGPpGPpGPPS	COL1A1	Collagen alpha-1(I) chain	1,177	1,193	92.98	84.14	9.91E-11	2.14E-09	2006.04	1515.88	1315.44	1187.92	0.66
e06186	SpGSPGpDGKTGPPGpAG	COL1A1	Collagen alpha-1(I) chain	543	560	99.44	98.58	6.95E-04	3.22E-03	1938.76	1007.57	1826.42	1626.89	0.94
e07678	TGSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	541	560	95.79	93.20	4.31E-04	2.14E-03	1791.99	1155.39	1653.49	1570.30	0.92
e06859	VGpPGpPGPpGPpGPPSAG	COL1A1	Collagen alpha-1(I) chain	1,177	1,195	67.98	74.79	6.83E-05	4.31E-04	1729.47	1784.65	2417.16	2239.36	1.40
e16118	GESGREGApGAEGSpGRDGSPGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,010	1,041	97.19	95.18	1.87E-08	2.61E-07	1615.95	1086.04	2358.41	1730.06	1.46
e02667	SpGPDGKTGpPGP	COL1A1	Collagen alpha-1(I) chain	546	558	97.47	95.18	1.52E-12	4.30E-11	1583.02	898.48	2237.97	1340.02	1.41
e10668	GpPGEAGKpGEQGVpGDLGAPGp	COL1A1	Collagen alpha-1(I) chain	650	672	97.75	94.33	2.34E-04	1.26E-03	1533.04	931.93	1892.66	1300.52	1.23
e10277	nGDDGEAGKpGRPGERGPPGp	COL1A1	Collagen alpha-1(I) chain	229	249	97.75	96.60	6.82E-19	5.54E-17	1377.88	1236.44	2706.86	3210.35	1.96
e03025	GQDGRpGPpGpPG	COL1A1	Collagen alpha-1(I) chain	560	572	87.92	64.31	4.06E-23	6.52E-21	1359.89	1220.03	643.06	930.82	0.47
e04843	GPpGpPGPpGpPGPPS	COL1A1	Collagen alpha-1(I) chain	1,178	1,193	74.16	67.99	5.76E-05	3.72E-04	1355.83	1714.29	1510.21	7496.84	1.11
e12661	GKNGDDGEAGKPGRpGERGPpGpQ	COL1A1	Collagen alpha-1(I) chain	227	250	96.91	92.35	9.64E-03	2.97E-02	1310.87	1171.40	1127.00	1032.53	0.86
e10025	NSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453	98.31	96.03	2.63E-14	1.04E-12	1271.31	766.62	1841.96	1081.78	1.45
e08916	DDGEAGKPGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	231	249	97.47	95.18	2.57E-07	2.83E-06	1267.14	890.85	1824.63	1502.82	1.44
e07944	GpPGEAGKpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	650	668	94.10	84.70	2.61E-08	3.54E-07	1197.22	899.95	883.97	843.14	0.74
e10953	DGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	820	843	97.47	97.73	1.06E-21	1.34E-19	1180.53	747.25	2042.48	1325.75	1.73
e01155	ApGDKGESGPS	COL1A1	Collagen alpha-1(I) chain	777	787	94.66	81.87	1.04E-03	4.56E-03	1163.01	1009.27	977.48	1024.14	0.84
e11850	ADGQPGAKGEpGDAGAKGDAGPPGpA	COL1A1	Collagen alpha-1(I) chain	819	844	86.80	62.89	1.25E-10	2.66E-09	1158.44	1179.19	762.72	1114.66	0.66
e17946	PpGPAGFAGPPGADGQPGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	807	846	94.10	89.24	1.24E-08	1.80E-07	1029.79	821.91	783.93	893.14	0.76
e07275	NGApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	700	719	88.20	77.34	6.88E-14	2.49E-12	1023.96	667.54	674.64	561.49	0.66
e03638	SpGSpGPDGKTGPp	COL1A1	Collagen alpha-1(I) chain	543	556	80.62	56.94	4.11E-15	1.89E-13	950.26	854.88	568.48	925.22	0.60
e08755	EGSpGRDGSpGAKGDRGET	COL1A1	Collagen alpha-1(I) chain	1,021	1,039	79.49	43.06	3.50E-22	4.88E-20	873.20	1761.80	373.25	609.20	0.43
e10657	AEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,020	1,041	92.98	78.19	1.66E-09	2.83E-08	865.85	840.54	635.23	861.30	0.73
e10437	AEGSPGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,020	1,041	91.85	82.72	9.10E-17	5.46E-15	859.71	899.32	403.89	474.49	0.47
e12508	KGNSGEpGAPGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	430	455	96.63	95.18	1.08E-11	2.71E-10	836.60	672.12	1408.79	1352.13	1.68
e17690	pPGADGQPGAKGEpGDAGAKGDAGppGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854	92.13	84.14	4.54E-12	1.20E-10	818.34	690.35	537.33	623.21	0.66
e17890	GPpGADGQPGAKGEpGDAGAKGDAGPPGpAGPAGPPGpIG	COL1A1	Collagen alpha-1(I) chain	815	854	92.13	84.42	4.91E-09	7.78E-08	803.09	663.91	600.21	723.42	0.75
e10326	SGEpGApGSKGDTGAKGEpGPVG	COL1A1	Collagen alpha-1(I) chain	433	455	92.98	90.93	2.19E-05	1.59E-04	737.91	510.85	933.92	636.73	1.27
e11002	AEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,020	1,042	87.08	54.96	3.30E-26	9.09E-24	726.96	740.59	316.26	598.21	0.44
e07807	GpPGpPGKNGDDGEAGKpG	COL1A1	Collagen alpha-1(I) chain	221	239	82.87	76.77	1.14E-04	6.70E-04	682.65	764.96	502.59	864.47	0.74
e16966	PpGESGREGApGAEGSpGRDGSPGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,008	1,041	93.82	82.72	2.24E-04	1.21E-03	663.78	555.40	561.50	606.07	0.85
e11678	ANGAPGNDGAKGDAGAPGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	699	725	83.43	75.92	2.31E-07	2.57E-06	652.82	670.10	510.20	790.00	0.78
e10141	PpGEAGKPGEQGVpGDLGApGP	COL1A1	Collagen alpha-1(I) chain	651	672	94.94	90.08	1.61E-03	6.56E-03	652.66	482.64	818.54	676.62	1.25
e07388	pPGEAGKpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	651	668	73.31	66.29	7.43E-09	1.13E-07	649.40	776.02	357.70	661.29	0.55
e07225	pPGEAGKpGEQGVPGDLG	COL1A1	Collagen alpha-1(I) chain	651	668	77.25	72.52	1.59E-10	3.33E-09	635.72	697.95	356.96	577.56	0.56
e17348	ppGESGREGAPGAEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,008	1,042	88.20	70.82	2.44E-18	1.85E-16	629.44	669.04	284.56	363.83	0.45
e09408	GDDGEAGKpGRPGERGPPGp	COL1A1	Collagen alpha-1(I) chain	230	249	93.82	90.37	1.12E-04	6.60E-04	624.34	517.48	916.61	873.25	1.47
e11533	pGEQGpSGASGPAGPRGPpGSAGApG	COL1A1	Collagen alpha-1(I) chain	1,126	1,151	76.97	62.89	1.56E-15	7.70E-14	621.94	782.92	220.54	312.82	0.35

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e11865	GADGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	818	843	79.21	82.72	5.19E-06	4.36E-05	610.22	597.37	933.49	857.21	1.53
e10771	DGQPGAKGEPGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	820	843	71.07	81.30	4.98E-03	1.71E-02	582.23	606.99	714.79	714.77	1.23
e10445	GNSGEpGApGSKGDTGAKGEPGp	COL1A1	Collagen alpha-1(I) chain	431	453	83.99	87.82	5.99E-04	2.83E-03	575.02	519.22	789.99	786.63	1.37
e12488	KGDRGETGpAGPPGApGAPGAPGPVGP	COL1A1	Collagen alpha-1(I) chain	1,033	1,059	96.35	97.17	1.36E-04	7.80E-04	558.85	467.25	696.08	567.94	1.25
e12366	GANGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	698	725	76.97	69.41	9.75E-08	1.17E-06	512.10	555.96	315.75	450.58	0.62
e14837	ERGSpGPAGPKGSpGEAGRpGEAGLpGAKG	COL1A1	Collagen alpha-1(I) chain	510	539	63.76	79.04	3.83E-12	1.03E-10	427.52	845.10	1379.25	3378.47	3.23
e11377	GNSGEPGApGSKGDTGAKGEpGPVG	COL1A1	Collagen alpha-1(I) chain	431	455	82.02	79.60	6.32E-04	2.97E-03	421.93	383.30	320.10	307.80	0.76
e02592	DDGEAGKpGRpG	COL1A1	Collagen alpha-1(I) chain	231	242	84.83	55.52	2.23E-28	8.94E-26	418.99	393.46	158.27	232.55	0.38
e10142	EGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,021	1,041	89.04	84.14	4.84E-05	3.21E-04	415.21	592.36	318.56	370.18	0.77
e06697	VGPpGpPGPpGPPGPPSAG	COL1A1	Collagen alpha-1(I) chain	1,177	1,195	46.63	58.36	1.65E-05	1.23E-04	401.17	643.46	691.50	913.20	1.72
e16606	ADGQpGAKGEpGDAGAKGDAGpPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	819	854	87.92	81.87	1.68E-09	2.87E-08	394.67	292.50	292.98	339.32	0.74
e01461	SpGEAGRpGEA	COL1A1	Collagen alpha-1(I) chain	522	532	28.09	62.61	1.74E-22	2.69E-20	391.41	991.14	1157.52	1386.06	2.96
e13817	AGPpGAPGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,042	1,071	90.45	94.05	2.25E-15	1.08E-13	356.25	300.58	596.86	462.83	1.68
e05236	SpGSpGPDGKTGppGP	COL1A1	Collagen alpha-1(I) chain	543	558	91.29	80.17	3.35E-06	2.94E-05	356.20	298.57	287.85	419.74	0.81
e09059	DDGEAGKPGRpGERGpPGp	COL1A1	Collagen alpha-1(I) chain	231	249	82.87	90.37	2.05E-13	6.68E-12	355.52	354.76	677.12	637.82	1.90
e14801	GPpGADGQPGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	815	846	89.89	83.29	4.32E-11	9.93E-10	352.66	262.32	258.92	392.47	0.73
e05353	GPpGKNGDDGEAGKpG	COL1A1	Collagen alpha-1(I) chain	224	239	78.65	67.99	2.29E-08	3.15E-07	344.70	375.44	214.13	334.25	0.62
e11537	GKNGDDGEAGKPGRpGERGPpGP	COL1A1	Collagen alpha-1(I) chain	227	249	85.67	86.40	8.85E-11	1.93E-09	343.22	308.05	589.67	499.34	1.72
e07799	GPpGEAGKpGEQGVPGDLG	COL1A1	Collagen alpha-1(I) chain	650	668	70.51	63.74	2.43E-04	1.30E-03	339.78	369.59	273.47	493.27	0.80
e13825	LTGPIGppGPAGAPGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	765	794	81.18	55.24	7.45E-23	1.18E-20	335.04	396.77	132.07	241.56	0.39
e17596	GPpGESGREGApGAEGSpGRDGSPGAKGDRGETGpA	COL1A1	Collagen alpha-1(I) chain	1,007	1,042	60.96	54.39	2.95E-03	1.10E-02	322.67	556.10	242.55	549.76	0.75
e11415	IGPpGPAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794	74.44	63.17	9.81E-11	2.12E-09	316.87	338.72	162.81	215.59	0.51
e02530	pGDRGEpGPpGP	COL1A1	Collagen alpha-1(I) chain	799	810	64.33	72.24	1.04E-06	1.00E-05	311.19	367.51	507.13	508.93	1.63
e06948	pPGPAGApGDKGESGPSGP	COL1A1	Collagen alpha-1(I) chain	771	789	69.66	59.49	2.66E-03	1.01E-02	311.01	347.05	303.92	562.60	0.98
e18831	DKGETGEQGDRGIKGHRGFSGLQGppGppGSPGEQGP	COL1A1	Collagen alpha-1(I) chain	1,095	1,131	67.70	84.70	1.28E-15	6.44E-14	310.86	987.39	1029.08	2695.34	3.31
e11777	ANGApGNDGAKGDAGApGApGSQGAPG	COL1A1	Collagen alpha-1(I) chain	699	725	80.90	77.05	1.66E-02	4.63E-02	310.54	285.99	266.00	274.89	0.86
e16771	GADGQpGAKGEpGDAGAKGDAGPPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	76.97	73.37	1.56E-02	4.39E-02	301.08	293.66	275.83	365.50	0.92
e06024	SpGSPGPDGKTGpPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560	90.73	79.60	1.25E-13	4.25E-12	299.85	248.99	212.94	397.02	0.71
e16548	ADGQpGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	819	854	85.11	75.35	1.38E-09	2.41E-08	297.17	259.35	216.86	340.06	0.73
e11554	GRTGDAGPVGPPGPpGppGpPGPPS	COL1A1	Collagen alpha-1(I) chain	1,169	1,193	52.53	28.61	1.32E-12	3.78E-11	291.37	528.98	96.56	258.38	0.33
e11641	GADGQPGAKGEPGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	818	843	62.08	38.81	1.30E-10	2.76E-09	288.36	356.87	163.59	308.66	0.57
e12986	ADGQpGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846	85.67	80.45	2.36E-03	9.12E-03	286.22	236.24	234.59	224.71	0.82
e11576	ADGQpGAKGEpGDAGAKGDAGppGP	COL1A1	Collagen alpha-1(I) chain	819	843	78.93	82.44	5.33E-03	1.82E-02	257.20	257.11	331.21	315.60	1.29
e02286	PpGEAGKpGEQG	COL1A1	Collagen alpha-1(I) chain	651	662	63.20	73.65	1.32E-02	3.84E-02	256.56	293.97	326.32	378.75	1.27
e15323	VQGPpGpAGEEGKRGARGEPGPTGLpGPpG	COL1A1	Collagen alpha-1(I) chain	456	485	60.67	53.26	5.60E-04	2.67E-03	255.38	363.63	184.75	425.74	0.72
e12851	LDGAKGDAGPAGPKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299	75.84	69.41	4.06E-03	1.44E-02	254.70	240.95	216.69	265.00	0.85
e00467	DGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	550	559	58.43	45.04	2.69E-08	3.63E-07	250.91	403.96	95.05	196.82	0.38
e08740	NSGEpGApGSKGDTGAKGEp	COL1A1	Collagen alpha-1(I) chain	432	451	60.39	46.18	5.13E-04	2.46E-03	250.25	362.68	204.83	398.54	0.82
e11536	NGDDGEAGKPGRpGERGPpGPQG	COL1A1	Collagen alpha-1(I) chain	229	251	71.91	67.14	4.34E-03	1.52E-02	245.68	299.46	215.53	364.74	0.88
e20010	ARGNDGATGAAGpPGPTGPAGPPGFPGAVGAKGEAGpQGpRGSEGpQG	COL1A1	Collagen alpha-1(I) chain	321	368	64.04	78.75	7.97E-04	3.63E-03	240.83	294.72	334.76	423.45	1.39
e12101	ADGQpGAKGEpGDAGAKGDAGPpGpA	COL1A1	Collagen alpha-1(I) chain	819	844	67.13	50.42	1.77E-08	2.49E-07	228.81	260.30	138.33	227.09	0.60
e01399	DGRpGPpGPpG	COL1A1	Collagen alpha-1(I) chain	562	572	60.11	26.35	4.02E-21	4.51E-19	227.30	323.55	71.70	184.80	0.32
e05423	VGpPGPPGpPGPPGPPS	COL1A1	Collagen alpha-1(I) chain	1,177	1,193	51.69	40.23	3.00E-04	1.55E-03	224.55	350.39	136.44	237.42	0.61
e11245	NGDDGEAGKpGRpGERGpPGPQ	COL1A1	Collagen alpha-1(I) chain	229	250	62.36	60.34	5.26E-03	1.80E-02	223.41	390.38	158.88	313.32	0.71
e09542	GDDGEAGKpGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	230	249	75.56	82.72	1.50E-06	1.40E-05	222.09	234.93	340.01	327.78	1.53

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e11270	ISVPGPMGPSGPRGLpGPpGApGP	COL1A1	Collagen alpha-1(I) chain	175	198	58.15	74.50	1.55E-06	1.45E-05	220.46	763.17	1598.12	8802.83	7.25
e09627	PpGPpGKNGDDGEAGKpGRp	COL1A1	Collagen alpha-1(I) chain	222	241	65.17	41.36	9.65E-12	2.45E-10	214.64	268.90	121.47	241.22	0.57
e08598	NSGEPGApGSKGDTGAKGEp	COL1A1	Collagen alpha-1(I) chain	432	451	64.61	54.96	4.53E-04	2.23E-03	201.73	251.55	142.94	204.19	0.71
e17949	GEPGPPGPAGFAGPPGADGQPGAKGEPGDAGAKGDAGPpG	COL1A1	Collagen alpha-1(I) chain	803	842	55.06	34.28	1.88E-08	2.62E-07	199.98	262.03	120.70	254.09	0.60
e09125	SpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,023	1,042	60.67	52.12	7.01E-03	2.28E-02	197.01	294.92	177.26	573.86	0.90
e12411	ApGPAGARGNDGATGAAGppGPTGPAGP	COL1A1	Collagen alpha-1(I) chain	315	342	52.81	30.59	3.80E-11	8.81E-10	195.11	362.17	71.60	172.98	0.37
e11734	ADGQPGAKGEPGDAGAKGDAGpPGPA	COL1A1	Collagen alpha-1(I) chain	819	844	57.87	44.19	2.78E-04	1.45E-03	189.71	265.49	146.53	288.45	0.77
e08888	pQGpGGPPGpKGNSGEPGApG	COL1A1	Collagen alpha-1(I) chain	420	440	67.98	56.37	5.17E-04	2.48E-03	188.56	226.07	150.56	228.37	0.80
e13065	ADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846	70.22	62.04	1.98E-04	1.09E-03	184.04	181.87	135.88	160.74	0.74
e14211	GPpGKNGDDGEAGKPGRpGERGPpGpQ	COL1A1	Collagen alpha-1(I) chain	224	250	59.27	51.27	7.24E-03	2.34E-02	172.33	274.38	127.85	226.09	0.74
e05704	DGQPGAKGEpGDAGAKG	COL1A1	Collagen alpha-1(I) chain	820	836	51.12	52.69	4.13E-03	1.46E-02	170.50	262.38	281.11	368.54	1.65
e05448	EpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	828	844	53.09	38.24	3.18E-08	4.21E-07	170.37	230.46	77.13	153.39	0.45
e13850	PpGKNGDDGEAGKPGRpGERGppGPQ	COL1A1	Collagen alpha-1(I) chain	225	250	49.16	40.51	1.68E-03	6.84E-03	169.45	323.26	97.74	213.16	0.58
e05703	ApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	702	719	69.94	79.89	1.08E-02	3.25E-02	165.43	197.04	202.44	243.11	1.22
e16015	NVGApGAKGARGSAGpPGATGFpGAAGRVGPpGP	COL1A1	Collagen alpha-1(I) chain	855	888	44.94	65.44	4.18E-10	8.07E-09	165.12	315.32	379.89	620.94	2.30
e12085	RTGDAGPVGpPGPpGPpGPpGPPSAG	COL1A1	Collagen alpha-1(I) chain	1,170	1,195	41.85	28.90	3.34E-06	2.93E-05	155.90	265.56	63.34	144.98	0.41
e08629	TGPIGpPGPAGApGDKGESGP	COL1A1	Collagen alpha-1(I) chain	766	786	39.89	66.29	3.97E-14	1.52E-12	151.00	307.21	391.16	662.05	2.59
e04666	GPpGEAGKpGEQGVP	COL1A1	Collagen alpha-1(I) chain	650	664	49.16	65.44	1.17E-06	1.12E-05	147.33	260.25	234.82	338.33	1.59
e13200	TGPIGpPGPAGAPGDKGESGpSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	766	794	61.80	53.26	1.00E-05	7.89E-05	147.18	198.31	79.58	122.91	0.54
e10653	SGREGApGAEGSpGRDGSpGAKG	COL1A1	Collagen alpha-1(I) chain	1,012	1,034	72.75	64.31	8.28E-04	3.73E-03	141.13	199.27	97.78	135.23	0.69
e13595	GpPGADGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	815	843	59.27	71.10	1.11E-03	4.82E-03	140.18	183.96	194.02	280.01	1.38
e04947	EpGKAGERGVPGpPG	COL1A1	Collagen alpha-1(I) chain	591	605	66.85	56.94	9.54E-05	5.75E-04	136.86	219.34	93.69	155.99	0.68
e05879	SpGSPGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560	50.00	42.21	1.48E-04	8.43E-04	131.39	227.59	70.32	125.94	0.54
e11836	GLpGpAGpPGEAGKPGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	644	668	44.94	39.66	8.51E-03	2.67E-02	128.34	216.43	78.16	190.52	0.61
e10135	SGNAGPpGPpGPAGKEGGKGPRG	COL1A1	Collagen alpha-1(I) chain	889	911	59.27	41.36	1.70E-07	1.95E-06	124.39	241.33	80.47	199.83	0.65
e09230	NGApGNDGAKGDAGApGApGSQ	COL1A1	Collagen alpha-1(I) chain	700	721	40.73	53.26	7.32E-04	3.37E-03	123.62	277.26	173.68	364.62	1.40
e13918	AGpPGApGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,042	1,071	47.47	61.19	7.67E-06	6.18E-05	116.59	201.08	238.25	388.32	2.04
e19986	ARGNDGATGAAGPpGPTGPAGPpGFpGAVGAKGEAGPQGPRGSEGPQG	COL1A1	Collagen alpha-1(I) chain	321	368	44.38	69.41	1.46E-11	3.60E-10	115.77	188.93	249.58	396.63	2.16
e17825	GPpGADGQPGAKGEPGDAGAKGDAGPPGpAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	815	854	40.45	31.44	2.06E-03	8.16E-03	115.06	221.99	70.86	160.90	0.62
e16056	GESGREGAPGAEGSpGRDGSPGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,010	1,041	34.55	55.52	6.04E-09	9.41E-08	111.81	251.07	223.15	349.81	2.00
e17438	AGRpGEVGpPGpPGPAGEKGSPGADGPAGAPGTPGPQG	COL1A1	Collagen alpha-1(I) chain	916	953	44.38	24.36	8.82E-08	1.07E-06	109.20	156.92	72.15	172.16	0.66
e05692	GSpGSpGPDGKTGpPGp	COL1A1	Collagen alpha-1(I) chain	542	558	39.04	28.90	3.67E-04	1.86E-03	108.52	227.14	54.91	135.41	0.51
e17626	pPGADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854	53.93	39.66	4.86E-07	5.04E-06	106.09	166.04	60.10	134.31	0.57
e06018	VGPpGPPGPpGPPGPPSA	COL1A1	Collagen alpha-1(I) chain	1,177	1,194	17.42	30.59	2.12E-04	1.16E-03	102.27	299.77	140.83	389.47	1.38
e06547	GSpGSpGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	542	560	47.47	36.83	1.14E-03	4.93E-03	102.14	155.51	80.29	199.80	0.79
e12949	LDGAKGDAGPAGpKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299	61.80	57.79	9.15E-03	2.84E-02	96.46	127.62	75.91	131.22	0.79
e12624	KGNSGEpGApGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	430	455	53.37	60.06	5.04E-04	2.43E-03	93.45	148.27	175.20	262.21	1.87
e17221	GPpGESGREGAPGAEGSpGRDGSPGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,007	1,041	31.74	47.59	1.31E-05	9.99E-05	92.54	242.38	172.85	397.73	1.87
e11527	IGPpGpAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794	50.28	36.26	1.04E-05	8.18E-05	91.72	137.63	53.57	106.27	0.58
e09124	SGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	433	453	43.82	64.02	1.03E-13	3.56E-12	89.64	166.13	217.86	268.95	2.43
e00214	SpGEAGRpG	COL1A1	Collagen alpha-1(I) chain	522	530	44.66	53.26	1.38E-02	3.96E-02	86.32	158.20	110.86	225.20	1.28
e13730	AGPpGAPGApGAPGPVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,042	1,071	47.19	68.56	9.01E-13	2.66E-11	82.53	137.49	186.05	245.71	2.25
e03372	DGQPGAKGEpGDAG	COL1A1	Collagen alpha-1(I) chain	820	833	35.67	21.25	6.05E-07	6.14E-06	77.50	126.72	31.61	74.60	0.41
e08489	SpGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,023	1,041	41.85	72.52	2.54E-26	7.20E-24	77.44	145.87	393.89	566.53	5.09
e18625	AAGEpGKAGERGVPGppGAVGPAGKDGEAGAQGpPGPAGPAG	COL1A1	Collagen alpha-1(I) chain	588	629	45.51	29.46	9.79E-06	7.74E-05	75.73	125.63	45.82	98.50	0.61

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e13056	AGpPGApGApGAPGpVGPAGKSGDRGET	COL1A1	Collagen alpha-1(I) chain	1,042	1,069	52.81	32.29	6.07E-11	1.36E-09	75.70	103.56	34.38	77.24	0.45
e06650	EGSpGRDGSpGAKGDRG	COL1A1	Collagen alpha-1(I) chain	1,021	1,037	49.72	41.08	1.21E-03	5.20E-03	72.72	133.07	49.44	142.25	0.68
e04177	PpGPpGPpGPPGPPS	COL1A1	Collagen alpha-1(I) chain	1,179	1,193	21.91	35.41	2.75E-04	1.44E-03	72.69	263.23	157.59	663.93	2.17
e06282	GPIGPpGPAGApGDKGES	COL1A1	Collagen alpha-1(I) chain	767	784	24.72	39.38	3.09E-05	2.15E-04	70.03	161.04	109.39	175.66	1.56
e12120	DGAKGDAGPAGpKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	274	299	24.44	38.53	1.78E-04	9.87E-04	69.97	443.16	54.77	124.87	0.78
e10057	GEpGEpGASGPMGPRGPpGPpG	COL1A1	Collagen alpha-1(I) chain	206	227	43.54	55.81	7.52E-04	3.45E-03	68.98	124.44	108.82	180.72	1.58
e09923	NSGEPGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453	42.13	69.41	4.28E-17	2.72E-15	68.91	134.74	332.23	1635.87	4.82
e01166	DGRPGPPGPpG	COL1A1	Collagen alpha-1(I) chain	562	572	28.09	51.84	3.11E-11	7.27E-10	66.84	145.56	156.76	252.44	2.35
e02810	GPpGEAGKpGEQG	COL1A1	Collagen alpha-1(I) chain	650	662	32.87	24.36	3.06E-03	1.14E-02	65.94	135.63	46.15	185.33	0.70
e04281	ApGDRGEPGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812	36.80	28.90	2.29E-03	8.93E-03	64.11	121.78	35.79	89.41	0.56
e16078	VMGFpGPKGAAGEpGKAGERGVPGppGAVGPAG	COL1A1	Collagen alpha-1(I) chain	579	611	25.84	48.16	7.42E-11	1.64E-09	63.05	146.95	208.83	432.18	3.31
e01213	pGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	799	808	35.67	18.70	2.69E-08	3.64E-07	62.48	129.52	22.29	74.56	0.36
e11672	NGDDGEAGKPGRPGERGppGpQG	COL1A1	Collagen alpha-1(I) chain	229	251	45.51	39.38	1.46E-02	4.14E-02	62.37	103.09	43.22	89.44	0.69
e02517	QDGRpGpPGPpG	COL1A1	Collagen alpha-1(I) chain	561	572	33.99	15.01	6.21E-09	9.68E-08	61.23	113.77	26.79	79.13	0.44
e13207	PpGADGQpGAKGEPGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	816	843	36.52	47.88	8.44E-04	3.79E-03	60.10	120.68	82.65	128.30	1.38
e09321	EAGKpGEQGVpGDLGApGPSG	COL1A1	Collagen alpha-1(I) chain	654	674	31.46	51.84	3.76E-08	4.94E-07	58.49	128.55	114.67	355.04	1.96
e02804	SpGPDGKTGppGP	COL1A1	Collagen alpha-1(I) chain	546	558	19.66	31.16	9.79E-05	5.88E-04	57.87	295.50	118.11	411.50	2.04
e11264	NGApGNDGAKGDAGAPGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	700	725	24.44	43.06	6.41E-08	7.99E-07	51.98	128.59	109.13	190.79	2.10
e15935	ESGREGApGAEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,011	1,041	48.88	65.44	4.02E-07	4.25E-06	51.82	76.54	92.79	150.92	1.79
e16624	GPpGESGREGApGAEGSpGRDGSpGAKGDRGET	COL1A1	Collagen alpha-1(I) chain	1,007	1,039	30.90	10.48	2.01E-12	5.61E-11	51.11	115.47	9.20	38.64	0.18
e09008	GNAGPpGPpGPAGKEGGKGPR	COL1A1	Collagen alpha-1(I) chain	890	910	25.28	50.42	3.09E-14	1.21E-12	50.50	245.86	119.97	211.91	2.38
e11538	GKNGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	227	249	34.55	55.81	3.70E-09	5.97E-08	50.36	124.44	102.07	171.45	2.03
e05810	PpGEAGKpGEQGVpGD	COL1A1	Collagen alpha-1(I) chain	651	666	30.06	44.76	2.03E-05	1.48E-04	48.70	123.32	78.23	129.60	1.61
e10192	ApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	702	725	27.25	40.51	1.34E-03	5.62E-03	48.54	147.01	53.83	119.38	1.11
e05458	GPpGPpGPpGPpGPPSA	COL1A1	Collagen alpha-1(I) chain	1,178	1,194	25.84	52.97	8.34E-14	2.96E-12	46.78	132.32	157.76	343.68	3.37
e15755	RGPpGPpGKNGDDGEAGKPGRpGERGPpGP	COL1A1	Collagen alpha-1(I) chain	220	249	2.25	32.01	1.49E-25	3.53E-23	45.53	573.87	825.99	2909.46	18.14
e01561	DGEAGKpGRpG	COL1A1	Collagen alpha-1(I) chain	232	242	41.85	24.36	7.68E-08	9.43E-07	42.52	86.68	20.53	97.54	0.48
e07917	DGEAGKPGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	232	249	24.44	56.09	6.83E-22	8.73E-20	41.42	96.18	205.85	350.74	4.97
e11940	GESGREGApGAEGSpGRDGSpGAKG	COL1A1	Collagen alpha-1(I) chain	1,010	1,034	32.58	19.26	1.30E-06	1.24E-05	36.57	93.01	12.18	50.68	0.33
e04497	GRpGEVGPpGPpGPA	COL1A1	Collagen alpha-1(I) chain	917	931	21.63	38.53	1.40E-08	2.01E-07	34.80	101.39	138.00	335.36	3.97
e02579	KpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	657	668	22.19	39.94	4.80E-08	6.17E-07	34.80	108.07	90.47	236.70	2.60
e01983	DGRpGPpGPpGA	COL1A1	Collagen alpha-1(I) chain	562	573	38.20	20.68	9.81E-09	1.46E-07	31.98	68.01	11.11	34.98	0.35
e18181	ERGEQGPAGSpGFQGLpGPAGPpGEAGKpGEQGVPGD	COL1A1	Collagen alpha-1(I) chain	630	666	13.76	30.03	4.18E-07	4.40E-06	30.23	131.58	77.74	235.94	2.57
e13342	GADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	818	846	19.66	34.56	4.04E-05	2.73E-04	27.42	71.85	40.48	74.86	1.48
e05202	DGRpGPpGPpGARGQ	COL1A1	Collagen alpha-1(I) chain	562	576	16.57	37.39	1.09E-09	1.94E-08	26.92	88.54	166.02	1002.84	6.17
e11286	KGNSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	430	453	20.51	34.56	3.14E-06	2.78E-05	25.85	74.02	95.31	227.18	3.69
e18806	ARGNDGATGAAGPpGPTGPAGpPGFpGAVGAKGEAGpQGPRG	COL1A1	Collagen alpha-1(I) chain	321	362	23.31	33.43	2.19E-03	8.59E-03	23.28	57.23	48.93	152.65	2.10
e13322	GPpGKNGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	224	249	26.69	57.51	2.14E-21	2.52E-19	23.03	53.27	101.43	147.31	4.40
e14893	GPpGADGQpGAKGEpGDAGAKGDAGpPGPAGP	COL1A1	Collagen alpha-1(I) chain	815	846	25.28	35.98	3.01E-03	1.13E-02	22.39	53.14	33.65	76.94	1.50
e08350	GEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	434	453	16.57	48.73	2.41E-22	3.59E-20	19.38	64.39	112.79	196.31	5.82
e00131	DGKTGPpGP	COL1A1	Collagen alpha-1(I) chain	550	558	16.57	37.39	1.62E-09	2.78E-08	18.08	51.00	43.27	89.37	2.39
e13043	PpGKNGDDGEAGKPGRPGERGppGP	COL1A1	Collagen alpha-1(I) chain	225	249	18.26	42.49	4.46E-14	1.68E-12	17.52	50.96	71.86	129.02	4.10
e13410	GPpGKNGDDGEAGKpGRPGERGppGP	COL1A1	Collagen alpha-1(I) chain	224	249	20.51	47.31	1.13E-15	5.71E-14	14.17	39.50	58.18	110.43	4.11
e15607	GFAGPpGADGQpGAKGEpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	812	844	13.76	31.16	5.13E-08	6.55E-07	12.11	39.40	34.80	103.42	2.87
e09729	SGNAGPpGPpGPAGKEGGKGPR	COL1A1	Collagen alpha-1(I) chain	889	910	16.29	35.98	6.10E-10	1.14E-08	11.59	35.48	47.54	247.12	4.10

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e19228	PGLPGPSGEpGKQGpSGASGERGPPGPMGPPGLAGppGESGR	COL1A1	Collagen alpha-1(I) chain	973	1,014	8.15	34.28	1.69E-17	1.14E-15	9.42	52.91	46.32	102.60	4.92
e13136	PpGKNGDDGEAGKPGRpGERGppGP	COL1A1	Collagen alpha-1(I) chain	225	249	14.61	32.29	2.44E-08	3.33E-07	9.16	32.12	24.89	58.94	2.72
e11128	KNGDDGEAGKPGRPGERGPpGp	COL1A1	Collagen alpha-1(I) chain	228	249	16.29	34.28	3.76E-08	4.94E-07	8.43	22.27	23.46	53.50	2.78
e17212	RTGEVGAVGPpGFAGEKGPSGEAGTAGpPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	830	865	97.19	94.33	1.04E-04	6.19E-04	1192.45	721.02	1058.40	848.98	0.89
e03691	YDGKGVGLGPGPMG	COL1A2	Collagen alpha-2(I) chain	81	94	78.09	52.97	3.98E-22	5.40E-20	680.43	965.74	232.47	475.07	0.34
e07217	GSpGNIGPAGKEGPVGLpG	COL1A2	Collagen alpha-2(I) chain	454	472	46.63	28.05	2.42E-08	3.31E-07	607.46	1748.00	236.14	636.61	0.39
e06182	GpAGPRGERGPpGESGA	COL1A2	Collagen alpha-2(I) chain	583	617	93.26	80.74	1.93E-03	7.71E-03	604.56	662.56	985.50	1174.23	1.63
e19745	SKGESGNKGEpGSAGPQGPpGpSGEEGKRGPNGEAGSAGPPGPpG	COL1A2	Collagen alpha-2(I) chain	353	397	87.36	77.62	1.58E-02	4.45E-02	521.33	494.99	510.55	657.19	0.98
e00421	DpGKNGDKG	COL1A2	Collagen alpha-2(I) chain	503	511	83.71	90.08	3.36E-14	1.30E-12	474.10	511.54	830.71	760.46	1.75
e08546	NGApGEAGRDGNPGNDGPpG	COL1A2	Collagen alpha-2(I) chain	918	937	48.03	26.63	1.39E-08	2.00E-07	353.68	514.12	216.65	513.62	0.61
e06154	EDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	143	157	82.58	76.49	8.15E-03	2.58E-02	323.89	331.08	266.63	280.15	0.82
e07808	KGPSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	846	865	64.89	43.91	6.05E-15	2.70E-13	308.04	407.32	109.10	209.43	0.35
e15593	NGEAGSAGpPGppGLRGSpGSRGLPGADGRAG	COL1A2	Collagen alpha-2(I) chain	384	415	70.79	43.91	4.53E-15	2.06E-13	253.88	285.13	121.35	203.30	0.48
e02933	GppGPDGNKGEpG	COL1A2	Collagen alpha-2(I) chain	613	625	80.34	82.44	3.40E-04	1.73E-03	223.19	247.98	291.39	288.43	1.31
e15467	GRDGNpGNDGPpGRDGQpGHKGERGYpG	COL1A2	Collagen alpha-2(I) chain	925	952	75.28	78.47	8.66E-03	2.71E-02	215.28	256.75	354.71	535.71	1.65
e19752	GEVGPAGpNGFAGpAGAAGQpGAKGERGAKGPKGENGVVGPTGpVG	COL1A2	Collagen alpha-2(I) chain	715	760	51.69	37.96	2.54E-05	1.81E-04	185.13	298.62	145.74	388.81	0.79
e09529	EEGKRGPNGEAGSAGPpGPpG	COL1A2	Collagen alpha-2(I) chain	377	397	56.18	54.11	1.14E-02	3.39E-02	177.03	241.71	181.88	846.88	1.03
e15679	TGEVGAVGPPGFAGEKGpSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	831	863	48.60	66.29	6.73E-07	6.77E-06	148.13	225.48	237.18	299.00	1.60
e02052	ApGEAGRDGNpG	COL1A2	Collagen alpha-2(I) chain	920	931	50.00	61.19	4.37E-03	1.53E-02	125.36	176.70	156.24	182.36	1.25
e10318	GEpGPAGSKGESGNKGEpGSAGP	COL1A2	Collagen alpha-2(I) chain	346	368	58.71	49.01	2.14E-04	1.16E-03	114.48	141.58	78.86	137.79	0.69
e18516	EVGKpGERGLHGEFGLpGpAGpRGERGPPGESGAAGP	COL1A2	Collagen alpha-2(I) chain	566	602	50.00	74.50	4.09E-14	1.56E-12	111.25	208.43	245.17	356.64	2.20
e04597	ApGENGTpGQTGARG	COL1A2	Collagen alpha-2(I) chain	203	217	32.30	5.10	2.45E-21	2.82E-19	110.53	278.93	10.03	83.49	0.09
e11265	NDGPpGRDGQpGHKGERGYpG	COL1A2	Collagen alpha-2(I) chain	932	952	51.69	42.21	1.18E-03	5.08E-03	97.38	176.40	63.19	155.13	0.65
e06839	GEDGHpGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	142	157	54.49	64.31	1.65E-02	4.62E-02	96.58	145.57	122.84	198.85	1.27
e04647	DGPpGRDGQpGHKG	COL1A2	Collagen alpha-2(I) chain	933	946	66.01	45.89	3.13E-18	2.31E-16	87.37	103.74	28.12	46.86	0.32
e15400	LkGQpGApGVkGEpGApGENGTpGQTGARG	COL1A2	Collagen alpha-2(I) chain	188	217	30.34	66.01	2.89E-28	1.12E-25	86.82	328.42	525.95	857.67	6.06
e17585	GDPGKNGDKGHAGLAGARGApGPDGNNGAQGPpGPQG	COL1A2	Collagen alpha-2(I) chain	502	538	51.69	66.29	1.71E-04	9.53E-04	77.25	108.09	130.88	211.10	1.69
e18887	AGEVGKpGERGLHGEFGLPGpAGPRGERGppGESGAAGP	COL1A2	Collagen alpha-2(I) chain	564	602	17.13	32.58	2.53E-06	2.28E-05	71.60	241.63	156.07	355.08	2.18
e17388	GPpGppGRDGEDGPTGPpGPPGPPGPPGLGGNFAAQ	COL1A2	Collagen alpha-2(I) chain	45	80	36.24	58.36	1.61E-09	2.77E-08	68.60	131.14	128.01	183.81	1.87
e17490	ERGppGESGAAGPTGpIGSRGPSGPPGPDGNKGEpG	COL1A2	Collagen alpha-2(I) chain	590	625	29.78	45.33	2.62E-05	1.87E-04	65.26	145.26	98.99	155.22	1.52
e15659	QGVQGGKGEQGpPGppGFQGLPGpSGPAGEV	COL1A2	Collagen alpha-2(I) chain	537	567	32.58	46.18	8.80E-04	3.93E-03	62.38	118.97	104.78	219.86	1.68
e08253	GRTGppGPSGISGPpGPpGP	COL1A2	Collagen alpha-2(I) chain	793	812	22.47	33.43	2.25E-03	8.78E-03	58.41	204.29	85.63	310.43	1.47
e16604	TGEVGAVGppGFAGEKGPSGEAGTAGpPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	831	865	19.66	31.73	3.73E-04	1.88E-03	51.60	147.67	76.54	170.09	1.48
e16340	EAGRDGNPGNDGppGRDGQpGHKGERGYPG	COL1A2	Collagen alpha-2(I) chain	923	952	17.98	32.01	1.05E-05	8.23E-05	47.74	257.99	354.51	2106.48	7.43
e13164	AVGPPGFAGEKGpSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	836	863	30.34	15.58	8.83E-08	1.07E-06	44.41	104.70	9.75	40.97	0.22
e09700	FAGEKGPSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	842	863	19.38	32.01	2.02E-04	1.10E-03	36.64	99.46	71.00	206.78	1.94
e14285	EAGRDGNPGNDGPpGRDGQpGHKGER	COL1A2	Collagen alpha-2(I) chain	923	948	20.22	42.21	4.82E-11	1.10E-09	35.88	115.76	196.40	735.07	5.47
e10519	GApGVKGEpGApGENGTPGQTG	COL1A2	Collagen alpha-2(I) chain	193	214	26.12	42.78	5.60E-06	4.66E-05	34.66	79.04	66.24	152.38	1.91
e10651	PpGKAGEDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	137	157	19.38	49.86	3.08E-19	2.66E-17	31.48	197.51	104.66	326.53	3.32
e11003	GPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	136	157	20.22	50.42	6.44E-19	5.30E-17	31.27	197.01	124.29	304.72	3.97
e18620	DQGPVGRTGEVGAVGppGFAGEKGPSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	824	863	33.15	43.06	4.96E-03	1.71E-02	26.64	56.33	48.93	106.27	1.84
e11629	AGPpGKAGEDGHpGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	135	157	19.94	45.04	3.86E-14	1.49E-12	22.90	107.43	131.17	430.96	5.73
e05776	DGPpGRDGQpGHKGE	COL1A2	Collagen alpha-2(I) chain	933	947	23.60	40.23	1.35E-06	1.28E-05	21.92	57.29	43.06	80.40	1.96
e16390	pNGPPGpAGSRGDGGpPGMTGFPGAAGRTGPpGP	COL1A2	Collagen alpha-2(I) chain	767	800	21.63	36.54	1.79E-05	1.33E-04	17.51	42.51	43.27	149.20	2.47
e10635	DGppGRDGQpGHKGERGYpG	COL1A2	Collagen alpha-2(I) chain	933	952	26.12	36.26	9.22E-03	2.86E-02	17.37	40.57	22.12	43.22	1.27

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e12793	GpAGPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	133	157	13.76	49.86	3.74E-28	1.42E-25	11.26	52.90	115.23	212.83	10.23
e05677	pGKDGDTGPTGPQGPQ	COL22A1	Collagen alpha-1(XXII) chain	1,305	1,320	98.60	98.30	1.88E-07	2.12E-06	4948.30	3046.24	3869.82	2690.31	0.78
e16219	ppGAKGQEGAHGAPGAAGNPGAPGHVGAPGPSGpP	COL22A1	Collagen alpha-1(XXII) chain	899	933	70.79	84.99	4.30E-11	9.88E-10	205.66	279.24	446.71	695.21	2.17
e15713	pGpLGTKGDRGAPGIPGSPGSRGDpGIGVAGp	COL22A1	Collagen alpha-1(XXII) chain	998	1,029	51.69	71.10	2.56E-11	6.08E-10	173.73	271.19	333.35	397.21	1.92
e09447	pGAAGNpGAPGHVGApGPSGPpG	COL22A1	Collagen alpha-1(XXII) chain	912	934	32.87	60.91	3.06E-19	2.66E-17	37.82	79.47	143.75	206.39	3.80
e09697	PGpPGPHGPPGpmGPHGLpGP	COL25A1	Collagen alpha-1(XXV) chain	531	551	94.66	92.07	6.82E-14	2.48E-12	1275.51	947.89	869.63	1306.99	0.68
e13646	QGpPGPpGPQGLQGPKGEQGSPGIPGM	COL25A1	Collagen alpha-1(XXV) chain	449	474	17.98	38.81	7.32E-11	1.62E-09	19.09	62.27	56.94	106.68	2.98
e04644	PpGPAGNPGpSpNSp	COL26A1	Collagen alpha-1(XXVI) chain	257	271	49.44	30.59	8.42E-07	8.30E-06	227.00	732.38	208.46	1444.12	0.92
e08201	NKGEPGpPGpYGSpGAPGI	COL28A1	Collagen alpha-1(XXVIII) chain	341	359	26.97	36.26	2.75E-03	1.04E-02	67.11	160.36	106.57	217.35	1.59
e09456	PGppGpPGYGSQGIKGEQGp	COL28A1	Collagen alpha-1(XXVIII) chain	698	717	24.72	42.78	2.82E-07	3.08E-06	39.10	110.09	107.00	406.14	2.74
e16656	FAGpPGADGQpGAKGEQGEAGQKGDAGApGpQGP	COL2A1	Collagen alpha-1(II) chain	835	868	94.66	94.05	7.02E-03	2.28E-02	636.22	451.68	737.51	507.86	1.16
e13033	GpAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	948	974	89.04	82.15	3.69E-07	3.93E-06	554.00	508.69	400.15	472.81	0.72
e12156	GPAGpPGEKGEPGDDGPSGAEGPPGp	COL2A1	Collagen alpha-1(II) chain	948	973	85.96	69.69	2.03E-05	1.48E-04	517.20	515.65	426.19	552.82	0.82
e12714	pAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	949	974	87.36	81.02	4.82E-08	6.19E-07	491.19	447.76	345.36	431.27	0.70
e04199	PVGpSGKDGANGIpG	COL2A1	Collagen alpha-1(II) chain	1,168	1,182	71.63	54.96	3.32E-14	1.29E-12	201.48	232.46	83.34	135.81	0.41
e17673	GpPGPAGFAGpPGADGQpGAKGEQGEAGQKGDAGAPGP	COL2A1	Collagen alpha-1(II) chain	828	865	18.54	44.19	3.72E-13	1.16E-11	189.68	897.85	2141.99	11230.08	11.29
e12007	pGADGQpGAKGEQGEAGQKGDAGAp	COL2A1	Collagen alpha-1(II) chain	839	863	44.66	24.08	2.93E-08	3.93E-07	189.22	429.64	117.90	376.99	0.62
e12658	AGppGEKGEPGDDGpSGAEGPpGPQG	COL2A1	Collagen alpha-1(II) chain	950	975	44.10	21.53	2.66E-12	7.33E-11	151.50	296.16	58.77	257.50	0.39
e19147	GAKGEAGAPGVKGESGSpGENGSPGPmGpRGLPGERGRTGP	COL2A1	Collagen alpha-1(II) chain	297	337	45.51	65.16	3.58E-11	8.32E-10	116.27	242.04	418.24	874.59	3.60
e02280	ApGEDGRpGPpG	COL2A1	Collagen alpha-1(II) chain	580	591	40.45	50.14	8.72E-03	2.72E-02	54.39	97.64	87.59	182.80	1.61
e09547	GPpGEGGKpGDQGVpGEAGApG	COL2A1	Collagen alpha-1(II) chain	672	693	32.58	23.51	1.18E-03	5.06E-03	40.88	84.56	29.32	180.17	0.72
e02994	NGNPGpPGpPGPSG	COL2A1	Collagen alpha-1(II) chain	911	924	15.73	42.78	1.02E-16	6.02E-15	38.01	120.11	188.87	373.76	4.97
e03354	SpGERGETGPpGP	COL3A1	Collagen alpha-1(III) chain	796	808	96.35	98.02	7.85E-16	4.05E-14	4712.69	3524.52	7544.53	4623.23	1.60
e06584	DGApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	587	604	98.60	97.17	1.29E-03	5.48E-03	4399.13	2264.86	4909.51	2370.87	1.12
e07676	NDGAPGKNGERGGpGGpGp	COL3A1	Collagen alpha-1(III) chain	586	604	99.16	100.00	1.93E-04	1.06E-03	4352.32	2062.92	3869.39	1885.97	0.89
e03389	EpGRDGVpGGPGm	COL3A1	Collagen alpha-1(III) chain	523	535	92.98	86.69	2.64E-19	2.33E-17	2897.80	2967.98	1365.83	1731.25	0.47
e15411	PQGPpGPTGpGGDKGDTGPpGPQGLQGLpGT	COL3A1	Collagen alpha-1(III) chain	616	646	96.07	88.67	6.18E-08	7.71E-07	2737.24	2193.54	1915.24	1666.92	0.70
e08526	GLpGTGGPpGENGKpGEpGP	COL3A1	Collagen alpha-1(III) chain	642	661	87.92	90.08	4.18E-13	1.29E-11	2681.17	4364.29	6180.54	5905.83	2.31
e01923	SpGERGETGPp	COL3A1	Collagen alpha-1(III) chain	796	806	89.33	70.54	8.09E-13	2.41E-11	2439.01	1953.69	1666.98	2311.55	0.68
e13707	GApGQNGEPGGKGERGApGEKGEGGppG	COL3A1	Collagen alpha-1(III) chain	813	840	96.91	98.30	4.10E-13	1.27E-11	2142.52	1909.99	3587.65	2969.55	1.67
e08188	GNDGApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	585	604	94.66	92.07	3.56E-06	3.10E-05	1763.05	1123.39	1372.46	942.47	0.78
e10257	GSNGNpGpPGPSGSpGKDGPpGP	COL3A1	Collagen alpha-1(III) chain	885	907	94.10	86.97	1.47E-02	4.17E-02	1703.82	1093.24	1996.73	1462.09	1.17
e17922	NTGApGSPGVSGPKGDAGQpGEKGSpGAQGpPGAPGPLG	COL3A1	Collagen alpha-1(III) chain	910	948	94.66	93.48	1.19E-02	3.51E-02	1400.99	976.01	1323.64	1193.57	0.94
e14735	KNGETGPQGPPGpTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	98.60	96.60	5.70E-10	1.07E-08	1189.02	742.92	927.77	838.39	0.78
e06068	NDGApGKNGERGGpGGP	COL3A1	Collagen alpha-1(III) chain	586	602	98.60	91.50	2.85E-19	2.49E-17	1130.08	704.54	675.09	407.26	0.60
e04824	GLpGTGGPpGENGKPG	COL3A1	Collagen alpha-1(III) chain	642	657	48.60	28.61	2.24E-08	3.09E-07	727.66	1393.40	356.92	980.71	0.49
e08405	GLpGTGGPpGENGKPGEpGP	COL3A1	Collagen alpha-1(III) chain	642	661	59.55	73.94	5.72E-15	2.58E-13	700.20	1376.37	1758.87	1857.91	2.51
e15129	ERGEAGIpGVpGAKGEDGKDGSPGEpGANG	COL3A1	Collagen alpha-1(III) chain	448	477	92.42	86.40	3.80E-03	1.37E-02	667.35	529.10	569.38	519.73	0.85
e10876	GDAGApGApGGKGDAGApGERGPpG	COL3A1	Collagen alpha-1(III) chain	663	687	87.08	92.35	3.88E-07	4.13E-06	552.15	628.13	701.84	564.55	1.27
e08539	ApGApGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	667	687	92.70	95.18	2.78E-09	4.57E-08	543.09	981.91	1434.18	10910.71	2.64
e10072	GLpGTGGPpGENGKpGEpGPKG	COL3A1	Collagen alpha-1(III) chain	642	663	89.89	80.74	1.27E-02	3.70E-02	502.26	429.49	588.10	1279.36	1.17
e05577	GGAGEpGKNGAKGEpGP	COL3A1	Collagen alpha-1(III) chain	429	445	63.48	56.66	4.03E-03	1.44E-02	479.81	643.72	336.51	477.16	0.70
e10902	AGpPGPEGGKGAAGPpGPpGAAGTpG	COL3A1	Collagen alpha-1(III) chain	698	723	81.74	69.41	7.80E-05	4.84E-04	428.24	439.89	412.30	612.77	0.96
e11904	GPAGFpGApGQNGEpGGKGERGApG	COL3A1	Collagen alpha-1(III) chain	807	831	77.53	61.47	5.27E-11	1.19E-09	404.27	428.75	235.47	345.94	0.58
e03940	SpGGpGSDGKpGpPG	COL3A1	Collagen alpha-1(III) chain	541	555	71.07	79.60	1.36E-02	3.91E-02	400.65	408.53	489.30	483.45	1.22

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e09521	EGGKGAAGpPGPpGAAGTpGLQG	COL3A1	Collagen alpha-1(III) chain	704	726	89.33	78.47	1.29E-05	9.88E-05	399.90	287.57	322.53	315.46	0.81
e07586	GPPGPTGPGGDKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	618	637	60.39	78.19	5.13E-04	2.46E-03	390.86	534.14	451.12	442.82	1.15
e14315	NRGERGSEGSPGHpGQpGPPGpPGApGP	COL3A1	Collagen alpha-1(III) chain	865	892	68.82	83.57	8.74E-13	2.60E-11	312.67	393.14	607.02	687.43	1.94
e11222	NDGApGKNGERGGpGGpGPQGPpG	COL3A1	Collagen alpha-1(III) chain	586	609	72.19	77.34	1.03E-02	3.15E-02	268.23	293.05	325.40	344.39	1.21
e01544	GpGSDGKpGPpG	COL3A1	Collagen alpha-1(III) chain	544	555	35.11	49.86	5.44E-10	1.03E-08	258.45	451.29	776.24	1071.88	3.00
e11911	GIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	453	477	54.21	39.94	3.18E-05	2.21E-04	256.18	372.69	149.48	243.78	0.58
e12235	GQNGEpGGKGERGApGEKGEGGPpG	COL3A1	Collagen alpha-1(III) chain	816	840	65.17	78.75	5.42E-18	3.90E-16	245.06	284.22	551.21	505.36	2.25
e10613	GPGMRGMPGSPGGpGSDGKpGpP	COL3A1	Collagen alpha-1(III) chain	532	554	82.30	69.69	2.52E-05	1.80E-04	229.29	213.17	192.07	258.72	0.84
e09891	SEGSPGHpGQPGpPGpPGApGP	COL3A1	Collagen alpha-1(III) chain	871	892	74.16	81.87	7.20E-09	1.10E-07	225.85	240.34	415.60	455.68	1.84
e13816	ERGEAGIpGVpGAKGEDGKDGSpGEpG	COL3A1	Collagen alpha-1(III) chain	448	474	74.72	86.12	7.90E-11	1.74E-09	223.63	216.83	355.70	291.81	1.59
e05568	TGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	623	639	44.38	25.50	1.53E-09	2.65E-08	215.87	311.16	93.47	215.22	0.43
e10938	QGLpGTGGpPGENGKpGEpGPKG	COL3A1	Collagen alpha-1(III) chain	641	663	31.18	52.41	5.35E-12	1.40E-10	208.01	585.63	694.51	1403.88	3.34
e07668	GTGGPpGENGKpGEpGPKG	COL3A1	Collagen alpha-1(III) chain	645	663	50.56	42.21	5.99E-05	3.85E-04	199.92	283.78	115.71	280.52	0.58
e07880	pGARGLpGpPGSNGNPGpP	COL3A1	Collagen alpha-1(III) chain	875	893	59.27	43.06	3.67E-07	3.92E-06	193.21	274.58	118.70	241.66	0.61
e16286	RGERGEAGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	446	477	63.48	71.10	5.38E-05	3.51E-04	158.22	224.25	320.33	501.45	2.02
e14712	AKGEDGKDGSpGEpGANGLpGAAGERGApG	COL3A1	Collagen alpha-1(III) chain	460	489	59.55	54.11	2.82E-03	1.06E-02	154.40	253.75	98.43	183.25	0.64
e05918	GTGGPpGENGKpGEpGP	COL3A1	Collagen alpha-1(III) chain	645	661	71.07	75.35	8.78E-04	3.92E-03	152.38	236.62	233.49	342.87	1.53
e03651	DGApGKNGERGGpG	COL3A1	Collagen alpha-1(III) chain	587	600	57.87	24.65	3.83E-22	5.23E-20	151.70	195.42	44.96	116.95	0.30
e09856	SNGNPGppGPSGSpGKDGPPGp	COL3A1	Collagen alpha-1(III) chain	886	907	61.52	54.96	1.76E-02	4.87E-02	151.26	172.94	134.85	216.80	0.89
e12496	AGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	452	477	61.24	38.81	4.54E-12	1.20E-10	141.92	184.57	66.10	130.23	0.47
e00259	ApGERGPpG	COL3A1	Collagen alpha-1(III) chain	679	687	65.17	88.10	1.94E-18	1.49E-16	132.10	191.93	239.81	248.88	1.82
e12333	TSGHPGSpGSpGYQGPpGEpGQAGP	COL3A1	Collagen alpha-1(III) chain	187	211	47.19	26.91	8.94E-09	1.34E-07	122.98	224.19	58.63	144.52	0.48
e01935	DGESGRpGRpG	COL3A1	Collagen alpha-1(III) chain	230	240	53.37	28.90	1.70E-15	8.34E-14	116.71	175.75	37.02	105.53	0.32
e10096	GEpGGKGERGApGEKGEGGPpG	COL3A1	Collagen alpha-1(III) chain	819	840	55.34	78.47	3.68E-17	2.37E-15	116.59	145.30	244.87	238.38	2.10
e08150	GNpGPpGPSGSpGKDGPPGp	COL3A1	Collagen alpha-1(III) chain	888	907	39.04	28.05	4.20E-04	2.09E-03	114.12	333.79	81.31	348.15	0.71
e03194	DGVPGKDGPRGPT	COL3A1	Collagen alpha-1(III) chain	752	764	49.44	20.68	2.65E-19	2.33E-17	108.81	180.03	45.54	316.52	0.42
e12891	RGGAGPPGpEGGKGAAGPpGpPGAAGTpG	COL3A1	Collagen alpha-1(III) chain	695	723	54.21	68.56	6.10E-10	1.14E-08	103.95	166.98	211.30	323.34	2.03
e06307	ApGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	670	687	53.09	71.39	3.67E-10	7.14E-09	102.11	155.76	213.52	295.43	2.09
e09629	QGLpGTGGPpGENGKpGEpGP	COL3A1	Collagen alpha-1(III) chain	641	661	55.62	69.69	5.82E-07	5.94E-06	94.37	122.07	173.44	229.44	1.84
e09061	GApGApGGKGDAGAPGERGppG	COL3A1	Collagen alpha-1(III) chain	666	687	42.42	73.37	1.63E-20	1.70E-18	76.33	172.23	189.54	342.13	2.48
e02032	GGpGSDGKpGPpG	COL3A1	Collagen alpha-1(III) chain	543	555	44.38	52.41	1.33E-02	3.85E-02	74.62	110.70	101.30	139.49	1.36
e12313	TGGpPGENGKPGEpGpKGDAGApGAP	COL3A1	Collagen alpha-1(III) chain	646	671	33.15	21.25	4.66E-05	3.11E-04	74.25	148.92	30.71	84.17	0.41
e13362	ApGQNGEPGGkGERGAPGEkGEGGPpG	COL3A1	Collagen alpha-1(III) chain	814	840	44.38	68.56	1.43E-12	4.08E-11	74.12	130.72	149.86	199.20	2.02
e05118	ApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	589	604	22.47	50.42	4.59E-18	3.33E-16	67.10	206.01	361.14	599.85	5.38
e14644	KNGETGPQGPPGPTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	44.66	35.69	3.66E-03	1.33E-02	59.18	98.57	49.40	122.67	0.83
e02169	EpGRDGVpGGpG	COL3A1	Collagen alpha-1(III) chain	523	534	40.17	46.74	2.43E-03	9.34E-03	57.38	191.31	120.43	351.43	2.10
e14224	NRGERGSEGSPGHpGQPGPpGPPGApGP	COL3A1	Collagen alpha-1(III) chain	865	892	32.02	48.73	4.22E-06	3.62E-05	49.09	105.36	98.33	184.97	2.00
e09966	GARGNDGARGSDGQPGPpGPpG	COL3A1	Collagen alpha-1(III) chain	318	339	27.53	43.63	3.40E-06	2.98E-05	48.58	132.40	164.65	573.23	3.39
e10992	GLAGTAGEpGRDGNpGSDGLpGR	COL3A1	Collagen alpha-1(III) chain	1,002	1,024	31.74	41.08	9.17E-03	2.84E-02	45.68	102.75	60.76	112.60	1.33
e01422	GpGSDGKPGPpG	COL3A1	Collagen alpha-1(III) chain	544	555	34.27	46.74	8.90E-05	5.41E-04	45.58	105.66	78.06	129.96	1.71
e00336	PpGENGKpG	COL3A1	Collagen alpha-1(III) chain	649	657	35.11	49.86	7.05E-06	5.74E-05	35.38	72.06	67.22	142.66	1.90
e01956	GpAGPpGpPGPpG	COL3A1	Collagen alpha-1(III) chain	174	186	20.51	33.43	5.23E-05	3.43E-04	33.39	91.71	77.55	257.82	2.32
e16231	pPGKNGETGPQGppGPTGPGGDKGDTGPPGpQG	COL3A1	Collagen alpha-1(III) chain	607	639	22.75	36.83	7.21E-05	4.51E-04	23.53	56.24	40.45	77.21	1.72
e20610	GLAGTAGEpGRDGNPGSDGLPGRDGSpGGKGDRGENGSpGAPGAPGHPGPPGp	COL3A1	Collagen alpha-1(III) chain	1,002	1,054	5.06	37.96	4.41E-26	1.20E-23	22.07	156.84	216.48	533.19	9.81
e11885	ENGKpGEPGpKGDAGApGApGGKGD	COL3A1	Collagen alpha-1(III) chain	652	676	21.63	33.43	4.40E-04	2.17E-03	21.27	91.98	28.38	57.77	1.33

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e00635	SpGKDGPpGP	COL3A1	Collagen alpha-1(III) chain	898	907	17.98	43.06	1.85E-14	7.52E-13	17.86	187.19	91.51	518.27	5.12
e14434	GEpGRDGNpGSDGLpGRDGSpGGKGDRG	COL3A1	Collagen alpha-1(III) chain	1,008	1,035	17.70	38.81	7.84E-10	1.43E-08	13.00	38.60	32.55	69.86	2.50
e00753	DKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	628	637	25.00	45.61	1.45E-08	2.07E-07	9.04	20.30	30.48	228.84	3.37
e14727	KNGERGGpGGPGPQGpPGKNGETGpQGpP	COL3A1	Collagen alpha-1(III) chain	592	620	3.65	30.31	1.81E-21	2.17E-19	5.51	49.17	94.08	391.13	17.09
e05864	GppGFTGPpGpPGPPGP	COL4A1	Collagen alpha-1(IV) chain	197	213	88.76	72.24	6.79E-37	1.14E-33	2701.70	2612.81	793.91	1117.35	0.29
e05726	GPpGFTGppGPPGPPGP	COL4A1	Collagen alpha-1(IV) chain	197	213	72.47	28.33	2.79E-40	6.99E-37	435.10	655.23	56.63	154.70	0.13
e08436	PGSRGDTGPpGpPGYGPAGP	COL4A1	Collagen alpha-1(IV) chain	594	613	32.02	22.38	1.24E-02	3.63E-02	114.16	225.53	109.81	307.76	0.96
e12014	DGAPGQKGEMGpAGpTGpRGFPGp	COL4A1	Collagen alpha-1(IV) chain	1,401	1,424	34.27	23.51	6.38E-05	4.06E-04	106.90	250.47	31.70	90.49	0.30
e11768	pGFPGAQGEPGSQGEpGDpGLpGP	COL4A2	Collagen alpha-2(IV) chain	365	388	22.47	35.41	2.20E-04	1.19E-03	44.83	146.36	82.52	231.43	1.84
e15360	GpKGDpGIpGLDRSGFpGETGSPGIPGHQ	COL4A3	Collagen alpha-3(IV) chain	836	864	97.19	88.39	1.33E-28	5.66E-26	1518.84	1734.64	480.74	545.99	0.32
e07481	KGPPGDHGLPGYLGSPGI	COL4A3	Collagen alpha-3(IV) chain	445	462	53.37	39.66	1.06E-05	8.25E-05	943.87	3122.98	394.24	1070.61	0.42
e07037	PGPPGTPGEpGMQGEPGP	COL4A3	Collagen alpha-3(IV) chain	1,360	1,377	57.58	51.56	3.89E-04	1.95E-03	660.65	1003.15	381.13	684.22	0.58
e06771	PGpPGpPGPPGHPGPQGp	COL4A3	Collagen alpha-3(IV) chain	655	672	51.12	46.18	7.36E-03	2.37E-02	190.10	242.09	135.86	195.97	0.71
e11819	NEGLDGPRGDpGQPGpPGEQGpP	COL4A3	Collagen alpha-3(IV) chain	784	806	35.96	18.70	1.05E-07	1.26E-06	103.30	201.86	55.74	194.27	0.54
e08406	HEDATpGGKGFPGPLGpPG	COL4A4	Collagen alpha-4(IV) chain	604	622	53.37	66.29	8.35E-07	8.25E-06	116.90	174.10	214.88	321.53	1.84
e15320	LPGFPGpEGPPGpRGQKGDDGIpGpPGPK	COL4A5	Collagen alpha-5(IV) chain	61	89	79.49	84.70	6.47E-03	2.14E-02	565.35	748.01	640.81	770.96	1.13
e07901	QKGDQGLPGDRGpPGpPG	COL4A5	Collagen alpha-5(IV) chain	256	273	50.28	29.18	1.15E-13	3.95E-12	124.42	223.96	24.50	63.45	0.20
e08942	pGFPGTpGLpGmPGHDGAPG	COL4A5	Collagen alpha-5(IV) chain	98	117	42.98	33.99	8.53E-03	2.67E-02	75.60	115.86	60.48	123.18	0.80
e09844	GLDGERGRPGPAGppGppGPS	COL4A6	Collagen alpha-6(IV) chain	1,240	1,260	37.92	26.35	1.87E-03	7.51E-03	217.09	953.46	126.93	372.17	0.58
e02526	GPpGPPGpSSNQG	COL4A6	Collagen alpha-6(IV) chain	1,252	1,264	48.88	28.05	1.31E-12	3.76E-11	151.30	260.64	53.61	287.71	0.35
e14398	PGMPGADGpPGHPGKEGppGEKGGQGpPG	COL5A1	Collagen alpha-1(V) chain	753	781	98.03	99.15	1.48E-31	1.24E-28	1767.53	1211.49	3197.88	1820.59	1.81
e03055	GEAGHPGPPGPpGP	COL5A1	Collagen alpha-1(V) chain	1,555	1,568	67.70	45.04	5.99E-15	2.68E-13	312.76	373.90	152.26	455.49	0.49
e05011	pGPPGEPGPAGQDGPP	COL5A1	Collagen alpha-1(V) chain	1,347	1,362	21.07	38.53	6.96E-06	5.68E-05	176.82	807.82	416.47	3140.66	2.36
e11679	EGpPGKPGEDGEpGRNGNpGEVG	COL5A2	Collagen alpha-2(V) chain	257	279	67.70	67.71	1.10E-03	4.79E-03	1345.34	2827.89	1969.53	2796.03	1.46
e06214	GSPGTSGppGSAGpPGSpG	COL5A2	Collagen alpha-2(V) chain	435	453	55.34	18.41	5.85E-26	1.53E-23	530.38	1312.68	71.70	251.39	0.14
e15375	GpMGAMGpLGPRGMpGERGRLGpQGAPGQ	COL5A2	Collagen alpha-2(V) chain	327	355	55.34	34.84	3.34E-15	1.57E-13	207.79	337.97	45.56	99.46	0.22
e11763	GpEGppGKpGEDGEPGRNGNPGE	COL5A2	Collagen alpha-2(V) chain	255	277	46.07	35.98	1.53E-03	6.29E-03	190.28	294.16	132.83	263.62	0.70
e11008	pPGEEGKRGPRGDpGTVGPpGP	COL5A2	Collagen alpha-2(V) chain	496	517	63.20	48.16	2.07E-07	2.33E-06	112.19	182.64	77.30	183.94	0.69
e13650	GpTGATGDKGPPGPVGPPGSNGpVGEpGP	COL5A2	Collagen alpha-2(V) chain	1,020	1,048	26.97	45.89	2.97E-06	2.64E-05	49.74	126.95	89.76	220.11	1.80
e15580	GpSGpVGpPGLAGERGEQGPpGPTGFQGLPG	COL5A2	Collagen alpha-2(V) chain	651	681	27.53	55.81	1.61E-14	6.67E-13	46.37	118.70	126.31	270.41	2.72
e15594	PGSRGENGpTGAVGFAGPQGPDGQPGVKGEP	COL5A2	Collagen alpha-2(V) chain	833	863	26.69	45.61	4.03E-07	4.26E-06	43.93	99.57	114.66	295.28	2.61
e05200	GPpGPpGFPGDpGPpG	COL5A3	Collagen alpha-3(V) chain	407	422	85.96	64.87	1.93E-24	3.91E-22	1215.94	2095.92	619.10	2442.22	0.51
e05060	GPpGPpGFpGDPGPPG	COL5A3	Collagen alpha-3(V) chain	407	422	76.40	47.59	7.37E-26	1.85E-23	597.14	837.43	264.78	1456.00	0.44
e08177	DGpEGPKGQAGQAGEEGPP	COL5A3	Collagen alpha-3(V) chain	760	778	69.38	55.52	1.60E-09	2.75E-08	433.58	823.15	178.62	411.87	0.41
e09921	pGVSGIDGSpGEKGDpGDVGGP	COL5A3	Collagen alpha-3(V) chain	1,273	1,294	18.26	36.54	5.65E-08	7.14E-07	24.79	91.22	52.01	104.26	2.10
e16717	DPGLMGERGEDGpAGNGTEGFPGFPGYpGNR	COL6A1	Collagen alpha-1(VI) chain	501	531	45.51	67.71	1.52E-14	6.34E-13	141.87	236.50	359.63	441.95	2.53
e05521	GQSRDAEEAISQTI	COL6A1	Collagen alpha-1(VI) chain	219	232	31.18	8.50	3.37E-15	1.57E-13	64.06	141.69	8.31	38.76	0.13
e07801	RGDEGPPGSEGARGAPGpA	COL6A1	Collagen alpha-1(VI) chain	478	496	21.35	32.01	2.63E-03	1.00E-02	35.83	99.86	56.52	185.06	1.58
e11369	GPpGEPGPRGPRGVpGpEGEpGP	COL6A2	Collagen alpha-2(VI) chain	561	583	93.54	87.82	1.61E-13	5.33E-12	707.30	517.84	468.90	497.52	0.66
e10376	GEKGDPGSQGSPGSRGApGqYG	COL6A5	Collagen alpha-5(VI) chain	1,485	1,506	16.57	31.73	2.31E-06	2.10E-05	30.40	278.36	37.21	105.60	1.22
e09719	KGDPGPSGppGpRGPLGDpGP	COL7A1	Collagen alpha-1(VII) chain	1,367	1,387	33.71	21.81	2.82E-04	1.47E-03	200.65	760.66	103.89	370.37	0.52
e13387	KGEKGDSEDGApGLpGQPGSpGEQGp	COL7A1	Collagen alpha-1(VII) chain	1,444	1,469	20.51	30.31	6.43E-03	2.13E-02	19.24	57.07	29.26	92.84	1.52
e02172	GPpGpPGPPGPpA	COL8A1	Collagen alpha-1(VIII) chain	560	572	23.88	35.13	9.57E-03	2.95E-02	40.63	99.33	53.93	179.87	1.33
e08435	GpPGEGRAGEpGTAGpTGpP	COL8A2	Collagen alpha-2(VIII) chain	490	509	35.39	26.35	1.18E-02	3.48E-02	96.41	231.01	89.78	291.86	0.93
e05738	pGPDGpSGpPGPpGKPG	COL9A2	Collagen alpha-2(IX) chain	131	147	40.45	27.76	1.97E-06	1.81E-05	112.14	368.59	96.13	1010.25	0.86

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e01532	DGEkGDPGPpG	COL9A3	Collagen alpha-3(IX) chain	207	217	97.19	92.63	5.43E-03	1.85E-02	2464.95	1810.27	2799.23	1883.67	1.14
e16278	mPGFKGpTGYKGEQGEVGKDGEKGDpGpPG	COL9A3	Collagen alpha-3(IX) chain	151	180	82.58	49.58	9.53E-34	9.57E-31	577.68	625.07	153.68	240.12	0.27
e11916	QGDRGDKGAAGAGLDGpEGDQGpQ	COL9A3	Collagen alpha-3(IX) chain	598	621	58.43	27.48	5.97E-21	6.56E-19	206.76	328.72	48.79	121.74	0.24
e11161	DQGpQGPQGVPGTSKDGQDGApG	COL9A3	Collagen alpha-3(IX) chain	617	639	37.64	17.00	1.10E-11	2.75E-10	108.78	233.92	25.97	109.33	0.24
e11487	TpGVAGPSGEpGmpGKDGQNGVPG	COL9A3	Collagen alpha-3(IX) chain	290	313	23.31	33.71	9.63E-04	4.26E-03	24.09	75.17	64.53	296.70	2.68
e10976	TpGVAGpSGEPGMpGKDGQNGVP	COL9A3	Collagen alpha-3(IX) chain	290	312	19.66	34.84	2.66E-05	1.89E-04	23.70	65.95	40.76	100.45	1.72
e00676	VAMTPRSEG	F2	Prothrombin	193	201	20.79	46.46	4.48E-15	2.05E-13	18.38	54.40	73.18	149.84	3.98
e12790	TDGALVQHQEWDGKESTITRK	FABP5P3	Putative fatty acid-binding protein 5-like protein 3	56	76	14.61	34.84	9.70E-12	2.46E-10	26.72	93.13	140.38	277.90	5.25
e13727	ATPLYINI	FAT1	Protocadherin Fat 1	654	661	43.26	67.71	1.15E-17	7.93E-16	59.27	105.72	181.44	235.76	3.06
e08360	tGYTGKMCESSVNYCE	FAT4	Protocadherin Fat 4	3,928	3,943	98.60	96.32	3.01E-08	4.02E-07	4265.49	2428.44	3471.44	2654.90	0.81
e08978	DEAGSEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	605	622	99.72	97.45	6.05E-05	3.88E-04	22185.01	5670.01	19731.10	8022.41	0.89
e14283	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629	67.70	76.49	3.61E-10	7.02E-09	2267.31	4548.89	10741.67	27698.25	4.74
e13674	DEAGSEADHEGTHSTKRGHAKSRP	FGA	Fibrinogen alpha chain	605	628	67.98	83.29	4.38E-19	3.74E-17	909.22	1626.45	4331.72	12802.08	4.76
e11627	SESGSFRPDSPGSGNARPNNPD	FGA	Fibrinogen alpha chain	388	409	87.36	86.40	7.00E-06	5.71E-05	713.04	672.96	494.99	529.10	0.69
e07002	DEAGSEADHEGTHSTK	FGA	Fibrinogen alpha chain	605	620	86.24	71.10	1.60E-28	6.70E-26	476.65	504.53	237.26	1285.43	0.50
e17491	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629	65.73	77.34	2.00E-09	3.35E-08	372.55	537.57	776.47	918.07	2.08
e07971	EAGSEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	606	622	72.19	75.35	4.85E-03	1.68E-02	238.68	602.33	270.25	265.58	1.13
e04994	DEAGSEADHEGTHS	FGA	Fibrinogen alpha chain	605	618	70.79	39.09	1.81E-24	3.78E-22	237.21	259.27	78.82	151.24	0.33
e02915	DHEGTHSTKRG	FGA	Fibrinogen alpha chain	612	622	27.53	52.12	2.33E-11	5.58E-10	200.78	631.23	344.42	677.83	1.72
e07900	DEAAFFDTASTGKTFPG	FGA	Fibrinogen alpha chain	515	531	50.28	63.74	5.93E-05	3.82E-04	138.39	231.61	217.32	303.57	1.57
e12086	DEAGSEADHEGTHSTKRGHAKS	FGA	Fibrinogen alpha chain	605	626	47.75	59.77	1.34E-05	1.02E-04	127.56	407.03	184.67	299.78	1.45
e00860	EGTHSTKRG	FGA	Fibrinogen alpha chain	614	622	16.29	38.53	7.94E-10	1.45E-08	52.49	165.70	110.05	333.00	2.10
e10596	DEAGSEADHEGTHSTKRGHA	FGA	Fibrinogen alpha chain	605	624	36.80	52.97	1.37E-05	1.04E-04	48.76	222.06	129.55	639.93	2.66
e05580	SEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	609	622	31.18	47.88	3.75E-07	4.00E-06	24.85	58.39	60.67	147.84	2.44
e06067	GSEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	608	622	25.56	35.13	1.66E-02	4.65E-02	19.05	77.19	29.50	181.52	1.55
e11931	SEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	609	629	15.45	40.79	1.58E-14	6.56E-13	14.97	63.17	82.83	278.62	5.53
e08185	EEAPSLRPAPPPISGGGY	FGB	Fibrinogen beta chain	54	71	70.79	60.91	7.42E-07	7.39E-06	362.42	475.74	298.92	791.94	0.82
e06733	AGSEADHEGTHSTKRG	FIBA	Fibrinogen alpha chain	607	622	98.60	93.77	1.24E-17	8.47E-16	1715.82	863.17	1165.74	601.94	0.68
e01784	DGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	7	18	73.31	47.31	5.22E-19	4.37E-17	284.50	307.03	123.94	229.02	0.44
e07648	TGLSMDGGGSPKGDVDPF	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	2	19	44.94	34.84	4.57E-05	3.06E-04	225.65	353.08	114.99	203.78	0.51
e05387	GLSMDGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	3	18	64.61	61.19	4.99E-03	1.72E-02	198.79	289.32	143.92	231.78	0.72
e00553	GGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	9	18	16.57	39.09	2.07E-10	4.22E-09	9.71	58.76	20.11	92.20	2.07
e15365	SWYDNEFGYSNRVVDLMAHMASKE	GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	312	335	56.74	36.54	1.17E-13	3.99E-12	225.50	450.24	67.64	231.55	0.30
e07622	WVGTGASEAEKTGAQEL	GSN	Gelsolin	605	621	85.96	78.47	7.04E-07	7.05E-06	1990.04	1725.64	1395.90	1416.91	0.70
e11826	SETAPAAPAAPAPAEKTPVKKKA	H14	Histone H1.4	2	24	42.70	61.47	2.13E-08	2.95E-07	98.21	161.97	227.83	565.43	2.32
e13087	SETAPAETATPAPVEKSPAKKKAT	H15	Histone H1.5	2	25	17.70	47.59	4.69E-19	3.98E-17	15.40	44.60	79.83	206.05	5.18
e07959	VAHVDDMPNALSALSDL	HBA1	Hemoglobin subunit alpha	71	82	80.90	73.94	4.48E-08	5.80E-07	1084.82	1659.82	882.14	2227.00	0.81

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviatio

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e04294	PEPAKSAPAPKKGS	H2B1K	Histone H2B type 1-K	2	15	8.99	41.36	8.86E-23	1.39E-20	13.80	56.04	125.10	531.56	9.07
e00274	TVEAPMPK	HSPB1	Heat shock protein beta-1	164	171	15.73	46.18	4.11E-19	3.52E-17	9.07	32.49	33.03	57.88	3.64
e07356	TTTAPTPA	HUWE1	E3 ubiquitin-protein ligase HUWE1	1,090	1,097	44.10	52.12	1.57E-02	4.43E-02	690.18	1059.97	915.93	1270.15	1.33
e14820	LIALPTQDPAHGGAPPEMASN	IGF2	Insulin-like growth factor II	158	178	18.26	37.96	3.57E-10	6.97E-09	43.13	147.12	171.05	353.61	3.97
e03199	VDVSHEDPEVK	IGHG1	Immunoglobulin heavy constant gamma 1	266	276	30.06	19.83	3.72E-04	1.88E-03	28.72	56.79	20.21	123.84	0.70
e05105	VVVDVSHEDPEVK	IGHG1	Immunoglobulin heavy constant gamma 1	264	276	13.20	30.31	8.68E-09	1.31E-07	13.76	50.48	58.58	131.10	4.26
e09692	ASTRESGVPDRFSGSGSGTD	IGKV4-1	Immunoglobulin kappa variable 4-1	77	96	55.06	76.20	1.21E-07	1.42E-06	191.14	257.11	438.90	3116.57	2.30
e00433	DVVPIEPH	IL1RN	Interleukin-1 receptor antagonist protein	72	79	33.43	58.36	6.78E-11	1.51E-09	35.02	127.71	71.42	214.38	2.04
e11944	KDNDVDEEDEEDELDQSQH	IRF6	Interferon regulatory factor 6	137	155	35.67	56.94	8.22E-07	8.15E-06	251.67	1016.83	291.91	799.30	1.16
e08496	LLRDTDRFSSHVGGTLG	ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	865	881	12.08	31.16	1.07E-09	1.91E-08	85.81	683.74	533.63	3077.57	6.22
e05450	SVMPGLKMTMDKTG	ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	825	838	46.63	62.61	8.82E-05	5.38E-04	44.06	76.20	59.86	83.77	1.36
e01692	SSHVGGTLGQF	ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	873	883	23.03	30.88	1.32E-02	3.83E-02	24.02	76.78	43.54	115.17	1.81
e10519	FARSIEMMDIVVEKNGEN	KCNB1	Potassium voltage-gated channel subfamily B member 1	454	471	70.51	65.72	5.78E-06	4.80E-05	475.94	582.85	307.32	758.02	0.65
e09412	GSGGSSYGSGGGSYGSGGGGGGGRG	KRT1	Keratin; type II cytoskeletal 1	526	550	84.55	73.65	6.62E-14	2.42E-12	429.81	513.41	205.90	256.38	0.48
e06292	ASYLDKVRALEESN	KRT10	Keratin, type I cytoskeletal 10	158	171	72.19	55.81	8.94E-11	1.94E-09	355.71	391.66	183.64	237.67	0.52
e09390	LSMDNNRNLDLDSIIAE	KRT4	Keratin; type II cytoskeletal 4	274	290	38.76	51.27	2.19E-03	8.61E-03	68.97	113.35	95.13	145.94	1.38
e01849	AQYEEIAQR	KRT4	Keratin; type II cytoskeletal 4	354	362	20.79	37.68	1.41E-07	1.64E-06	25.51	77.33	52.44	98.25	2.06
e10169	FGASAGTGDLSDNHDIISMK	LMAN2	Vesicular integral-membrane protein VIP36	253	272	49.72	58.64	5.37E-06	4.50E-05	172.68	374.99	508.81	1060.65	2.95
e09606	LDTYPNDETTERVFPY	LMAN2	Vesicular integral-membrane protein VIP36	161	176	21.63	32.58	2.45E-04	1.31E-03	75.48	237.76	192.77	487.33	2.55
e01343	YSNEKPFTG	MASP2	Mannan-binding lectin serine protease 2	121	129	48.60	60.91	6.59E-05	4.17E-04	58.38	280.82	90.85	263.97	1.56
e04940	GKVEADIPGHGQEV	MB	Myoglobin	16	29	38.48	55.24	8.50E-05	5.22E-04	49.31	203.56	109.65	821.44	2.22
e05961	GPITLEPTEDGMAGVA	MEGF8	Multiple epidermal growth factor-like domains protein 8	2,766	2,781	50.28	68.27	1.33E-04	7.68E-04	417.30	642.56	507.71	605.57	1.22
e01132	cDDYRLcE	MGP	Matrix Gla Protein	73	90	99.72	98.02	4.28E-30	2.66E-27	3670.90	3205.36	8548.56	7563.89	2.33
e00340	cDDYRLc	MGP	Matrix Gla Protein	73	79	82.58	92.35	1.14E-25	2.75E-23	450.32	561.62	1142.97	1244.67	2.54
e03142	DTHFDSDEPW	MMP24	Matrix metalloproteinase-24	255	264	96.91	91.22	2.83E-05	2.00E-04	1490.26	1015.94	1223.36	1003.85	0.82
e17804	TTLSPSSSTTHEGEPTTFQSWPSSKDTSPAPSG	MUC12	Mucin-12	404	436	37.92	28.90	6.85E-03	2.23E-02	40.32	76.14	31.60	86.06	0.78
e12382	DGLSPDQTRSEDPQNSAGSPPDA	MYOCD	Myocardin	160	182	67.13	63.74	4.40E-05	2.95E-04	236.21	265.65	148.60	193.52	0.63
e00161	DQITGKW	ORM1	Alpha-1-acid glycoprotein 1	37	43	25.28	35.69	6.58E-03	2.17E-02	11.60	25.99	17.11	39.59	1.47
e03544	KELDINTDGAVN	S100A8	Protein S100-A8	56	67	40.73	17.28	2.46E-13	7.90E-12	148.50	355.81	34.73	135.14	0.23
e03248	EATEMcTQEc	PCDH9	Protocadherin-9	1,124	1,133	91.57	79.89	6.73E-10	1.25E-08	4659.44	3273.31	3346.05	3400.11	0.72

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA	Frequency Control (%)	Frequency CRS (%)	Unadjusted p-value (Mann-Whitney)	BH Adjusted p-value	Average Control	St Dev Control	Average CRS	St Dev CRS	Fold change
e06511	PGMFPSGTPGGPYGGAAP	PEF1	Peflin	69	86	67.70	39.09	1.00E-17	7.00E-16	317.50	522.57	122.42	301.23	0.39
e08564	LTDEEKRLMVELHNL	PI16	Peptidase inhibitor 16	28	42	9.27	36.54	6.92E-18	4.95E-16	43.00	238.09	266.93	825.53	6.21
e15907	AVADTRDQADGSRASVDSGSSEEQGGSSRA	PIGR	Polymeric-immunoglobulin receptor	610	639	33.71	45.89	7.77E-03	2.47E-02	113.40	274.56	122.00	252.06	1.08
e14560	TRDQADGSRASVDSGSSEEQGGSSRAL	PIGR	Polymeric-immunoglobulin receptor	614	640	44.38	62.32	1.86E-08	2.59E-07	56.34	226.14	90.98	137.87	1.61
e14638	AVADTRDQADGSRASVDSGSSEEQGGSS	PIGR	Polymeric-immunoglobulin receptor	610	637	36.80	28.61	7.05E-03	2.29E-02	47.79	80.29	34.17	81.16	0.72
e19279	TSPSGQLIPVKNLSENIEIL	PK1L2	Polycystic kidney disease protein 1-like 2	1,142	1,161	78.09	74.22	1.65E-04	9.25E-04	205.20	210.06	151.33	188.64	0.74
e00166	FAGDDAPR	POTEF	POTE ankyrin domain family member F	721	728	33.99	46.74	6.07E-05	3.89E-04	17.42	36.12	34.81	65.77	2.00
e06714	GYISGPLVSDMDTDAP	ROBO1	Roundabout homolog 1	1,312	1,327	35.67	51.84	2.58E-07	2.84E-06	175.30	377.01	380.02	616.57	2.17
e06220	GHPDTLNQGEFKEL	S100A9	Protein S100-A9	27	40	86.24	81.30	1.41E-03	5.85E-03	322.87	269.76	259.34	235.38	0.80
e00317	KLGHPDTL	S100A9	Protein S100-A9	25	32	36.24	46.46	1.35E-02	3.91E-02	46.09	109.84	69.29	178.05	1.50
e10432	HQYSVKLGHPDTLNQGEF	S100A9	Protein S100-A9	20	37	34.83	24.93	1.19E-03	5.11E-03	31.71	61.70	40.91	228.66	1.29
e00191	KPGLGEGTP	S100A9	Protein S100-A9	106	114	14.89	42.49	1.66E-16	9.52E-15	12.24	56.79	42.71	101.63	3.49
e18617	FGHGAEDSLADQAANEWGRSGKDPNHFRPAGLPE	SAA1	Serum amyloid A-1 protein	87	120	12.36	36.54	1.60E-14	6.62E-13	13.53	57.62	138.31	580.89	10.22
e05292	TGRGAEDSLADQAAN	SAA2	Serum amyloid A-2 protein	87	101	67.98	86.40	1.01E-04	6.02E-04	636.75	653.55	788.80	577.17	1.24
e09609	LTGRGAEDSLADQAANKWG	SAA2	Serum amyloid A-2 protein	86	104	16.57	33.99	1.26E-08	1.83E-07	151.78	892.21	2335.14	17920.48	15.39
e12387	HLVGHQRNNRQVTLEVSGAEP	SECTM1	Secreted and transmembrane protein 1	118	138	14.04	39.66	1.10E-14	4.69E-13	35.04	140.39	214.40	727.87	6.12
e08607	RAHGQESAIFNEVAPGY	SECTM1	Secreted and transmembrane protein 1	69	85	19.10	32.86	3.86E-06	3.35E-05	22.40	80.26	149.33	590.32	6.67
e10000	VANEESEHNQGASEENGLP	SHANK1	SH3 and multiple ankyrin repeat domains protein 1	1,536	1,543	90.17	90.37	3.50E-12	9.46E-11	473.35	408.25	854.69	814.82	1.81
e15314	IPVKQADSGSSEEKQLYNKYPDAVAT	SPP1	Osteopontin	17	42	26.69	42.49	2.33E-05	1.68E-04	629.68	1966.12	1176.76	3278.17	1.87
e05742	DITSHMESEELNGA	SPP1	Osteopontin	188	201	56.46	27.76	9.04E-20	8.65E-18	88.74	219.69	30.83	197.84	0.35
e13231	NKTPIR	TITIN	Titin	21,153	21,158	56.74	61.76	3.78E-03	1.37E-02	710.10	982.28	1070.34	1394.13	1.51
e20740	sDKPDMAEIEKFDKSKLKKTETQEKNPLPSKETIEQEKQAGES	TMSB4X	Thymosin beta-4	2	44	55.90	67.99	8.85E-05	5.39E-04	774.61	3369.95	4551.40	18657.84	5.88
e14519	TETQEKNPLPSKETIEQEKQAGES	TMSB4X	Thymosin beta-4	21	44	62.36	80.17	1.11E-12	3.21E-11	112.19	171.80	248.55	671.13	2.22
e00773	GFQLTHSLG	TUBB3	Tubulin beta-3 chain	132	140	32.30	49.01	1.64E-07	1.89E-06	27.53	85.26	121.67	1271.13	4.42
e06064	GSEEEPAPSSLQPGSP	UBAP1L	Ubiquitin-associated protein 1-like	118	133	34.55	10.76	6.65E-16	3.48E-14	323.43	998.48	31.05	227.30	0.10
e09213	SGSVIDQSRVLNLGPITR	UMOD	Uromodulin	589	606	96.63	99.15	1.39E-04	8.00E-04	37066.10	37704.90	27980.88	33288.29	0.75
e07093	VIDQSRVLNLGPITR	UMOD	Uromodulin	592	606	82.87	78.19	3.13E-03	1.17E-02	8505.12	15192.06	5435.61	8383.68	0.64
e07964	SVIDQSRVLNLGPITR	UMOD	Uromodulin	591	606	93.82	88.67	3.96E-13	1.23E-11	8089.96	10963.23	5031.72	11586.38	0.62
e07848	SGSVIDQSRVLNLGPIT	UMOD	Uromodulin	589	605	69.66	60.06	3.93E-09	6.31E-08	3515.59	6270.27	1637.32	2426.25	0.47
e06877	SGSVIDQSRVLNLGPI	UMOD	Uromodulin	589	604	83.43	81.59	4.95E-07	5.13E-06	3028.78	4310.47	1756.88	2803.54	0.58
e10189	SGSVIDQSRVLNLGPITRK	UMOD	Uromodulin	589	607	69.66	65.16	1.54E-04	8.67E-04	953.33	1538.73	603.26	1284.05	0.63
e06451	SVIDQSRVLNLGPIT	UMOD	Uromodulin	591	605	59.27	32.29	8.32E-15	3.65E-13	853.41	1357.91	336.34	766.25	0.39
e08455	GSVIDQSRVLNLGPITR	UMOD	Uromodulin	590	606	48.60	24.08	7.26E-15	3.22E-13	774.86	1815.63	172.20	743.80	0.22
e05684	VIDQSRVLNLGPIT	UMOD	Uromodulin	592	605	53.09	21.81	9.70E-20	9.24E-18	475.06	752.50	139.59	396.54	0.29
e06194	IDQSRVLNLGPITR	UMOD	Uromodulin	593	606	38.76	21.25	1.25E-07	1.47E-06	451.27	1402.68	191.09	925.80	0.42
e02332	SGSVIDQSRVL	UMOD	Uromodulin	589	599	41.29	24.93	1.37E-07	1.60E-06	282.51	605.07	169.57	971.16	0.60
e00923	VLNLGPITR	UMOD	Uromodulin	598	606	53.09	39.66	4.33E-06	3.70E-05	269.34	638.27	124.90	336.54	0.46
e00683	SGSVIDQSR	UMOD	Uromodulin	589	597	37.64	51.56	9.51E-03	2.93E-02	93.89	202.46	90.59	172.45	0.96
e02788	VENGESSQGRF	UMOD	Uromodulin	538	548	33.43	41.08	1.51E-02	4.28E-02	59.82	121.89	90.31	159.95	1.51
e01448	IDQSRVLNL	UMOD	Uromodulin	593	601	17.70	41.08	4.67E-13	1.43E-11	23.75	80.47	118.92	318.15	5.01
e05240	DQSRVLNLGPITR	UMOD	Uromodulin	594	606	53.09	40.51	7.43E-06	6.02E-05	1112.87	2263.83	457.25	1043.23	0.41
e17439	GRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAPE	VGF	Neurosecretory protein VGF	26	58	54.78	42.21	1.29E-05	9.89E-05	110.26	157.25	65.40	133.73	0.59

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Supplementary Table S2. List of the 31 differentially excreted peptides, commonly identified in chronic kidney disease (CKD) and CRS patients (Sci Rep. 2021 Aug 10;11(1):16219. doi: 10.1038/s41598-021-95695-z).

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e03372	DGQPGAKGEpGDAG	COL1A1	Collagen alpha-1(I) chain	820	833
e04419	ApGDRGEpGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812
e03194	DGVPGKDGPRGPT	COL3A1	Collagen alpha-1(III) chain	752	764
e11678	ANGAPGNDGAKGDAGAPGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	699	725
e07002	DEAGSEADHEGTHSTK	FGA	Fibrinogen alpha chain	605	620
e04994	DEAGSEADHEGTHS	FGA	Fibrinogen alpha chain	605	618
e12950	LREGETKAVKTVRTPGAAANLEL	A1BG	Alpha-1B-glycoprotein	435	457
e12127	LREGETKAVKTVRTPGAAANLE	A1BG	Alpha-1B-glycoprotein	435	456
e12741	MIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	398	418
e13340	LMIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	397	418
e05929	TIDEKGTEAAGAMFL	A1AT	Alpha-1-antitrypsin	363	377
e07656	VVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	324	340
e09323	MGVVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	322	340
e11895	FFLPDEGKLQHLENELTHD	A1AT	Alpha-1-antitrypsin	276	294
e06716	LSALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	254	267
e10169	FGASAGTGDLSDNHDIISMK	LMAN2	Vesicular integral-membrane protein VIP36	253	272
e12606	LSSLTETIEGVDAEDGHGPGEQQ	CFB	Complement factor B	236	257
e05683	SALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	233	245
e16206	DGVSGGEGKGGSDGGGSHRKEGEEADAPGVIPG	CD99	CD99 antigen	140	172
e13955	LKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	60	81
e14596	LLKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	59	81
e14633	VDVLKDSGRDYVSQFEGSALGKQLN	APOA1	Apolipoprotein A-I	43	67
e08564	LTDEEKRLMVELHNL	PI16	Peptidase inhibitor 16	28	42
e14191	DAHKSEVAHRFKDLGEENFKALV	ALB	Albumin	27	49
e18378	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAE	A1AT	Alpha-1-antitrypsin	25	56
e13562	DAHKSEVAHRFKDLGEENFKAL	ALB	Albumin	25	46
e12970	DAHKSEVAHRFKDLGEENFKA	ALB	Albumin	25	45
e12518	DAHKSEVAHRFKDLGEENFK	ALB	Albumin	25	44
e14790	DAHKSEVAHRFKDLGEENFKALVL	ALB	Albumin	25	48
e15314	IPVKQADSGSSEEKQLYNKYPDAVAT	SPP1	Osteopontin	17	42
e01784	DGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	7	18

AA: Amino acid

Supplementary Table S3. List of the 341 differentially excreted peptides, commonly identified in heart failure (HF) and CRS patients. (Sci Rep. 2021 Aug 10;11(1):16219. doi: 10.1038/s41598-021-95695-z).

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e07000	FSNGADL	A1AT	Alpha-1-antitrypsin	336	342
e13865	LPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	278	299
e11895	FFLPDEGKLQHLENELTHD	A1AT	Alpha-1-antitrypsin	276	294
e12271	EDPQGDAAQKTDTSHHDQDHP	A1AT	Alpha-1-antitrypsin	25	45
e05548	VVSLGSPSGEVSHPR	AHSG	Alpha-2-HS-glycoprotein	324	338
e04435	AILDETKGDYEK	ANXA1	Annexin	326	337
e03546	LGPHAGDVEGHLS	APOA4	Apolipoprotein A-IV	329	341
e11210	FWDLDPEVRPTSA	APOC3	Apolipoprotein C-III	84	96
e00153	NGERIEK	B2M	Beta-2-microglobulin	62	68
e00145	FHPSDIE	B2M	Beta-2-microglobulin	50	56
e01453	FHPSDIEVD	B2M	Beta-2-microglobulin	50	58
e00957	SGFHPSDIE	B2M	Beta-2-microglobulin	48	56
e00152	VSGFHPSD	B2M	Beta-2-microglobulin	47	54
e17006	SSQGGSLPSEEKGHPQEESEESNVSMASLGE	CHGB	Secretogranin-1	293	323
e05622	FDSDPITVTVPVEV	CLU	Clusterin	410	423
e18263	ASHTSDSDVPSGVTEVVVKLFDSDPITVTVPVEV	CLU	Clusterin	390	423
e02160	DKGDTGPPGPQG	COL3A1	Collagen alpha-1(III) chain	628	639
e04847	GGDkGEDGDPGQPGp	COL11A1	Collagen alpha-1(XI) chain	1,332	1,346
e11542	pGpSGEKGETGDVGPMGpPGPpGP	COL11A2	Collagen alpha-2(XI) chain	1,161	1,184
e11726	pGVVGPQGAAGETGPmGERGHpGP	COL11A2	Collagen alpha-2(XI) chain	924	947
e07199	pGPpGQQGTPGTQGLpGP	COL11A2	Collagen alpha-2(XI) chain	645	662
e09631	EPGppGQQGTpGTQGLpGPQ	COL11A2	Collagen alpha-2(XI) chain	644	663
e15200	GIpGGVGSpGRDGSpGQRGLPGKDGSSGPpG	COL14A1	Collagen alpha-1(XIV) chain	1,536	1,566
e02352	GDpGPpGPpGPpG	COL15A1	Collagen alpha-1(XV) chain	1,093	1,105
e17903	AGERGHPGApGPSGSPGLpGVPGSMGDMVNYDEIK	COL16A1	Collagen alpha-1(XVI) chain	1,406	1,440
e10985	NSGEKGDQGFQGQPGFPGPPGP	COL16A1	Collagen alpha-1(XVI) chain	1,145	1,166
e11495	GNSGEKGDQGFQGQPGFPGPpGP	COL16A1	Collagen alpha-1(XVI) chain	1,144	1,166
e12384	EGpmGQRGREGPMGpRGEAGPpG	COL17A1	Collagen alpha-1(XVII) chain	617	639
e04863	SVPGPpGPpGPpGPpG	COL18A1	Collagen alpha-1(XVIII) chain	1,422	1,437
e04820	GVNVpSYPGpPGPPG	COL19A1	Collagen alpha-1(XIX) chain	834	848
e05458	GPpGPpGPpGPpGPPSA	COL1A1	Collagen alpha-1(I) chain	1,178	1,194
e06018	VGPpGPPGPpGPPGPPSA	COL1A1	Collagen alpha-1(I) chain	1,177	1,194
e05682	VGPpGPpGPpGPpGPPS	COL1A1	Collagen alpha-1(I) chain	1,177	1,193
e05551	VGPpGPPGPpGPpGPPS	COL1A1	Collagen alpha-1(I) chain	1,177	1,193
e05423	VGpPGPPGpPGPPGPPS	COL1A1	Collagen alpha-1(I) chain	1,177	1,193
e12085	RTGDAGPVGpPGPpGPpGPpGPPSAG	COL1A1	Collagen alpha-1(I) chain	1,170	1,195
e11554	GRTGDAGPVGPPGPpGppGpPGPPS	COL1A1	Collagen alpha-1(I) chain	1,169	1,193
e11533	pGEQGpSGASGPAGPRGPpGSAGApG	COL1A1	Collagen alpha-1(I) chain	1,126	1,151
e13730	AGPpGAPGApGAPGPVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,042	1,071
e13817	AGPpGAPGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,042	1,071
e13056	AGpPGApGApGAPGpVGPAGKSGDRGET	COL1A1	Collagen alpha-1(I) chain	1,042	1,069
e08489	SpGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,023	1,041

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e10032	EGSpGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,021	1,041
e10554	EGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,021	1,042
e10142	EGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,021	1,041
e06650	EGSpGRDGSpGAKGDRG	COL1A1	Collagen alpha-1(I) chain	1,021	1,037
e08755	EGSpGRDGSpGAKGDRGET	COL1A1	Collagen alpha-1(I) chain	1,021	1,039
e10657	AEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,020	1,041
e11002	AEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,020	1,042
e10437	AEGSPGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,020	1,041
e10653	SGREGApGAEGSpGRDGSpGAKG	COL1A1	Collagen alpha-1(I) chain	1,012	1,034
e15935	ESGREGApGAEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,011	1,041
e16177	ESGREGApGAEGSPGRDGSpGAKGDRGETGpA	COL1A1	Collagen alpha-1(I) chain	1,011	1,042
e16056	GESGREGAPGAEGSpGRDGSPGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,010	1,041
e16118	GESGREGApGAEGSpGRDGSPGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,010	1,041
e17348	ppGESGREGAPGAEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,008	1,042
e17596	GPpGESGREGApGAEGSpGRDGSPGAKGDRGETGpA	COL1A1	Collagen alpha-1(I) chain	1,007	1,042
e04497	GRpGEVGPpGPpGPA	COL1A1	Collagen alpha-1(I) chain	917	931
e09008	GNAGPpGPpGPAGKEGGKGPR	COL1A1	Collagen alpha-1(I) chain	890	910
e09729	SGNAGPpGPpGPAGKEGGKGPR	COL1A1	Collagen alpha-1(I) chain	889	910
e10135	SGNAGPpGPpGPAGKEGGKGPRG	COL1A1	Collagen alpha-1(I) chain	889	911
e16015	NVGApGAKGARGSAGpPGATGFpGAAGRVGPpGP	COL1A1	Collagen alpha-1(I) chain	855	888
e05704	DGQPGAKGEpGDAGAKG	COL1A1	Collagen alpha-1(I) chain	820	836
e10953	DGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	820	843
e10771	DGQPGAKGEPGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	820	843
e10863	DGQPGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	820	843
e03372	DGQPGAKGEpGDAG	COL1A1	Collagen alpha-1(I) chain	820	833
e11576	ADGQpGAKGEpGDAGAKGDAGppGP	COL1A1	Collagen alpha-1(I) chain	819	843
e16606	ADGQpGAKGEpGDAGAKGDAGpPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	819	854
e11972	ADGQpGAKGEPGDAGAKGDAGppGPA	COL1A1	Collagen alpha-1(I) chain	819	844
e16548	ADGQpGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	819	854
e11850	ADGQPGAKGEpGDAGAKGDAGPPGpA	COL1A1	Collagen alpha-1(I) chain	819	844
e11734	ADGQPGAKGEPGDAGAKGDAGpPGPA	COL1A1	Collagen alpha-1(I) chain	819	844
e13342	GADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	818	846
e11865	GADGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	818	843
e11641	GADGQPGAKGEPGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	818	843
e13207	PpGADGQpGAKGEPGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	816	843
e14893	GPpGADGQpGAKGEpGDAGAKGDAGpPGPAGP	COL1A1	Collagen alpha-1(I) chain	815	846
e13595	GpPGADGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	815	843
e17890	GPpGADGQPGAKGEpGDAGAKGDAGPPGpAGPAGPPGpIG	COL1A1	Collagen alpha-1(I) chain	815	854
e14801	GPpGADGQPGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	815	846
e17946	PpGPAGFAGPPGADGQPGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	807	846
e17949	GEPGPPGPAGFAGPPGADGQPGAKGEPGDAGAKGDAGPpG	COL1A1	Collagen alpha-1(I) chain	803	842
e02530	pGDRGEpGPpGP	COL1A1	Collagen alpha-1(I) chain	799	810

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e01213	pGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	799	808
e03180	ApGDRGEpGPPGp	COL1A1	Collagen alpha-1(I) chain	798	810
e04419	ApGDRGEpGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812
e03890	ApGDRGEpGPpGPA	COL1A1	Collagen alpha-1(I) chain	798	811
e01758	ApGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	798	808
e04281	ApGDRGEPGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812
e06948	pPGPAGApGDKGESGPSGP	COL1A1	Collagen alpha-1(I) chain	771	789
e11415	IGPpGPAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794
e06282	GPIGPpGPAGApGDKGES	COL1A1	Collagen alpha-1(I) chain	767	784
e08629	TGPIGpPGPAGApGDKGESGP	COL1A1	Collagen alpha-1(I) chain	766	786
e13825	LTGPIGppGPAGAPGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	765	794
e05703	ApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	702	719
e11264	NGApGNDGAKGDAGAPGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	700	725
e09230	NGApGNDGAKGDAGApGApGSQ	COL1A1	Collagen alpha-1(I) chain	700	721
e11375	NGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	700	725
e07275	NGApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	700	719
e11678	ANGAPGNDGAKGDAGAPGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	699	725
e12366	GANGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	698	725
e02579	KpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	657	668
e09321	EAGKpGEQGVpGDLGApGPSG	COL1A1	Collagen alpha-1(I) chain	654	674
e05810	PpGEAGKpGEQGVpGD	COL1A1	Collagen alpha-1(I) chain	651	666
e10141	PpGEAGKPGEQGVpGDLGApGP	COL1A1	Collagen alpha-1(I) chain	651	672
e07388	pPGEAGKpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	651	668
e07225	pPGEAGKpGEQGVPGDLG	COL1A1	Collagen alpha-1(I) chain	651	668
e04666	GPpGEAGKpGEQGVP	COL1A1	Collagen alpha-1(I) chain	650	664
e07799	GPpGEAGKpGEQGVPGDLG	COL1A1	Collagen alpha-1(I) chain	650	668
e07944	GpPGEAGKpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	650	668
e02810	GPpGEAGKpGEQG	COL1A1	Collagen alpha-1(I) chain	650	662
e16078	VMGFpGPKGAAGEpGKAGERGVPGppGAVGPAG	COL1A1	Collagen alpha-1(I) chain	579	611
e01166	DGRPGPPGPpG	COL1A1	Collagen alpha-1(I) chain	562	572
e05202	DGRpGPpGPpGARGQ	COL1A1	Collagen alpha-1(I) chain	562	576
e01983	DGRpGPpGPpGA	COL1A1	Collagen alpha-1(I) chain	562	573
e01399	DGRpGPpGPpG	COL1A1	Collagen alpha-1(I) chain	562	572
e02517	QDGRpGpPGPpG	COL1A1	Collagen alpha-1(I) chain	561	572
e03025	GQDGRpGPpGpPG	COL1A1	Collagen alpha-1(I) chain	560	572
e00131	DGKTGPpGP	COL1A1	Collagen alpha-1(I) chain	550	558
e02804	SpGPDGKTGppGP	COL1A1	Collagen alpha-1(I) chain	546	558
e02667	SpGPDGKTGpPGP	COL1A1	Collagen alpha-1(I) chain	546	558
e03322	SpGPDGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	546	559
e06024	SpGSPGPDGKTGpPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560
e03638	SpGSpGPDGKTGPp	COL1A1	Collagen alpha-1(I) chain	543	556
e07678	TGSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	541	560

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e01461	SpGEAGRpGEA	COL1A1	Collagen alpha-1(I) chain	522	532
e00214	SpGEAGRpG	COL1A1	Collagen alpha-1(I) chain	522	530
e08350	GEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	434	453
e09124	SGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	433	453
e10326	SGEpGApGSKGDTGAKGEpGPVG	COL1A1	Collagen alpha-1(I) chain	433	455
e10025	NSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453
e08740	NSGEpGApGSKGDTGAKGEp	COL1A1	Collagen alpha-1(I) chain	432	451
e08598	NSGEPGApGSKGDTGAKGEp	COL1A1	Collagen alpha-1(I) chain	432	451
e10445	GNSGEpGApGSKGDTGAKGEPGp	COL1A1	Collagen alpha-1(I) chain	431	453
e11498	GNSGEpGApGSKGDTGAKGEPGpVG	COL1A1	Collagen alpha-1(I) chain	431	455
e11377	GNSGEPGApGSKGDTGAKGEpGPVG	COL1A1	Collagen alpha-1(I) chain	431	455
e11613	GNSGEpGApGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	431	455
e08888	pQGpGGPPGpKGNSGEPGApG	COL1A1	Collagen alpha-1(I) chain	420	440
e18806	ARGNDGATGAAGPpGPTGPAGpPGFpGAVGAKGEAGpQGPRG	COL1A1	Collagen alpha-1(I) chain	321	362
e19986	ARGNDGATGAAGPpGPTGPAGPpGFpGAVGAKGEAGPQGPRGSEGPQG	COL1A1	Collagen alpha-1(I) chain	321	368
e20010	ARGNDGATGAAGpPGPTGPAGPPGFPGAVGAKGEAGpQGpRGSEGpQG	COL1A1	Collagen alpha-1(I) chain	321	368
e12411	ApGPAGARGNDGATGAAGppGPTGPAGP	COL1A1	Collagen alpha-1(I) chain	315	342
e12120	DGAKGDAGPAGpKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	274	299
e07917	DGEAGKPGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	232	249
e09059	DDGEAGKPGRpGERGpPGp	COL1A1	Collagen alpha-1(I) chain	231	249
e08916	DDGEAGKPGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	231	249
e02592	DDGEAGKpGRpG	COL1A1	Collagen alpha-1(I) chain	231	242
e09408	GDDGEAGKpGRPGERGPPGp	COL1A1	Collagen alpha-1(I) chain	230	249
e09542	GDDGEAGKpGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	230	249
e10277	nGDDGEAGKpGRPGERGPPGp	COL1A1	Collagen alpha-1(I) chain	229	249
e10395	NGDDGEAGKpGRPGERGpPGp	COL1A1	Collagen alpha-1(I) chain	229	249
e10266	NGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	229	249
e11128	KNGDDGEAGKPGRPGERGPpGp	COL1A1	Collagen alpha-1(I) chain	228	249
e11537	GKNGDDGEAGKPGRpGERGPpGP	COL1A1	Collagen alpha-1(I) chain	227	249
e13043	PpGKNGDDGEAGKPGRPGERGppGP	COL1A1	Collagen alpha-1(I) chain	225	249
e13136	PpGKNGDDGEAGKPGRpGERGppGP	COL1A1	Collagen alpha-1(I) chain	225	249
e13322	GPpGKNGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	224	249
e13410	GPpGKNGDDGEAGKpGRPGERGppGP	COL1A1	Collagen alpha-1(I) chain	224	249
e05353	GPpGKNGDDGEAGKpG	COL1A1	Collagen alpha-1(I) chain	224	239
e09627	PpGPpGKNGDDGEAGKpGRp	COL1A1	Collagen alpha-1(I) chain	222	241
e07807	GpPGpPGKNGDDGEAGKpG	COL1A1	Collagen alpha-1(I) chain	221	239
e11270	ISVPGPMGPSGPRGLpGPpGApGP	COL1A1	Collagen alpha-1(I) chain	175	198
e05776	DGPpGRDGQpGHKGE	COL1A2	Collagen alpha-2(I) chain	933	947
e10635	DGppGRDGQpGHKGERGYpG	COL1A2	Collagen alpha-2(I) chain	933	952
e04647	DGPpGRDGQpGHKG	COL1A2	Collagen alpha-2(I) chain	933	946
e02052	ApGEAGRDGNpG	COL1A2	Collagen alpha-2(I) chain	920	931
e08546	NGApGEAGRDGNPGNDGPpG	COL1A2	Collagen alpha-2(I) chain	918	937

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e07808	KGPSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	846	865
e15679	TGEVGAVGPPGFAGEKGpSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	831	863
e16604	TGEVGAVGppGFAGEKGPSGEAGTAGpPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	831	865
e17212	RTGEVGAVGPpGFAGEKGPSGEAGTAGpPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	830	865
e16390	pNGPPGpAGSRGDGGpPGMTGFPGAAGRTGPpGP	COL1A2	Collagen alpha-2(I) chain	767	800
e19752	GEVGPAGpNGFAGpAGAAGQpGAKGERGAKGPKGENGVVGPTGpVG	COL1A2	Collagen alpha-2(I) chain	715	760
e02933	GppGPDGNKGEpG	COL1A2	Collagen alpha-2(I) chain	613	625
e17490	ERGppGESGAAGPTGpIGSRGPSGPPGPDGNKGEpG	COL1A2	Collagen alpha-2(I) chain	590	625
e06182	GpAGPRGERGPpGESGA	COL1A2	Collagen alpha-2(I) chain	583	617
e18516	EVGKpGERGLHGEFGLpGpAGpRGERGPPGESGAAGP	COL1A2	Collagen alpha-2(I) chain	566	602
e15659	QGVQGGKGEQGpPGppGFQGLPGpSGPAGEV	COL1A2	Collagen alpha-2(I) chain	537	567
e00421	DpGKNGDKG	COL1A2	Collagen alpha-2(I) chain	503	511
e17585	GDPGKNGDKGHAGLAGARGApGPDGNNGAQGPpGPQG	COL1A2	Collagen alpha-2(I) chain	502	538
e07217	GSpGNIGPAGKEGPVGLpG	COL1A2	Collagen alpha-2(I) chain	454	472
e15593	NGEAGSAGpPGppGLRGSpGSRGLPGADGRAG	COL1A2	Collagen alpha-2(I) chain	384	415
e19745	SKGESGNKGEpGSAGPQGPpGpSGEEGKRGPNGEAGSAGPPGPpG	COL1A2	Collagen alpha-2(I) chain	353	397
e10318	GEpGPAGSKGESGNKGEpGSAGP	COL1A2	Collagen alpha-2(I) chain	346	368
e15400	LkGQpGApGVkGEpGApGENGTpGQTGARG	COL1A2	Collagen alpha-2(I) chain	188	217
e10651	PpGKAGEDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	137	157
e11003	GPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	136	157
e12793	GpAGPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	133	157
e03691	YDGKGVGLGPGPMG	COL1A2	Collagen alpha-2(I) chain	81	94
e05677	pGKDGDTGPTGPQGPQ	COL22A1	Collagen alpha-1(XXII) chain	1,305	1,320
e09447	pGAAGNpGAPGHVGApGPSGPpG	COL22A1	Collagen alpha-1(XXII) chain	912	934
e16219	ppGAKGQEGAHGAPGAAGNPGAPGHVGAPGPSGpP	COL22A1	Collagen alpha-1(XXII) chain	899	933
e09697	PGpPGPHGPPGpmGPHGLpGP	COL25A1	Collagen alpha-1(XXV) chain	531	551
e13646	QGpPGPpGPQGLQGPKGEQGSPGIPGM	COL25A1	Collagen alpha-1(XXV) chain	449	474
e09456	PGppGpPGYGSQGIKGEQGp	COL28A1	Collagen alpha-1(XXVIII) chain	698	717
e04199	PVGpSGKDGANGIpG	COL2A1	Collagen alpha-1(II) chain	1,168	1,182
e12658	AGppGEKGEPGDDGpSGAEGPpGPQG	COL2A1	Collagen alpha-1(II) chain	950	975
e13033	GpAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	948	974
e12156	GPAGpPGEKGEPGDDGPSGAEGPPGp	COL2A1	Collagen alpha-1(II) chain	948	973
e02994	NGNPGpPGpPGPSG	COL2A1	Collagen alpha-1(II) chain	911	924
e02280	ApGEDGRpGPpG	COL2A1	Collagen alpha-1(II) chain	580	591
e14434	GEpGRDGNpGSDGLpGRDGSpGGKGDRG	COL3A1	Collagen alpha-1(III) chain	1,008	1,035
e10992	GLAGTAGEpGRDGNpGSDGLpGR	COL3A1	Collagen alpha-1(III) chain	1,002	1,024
e17922	NTGApGSPGVSGPKGDAGQpGEKGSpGAQGpPGAPGPLG	COL3A1	Collagen alpha-1(III) chain	910	948
e00635	SpGKDGPpGP	COL3A1	Collagen alpha-1(III) chain	898	907
e10257	GSNGNpGpPGPSGSpGKDGPpGP	COL3A1	Collagen alpha-1(III) chain	885	907
e07880	pGARGLpGpPGSNGNPGpP	COL3A1	Collagen alpha-1(III) chain	875	893
e09891	SEGSPGHpGQPGpPGpPGApGP	COL3A1	Collagen alpha-1(III) chain	871	892
e14224	NRGERGSEGSPGHpGQPGPpGPPGApGP	COL3A1	Collagen alpha-1(III) chain	865	892

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e14315	NRGERGSEGSPGHpGQpGPPGpPGApGP	COL3A1	Collagen alpha-1(III) chain	865	892
e10096	GEpGGKGERGApGEKGEGGPpG	COL3A1	Collagen alpha-1(III) chain	819	840
e12235	GQNGEpGGKGERGApGEKGEGGPpG	COL3A1	Collagen alpha-1(III) chain	816	840
e13362	ApGQNGEPGGkGERGAPGEkGEGGPpG	COL3A1	Collagen alpha-1(III) chain	814	840
e11904	GPAGFpGApGQNGEpGGKGERGApG	COL3A1	Collagen alpha-1(III) chain	807	831
e03354	SpGERGETGPpGP	COL3A1	Collagen alpha-1(III) chain	796	808
e01923	SpGERGETGPp	COL3A1	Collagen alpha-1(III) chain	796	806
e03194	DGVPGKDGPRGPT	COL3A1	Collagen alpha-1(III) chain	752	764
e09521	EGGKGAAGpPGPpGAAGTpGLQG	COL3A1	Collagen alpha-1(III) chain	704	726
e10902	AGpPGPEGGKGAAGPpGPpGAAGTpG	COL3A1	Collagen alpha-1(III) chain	698	723
e12891	RGGAGPPGpEGGKGAAGPpGpPGAAGTpG	COL3A1	Collagen alpha-1(III) chain	695	723
e00259	ApGERGPpG	COL3A1	Collagen alpha-1(III) chain	679	687
e06307	ApGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	670	687
e09061	GApGApGGKGDAGAPGERGppG	COL3A1	Collagen alpha-1(III) chain	666	687
e10876	GDAGApGApGGKGDAGApGERGPpG	COL3A1	Collagen alpha-1(III) chain	663	687
e11885	ENGKpGEPGpKGDAGApGApGGKGD	COL3A1	Collagen alpha-1(III) chain	652	676
e00336	PpGENGKpG	COL3A1	Collagen alpha-1(III) chain	649	657
e05918	GTGGPpGENGKpGEpGP	COL3A1	Collagen alpha-1(III) chain	645	661
e07668	GTGGPpGENGKpGEpGPKG	COL3A1	Collagen alpha-1(III) chain	645	663
e08405	GLpGTGGPpGENGKPGEpGP	COL3A1	Collagen alpha-1(III) chain	642	661
e08526	GLpGTGGPpGENGKpGEpGP	COL3A1	Collagen alpha-1(III) chain	642	661
e04824	GLpGTGGPpGENGKPG	COL3A1	Collagen alpha-1(III) chain	642	657
e09629	QGLpGTGGPpGENGKpGEpGP	COL3A1	Collagen alpha-1(III) chain	641	661
e10938	QGLpGTGGpPGENGKpGEpGPKG	COL3A1	Collagen alpha-1(III) chain	641	663
e00753	DKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	628	637
e05568	TGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	623	639
e14735	KNGETGPQGPPGpTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639
e16231	pPGKNGETGPQGppGPTGPGGDKGDTGPPGpQG	COL3A1	Collagen alpha-1(III) chain	607	639
e05118	ApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	589	604
e06584	DGApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	587	604
e03651	DGApGKNGERGGpG	COL3A1	Collagen alpha-1(III) chain	587	600
e07676	NDGAPGKNGERGGpGGpGp	COL3A1	Collagen alpha-1(III) chain	586	604
e06068	NDGApGKNGERGGpGGP	COL3A1	Collagen alpha-1(III) chain	586	602
e08188	GNDGApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	585	604
e01544	GpGSDGKpGPpG	COL3A1	Collagen alpha-1(III) chain	544	555
e01422	GpGSDGKPGPpG	COL3A1	Collagen alpha-1(III) chain	544	555
e02032	GGpGSDGKpGPpG	COL3A1	Collagen alpha-1(III) chain	543	555
e02169	EpGRDGVpGGpG	COL3A1	Collagen alpha-1(III) chain	523	534
e03389	EpGRDGVpGGPGm	COL3A1	Collagen alpha-1(III) chain	523	535
e14712	AKGEDGKDGSpGEpGANGLpGAAGERGApG	COL3A1	Collagen alpha-1(III) chain	460	489
e11911	GIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	453	477
e12496	AGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	452	477

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e13816	ERGEAGIpGVpGAKGEDGKDGSpGEpG	COL3A1	Collagen alpha-1(III) chain	448	474
e01935	DGESGRpGRpG	COL3A1	Collagen alpha-1(III) chain	230	240
e12333	TSGHPGSpGSpGYQGPpGEpGQAGP	COL3A1	Collagen alpha-1(III) chain	187	211
e01956	GpAGPpGpPGPpG	COL3A1	Collagen alpha-1(III) chain	174	186
e12014	DGAPGQKGEMGpAGpTGpRGFPGp	COL4A1	Collagen alpha-1(IV) chain	1,401	1,424
e05864	GppGFTGPpGpPGPPGP	COL4A1	Collagen alpha-1(IV) chain	197	213
e05726	GPpGFTGppGPPGPPGP	COL4A1	Collagen alpha-1(IV) chain	197	213
e07037	PGPPGTPGEpGMQGEPGP	COL4A3	Collagen alpha-3(IV) chain	1,360	1,377
e15360	GpKGDpGIpGLDRSGFpGETGSPGIPGHQ	COL4A3	Collagen alpha-3(IV) chain	836	864
e11819	NEGLDGPRGDpGQPGpPGEQGpP	COL4A3	Collagen alpha-3(IV) chain	784	806
e07481	KGPPGDHGLPGYLGSPGI	COL4A3	Collagen alpha-3(IV) chain	445	462
e07901	QKGDQGLPGDRGpPGpPG	COL4A5	Collagen alpha-5(IV) chain	256	273
e02526	GPpGPPGpSSNQG	COL4A6	Collagen alpha-6(IV) chain	1,252	1,264
e14398	PGMPGADGpPGHPGKEGppGEKGGQGpPG	COL5A1	Collagen alpha-1(V) chain	753	781
e15580	GpSGpVGpPGLAGERGEQGPpGPTGFQGLPG	COL5A2	Collagen alpha-2(V) chain	651	681
e11008	pPGEEGKRGPRGDpGTVGPpGP	COL5A2	Collagen alpha-2(V) chain	496	517
e06214	GSPGTSGppGSAGpPGSpG	COL5A2	Collagen alpha-2(V) chain	435	453
e15375	GpMGAMGpLGPRGMpGERGRLGpQGAPGQ	COL5A2	Collagen alpha-2(V) chain	327	355
e09921	pGVSGIDGSpGEKGDpGDVGGP	COL5A3	Collagen alpha-3(V) chain	1,273	1,294
e05200	GPpGPpGFPGDpGPpG	COL5A3	Collagen alpha-3(V) chain	407	422
e05060	GPpGPpGFpGDPGPPG	COL5A3	Collagen alpha-3(V) chain	407	422
e16717	DPGLMGERGEDGpAGNGTEGFPGFPGYpGNR	COL6A1	Collagen alpha-1(VI) chain	501	531
e07801	RGDEGPPGSEGARGAPGpA	COL6A1	Collagen alpha-1(VI) chain	478	496
e11369	GPpGEPGPRGPRGVpGpEGEpGP	COL6A2	Collagen alpha-2(VI) chain	561	583
e08435	GpPGEGRAGEpGTAGpTGpP	COL8A2	Collagen alpha-2(VIII) chain	490	509
e05738	pGPDGpSGpPGPpGKPG	COL9A2	Collagen alpha-2(IX) chain	131	147
e11161	DQGpQGPQGVPGTSKDGQDGApG	COL9A3	Collagen alpha-3(IX) chain	617	639
e11916	QGDRGDKGAAGAGLDGpEGDQGpQ	COL9A3	Collagen alpha-3(IX) chain	598	621
e11487	TpGVAGPSGEpGmpGKDGQNGVPG	COL9A3	Collagen alpha-3(IX) chain	290	313
e10976	TpGVAGpSGEPGMpGKDGQNGVP	COL9A3	Collagen alpha-3(IX) chain	290	312
e01532	DGEkGDPGPpG	COL9A3	Collagen alpha-3(IX) chain	207	217
e16278	mPGFKGpTGYKGEQGEVGKDGEKGDpGpPG	COL9A3	Collagen alpha-3(IX) chain	151	180
e00676	VAMTPRSEG	F2	Prothrombin	193	201
e12790	TDGALVQHQEWDGKESTITRK	FABP5P3	Putative fatty acid-binding protein 5-like protein 3	56	76
e13727	ATPLYINI	FAT1	Protocadherin Fat 1	654	661
e00860	EGTHSTKRG	FGA	Fibrinogen alpha chain	614	622
e02915	DHEGTHSTKRG	FGA	Fibrinogen alpha chain	612	622
e05580	SEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	609	622
e06067	GSEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	608	622
e07971	EAGSEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	606	622
e12086	DEAGSEADHEGTHSTKRGHAKS	FGA	Fibrinogen alpha chain	605	626
e13674	DEAGSEADHEGTHSTKRGHAKSRP	FGA	Fibrinogen alpha chain	605	628

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e17491	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629
e07002	DEAGSEADHEGTHSTK	FGA	Fibrinogen alpha chain	605	620
e04994	DEAGSEADHEGTHS	FGA	Fibrinogen alpha chain	605	618
e11627	SESGSFRPDSPGSGNARPNNPD	FGA	Fibrinogen alpha chain	388	409
e08185	EEAPSLRPAPPPISGGGY	FGB	Fibrinogen beta chain	54	71
e06733	AGSEADHEGTHSTKRG	FIBA	Fibrinogen alpha chain	607	622
e15365	SWYDNEFGYSNRVVDLMAHMASKE	GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	312	335
e07622	WVGTGASEAEKTGAQEL	GSN	Gelsolin	605	621
e11826	SETAPAAPAAPAPAEKTPVKKKA	H14	Histone H1.4	2	24
e13087	SETAPAETATPAPVEKSPAKKKAT	H15	Histone H1.5	2	25
e07959	VAHVDDMPNALSALSDL	HBA1	Hemoglobin subunit alpha	71	82
e04294	PEPAKSAPAPKKGS	H2B1K	Histone H2B type 1-K	2	15
e00274	TVEAPMPK	HSPB1	Heat shock protein beta-1	164	171
e09692	ASTRESGVPDRFSGSGSGTD	IGKV4-1	Immunoglobulin kappa variable 4-1	77	96
e00433	DVVPIEPH	IL1RN	Interleukin-1 receptor antagonist protein	72	79
e01692	SSHVGGTLGQF	ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	873	883
e05450	SVMPGLKMTMDKTG	ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	825	838
e10519	FARSIEMMDIVVEKNGEN	KCNB1	Potassium voltage-gated channel subfamily B member 1	454	471
e06292	ASYLDKVRALEESN	KRT10	Keratin, type I cytoskeletal 10	158	171
e01849	AQYEEIAQR	KRT4	Keratin; type II cytoskeletal 4	354	362
e09390	LSMDNNRNLDLDSIIAE	KRT4	Keratin; type II cytoskeletal 4	274	290
e01343	YSNEKPFTG	MASP2	Mannan-binding lectin serine protease 2	121	129
e04940	GKVEADIPGHGQEV	MB	Myoglobin	16	29
e05961	GPITLEPTEDGMAGVA	MEGF8	Multiple epidermal growth factor-like domains protein 8	2,766	2,781
e00340	cDDYRLc	MGP	Matrix Gla Protein	73	79
e01132	cDDYRLcE	MGP	Matrix Gla Protein	73	90
e12382	DGLSPDQTRSEDPQNSAGSPPDA	MYOCD	Myocardin	160	182
e00161	DQITGKW	ORM1	Alpha-1-acid glycoprotein 1	37	43
e03544	KELDINTDGAVN	S100A8	Protein S100-A8	56	67
e03248	EATEMcTQEc	PCDH9	Protocadherin-9	1,124	1,133
e06511	PGMFPSGTPGGPYGGAAP	PEF1	Peflin	69	86
e00166	FAGDDAPR	POTEF	POTE ankyrin domain family member F	721	728
e00191	KPGLGEGTP	S100A9	Protein S100-A9	106	114
e06220	GHPDTLNQGEFKEL	S100A9	Protein S100-A9	27	40
e00317	KLGHPDTL	S100A9	Protein S100-A9	25	32
e05292	TGRGAEDSLADQAAN	SAA2	Serum amyloid A-2 protein	87	101
e05742	DITSHMESEELNGA	SPP1	Osteopontin	188	201
e14519	TETQEKNPLPSKETIEQEKQAGES	TMSB4X	Thymosin beta-4	21	44
e00773	GFQLTHSLG	TUBB3	Tubulin beta-3 chain	132	140
e01448	IDQSRVLNL	UMOD	Uromodulin	593	601
e07093	VIDQSRVLNLGPITR	UMOD	Uromodulin	592	606
e05684	VIDQSRVLNLGPIT	UMOD	Uromodulin	592	605

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e06451	SVIDQSRVLNLGPIT	UMOD	Uromodulin	591	605
e07964	SVIDQSRVLNLGPITR	UMOD	Uromodulin	591	606
e06877	SGSVIDQSRVLNLGPI	UMOD	Uromodulin	589	604
e02788	VENGESSQGRF	UMOD	Uromodulin	538	548
e05240	DQSRVLNLGPITR	UMOD	Uromodulin	594	606

AA: Amino acid

Supplementary Table S4. List of the 193 differentially excreted CRS-associated peptides. (Sci Rep. 2021 Aug 10;11(1):16219. doi: 10.1038/s41598-021-95695-z).

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e14697	FLPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	277	299
e11793	FKGKWERPFEVKDTEEED	A1AT	Alpha-1-antitrypsin	214	231
e05113	EAGSPPVVE	ANR17	Ankyrin repeat domain-containing protein 17	2,078	2,086
e10106	SNNAKEAVEHLQKSELTQ	APOA4	Apolipoprotein A-IV	39	56
e04609	SIAAGGEGLTDVSPE	ATG12	Ubiquitin-like protein ATG12	14	28
e03035	WKYYYDGKD	AZGP1	Zinc-alpha-2-glycoprotein	135	143
e12566	NGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	62	81
e12280	LLKNGERIEKVEHSDLSFSK	B2M	Beta-2-microglobulin	59	78
e00402	LDLSHNSL	CD14	Monocyte differentiation antigen CD14	254	261
e10450	VSGGEGKGGSDGGGSHRKEGEE	CD99	CD99 antigen	99	120
e09580	NPPKPMPNPNPNHPSSSGS	CD99	CD99 antigen	71	89
e14231	DDPRPPNPPKPmPNPNPNHPSSSGS	CD99	CD99 antigen	65	89
e10043	FSHAVSSNGNAVEDPMEIL	CDH1	Cadherin 1	179	197
e09883	ETLAEPEISGLWNEDYK	CFAP74	Cilia- and flagella-associated protein 74	448	464
e04757	SHTSDSDVPSGVTE	CLU	Clusterin	391	404
e06239	VASHTSDSDVPSGVTE	CLU	Clusterin	389	404
e14337	IHEAQQAMDIHFHSPAFQHPPTE	CLU	Clusterin	251	273
e12945	DGpQGPpGSVGSVGGVGEKGEPGEAGN	COL11A1	Collagen alpha-1(XI) chain	1,236	1,262
e05574	GpKGTSGGDGpPGpPGE	COL11A1	Collagen alpha-1(XI) chain	901	917
e14204	GNEGpSGPPGpAGSPGERGAAGSGGPIGpPG	COL11A2	Collagen alpha-2(XI) chain	1,003	1,033
e07106	EAGEKGNPGAEGLQGVpG	COL13A1	Collagen alpha-1(XIII) chain	555	572
e09468	GDKGAIGMpGRVGVKGQpGE	COL13A1	Collagen alpha-1(XIII) chain	134	153
e17751	pPGPQGPSGLSIQGMpGmpGEKGEKGDTGLPGPQG	COL14A1	Collagen alpha-1(XIV) chain	1,502	1,536
e05351	DKGEpGPPGQPGYpG	COL16A1	Collagen alpha-1(XVI) chain	1,079	1,093
e11015	PKGDKGDPGVGERGppGpQGpP	COL18A1	Collagen alpha-1(XVIII) chain	848	869
e19753	GPEGPSGKpGINGKDGIPGAQGImGKpGDRGpKGERGDQGIP	COL19A1	Collagen alpha-1(XIX) chain	917	958
e04177	PpGPpGPpGPPGPPS	COL1A1	Collagen alpha-1(I) chain	1,179	1,193
e04843	GPpGpPGPpGpPGPPS	COL1A1	Collagen alpha-1(I) chain	1,178	1,193
e06697	VGPpGpPGPpGPPGPPSAG	COL1A1	Collagen alpha-1(I) chain	1,177	1,195
e06859	VGpPGpPGPpGPpGPPSAG	COL1A1	Collagen alpha-1(I) chain	1,177	1,195
e18831	DKGETGEQGDRGIKGHRGFSGLQGppGppGSPGEQGP	COL1A1	Collagen alpha-1(I) chain	1,095	1,131
e13918	AGpPGApGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,042	1,071
e12488	KGDRGETGpAGPPGApGAPGAPGPVGP	COL1A1	Collagen alpha-1(I) chain	1,033	1,059
e09125	SpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1,023	1,042
e11940	GESGREGApGAEGSpGRDGSpGAKG	COL1A1	Collagen alpha-1(I) chain	1,010	1,034
e16966	PpGESGREGApGAEGSpGRDGSPGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1,008	1,041
e16624	GPpGESGREGApGAEGSpGRDGSpGAKGDRGET	COL1A1	Collagen alpha-1(I) chain	1,007	1,039
e17221	GPpGESGREGAPGAEGSpGRDGSPGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,007	1,041
e17288	GPpGESGREGAPGAEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1,007	1,041
e19228	PGLPGPSGEpGKQGpSGASGERGPPGPMGPPGLAGppGESGR	COL1A1	Collagen alpha-1(I) chain	973	1,014
e17438	AGRpGEVGpPGpPGPAGEKGSPGADGPAGAPGTPGPQG	COL1A1	Collagen alpha-1(I) chain	916	953
e05448	EpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	828	844

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e05259	DGQPGAKGEpGDAGAK	COL1A1	Collagen alpha-1(I) chain	820	835
e12101	ADGQpGAKGEpGDAGAKGDAGPpGpA	COL1A1	Collagen alpha-1(I) chain	819	844
e11452	ADGQpGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843
e13065	ADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846
e12986	ADGQpGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846
e11325	ADGQPGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843
e16771	GADGQpGAKGEpGDAGAKGDAGPPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	818	854
e17690	pPGADGQPGAKGEpGDAGAKGDAGppGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854
e17626	pPGADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854
e17825	GPpGADGQPGAKGEPGDAGAKGDAGPPGpAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	815	854
e15607	GFAGPpGADGQpGAKGEpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	812	844
e01155	ApGDKGESGPS	COL1A1	Collagen alpha-1(I) chain	777	787
e11527	IGPpGpAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794
e13200	TGPIGpPGPAGAPGDKGESGpSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	766	794
e10192	ApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	702	725
e11777	ANGApGNDGAKGDAGApGApGSQGAPG	COL1A1	Collagen alpha-1(I) chain	699	725
e02286	PpGEAGKpGEQG	COL1A1	Collagen alpha-1(I) chain	651	662
e10668	GpPGEAGKpGEQGVpGDLGAPGp	COL1A1	Collagen alpha-1(I) chain	650	672
e11836	GLpGpAGpPGEAGKPGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	644	668
e18181	ERGEQGPAGSpGFQGLpGPAGPpGEAGKpGEQGVPGD	COL1A1	Collagen alpha-1(I) chain	630	666
e04947	EpGKAGERGVPGpPG	COL1A1	Collagen alpha-1(I) chain	591	605
e18625	AAGEpGKAGERGVPGppGAVGPAGKDGEAGAQGpPGPAGPAG	COL1A1	Collagen alpha-1(I) chain	588	629
e00467	DGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	550	559
e05236	SpGSpGPDGKTGppGP	COL1A1	Collagen alpha-1(I) chain	543	558
e05879	SpGSPGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560
e06186	SpGSPGpDGKTGPPGpAG	COL1A1	Collagen alpha-1(I) chain	543	560
e06709	GSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	542	560
e05692	GSpGSpGPDGKTGpPGp	COL1A1	Collagen alpha-1(I) chain	542	558
e06547	GSpGSpGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	542	560
e14837	ERGSpGPAGPKGSpGEAGRpGEAGLpGAKG	COL1A1	Collagen alpha-1(I) chain	510	539
e15323	VQGPpGpAGEEGKRGARGEPGPTGLpGPpG	COL1A1	Collagen alpha-1(I) chain	456	485
e09923	NSGEPGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453
e12508	KGNSGEpGAPGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	430	455
e11286	KGNSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	430	453
e12624	KGNSGEpGApGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	430	455
e07132	EpGSpGENGAPGQmGPR	COL1A1	Collagen alpha-1(I) chain	288	304
e12851	LDGAKGDAGPAGPKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299
e12949	LDGAKGDAGPAGpKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299
e01561	DGEAGKpGRpG	COL1A1	Collagen alpha-1(I) chain	232	242
e11536	NGDDGEAGKPGRpGERGPpGPQG	COL1A1	Collagen alpha-1(I) chain	229	251
e11245	NGDDGEAGKpGRpGERGpPGPQ	COL1A1	Collagen alpha-1(I) chain	229	250
e11672	NGDDGEAGKPGRPGERGppGpQG	COL1A1	Collagen alpha-1(I) chain	229	251

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e11538	GKNGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	227	249
e12661	GKNGDDGEAGKPGRpGERGPpGpQ	COL1A1	Collagen alpha-1(I) chain	227	250
e13850	PpGKNGDDGEAGKPGRpGERGppGPQ	COL1A1	Collagen alpha-1(I) chain	225	250
e14211	GPpGKNGDDGEAGKPGRpGERGPpGpQ	COL1A1	Collagen alpha-1(I) chain	224	250
e15755	RGPpGPpGKNGDDGEAGKPGRpGERGPpGP	COL1A1	Collagen alpha-1(I) chain	220	249
e10057	GEpGEpGASGPMGPRGPpGPpG	COL1A1	Collagen alpha-1(I) chain	206	227
e11265	NDGPpGRDGQpGHKGERGYpG	COL1A2	Collagen alpha-2(I) chain	932	952
e15467	GRDGNpGNDGPpGRDGQpGHKGERGYpG	COL1A2	Collagen alpha-2(I) chain	925	952
e14285	EAGRDGNPGNDGPpGRDGQpGHKGER	COL1A2	Collagen alpha-2(I) chain	923	948
e16340	EAGRDGNPGNDGppGRDGQpGHKGERGYPG	COL1A2	Collagen alpha-2(I) chain	923	952
e09700	FAGEKGPSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	842	863
e13164	AVGPPGFAGEKGpSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	836	863
e18620	DQGPVGRTGEVGAVGppGFAGEKGPSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	824	863
e08253	GRTGppGPSGISGPpGPpGP	COL1A2	Collagen alpha-2(I) chain	793	812
e18887	AGEVGKpGERGLHGEFGLPGpAGPRGERGppGESGAAGP	COL1A2	Collagen alpha-2(I) chain	564	602
e09529	EEGKRGPNGEAGSAGPpGPpG	COL1A2	Collagen alpha-2(I) chain	377	397
e04597	ApGENGTpGQTGARG	COL1A2	Collagen alpha-2(I) chain	203	217
e06154	EDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	143	157
e06839	GEDGHpGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	142	157
e11629	AGPpGKAGEDGHpGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	135	157
e17388	GPpGppGRDGEDGPTGPpGPPGPPGPPGLGGNFAAQ	COL1A2	Collagen alpha-2(I) chain	45	80
e15713	pGpLGTKGDRGAPGIPGSPGSRGDpGIGVAGp	COL22A1	Collagen alpha-1(XXII) chain	998	1,029
e04644	PpGPAGNPGpSpNSp	COL26A1	Collagen alpha-1(XXVI) chain	257	271
e08201	NKGEPGpPGpYGSpGAPGI	COL28A1	Collagen alpha-1(XXVIII) chain	341	359
e12714	pAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	949	974
e12007	pGADGQpGAKGEQGEAGQKGDAGAp	COL2A1	Collagen alpha-1(II) chain	839	863
e16656	FAGpPGADGQpGAKGEQGEAGQKGDAGApGpQGP	COL2A1	Collagen alpha-1(II) chain	835	868
e17673	GpPGPAGFAGpPGADGQpGAKGEQGEAGQKGDAGAPGP	COL2A1	Collagen alpha-1(II) chain	828	865
e09547	GPpGEGGKpGDQGVpGEAGApG	COL2A1	Collagen alpha-1(II) chain	672	693
e19147	GAKGEAGAPGVKGESGSpGENGSPGPmGpRGLPGERGRTGP	COL2A1	Collagen alpha-1(II) chain	297	337
e20610	GLAGTAGEpGRDGNPGSDGLPGRDGSpGGKGDRGENGSpGAPGAPGHPGPPGp	COL3A1	Collagen alpha-1(III) chain	1,002	1,054
e08150	GNpGPpGPSGSpGKDGPPGp	COL3A1	Collagen alpha-1(III) chain	888	907
e09856	SNGNPGppGPSGSpGKDGPPGp	COL3A1	Collagen alpha-1(III) chain	886	907
e13707	GApGQNGEPGGKGERGApGEKGEGGppG	COL3A1	Collagen alpha-1(III) chain	813	840
e08539	ApGApGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	667	687
e12313	TGGpPGENGKPGEpGpKGDAGApGAP	COL3A1	Collagen alpha-1(III) chain	646	671
e10072	GLpGTGGPpGENGKpGEpGPKG	COL3A1	Collagen alpha-1(III) chain	642	663
e07586	GPPGPTGPGGDKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	618	637
e15411	PQGPpGPTGpGGDKGDTGPpGPQGLQGLpGT	COL3A1	Collagen alpha-1(III) chain	616	646
e14644	KNGETGPQGPPGPTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639
e14727	KNGERGGpGGPGPQGpPGKNGETGpQGpP	COL3A1	Collagen alpha-1(III) chain	592	620
e11222	NDGApGKNGERGGpGGpGPQGPpG	COL3A1	Collagen alpha-1(III) chain	586	609

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e03940	SpGGpGSDGKpGpPG	COL3A1	Collagen alpha-1(III) chain	541	555
e10613	GPGMRGMPGSPGGpGSDGKpGpP	COL3A1	Collagen alpha-1(III) chain	532	554
e15129	ERGEAGIpGVpGAKGEDGKDGSPGEpGANG	COL3A1	Collagen alpha-1(III) chain	448	477
e16286	RGERGEAGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	446	477
e05577	GGAGEpGKNGAKGEpGP	COL3A1	Collagen alpha-1(III) chain	429	445
e09966	GARGNDGARGSDGQPGPpGPpG	COL3A1	Collagen alpha-1(III) chain	318	339
e08436	PGSRGDTGPpGpPGYGPAGP	COL4A1	Collagen alpha-1(IV) chain	594	613
e11768	pGFPGAQGEPGSQGEpGDpGLpGP	COL4A2	Collagen alpha-2(IV) chain	365	388
e06771	PGpPGpPGPPGHPGPQGp	COL4A3	Collagen alpha-3(IV) chain	655	672
e08406	HEDATpGGKGFPGPLGpPG	COL4A4	Collagen alpha-4(IV) chain	604	622
e08942	pGFPGTpGLpGmPGHDGAPG	COL4A5	Collagen alpha-5(IV) chain	98	117
e15320	LPGFPGpEGPPGpRGQKGDDGIpGpPGPK	COL4A5	Collagen alpha-5(IV) chain	61	89
e09844	GLDGERGRPGPAGppGppGPS	COL4A6	Collagen alpha-6(IV) chain	1,240	1,260
e03055	GEAGHPGPPGPpGP	COL5A1	Collagen alpha-1(V) chain	1,555	1,568
e05011	pGPPGEPGPAGQDGPP	COL5A1	Collagen alpha-1(V) chain	1,347	1,362
e13650	GpTGATGDKGPPGPVGPPGSNGpVGEpGP	COL5A2	Collagen alpha-2(V) chain	1,020	1,048
e15594	PGSRGENGpTGAVGFAGPQGPDGQPGVKGEP	COL5A2	Collagen alpha-2(V) chain	833	863
e11679	EGpPGKPGEDGEpGRNGNpGEVG	COL5A2	Collagen alpha-2(V) chain	257	279
e11763	GpEGppGKpGEDGEPGRNGNPGE	COL5A2	Collagen alpha-2(V) chain	255	277
e08177	DGpEGPKGQAGQAGEEGPP	COL5A3	Collagen alpha-3(V) chain	760	778
e05521	GQSRDAEEAISQTI	COL6A1	Collagen alpha-1(VI) chain	219	232
e10376	GEKGDPGSQGSPGSRGApGqYG	COL6A5	Collagen alpha-5(VI) chain	1,485	1,506
e13387	KGEKGDSEDGApGLpGQPGSpGEQGp	COL7A1	Collagen alpha-1(VII) chain	1,444	1,469
e09719	KGDPGPSGppGpRGPLGDpGP	COL7A1	Collagen alpha-1(VII) chain	1,367	1,387
e02172	GPpGpPGPPGPpA	COL8A1	Collagen alpha-1(VIII) chain	560	572
e08360	tGYTGKMCESSVNYCE	FAT4	Protocadherin Fat 4	3,928	3,943
e11931	SEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	609	629
e14283	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629
e10596	DEAGSEADHEGTHSTKRGHA	FGA	Fibrinogen alpha chain	605	624
e08978	DEAGSEADHEGTHSTKRG	FGA	Fibrinogen alpha chain	605	622
e07900	DEAAFFDTASTGKTFPG	FGA	Fibrinogen alpha chain	515	531
e00553	GGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	9	18
e05387	GLSMDGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	3	18
e07648	TGLSMDGGGSPKGDVDPF	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	2	19
e07356	TTTAPTPA	HUWE1	E3 ubiquitin-protein ligase HUWE1	1,090	1,097
e14820	LIALPTQDPAHGGAPPEMASN	IGF2	Insulin-like growth factor II	158	178
e03199	VDVSHEDPEVK	IGHG1	Immunoglobulin heavy constant gamma 1	266	276
e05105	VVVDVSHEDPEVK	IGHG1	Immunoglobulin heavy constant gamma 1	264	276
e11944	KDNDVDEEDEEDELDQSQH	IRF6	Interferon regulatory factor 6	137	155
e08496	LLRDTDRFSSHVGGTLG	ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	865	881
e09412	GSGGSSYGSGGGSYGSGGGGGGGRG	KRT1	Keratin; type II cytoskeletal 1	526	550
e09606	LDTYPNDETTERVFPY	LMAN2	Vesicular integral-membrane protein VIP36	161	176

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein Name	Start AA	Stop AA
e03142	DTHFDSDEPW	MMP24	Matrix metalloproteinase-24	255	264
e17804	TTLSPSSSTTHEGEPTTFQSWPSSKDTSPAPSG	MUC12	Mucin-12	404	436
e14560	TRDQADGSRASVDSGSSEEQGGSSRAL	PIGR	Polymeric-immunoglobulin receptor	614	640
e14638	AVADTRDQADGSRASVDSGSSEEQGGSS	PIGR	Polymeric-immunoglobulin receptor	610	637
e15907	AVADTRDQADGSRASVDSGSSEEQGGSSRA	PIGR	Polymeric-immunoglobulin receptor	610	639
e19279	TSPSGQLIPVKNLSENIEIL	PK1L2	Polycystic kidney disease protein 1-like 2	1,142	1,161
e06714	GYISGPLVSDMDTDAP	ROBO1	Roundabout homolog 1	1,312	1,327
e10432	HQYSVKLGHPDTLNQGEF	S100A9	Protein S100-A9	20	37
e18617	FGHGAEDSLADQAANEWGRSGKDPNHFRPAGLPE	SAA1	Serum amyloid A-1 protein	87	120
e09609	LTGRGAEDSLADQAANKWG	SAA2	Serum amyloid A-2 protein	86	104
e12387	HLVGHQRNNRQVTLEVSGAEP	SECTM1	Secreted and transmembrane protein 1	118	138
e08607	RAHGQESAIFNEVAPGY	SECTM1	Secreted and transmembrane protein 1	69	85
e10000	VANEESEHNQGASEENGLP	SHANK1	SH3 and multiple ankyrin repeat domains protein 1	1,536	1,543
e13231	NKTPIR	TITIN	Titin	21,153	21,158
e20740	sDKPDMAEIEKFDKSKLKKTETQEKNPLPSKETIEQEKQAGES	TMSB4X	Thymosin beta-4	2	44
e06064	GSEEEPAPSSLQPGSP	UBAP1L	Ubiquitin-associated protein 1-like	118	133
e00923	VLNLGPITR	UMOD	Uromodulin	598	606
e06194	IDQSRVLNLGPITR	UMOD	Uromodulin	593	606
e08455	GSVIDQSRVLNLGPITR	UMOD	Uromodulin	590	606
e07848	SGSVIDQSRVLNLGPIT	UMOD	Uromodulin	589	605
e02332	SGSVIDQSRVL	UMOD	Uromodulin	589	599
e09213	SGSVIDQSRVLNLGPITR	UMOD	Uromodulin	589	606
e10189	SGSVIDQSRVLNLGPITRK	UMOD	Uromodulin	589	607
e00683	SGSVIDQSR	UMOD	Uromodulin	589	597
e17439	GRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAPE	VGF	Neurosecretory protein VGF	26	58

AA: Amino acid

Supplementary Table S5. List of the protein precursors which were found only in CRS when comparing with HF and CKD (Sci Rep. 2021 Aug 10;11(1):16219. doi: 10.1038/s41598-021-95695-z).

Protein Symbol	Protein Name
ANR17	Ankyrin repeat domain-containing protein 17
ATG12	Ubiquitin-like protein ATG12
AZGP1	Zinc-alpha-2-glycoprotein
CD14	Monocyte differentiation antigen CD14
CDH1	Cadherin 1
CFAP74	Cilia- and flagella-associated protein 74
COL13A1	Collagen alpha-1(XIII) chain
COL26A1	Collagen alpha-1(XXVI) chain
COL4A2	Collagen alpha-2(IV) chain
COL4A4	Collagen alpha-4(IV) chain
COL6A5	Collagen alpha-5(VI) chain
COL7A1	Collagen alpha-1(VII) chain
COL8A1	Collagen alpha-1(VIII) chain
FAT4	Protocadherin Fat 4
HUWE1	E3 ubiquitin-protein ligase HUWE1
IGF2	Insulin-like growth factor II
IGHG1	Immunoglobulin heavy constant gamma 1
IRF6	Interferon regulatory factor 6
KRT1	Keratin; type II cytoskeletal 1
MMP24	Matrix metalloproteinase-24
MUC12	Mucin-12
PIGR	Polymeric-immunoglobulin receptor
PK1L2	Polycystic kidney disease protein 1-like 2
ROBO1	Roundabout homolog 1
SAA1	Serum amyloid A-1 protein
SECTM1	Secreted and transmembrane protein 1
SHANK1	SH3 and multiple ankyrin repeat domains protein 1
TITIN	Titin
UBAP1L	Ubiquitin-associated protein 1-like
VGF	Neurosecretory protein VGF

PLOS ONE

RESEARCH ARTICLE

Urine peptidome in combination with transcriptomics analysis highlights MMP7, MMP14 and PCSK5 for further investigation in chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is characterized by the loss of kidney function. The molecular mechanisms underlying the development and progression of CKD are still not fully understood. Among others, the urinary peptidome has been extensively studied, with several urinary peptides effectively detecting disease progression. However, their link to proteolytic events has not been made yet. This study aimed to predict the proteases involved in the generation of CKD-associated urinary excreted peptides in a well-matched (for age, sex, lack of heart disease) case-control study. The urinary peptide profiles from CKD (n = 241) and controls (n = 240) were compared and statistically analyzed. The *in-silico* analysis of the involved proteases was performed using Proteasix and proteases activity was predicted based on the abundance changes of the associated peptides. Predictions were cross-correlated to transcriptomics datasets by using the Nephroseq database. Information on the respective protease inhibitors was also retrieved from the MEROPS database. Totally, 303 urinary peptides were significantly associated with CKD. Among the most frequently observed were fragments of collagen types I, II and III, uromodulin, albumin and beta-2-microglobulin. Proteasix predicted 16 proteases involved in their generation. Through investigating CKD-associated transcriptomics datasets, several proteases are highlighted including members of matrix metalloproteinases (*MMP7*, *MMP14*) and serine proteases (*PCSK5*); laying the foundation for further studies towards elucidating their role in CKD pathophysiology.

Introduction

Chronic kidney disease (CKD) is one of the leading causes of death worldwide [1]. CKD is characterized by a reduced kidney function reflected in decreased glomerular filtration rate (GFR) < 60 mL/min/1.73m^2, for three months or longer [2]. The cellular and molecular mechanisms underlying the development and progression of CKD are not fully understood whereas

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the therapeutic methods are limited [3]. Specifically, several mechanisms including endocrine and metabolic complications as well as cardiovascular disease have a significant effect on the development and progression of CKD [2]. Furthermore, factors like proteinuria, kidney fibrosis and hypertension are associated with an increased risk of progression of CKD through the renin-angiotensin-aldosterone system (RAAS) [4].

Altered activation of proteases, breaking peptide bonds between the amino acids and generating protein fragments, are involved in key cellular mechanisms including, immune response, transcription, cell proliferation, differentiation, signalling and extracellular matrix (ECM) remodelling [5, 6]. Given the complexity of CKD pathophysiology, proteolysis is considered to play an essential role in the glomerular basal membrane breakdown, kidney damage and fibrosis [5]. Specifically, matrix metalloproteinases (MMPs), a family of zinc-containing endopeptidases, such as *MMP2* and *MMP9* have been linked to alterations of the tubular basement membrane, leading to renal fibrosis and tubular atrophy [7–9]. Furthermore, *MMP1* and *MMP7* are associated with the inflammatory process resulting in the development of renal fibrosis [7, 10–12]. The activation or inhibition of MMPs is regulated by, among others, inhibitors of metalloproteinases (TIMPs), α2-macro-globulin, netrins, tissue factor inhibitor 2 and the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) [5, 7]. Disparate evidence is available supporting changes in levels or activities of various proteases in association to CKD (reviewed in [13]), yet links to specific proteolytic events are generally lacking.

Based on the novel high-throughput technologies, the discovery and development of non-invasive CKD biomarkers is highlighted increasingly in the last decade. The urinary peptidome has been extensively studied, suggesting that several urinary peptides/biomarkers can effectively detect the progression of CKD [14–19]. Notably, a panel of 273 urinary differentially excreted peptides between CKD patients and controls, known as the "*CKD273 classifier*" [16], has been used for diagnostic and prognostic purposes in all CKD stages [15, 19–21]. In addition, this urinary proteomic classifier CKD273 has been successfully used for the stratification of CKD patients in large clinical trials [22].

Prompted by this lack of links between proteases and generated peptides in association to CKD, we aimed to predict the proteases involved in the generation of CKD-associated urinary excreted peptides in a well-matched case-control study. Through cross-correlating our predictions to CKD-associated transcriptomics datasets, several proteases are highlighted including members of MMPs (*MMP7*, *MMP14*) and serine proteases (*PCSK5*), laying the foundation for further studies towards elucidating their role in CKD pathophysiology.

Materials and methods

Patient data and peptide data collection

Urinary peptidomics data from CKD and non-CKD individuals were retrieved from the Human Urinary Proteome database of capillary electrophoresis mass spectrometry (CE-MS) [23]. These urine sample datasets were obtained from published studies on CKD and kidney failure and described before [19, 24, 25]. The datasets were examined for the accessibility of information on kidney failure and estimated glomerular filtration rate (eGFR). In addition, since cardiovascular disease is a major confounder, data were also screened for ejection fraction (EF) and heart failure diagnosis. All participants with EF $< 55\%$ and/or heart failure diagnoses were excluded from the study. The kidney function was estimated by the eGFR assessed based on ´Chronic Kidney Disease Epidemiology Collaboration´ (CKD-EPI) and the eGFR values were single measurements. Further patient characteristics and information including sex, age, body mass index (BMI), smoking status, serum creatinine, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were extracted. These accessible datasets were then

divided into two groups; CKD and non-CKD individuals where CKD was defined based on kidney function (eGFR < 60 ml/min/1.73 m^2) including mainly diabetic nephropathy (DN), glomerulonephritis (GN) and focal segmental glomerulosclerosis (FSGS) as the associated CKD aetiologies. The non-CKD cohort had an eGFR > 60 ml/min/1.73 m^2. This study was conducted following the ethics approval (163/19 Ethik-Commission of the medical faculty of the RWTH Aachen), fulfilling all the requirements of the protection of the individuals participating in medical research and accordance with the principles of the Declaration of Helsinki. All data sets received were anonymized. All experiments were performed by relevant named guidelines and regulations.

Capillary electrophoresis mass spectrometry (CE-MS)

Processing of the urine samples for CE-MS was performed as previously reported in Mischak et al. [26]. The P/ACE MDQ capillary electrophoresis system (Beckman Coulter, USA) coupled to a micro-TOF-MS (Bruker Daltonic, Germany) was utilized to perform CE-MS analysis. RAW MS data were assessed by the MosaFinder software [23]. CE-MS data normalization was performed by 29 collagen types that were not affected by the disease [27].

Statistical analysis

The Kolmogorov-Smirnov normality test was used to determine the distribution of the urine peptidome data. Statistical analysis of the urinary peptides was performed by the non-parametric Mann-Whitney test, followed by correction for multiple testing using the Benjamini-Hochberg (BH) method. A BH adjusted P-value <0.05 was considered statistically significant. The frequency threshold of 30% in cases or controls was applied. The Spearman's rank-order correlation was performed using Python 3.8.0. Data visualization and graphical plots were created using GraphPad Prism version 7.0 (GraphPad Software, La Jolla, California, USA) and Python 3.8.0. Data are presented as mean ± SD (standard deviation) ($^*P < 0.05$).

Bioinformatic analysis

The open-source tool "*Proteasix*" (www.proteasix.org) was used to predict proteases that were potentially responsible for the generation of the CKD-associated peptides [28]. In brief, "*Proteasix*" retrieves information on the naturally occurring protease/cleavage site associations from protease databases (MEROPS, www.ebi.ac.uk/merops; UniProt, www.uniprot.org; BRENDA, www.brenda-enzymes.org) along with the cleavage site restrictions database (ENZYME database, www.brenda-enzymes.org). A list of two types of proteases is generated; 1) the observed proteases (proteases collected from the literature) and 2) the predicted proteases (the proteolysis is calculated by the MEROPS database). In this study, to improve the reliability of the data, the analysis was focused only on the observed proteases. The predicted protease activity score was calculated as previously described [17]. Pathway enrichment analysis was performed with the "*Metascape*" (www.metascape.org) with the Reactome pathway database used as an ontology source [29]. Information about the available protease inhibitors was retrieved from the MEROPS database (www.ebi.ac.uk) [30].

Transcriptomics data

The transcriptomic data were extracted from the Nephroseq (www.nephroseq.org, University of Michigan, Ann Arbor, MI). The 16 shortlisted proteases were uploaded to the Nephroseq database and the corresponding gene expression patterns were identified in CKD databases. Four different databases where CKD, as compared to controls, were available and used: (1)

Nakagawa CKD Kidney (Discovery Set) [31], (2) Nakagawa CKD Kidney (Validation Set) [31], (3) Ju CKD TubInt [32] and (4) Ju CKD Glom [33]. The main CKD aetiologies included in datasets were DN (Ju CKD Glom; n = 12, Ju CKD TubInt; n = 17), FSGS (Ju CKD Glom; n = 25, Ju CKD TubInt; n = 17), IgA nephropathy (Ju CKD Glom; n = 27, Ju CKD TubInt; n = 25), membranous glomerulonephropathy (Ju CKD Glom; n = 21, Ju CKD TubInt; n = 18), thin basement membrane disease (Ju CKD Glom; n = 3, Ju CKD TubInt; n = 6) and vasculitis (Ju CKD Glom; n = 23, Ju CKD TubInt; n = 21). Lupus nephritis and tumour nephrectomy were excluded from Ju CKD TubInt and Ju CKD Glom studies to better match with the peptidomics data. The threshold was set at $P < 0.05$. The transcriptomic data of the four CKD databases were compared with the predicted activity of the proteases.

Results

Cohort characteristics

3463 datasets of the "*Human Proteome database*" were screened for the availability of renal and heart disease as well as eGFR values. Following case-control matching (no evidence for heart disease, similar age and sex distribution), two groups were generated; non-CKD (controls, with an eGFR > 60 ml/min/1.73 m^2, n = 240) and CKD (with an eGFR < 60 ml/min/1.73 m^2, n = 241). The mean eGFR value of the CKD cohort was 41.0 ml/min/1.73 m^2 whereas the double value (i.e. 82.0 ml/min/1.73 m^2) was observed for the non-CKD cohort. The majority (75%; n = 181) of CKD patients were at stage 3 (30–45 ml/min/1.73 m^2) followed by patients at stage 4 (n = 38, 15–29 ml/min/1.73 m^2) and 5 (n = 22, less than 15 ml/min/1.73 m^2). No significant differences between the two groups were observed in the levels of N-terminal pro-b-type natriuretic peptide (*NT-proBNP*), SBP and DBP. Serum creatinine was significantly higher in CKD patients. Clinical characteristics of the matched non-CKD and CKD patients are presented in **Table 1**.

Table 1. Characteristics of the matched non-CKD and CKD patients.

	non-CKD	CKD
Number	240	241
Sex, male, (%)	58	59
Age, years	71 ± 8	71 ± 8
BMI	26.59 ± 4.15	27.84 ± 4.16
Smoking Status (Yes, %)	5.1	8.9 *
eGFR (CKD-EPI), (ml/min/1.73 m^2)	82.0 ± 21.4	41.0 ± 15.4 *
CKD Stage 5, (%)	N/A	9
CKD Stage 4, (%)	N/A	16
CKD Stage 3, (%)	N/A	75
NT-proBNP (pg/mL)	203.34 ± 220.57	271.24 ± 159.45
Serum creatinine (μmol/L)	75.37 ± 11.82	106.83 ± 17.85 *
Systolic BP (mmHg)	143.59 ± 18.61	146.58 ± 21.89
Diastolic BP (mmHg)	79.59 ± 8.99	79.14 ± 9.09

Data are presented as mean ± SD (standard deviation) or number (%). Differences between non-CKD and CKD have been evaluated by the Mann-Whitney U test (for continuous variables) or Chi-Square test (for categorical variables) and are marked with * when $P < 0.05$. Abbreviations: CKD = chronic kidney disease; BMI = body mass index; eGFR = estimated glomerular filtration rate; CKD-EPI = chronic kidney disease epidemiology collaboration; NT-proBNP = N-terminal pro b-type natriuretic peptide; BP = blood pressure.

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Urine peptidomic analysis

In the present study, 3184 discriminatory sequenced urinary peptides were initially identified between CKD and the compared non-CKD groups. Overall, 303 urinary peptides were still significantly differentially excreted after applying multiple testing corrections (Benjamini-Hochberg (BH), $P < 0.05$) and the frequency threshold of 30% in cases or controls (S1 Table). A volcano plot showing the fold change difference in the 303 differentially excreted peptides is presented in Fig 1A. The majority of the differentially excreted peptides (n = 199, 65,7%) showed decreased abundance, whereas 104 (34.3%) peptides were detected with increased abundance in CKD patients versus controls. Among the former, showing the most decreased levels in CKD, were fragments of collagen types I, II, III and XI, clusterin (*CLU*), uromodulin (*UMOD*) and mucin-12 (*MUC12*); whereas peptides originated from albumin, beta-2-microglobulin (*B2M*) and alpha-1-antitrypsin (*A1AT*) were the most increased. The top 20 most up-regulated or down-regulated peptides between the two groups are presented in the heatmap (Fig 1B).

On a protein level, these 303 CKD-associated peptides originated from 69 unique protein precursors. The top 15 most frequently detected protein precursors, that covered 76%

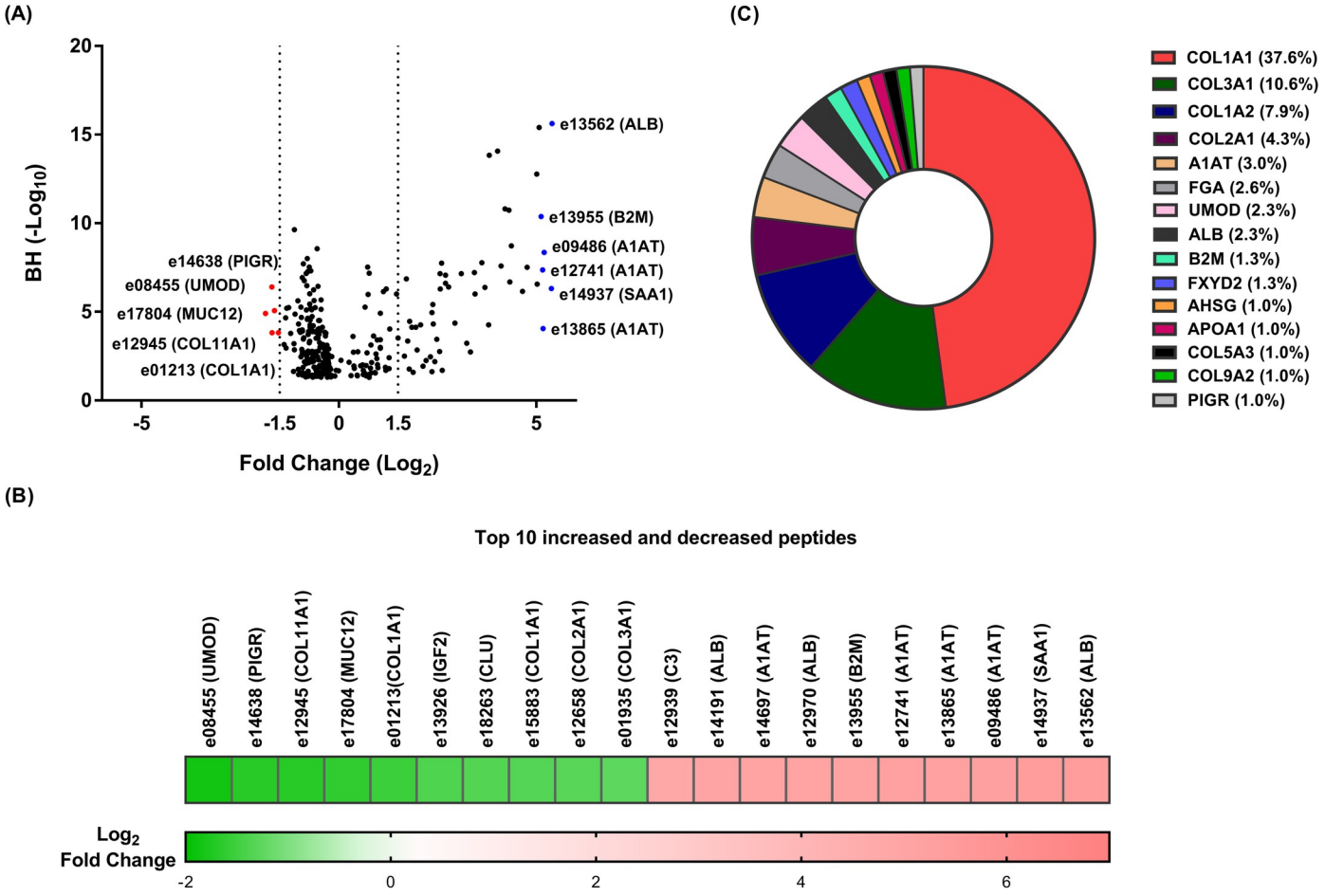


Fig 1. Urinary peptides in CKD. (**A**) Volcano plot showing the fold change (log_2 CKD/non-CKD) plotted against the BH p-value ($-log_{10}$) of the 303 differentially excreted CKD-associated peptides. The top five most increased and decreased abundance peptides in CKD patients are highlighted in blue (for increased) and red (for decreased) colours. (**B**) Heatmap of the log_2 transformed fold change of the top 10 most increased and decreased peptides in CKD patients. In each case, the peptide codes are provided in the S1 Table. (**C**) Pie chart of the top 15 most frequently observed protein precursors, that covered 76% (n = 230) of differentially excreted CKD-associated peptides. The percentage of the differentially excreted peptides per protein precursor is presented.

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(n = 230) of differentially excreted CKD-associated peptides are presented in Fig 1C. About 31% (n = 94) of these 303 CKD-associated peptides were non-collagen and 69% (n = 209) were collagen peptides. Overall, these 209 peptides originated from 22 different collagen types with the vast majority (n = 183) deriving from fibril-forming collagens (i.e. types I, II and III).

We further investigated which of the protein precursors were represented by peptides that showed a consistent directional change in abundance. Five protein precursors including, albumin (*ALB*, number of peptides = 7), *B2M* (number of peptides = 4), apolipoprotein A-I (*APOA1*, number of peptides = 3), alpha-2-HS-glycoprotein (*AHSG*, number of peptides = 3) and alpha-1B-glycoprotein (*A1BG*, number of peptides = 2) were represented by increased peptides whereas seven protein precursors including *UMOD* (number of peptides = 8), sodium/potassium-transporting ATPase subunit gamma (*FXYD2*, number of peptides = 4), *COL9A2* (number of peptides = 3), *COL5A3* (number of peptides = 3), *COL16A1* (number of peptides = 2) and *CLU* (number of peptides = 2) were represented by peptides all at decreased abundance in CKD when compared to controls. To further investigate the association of these peptides with kidney function, we calculated the correlation between the abundance of these peptides and eGFR. A significant negative correlation was observed between all peptides originating from *ALB* (rho (range): -0.18 to -0.53, $P < 0.05$), *A1BG* (rho (range): -0.31 to -0.34, $P < 0.05$), *AHSG* (rho (range): -0.18 to -0.47, $P < 0.05$), *APOA1* (rho (range): -0.38 to -0.52, $P < 0.05$), *B2M* (rho (range): -0.17 to -0.59, $P < 0.05$) and eGFR in CKD (S2 Table), whereas the same peptides were not correlated with eGFR in the controls ($P > 0.05$). Along the same lines, a significant positive correlation was detected between all peptides of *COL16A1* (rho (range): 0.13 to 0.26, $P < 0.05$), *FXYD2* (rho (range): 0.15 to 0.33, $P < 0.05$) and eGFR in CKD patients (S2 Table).

In-silico protease and protease inhibitor analysis

In-silico analysis by Proteasix revealed the 24 predicted proteases which possibly were involved in the endogenous cleavage of the CKD-associated peptides (Fig 2A). Of these 24, 16 proteases had a percentage of cleavage events above 1% and are presented in Fig 2A. These 16 shortlisted proteases were classified into two groups; a) MMPs including 11 family members (*MMP9*, *MMP13*, *MMP2*, *MMP14*, *MMP3*, *MMP12*, *MMP8*, *MMP20*, *MMP1*, *MMP7*, *MMP26*) and b) serine proteinases including 4 protein convertases (*PCSK6*, *PCSK7*, *PCSK4*, *PCSK5*) and kallikrein 4 (*KLK4*). About 48% of the cleavage events were predicted to be performed by *MMP9*, *MMP13 and MMP2*. However, interestingly, the proteolytic products of the 4 protein convertases and *KLK4* were among the most abundant endogenous peptides, as illustrated in the heatmap (Fig 2B). We further calculated the predicted proteolytic activity of the shortlisted proteases (**Methods and** S3 Table). Among the predicted proteases, four protein convertases, *KLK4* and *MMP7* exhibited an increased proteolytic activity whereas several MMPs (*MMP13*, *MMP9*, *MMP2*, *MMP14*, *MMP3*, *MMP12*, *MMP20*, *MMP8*, *MMP1*) were predicted at decreased activity levels, as presented in the heatmap (Fig 2C).

Pathway enrichment analysis of the 16 shortlisted proteases along with the 69 unique protein precursors of the CKD-associated peptides was performed using the Reactome pathway database. This analysis highlighted that the shortlisted proteases along with the protein precursors were significantly linked with several enriched terms including the ECM-related, metabolism, platelet signalling and vesicle-mediated transport.

Of the most pronounced, together, the predicted MMPs including *MMP9*, *MMP2*, *MMP1*, *MMP3*, *MMP12*, *MMP14*, *MMP7*, *MMP13*, *MMP8*, and *MMP20* along with several collagen types (I, II, III, IV, V, VI, VII, VIII, IX, XI, XIII, XIV, XVI, XVII, XIX, XXII and XXV) were involved in collagen-related and ECM-related pathways. The ten most significant clusters are presented in Fig 3.

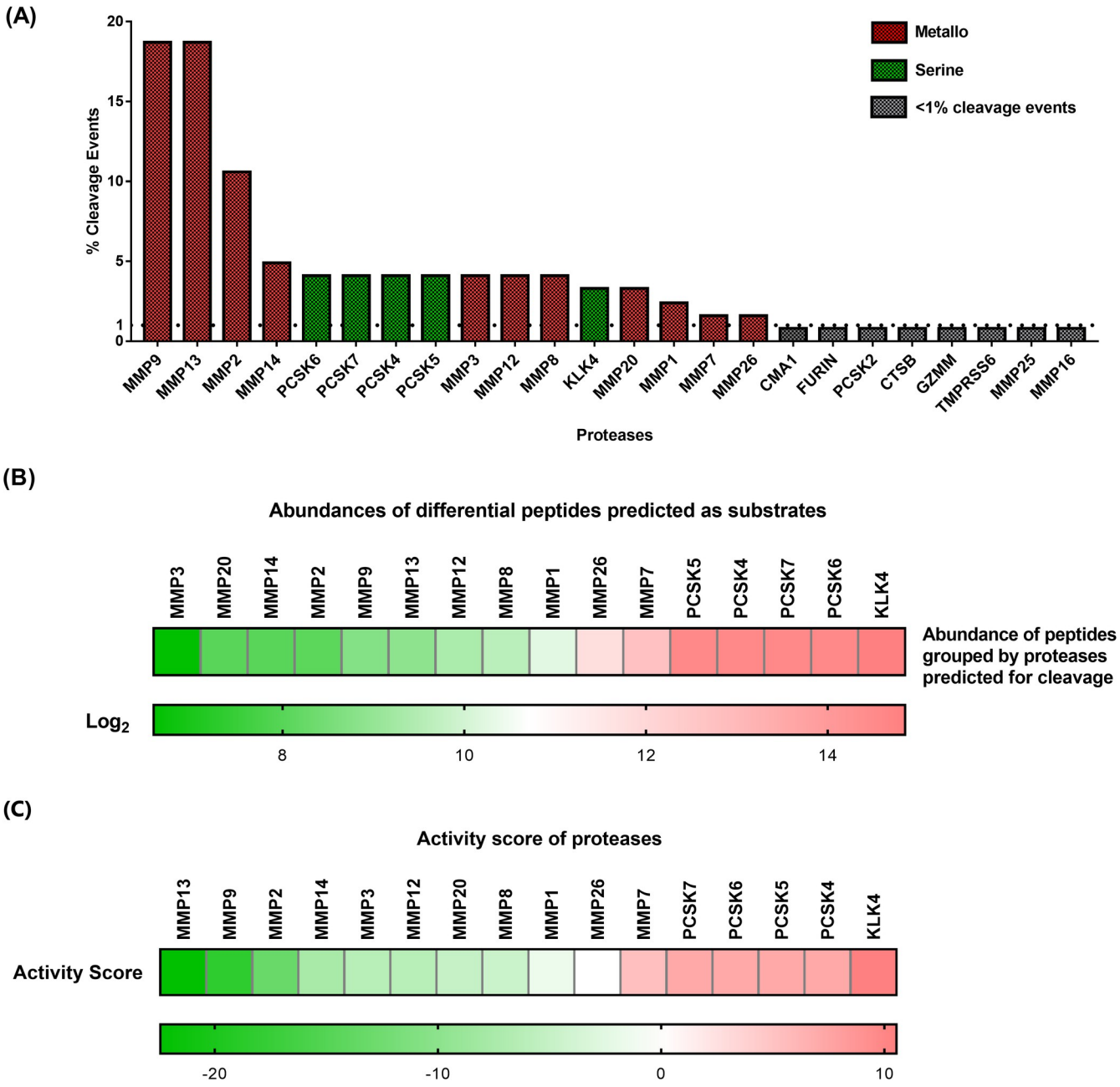
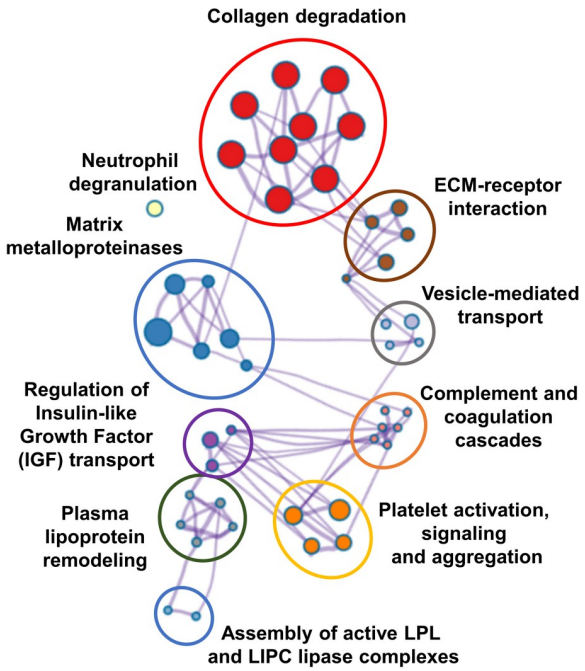


Fig 2. ***In-silico*** **predicted proteases.** (**A**) The 24 predicted proteases which possibly involved in the endogenous cleavage of the CKD-associated peptides are presented. Of these 24, 16 proteases had > 1% of cleavage events and are highlighted in red and green colours. Eleven metalloproteinases (highlighted in red) and 5 serine proteases (highlighted in green) are presented. (**B**) Heatmap of the $\log_2$ transformed abundance of the differentially excreted peptides grouped based on the predicted proteases. These peptides were used as substrates by the 16 shortlisted proteases. (**C**) Heatmap of the shortlisted proteases with their calculated activity score. The activated proteases are highlighted in red whereas the deactivated proteases are highlighted in green.

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Given the dependence of protease activities on protease inhibitors, we also investigated the involved inhibitors of the 16 shortlisted proteases. Along the lines of the protease analysis, information on the inhibitors was retrieved from the MEROPS protease database (www.ebi.ac.uk/merops/inhibitors/). *TIMP-1*, *TIMP-2* and *TIMP-3* were listed as regulating the activity of 8 MMPs (summarized in **Table 2**). Furthermore, four different inhibitors of serine proteases



Pathways	Associated Genes
Collagen degradation (P= 8.62E-60)	COL1A1|COL1A2|COL2A1|COL3A1|COL4A5|COL4A6|COL5A1|COL5A2|COL6A1|COL6A2|COL7A1|COL8A1|COL9A2|COL11A1|COL13A1|COL16A1|COL17A1|COL19A1|MMP1|MMP2|MMP3|MMP7|MMP8|MMP9|MMP12|MMP13|MMP14|COL14A1|MMP20|COL5A3|COL25A1
Matrix metalloproteinases (P= 3.48E-18)	MMP1|MMP2|MMP3|MMP7|MMP8|MMP9|MMP12|MMP13|MMP14|MMP20|MMP26
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Protein (P= 5.01E-11)	AHSG|ALB|APOA1|C3|FGA|IGF2|MMP1|MMP2|SERPINA1|SPP1|VGF
Platelet activation, signaling and aggregation (P= 3.66E-10)	A1BG|AHSG|ALB|APOA1|CLU|COL1A1|COL1A2|FGA|FGB|IGF2|PCDH7|SERPINA1|TMSB4X
ECM-receptor interaction (P= 1.07E-09)	COL1A1|COL1A2|COL2A1|COL4A5|COL4A6|COL6A1|COL6A2|COL9A2|SPP1
Plasma lipoprotein remodeling (P= 1.34E-07)	ALB|APOA1|APOA4|APOC3|PCSK6|PCSK5
Neutrophil degranulation (P= 3.19E-05)	A1BG|AHSG|B2M|C3|HSP90AB1|KRT1|MMP8|MMP9|SERPINA1|PIGR|S100A8
Complement and coagulation cascades (P= 5.96E-04)	C3|CLU|FGA|FGB|SERPINA1
Assembly of active LPL and LIPC lipase complexes (P= 3.01E-03)	APOA4|PCSK6|PCSK5
Vesicle-mediated transport (P= 3.23E-03)	ALB|APOA1|COL1A1|COL1A2|COL3A1|COL7A1|MAN1A1|SERPINA1|SAA1|LMAN2

Fig 3. Pathway enrichment analysis. Pathway enrichment analysis of the 16 shortlisted proteases along with the 69 protein precursors of the differentially excreted peptides was performed by the Reactome pathway database. The 10 most significant clusters are presented in different colours and the most significant term of each cluster is selected as a label. The associated proteases are highlighted in red colour.

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namely *SPINK6*, *SERPINA1*, *SERPINC1* and *SERPINF2* were linked to the activity of *KLK4* (Table 2). No data were available for the *MMP20*, *MMP26*, *PCSK6*, *PCSK7*, *PCSK4* and *PCSK5* proteases.

Table 2. List of protease inhibitors and associated proteases (according to MEROPS).

Inhibitors	Proteases									
Reversion-inducing cysteine-rich protein with Kazal motifs (RECK)	MMP9		MMP2	MMP14						
Metalloproteinase inhibitor 1 (TIMP1)	MMP9	MMP13	MMP2		MMP3	MMP12	MMP8	MMP1	MMP7	
Metalloproteinase inhibitor 2 (TIMP2)	MMP9	MMP13	MMP2	MMP14	MMP3		MMP8	MMP1	MMP7	
Metalloproteinase inhibitor 3 (TIMP3)	MMP9	MMP13	MMP2	MMP14	MMP3		MMP8	MMP1	MMP7	
Metalloproteinase inhibitor 4 (TIMP4)	MMP9		MMP2	MMP14	MMP3			MMP1	MMP7	
Alpha-2-macroglobulin (A2M)	MMP9		MMP2				MMP8	MMP1		
Pregnancy zone protein (PZP)	MMP9		MMP2							
Testican-1 (SPOCK1)				MMP14						
Testican-3 (SPOCK3)				MMP14						
Serine protease inhibitor Kazal-type 6 (SPINK6)										KLK4
Alpha-1-antitrypsin (SERPINA1)										KLK4
Antithrombin-III (SERPINC1)										KLK4
Alpha-2-antiplasmin (SERPINF2)										KLK4

Abbreviations: MMP = Matrix metalloproteinase; KLK4 = Kallikrein-4

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Validation of predicted proteases

To evaluate the validity of the predictions, kidney transcriptome datasets from CKD were retrieved from the Nephroseq database (www.nephroseq.org). Four datasets where the mRNA levels of expression of CKD patients were compared to healthy controls (threshold $P < 0.05$) were available in the Nephroseq database; in which the transcriptomic data related to the 16 predicted proteases were evaluated. Interestingly, the activity trend of 3 predicted proteases including *MMP7*, *PCSK5* and *MMP14* was in agreement with all transcriptomic datasets (**Table 3**). In addition, in the case of *KLK4*, the predicted activity trend was in agreement with the transcriptomic data of one dataset, whereas no data were available in the other 3 datasets. In contrast, *MMP1* and *MMP3* were found at increased mRNA levels in 3 of the transcriptomics datasets in contrary to their predicted decreased protease activity based on the peptidomics analysis (**Table 3**). In the case of the rest proteases, data were less conclusive due to inconsistencies among the different transcriptomics datasets. No transcriptomic data were available for the *PCSK4* protease (**Table 3**).

To enhance the reliability of these results, we further retrieved the relevant kidney transcriptomics data for the protease inhibitors regulating the activity of the 16 proteases from the Nephroseq database (**Table 4**). In CKD patients, *TIMP1* was found at increased mRNA levels in three of the transcriptomics datasets while *TIMP2* and *A2M* were found at increased mRNA levels in two of the transcriptomics datasets. In addition, two serpins, *SERPINC1* and *SERPINF2* exhibited decreased mRNA levels, in at least three transcriptomics datasets, in CKD versus controls (**Table 4**). We also correlated the transcriptomics data of the inhibitors with expression data as reported by scientific publications. We found that the mRNA expression trend was in agreement for 2 inhibitors, namely *TIMP1* and *SERPINA1* whereas no data were available for the other protease inhibitors in CKD patients.

Discussion

Considering that urine is produced by the kidney, the urinary peptidome has been extensively studied to investigate kidney dysfunction. Proteases play a key role in the generation of peptides, yet their study is still limited. The presented *in-silico* analysis describes the predicted proteases involved in the proteolytic cleavage events of the CKD-associated peptides following comparison of large sample sizes of well-matched, (placing also emphasis on the main confounder -cardiovascular disease) case-control groups. The most prominent changes of the related pathways are associated with ECM remodelling, immune system and metabolism with specific peptides affected in CKD patients.

MMPs may play an important role in key cellular functions such as cell differentiation, migration, apoptosis, angiogenesis, fibrosis and inflammation through their interaction with both ECM and non-ECM substrates such as growth factors and cell adhesion molecules [7]. In the kidney, MMPs are synthesized by the tubular epithelial and the glomerular intrinsic cells [5]. *In-silico* analysis of our data pointed out that MMPs and protein convertases were possibly mainly responsible for the generation of the CKD-associated peptides. Specifically, it was predicted that for the vast majority of MMPs, except *MMP7*, a decrease in proteolytic activity is expected. These predictions were further confirmed at the mRNA level in the case of *MMP7* and *MMP14* and also enhanced by the observed increased mRNA expression levels of several inhibitors (*TIMP1*, *TIMP2*). Interestingly, some studies have reported the importance of *MMP7* in CKD, highlighting this protease as a key regulator of renal fibrosis through three main pathways, transforming growth factor-beta (TGF-β) signalling, epithelial-mesenchymal transition (EMT) and ECM deposition [34, 35]. In addition, it has been proposed that *MMP7* is activated by the Wnt/ β-catenin signalling, a pathway that is associated with kidney injury

Table 3. List of predicted proteases with calculated activity score.

	Activity Score (Peptide database)	Nakagawa CKD Kidney (Discovery Set)	Nakagawa CKD Kidney (Validation Set)	Ju CKD Glom	Ju CKD TubInt	Protein expression
Proteases		**CKD cohort**	**CKD cohort**	**CKD cohort**	**CKD cohort**	**CKD cohort**
MMP9	-18.47	Increase	Not significant*	Not significant*	Not significant*	inconclusive*
MMP13	-22.44	Increase	Increase	Not significant*	Not significant*	-
MMP2	-13.28	Decrease	Not Significant*	Increase	Increase	inconclusive*
MMP14	-7.59	Decrease	Decrease	Decrease	Not significant*	-
PCSK6	7.08	Decrease	Increase	Decrease	Decrease	-
PCSK7	7.08	Decrease	Increase	Increase	Not significant*	-
PCSK4	7.08	No data	No data	No data	No data	-
PCSK5	7.08	Increase	Increase	Increase	Increase	-
MMP3	-6.33	Increase	Increase	Increase	Not significant*	-
MMP12	-6.33	Decrease	Increase	Not significant*	Not significant*	Increase [61]
MMP8	-4.62	Increase	Increase	Not significant*	Not significant*	-
KLK4	10.53	Increase	No data	No data	No data	-
MMP20	-5.06	Increase	Increase	Not significant*	Not significant*	-
MMP1	-1.72	Increase	Not Significant*	Increase	Increase	-
MMP7	5.26	Increase	Increase	Increase	Increase	Increase [11, 62]
MMP26	0	Increase	Not Significant*	Decrease	Not significant*	-

* Not significant: $P > 0.05$, inconclusive*: some studies reported increased, some decreased protein expression levels in CKD and some reported no statistically significant difference between CKD and the compared groups. Abbreviations: MMP = Matrix metalloproteinase; PCSK = Proprotein convertase subtilisin/kexin type; KLK4 = Kallikrein-4.

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[12, 36, 37]. In the case of *MMP14*, which is predicted to be at decreased activity based on the peptide and Nephroseq data, evidence that it acts as a regulatory molecule for pro-MMP2 and pro-MMP9 leading to the formation of the activated *MMP9* and *MMP2* through the complex proMMP-2/TIMP-2/MMP-14 has also been accumulated [38, 39]. Based on our results, *MMP2* and *9* may be involved in a large number of the observed peptide changes in CKD; in agreement with our predictions, it has been described that *MMP9* and *MMP2* activity is reduced with the progression of CKD due to the excessive formation of fibrosis and hypoxia [38, 40]. Overall, *MMP2* and *MMP9* may regulate the CKD pathophysiology through their interactions with tumour necrosis factors (TNFs), oxidative stress (OS), growth factors (GFs) and monocyte chemoattractant proteins (MCPs) [38]. Furthermore, it has been reported that *MMP2* and *MMP9* are differentially expressed in patients with minimal change disease, focal segmental glomerulosclerosis and membranous nephropathy [41, 42]. In addition, it has been shown that reduced expression of *MMP9* in the cytoplasm of normal tubular cells is associated with renal fibrosis, whereas *MMP2* is associated with structural changes in the tubular basement membrane leading to tubular atrophy and fibrosis [9, 41]. Regarding the inflammatory response, it has been reported that both *MMP7* and *MMP9* may increase the inflammatory process through their chemotactic effect on human dendric cells while *MMP14* may serve as

Table 4. List of protease inhibitors with transcriptomics and protein expression.

	Nakagawa CKD Kidney (Discovery Set)	Nakagawa CKD Kidney (Validation Set)	Ju CKD Glom	Ju CKD TubInt	Protein expression
Inhibitors	**CKD cohort**	**CKD cohort**	**CKD cohort**	**CKD cohort**	**CKD cohort**
Reversion-inducing cysteine-rich protein with Kazal motifs (RECK)	Increase	Increase	Decrease	Not significant*	-
Metalloproteinase inhibitor 1 (TIMP1)	Increase	Not significant*	Increase	Increase	Increase [45]
Metalloproteinase inhibitor 2 (TIMP2)	Increase	Increase	Not significant*	Not significant*	-
Metalloproteinase inhibitor 3 (TIMP3)	Increase	Increase	Not significant*	Decrease	-
Metalloproteinase inhibitor 4 (TIMP4)	Decrease	Not significant*	Not significant*	Not significant*	-
Alpha-2-macroglobulin (A2M)	Not significant*	Not significant*	Increase	Increase	-
Pregnancy zone protein (PZP)	Decrease	Not significant*	Not significant*	Not significant*	-
Testican-1 (SPOCK1)	Not significant*	Not significant*	Decrease	Decrease	-
Testican-3 (SPOCK3)	Not significant*	Not significant*	Not significant*	Not significant*	-
Serine protease inhibitor Kazal-type 6 (SPINK6)	Increase	Not significant*	No data	No data	-
Alpha-1-antitrypsin (SERPINA1)	Increase	Not significant*	Not significant*	Not significant*	Increase [63]
Antithrombin-III (SERPINC1)	Decrease	Decrease	Decrease	Not significant*	inconclusive*
Alpha-2-antiplasmin (SERPINF2)	Decrease	Decrease	Decrease	Decrease	-

Not significant*: $P > 0.05$, inconclusive*: some studies reported increased and some decreased protein expression levels in CKD.

https://doi.org/10.1371/journal.pone.0262667.t004

an anti-inflammatory mediator [41–43]. Given the abovementioned interactions of these proteases, the predicted decreased activities of all three *MMP2*, *9*, *14* in our study, is further enhanced, collectively suggesting for a more thorough investigation of these proteases in the CKD development and progression.

Four known enzymes namely *TIMP1* to *TIMP4* regulate either the activation and/or inhibition of MMPs. It is supported that the activity of the MMPs is regulated either intracellularly (transcriptional and posttranscriptional levels) and/or extracellularly (enzymatic activity). According to our results, we can conclude that the increased mRNA levels of TIMPs may lead to decreased activity of MMPs. Consequently, imbalances in the expression levels of MMPs and their inhibitors have been associated with essential cellular functions that lead to the development of CKD [43]. Even though the expression of MMPs and TIMPs in the kidneys has not been completely characterized, it has been reported that imbalanced levels of MMPs/TIMPs lead to dysregulated ECM formation/ breakdown and tissue remodelling [44]. Additionally, several cellular processes such as apoptosis, proliferation, inflammation, chemokine and cytokine production are regulated by MMPs/TIMPs imbalance, thus promoting the vascular, glomerular and tubular changes found in CKD [45]. Specifically, *MMP1*, *3,7* and *9* are mainly regulated by *TIMP1* while *TIMP2* is a major *MMP2* inhibitor [46]. Several studies have shown elevated levels of *TIMP1* in the urine and serum of CKD patients [47]. Furthermore, *TIMP1* may promote renal interstitial fibrosis [48]. In addition, both *TIMP1* and *TIMP2* are associated with glomerulosclerosis [5]. *TIMP3* is highly expressed in the kidney and inhibits mainly the activation of *MMP2*,*7* and *9* [49]. It has been shown that *TIMP3* may protect kidneys from damage [49, 50]. Although *TIMP4* expression in tissues is limited, studies support that it may inhibit *MMP14* leading to ECM deposition and inflammation [51]. Another reported inhibitor

of MMPs is the membrane-anchored protein RECK whose expression is increased by hyperglycemia [52]. An analysis showed that empagliflozin may reverse the renal suppression of RECK in human proximal tubular epithelial cells [52]. In summary, our data demonstrate that the TIMPs and RECK proteins have a distinct role in renal injury.

In addition to the MMPs, four proprotein convertases (*PCSK6*, *PCSK7*, *PCSK4* and *PCSK5*) were also predicted to be involved in the generation of the peptide data in our study. Two of these proprotein convertases have been previously associated with kidney disease: specifically, in the kidney, a high-salt diet induces the PCSK6-corin-ANP-AQP2/β-ENaC pathway suggesting the importance of *PCSK6* in renal failure [53], whereas *PCSK7* is linked to end-stage renal disease (ESRD) [54]. Notably, *PCSK6* is also considered a key regulator of smooth muscle cell function in vascular remodelling [55], a mechanism that is involved in CKD development. The role of *PCSK4* and *PCSK5* in CKD has not been investigated yet. However, the single-cell transcriptomic analysis revealed that *PCSK5* was differentially expressed in early human diabetic nephropathy [56]. Interestingly, *PSCK5*, predicted to be at increased activity in CKD based on our data and also supported by the mRNA Nephroseq expression pattern, has been reported as one of the enzymes involved in posttranslational processing and stability of fibroblast growth factor 23 (*Fgf23*), a protein which plays an important role in CKD development as it regulates phosphorus and vitamin D metabolism [57]. Nonetheless, knowledge of the inhibitors of the proprotein convertases is still very limited. Given our results, further investigation of *PCSK5* in CKD is warranted. Finally, *KLK4*, another serine protease with putative renoprotective properties [58], was predicted to have increased proteolytic activity in our study. Interestingly and in line with our prediction, decreased mRNA levels of the *KLK4* inhibitors *SERPINAC1* and *SERPINF2* have been observed in CKD, based on our analysis. Overall, 4 serine proteases including *SPINK6*, *SERPINA1*, *SERPINAC1* and *SERPINF2* inhibit the activity of *KLK4*. Several studies have reported the role of *SERPINF2* in the development of fibrosis [59, 60].

Among the strengths of our study are the large sample size and case-control matching, taking into consideration also the heart condition, suggesting high validity of our findings. Additionally, the same analytical platform (CE-MS) and protocols were used for the analysis of all urinary peptide datasets, leading to the generation of highly comparable data.

Limitations included that CKD and non-CKD individuals were acquired from different cohorts and studies. However, the large sample size, the case-control matching and the high significance of the findings reduce the risk of this bias. Additionally, the results of this study can only distinguish the effects of the two phases (CKD with eGFR $<$ 60 ml/min/1.73 m^2 and non-CKD with eGFR $>$ 60 ml/min/1.73 m^2) and cannot explain the molecular mechanisms of CKD development. We should however point that similar results were obtained when a different eGFR cut-off was applied (e.g. eGFR $>$70 versus eGFR $<$50; data not shown). Further, the weakness of our study is related to the fact that the predicted proteases are supported by the *in-silico* analysis and not by in vitro and/or in vivo experiments. It is expected that transcriptomics data and activity levels of the predicted proteases are not always in agreement. In addition, in the Nephroseq datasets, 'CKD' was not defined always in the same way, which may also explain the observed inconsistencies. However, our spherical approach, involving the cross-omics analysis, together with the in-depth literature mining generates a reliable shortlist of proteases and enhances the reliability of the observed agreements among the proteomics and multiple transcriptomics datasets opening up avenues for further investigation in future studies.

Conclusions

In conclusion, our study revealed several interesting proteases including *MMP 7*, *14* and their interactions with *MMP2* and *MMP9* as well as *PCSK5* which may be involved in the generation

of CKD-associated urine peptides. These predicted proteases should be further investigated in the context of CKD development and progression and may be considered as putative therapeutic targets. With this study, we contribute to a better understanding of the proteolytic mechanisms involved in CKD and propose multiple proteases of possible significance in CKD pathogenesis.

Supporting information

S1 Table. List of the 303 Chronic kidney disease (CKD) differentially excreted peptides.
(XLSX)

S2 Table. Spearman's rank-order correlation analysis between the amplitude of the 303 CKD-associated peptides and eGFR of CKD patients.
(XLSX)

S3 Table. List of predicted proteases with calculated activity score.
(XLSX)

Author Contributions

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Validation: Eleni Petra.

Visualization: Eleni Petra.

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Supplementary S1 Table. List of the 303 Chronic kidney disease (CKD) differentially excreted peptides (PLoS One. 2022 Jan 19;17(1):e0262667. doi: 10.1371/journal.pone.0262667).

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e09486	EAIPMSIPPEVKFNKPF	A1AT	Alpha-1-antitrypsin	378	394	11.25	36.51	9.51E-12	4.43E-09	516.74	3781.05	18972.90	104770.26	36.72
e13865	LPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	278	299	15.83	32.78	2.18E-06	8.93E-05	54.47	306.84	1955.68	12362.95	35.91
e12741	MIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	398	418	14.58	38.17	1.51E-10	4.26E-08	677.06	3974.24	24221.79	114720.83	35.77
e14697	FLPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	277	299	9.17	30.29	1.63E-09	2.78E-07	175.31	1061.14	5705.11	27109.19	32.54
e13340	LMIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	397	418	12.08	32.78	5.61E-09	7.13E-07	509.73	3060.31	12786.19	61083.49	25.08
e18378	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAE	A1AT	Alpha-1-antitrypsin	25	56	30.83	52.70	8.58E-09	9.91E-07	631.50	2852.92	6902.08	30042.69	10.93
e11895	FFLPDEGKLQHLENELTHD	A1AT	Alpha-1-antitrypsin	276	294	54.58	63.90	2.32E-03	1.97E-02	86.22	146.93	530.52	3062.05	6.15
e04988	TIDEKGTEAAGAMF	A1AT	Alpha-1-antitrypsin	363	376	11.67	30.29	1.65E-07	1.11E-05	137.65	659.27	704.75	2151.29	5.12
e12271	EDPQGDAAQKTDTSHHDQDHP	A1AT	Alpha-1-antitrypsin	25	45	68.75	48.13	3.71E-06	1.33E-04	174.19	225.84	109.38	208.80	0.63
e12127	LREGETKAVKTVRTPGAAANLE	A1BG	Alpha-1B-glycoprotein	435	456	12.08	36.10	7.88E-11	2.59E-08	75.20	445.77	1296.42	6689.48	17.24
e12950	LREGETKAVKTVRTPGAAANLEL	A1BG	Alpha-1B-glycoprotein	435	457	17.08	41.49	4.16E-10	8.56E-08	245.15	1325.87	1591.44	5880.31	6.49
e09323	MGVVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	322	340	17.08	39.00	2.87E-09	4.17E-07	90.02	495.07	1171.82	4245.78	13.02
e07656	VVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	324	340	23.75	45.64	4.77E-08	3.92E-06	266.70	1141.57	1387.35	5544.99	5.20
e05548	VVSLGSPSGEVSHPR	AHSG	Alpha-2-HS-glycoprotein	324	338	20.42	30.71	6.20E-03	4.09E-02	62.93	274.25	106.51	277.81	1.69
e13562	DAHKSEVAHRFKDLGEENFKAL	ALB	Albumin	25	46	17.08	53.94	4.90E-20	2.42E-16	324.79	2858.40	13710.03	77152.82	42.21
e12970	DAHKSEVAHRFKDLGEENFKA	ALB	Albumin	25	45	10.42	45.64	1.21E-19	4.00E-16	80.35	857.06	2691.67	11300.82	33.50
e14191	DAHKSEVAHRFKDLGEENFKALV	ALB	Albumin	27	49	12.50	44.81	1.02E-16	1.69E-13	321.00	3039.20	10347.49	41762.54	32.24
e12518	DAHKSEVAHRFKDLGEENFK	ALB	Albumin	25	44	11.67	40.25	1.38E-14	1.82E-11	45.83	262.77	907.64	2900.24	19.80
e14790	DAHKSEVAHRFKDLGEENFKALVL	ALB	Albumin	25	48	30.42	64.32	7.47E-18	1.48E-14	7165.85	92216.77	100667.92	512710.16	14.05
e07463	VRYTKKVPQVSTPTL	ALB	Albumin	433	447	19.17	34.85	2.31E-05	5.85E-04	715.83	4551.85	6768.18	32512.23	9.46
e15827	DAHKSEVAHRFKDLGEENFKALVLIA	ALB	Albumin	27	52	9.58	30.29	2.71E-09	4.02E-07	781.04	10493.12	5363.97	25665.00	6.87
e05113	EAGSPPVVE	ANR17	Ankyrin repeat domain-containing protein 17	2078	2086	13.75	36.93	2.52E-10	6.01E-08	25.48	171.99	274.63	914.49	10.78
e04435	AILDETKGDYEK	ANXA1	Annexin A1	326	337	43.75	61.41	1.81E-07	1.21E-05	145.01	362.93	299.73	440.18	2.07
e06716	LSALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	254	267	12.08	36.51	4.27E-11	1.69E-08	236.64	1383.56	2911.92	8756.99	12.31
e14633	VDVLKDSGRDYVSQFEGSALGKQLN	APOA1	Apolipoprotein A-I	43	67	27.08	52.70	4.88E-11	1.79E-08	176.20	1260.20	1067.05	3716.11	6.06
e05683	SALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	233	245	40.42	51.45	9.28E-05	1.72E-03	101.76	293.43	597.61	1756.23	5.87
e10106	SNNAKEAVEHLQKSELTQ	APOA4	Apolipoprotein A-IV	39	56	24.58	39.42	1.23E-05	3.51E-04	52.63	168.64	294.11	1379.17	5.59
e08260	PEVRPTSA	APOC3	Apolipoprotein C-III	89	96	48.75	35.68	7.77E-03	4.77E-02	72.84	148.62	53.39	115.42	0.73
e04609	SIAAGGEGLTDVSPE	ATG12	Ubiquitin-like protein ATG12	14	28	30.83	19.92	5.70E-03	3.84E-02	102.20	264.58	54.17	164.69	0.53
e03035	WKYYYDGKD	AZGP1	Zinc-alpha-2-glycoprotein	135	143	35.00	23.24	4.71E-03	3.31E-02	42.29	104.18	23.58	59.46	0.56
e13955	LKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	60	81	9.17	37.34	3.97E-14	4.13E-11	287.26	2562.93	9980.45	49990.41	34.74
e14596	LLKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	59	81	16.25	46.47	1.09E-14	1.54E-11	2654.68	29165.56	49264.02	304074.20	18.56
e12566	NGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	62	81	20.00	42.74	3.84E-09	5.12E-07	33.89	218.03	200.77	573.06	5.92
e00152	VSGFHPSD	B2M	Beta-2-microglobulin	47	54	20.42	32.78	2.38E-03	2.01E-02	32.84	151.41	50.54	148.75	1.54
e12939	LQGTPVAQMTEDAVDAERLKHL	C3	Complement C3	982	1003	8.33	30.71	1.04E-10	3.06E-08	29.16	137.39	793.25	3631.26	27.20
e14818	FPGMPGPPGQpGPRGSMGPMGPSPDLSH	CCBE1	Collagen and calcium-binding EGF domain-containing protein 1	269	296	46.25	37.34	6.91E-03	4.39E-02	67.67	99.08	47.73	102.61	0.71
e14231	DDPRPPNPPKPmPNPNPNHPSSSGS	CD99	CD99 antigen	65	89	32.08	45.23	3.74E-03	2.80E-02	29.60	62.73	51.91	137.19	1.75
e10450	VSGGEGKGGSDGGGSHRKEGEE	CD99	CD99 antigen	99	120	63.75	42.32	1.10E-04	1.95E-03	78.72	109.83	51.17	79.47	0.65
e13010	DGSPHPDPSAGAKPcGSSSAGKIPc	CDSN	Corneodesmosin	472	496	15.42	31.54	1.00E-05	2.98E-04	39.48	147.91	111.91	270.69	2.83
e04757	SHTSDSDVPSGVTE	CLU	Clusterin	391	404	30.83	19.92	4.16E-03	3.02E-02	128.10	276.06	66.10	184.65	0.52
e18263	ASHTSDSDVPSGVTEVVVKLFDSDPITVTVPVEV	CLU	Clusterin	390	423	56.67	36.10	3.88E-07	2.19E-05	641.25	1207.28	252.26	656.02	0.39
e12945	DGpQGPpGSVGSVGGVGEKGEPGEAGN	COL11A1	Collagen alpha-1(XI) chain	1236	1262	32.50	15.77	4.40E-06	1.52E-04	59.69	116.26	18.51	58.57	0.31
e07106	EAGEKGNPGAEGLQGVpG	COL13A1	Collagen alpha-1(XIII) chain	555	572	38.33	52.28	1.66E-03	1.54E-02	327.29	699.66	427.57	572.28	1.31
e15200	GIpGGVGSpGRDGSpGQRGLPGKDGSSGPpG	COL14A1	Collagen alpha-1(XIV) chain	1536	1566	39.17	52.70	4.65E-05	1.01E-03	49.27	90.26	101.74	145.38	2.06

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e17751	pPGPQGPSGLSIQGMpGmpGEKGEKGDTGLPGPQG	COL14A1	Collagen alpha-1(XIV) chain	1502	1536	92.08	79.25	2.20E-10	5.50E-08	792.10	698.08	458.29	504.03	0.58
e11191	NSGEKGDQGFQGQpGFPGPpGP	COL16A1	Collagen alpha-1(XVI) chain	1145	1166	74.58	62.66	4.97E-04	6.27E-03	167.71	167.06	130.81	190.52	0.78
e05351	DKGEpGPPGQPGYpG	COL16A1	Collagen alpha-1(XVI) chain	1079	1093	40.42	28.22	4.93E-03	3.43E-02	53.49	241.71	28.37	82.46	0.53
e12384	EGpmGQRGREGPMGpRGEAGPpG	COL17A1	Collagen alpha-1(XVII) chain	617	639	32.92	42.32	3.52E-03	2.68E-02	39.61	99.97	74.60	134.81	1.88
e19753	GPEGPSGKpGINGKDGIPGAQGImGKpGDRGpKGERGDQGIP	COL19A1	Collagen alpha-1(XIX) chain	917	958	3.33	34.85	3.85E-18	8.46E-15	82.00	565.17	1332.86	3681.94	16.25
e18831	DKGETGEQGDRGIKGHRGFSGLQGppGppGSPGEQGP	COL1A1	Collagen alpha-1(I) chain	1095	1131	68.33	80.91	1.44E-09	2.48E-07	294.65	859.70	1916.06	5917.15	6.50
e09923	NSGEPGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453	43.75	55.19	4.22E-04	5.57E-03	73.55	142.82	339.19	1483.22	4.61
e11286	KGNSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	430	453	20.42	38.17	1.12E-06	5.34E-05	26.02	75.10	108.95	248.07	4.19
e04497	GRpGEVGPpGPpGPA	COL1A1	Collagen alpha-1(I) chain	917	931	20.42	30.29	3.31E-03	2.57E-02	32.57	90.75	119.61	326.16	3.67
e13322	GPpGKNGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	224	249	28.75	42.32	1.67E-05	4.51E-04	22.49	51.79	75.18	135.16	3.34
e13410	GPpGKNGDDGEAGKpGRPGERGppGP	COL1A1	Collagen alpha-1(I) chain	224	249	20.00	32.78	2.06E-04	3.20E-03	13.53	38.53	42.73	96.36	3.16
e07917	DGEAGKPGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	232	249	19.58	31.12	1.71E-03	1.58E-02	38.41	101.63	92.60	222.03	2.41
e14837	ERGSpGPAGPKGSpGEAGRpGEAGLpGAKG	COL1A1	Collagen alpha-1(I) chain	510	539	65.42	79.67	5.79E-09	7.28E-07	440.38	934.93	962.24	1859.25	2.19
e08629	TGPIGpPGPAGApGDKGESGP	COL1A1	Collagen alpha-1(I) chain	766	786	41.67	58.92	1.34E-05	3.77E-04	169.30	341.77	350.55	757.17	2.07
e19986	ARGNDGATGAAGPpGPTGPAGPpGFpGAVGAKGEAGPQGPRGSEGPQG	COL1A1	Collagen alpha-1(I) chain	321	368	45.42	55.19	1.51E-03	1.43E-02	110.98	183.20	220.19	373.55	1.98
e13918	AGpPGApGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1042	1071	51.25	60.17	3.12E-04	4.38E-03	120.12	189.42	233.09	359.76	1.94
e09124	SGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	433	453	41.25	53.53	1.44E-04	2.41E-03	86.87	166.90	166.87	231.85	1.92
e01461	SpGEAGRpGEA	COL1A1	Collagen alpha-1(I) chain	522	532	29.58	45.64	3.20E-05	7.44E-04	425.43	1100.22	748.09	1100.83	1.76
e04666	GPpGEAGKpGEQGVP	COL1A1	Collagen alpha-1(I) chain	650	664	50.42	57.68	1.62E-03	1.52E-02	153.72	283.51	267.69	374.49	1.74
e10277	nGDDGEAGKpGRPGERGPPGp	COL1A1	Collagen alpha-1(I) chain	229	249	97.08	98.34	9.12E-09	1.04E-06	1348.66	1340.60	2251.87	2208.64	1.67
e13730	AGPpGAPGApGAPGPVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1042	1071	47.50	63.49	1.19E-04	2.08E-03	88.75	150.29	144.96	200.33	1.63
e16015	NVGApGAKGARGSAGpPGATGFpGAAGRVGPpGP	COL1A1	Collagen alpha-1(I) chain	855	888	44.58	52.28	6.25E-03	4.10E-02	164.23	323.79	265.18	404.73	1.61
e12508	KGNSGEpGAPGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	430	455	96.67	95.44	6.84E-08	5.40E-06	812.33	677.81	1287.05	1104.02	1.58
e10953	DGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	820	843	96.67	98.76	9.76E-05	1.78E-03	1161.02	743.86	1619.35	1214.66	1.39
e01166	DGRPGPPGPpG	COL1A1	Collagen alpha-1(I) chain	562	572	29.58	42.32	5.38E-03	3.68E-02	76.51	162.11	105.22	178.69	1.38
e13817	AGPpGAPGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1042	1071	91.67	94.19	1.04E-03	1.11E-02	378.23	300.74	492.51	428.54	1.30
e11325	ADGQPGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843	91.25	96.27	7.86E-06	2.45E-04	5939.79	3540.17	7620.35	4085.55	1.28
e10025	NSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453	98.33	97.51	6.02E-03	4.02E-02	1292.79	796.45	1601.09	1116.73	1.24
e11452	ADGQpGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843	96.67	98.34	5.58E-04	6.84E-03	4728.95	2493.39	5667.82	2822.30	1.20
e06650	EGSpGRDGSpGAKGDRG	COL1A1	Collagen alpha-1(I) chain	1021	1037	47.50	34.44	6.53E-03	4.21E-02	70.47	138.72	65.69	276.02	0.93
e06186	SpGSPGpDGKTGPPGpAG	COL1A1	Collagen alpha-1(I) chain	543	560	99.58	98.34	2.14E-04	3.29E-03	1925.41	966.19	1698.14	1401.98	0.88
e04843	GPpGpPGPpGpPGPPS	COL1A1	Collagen alpha-1(I) chain	1178	1193	75.83	70.12	7.55E-03	4.69E-02	1505.38	1852.68	1309.47	2290.06	0.87
e17047	PpGESGREGApGAEGSpGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1008	1041	98.75	96.68	1.42E-03	1.38E-02	5007.30	2685.83	4261.89	3157.12	0.85
e12851	LDGAKGDAGPAGPKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299	74.58	66.39	6.64E-03	4.27E-02	257.16	247.35	217.30	289.60	0.85
e06709	GSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	542	560	95.83	93.36	1.74E-04	2.76E-03	2077.16	1130.40	1737.91	1174.40	0.84
e12661	GKNGDDGEAGKPGRpGERGPpGpQ	COL1A1	Collagen alpha-1(I) chain	227	250	96.25	90.04	2.82E-03	2.26E-02	1309.28	1069.23	1094.14	1085.06	0.84
e07944	GpPGEAGKpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	650	668	94.58	86.72	7.34E-04	8.54E-03	1256.31	904.41	1046.39	967.10	0.83
e05353	GPpGKNGDDGEAGKpG	COL1A1	Collagen alpha-1(I) chain	224	239	77.92	65.56	4.67E-03	3.28E-02	360.27	394.30	298.42	411.81	0.83
e10875	GEQGPSGASGpAGpRGpPGSAGApG	COL1A1	Collagen alpha-1(I) chain	1127	1151	38.75	26.97	3.73E-03	2.79E-02	63.18	112.87	52.23	168.31	0.83
e11902	ANGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	699	725	99.58	98.34	1.46E-04	2.44E-03	6120.71	3239.02	5041.89	3099.81	0.82
e06024	SpGSPGPDGKTGpPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560	91.67	80.08	3.28E-05	7.60E-04	315.19	260.37	256.56	352.36	0.81
e16177	ESGREGApGAEGSPGRDGSpGAKGDRGETGpA	COL1A1	Collagen alpha-1(I) chain	1011	1042	94.17	85.48	6.23E-04	7.48E-03	4725.65	3882.93	3839.38	4094.17	0.81
e12986	ADGQpGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846	85.83	74.69	1.20E-03	1.23E-02	292.74	243.18	236.61	256.11	0.81
e11850	ADGQPGAKGEpGDAGAKGDAGPPGpA	COL1A1	Collagen alpha-1(I) chain	819	844	86.67	75.52	3.33E-03	2.59E-02	1210.52	1156.55	962.50	1121.41	0.80
e10554	EGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1021	1042	100.00	97.10	7.15E-06	2.27E-04	7130.03	3962.88	5630.94	3940.67	0.79

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e07132	EpGSpGENGAPGQmGPR	COL1A1	Collagen alpha-1(I) chain	288	304	61.67	47.30	4.25E-03	3.07E-02	2598.68	2544.62	2048.87	2715.19	0.79
e11193	NSGEpGApGSKGDTGAkGEpGPVG	COL1A1	Collagen alpha-1(I) chain	432	455	97.08	86.31	4.03E-05	9.02E-04	1614.38	950.03	1263.43	932.93	0.78
e08228	GEpGSpGENGApGQMGPRG	COL1A1	Collagen alpha-1(I) chain	287	305	90.00	84.65	2.16E-04	3.32E-03	687.06	479.84	531.87	411.16	0.77
e10657	AEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1020	1041	92.92	82.16	1.61E-03	1.51E-02	845.17	838.40	645.77	727.84	0.76
e06309	VGPpGPpGPpGPpGPPSA	COL1A1	Collagen alpha-1(I) chain	1177	1194	90.42	82.57	2.21E-04	3.37E-03	1078.08	820.30	823.06	771.95	0.76
e06520	NSGEpGApGSKGDTGAKG	COL1A1	Collagen alpha-1(I) chain	432	449	39.58	27.80	4.29E-03	3.09E-02	84.46	137.38	64.25	179.57	0.76
e12198	AGppGEAGKPGEQGVpGDLGApGPSG	COL1A1	Collagen alpha-1(I) chain	649	674	65.00	48.55	5.97E-04	7.24E-03	246.16	281.41	187.11	298.17	0.76
e05551	VGPpGPPGPpGPpGPPS	COL1A1	Collagen alpha-1(I) chain	1177	1193	92.92	87.55	2.95E-05	7.04E-04	2041.22	1529.91	1546.74	1481.01	0.76
e17348	ppGESGREGAPGAEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1008	1042	88.75	69.71	4.88E-05	1.06E-03	604.19	596.11	456.85	568.29	0.76
e07275	NGApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	700	719	86.67	87.97	2.87E-05	6.90E-04	1029.05	692.53	771.68	539.90	0.75
e05879	SpGSPGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560	50.42	42.32	4.80E-03	3.36E-02	137.95	250.15	103.31	265.26	0.75
e12101	ADGQpGAKGEpGDAGAKGDAGPpGpA	COL1A1	Collagen alpha-1(I) chain	819	844	68.33	57.68	2.92E-03	2.33E-02	221.83	232.41	165.61	210.65	0.75
e16966	PpGESGREGApGAEGSpGRDGSPGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1008	1041	93.33	72.20	1.72E-06	7.44E-05	606.49	523.49	451.80	548.93	0.74
e11777	ANGApGNDGAKGDAGApGApGSQGAPG	COL1A1	Collagen alpha-1(I) chain	699	725	79.58	73.03	1.14E-03	1.19E-02	315.02	281.84	231.90	245.41	0.74
e07678	TGSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	541	560	96.67	88.80	9.86E-08	7.25E-06	1884.23	1239.83	1384.06	1351.21	0.73
e01758	ApGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	798	808	87.08	78.84	4.48E-05	9.86E-04	3177.74	2859.94	2295.92	2732.38	0.72
e03890	ApGDRGEpGPpGPA	COL1A1	Collagen alpha-1(I) chain	798	811	92.08	95.44	4.56E-05	9.99E-04	7690.15	5871.30	5524.95	4534.50	0.72
e17946	PpGPAGFAGPPGADGQPGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	807	846	94.17	90.87	3.13E-06	1.17E-04	1052.47	836.86	752.14	697.62	0.71
e11536	NGDDGEAGKPGRpGERGPpGPQG	COL1A1	Collagen alpha-1(I) chain	229	251	67.50	56.02	9.89E-04	1.07E-02	215.20	269.61	153.62	259.29	0.71
e13065	ADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846	70.42	60.17	3.78E-04	5.13E-03	181.29	176.14	127.32	158.87	0.70
e01155	ApGDKGESGPS	COL1A1	Collagen alpha-1(I) chain	777	787	95.00	88.38	8.15E-05	1.57E-03	1303.27	1106.86	910.31	838.79	0.70
e05703	ApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	702	719	71.25	59.34	1.23E-03	1.25E-02	170.98	206.02	118.86	156.83	0.70
e17890	GPpGADGQPGAKGEpGDAGAKGDAGPPGpAGPAGPPGpIG	COL1A1	Collagen alpha-1(I) chain	815	854	91.67	87.97	2.37E-06	9.51E-05	829.94	686.67	575.92	553.36	0.69
e03638	SpGSpGPDGKTGPp	COL1A1	Collagen alpha-1(I) chain	543	556	81.25	64.73	1.06E-05	3.12E-04	934.59	853.77	646.52	801.88	0.69
e08462	GANGApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	698	719	48.33	36.93	2.78E-03	2.23E-02	265.06	379.16	181.99	338.60	0.69
e04419	ApGDRGEpGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812	97.08	97.10	5.12E-12	2.73E-09	2090.75	1147.48	1428.15	1006.52	0.68
e06547	GSpGSpGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	542	560	47.50	36.10	1.92E-03	1.73E-02	101.21	138.13	67.06	130.74	0.66
e03025	GQDGRpGPpGpPG	COL1A1	Collagen alpha-1(I) chain	560	572	90.00	78.01	7.45E-08	5.75E-06	1554.26	1321.93	1024.41	1236.45	0.66
e17438	AGRpGEVGpPGpPGPAGEKGSPGADGPAGAPGTPGPQG	COL1A1	Collagen alpha-1(I) chain	916	953	46.25	31.54	2.23E-04	3.39E-03	110.56	155.68	72.63	175.51	0.66
e01100	DRGEpGPpGP	COL1A1	Collagen alpha-1(I) chain	801	810	38.75	24.48	1.32E-03	1.32E-02	38.64	76.26	24.99	64.22	0.65
e14847	FAGPpGADGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	813	843	68.75	56.43	4.62E-04	5.97E-03	103.45	147.25	66.47	89.80	0.64
e03322	SpGPDGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	546	559	99.17	96.27	4.35E-09	5.69E-07	3624.33	2923.88	2325.80	2456.93	0.64
e12366	GANGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	698	725	77.50	64.32	3.35E-06	1.22E-04	542.60	573.86	345.49	526.95	0.64
e14501	pPGADGQPGAKGEpGDAGAKGDAGpPGPAGP	COL1A1	Collagen alpha-1(I) chain	816	846	48.33	40.25	7.99E-03	4.81E-02	86.07	119.89	54.55	88.08	0.63
e12949	LDGAKGDAGPAGpKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299	61.67	44.81	1.16E-04	2.03E-03	100.82	137.00	63.39	110.88	0.63
e04947	EpGKAGERGVPGpPG	COL1A1	Collagen alpha-1(I) chain	591	605	66.25	50.62	3.91E-04	5.26E-03	149.31	248.10	93.79	154.72	0.63
e13056	AGpPGApGApGAPGpVGPAGKSGDRGET	COL1A1	Collagen alpha-1(I) chain	1042	1069	54.17	36.10	9.15E-05	1.71E-03	79.38	106.91	49.62	88.26	0.63
e01983	DGRpGPpGPpGA	COL1A1	Collagen alpha-1(I) chain	562	573	38.75	24.90	5.40E-04	6.68E-03	35.72	74.38	22.22	68.87	0.62
e11002	AEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1020	1042	90.42	67.63	1.89E-10	4.91E-08	791.76	731.98	484.96	702.31	0.61
e08755	EGSpGRDGSpGAKGDRGET	COL1A1	Collagen alpha-1(I) chain	1021	1039	79.17	52.70	5.31E-07	2.86E-05	882.95	2082.12	534.10	708.42	0.60
e08888	pQGpGGPPGpKGNSGEPGApG	COL1A1	Collagen alpha-1(I) chain	420	440	68.75	50.21	1.17E-06	5.48E-05	198.02	218.60	119.76	190.01	0.60
e16771	GADGQpGAKGEpGDAGAKGDAGPPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	75.83	58.92	4.36E-08	3.65E-06	311.79	302.67	187.12	262.73	0.60
e16548	ADGQpGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	819	854	84.58	65.15	8.15E-09	9.52E-07	302.87	264.74	181.76	217.84	0.60
e05448	EpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	828	844	54.17	36.51	1.71E-05	4.59E-04	167.45	220.17	100.15	217.85	0.60
e16606	ADGQpGAKGEpGDAGAKGDAGpPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	819	854	87.50	72.61	9.63E-11	2.97E-08	409.21	300.23	243.11	251.94	0.59

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e13850	PpGKNGDDGEAGKPGRpGERGppGPQ	COL1A1	Collagen alpha-1(I) chain	225	250	50.83	36.93	6.19E-04	7.46E-03	167.46	286.68	98.74	226.01	0.59
e13673	PpGADGQpGAKGEpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	816	844	65.42	49.79	4.52E-06	1.56E-04	110.42	127.82	64.68	102.62	0.59
e11527	IGPpGpAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794	52.92	37.76	8.48E-05	1.62E-03	92.68	127.14	53.96	104.39	0.58
e17825	GPpGADGQPGAKGEPGDAGAKGDAGPPGpAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	815	854	40.00	30.71	6.84E-03	4.35E-02	116.45	217.35	67.75	153.21	0.58
e18625	AAGEpGKAGERGVPGppGAVGPAGKDGEAGAQGpPGPAGPAG	COL1A1	Collagen alpha-1(I) chain	588	629	47.08	31.12	3.85E-04	5.21E-03	79.19	131.49	46.02	98.68	0.58
e17690	pPGADGQPGAKGEpGDAGAKGDAGppGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854	91.67	79.67	2.29E-11	9.74E-09	836.69	718.99	481.54	547.69	0.58
e16845	GADGQpGAKGEpGDAGAKGDAGPpGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	65.42	44.81	1.14E-07	7.97E-06	296.08	315.69	168.11	277.34	0.57
e02517	QDGRpGpPGPpG	COL1A1	Collagen alpha-1(I) chain	561	572	35.00	19.50	1.90E-04	2.99E-03	66.36	120.66	37.58	98.42	0.57
e09627	PpGPpGKNGDDGEAGKpGRp	COL1A1	Collagen alpha-1(I) chain	222	241	67.08	36.93	3.03E-10	6.73E-08	217.07	270.80	121.74	252.87	0.56
e10135	SGNAGPpGPpGPAGKEGGKGPRG	COL1A1	Collagen alpha-1(I) chain	889	911	58.33	42.74	7.31E-04	8.52E-03	134.86	278.40	75.42	133.84	0.56
e16708	GADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	31.67	18.67	5.34E-04	6.62E-03	42.17	85.97	23.00	72.05	0.55
e11415	IGPpGPAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794	76.25	55.60	9.34E-10	1.72E-07	339.21	330.79	184.94	279.70	0.55
e05423	VGpPGPPGpPGPPGPPS	COL1A1	Collagen alpha-1(I) chain	1177	1193	53.75	36.10	9.53E-06	2.87E-04	226.11	353.55	122.40	281.20	0.54
e02592	DDGEAGKpGRpG	COL1A1	Collagen alpha-1(I) chain	231	242	83.75	61.00	5.55E-11	1.96E-08	441.91	418.53	236.51	315.86	0.54
e03372	DGQPGAKGEpGDAG	COL1A1	Collagen alpha-1(I) chain	820	833	36.25	24.90	1.45E-03	1.39E-02	77.90	125.86	41.49	93.02	0.53
e01399	DGRpGPpGPpG	COL1A1	Collagen alpha-1(I) chain	562	572	62.08	43.98	3.33E-06	1.22E-04	261.22	360.52	137.89	313.43	0.53
e06176	VGPpGPpGPPGPpGPPSA	COL1A1	Collagen alpha-1(I) chain	1177	1194	50.42	34.85	8.96E-05	1.68E-03	345.15	503.90	181.11	344.78	0.52
e11940	GESGREGApGAEGSpGRDGSpGAKG	COL1A1	Collagen alpha-1(I) chain	1010	1034	34.17	18.26	6.57E-05	1.32E-03	36.51	85.44	18.97	79.37	0.52
e13200	TGPIGpPGPAGAPGDKGESGpSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	766	794	61.25	41.08	3.63E-07	2.07E-05	153.58	204.02	79.57	151.12	0.52
e18580	FAGpPGADGQPGAKGEpGDAGAKGDAGpPGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	813	854	51.67	32.37	3.05E-06	1.15E-04	97.52	138.10	48.73	95.43	0.50
e17949	GEPGPPGPAGFAGPPGADGQPGAKGEPGDAGAKGDAGPpG	COL1A1	Collagen alpha-1(I) chain	803	842	56.25	37.76	1.02E-06	4.93E-05	216.72	273.59	106.91	194.23	0.49
e17626	pPGADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854	52.50	28.22	2.62E-08	2.38E-06	100.77	156.39	49.08	119.73	0.49
e12011	GpAGPpGEAGKPGEQGVPGDLGAPGP	COL1A1	Collagen alpha-1(I) chain	647	672	50.42	28.22	2.12E-07	1.34E-05	66.70	99.59	30.83	68.64	0.46
e13825	LTGPIGppGPAGAPGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	765	794	81.25	53.53	2.86E-13	2.35E-10	332.98	354.66	152.43	239.04	0.46
e14583	pPGADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	816	846	32.92	17.43	6.84E-05	1.37E-03	32.70	60.18	14.95	38.39	0.46
e10829	DGKTGpPGPAGQDGRpGPpGPpG	COL1A1	Collagen alpha-1(I) chain	550	572	31.25	20.75	2.83E-03	2.26E-02	25.69	52.31	11.61	27.39	0.45
e00467	DGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	550	559	59.58	44.40	4.88E-06	1.66E-04	296.62	457.63	127.29	324.97	0.43
e15883	NSGEpGApGSKGDTGAKGEpGPVGVQGPpGPAG	COL1A1	Collagen alpha-1(I) chain	432	464	31.67	17.01	5.15E-05	1.09E-03	36.24	68.40	14.28	37.59	0.39
e01213	pGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	799	808	35.83	17.84	4.36E-06	1.51E-04	65.79	136.16	22.81	66.23	0.35
e11629	AGPpGKAGEDGHpGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	135	157	20.00	37.76	9.79E-07	4.80E-05	25.35	125.58	132.51	425.89	5.23
e12793	GpAGPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	133	157	12.92	30.71	6.76E-07	3.47E-05	11.86	58.23	40.94	108.06	3.45
e15400	LkGQpGApGVkGEpGApGENGTpGQTGARG	COL1A2	Collagen alpha-2(I) chain	188	217	33.33	54.77	7.21E-10	1.38E-07	104.86	386.40	342.71	696.59	3.27
e11003	GPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	136	157	18.75	35.68	7.43E-06	2.34E-04	37.96	237.29	69.94	207.36	1.84
e18516	EVGKpGERGLHGEFGLpGpAGpRGERGPPGESGAAGP	COL1A2	Collagen alpha-2(I) chain	566	602	51.25	61.83	6.14E-03	4.06E-02	109.97	212.59	152.78	215.93	1.39
e10651	PpGKAGEDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	137	157	18.75	31.95	4.20E-04	5.55E-03	38.80	236.61	40.24	105.90	1.04
e19745	SKGESGNKGEpGSAGPQGPpGpSGEEGKRGPNGEAGSAGPPGPpG	COL1A2	Collagen alpha-2(I) chain	353	397	88.75	71.37	1.95E-03	1.75E-02	533.69	497.69	451.23	547.12	0.85
e06154	EDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	143	157	82.50	67.63	7.61E-04	8.76E-03	322.33	335.51	254.69	325.02	0.79
e17212	RTGEVGAVGPpGFAGEKGPSGEAGTAGpPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	830	865	97.50	90.87	3.98E-06	1.41E-04	1201.22	726.57	936.47	745.83	0.78
e10318	GEpGPAGSKGESGNKGEpGSAGP	COL1A2	Collagen alpha-2(I) chain	346	368	60.00	45.23	1.79E-03	1.64E-02	117.88	138.89	90.68	140.98	0.77
e19107	DQGPVGRTGEVGAVGPpGFAGEKGpSGEAGTAGPPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	824	865	62.92	48.96	5.91E-04	7.19E-03	157.76	214.89	120.08	259.26	0.76
e17585	GDPGKNGDKGHAGLAGARGApGPDGNNGAQGPpGPQG	COL1A2	Collagen alpha-2(I) chain	502	538	52.08	38.17	1.40E-03	1.36E-02	83.91	111.04	62.03	114.34	0.74
e09796	GApGVKGEpGApGENGTPGQTG	COL1A2	Collagen alpha-2(I) chain	193	214	30.83	19.92	5.26E-03	3.61E-02	39.67	82.15	29.06	121.23	0.73
e07808	KGPSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	846	865	66.25	58.09	3.84E-03	2.86E-02	334.67	427.44	243.63	397.43	0.73
e09435	GEKGPSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	844	865	76.67	58.09	5.61E-06	1.87E-04	222.25	241.86	156.87	261.10	0.71
e08951	GEKGPSGEAGTAGpPGTpGPQ	COL1A2	Collagen alpha-2(I) chain	844	864	51.67	33.20	5.75E-06	1.90E-04	127.82	185.44	89.01	270.25	0.70

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e11186	GPpGpAGSRGDGGPpGMTGFpGAAG	COL1A2	Collagen alpha-2(I) chain	769	793	47.50	36.93	6.92E-03	4.39E-02	105.82	152.87	71.48	128.43	0.68
e19752	GEVGPAGpNGFAGpAGAAGQpGAKGERGAKGPKGENGVVGPTGpVG	COL1A2	Collagen alpha-2(I) chain	715	760	52.92	40.66	3.36E-03	2.60E-02	201.76	321.23	135.55	260.75	0.67
e13164	AVGPPGFAGEKGpSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	836	863	30.83	19.92	6.52E-03	4.21E-02	43.78	106.14	29.03	86.90	0.66
e14368	EAGRDGNpGNDGpPGRDGQpGHKGER	COL1A2	Collagen alpha-2(I) chain	923	948	30.00	19.09	6.88E-03	4.37E-02	25.95	55.38	16.89	46.65	0.65
e04647	DGPpGRDGQpGHKG	COL1A2	Collagen alpha-2(I) chain	933	946	65.83	46.06	2.28E-06	9.23E-05	90.31	109.02	55.16	107.53	0.61
e15593	NGEAGSAGpPGppGLRGSpGSRGLPGADGRAG	COL1A2	Collagen alpha-2(I) chain	384	415	69.58	47.30	1.64E-06	7.21E-05	241.43	276.15	145.24	211.85	0.60
e03691	YDGKGVGLGPGPMG	COL1A2	Collagen alpha-2(I) chain	81	94	79.58	65.56	4.97E-07	2.70E-05	724.11	943.01	415.81	673.91	0.57
e09564	GEKGpSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	844	865	37.92	20.75	1.20E-05	3.45E-04	51.63	93.19	27.74	110.97	0.54
e15713	pGpLGTKGDRGAPGIPGSPGSRGDpGIGVAGp	COL22A1	Collagen alpha-1(XXII) chain	998	1029	49.17	69.29	3.80E-09	5.11E-07	166.03	267.94	382.61	504.13	2.30
e05677	pGKDGDTGPTGPQGPQ	COL22A1	Collagen alpha-1(XXII) chain	1305	1320	98.75	97.51	1.62E-04	2.62E-03	5061.45	3123.41	4027.35	2590.78	0.80
e09697	PGpPGPHGPPGpmGPHGLpGP	COL25A1	Collagen alpha-1(XXV) chain	531	551	94.17	85.89	5.79E-07	3.07E-05	1290.53	976.48	906.03	895.95	0.70
e17673	GpPGPAGFAGpPGADGQpGAKGEQGEAGQKGDAGAPGP	COL2A1	Collagen alpha-1(II) chain	828	865	17.92	41.08	1.22E-09	2.11E-07	209.52	1035.65	4205.69	41827.09	20.07
e19147	GAKGEAGAPGVKGESGSpGENGSPGPmGpRGLPGERGRTGP	COL2A1	Collagen alpha-1(II) chain	297	337	47.08	60.58	2.31E-06	9.31E-05	121.71	265.97	296.87	587.70	2.44
e06597	DQGASGpAGpSGpRGPpG	COL2A1	Collagen alpha-1(II) chain	1150	1167	41.25	56.43	9.13E-04	9.99E-03	322.80	619.03	490.96	794.34	1.52
e18864	SGPPGRAGEPGLQGPAGPpGEKGEPGDDGpSGAEGPpGPQG	COL2A1	Collagen alpha-1(II) chain	935	975	74.17	61.83	5.10E-04	6.40E-03	222.25	250.18	184.79	342.61	0.83
e01661	DGpSGAEGpPGp	COL2A1	Collagen alpha-1(II) chain	962	973	98.75	97.10	2.92E-04	4.15E-03	2465.66	1597.30	2044.32	1587.01	0.83
e12156	GPAGpPGEKGEPGDDGPSGAEGPPGp	COL2A1	Collagen alpha-1(II) chain	948	973	85.00	78.84	4.25E-03	3.07E-02	546.25	549.01	410.81	432.68	0.75
e13033	GpAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	948	974	87.92	80.50	1.04E-05	3.07E-04	586.26	526.32	392.73	402.58	0.67
e13138	GpEGAQGPRGEpGTpGSPGPAGASGNPG	COL2A1	Collagen alpha-1(II) chain	384	411	35.83	23.65	2.76E-03	2.22E-02	32.48	68.77	18.87	51.64	0.58
e04199	PVGpSGKDGANGIpG	COL2A1	Collagen alpha-1(II) chain	1168	1182	73.75	53.94	4.09E-07	2.28E-05	217.03	239.90	125.14	183.57	0.58
e12714	pAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	949	974	86.67	75.52	2.05E-09	3.30E-07	507.48	436.78	290.20	320.24	0.57
e09547	GPpGEGGKpGDQGVpGEAGApG	COL2A1	Collagen alpha-1(II) chain	672	693	31.67	21.58	4.30E-03	3.10E-02	41.75	83.96	23.04	77.06	0.55
e13127	GpAGpPGEKGEPGDDGPSGAEGpPGPQ	COL2A1	Collagen alpha-1(II) chain	948	974	30.83	14.94	2.52E-05	6.26E-04	34.23	72.65	15.54	52.57	0.45
e12658	AGppGEKGEPGDDGpSGAEGPpGPQG	COL2A1	Collagen alpha-1(II) chain	950	975	46.67	24.48	8.28E-08	6.24E-06	163.81	285.13	65.73	185.65	0.40
e09966	GARGNDGARGSDGQPGPpGPpG	COL3A1	Collagen alpha-1(III) chain	318	339	26.67	38.17	3.02E-03	2.39E-02	48.03	121.82	247.09	1891.08	5.14
e03194	DGVPGKDGPRGPT	COL3A1	Collagen alpha-1(III) chain	752	764	47.92	30.29	1.14E-03	1.19E-02	107.71	191.11	471.72	2758.12	4.38
e16173	LGSPGpKGDKGEpGGpGADGVPGKDGPRGPTGP	COL3A1	Collagen alpha-1(III) chain	734	766	16.25	33.61	1.69E-06	7.40E-05	45.98	206.35	177.60	490.79	3.86
e03922	TGPGGDKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	623	637	29.58	45.64	5.56E-05	1.14E-03	141.24	329.92	293.31	563.19	2.08
e09061	GApGApGGKGDAGAPGERGppG	COL3A1	Collagen alpha-1(III) chain	666	687	42.92	52.28	3.81E-03	2.84E-02	82.97	197.57	157.18	347.15	1.89
e16286	RGERGEAGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	446	477	62.08	69.71	5.97E-04	7.24E-03	157.52	232.82	280.44	400.99	1.78
e13707	GApGQNGEPGGKGERGApGEKGEGGppG	COL3A1	Collagen alpha-1(III) chain	813	840	96.67	97.93	2.93E-10	6.58E-08	2052.21	1899.96	3494.56	3029.44	1.70
e12235	GQNGEpGGKGERGApGEKGEGGPpG	COL3A1	Collagen alpha-1(III) chain	816	840	62.08	70.95	1.00E-03	1.08E-02	229.59	292.01	369.42	454.90	1.61
e08539	ApGApGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	667	687	93.33	89.21	4.99E-03	3.46E-02	575.49	1173.88	885.22	1855.44	1.54
e13566	KNGETGPQGPPGPTGPGGDKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	610	637	58.75	45.64	2.37E-03	2.00E-02	100.09	125.43	95.66	251.33	0.96
e07676	NDGAPGKNGERGGpGGpGp	COL3A1	Collagen alpha-1(III) chain	586	604	98.75	99.17	1.92E-03	1.73E-02	4293.28	2093.89	3714.67	1830.94	0.87
e09989	DGESGRpGRpGERGLpGPpG	COL3A1	Collagen alpha-1(III) chain	230	249	98.33	95.85	3.05E-03	2.41E-02	2262.69	2054.01	1868.15	1259.75	0.83
e09521	EGGKGAAGpPGPpGAAGTpGLQG	COL3A1	Collagen alpha-1(III) chain	704	726	87.92	82.99	2.47E-03	2.06E-02	407.33	298.92	334.04	298.17	0.82
e06068	NDGApGKNGERGGpGGP	COL3A1	Collagen alpha-1(III) chain	586	602	98.75	92.12	4.61E-06	1.59E-04	1108.28	700.45	881.89	765.33	0.80
e08188	GNDGApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	585	604	94.58	83.82	2.02E-04	3.15E-03	1771.67	1124.24	1403.98	1125.81	0.79
e18092	NTGApGSpGVSGpKGDAGQpGEKGSpGAQGpPGAPGpLG	COL3A1	Collagen alpha-1(III) chain	910	948	95.83	95.85	8.62E-05	1.64E-03	3594.75	2122.95	2822.52	1901.87	0.79
e11904	GPAGFpGApGQNGEpGGKGERGApG	COL3A1	Collagen alpha-1(III) chain	807	831	77.08	68.88	1.22E-03	1.24E-02	421.86	425.05	322.06	426.44	0.76
e13253	EDGKDGSpGEpGANGLpGAAGERGApG	COL3A1	Collagen alpha-1(III) chain	463	489	81.25	72.61	1.02E-03	1.09E-02	259.72	256.02	196.21	242.49	0.76
e10769	SNGNPGppGPSGSpGKDGPpGPAG	COL3A1	Collagen alpha-1(III) chain	886	909	49.58	37.76	6.78E-03	4.33E-02	90.86	136.62	66.66	127.22	0.73
e01923	SpGERGETGPp	COL3A1	Collagen alpha-1(III) chain	796	806	90.42	73.44	5.89E-07	3.11E-05	2423.68	1927.73	1725.69	2041.41	0.71
e10781	GDAGApGAPGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	663	687	33.33	21.58	6.11E-03	4.05E-02	51.67	104.15	36.77	92.56	0.71

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e14735	KNGETGPQGPPGpTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	98.33	95.02	2.39E-09	3.66E-07	1184.95	734.00	823.01	631.56	0.69
e12496	AGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	452	477	60.00	48.13	2.28E-03	1.95E-02	145.82	193.10	99.52	156.75	0.68
e07880	pGARGLpGpPGSNGNPGpP	COL3A1	Collagen alpha-1(III) chain	875	893	57.50	43.15	1.90E-03	1.72E-02	191.20	281.56	129.63	231.14	0.68
e05568	TGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	623	639	44.58	33.61	4.20E-03	3.05E-02	228.61	330.81	154.80	312.34	0.68
e15411	PQGPpGPTGpGGDKGDTGPpGPQGLQGLpGT	COL3A1	Collagen alpha-1(III) chain	616	646	95.83	90.04	2.42E-08	2.27E-06	2698.45	2117.04	1738.52	1601.57	0.64
e13472	LRGGAGpPGPEGGKGAAGPpGPpGAAGTpG	COL3A1	Collagen alpha-1(III) chain	694	723	65.42	55.19	2.68E-04	3.91E-03	246.64	300.29	153.66	228.80	0.62
e09856	SNGNPGppGPSGSpGKDGPPGp	COL3A1	Collagen alpha-1(III) chain	886	907	61.25	45.64	3.15E-06	1.17E-04	159.15	181.84	96.24	191.12	0.60
e03651	DGApGKNGERGGpG	COL3A1	Collagen alpha-1(III) chain	587	600	56.67	35.27	5.77E-06	1.90E-04	139.77	185.13	81.47	146.78	0.58
e14644	KNGETGPQGPPGPTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	42.92	32.78	3.41E-03	2.63E-02	58.95	103.78	31.08	62.07	0.53
e14821	KNGETGPQGppGPTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	37.92	21.99	1.38E-04	2.33E-03	39.38	68.97	20.73	47.62	0.53
e01935	DGESGRpGRpG	COL3A1	Collagen alpha-1(III) chain	230	240	51.67	30.29	7.63E-08	5.82E-06	119.01	185.26	49.30	117.49	0.41
e08942	pGFPGTpGLpGmPGHDGAPG	COL4A5	Collagen alpha-5(IV) chain	98	117	45.00	26.97	4.07E-06	1.43E-04	86.71	125.27	44.07	110.46	0.51
e09844	GLDGERGRPGPAGppGppGPS	COL4A6	Collagen alpha-6(IV) chain	1240	1260	39.17	28.63	7.47E-03	4.65E-02	243.95	1075.92	136.75	528.67	0.56
e14398	PGMPGADGpPGHPGKEGppGEKGGQGpPG	COL5A1	Collagen alpha-1(V) chain	753	781	97.92	99.17	1.08E-04	1.92E-03	1686.22	1180.22	2173.03	1418.60	1.29
e03055	GEAGHPGPPGPpGP	COL5A1	Collagen alpha-1(V) chain	1555	1568	70.83	50.62	6.95E-08	5.47E-06	341.97	388.25	176.04	271.07	0.51
e11679	EGpPGKPGEDGEpGRNGNpGEVG	COL5A2	Collagen alpha-2(V) chain	257	279	67.92	84.23	1.02E-10	3.05E-08	1448.76	3353.27	2401.50	2474.06	1.66
e05060	GPpGPpGFpGDPGPPG	COL5A3	Collagen alpha-3(V) chain	407	422	77.92	63.07	2.62E-03	2.13E-02	647.94	889.25	643.73	1597.65	0.99
e05200	GPpGPpGFPGDpGPpG	COL5A3	Collagen alpha-3(V) chain	407	422	87.50	73.44	2.20E-06	8.96E-05	1360.55	2372.49	963.64	1658.74	0.71
e08177	DGpEGPKGQAGQAGEEGPP	COL5A3	Collagen alpha-3(V) chain	760	778	69.58	58.51	2.33E-04	3.51E-03	447.31	864.87	229.85	518.78	0.51
e16717	DPGLMGERGEDGpAGNGTEGFPGFPGYpGNR	COL6A1	Collagen alpha-1(VI) chain	501	531	45.83	55.19	4.30E-03	3.10E-02	143.26	237.47	228.38	315.73	1.59
e11369	GPpGEPGPRGPRGVpGpEGEpGP	COL6A2	Collagen alpha-2(VI) chain	561	583	93.33	85.06	2.48E-04	3.70E-03	718.02	535.14	582.19	594.65	0.81
e03632	GApGLAGpAGpQGpS	COL7A1	Collagen alpha-1(VII) chain	2189	2203	16.67	30.29	2.68E-04	3.91E-03	38.83	161.01	93.49	286.29	2.41
e02311	GpPGPpGPpGPpA	COL8A1	Collagen alpha-1(VIII) chain	560	572	74.17	63.07	3.20E-03	2.50E-02	727.88	897.52	554.77	884.15	0.76
e12015	PpGppGPpGVPGSDGIDGDNGPPGK	COL9A2	Collagen alpha-2(IX) chain	23	47	87.50	77.18	2.05E-05	5.31E-04	426.94	351.99	304.94	311.41	0.71
e06314	PGpKGEpGKAGpDGpDG	COL9A2	Collagen alpha-2(IX) chain	51	67	52.92	44.81	5.59E-03	3.78E-02	133.47	182.16	83.27	133.22	0.62
e00307	GPpGpPGPpG	COL9A2	Collagen alpha-2(IX) chain	33	42	55.83	47.72	4.96E-03	3.44E-02	303.61	608.69	149.92	315.98	0.49
e15390	SQTSQAVTGGHTQIQAGSHTETVEQDR	CRNN	Cornulin	336	362	34.17	44.81	8.35E-03	4.99E-02	56.40	126.74	96.10	190.88	1.70
e11931	SEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	609	629	15.00	31.95	8.39E-07	4.24E-05	13.76	64.90	105.54	344.34	7.67
e14283	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629	70.42	71.78	2.31E-04	3.48E-03	2311.19	4600.54	11577.41	26450.64	5.01
e13674	DEAGSEADHEGTHSTKRGHAKSRP	FGA	Fibrinogen alpha chain	605	628	69.58	76.76	1.74E-06	7.49E-05	957.95	1750.38	3444.75	7569.14	3.60
e17491	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629	66.67	72.20	8.69E-04	9.59E-03	370.63	492.49	729.47	1054.36	1.97
e02915	DHEGTHSTKRG	FGA	Fibrinogen alpha chain	612	622	29.58	43.57	1.03E-03	1.10E-02	193.73	623.38	283.05	781.98	1.46
e08463	DEAGSEADHEGTHSTKR	FGA	Fibrinogen alpha chain	605	621	97.08	94.61	5.74E-03	3.86E-02	2000.63	852.80	1762.82	908.81	0.88
e07002	DEAGSEADHEGTHSTK	FGA	Fibrinogen alpha chain	605	620	85.83	69.71	2.22E-08	2.13E-06	491.94	520.67	360.73	1032.51	0.73
e04994	DEAGSEADHEGTHS	FGA	Fibrinogen alpha chain	605	618	70.42	47.72	3.06E-07	1.82E-05	227.16	254.10	141.47	243.60	0.62
e08185	EEAPSLRPAPPPISGGGY	FGB	Fibrinogen beta chain	54	71	72.50	63.07	1.59E-04	2.59E-03	408.28	536.01	271.30	421.90	0.66
e06733	AGSEADHEGTHSTKRG	FIBA	Fibrinogen alpha chain	607	622	98.75	96.68	6.13E-05	1.24E-03	1684.87	875.98	1407.54	911.22	0.84
e05387	GLSMDGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	3	18	65.00	50.21	1.44E-04	2.41E-03	201.58	302.40	152.48	301.16	0.76
e01784	DGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	7	18	75.00	58.92	1.35E-06	6.14E-05	311.76	328.21	198.96	297.70	0.64
e06256	TGLSMDGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	2	18	71.67	52.70	1.08E-07	7.62E-06	301.31	329.69	187.26	348.39	0.62

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Frequency non-CKD (%)	Frequency CKD (%)	Unadjusted p value (Mann Whitney)	BH Adjusted p-value	Average non-CKD	St. Dev. non-CKD	Average CKD	St. Dev. CKD	Fold change
e07648	TGLSMDGGGSPKGDVDPF	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	2	19	43.33	29.05	3.04E-04	4.29E-03	221.28	336.90	127.14	267.41	0.57
e11826	SETAPAAPAAPAPAEKTPVKKKA	H1-4	Histone H1.4	2	24	42.08	51.87	2.34E-03	1.98E-02	93.43	159.77	213.24	1071.11	2.28
e13087	SETAPAETATPAPVEKSPAKKKAT	H1-5	Histone H1.5	2	25	19.17	33.61	1.01E-04	1.84E-03	17.22	47.53	172.89	1970.59	10.04
e03285	PEDEEEKKKM	HSP90AB1	Heat shock protein HSP 90-beta	544	553	15.42	32.37	1.16E-06	5.44E-05	15.29	99.27	212.12	923.39	13.87
e13926	DVSTPPTVLPDNFPR	IGF2	Insulin-like growth factor II	93	107	30.42	14.94	2.89E-05	6.91E-04	35.51	81.62	13.57	46.82	0.38
e15015	WKADGSPVKAGVETTKPSKQSNNKYA	IGLL5	Immunoglobulin lambda-like polypeptide 5	150	175	10.83	34.02	3.18E-10	6.91E-08	936.45	12199.09	8033.90	60110.47	8.58
e09412	GSGGSSYGSGGGSYGSGGGGGGGRG	KRT1	Keratin; type II cytoskeletal 1	526	550	85.83	65.98	4.14E-06	1.45E-04	431.98	529.63	288.69	380.81	0.67
e08691	SSSKGSLGGGFSSGGFSGGSF	KRT10	Keratin, type I cytoskeletal 10	37	57	57.08	47.72	5.40E-03	3.69E-02	161.70	231.23	100.36	144.83	0.62
e06292	ASYLDKVRALEESN	KRT10	Keratin, type I cytoskeletal 10	158	171	71.25	46.47	5.86E-10	1.17E-07	350.33	369.08	184.29	302.82	0.53
e10169	FGASAGTGDLSDNHDIISMK	LMAN2	Vesicular integral-membrane protein VIP36	253	272	50.42	62.24	7.39E-05	1.45E-03	188.46	391.28	741.25	1842.88	3.93
e09606	LDTYPNDETTERVFPY	LMAN2	Vesicular integral-membrane protein VIP36	161	176	21.25	33.20	1.39E-03	1.36E-02	84.02	252.35	190.23	452.78	2.26
e08039	FGASAGTGDLSDNHDIIS	LMAN2	Vesicular integral-membrane protein VIP36	253	270	75.83	68.46	2.85E-03	2.28E-02	637.75	706.55	531.51	799.28	0.83
e01666	SREPADAAIR	MAN1A1	Mannosyl-oligosaccharide 1;2-alpha-mannosidase IA	184	193	57.50	39.42	2.17E-05	5.57E-04	123.58	168.34	73.24	139.11	0.59
e11919	QSKHPGDFGADAQGAMNKALEL	MB	Myoglobin	117	138	34.17	44.81	1.85E-03	1.69E-02	31.95	73.10	109.78	402.32	3.44
e17804	TTLSPSSSTTHEGEPTTFQSWPSSKDTSPAPSG	MUC12	Mucin-12	404	436	37.50	17.01	1.22E-07	8.45E-06	40.49	74.15	13.08	39.01	0.32
e12382	DGLSPDQTRSEDPQNSAGSPPDA	MYOCD	Myocardin	160	182	67.50	61.00	4.13E-03	3.00E-02	241.99	271.52	186.48	293.19	0.77
e03544	KELDINTDGAVN	S100A8	Protein S100-A8	56	67	42.92	26.14	1.17E-04	2.04E-03	163.05	384.67	96.72	280.99	0.59
e05899	SAPYPGGGGNGASGGGSGGS	PCDH7	Protocadherin-7	203	222	71.67	60.17	3.53E-06	1.28E-04	441.50	465.68	259.56	377.83	0.59
e07343	DHDVGSELPPEGVLGAL	PCSK1N	ProSAAS	223	239	40.42	26.97	1.72E-03	1.59E-02	169.91	465.73	116.03	331.93	0.68
e18732	LFAEEKAVADTRDQADGSRASVDSGSSEEQGGSSRA	PIGR	Polymeric-immunoglobulin receptor	604	639	83.75	87.55	1.38E-05	3.87E-04	719.39	862.10	1411.01	2061.42	1.96
e15907	AVADTRDQADGSRASVDSGSSEEQGGSSRA	PIGR	Polymeric-immunoglobulin receptor	610	639	32.08	44.81	4.99E-03	3.46E-02	119.67	299.65	204.44	554.06	1.71
e14638	AVADTRDQADGSRASVDSGSSEEQGGSS	PIGR	Polymeric-immunoglobulin receptor	610	637	37.08	14.11	2.63E-09	3.97E-07	50.69	83.77	15.58	50.32	0.31
e19279	TSPSGQLIPVKNLSENIEIL	PK1L2	Polycystic kidney disease protein 1-like 2	1142	1161	77.92	60.17	8.23E-08	6.24E-06	211.83	213.46	128.91	178.66	0.61
e14937	DQAANEWGRSGKDPNHFRPAGLPEK	SAA1	Serum amyloid A-1 protein	97	121	10.42	30.71	3.58E-09	4.93E-07	17.57	94.27	730.23	3779.20	41.56
e09609	LTGRGAEDSLADQAANKWG	SAA2	Serum amyloid A-2 protein	86	104	15.83	42.74	3.17E-12	1.90E-09	169.59	1046.36	3516.42	15176.87	20.73
e06246	LTGRGAEDSLADQAAN	SAA2	Serum amyloid A-2 protein	86	101	49.17	35.68	1.71E-03	1.59E-02	78.38	119.87	61.14	147.73	0.78
e12387	HLVGHQRNNRQVTLEVSGAEP	SECTM1	Secreted and transmembrane protein 1	118	138	12.92	37.34	3.21E-10	6.91E-08	36.53	153.79	215.42	550.68	5.90
e05742	DITSHMESEELNGA	SPP1	Osteopontin	188	201	57.92	40.25	9.58E-05	1.76E-03	99.27	257.91	65.90	151.30	0.66
e20740	sDKPDMAEIEKFDKSKLKKTETQEKNPLPSKETIEQEKQAGES	TMSB4X	Thymosin beta-4	2	44	59.58	67.22	5.09E-04	6.40E-03	956.19	4002.29	5141.20	15012.23	5.38
e07964	SVIDQSRVLNLGPITR	UMOD	Uromodulin	591	606	93.75	92.53	1.52E-03	1.44E-02	8252.83	10762.73	6875.41	11843.48	0.83
e09213	SGSVIDQSRVLNLGPITR	UMOD	Uromodulin	589	606	96.67	95.44	8.10E-03	4.86E-02	38247.25	38606.80	31239.53	38747.56	0.82
e10189	SGSVIDQSRVLNLGPITRK	UMOD	Uromodulin	589	607	70.83	61.41	3.96E-03	2.92E-02	1007.08	1589.06	782.63	2071.09	0.78
e06451	SVIDQSRVLNLGPIT	UMOD	Uromodulin	591	605	59.17	40.66	2.14E-04	3.29E-03	856.03	1384.83	589.02	1168.19	0.69
e07848	SGSVIDQSRVLNLGPIT	UMOD	Uromodulin	589	605	69.58	63.49	1.20E-04	2.09E-03	3818.84	7300.05	2101.01	3547.27	0.55
e02332	SGSVIDQSRVL	UMOD	Uromodulin	589	599	41.25	22.41	2.72E-06	1.05E-04	342.85	694.07	180.45	764.44	0.53
e00923	VLNLGPITR	UMOD	Uromodulin	598	606	52.92	42.32	1.91E-03	1.73E-02	304.84	740.96	149.71	288.92	0.49
e08455	GSVIDQSRVLNLGPITR	UMOD	Uromodulin	590	606	50.00	30.29	1.90E-07	1.23E-05	738.79	1551.44	203.23	566.99	0.28
e18782	GRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAPEVRGA	VGF	Neurosecretory protein VGF	26	62	75.00	84.65	8.51E-09	9.89E-07	483.97	761.81	1331.07	2239.85	2.75
e07573	ESVVLEPEAT	X3CL1	Fractalkine	123	132	52.92	41.08	5.00E-03	3.47E-02	179.08	257.27	134.29	293.05	0.75

AA: Amino acid, BH: Benjamini-Hochberg, St. Dev: Standard deviation

Supplementary S2 Table. Spearman's rank-order correlation analysis between the amplitude of the 303 CKD-associated peptides and eGFR in CKD patients. (PLoS One. 2022 Jan 19; 17(1): e0262667. doi: 10.1371/journal.pone.0262667).

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e12741	MIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	398	418	-0.48	3.68E-15
e13340	LMIEQNTKSPLFMGKVVNPTQK	A1AT	Alpha-1-antitrypsin	397	418	-0.46	7.37E-14
e09486	EAIPMSIPPEVKFNKPF	A1AT	Alpha-1-antitrypsin	378	394	-0.41	3.26E-11
e14697	FLPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	277	299	-0.39	5.02E-10
e18378	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAE	A1AT	Alpha-1-antitrypsin	25	56	-0.34	6.55E-08
e13865	LPDEGKLQHLENELTHDIITKF	A1AT	Alpha-1-antitrypsin	278	299	-0.29	6.53E-06
e04988	TIDEKGTEAAGAMF	A1AT	Alpha-1-antitrypsin	363	376	-0.27	1.55E-05
e12271	EDPQGDAAQKTDTSHHDQDHP	A1AT	Alpha-1-antitrypsin	25	45	0.21	8.69E-04
e11895	FFLPDEGKLQHLENELTHD	A1AT	Alpha-1-antitrypsin	276	294	-0.13	4.50E-02
e12950	LREGETKAVKTVRTPGAAANLEL	A1BG	Alpha-1B-glycoprotein	435	457	-0.34	7.95E-08
e12127	LREGETKAVKTVRTPGAAANLE	A1BG	Alpha-1B-glycoprotein	435	456	-0.31	1.19E-06
e09323	MGVVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	322	340	-0.47	2.46E-14
e07656	VVSLGSPSGEVSHPRKT	AHSG	Alpha-2-HS-glycoprotein	324	340	-0.38	1.13E-09
e05548	VVSLGSPSGEVSHPR	AHSG	Alpha-2-HS-glycoprotein	324	338	-0.18	4.64E-03
e13562	DAHKSEVAHRFKDLGEENFKAL	ALB	Albumin	25	46	-0.53	6.34E-19
e12518	DAHKSEVAHRFKDLGEENFK	ALB	Albumin	25	44	-0.51	4.13E-17
e14191	DAHKSEVAHRFKDLGEENFKALV	ALB	Albumin	27	49	-0.48	1.88E-15
e14790	DAHKSEVAHRFKDLGEENFKALVL	ALB	Albumin	25	48	-0.41	5.12E-11
e12970	DAHKSEVAHRFKDLGEENFKA	ALB	Albumin	25	45	-0.40	1.13E-10
e15827	DAHKSEVAHRFKDLGEENFKALVLIA	ALB	Albumin	27	52	-0.33	1.56E-07
e07463	VRYTKKVPQVSTPTL	ALB	Albumin	433	447	-0.18	4.82E-03
e05113	EAGSPPVVE	ANR17	Ankyrin repeat domain-containing protein 17	2078	2086	-0.33	2.13E-07
e04435	AILDETKGDYEK	ANXA1	Annexin A1	326	337	-0.33	1.89E-07
e06716	LSALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	254	267	-0.52	3.07E-18
e14633	VDVLKDSGRDYVSQFEGSALGKQLN	APOA1	Apolipoprotein A-I	43	67	-0.41	5.38E-11
e05683	SALEEYTKKLNTQ	APOA1	Apolipoprotein A-I	233	245	-0.38	8.00E-10
e10106	SNNAKEAVEHLQKSELTQ	APOA4	Apolipoprotein A-IV	39	56	-0.21	1.15E-03
e08260	PEVRPTSA	APOC3	Apolipoprotein C-III	89	96	0.11	8.22E-02
e04609	SIAAGGEGLTDVSPE	ATG12	Ubiquitin-like protein ATG12	14	28	0.17	1.01E-02
e03035	WKYYYDGKD	AZGP1	Zinc-alpha-2-glycoprotein	135	143	0.07	2.51E-01
e14596	LLKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	59	81	-0.59	3.38E-24
e13955	LKNGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	60	81	-0.56	5.42E-21
e12566	NGERIEKVEHSDLSFSKDWS	B2M	Beta-2-microglobulin	62	81	-0.38	1.69E-09
e00152	VSGFHPSD	B2M	Beta-2-microglobulin	47	54	-0.17	7.48E-03
e12939	LQGTPVAQMTEDAVDAERLKHL	C3	Complement C3	982	1003	-0.25	8.82E-05
e14818	FPGMPGPPGQpGPRGSMGPMGPSPDLSH	CCBE1	Collagen and calcium-binding EGF domain-containing protein 1	269	296	0.14	3.16E-02
e10450	VSGGEGKGGSDGGGSHRKEGEE	CD99	CD99 antigen	99	120	0.34	6.84E-08
e14231	DDPRPPNPPKPmPNPNPNHPSSSGS	CD99	CD99 antigen	65	89	0.03	6.87E-01
e13010	DGSPHPDPSAGAKPcGSSSAGKIPc	CDSN	Corneodesmosin	472	496	-0.16	1.55E-02
e18263	ASHTSDSDVPSGVTEVVVKLFDSDPITVTVPVEV	CLU	Clusterin	390	423	0.24	1.93E-04
e04757	SHTSDSDVPSGVTE	CLU	Clusterin	391	404	0.12	5.95E-02
e12945	DGpQGPpGSVGSVGGVGEKGEPGEAGN	COL11A1	Collagen alpha-1(XI) chain	1236	1262	0.26	5.00E-05
e07106	EAGEKGNPGAEGLQGVpG	COL13A1	Collagen alpha-1(XIII) chain	555	572	-0.05	4.86E-01
e17751	pPGPQGPSGLSIQGMpGmpGEKGEKGDTGLPGPQG	COL14A1	Collagen alpha-1(XIV) chain	1502	1536	0.58	8.57E-23
e15200	GIpGGVGSpGRDGSpGQRGLPGKDGSSGPpG	COL14A1	Collagen alpha-1(XIV) chain	1536	1566	-0.17	8.04E-03

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e11191	NSGEKGDQGFQGQpGFPGPpGP	COL16A1	Collagen alpha-1(XVI) chain	1145	1166	0.26	5.81E-05
e05351	DKGEpGPPGQPGYpG	COL16A1	Collagen alpha-1(XVI) chain	1079	1093	0.13	4.10E-02
e12384	EGpmGQRGREGPMGpRGEAGPpG	COL17A1	Collagen alpha-1(XVII) chain	617	639	-0.17	7.27E-03
e19753	GPEGPSGKpGINGKDGIPGAQGImGKpGDRGpKGERGDQGIP	COL19A1	Collagen alpha-1(XIX) chain	917	958	-0.61	6.67E-26
e16708	GADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	0.23	0.00E+00
e01983	DGRpGPpGPpGA	COL1A1	Collagen alpha-1(I) chain	562	573	0.27	0.00E+00
e12198	AGppGEAGKPGEQGVpGDLGApGPSG	COL1A1	Collagen alpha-1(I) chain	649	674	0.26	0.00E+00
e16177	ESGREGApGAEGSPGRDGSpGAKGDRGETGpA	COL1A1	Collagen alpha-1(I) chain	1011	1042	0.23	0.00E+00
e11536	NGDDGEAGKPGRpGERGPpGPQG	COL1A1	Collagen alpha-1(I) chain	229	251	0.32	0.00E+00
e11777	ANGApGNDGAKGDAGApGApGSQGAPG	COL1A1	Collagen alpha-1(I) chain	699	725	0.26	0.00E+00
e12986	ADGQpGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846	0.30	0.00E+00
e17047	PpGESGREGApGAEGSpGRDGSpGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1008	1041	0.37	0.00E+00
e17690	pPGADGQPGAKGEpGDAGAKGDAGppGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854	0.56	3.73E-21
e17946	PpGPAGFAGPPGADGQPGAKGEpGDAGAKGDAGPPGPAGP	COL1A1	Collagen alpha-1(I) chain	807	846	0.44	8.46E-13
e17890	GPpGADGQPGAKGEpGDAGAKGDAGPPGpAGPAGPPGpIG	COL1A1	Collagen alpha-1(I) chain	815	854	0.44	1.14E-12
e16845	GADGQpGAKGEpGDAGAKGDAGPpGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	0.43	3.01E-12
e04419	ApGDRGEpGPpGPAG	COL1A1	Collagen alpha-1(I) chain	798	812	0.43	3.86E-12
e16606	ADGQpGAKGEpGDAGAKGDAGpPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	819	854	0.42	8.18E-12
e13825	LTGPIGppGPAGAPGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	765	794	0.41	5.75E-11
e11415	IGPpGPAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794	0.40	1.83E-10
e10277	nGDDGEAGKpGRPGERGPPGp	COL1A1	Collagen alpha-1(I) chain	229	249	-0.39	4.15E-10
e16771	GADGQpGAKGEpGDAGAKGDAGPPGPAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	818	854	0.38	1.54E-09
e02592	DDGEAGKpGRpG	COL1A1	Collagen alpha-1(I) chain	231	242	0.37	2.66E-09
e16548	ADGQpGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	819	854	0.37	3.04E-09
e16966	PpGESGREGApGAEGSpGRDGSPGAKGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1008	1041	0.36	1.32E-08
e17626	pPGADGQPGAKGEpGDAGAKGDAGPpGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	816	854	0.35	1.80E-08
e11902	ANGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	699	725	0.34	7.79E-08
e09627	PpGPpGKNGDDGEAGKpGRp	COL1A1	Collagen alpha-1(I) chain	222	241	0.34	8.10E-08
e17348	ppGESGREGAPGAEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1008	1042	0.31	7.27E-07
e06186	SpGSPGpDGKTGPPGpAG	COL1A1	Collagen alpha-1(I) chain	543	560	0.30	1.42E-06
e08755	EGSpGRDGSpGAKGDRGET	COL1A1	Collagen alpha-1(I) chain	1021	1039	0.30	1.61E-06
e07678	TGSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	541	560	0.28	8.07E-06
e06709	GSpGSpGPDGKTGPpGPAG	COL1A1	Collagen alpha-1(I) chain	542	560	0.28	8.92E-06
e07275	NGApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	700	719	0.28	9.67E-06
e17949	GEPGPPGPAGFAGPPGADGQPGAKGEPGDAGAKGDAGPpG	COL1A1	Collagen alpha-1(I) chain	803	842	0.28	9.78E-06
e13200	TGPIGpPGPAGAPGDKGESGpSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	766	794	0.28	1.37E-05
e06024	SpGSPGPDGKTGpPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560	0.27	1.86E-05
e13065	ADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	819	846	0.27	2.48E-05
e14583	pPGADGQpGAKGEpGDAGAKGDAGPpGPAGP	COL1A1	Collagen alpha-1(I) chain	816	846	0.27	2.79E-05
e18831	DKGETGEQGDRGIKGHRGFSGLQGppGppGSPGEQGP	COL1A1	Collagen alpha-1(I) chain	1095	1131	-0.26	3.76E-05
e14837	ERGSpGPAGPKGSpGEAGRpGEAGLpGAKG	COL1A1	Collagen alpha-1(I) chain	510	539	-0.26	3.80E-05
e13056	AGpPGApGApGAPGpVGPAGKSGDRGET	COL1A1	Collagen alpha-1(I) chain	1042	1069	0.26	6.10E-05
e11193	NSGEpGApGSKGDTGAkGEpGPVG	COL1A1	Collagen alpha-1(I) chain	432	455	0.25	7.70E-05
e18625	AAGEpGKAGERGVPGppGAVGPAGKDGEAGAQGpPGPAGPAG	COL1A1	Collagen alpha-1(I) chain	588	629	0.24	1.27E-04
e11527	IGPpGpAGApGDKGESGPSGPAGPTG	COL1A1	Collagen alpha-1(I) chain	769	794	0.24	1.49E-04

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e05551	VGPpGPPGPpGPpGPPS	COL1A1	Collagen alpha-1(I) chain	1177	1193	0.24	1.66E-04
e06650	EGSpGRDGSpGAKGDRG	COL1A1	Collagen alpha-1(I) chain	1021	1037	0.24	1.87E-04
e08228	GEpGSpGENGApGQMGPRG	COL1A1	Collagen alpha-1(I) chain	287	305	0.24	1.96E-04
e01399	DGRpGPpGPpG	COL1A1	Collagen alpha-1(I) chain	562	572	0.24	2.01E-04
e16015	NVGApGAKGARGSAGpPGATGFpGAAGRVGPpGP	COL1A1	Collagen alpha-1(I) chain	855	888	-0.24	2.07E-04
e18580	FAGpPGADGQPGAKGEpGDAGAKGDAGpPGPAGPAGPPGPIG	COL1A1	Collagen alpha-1(I) chain	813	854	0.23	3.06E-04
e12851	LDGAKGDAGPAGPKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299	0.23	3.39E-04
e11002	AEGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1020	1042	0.23	3.70E-04
e00467	DGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	550	559	0.23	3.83E-04
e12949	LDGAKGDAGPAGpKGEpGSpGENGApG	COL1A1	Collagen alpha-1(I) chain	273	299	0.23	4.07E-04
e01213	pGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	799	808	0.22	4.39E-04
e08888	pQGpGGPPGpKGNSGEPGApG	COL1A1	Collagen alpha-1(I) chain	420	440	0.22	4.72E-04
e12011	GpAGPpGEAGKPGEQGVPGDLGAPGP	COL1A1	Collagen alpha-1(I) chain	647	672	0.22	6.61E-04
e13850	PpGKNGDDGEAGKPGRpGERGppGPQ	COL1A1	Collagen alpha-1(I) chain	225	250	0.21	1.00E-03
e07917	DGEAGKPGRpGERGpPGP	COL1A1	Collagen alpha-1(I) chain	232	249	-0.21	1.00E-03
e10829	DGKTGpPGPAGQDGRpGPpGPpG	COL1A1	Collagen alpha-1(I) chain	550	572	0.21	1.00E-03
e05423	VGpPGPPGpPGPPGPPS	COL1A1	Collagen alpha-1(I) chain	1177	1193	0.20	1.80E-03
e13817	AGPpGAPGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1042	1071	-0.20	2.00E-03
e04666	GPpGEAGKpGEQGVP	COL1A1	Collagen alpha-1(I) chain	650	664	-0.20	2.00E-03
e12508	KGNSGEpGAPGSKGDTGAKGEpGpVG	COL1A1	Collagen alpha-1(I) chain	430	455	-0.20	2.05E-03
e12366	GANGApGNDGAKGDAGApGApGSQGApG	COL1A1	Collagen alpha-1(I) chain	698	725	0.20	2.11E-03
e13673	PpGADGQpGAKGEpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	816	844	0.19	2.53E-03
e17825	GPpGADGQPGAKGEPGDAGAKGDAGPPGpAGPAGPpGPIG	COL1A1	Collagen alpha-1(I) chain	815	854	0.19	2.95E-03
e10554	EGSpGRDGSpGAKGDRGETGPA	COL1A1	Collagen alpha-1(I) chain	1021	1042	0.19	3.08E-03
e03638	SpGSpGPDGKTGPp	COL1A1	Collagen alpha-1(I) chain	543	556	0.19	3.30E-03
e09923	NSGEPGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453	-0.19	3.66E-03
e10953	DGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	820	843	-0.19	3.72E-03
e15883	NSGEpGApGSKGDTGAKGEpGPVGVQGPpGPAG	COL1A1	Collagen alpha-1(I) chain	432	464	0.19	3.81E-03
e12661	GKNGDDGEAGKPGRpGERGPpGpQ	COL1A1	Collagen alpha-1(I) chain	227	250	0.18	4.00E-03
e14501	pPGADGQPGAKGEpGDAGAKGDAGpPGPAGP	COL1A1	Collagen alpha-1(I) chain	816	846	0.18	4.10E-03
e13730	AGPpGAPGApGAPGPVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1042	1071	-0.18	5.25E-03
e06309	VGPpGPpGPpGPpGPPSA	COL1A1	Collagen alpha-1(I) chain	1177	1194	0.18	5.33E-03
e01758	ApGDRGEpGPp	COL1A1	Collagen alpha-1(I) chain	798	808	0.17	7.06E-03
e01461	SpGEAGRpGEA	COL1A1	Collagen alpha-1(I) chain	522	532	-0.17	7.18E-03
e13918	AGpPGApGApGAPGpVGPAGKSGDRGETGP	COL1A1	Collagen alpha-1(I) chain	1042	1071	-0.17	7.24E-03
e10875	GEQGPSGASGpAGpRGpPGSAGApG	COL1A1	Collagen alpha-1(I) chain	1127	1151	0.17	7.59E-03
e01100	DRGEpGPpGP	COL1A1	Collagen alpha-1(I) chain	801	810	0.17	8.00E-03
e14847	FAGPpGADGQpGAKGEpGDAGAKGDAGPpGP	COL1A1	Collagen alpha-1(I) chain	813	843	0.17	9.48E-03
e06176	VGPpGPpGPPGPpGPPSA	COL1A1	Collagen alpha-1(I) chain	1177	1194	0.16	1.20E-02
e03890	ApGDRGEpGPpGPA	COL1A1	Collagen alpha-1(I) chain	798	811	0.16	1.26E-02
e06547	GSpGSpGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	542	560	0.16	1.40E-02
e13322	GPpGKNGDDGEAGKpGRpGERGPPGP	COL1A1	Collagen alpha-1(I) chain	224	249	-0.16	1.47E-02
e04497	GRpGEVGPpGPpGPA	COL1A1	Collagen alpha-1(I) chain	917	931	-0.15	1.70E-02
e09124	SGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	433	453	-0.15	1.90E-02
e05353	GPpGKNGDDGEAGKpG	COL1A1	Collagen alpha-1(I) chain	224	239	0.15	1.92E-02

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e13410	GPpGKNGDDGEAGKpGRPGERGppGP	COL1A1	Collagen alpha-1(I) chain	224	249	-0.15	2.15E-02
e12101	ADGQpGAKGEpGDAGAKGDAGPpGpA	COL1A1	Collagen alpha-1(I) chain	819	844	0.14	2.90E-02
e10135	SGNAGPpGPpGPAGKEGGKGPRG	COL1A1	Collagen alpha-1(I) chain	889	911	0.14	3.30E-02
e05879	SpGSPGPDGKTGPPGPAG	COL1A1	Collagen alpha-1(I) chain	543	560	0.14	3.31E-02
e03372	DGQPGAKGEpGDAG	COL1A1	Collagen alpha-1(I) chain	820	833	0.13	3.80E-02
e05703	ApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	702	719	0.13	4.50E-02
e11286	KGNSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	430	453	-0.13	4.88E-02
e19986	ARGNDGATGAAGPpGPTGPAGPpGFpGAVGAKGEAGPQGPRGSEGPQG	COL1A1	Collagen alpha-1(I) chain	321	368	-0.12	6.50E-02
e02517	QDGRpGpPGPpG	COL1A1	Collagen alpha-1(I) chain	561	572	0.12	6.76E-02
e10657	AEGSpGRDGSpGAKGDRGETGp	COL1A1	Collagen alpha-1(I) chain	1020	1041	0.12	7.10E-02
e03025	GQDGRpGPpGpPG	COL1A1	Collagen alpha-1(I) chain	560	572	0.11	8.83E-02
e07132	EpGSpGENGAPGQmGPR	COL1A1	Collagen alpha-1(I) chain	288	304	0.10	1.17E-01
e05448	EpGDAGAKGDAGPpGPA	COL1A1	Collagen alpha-1(I) chain	828	844	0.10	1.32E-01
e04947	EpGKAGERGVPGpPG	COL1A1	Collagen alpha-1(I) chain	591	605	0.09	1.63E-01
e11850	ADGQPGAKGEpGDAGAKGDAGPPGpA	COL1A1	Collagen alpha-1(I) chain	819	844	0.09	1.70E-01
e03322	SpGPDGKTGPpGPA	COL1A1	Collagen alpha-1(I) chain	546	559	0.09	1.84E-01
e11940	GESGREGApGAEGSpGRDGSpGAKG	COL1A1	Collagen alpha-1(I) chain	1010	1034	0.08	2.05E-01
e11452	ADGQpGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843	0.07	2.82E-01
e01166	DGRPGPPGPpG	COL1A1	Collagen alpha-1(I) chain	562	572	-0.06	3.32E-01
e08629	TGPIGpPGPAGApGDKGESGP	COL1A1	Collagen alpha-1(I) chain	766	786	-0.05	4.26E-01
e07944	GpPGEAGKpGEQGVpGDLG	COL1A1	Collagen alpha-1(I) chain	650	668	0.05	4.55E-01
e10025	NSGEpGApGSKGDTGAKGEpGP	COL1A1	Collagen alpha-1(I) chain	432	453	-0.05	4.75E-01
e08462	GANGApGNDGAKGDAGApGApG	COL1A1	Collagen alpha-1(I) chain	698	719	0.04	5.35E-01
e11325	ADGQPGAKGEpGDAGAKGDAGPPGp	COL1A1	Collagen alpha-1(I) chain	819	843	-0.04	5.54E-01
e01155	ApGDKGESGPS	COL1A1	Collagen alpha-1(I) chain	777	787	0.04	5.78E-01
e17438	AGRpGEVGpPGpPGPAGEKGSPGADGPAGAPGTPGPQG	COL1A1	Collagen alpha-1(I) chain	916	953	0.02	7.39E-01
e06520	NSGEpGApGSKGDTGAKG	COL1A1	Collagen alpha-1(I) chain	432	449	0.01	9.11E-01
e04843	GPpGpPGPpGpPGPPS	COL1A1	Collagen alpha-1(I) chain	1178	1193	0.00	9.69E-01
e15593	NGEAGSAGpPGppGLRGSpGSRGLPGADGRAG	COL1A2	Collagen alpha-2(I) chain	384	415	0.49	3.72E-16
e15400	LkGQpGApGVkGEpGApGENGTpGQTGARG	COL1A2	Collagen alpha-2(I) chain	188	217	-0.42	1.10E-11
e06154	EDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	143	157	0.41	5.73E-11
e17212	RTGEVGAVGPpGFAGEKGPSGEAGTAGpPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	830	865	0.40	7.13E-11
e11629	AGPpGKAGEDGHpGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	135	157	-0.33	2.18E-07
e19745	SKGESGNKGEpGSAGPQGPpGpSGEEGKRGPNGEAGSAGPPGPpG	COL1A2	Collagen alpha-2(I) chain	353	397	0.32	5.15E-07
e04647	DGPpGRDGQpGHKG	COL1A2	Collagen alpha-2(I) chain	933	946	0.30	1.57E-06
e19107	DQGPVGRTGEVGAVGPpGFAGEKGpSGEAGTAGPPGTpGPQG	COL1A2	Collagen alpha-2(I) chain	824	865	0.29	5.91E-06
e17585	GDPGKNGDKGHAGLAGARGApGPDGNNGAQGPpGPQG	COL1A2	Collagen alpha-2(I) chain	502	538	0.28	9.83E-06
e10318	GEpGPAGSKGESGNKGEpGSAGP	COL1A2	Collagen alpha-2(I) chain	346	368	0.28	9.83E-06
e19752	GEVGPAGpNGFAGpAGAAGQpGAKGERGAKGPKGENGVVGPTGpVG	COL1A2	Collagen alpha-2(I) chain	715	760	0.27	1.87E-05
e09435	GEKGPSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	844	865	0.22	5.14E-04
e13164	AVGPPGFAGEKGpSGEAGTAGPpGTpGP	COL1A2	Collagen alpha-2(I) chain	836	863	0.22	7.62E-04
e09564	GEKGpSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	844	865	0.21	1.34E-03
e12793	GpAGPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	133	157	-0.20	2.22E-03
e11003	GPpGKAGEDGHPGKpGRpGERG	COL1A2	Collagen alpha-2(I) chain	136	157	-0.18	4.60E-03
e10651	PpGKAGEDGHpGKPGRpGERG	COL1A2	Collagen alpha-2(I) chain	137	157	-0.18	5.44E-03

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e07808	KGPSGEAGTAGPpGTpGPQG	COL1A2	Collagen alpha-2(I) chain	846	865	0.17	9.55E-03
e11186	GPpGpAGSRGDGGPpGMTGFpGAAG	COL1A2	Collagen alpha-2(I) chain	769	793	0.16	1.04E-02
e14368	EAGRDGNpGNDGpPGRDGQpGHKGER	COL1A2	Collagen alpha-2(I) chain	923	948	0.12	6.26E-02
e08951	GEKGPSGEAGTAGpPGTpGPQ	COL1A2	Collagen alpha-2(I) chain	844	864	0.11	9.23E-02
e09796	GApGVKGEpGApGENGTPGQTG	COL1A2	Collagen alpha-2(I) chain	193	214	0.09	1.76E-01
e03691	YDGKGVGLGPGPMG	COL1A2	Collagen alpha-2(I) chain	81	94	0.08	2.09E-01
e18516	EVGKpGERGLHGEFGLpGpAGpRGERGPPGESGAAGP	COL1A2	Collagen alpha-2(I) chain	566	602	-0.02	7.93E-01
e15713	pGpLGTKGDRGAPGIPGSPGSRGDpGIGVAGp	COL22A1	Collagen alpha-1(XXII) chain	998	1029	-0.24	1.48E-04
e05677	pGKDGDTGPTGPQGPQ	COL22A1	Collagen alpha-1(XXII) chain	1305	1320	0.19	3.66E-03
e09697	PGpPGPHGPPGpmGPHGLpGP	COL25A1	Collagen alpha-1(XXV) chain	531	551	0.30	1.48E-06
e12714	pAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	949	974	0.49	5.29E-16
e13033	GpAGPPGEKGEPGDDGPSGAEGPpGPQ	COL2A1	Collagen alpha-1(II) chain	948	974	0.36	7.12E-09
e18864	SGPPGRAGEPGLQGPAGPpGEKGEPGDDGpSGAEGPpGPQG	COL2A1	Collagen alpha-1(II) chain	935	975	0.34	9.33E-08
e17673	GpPGPAGFAGpPGADGQpGAKGEQGEAGQKGDAGAPGP	COL2A1	Collagen alpha-1(II) chain	828	865	-0.32	3.72E-07
e01661	DGpSGAEGpPGp	COL2A1	Collagen alpha-1(II) chain	962	973	0.28	1.29E-05
e19147	GAKGEAGAPGVKGESGSpGENGSPGPmGpRGLPGERGRTGP	COL2A1	Collagen alpha-1(II) chain	297	337	-0.27	2.92E-05
e13127	GpAGpPGEKGEPGDDGPSGAEGpPGPQ	COL2A1	Collagen alpha-1(II) chain	948	974	0.25	6.84E-05
e13138	GpEGAQGPRGEpGTpGSPGPAGASGNPG	COL2A1	Collagen alpha-1(II) chain	384	411	0.24	2.16E-04
e12156	GPAGpPGEKGEPGDDGPSGAEGPPGp	COL2A1	Collagen alpha-1(II) chain	948	973	0.23	2.47E-04
e09547	GPpGEGGKpGDQGVpGEAGApG	COL2A1	Collagen alpha-1(II) chain	672	693	0.23	3.52E-04
e04199	PVGpSGKDGANGIpG	COL2A1	Collagen alpha-1(II) chain	1168	1182	0.21	9.47E-04
e12658	AGppGEKGEPGDDGpSGAEGPpGPQG	COL2A1	Collagen alpha-1(II) chain	950	975	0.16	1.19E-02
e06597	DQGASGpAGpSGpRGPpG	COL2A1	Collagen alpha-1(II) chain	1150	1167	-0.09	1.44E-01
e14735	KNGETGPQGPPGpTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	0.54	2.42E-19
e18092	NTGApGSpGVSGpKGDAGQpGEKGSpGAQGpPGAPGpLG	COL3A1	Collagen alpha-1(III) chain	910	948	0.37	3.10E-09
e08188	GNDGApGKNGERGGpGGpGP	COL3A1	Collagen alpha-1(III) chain	585	604	0.36	8.19E-09
e09856	SNGNPGppGPSGSpGKDGPPGp	COL3A1	Collagen alpha-1(III) chain	886	907	0.36	1.12E-08
e06068	NDGApGKNGERGGpGGP	COL3A1	Collagen alpha-1(III) chain	586	602	0.35	1.75E-08
e15411	PQGPpGPTGpGGDKGDTGPpGPQGLQGLpGT	COL3A1	Collagen alpha-1(III) chain	616	646	0.34	6.32E-08
e07676	NDGAPGKNGERGGpGGpGp	COL3A1	Collagen alpha-1(III) chain	586	604	0.33	2.38E-07
e03651	DGApGKNGERGGpG	COL3A1	Collagen alpha-1(III) chain	587	600	0.31	8.15E-07
e14821	KNGETGPQGppGPTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	0.31	8.62E-07
e10781	GDAGApGAPGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	663	687	0.30	2.94E-06
e14644	KNGETGPQGPPGPTGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	610	639	0.29	6.71E-06
e16173	LGSPGpKGDKGEpGGpGADGVPGKDGPRGPTGP	COL3A1	Collagen alpha-1(III) chain	734	766	-0.28	1.29E-05
e01935	DGESGRpGRpG	COL3A1	Collagen alpha-1(III) chain	230	240	0.28	1.39E-05
e13707	GApGQNGEPGGKGERGApGEKGEGGppG	COL3A1	Collagen alpha-1(III) chain	813	840	-0.26	3.60E-05
e10769	SNGNPGppGPSGSpGKDGPpGPAG	COL3A1	Collagen alpha-1(III) chain	886	909	0.21	9.38E-04
e13472	LRGGAGpPGPEGGKGAAGPpGPpGAAGTpG	COL3A1	Collagen alpha-1(III) chain	694	723	0.20	2.14E-03
e01923	SpGERGETGPp	COL3A1	Collagen alpha-1(III) chain	796	806	0.18	4.02E-03
e03922	TGPGGDKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	623	637	-0.18	4.20E-03
e09061	GApGApGGKGDAGAPGERGppG	COL3A1	Collagen alpha-1(III) chain	666	687	-0.18	5.92E-03
e09966	GARGNDGARGSDGQPGPpGPpG	COL3A1	Collagen alpha-1(III) chain	318	339	-0.17	7.35E-03
e05568	TGPGGDKGDTGPpGPQG	COL3A1	Collagen alpha-1(III) chain	623	639	0.16	1.05E-02
e09521	EGGKGAAGpPGPpGAAGTpGLQG	COL3A1	Collagen alpha-1(III) chain	704	726	0.16	1.12E-02

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e12496	AGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	452	477	0.15	1.73E-02
e11904	GPAGFpGApGQNGEpGGKGERGApG	COL3A1	Collagen alpha-1(III) chain	807	831	0.15	2.11E-02
e13566	KNGETGPQGPPGPTGPGGDKGDTGPpGP	COL3A1	Collagen alpha-1(III) chain	610	637	0.11	8.65E-02
e08539	ApGApGGKGDAGApGERGpPG	COL3A1	Collagen alpha-1(III) chain	667	687	-0.11	9.33E-02
e03194	DGVPGKDGPRGPT	COL3A1	Collagen alpha-1(III) chain	752	764	0.10	1.13E-01
e09989	DGESGRpGRpGERGLpGPpG	COL3A1	Collagen alpha-1(III) chain	230	249	0.10	1.16E-01
e07880	pGARGLpGpPGSNGNPGpP	COL3A1	Collagen alpha-1(III) chain	875	893	0.09	1.55E-01
e12235	GQNGEpGGKGERGApGEKGEGGPpG	COL3A1	Collagen alpha-1(III) chain	816	840	-0.07	3.15E-01
e16286	RGERGEAGIpGVpGAKGEDGKDGSpGEpGANG	COL3A1	Collagen alpha-1(III) chain	446	477	-0.01	8.19E-01
e13253	EDGKDGSpGEpGANGLpGAAGERGApG	COL3A1	Collagen alpha-1(III) chain	463	489	-0.01	8.23E-01
e08942	pGFPGTpGLpGmPGHDGAPG	COL4A5	Collagen alpha-5(IV) chain	98	117	0.22	4.62E-04
e09844	GLDGERGRPGPAGppGppGPS	COL4A6	Collagen alpha-6(IV) chain	1240	1260	-0.05	4.74E-01
e03055	GEAGHPGPPGPpGP	COL5A1	Collagen alpha-1(V) chain	1555	1568	0.19	2.41E-03
e14398	PGMPGADGpPGHPGKEGppGEKGGQGpPG	COL5A1	Collagen alpha-1(V) chain	753	781	-0.11	8.23E-02
e11679	EGpPGKPGEDGEpGRNGNpGEVG	COL5A2	Collagen alpha-2(V) chain	257	279	-0.26	3.87E-05
e08177	DGpEGPKGQAGQAGEEGPP	COL5A3	Collagen alpha-3(V) chain	760	778	0.20	1.62E-03
e05200	GPpGPpGFPGDpGPpG	COL5A3	Collagen alpha-3(V) chain	407	422	-0.06	3.67E-01
e05060	GPpGPpGFpGDPGPPG	COL5A3	Collagen alpha-3(V) chain	407	422	0.02	7.40E-01
e16717	DPGLMGERGEDGpAGNGTEGFPGFPGYpGNR	COL6A1	Collagen alpha-1(VI) chain	501	531	-0.24	2.13E-04
e11369	GPpGEPGPRGPRGVpGpEGEpGP	COL6A2	Collagen alpha-2(VI) chain	561	583	0.17	7.98E-03
e03632	GApGLAGpAGpQGpS	COL7A1	Collagen alpha-1(VII) chain	2189	2203	-0.16	1.23E-02
e02311	GpPGPpGPpGPpA	COL8A1	Collagen alpha-1(VIII) chain	560	572	0.07	2.72E-01
e12015	PpGppGPpGVPGSDGIDGDNGPPGK	COL9A2	Collagen alpha-2(IX) chain	23	47	0.29	3.40E-06
e06314	PGpKGEpGKAGpDGpDG	COL9A2	Collagen alpha-2(IX) chain	51	67	0.14	3.36E-02
e00307	GPpGpPGPpG	COL9A2	Collagen alpha-2(IX) chain	33	42	-0.04	4.87E-01
e15390	SQTSQAVTGGHTQIQAGSHTETVEQDR	CRNN	Cornulin	336	362	-0.29	6.75E-06
e14283	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629	-0.41	2.62E-11
e13674	DEAGSEADHEGTHSTKRGHAKSRP	FGA	Fibrinogen alpha chain	605	628	-0.38	9.17E-10
e04994	DEAGSEADHEGTHS	FGA	Fibrinogen alpha chain	605	618	0.37	4.13E-09
e11931	SEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	609	629	-0.33	1.47E-07
e08463	DEAGSEADHEGTHSTKR	FGA	Fibrinogen alpha chain	605	621	0.30	1.61E-06
e07002	DEAGSEADHEGTHSTK	FGA	Fibrinogen alpha chain	605	620	0.29	3.27E-06
e17491	DEAGSEADHEGTHSTKRGHAKSRPV	FGA	Fibrinogen alpha chain	605	629	-0.21	9.31E-04
e02915	DHEGTHSTKRG	FGA	Fibrinogen alpha chain	612	622	-0.14	3.35E-02
e08185	EEAPSLRPAPPPISGGGY	FGB	Fibrinogen beta chain	54	71	0.17	9.64E-03
e06733	AGSEADHEGTHSTKRG	FIBA	Fibrinogen alpha chain	607	622	0.28	1.09E-05
e01784	DGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	7	18	0.33	1.13E-07
e06256	TGLSMDGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	2	18	0.17	7.37E-03
e07648	TGLSMDGGGSPKGDVDPF	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	2	19	0.16	1.41E-02
e05387	GLSMDGGGSPKGDVDP	FXYD2	Sodium/potassium-transporting ATPase subunit gamma	3	18	0.15	2.39E-02
e11826	SETAPAAPAAPAPAEKTPVKKKA	H1-4	Histone H1.4	2	24	-0.04	5.44E-01
e13087	SETAPAETATPAPVEKSPAKKKAT	H1-5	Histone H1.5	2	25	-0.18	4.71E-03
e03285	PEDEEEKKKM	HSP90AB1	Heat shock protein HSP 90-beta	544	553	-0.24	2.00E-04
e13926	DVSTPPTVLPDNFPR	IGF2	Insulin-like growth factor II	93	107	0.19	3.12E-03
e15015	WKADGSPVKAGVETTKPSKQSNNKYA	IGLL5	Immunoglobulin lambda-like polypeptide 5	150	175	-0.35	1.56E-08

AA: Amino acid

Peptide ID	Sequence	Protein Symbol	Protein name	Start AA	Stop AA	Spearman's rank-order correlation	p-values
e09412	GSGGSSYGSGGGSYGSGGGGGGGRG	KRT1	Keratin; type II cytoskeletal 1	526	550	0.31	7.37E-07
e06292	ASYLDKVRALEESN	KRT10	Keratin, type I cytoskeletal 10	158	171	0.34	7.49E-08
e08691	SSSKGSLGGGFSSGGFSGGSF	KRT10	Keratin, type I cytoskeletal 10	37	57	0.12	7.12E-02
e10169	FGASAGTGDLSDNHDIISMK	LMAN2	Vesicular integral-membrane protein VIP36	253	272	-0.29	4.44E-06
e09606	LDTYPNDETTERVFPY	LMAN2	Vesicular integral-membrane protein VIP36	161	176	-0.21	1.00E-03
e08039	FGASAGTGDLSDNHDIIS	LMAN2	Vesicular integral-membrane protein VIP36	253	270	0.05	4.30E-01
e01666	SREPADAAIR	MAN1A1	Mannosyl-oligosaccharide 1;2-alpha-mannosidase IA	184	193	0.22	7.16E-04
e11919	QSKHPGDFGADAQGAMNKALEL	MB	Myoglobin	117	138	-0.11	8.97E-02
e17804	TTLSPSSSTTHEGEPTTFQSWPSSKDTSPAPSG	MUC12	Mucin-12	404	436	0.30	1.48E-06
e12382	DGLSPDQTRSEDPQNSAGSPPDA	MYOCD	Myocardin	160	182	0.19	3.31E-03
e03544	KELDINTDGAVN	S100A8	Protein S100-A8	56	67	0.08	2.25E-01
e05899	SAPYPGGGGNGASGGGSGGS	PCDH7	Protocadherin-7	203	222	0.16	1.36E-02
e07343	DHDVGSELPPEGVLGAL	PCSK1N	ProSAAS	223	239	0.09	1.65E-01
e18732	LFAEEKAVADTRDQADGSRASVDSGSSEEQGGSSRA	PIGR	Polymeric-immunoglobulin receptor	604	639	-0.18	4.51E-03
e14638	AVADTRDQADGSRASVDSGSSEEQGGSS	PIGR	Polymeric-immunoglobulin receptor	610	637	0.12	6.35E-02
e15907	AVADTRDQADGSRASVDSGSSEEQGGSSRA	PIGR	Polymeric-immunoglobulin receptor	610	639	0.01	9.30E-01
e19279	TSPSGQLIPVKNLSENIEIL	PK1L2	Polycystic kidney disease protein 1-like 2	1142	1161	0.29	3.48E-06
e14937	DQAANEWGRSGKDPNHFRPAGLPEK	SAA1	Serum amyloid A-1 protein	97	121	-0.48	2.00E-15
e09609	LTGRGAEDSLADQAANKWG	SAA2	Serum amyloid A-2 protein	86	104	-0.34	6.15E-08
e06246	LTGRGAEDSLADQAAN	SAA2	Serum amyloid A-2 protein	86	101	0.20	1.46E-03
e12387	HLVGHQRNNRQVTLEVSGAEP	SECTM1	Secreted and transmembrane protein 1	118	138	-0.39	4.46E-10
e05742	DITSHMESEELNGA	SPP1	Osteopontin	188	201	0.19	3.11E-03
e20740	sDKPDMAEIEKFDKSKLKKTETQEKNPLPSKETIEQEKQAGES	TMSB4X	Thymosin beta-4	2	44	-0.38	9.59E-10
e02332	SGSVIDQSRVL	UMOD	Uromodulin	589	599	0.31	1.09E-06
e00923	VLNLGPITR	UMOD	Uromodulin	598	606	0.25	8.96E-05
e06451	SVIDQSRVLNLGPIT	UMOD	Uromodulin	591	605	0.23	4.19E-04
e07964	SVIDQSRVLNLGPITR	UMOD	Uromodulin	591	606	0.20	2.17E-03
e07848	SGSVIDQSRVLNLGPIT	UMOD	Uromodulin	589	605	0.19	3.04E-03
e08455	GSVIDQSRVLNLGPITR	UMOD	Uromodulin	590	606	0.18	6.00E-03
e10189	SGSVIDQSRVLNLGPITRK	UMOD	Uromodulin	589	607	0.11	9.27E-02
e09213	SGSVIDQSRVLNLGPITR	UMOD	Uromodulin	589	606	0.03	6.86E-01
e18782	GRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAPEVRGA	VGF	Neurosecretory protein VGF	26	62	-0.22	6.33E-04
e07573	ESVVLEPEAT	X3CL1	Fractalkine	123	132	0.06	3.63E-01

AA: Amino acid

Supplementary S3 Table. List of predicted proteases with calculated activity scores. (PLoS One. 2022 Jan 19;17(1):e0262667. doi: 10.1371/journal.pone.0262667).

The 16 proteases with > 1% of proteolytic cleavage events.								
Proteases	**Downregulated peptides**	**Upregulated peptides**	**All peptides**	**freq%(up)**	**freq%(down)**	**%freq [% frequency difference ratio]**	**Weight**	**Score**
MMP13	18	2	20	0.10	0.90	-80.00	0.28	-22.44
MMP9	16	4	20	0.20	0.80	-60.00	0.31	-18.47
MMP2	11	2	13	0.15	0.85	-69.23	0.19	-13.28
MMP14	6	0	6	0.00	1.00	-100.00	0.08	-7.59
MMP3	5	0	5	0.00	1.00	-100.00	0.06	-6.33
MMP12	5	0	5	0.00	1.00	-100.00	0.06	-6.33
MMP20	4	0	4	0.00	1.00	-100.00	0.05	-5.06
MMP8	4	1	5	0.20	0.80	-60.00	0.08	-4.62
MMP1	2	1	3	0.33	0.67	-33.33	0.05	-1.72
MMP26	1	1	2	0.50	0.50	0.00	0.04	0.00
MMP7	0	2	2	1.00	0.00	100.00	0.05	5.26
PCSK7	1	4	5	0.80	0.20	60.00	0.12	7.08
PCSK6	1	4	5	0.80	0.20	60.00	0.12	7.08
PCSK5	1	4	5	0.80	0.20	60.00	0.12	7.08
PCSK4	1	4	5	0.80	0.20	60.00	0.12	7.08
KLK4	0	4	4	1.00	0.00	100.00	0.11	10.53
The 8 proteases with < 1% of proteolytic cleavage events.								
FURIN	1	0	1	0.00	1.00	-100.00	0.01	-1.27
PCSK2	1	0	1	0.00	1.00	-100.00	0.01	-1.27
MMP16	1	0	1	0.00	1.00	-100.00	0.01	-1.27
TMPRSS6	0	1	1	1.00	0.00	100.00	0.03	2.63
MMP25	0	1	1	1.00	0.00	100.00	0.03	2.63
GZMM	0	1	1	1.00	0.00	100.00	0.03	2.63
CTSB	0	1	1	1.00	0.00	100.00	0.03	2.63
CMA1	0	1	1	1.00	0.00	100.00	0.03	2.63

freq% (up): Frequency % (upregulated), freq% (down): Frequency % (downregulated)

6. Acknowledgement

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Affidavit according to §5(1) for Data Retention

I hereby declare that the original data forming the basis of this doctoral thesis are stored

-by me personally, ***Eleni Petra, Roussospiti, Rethymno, Crete, 74150, Greece***

Affidavit according to § 5 (1) and (2), and § 11 (3) 12 of the doctoral studies regulations

I, **Eleni Petra,** hereby declare on oath that I have contributed a significant part, and thus majority, of the publication:

Eleni Petra, Tianlin He, Vasiliki Lygirou, Agnieszka Latosinska, Harald Mischak, Antonia Vlahou, Joachim Jankowski (2021)**:** Urine peptidome analysis in cardiorenal syndrome reflects molecular processes; *Scientific Reports*; 11(1):16219. doi:10.1038/s41598-021-95695-z.

The contributions to the publication were as follows:

	Eleni Petra	Tianlin He	Vasiliki Lygirou	Agnieszka Latosinska	Harald Mischak	Antonia Vlahou	Joachim Jankowski	Sum (%)
Study supervision						80	20	100
Study design/conception	20				20	30	30	100
Data evaluation	100							100
Performing experiments	95		5					100
Statistical evaluation	100							100
Delivery of materials		25		25	50			100
Interpretation of data evaluation	100							100
Writing/draft of the manuscript	100							100
Correction of the manuscript	10	10	10	10	10	25	25	100

The position as the first author obviously arises from this significant contribution.

_____

Signature of the doctoral candidate

As supervisor and/or corresponding author I confirm the statements of **Eleni Petra** and as a representative of the collaborative partners.

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Signature of the doctoral supervisor

As co-author I endorse the statement of Prof. Dr. Joachim Jankowski

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Affidavit according to § 5 (1) and (2), and § 11 (3) 12 of the doctoral studies regulations

I, **Eleni Petra**, hereby declare on oath that I have contributed a significant part, and thus majority, of the publication:

Eleni Petra, Justyna Siwy, Antonia Vlahou, Joachim Jankowski (2022)**:** Urine peptidome in combination with transcriptomics analysis highlights MMP7, MMP14 and PCSK5 for further investigation in chronic kidney disease; *Plos One*;17(1):e0262667. doi:10.1371/journal.pone.0262667.

The contributions to the publication were as follows:

	Eleni Petra	Justyna Siwy	Antonia Vlahou	Joachim Jankowski	Sum (%)
Study supervision			80	20	100
Study design/conception	50		25	25	100
Data evaluation	100				100
Performing experiments	100				100
Statistical Evaluation	100				100
Delivery of Materials		100			100
Interpretation of data evaluation	100				100
Writing/draft of the manuscript	100				100
Correction of the Manuscript	15	15	35	35	100

The position as the first author obviously arises from this significant contribution.

Signature of the doctoral candidate

As supervisor and/or corresponding author I confirm the statements of **Eleni Petra** and as a representative of the collaborative partners

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Dr. Justyna Siwy Prof. Dr. Antonia Vlahou

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09/2006-07/2010: BSc (Hons) in Genetics-Immunology, The School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, UK

09/2012-09/2013: MSc in Molecular Medicine, Faculty of Medicine, Imperial College London, UK

09/2014-12/2017: Research Assistant, Spanish National Centre for Cardiovascular Research (CNIC) - working group of Prof. Dr. Juan Bernal (Madrid, Spain)

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Feb 2021: Cardiorenal Winter School, **oral presentation**, 'Efforts to differentiate the cardiorenal syndrome from heart failure and chronic kidney disease on a molecular level', Eleni Petra, Tianlin He, Agnieszka Latosinska, Vasiliki Lygiriou, Harald Mischak, Antonia Vlahou and Joachim Jankowski, **Online**, **due to COVID19 pandemic**

May 2020: 57th ERA-EDTA Congress, **poster presentation**, 'Urine peptidome analysis in heart failure, chronic kidney disease and cardiorenal syndrome towards the definition of disease-specific markers', Eleni Petra, Tianlin He, Agnieszka Latosinska, Rafael Stroggilos, Harald Mischak and Antonia Vlahou, **Online**, **due to COVID19 pandemic**

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July 2019: Proteomics bioinformatics (training course), **poster presentation**, 'Plasma and tissue proteomics to identify cardiorenal syndrome biomarkers', Eleni Petra, Jerome Zoidakis and Antonia Vlahou, **EMBL-EBI**, **Cambridge**, **UK**

May 2019: 45th Annual Panhellenic Medical Conference, **oral presentation**, 'Protein biomarkers for cardiorenal syndrome', Eleni Petra, Jerome Zoidakis and Antonia Vlahou, **Athens**, **Greece**

Mar 2019: European Uremic Toxin (EUTox) working group meeting 2019, **oral presentation**, 'Elucidating the cardiorenal syndrome (CRS). Molecular phenotype by proteomics', Eleni Petra, Georgia Kontostathi, Manousos Makridakis, Flore Duraton, Angel Argiles, Jerome Zoidakis and Antonia Vlahou, **Vaals**, **The Netherlands**

Mar 2019: Cardiorenal Winter School, **oral and poster presentations**, 'Elucidating the cardiorenal syndrome (CRS). Molecular phenotype by proteomics', Eleni Petra, Georgia Kontostathi, Manousos Makridakis, Flore Duraton, Angel Argiles, Jerome Zoidakis and Antonia Vlahou, **Aachen**, **Germany**

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Training courses/seminars

Feb 2021-May 2021: Data science, online course, Hannover, Germany

Sep 2020-Feb 2021: Medical statistics, online course, Vienna, Austria

July 2019: Proteomics bioinformatics, EMBL-EBI, Cambridge, UK

Mar 2019-June 2019: IBM SPSS statistics software, Athens, Greece

Skills

Molecular Biology: DNA/RNA/protein extraction (cells and tissues samples), gel electrophoresis (agarose), western blot, PCR, RT-qPCR

Cell Biology: cell culture (cell culture maintenance: HEK293 and HL-1), transfection, immunofluorescence, immunohistochemistry, fluorescence and confocal microscopes, image analysis (ImageJ), flow cytometry (FACS) and analysis (FlowJo), cell sorting

Animal models: mouse handling and dissection, oral gavage, maintenance and culture of *C. elegans*

Bioinformatics tools for –omics data: proteomics data handling, bioinformatics software: GeneCards: The Human Gene Database, ProteomicsDB, Uniprot, Nephroseq, The Human Protein Atlas, Reactome Pathway Database, KEGG PATHWAY Database, STRING Database, IntAct Molecular Interaction Database, GOrilla, Proteasix, Metascape, Cytoscape, Skyline, SPSS software and GraphPad Prism software

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