Differences on salivary proteome at rest and in response to an acute exercise in men and women: a pilot study

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Compliance with Ethical Standards

Conflict of Interest: Lorena Franco-Martínez declares that she has no conflict of interest. Jorge Miguel González Hernández declares that he has no conflict of interest. Anita Horvatić declares that she has no conflict of interest. Nicolas Guillemin declares that he has no conflict of interest. José Cerón declares that he has no conflict of interest. Silvia Martínez-Subiela declares that she has no conflict of interest. Miguel Ángel Sentandreu declares that he has no conflict of interest. Mirna Brkljačić declares that she has no conflict of interest. Vladimir Mrljak declares that he has no conflict of interest. Asta Tvarijonaviciute declares that she has no conflict of interest. Pedro Jiménez Reyes declares that he has no conflict of interest.

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Abstract

The aim of the present study was to evaluate the differences in salivary proteome at rest and in response to an acute exercise in men and women. For this, unstimulated whole saliva samples in rest and after a bout resistance exercise leading to failure (ELF) of both men and women (n = 5 for each sex) were subjected to isobaric Tandem Mass Tags (TMT) labelling followed by LC-MS/MS. A total of 274 proteins were identified and met the inclusion criteria. 16 proteins were modulated for the interaction sex*exercise, 6 were modulated because of the exercise, and 65 were differentially expressed between men and women at rest. In conclusion, these results indicate sex-related differences in the salivary proteome at rest and after an acute exercise, pointing out possible candidate biomarkers for sports performance and allowing further knowledge of the physiological processes occurring during ELF.

Significance

The present study describes for the first time the changes that occur in salivary proteome detected by TMT-based proteomics in response to an acute exercise and the differences in these changes depending on sex. Of the 274 protein identified, the 87 differentially expressed proteins and their related pathways were discussed, focusing on the sex- and exercise-related differences in the salivary proteome.

Keywords: exercise, label-based proteomics, resistance training, saliva, sex influence.

1. Introduction

Whole saliva is a non-invasive and easily accessible biological fluid which is composed mainly of the secretions of the salivary glands, gingival crevicular fluid, microorganisms, cell debris, and bronchoalveolar and nasal secretions [1]. This biofluid is easier to collect, safer for the personnel and the patient, pain-free and causes low-to-none stress associated with sampling in comparison to blood collection. For this reason, there is a growing interest in the saliva as a sample of choice for the evaluation of physiological and physiopathological processes, as well as for the screening of biomarkers that may reflect local and systemic health status. However, there are many factors that may influence saliva composition such as sex, age, taste stimulation, circadian rhythms, or inter-individual variability [2,3].

Proteomic analyses are ideal to get a general picture of protein composition of the sample (proteome) and to detect subtle differences due to different conditions since all proteins can be analysed simultaneously. In the last years, novel proteomic technologies such as the use of isobaric Tandem Mass Tags (TMT, Thermo Fisher) have greatly increased the sensitivity of the analysis in saliva. Therefore, this technology could help to increase the number of proteins identified in comparison with gel-based techniques. Up to date, sex-related differences have been described in sport response and recovery, especially related to differences in muscle blood flow, velocity of contraction, muscle strength, muscle groups involved or the intensity of the exercise [4,5]. However, to the best of the author's knowledge, no studies have been made to identify possible sex-and exercise-related differences in the salivary proteome.

Resistance training is widely performed for improving strength, power, and hypertrophy. Exercise leading to failure (ELF) is a resistance training usually employed in order to improve muscular strength and hypertrophy [6,7]. After acute exercise such as ELF, muscular tissue may be damaged by metabolic and mechanical factors and would leak intracellular components such as creatine kinase, myoglobin, or troponin, among others, into the extracellular compartment [8]. These leaked intracellular compounds would spread through the blood torrent and subsequently could reach saliva by active or passive flow [9]. Therefore, resistance training could be a suitable model for the evaluation of changes of proteins in saliva that can be produced after an acute exercise.

Taking overall, we hypothesize that salivary proteome could change after an intensive exercise in a sex-dependent manner. Therefore, the objective of the present work was to study the possible sex influence on salivary proteome at rest and after an acute session of exercise leading to failure. This data could improve the understanding of the biological differences among sexes in salivary composition, as well as enhance the potential of saliva for biomarker discovery in sports sciences.

2. Materials and methods

2.1. Participants and study design

A total of ten trained individuals volunteered to participate in the study, five men (age 23.6 ± 1.5 , height 178.2 ± 6.6 cm, body mass 76.5 ± 9.9 kg) and five women (age 25.6 ± 5.1 , height 167.2 ± 2.5 cm, body mass 60.2 ± 6.9 kg). All subjects were physically active sports science students with resistance training

and full squat exercise experience. Participants were healthy and injury-free for at least the last year and they did not take any medications, drugs or supplements that could influence physical performance. Participants were fully informed of any possible risks and discomforts related to the experimental procedures and signed the written informed consent to participate in the study. The present study was approved by the local ethical committee of the Catholic University of San Antonio (Murcia) in agreement with the Declaration of Helsinki.

Participants were asked not to exercise during the day before or the same day of the experiment. They were also asked not to eat, drink, smoke, or brush their teeth one hour prior to their participation in the study. In addition, the intake of caffeine was forbidden before the sessions. Unstimulated whole saliva was collected for 1 minute by passive drool under supervision before (rest group, T0) and 24 hours (T1) after the ELF protocol.

The ELF protocol consisted of 6 sets of 10 repetitions maximum (RM) of full squat with 10RM load, and 5 minutes of inter-set rest. Three familiarization sessions with saliva extraction and full squat technique exercise were performed prior to the study. Sessions were achieved in the morning between 8-10 am, and under constant environmental conditions (20°C and 60% humidity). Immediately after the collection, saliva was stored on ice until arrival at the laboratory, centrifuged (4000 x g, 10 min, 4°C) and the supernatant was immediately transferred to 1.5 mL Eppendorf tubes and stored at -80°C until analysis.

2.2. TMT-based proteomic analysis

From each sample, TMT-based proteomic analysis was performed according to the manufacturer's instructions (Thermo Scientific), with minor modifications. Briefly, 150µl of whole saliva from each sample was individually precipitated in ice-cold acetone (1:6) (VWR, Pennsylvania, USA) overnight at -20°C. The samples were centrifuged, the pellet was resuspended in 100 mM TEAB 10% SDS buffer and protein concentration was calculated using Bradford assay [10]. Then, 35 µg of each sample acetone-precipitated proteins as well as internal standards consisting of pools of 35 µg of acetone-precipitated from all samples were reduced with 200 mM DTT (Sigma-Aldrich) for one hour at 55°C, alkylated with 375 mM iodoacetamide (Sigma- Aldrich) for 30 minutes at room temperature and dark, and precipitated with ice-cold acetone (1:6) overnight at -20°C. Samples were then centrifuged and acetone was decanted. Pellets were resuspended with 50 µL of 100 mM TEAB buffer and digested with trypsin (Promega) overnight at 37°C, according to manufacturer's instructions. Each 0.8 mg vial of TMT label reagents were equilibrated to room temperature, resuspended in 41 µl anhydrous acetonitrile LC-MS grade (Thermo Scientific) and added to each sample and internal standard. Labelling reaction was incubated for 1 hour at room temperature and quenched by adding 5% hydroxylamine (Thermo Scientific) for 15 minutes. Samples were then combined at equal volume and 5 µg of each mixed sample was vacuum-dried and stored at -80°C before further LC-MS/MS analysis.

The LC-MS/MS analysis was performed on Dionex Ultimate 3000 RSLC nanoflow system (Dionex, Camberley, UK) and Q Exactive Plus mass spectrometer (Thermo Fisher Scientific) as described elsewhere [11]. SEQUEST algorithm, Proteome Discoverer (version 2.0., Thermo Fisher Scientific), was used for peptide identification and relative quantification. Database search against Homo Sapiens FASTA

files, NCBI database, was performed considering two trypsin missed cleavage sites, precursor and fragment mass tolerances of 10 ppm and 0.02 Da, respectively. Percolator algorithm in the Proteome Discoverer workflow based on the search results against a decoy database was used to determine the false discovery rate (FDR) for peptide identification. FDR was set at 1%.

2.4. Alpha-amylase verification

For alpha-amylase verification, saliva samples (12 men, 12 women) at rest were used. Alpha-amylase (sAA) activity in saliva was measured using a colorimetric commercial kit (Alpha-Amylase, Beckman Coulter Inc., Fullerton, CA, USA) following the International Medicine (IFCC) method [12], which was previously validated [13]. Results for sAA were expressed in UI/L.

2.5. Statistical analysis

First, proteins with less than two unique peptides and the ones with 30% or more missing data were removed from further analysis. Univariate analysis of variance (ANOVA) was performed to evaluate the effect of the interaction of exercise (before and after exercise leading to failure) and sex (men and women) on salivary biomarkers identified by proteomic analysis. To evaluate possible differences in salivary biomarkers between the two sexes at rest, Mann-Whitney test was performed. Missing values were replaced with 1/3 of the minimum amount detected for each protein. In all cases, values of $P < 0.05$ were considered to be significant. The results for sAA were evaluated for normality of distribution using D'Agostino and Pearson omnibus normality test. Since not all data were normally distributed, unpaired two-tails Mann-Whitney U tests were used to compare sAA concentration.

Statistics were performed with SPSS software 22 (SPSS Inc, IBM, IL, USA).

2.6. GO pathways

Genes encoding the differentially expressed proteins with respect to exercise and sex were used to determine their associated GO terms using Protein Analysis Through Evolutionary Relationships (PANTHER) classification tool (<http://www.pantherdb.org/>).

3. Results

The high-resolution quantitative proteomic analysis allowed the identification of 274 proteins (at least 2 unique peptides, present in at least 70% of samples and NMT 5% FDR) in the whole saliva samples (Supplementary Table 1). Of those, a total of 87 proteins were found to be differentially modulated in saliva.

3.1. Proteins differentially modulated by exercise

Six proteins changed significantly in abundance after the exercise, showing 0.87 to 0.19- fold lower abundance after the ELF protocol (Table 1). According to PANTHER classification system, 5 genes were

identified corresponding to 4 molecular functions namely binding (50%), catalytic activity, molecular function regulator, and structural molecule activity (16.7% for each case). These genes were involved in 24 pathways hits, classified in 8 categories specifically Alzheimer disease-presenilin pathway, cadherin signaling pathway, cytoskeletal regulation by Rho GTPase, Huntington disease, inflammation mediated by chemokine and cytokine signaling pathway, integrin signalling pathway, nicotinic acetylcholine receptor signaling pathway, and wnt signaling pathway (12.5% for each pathway).

Table 1. Proteins differentially modulated in saliva between pre- and post-exercise measurements.

Accession	Description	Pre (min - max)	Post (min -max)	P
P68133	Actin, alpha skeletal muscle	(0.23 - 1.45)	(0.23 - 1.08)	0.036
P62736	Actin, aortic smooth muscle	(0.23 - 1.45)	(0.23 - 1.08)	0.036
P63267-1	Actin, gamma-enteric smooth muscle	(0.23 - 1.45)	(0.23 - 1.08)	0.036
P68032	Actin, alpha cardiac muscle 1	(0.23 - 1.45)	(0.23 - 1.08)	0.036
P30041	Peroxiredoxin-6	(0.25 - 1.28)	(0.25 - 1.11)	0.037
P04080	Cystatin-B	(0.73 - 1.46)	(0.61 - 1.1)	0.035

3.2. Proteins differentially modulated by the interaction of sex and exercise.

Sixteen proteins were significantly differentially modulated by exercise in participants of different sexes (Table 2). These proteins were related with binding (40%), catalytic activity (30%), molecular function regulator (20%), and molecular transducer activity (10%) molecular functions. A total of 23 biological processes were related, classified into 9 categories; being cellular process the majoritarian (21.7%), followed by response to stimulus (17,4%), biological regulation, localization and metabolic process (13% each), immune system process (8.7%), and developmental process, multicellular organismal process, and biological adhesion (4.3% for each biological process). No hit for pathways was obtained using PANTHER for those proteins.

In men keratin type II cytoskeletal 6A decreased, while keratin, type I cytoskeletal (16 and 14), Ig lambda-7 chain C region, and suprabasin increased their concentration after EFL. The remaining 15 proteins including ceruloplasmin, catalase, protein S100-P and alpha-1-acid glycoprotein 1 were downregulated in women after the exercise.

Table 2. Salivary proteins significantly modulated in abundance by sex and exercise.

Accession	Description	Pre (min - max)	Post (min -max)	P
P20742-2	Isoform 2 of Pregnancy zone protein	(0.26 - 1.72)	(0.26 - 1.12)	0.008
P20742	Pregnancy zone protein	(0.26 - 1.72)	(0.26 - 1.12)	0.008
P02538	Keratin, type II cytoskeletal 6A	(0.25 - 1.54)	(0.25 - 1.14)	0.009
P11142-1	Heat shock cognate 71 kDa protein	(0.26 - 1.42)	(0.26 - 1.29)	0.016
P08779	Keratin, type I cytoskeletal 16	(0.23 - 1.05)	(0.23 - 1.25)	0.019
P02533	Keratin, type I cytoskeletal 14	(0.23 - 1.05)	(0.23 - 1.25)	0.019
P00450	Ceruloplasmin	(0.29 - 1.33)	(0.29 - 1.1)	0.023
A0M8Q6	Ig lambda-7 chain C region	(0.27 - 1.14)	(0.27 - 1.93)	0.025
P25815	Protein S100-P	(0.28 - 1.49)	(0.28 - 1.22)	0.027
P11142-2	Isoform 2 of Heat shock cognate 71 kDa protein	(0.26 - 1.35)	(0.26 - 1.25)	0.031
P04406-2	Isoform 2 of Glyceraldehyde-3-phosphate dehydrogenase	(0.22 - 1.29)	(0.22 - 1.15)	0.035
P02763	Alpha-1-acid glycoprotein 1	(0.25 - 1.46)	(0.25 - 1.26)	0.036
P04040	Catalase	(0.23 - 1.53)	(0.23 - 1.39)	0.041
Q6UWP8-1	Suprabasin	(0.19 - 1.51)	(0.19 - 1.41)	0.042
P04083	Annexin A1	(0.27 - 1.5)	(0.27 - 1.21)	0.045
P63104-2	Isoform 2 of 14-3-3 protein zeta/delta	(0.18 - 1.26)	(0.18 - 1.18)	0.049

3.3. Proteins differentially modulated by sex at rest.

Since exercise effects were not the same for men and women, we also aimed to evaluate the possible sex-related differences at rest (T0). The analyses revealed 65 proteins (corresponding to 42 genes) with different abundance between sexes at rest (Table 3). The analysis of the differentially expressed genes allowed the identification of 55 over-represented GO-terms, which were filtered for redundancies and grouped into 9 functional groups including canonical glycolysis, neutrophil degranulation, defence response to bacterium, and endodermal cell differentiation, among others. The GO-terms most represented in this comparison after being filtered by REVIGO and depicted by Cytoscape are shown in Figure 1. Accordingly, canonical glycolysis and neutrophil degranulation nodes were observed to be involved in many of the pathways which differ significantly among men and women at rest (Figure 2).

211 **Table 3.** Salivary proteins with different abundance between men and women at rest.

Accession	Description	Fold (W/M)	P
P04746-2	Isoform 2 of Pancreatic alpha-amylase	1.33	0.024
P19961-2	Isoform 2 of Alpha-amylase 2B	1.28	0.023
P04745	Alpha-amylase 1	1.27	0.029
P04746	Pancreatic alpha-amylase	1.26	0.023
P19961	Alpha-amylase 2B	1.25	0.021
P0DN37	Peptidyl-prolyl cis-trans isomerase A-like 4G	1.25	0.025
P0DN26	Peptidyl-prolyl cis-trans isomerase A-like 4F	1.25	0.025
Q9Y536	Peptidyl-prolyl cis-trans isomerase A-like 4A	1.25	0.025
A0A0B4J2A2	Peptidyl-prolyl cis-trans isomerase A-like 4C	1.25	0.025
F5H284	Peptidyl-prolyl cis-trans isomerase A-like 4D	1.25	0.025
P13929-1	Beta-enolase	1.22	0.044
P13929-2	Isoform 2 of Beta-enolase	1.22	0.044
P13929-3	Isoform 3 of Beta-enolase	1.22	0.044
P09104	Gamma-enolase	1.22	0.044
P09104-2	Isoform 2 of Gamma-enolase	1.22	0.044
P62937	Peptidyl-prolyl cis-trans isomerase A	1.22	0.038
P04040	Catalase	1.22	0.008
P60174-1	Isoform 2 of Triosephosphate isomerase	1.21	0.020
P60174	Triosephosphate isomerase	1.21	0.020
P62937-2	Isoform 2 of Peptidyl-prolyl cis-trans isomerase A	1.20	0.049
P60174-4	Isoform 4 of Triosephosphate isomerase	1.19	0.020
P06744	Glucose-6-phosphate isomerase	1.17	0.029
P06744-2	Isoform 2 of Glucose-6-phosphate isomerase	1.17	0.029
P06703	Protein S100-A6	1.17	0.040
P29401-2	Isoform 2 of Transketolase	1.15	0.022
P29401	Transketolase	1.15	0.022
P12814-4	Isoform 4 of Alpha-actinin-1	1.13	0.025
P12814-3	Isoform 3 of Alpha-actinin-1	1.13	0.025
P12814-2	Isoform 2 of Alpha-actinin-1	1.13	0.025
P12814-1	Alpha-actinin-1	1.13	0.025
P06396	Gelsolin	1.12	0.039
P06396-2	Isoform 2 of Gelsolin	1.12	0.039
P06396-4	Isoform 4 of Gelsolin	1.12	0.039
P06396-3	Isoform 3 of Gelsolin	1.12	0.039
P00558	Phosphoglycerate kinase 1	1.11	0.019
P00558-2	Isoform 2 of Phosphoglycerate kinase 1	1.11	0.019
P32926	Desmoglein-3	0.90	0.033
P04208	Ig lambda chain V-I region WAH	0.90	0.035
P22079-2	Isoform 2 of Lactoperoxidase	0.88	0.005
P22079	Lactoperoxidase	0.88	0.005
Q08380	Galectin-3-binding protein	0.87	0.000
P01833	Polymeric immunoglobulin receptor	0.86	0.012

B9A064-1	Immunoglobulin lambda-like polypeptide 5	0.83	0.007
P0CG04	Ig lambda-1 chain C regions	0.83	0.012
P25311	Zinc-alpha-2-glycoprotein	0.83	0.001
P01591	Immunoglobulin J chain	0.81	0.021
Q06830	Peroxiredoxin-1	0.81	0.044
P01037	Cystatin-SN	0.80	0.035
P28799	Granulins	0.79	0.011
P28799-3	Isoform 3 of Granulins	0.79	0.011
P07602-2	Isoform Sap-mu-6 of Prosaposin	0.79	0.045
P07602-1	Prosaposin	0.79	0.045
P29508	Serpin B3	0.79	0.026
P29508-2	Isoform 2 of Serpin B3	0.79	0.026
Q14515	SPARC-like protein 1	0.74	0.044
P01598	Ig kappa chain V-I region EU	0.74	0.027
P28325	Cystatin-D	0.72	0.005
Q6P5S2	Protein LEG1 homolog	0.71	0.001
P12273	Prolactin-inducible protein	0.68	0.005
P54108-1	Cysteine-rich secretory protein 3	0.67	0.000
P54108-3	Isoform 3 of Cysteine-rich secretory protein 3	0.67	0.000
P54108-2	Isoform 2 of Cysteine-rich secretory protein 3	0.67	0.000
Q96DA0	Zymogen granule protein 16 homolog B	0.66	0.018
P03973	Antileukoproteinase	0.61	0.011
P61626	Lysozyme c	0.49	0.008

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213 The three proteins that were most overrepresented in men in comparison to women were lysozyme c,
214 antileukoproteinase, and zymogen granule protein 16 homolog B. On the other hand, alpha-amylase 2B,
215 pancreatic alpha-amylase, and alpha-amylase 1 were the three proteins most overrepresented in women
216 when compared to men at rest.

217 3.4. sAA verification

218 At rest, statistically higher sAA levels were observed in women in comparison to men (median $\pm$ 25-75%
219 interquartile range) (30.44 [17.95 – 40.48] and 17.58 [7.75 – 19.44] UI/L, respectively) ($P = 0.0343$).

220 4. Discussion

221 The present study describes for the first time the effects of an acute exercise in the salivary proteome
222 measured by TMT-based proteomics and the possible variations in the response due to sex. Of the 270
223 proteins that met the inclusion criteria, six were modulated after the exercise, sixteen proteins were
224 modulated differently after the exercise between men and females, and sixty-five showed sex-related
225 differences at rest.

226 Out of the six proteins found to be modulated by exercise, we identified peroxiredoxin, cystatin-b, and
227 four actins (actin, alpha skeletal muscle; actin, aortic smooth muscle; actin, gamma-enteric smooth

muscle; actin, alpha cardiac muscle 1). Peroxiredoxin showed a 0.23-fold decrease after the exercise and a similar abundance between males and females at T0 and T1. Peroxiredoxin is an antioxidant protein that is able to catalyze the hydrogen peroxide produced by skeletal muscle during exercise, forming stable oxidised dimers that can be secreted into the extracellular space [14]. Therefore, peroxiredoxin has been proposed as a biomarker of sports performance [15]. Cystatin-b was downregulated after the ELF protocol. Similarly to our results, plasma cystatin-b was reported to be inversely associated with exercise in a recent study, as well as with other factors that may be related with exercise [16] such as body fat and pulse pressure [17], and with incident myocardial infarction [18]. Finally, the four actins were downregulated after the exercise. This decrease will agree with the results obtained for actin in plasma at 24h after an eccentric exercise [19]. It could be postulated that actin will only increase in case of muscle damage, in which large amounts of actin might be released to the bloodstream from dead or dying cells [20].

A total of sixteen proteins were differentially modulated by the interaction of sex and exercise. In the case of catalase, our results agreed with a previous report in which sex-related differences in blood catalase was observed for football players after a match, in which men showed a higher peak in comparison to women [21]. However, there are no reports about sex-dependent modulation of the other proteins found differentially expressed in our study and there is controversy in the literature regarding the possible sex-related differences in response to exercise. While some authors did not find sex-related changes in the response to exercise [22], others described differences in several biomarkers such as tumour necrosis factor alpha [23]. Although there should be confirmed in a larger population and also in other types of exercise, these results indicate that sex-related influence should be taken into account for the search of biomarkers of sport performance, since, even if at rest the levels between the two sexes could be similar, they may show different behaviour in saliva in men and women.

When comparing both sexes at rest, in men the proteins with higher abundance in comparison with women were lysozyme c (LYZ), antileukoproteinase (SLPI), zymogen granule protein 16 homolog B (ZG16B), and cysteine-rich secretory protein 3 (CRISP3). Lysozymes such as LYZ possess bacteriolytic function, being related to the monocyte-macrophage system, enhancing the activity of immunoagents, and causing the lysis of oral bacterial cells. Our findings are in agreement with a previous report in which LYZ concentration in stimulated sublingual and submandibular saliva was higher in men than in women [24]. CRISP3 belongs to a family of cysteine-rich secretory proteins and participates in many important biological processes of defence response, such as innate immune response and neutrophil degranulation. Proteins of CRISP family have roles in the fertilization process and in sperm maturation. CRISP3 levels are androgen (dehydroepiandrosterone, DHEA) dependent, and submandibular gland acinar cells cultured with DHEA increased CRISP3 messenger RNA levels [25]. Serum DHEA levels are higher in adult men than in women, which is compatible with our findings. Although our results showing the increase of LYZ and CRISP3 in saliva of men agrees with previously described information, there are no published data addressing sex-related difference in concentrations of SLPI and ZG16B in saliva. It is known that SLPI modulates the inflammatory and immune response against bacterial infections and some intracellular parasites [26]. This protein is also required for normal wound healing and plays a role in the normal

differentiation and proliferation of bone marrow myeloid cells [27]. SLPI was found in a previous report at higher concentrations in saliva than in serum, which could suggest a local production related to the local promotion of tissue repair [28,29]. Zymogen granule membrane protein 16 is involved to carbohydrate binding and protein transport [30]. In humans, this protein is mainly expressed in the colon, followed by the small intestine and liver [30]. It has been suggested that ZG16 may keep bacteria further away from colon epithelium, being important in colon surveillance system [31]. ZG16 has been shown to be decreased in several cancers such as colorectal cancer or hepatocellular carcinoma [32].

On the other hand, the alpha-amylase 2B and 1, and pancreatic alpha-amylase were the proteins that most increased in abundance in saliva in women, compared to men. Salivary alpha-amylase (sAA) is secreted by the parotid gland as a response to adrenergic activity, being increased at physical or psychological stress situations [33]. To the best of the authors' knowledge, the present study shows for the first-time higher abundance of amylase 2B and 1, and pancreatic alpha-amylase in saliva in women at rest compared to men that would indicate that overall the activity of alpha-amylase would be higher in women than in men. These findings were further validated by the employment of a commercial colorimetric assay previously validated for its use in human saliva. The results of the colorimetric assay for sAA activity were in agreement with the proteomic results, showing higher sAA in women at rest. It should be noted that in addition to salivary sAA, in our study, pancreatic amylase was also present in saliva, which is in agreement with previous findings [35,36]. Further studies should be made to clarify the roles and physiological responses of pancreatic and salivary sAA in saliva. Overall, and in agreement with previous reports [2,37,38], our results suggest notable differences in physiological salivary proteome at rest between men and women, pointing out the need of sex-specific cohorts when analysing potential changes in saliva.

One of the limitations of the study is the sample size (n=5 for each sex and time point), which could limit the potential predictive power in the identification of proteins that are reproducibly modulated in concentration in saliva of men and women before and after ELF due to the biological inter-individual variations, although this number it was in line with previous proteomic studies [39] and higher than the minimum of three biological replicates recommended for proteomic studies [40]. Finally, for the present study, we only measured saliva, while the analysis of paired samples consisting of serum/plasma and saliva could help to elucidate which changes in saliva reflect systemic alterations. In addition, this study has been made with only one type of exercise and therefore results could not entirely be applied to other different exercises or sports. Thus, this study should be considered as a preliminary one, and further validation studies with a larger sample size are recommended in order to confirm our findings. Nevertheless, and despite these limitations, our preliminary results indicate that sex and exercise are independent factors that can modulate the salivary proteome affecting different biological processes.

Practical Applications

After a session of ELF, there are several changes in saliva protein composition that can be potentially used as biomarkers of sports performance. Our results showed three main findings: (1) there are changes

in salivary proteome after ELF regardless of the sex, (2) some proteins are modulated by ELF in a sex-dependant manner, and (3) there are differences in salivary proteome between men and women at rest.

Overall, our data provide an overview of the salivary proteome in both men and women at rest and as a response to exercise leading to failure, indicating differences between the two sexes, which should be taken into consideration for coaches, athletes and researches in sports sciences. Further large-scale population studies are desirable in order to confirm the validity of these results and discern the applicability of these protein markers in the measurement of sports performance.

Conclusions

Salivary proteome showed differences associated with sex at rest and after an exercise. Six proteins are shown to be modulated after exercise in both sexes, while 16 presented different behaviour after the exercise between men and women; being sex the factor that modulates a higher number of proteins. In addition, there were sixty-five proteins that different abundances between men and women at rest, mainly associated with catalytic activity and with binding processes.

This study points out the idea that sex-associated differences should be taken into consideration for the study of physiological changes associated with exercise and in the search of sport performance biomarkers in human whole saliva.

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446 **Supplementary Tables**

447 **Supplementary Table 1:** Proteins in saliva identified using TMT-based proteomic analysis with two or more unique peptides and presented in at least 70% of samples before
 448 (T0) and after exercise leading to failure (T1), and p values of Two-way ANOVA using exercise (P exercise) and sex & exercise interaction (P sex*exercise) as
 449 factors.

450

Accession	Description	PRE (min - max)	Post (min -max)	P (exercise)	P (Sex*exercise)
Q9HC84	Mucin-5B	(0,69 - 1,55)	(0,71 - 1,36)	0,491	0,675
P02768-1	Serum albumin	(0,65 - 2,42)	(0,5 - 1,59)	0,494	0,756
P02768-2	Isoform 2 of Serum albumin	(0,67 - 2,41)	(0,48 - 1,69)	0,553	0,823
P01833	Polymeric immunoglobulin receptor	(0,7 - 1,26)	(0,74 - 1,31)	0,758	0,594
P02768-3	Isoform 3 of Serum albumin	(0,61 - 2,41)	(0,48 - 1,61)	0,517	0,799
P02787	Serotransferrin	(0,77 - 1,79)	(0,68 - 1,55)	0,784	0,931
P02788	Lactotransferrin	(0,77 - 1,38)	(0,69 - 1,43)	0,593	0,706
A8K2U0	Alpha-2-macroglobulin-like protein 1	(0,77 - 1,43)	(0,68 - 1,58)	0,702	0,770
P01023	alpha-2-macroglobulin	(0,63 - 1,57)	(0,79 - 1,35)	0,726	0,506
P02788-2	Isoform DeltaLf of Lactotransferrin	(0,77 - 1,39)	(0,69 - 1,43)	0,600	0,628
P01024	Complement C3	(0,9 - 1,27)	(0,83 - 1,43)	0,389	0,404
P04745	alpha-amylase 1	(0,59 - 1,57)	(0,49 - 1,57)	0,358	0,507
P19961	Alpha-amylase 2B	(0,6 - 1,47)	(0,55 - 1,51)	0,353	0,594
P35908	Keratin, type II cytoskeletal 2 epidermal	(0,71 - 1,05)	(0,8 - 1,05)	0,660	0,791
P13645	Keratin, type I cytoskeletal 10	(0,64 - 1,09)	(0,68 - 1,17)	0,372	0,213
P04746	Pancreatic alpha-amylase	(0,6 - 1,54)	(0,52 - 1,51)	0,330	0,505
P04264	Keratin, type II cytoskeletal 1	(0,59 - 1,13)	(0,68 - 1,09)	1,000	0,976

P25311	Zinc-alpha-2-glycoprotein	(0,82 - 1,32)	(0,85 - 1,2)	0,774	0,113
Q9Y6R7	IgGfC-binding protein	(0,67 - 2,19)	(0,62 - 1,48)	0,482	0,241
P06733-1	alpha-enolase	(0,74 - 1,39)	(0,71 - 1,46)	0,405	0,517
P19961-2	Isoform 2 of Alpha-amylase 2B	(0,51 - 1,47)	(0,51 - 1,5)	0,362	0,728
A8K2U0-2	Isoform 2 of Alpha-2-macroglobulin-like protein 1	(0,84 - 1,36)	(0,67 - 1,41)	0,430	0,703
P35527	Keratin, type I cytoskeletal 9	(0,58 - 1,08)	(0,63 - 1,01)	0,445	0,581
P02774	vitamin D-binding protein	(0,8 - 1,82)	(0,74 - 1,73)	0,444	0,936
P02774-3	Isoform 3 of Vitamin D-binding protein	(0,8 - 1,82)	(0,74 - 1,73)	0,444	0,936
P13796	Plastin-2	(0,76 - 1,48)	(0,78 - 1,88)	0,866	0,637
P37837	Transaldolase	(0,84 - 1,19)	(0,72 - 1,38)	0,829	0,920
P06396	Gelsolin	(0,78 - 1,33)	(0,82 - 1,22)	0,830	0,247
P06396-2	Isoform 2 of Gelsolin	(0,78 - 1,33)	(0,82 - 1,22)	0,830	0,247
P06396-4	Isoform 4 of Gelsolin	(0,78 - 1,33)	(0,82 - 1,22)	0,830	0,247
Q96DR5	BPI fold-containing family A member 2	(0,56 - 1,35)	(0,57 - 2,09)	0,135	0,996
P06396-3	Isoform 3 of Gelsolin	(0,78 - 1,33)	(0,82 - 1,22)	0,830	0,247
P06733-2	Isoform MBP-1 of Alpha-enolase	(0,68 - 1,42)	(0,64 - 1,62)	0,401	0,410
P02774-2	Isoform 2 of Vitamin D-binding protein	(0,8 - 1,86)	(0,74 - 1,73)	0,498	0,927
Q9UBC9	Small proline-rich protein 3	(0,57 - 1,42)	(0,48 - 1,12)	0,120	0,994
P00738-2	Isoform 2 of Haptoglobin	(0,77 - 1,64)	(0,7 - 1,25)	0,457	0,757
P02647	Apolipoprotein A-I	(0,81 - 1,73)	(0,64 - 1,39)	0,379	0,834
P00738	Haptoglobin	(0,77 - 1,64)	(0,7 - 1,25)	0,457	0,757
P29508	Serpin B3	(0,28 - 1,94)	(0,28 - 1,41)	0,298	0,335
Q6P5S2	Protein LEG1 homolog	(0,75 - 1,63)	(0,75 - 1,35)	0,384	0,132
Q9UGM3-1	deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
Q9UGM3-4	Isoform 4 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
P52209	6-phosphogluconate dehydrogenase, decarboxylating	(0,83 - 1,28)	(0,74 - 1,29)	0,494	0,925
Q9UGM3-3	Isoform 3 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
Q9UGM3-6	Isoform 6 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497

P52209-2	Isoform 2 of 6-phosphogluconate dehydrogenase, decarboxylating	(0,83 - 1,28)	(0,74 - 1,29)	0,494	0,925
P29401-2	Isoform 2 of Transketolase	(0,77 - 1,36)	(0,74 - 1,16)	0,413	0,853
Q9UGM3-5	Isoform 5 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
P29508-2	Isoform 2 of Serpin B3	(0,28 - 1,94)	(0,28 - 1,41)	0,298	0,335
P29401	Transketolase	(0,77 - 1,36)	(0,74 - 1,16)	0,413	0,853
Q9UGM3-2	Isoform 2 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
P01009-1	alpha-1-antitrypsin	(0,61 - 2,25)	(0,77 - 2,47)	0,719	0,751
P04746-2	Isoform 2 of Pancreatic alpha-amylase	(0,44 - 1,57)	(0,47 - 1,61)	0,434	0,631
P32926	Desmoglein-3	(0,76 - 1,2)	(0,75 - 1,57)	0,431	0,356
P12273	Prolactin-inducible protein	(0,62 - 1,7)	(0,63 - 1,73)	0,591	0,839
Q9UGM3-8	Isoform 8 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
Q9UGM3-7	Isoform 7 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,63)	0,793	0,497
P06744	glucose-6-phosphate isomerase	(0,76 - 1,35)	(0,65 - 1,26)	0,289	0,201
P14618-2	Isoform M1 of Pyruvate kinase PKM	(0,7 - 1,24)	(0,68 - 1,25)	0,128	0,819
Q96DA0	Zymogen granule protein 16 homolog B	(0,37 - 1,75)	(0,59 - 1,93)	0,321	0,166
Q9UGM3-9	Isoform 9 of Deleted in malignant brain tumors 1 protein	(0,65 - 1,52)	(0,65 - 1,62)	0,930	0,576
P14618	Pyruvate kinase PKM	(0,7 - 1,24)	(0,68 - 1,25)	0,128	0,819
Q9UBG3	Cornulin	(0,56 - 1,44)	(0,52 - 1,36)	0,254	0,610
Q08380	Galectin-3-binding protein	(0,93 - 1,29)	(0,78 - 1,33)	0,401	0,088
P06744-2	Isoform 2 of Glucose-6-phosphate isomerase	(0,76 - 1,35)	(0,65 - 1,26)	0,289	0,201
P60174-1	Isoform 2 of Triosephosphate isomerase	(0,78 - 1,63)	(0,85 - 1,41)	0,522	0,288
P60174	Triosephosphate isomerase	(0,78 - 1,63)	(0,85 - 1,41)	0,522	0,288
P31025	Lipocalin-1	(0,53 - 2,93)	(0,4 - 2,18)	0,523	0,697
Q8N4F0	BPI fold-containing family B member 2	(0,65 - 1,41)	(0,76 - 1,28)	0,391	0,272
P63104-1	14-3-3 protein zeta/delta	(0,85 - 1,18)	(0,84 - 1,35)	0,913	0,698
Q8TDL5-1	BPI fold-containing family B member 1	(0,51 - 1,37)	(0,62 - 1,7)	0,967	0,823
P01876	Ig alpha-1 chain C region	(0,5 - 1,17)	(0,52 - 1,4)	0,871	0,204
P22079-2	Isoform 2 of Lactoperoxidase	(0,8 - 1,22)	(0,8 - 1,23)	0,924	0,083

P22079	lactoperoxidase	(0,8 - 1,22)	(0,8 - 1,23)	0,924	0,083
P20061	Transcobalamin-1	(0,81 - 1,37)	(0,45 - 1,24)	0,110	0,786
P00338-3	Isoform 3 of L-lactate dehydrogenase A chain	(0,88 - 1,28)	(0,84 - 1,17)	0,269	0,159
Q02413	Desmoglein-1	(0,63 - 1,27)	(0,9 - 1,36)	0,425	0,707
P00338-1	L-lactate dehydrogenase A chain	(0,88 - 1,28)	(0,84 - 1,17)	0,269	0,159
P09211	Glutathione S-transferase P	(0,78 - 1,81)	(0,73 - 1,77)	0,485	0,664
P01591	Immunoglobulin J chain	(0,51 - 1,26)	(0,78 - 1,33)	0,682	0,410
P04075	fructose-bisphosphate aldolase A	(0,92 - 1,41)	(0,7 - 1,22)	0,145	0,080
P04075-2	Isoform 2 of Fructose-bisphosphate aldolase A	(0,92 - 1,41)	(0,7 - 1,22)	0,145	0,080
P02790	Hemopexin	(0,85 - 1,44)	(0,86 - 1,62)	0,728	0,235
Q01518-1	adenylyl cyclase-associated protein 1	(0,74 - 1,97)	(0,81 - 1,83)	0,770	0,731
P02679-2	Isoform Gamma-A of Fibrinogen gamma chain	(0,83 - 1,3)	(0,87 - 1,31)	0,800	0,516
P60174-4	Isoform 4 of Triosephosphate isomerase	(0,78 - 1,52)	(0,86 - 1,45)	0,873	0,271
P11142-1	Heat shock cognate 71 kDa protein	(0,26 - 1,42)	(0,26 - 1,29)	0,197	0,016
Q02487-2	Isoform 2B of Desmocollin-2	(0,84 - 1,38)	(0,72 - 1,72)	0,459	0,324
P54108-1	Cysteine-rich secretory protein 3	(0,58 - 1,5)	(0,48 - 1,57)	0,597	0,567
P00338-4	Isoform 4 of L-lactate dehydrogenase A chain	(0,93 - 1,32)	(0,84 - 1,17)	0,127	0,137
P14618-3	Isoform 3 of Pyruvate kinase PKM	(0,7 - 1,38)	(0,68 - 1,25)	0,156	0,967
P00450	Ceruloplasmin	(0,29 - 1,33)	(0,29 - 1,1)	0,215	0,023
P02679	Fibrinogen gamma chain	(0,83 - 1,3)	(0,87 - 1,31)	0,800	0,516
P01040	Cystatin-A	(0,37 - 1,37)	(0,47 - 2,53)	0,289	0,134
Q08188	Protein-glutamine gamma-glutamyltransferase E	(0,19 - 1,53)	(0,19 - 1,66)	0,353	0,121
Q01518-2	Isoform 2 of Adenylyl cyclase-associated protein 1	(0,74 - 1,97)	(0,81 - 1,83)	0,770	0,731
P01009-2	Isoform 2 of Alpha-1-antitrypsin	(0,66 - 2,04)	(0,77 - 2,11)	0,760	0,513
P54108-3	Isoform 3 of Cysteine-rich secretory protein 3	(0,58 - 1,5)	(0,48 - 1,57)	0,597	0,567
P62937	peptidyl-prolyl cis-trans isomerase A	(0,76 - 1,68)	(0,63 - 1,32)	0,437	0,585
Q02487	Desmocollin-2	(0,84 - 1,38)	(0,72 - 1,72)	0,459	0,324
P05109	Protein S100-A8	(0,61 - 1,87)	(0,62 - 1,64)	0,655	0,218

P54108-2	Isoform 2 of Cysteine-rich secretory protein 3	(0,58 - 1,5)	(0,48 - 1,57)	0,597	0,567
P30740	Leukocyte elastase inhibitor	(0,8 - 1,14)	(0,73 - 1,23)	0,790	0,845
P06870-2	Isoform 2 of Kallikrein-1	(0,74 - 1,53)	(0,78 - 1,42)	0,941	0,926
P68871	Hemoglobin subunit beta	(0,39 - 1,84)	(0,37 - 6,3)	0,361	0,275
P52566	Rho GDP-dissociation inhibitor 2	(0,71 - 1,99)	(0,68 - 1,62)	0,868	0,735
P01834	Ig kappa chain C region	(0,67 - 1,16)	(0,6 - 1,36)	0,895	0,424
P09228	Cystatin-SA	(0,55 - 1,37)	(0,44 - 2,1)	0,776	0,147
Q8NBJ4	Golgi membrane protein 1	(0,55 - 1,27)	(0,67 - 1,33)	0,742	0,118
P31947-2	Isoform 2 of 14-3-3 protein sigma	(0,6 - 1,35)	(0,61 - 1,47)	0,249	0,973
P00338-2	Isoform 2 of L-lactate dehydrogenase A chain	(0,77 - 1,28)	(0,8 - 1,22)	0,628	0,586
Q8NBJ4-2	Isoform 2 of Golgi membrane protein 1	(0,55 - 1,27)	(0,67 - 1,33)	0,742	0,118
P31146	Coronin-1A	(0,69 - 1,38)	(0,53 - 1,31)	0,886	0,417
P06702	Protein S100-A9	(0,71 - 2,22)	(0,75 - 1,66)	0,781	0,321
P01871-1	Ig mu chain C region	(0,7 - 1,16)	(0,52 - 1,35)	0,444	0,088
P02671-1	Fibrinogen alpha chain	(0,85 - 1,27)	(0,66 - 2,38)	0,731	0,654
P02671-2	Isoform 2 of Fibrinogen alpha chain	(0,85 - 1,27)	(0,66 - 2,38)	0,731	0,654
P62937-2	Isoform 2 of Peptidyl-prolyl cis-trans isomerase A	(0,75 - 1,71)	(0,61 - 1,33)	0,290	0,689
P06870-1	Kallikrein-1	(0,74 - 1,53)	(0,78 - 1,42)	0,941	0,926
P01871-2	Isoform 2 of Ig mu chain C region	(0,7 - 1,16)	(0,52 - 1,35)	0,444	0,088
Q14515	SPARC-like protein 1	(0,7 - 2,94)	(0,8 - 1,92)	0,451	0,466
P80188	Neutrophil gelatinase-associated lipocalin	(0,84 - 1,15)	(0,82 - 1,24)	0,904	0,841
P07737	profilin-1	(0,22 - 1,41)	(0,22 - 1,27)	0,321	0,056
Q01469	Fatty acid-binding protein, epidermal	(0,68 - 2,34)	(0,55 - 1,77)	0,637	0,444
P27482	Calmodulin-like protein 3	(0,56 - 1,46)	(0,61 - 1,27)	0,980	0,407
P23280	Carbonic anhydrase 6	(0,72 - 1,43)	(0,74 - 1,36)	0,715	0,214
P07476	Involucrin	(0,76 - 1,31)	(0,62 - 1,36)	0,478	0,214
P31947-1	14-3-3 protein sigma	(0,6 - 1,35)	(0,61 - 1,47)	0,249	0,973
P01877	Ig alpha-2 chain C region	(0,41 - 1,18)	(0,6 - 1,31)	0,708	0,751

P00338-5	Isoform 5 of L-lactate dehydrogenase A chain	(0,77 - 1,28)	(0,8 - 1,22)	0,628	0,586
P04040	catalase	(0,23 - 1,53)	(0,23 - 1,39)	0,171	0,041
P62979	Ubiquitin-40S ribosomal protein S27a	(0,66 - 1,48)	(0,68 - 1,58)	0,658	0,256
P18510-4	Isoform 4 of Interleukin-1 receptor antagonist protein	(0,61 - 1,68)	(0,66 - 1,42)	0,426	0,527
Q14508	WAP four-disulfide core domain protein 2	(0,81 - 1,28)	(0,72 - 1,31)	0,844	0,274
P80188-2	Isoform 2 of Neutrophil gelatinase-associated lipocalin	(0,84 - 1,15)	(0,82 - 1,24)	0,969	0,783
P61626	lysozyme c	(0,38 - 2,51)	(0,42 - 1,71)	0,789	0,310
P60709	Actin, cytoplasmic 1	(0,77 - 1,45)	(0,78 - 1,19)	0,147	0,268
P07237	Protein disulfide-isomerase	(0,29 - 1,49)	(0,29 - 1,35)	0,092	0,074
P01857	Ig gamma-1 chain C region	(0,74 - 1,31)	(0,56 - 1,56)	0,500	0,780
P0CG47	Polyubiquitin-B	(0,66 - 1,48)	(0,68 - 1,58)	0,658	0,256
Q9NQ38-3	Isoform long of Serine protease inhibitor Kazal-type 5	(0,88 - 1,46)	(0,74 - 1,28)	0,059	0,346
P49913	cathelicidin antimicrobial peptide	(0,68 - 1,6)	(0,89 - 1,45)	0,281	0,841
P10599-1	thioredoxin	(0,64 - 1,44)	(0,61 - 1,16)	0,140	0,252
P18669	Phosphoglycerate mutase 1	(0,72 - 1,24)	(0,78 - 1,4)	0,574	0,936
P18510-2	Isoform 2 of Interleukin-1 receptor antagonist protein	(0,61 - 1,68)	(0,66 - 1,42)	0,426	0,527
P13797-3	Isoform 3 of Plastin-3	(0,76 - 1,63)	(0,78 - 1,88)	0,410	0,450
P08779	Keratin, type I cytoskeletal 16	(0,23 - 1,05)	(0,23 - 1,25)	0,757	0,019
Q9NQ38-1	Serine protease inhibitor Kazal-type 5	(0,88 - 1,46)	(0,74 - 1,28)	0,059	0,346
P01623	Ig kappa chain V-III region WOL	(0,76 - 1,16)	(0,82 - 1,18)	0,835	0,506
P00739-2	Isoform 2 of Haptoglobin-related protein	(0,75 - 1,82)	(0,68 - 1,32)	0,454	0,877
P18510-3	Isoform 3 of Interleukin-1 receptor antagonist protein	(0,61 - 1,68)	(0,66 - 1,42)	0,426	0,527
P23280-3	Isoform 3 of Carbonic anhydrase 6	(0,72 - 1,43)	(0,74 - 1,34)	0,674	0,203
P69905	Hemoglobin subunit alpha	(0,34 - 2)	(0,29 - 5,75)	0,305	0,184
P13797-2	Isoform 2 of Plastin-3	(0,76 - 1,63)	(0,78 - 1,88)	0,410	0,450
P0CG48	Polyubiquitin-C	(0,66 - 1,48)	(0,68 - 1,58)	0,658	0,256
P63104-2	Isoform 2 of 14-3-3 protein zeta/delta	(0,18 - 1,26)	(0,18 - 1,18)	0,129	0,049
P18510-1	Interleukin-1 receptor antagonist protein	(0,61 - 1,68)	(0,66 - 1,42)	0,426	0,527

P02533	Keratin, type I cytoskeletal 14	(0,23 - 1,05)	(0,23 - 1,25)	0,757	0,019
P62987	Ubiquitin-60S ribosomal protein L40	(0,66 - 1,48)	(0,68 - 1,58)	0,658	0,256
P63261	Actin, cytoplasmic 2	(0,77 - 1,45)	(0,78 - 1,19)	0,147	0,268
P01009-3	Isoform 3 of Alpha-1-antitrypsin	(0,72 - 2,06)	(0,65 - 2,11)	0,861	0,587
P01037	Cystatin-SN	(0,66 - 1,49)	(0,46 - 1,53)	0,648	0,495
P13797	Plastin-3	(0,76 - 1,63)	(0,78 - 1,88)	0,410	0,450
P01036	Cystatin-S	(0,55 - 1,66)	(0,51 - 1,77)	0,920	0,860
P23280-2	Isoform 2 of Carbonic anhydrase 6	(0,81 - 1,43)	(0,78 - 1,32)	0,714	0,568
P10599-2	Isoform 2 of Thioredoxin	(0,64 - 1,44)	(0,61 - 1,16)	0,140	0,252
Q8TAX7	Mucin-7	(0,56 - 2,41)	(0,51 - 3,09)	0,769	0,850
P00739-1	Haptoglobin-related protein	(0,75 - 1,82)	(0,68 - 1,32)	0,454	0,877
O95274	Ly6/PLAUR domain-containing protein 3	(0,65 - 1,56)	(0,75 - 1,59)	0,819	0,536
P28325	Cystatin-D	(0,65 - 1,68)	(0,62 - 1,98)	0,346	0,800
B9A064-1	Immunoglobulin lambda-like polypeptide 5	(0,7 - 1,25)	(0,76 - 1,36)	0,480	0,538
P06703	protein S100-A6	(0,68 - 1,39)	(0,61 - 1,31)	0,617	0,853
P13929-1	Beta-enolase	(0,72 - 1,85)	(0,74 - 1,68)	0,975	0,166
P04080	Cystatin-B	(0,73 - 1,46)	(0,61 - 1,1)	0,035	0,610
P11142-2	Isoform 2 of Heat shock cognate 71 kDa protein	(0,26 - 1,35)	(0,26 - 1,25)	0,205	0,031
P02042	Hemoglobin subunit delta	(0,12 - 1,11)	(0,12 - 2,08)	0,851	0,050
P13647	keratin, type II cytoskeletal 5	(0,18 - 2,63)	(0,18 - 1,1)	0,270	0,515
P23528	Cofilin-1	(0,41 - 1,72)	(0,62 - 1,46)	0,867	0,685
P62158	Calmodulin	(0,73 - 1,67)	(0,51 - 2,54)	0,701	0,221
P13929-2	Isoform 2 of Beta-enolase	(0,72 - 1,85)	(0,74 - 1,68)	0,975	0,166
P01620	Ig kappa chain V-III region SIE	(0,77 - 1,14)	(0,9 - 1,35)	0,658	0,918
Q14508-2	Isoform 2 of WAP four-disulfide core domain protein 2	(0,81 - 1,28)	(0,72 - 1,31)	0,777	0,273
Q6UWP8-1	Suprabasin	(0,19 - 1,51)	(0,19 - 1,41)	0,323	0,042
P80723	Brain acid soluble protein 1	(0,58 - 2,18)	(0,73 - 1,63)	0,805	0,388
Q9H299	SH3 domain-binding glutamic acid-rich-like protein 3	(0,98 - 1,35)	(0,88 - 1,22)	0,273	0,719

P0CG05	Ig lambda-2 chain C regions	(0,65 - 2,04)	(0,79 - 1,81)	0,240	0,184
P04259	keratin, type II cytoskeletal 6B	(0,59 - 1,22)	(0,7 - 1,14)	0,856	0,804
P04406-1	glyceraldehyde-3-phosphate dehydrogenase	(0,75 - 1,27)	(0,45 - 1,13)	0,201	0,651
Q9NQ38-2	Isoform short of Serine protease inhibitor Kazal-type 5	(0,27 - 1,4)	(0,27 - 1,39)	0,076	0,150
Q14515-2	Isoform 2 of SPARC-like protein 1	(0,59 - 3,06)	(0,65 - 1,92)	0,438	0,400
P01034	Cystatin-C	(0,17 - 1,25)	(0,17 - 1,38)	0,538	0,232
Q01546	Keratin, type II cytoskeletal 2 oral	(0,5 - 1,2)	(0,72 - 1,14)	1,000	0,296
P02763	Alpha-1-acid glycoprotein 1	(0,25 - 1,46)	(0,25 - 1,26)	0,165	0,036
P31151	Protein S100-A7	(0,5 - 2,51)	(0,5 - 2,97)	0,896	0,927
P98088	Mucin-5AC	(0,56 - 1,57)	(0,76 - 1,57)	0,987	0,412
P00558	phosphoglycerate kinase 1	(0,91 - 1,27)	(0,75 - 1,31)	0,134	1,000
P29034	protein S100-A2	(0,64 - 1,45)	(0,65 - 1,37)	0,555	0,736
P00558-2	Isoform 2 of Phosphoglycerate kinase 1	(0,91 - 1,27)	(0,75 - 1,31)	0,134	1,000
Q14508-3	Isoform 3 of WAP four-disulfide core domain protein 2	(0,81 - 1,28)	(0,72 - 1,31)	0,777	0,273
P04083	annexin A1	(0,27 - 1,5)	(0,27 - 1,21)	0,124	0,045
P13929-3	Isoform 3 of Beta-enolase	(0,72 - 1,85)	(0,74 - 1,68)	0,975	0,166
P18135	Ig kappa chain V-III region HAH	(0,71 - 1,19)	(0,81 - 1,21)	0,549	0,764
P12814-4	Isoform 4 of Alpha-actinin-1	(0,9 - 1,46)	(0,86 - 1,59)	0,942	0,843
P04208	Ig lambda chain V-I region WAH	(0,25 - 1,16)	(0,25 - 1,19)	0,337	0,077
P09104	Gamma-enolase	(0,72 - 1,85)	(0,74 - 1,68)	0,975	0,166
P0CG04	Ig lambda-1 chain C regions	(0,67 - 1,26)	(0,74 - 1,32)	0,331	0,501
P68133	Actin, alpha skeletal muscle	(0,23 - 1,45)	(0,23 - 1,08)	0,036	0,062
P0DMV8-2	Isoform 2 of Heat shock 70 kDa protein 1A	(0,78 - 1,43)	(0,58 - 1,42)	0,773	0,741
P20742-2	Isoform 2 of Pregnancy zone protein	(0,26 - 1,72)	(0,26 - 1,12)	0,122	0,008
P0DN37	peptidyl-prolyl cis-trans isomerase A-like 4G	(0,76 - 1,68)	(0,69 - 1,41)	0,838	0,964
P15259	phosphoglycerate mutase 2	(0,67 - 1,83)	(0,76 - 1,19)	0,061	0,701
P01617	Ig kappa chain V-II region TEW	(0,75 - 1,3)	(0,81 - 1,19)	0,910	0,181
P12814-3	Isoform 3 of Alpha-actinin-1	(0,9 - 1,46)	(0,86 - 1,59)	0,942	0,843

P0DN26	Peptidyl-prolyl cis-trans isomerase A-like 4F	(0,76 - 1,68)	(0,69 - 1,41)	0,838	0,964
P0DMV8	heat shock 70 kDa protein 1A	(0,78 - 1,43)	(0,58 - 1,42)	0,773	0,741
Q8TDL5-2	Isoform 2 of BPI fold-containing family B member 1	(0,19 - 1,28)	(0,19 - 1,87)	0,654	0,060
P01598	Ig kappa chain V-I region EU	(0,6 - 1,68)	(0,69 - 1,53)	0,158	0,637
Q7Z3Z0	Keratin, type I cytoskeletal 25	(0,56 - 1,14)	(0,68 - 1,33)	0,107	0,332
P62736	Actin, aortic smooth muscle	(0,23 - 1,45)	(0,23 - 1,08)	0,036	0,062
P31949	protein S100-A11	(0,69 - 1,33)	(0,57 - 1,48)	0,286	0,336
P28799	Granulins	(0,26 - 1,55)	(0,26 - 1,34)	0,233	0,532
P01703	Ig lambda chain V-I region NEWM	(0,81 - 1,28)	(0,91 - 1,31)	0,945	0,589
P12035	Keratin, type II cytoskeletal 3	(0,5 - 1,22)	(0,72 - 1,19)	0,743	0,271
Q06830	peroxiredoxin-1	(0,24 - 1,64)	(0,24 - 2,08)	0,493	0,144
Q9Y536	Peptidyl-prolyl cis-trans isomerase A-like 4A	(0,76 - 1,68)	(0,69 - 1,41)	0,838	0,964
P04406-2	Isoform 2 of Glyceraldehyde-3-phosphate dehydrogenase	(0,22 - 1,29)	(0,22 - 1,15)	0,329	0,035
P01859	Ig gamma-2 chain C region	(0,74 - 1,55)	(0,69 - 1,85)	0,758	0,635
P01622	Ig kappa chain V-III region TI	(0,76 - 1,11)	(0,9 - 1,35)	0,559	0,987
P03973	Antileukoproteinase	(0,48 - 2,54)	(0,65 - 1,65)	0,650	0,214
P02812	Basic salivary proline-rich protein 2	(0,08 - 4,82)	(0,13 - 2,14)	0,817	0,731
P59665	Neutrophil defensin 1	(0,63 - 1,7)	(0,55 - 2,4)	0,992	0,603
A0A0B4J2A2	Peptidyl-prolyl cis-trans isomerase A-like 4C	(0,76 - 1,68)	(0,69 - 1,41)	0,838	0,964
P02538	Keratin, type II cytoskeletal 6A	(0,25 - 1,54)	(0,25 - 1,14)	0,165	0,009
P04206	Ig kappa chain V-III region GOL	(0,76 - 1,11)	(0,9 - 1,35)	0,559	0,987
Q7Z3Y7	keratin, type I cytoskeletal 28	(0,56 - 1,14)	(0,68 - 1,33)	0,107	0,332
P20742	Pregnancy zone protein	(0,26 - 1,72)	(0,26 - 1,12)	0,122	0,008
P12814-2	Isoform 2 of Alpha-actinin-1	(0,9 - 1,46)	(0,86 - 1,59)	0,942	0,843
P07108-3	Isoform 3 of Acyl-CoA-binding protein	(0,2 - 2,01)	(0,2 - 2,24)	0,340	0,270
P80748	Ig lambda chain V-III region LOI	(0,73 - 1,2)	(0,93 - 1,28)	0,368	0,638
P59666	Neutrophil defensin 3	(0,63 - 1,7)	(0,55 - 2,4)	0,992	0,603
P63267-1	actin, gamma-enteric smooth muscle	(0,23 - 1,45)	(0,23 - 1,08)	0,036	0,062

P18136	Ig kappa chain V-III region HIC	(0,74 - 1,29)	(0,86 - 1,33)	0,757	0,717
F5H284	peptidyl-prolyl cis-trans isomerase A-like 4D	(0,76 - 1,68)	(0,69 - 1,41)	0,838	0,964
P25815	Protein S100-P	(0,28 - 1,49)	(0,28 - 1,22)	0,213	0,027
P07108-2	Isoform 2 of Acyl-CoA-binding protein	(0,2 - 2,01)	(0,2 - 2,24)	0,340	0,270
P07108-5	Isoform 5 of Acyl-CoA-binding protein	(0,2 - 2,01)	(0,2 - 2,24)	0,340	0,270
Q5VSP4	Putative lipocalin 1-like protein 1	(0,56 - 2,58)	(0,54 - 2,05)	0,554	0,670
P01593	Ig kappa chain V-I region AG	(0,58 - 1,6)	(0,65 - 1,3)	0,650	0,590
P68032	Actin, alpha cardiac muscle 1	(0,23 - 1,45)	(0,23 - 1,08)	0,036	0,062
Q6UWP8-2	Isoform 2 of Suprabasin	(0,19 - 1,51)	(0,19 - 1,41)	0,242	0,060
P01860	Ig gamma-3 chain C region	(0,4 - 1,39)	(0,57 - 1,56)	0,936	0,968
Q5XKE5	Keratin, type II cytoskeletal 79	(0,5 - 1,22)	(0,72 - 1,19)	0,743	0,271
P28799-3	Isoform 3 of Granulins	(0,26 - 1,55)	(0,26 - 1,34)	0,233	0,532
Q04695	Keratin, type I cytoskeletal 17	(0,27 - 1,23)	(0,27 - 1,18)	0,166	0,643
P12814-1	Alpha-actinin-1	(0,9 - 1,46)	(0,86 - 1,59)	0,942	0,843
P01714	Ig lambda chain V-III region SH	(0,73 - 1,85)	(0,59 - 1,35)	0,722	0,331
P80723-2	Isoform 2 of Brain acid soluble protein 1	(0,68 - 2,18)	(0,73 - 1,63)	0,655	0,385
P35321	Cornifin-A	(0,78 - 1,49)	(0,57 - 1,57)	0,824	0,941
P30041	Peroxiredoxin-6	(0,25 - 1,28)	(0,25 - 1,11)	0,037	0,308
P01613	Ig kappa chain V-I region Ni	(0,17 - 1,72)	(0,17 - 2,17)	0,427	0,334
P07108-4	Isoform 4 of Acyl-CoA-binding protein	(0,2 - 2,01)	(0,2 - 2,24)	0,340	0,270
P01701	Ig lambda chain V-I region NEW	(0,74 - 1,19)	(0,59 - 1,55)	0,876	0,372
A0M8Q6	Ig lambda-7 chain C region	(0,27 - 1,14)	(0,27 - 1,93)	0,957	0,025
Q7Z3Y8	Keratin, type I cytoskeletal 27	(0,56 - 1,14)	(0,68 - 1,33)	0,107	0,332
P09104-2	Isoform 2 of Gamma-enolase	(0,72 - 1,85)	(0,74 - 1,68)	0,975	0,166
P22532	small proline-rich protein 2D	(0,23 - 1,36)	(0,23 - 1,7)	0,218	0,054
P00751-1	Complement factor B	(0,26 - 1,87)	(0,26 - 1,31)	0,525	0,099
Q86SG5	Protein S100-A7A	(0,12 - 2,75)	(0,12 - 2,97)	0,787	0,348
P01765	Ig heavy chain V-III region TIL	(0,63 - 1,3)	(0,46 - 1,28)	0,587	0,073

451	P01766	Ig heavy chain V-III region BRO	(0,7 - 1,31)	(0,68 - 1,41)	0,325	0,138
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Figure 1

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Figure 2