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ORIGINAL RESEARCH

Impact of Kidney Function on the Blood Proteome and on Protein Cardiovascular Risk Biomarkers in Patients With Stable Coronary Heart Disease

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BACKGROUND: Chronic kidney disease (CKD) confers increased cardiovascular risk, not fully explained by traditional factors. Proteins regulate biological processes and inform the risk of diseases. Thus, in 938 patients with stable coronary heart disease from the Heart and Soul cohort, we quantified 1054 plasma proteins using modified aptamers (SOMAscan) to: (1) discern how reduced glomerular filtration influences the circulating proteome, (2) learn of the importance of kidney function to the prognostic information contained in recently identified protein cardiovascular risk biomarkers, and (3) identify novel and even unique cardiovascular risk biomarkers among individuals with CKD.

METHODS AND RESULTS: Plasma protein levels were correlated to estimated glomerular filtration rate (eGFR) using Spearman-rank correlation coefficients. Cox proportional hazard models were used to estimate the association between individual protein levels and the risk of the cardiovascular outcome (first among myocardial infarction, stroke, heart failure hospitalization, or mortality). Seven hundred and nine (67.3%) plasma proteins correlated with eGFR at $P<0.05$ (ρ 0.06–0.74); 218 (20.7%) proteins correlated with eGFR moderately or strongly (ρ 0.2–0.74). Among the previously identified 196 protein cardiovascular biomarkers, just 87 remained prognostic after correction for eGFR. Among patients with CKD (eGFR <60 mL/min per 1.73 m^2), we identified 21 protein cardiovascular risk biomarkers of which 8 are unique to CKD.

CONCLUSIONS: CKD broadly alters the composition of the circulating proteome. We describe protein biomarkers capable of predicting cardiovascular risk independently of glomerular filtration, and those that are prognostic of cardiovascular risk specifically in patients with CKD and even unique to patients with CKD.

Key Words: cardiovascular disease ■ chronic kidney disease ■ proteomics

See Editorial by Khalaf et al.

Chronic kidney disease (CKD) confers a substantial increase in cardiovascular risk.[1,2] While traditional risk factors such as diabetes mellitus and hypertension predict adverse cardiovascular outcomes in patients with CKD, they do not fully explain the excess cardiovascular risk in this population.[3] CKD is associated with changes in the concentrations of some circulating proteins, partly because of their reduced renal clearance, but also the result of biochemical alterations associated with the "uremic milieu".[4–6] Such changes in the circulating proteome may give rise to biomarkers that are strongly prognostic of cardiovascular risk in CKD and even unique to CKD.[7] Current approaches designed to elucidate the excess

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For Sources of Funding and Disclosures, see page 10.

CLINICAL PERSPECTIVE

What Is New?

- We used modified aptamers for high throughput proteomic analyses to identify the importance of kidney function on the circulating proteome.
- We determined the effect of kidney function on the prognostic information of previously identified cardiovascular risk biomarkers and newly identified novel and even unique cardiovascular biomarkers among the population of patients with chronic kidney disease.

What Are the Clinical Implications?

- Chronic kidney disease is known to confer significantly increased cardiovascular risk that is not fully explained by traditional risk factors such as hypertension and diabetes mellitus.
- Herein, we describe protein biomarkers capable of predicting cardiovascular risk that is independent of glomerular filtration.
- We also identify proteins that are prognostic of cardiovascular risk specifically in patients with chronic kidney disease and even unique to patients with impaired renal function.

Non-Standard Abbreviation and Acronym

IPA	Ingenuity Pathway Analysis

cardiovascular risk among CKD patients have targeted a relatively small number of candidate biomarkers to explain what is likely a complex mechanism. Large-scale proteomic scanning removes the limitations of educated guesses and has the potential to reveal a much larger set of cardiovascular risk biomarkers in CKD than has otherwise been possible.

The field of proteomics has matured over the past 2 decades.[8] Technologies have been developed that can currently measure the levels of hundreds and even thousands of proteins from a small sample of blood.[9–11] We recently used one such technology, modified aptamers, to successfully measure the levels of 1054 proteins in 938 participants with stable coronary heart disease from the Heart and Soul observational study.[9] We discovered 196 proteins that are prognostic of cardiovascular risk in this cohort. Notably, despite its relatively recent ascendance as a leading technology, aptamer-based proteomics has been well-validated. The assay's specificity has been confirmed by orthogonal approaches including mass spectrometry[12] and by linking the effects of cis-genetic variants to measurements of protein expression.[12–14]

Kidney function in the patients from the Heart and Soul cohort ranges from normal to moderately impaired and this cohort has been well-suited for investigations of kidney-related outcomes.[15–19] Specifically, the presence of CKD in Heart and Soul has been associated with increased cardiovascular risk.[16,17] Our proteomic analysis of the Heart and Soul cohort had 3 objectives: (1) To discern how reduced glomerular filtration rates impact the composition of the circulating proteome, by surveying the plasma concentrations of 1054 distinct proteins, (2) To learn of the importance of kidney function in the prognostic information contained in the previously identified 196 cardiovascular risk biomarkers[9] by correcting their hazard ratios for glomerular filtration rate; this correction also generates a set of biomarker proteins that are capable of predicting cardiovascular risk independently of kidney function and (3) To identify cardiovascular risk biomarkers specifically in patients with CKD by conducting a de novo biomarker discovery among the previously measured 1054 plasma proteins. Of great interest was discovery of any cardiovascular risk biomarkers that are unique to patients with CKD and to help identify the effect of variations in glomerular filtration rates on disease-related pathways involved in processes such as atherosclerosis, inflammation, and angiogenesis.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files).

Study population

The cohort and study protocol was approved by the appropriate institutional review boards: the University of California San Francisco Committee on Human Research, the Research and Development Committee at the San Francisco Veterans Affairs Medical Center, the Medical Human Subjects Committee at Stanford University, the Human Subjects Committee at the Veterans Affairs Palo Alto Health Care System, and the Data Governance Board of the Community Health Network of San Francisco. All participants provided written informed consent. The Heart and Soul is a prospective cohort of patients with stable coronary artery disease from 12 clinics in the San Francisco Bay Area. Participants were enrolled from September 2000 to December 2002, with last follow-up in November 2011.[9] They were recruited based on ≥1 of the following eligibility criteria: history of myocardial infarction (MI), angiographic evidence of at least 50% stenosis in ≥1 coronary vessels, prior evidence of inducible ischemia by stress testing, or history of coronary revascularization. Exclusion criteria included MI within the previous

6 months, those unable to walk a block, or those planning to relocate within 2 years. Race was self-identified in a questionnaire with categories of white, black, Asian, Latino, or other. The Heart and Soul study was approved by the appropriate institutional review board and all participants provided written informed consent.[9] Events were defined as the first among: myocardial infarction, stroke, heart failure hospitalization, or mortality.

Assessment of Kidney Function and Definition of CKD

The design of the present study is summarized in a flowchart in Figure 1. Consistent with prior publications from Heart and Soul, we defined CKD as estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2.[15,18–20] An important objective of this study was to evaluate the association of plasma proteins with cardiovascular risk that is independent of kidney function. For this purpose, we adjusted the cardiovascular risk hazard ratios of prognostic proteins for eGFR, using the creatinine based CKD-Epi equation.[21–23]

Quantification of Proteins in Human Plasma by Modified Aptamers

The proteomic analysis consisted of the 938 baseline plasma samples from the Heart and Soul study.[9] Sample collection was standardized with fasted samples collected at the same time of day and centrifuged and frozen within 1 hour of sample collection. The method of quantification of plasma proteins using modified aptamers has been described previously.[9,24,25] In brief, each of the 1130 individual proteins measured has its binding reagent made of chemically modified DNA, referred to as a modified aptamer. Each sample of plasma was incubated with the mixture of modified aptamers to generate modified aptamer-protein complexes under equilibrium conditions. Unbound modified aptamers and unbound or non-specifically bound proteins were eliminated by 2 bead-based immobilization steps. After eluting the modified aptamers from the target protein, the fluorescently labeled modified aptamers were directly quantified on a hybridization array (Agilent Technologies, Santa Clara, CA). Calibrators were included so that the degree of fluorescence was a consistent reflection of protein concentration. In a prior study we reported the repeatability of the modified aptamer assay by establishing the coefficients of variation for 1129 proteins (one fewer protein than in the current study).[25] The distribution of coefficients of variation across these 1129 proteins is provided in Table S1. The median coefficient of variation was 3.9% and 95% of proteins had a coefficient of variation ≤10.5%. The 1054 proteins that passed all the quality control metrics[9] are the focus of the analyses in the present study. We have reported that 200 proteins were prognostic of cardiovascular risk from the analyses of 2 cohorts, Heart and

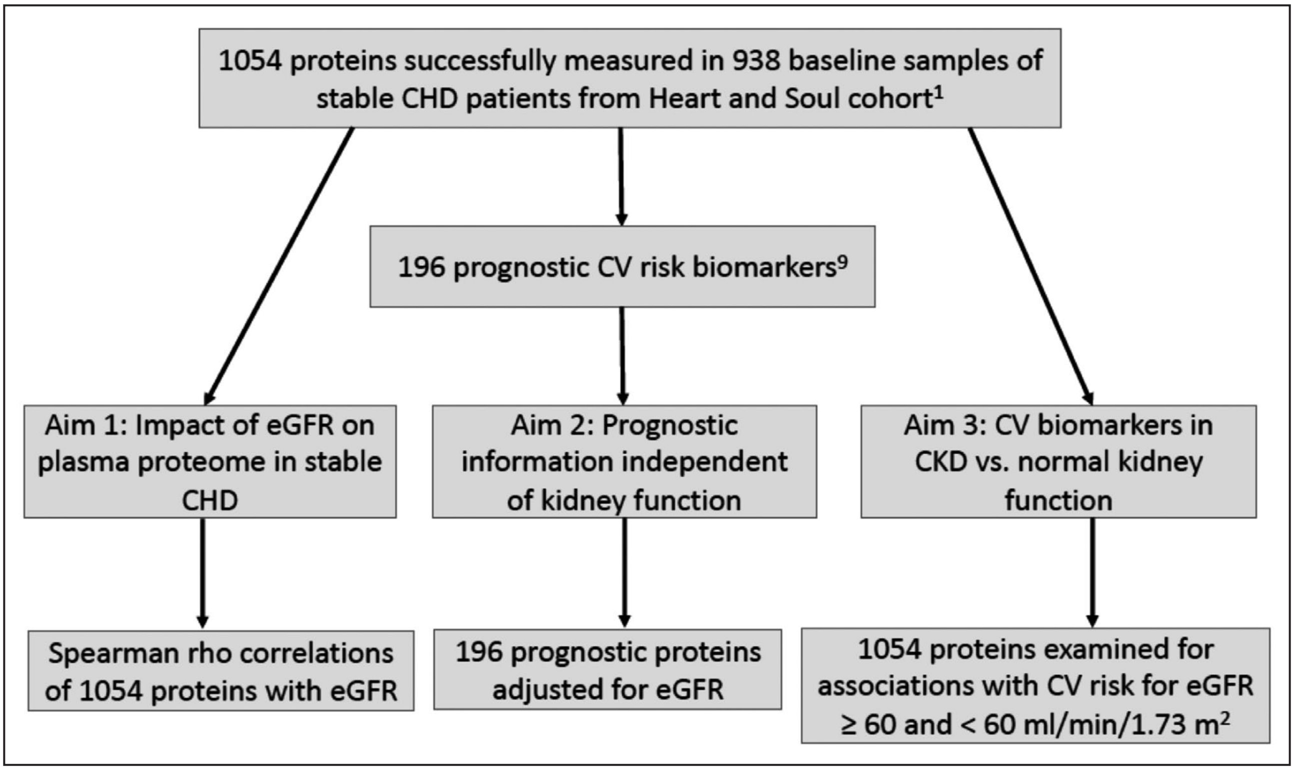

Figure 1. Study flowchart.[9]
CHD indicates coronary heart disease, CKD, chronic kidney disease; and eGFR, estimated glomerular filtration rate.

Table 1. Baseline Characteristics of the Study Participants

	Non-CKD	CKD	*P* value
No.	679	258	
Follow-up, y	8.9 (6–10)	7.6 (4–9)	<0.00001
Age, y	65 (57–72)	74 (66–79)	<0.00001
Men	555 (82)	217 (84)	0.39
Ethnicity			
White	401 (59)	164 (64)	0.6
Black	116 (17)	35 (14)	
Asian	80 (12)	27 (11)	
Latino	60 (9)	22 (9)	
Diabetes mellitus	166 (24)	80 (31)	0.04
Current smoker	152 (22)	32 (12)	0.003
Event rate, %/y	5.4	10.6	
Events during follow-up, No.	284 (42)	180 (70)	<0.00001
Time to event, y	8.9 (4.3–9)	5 (1.9–8.9)	<0.00001
BMI, kg/m^2	27.7 (24.8–31.4)	27.4 (24.9–30.5)	0.37
HDL-C, mg/dL	43 (36–54)	42 (34–52)	0.1
LDL-C, mg/dL	99 (82–124)	99 (82–119)	0.32
Total cholesterol, mg/dL	173 (150–199)	168 (146–195)	0.12
Triglycerides, mg/dL	108 (71–166)	119 (81–173)	0.12
Creatinine, mg/dL	0.8 (0.9–1.1)	1.4 (1.2–1.6)	<0.00001
eGFR, mL/min per 1.73 m^2	80.9 (71.1–93.1)	50.0 (40.1–55.4)	<0.00001
CRP, mg/L	2.1 (0.8–4.7)	2.7 (1.1–6.3)	0.004
Systolic blood pressure, mm Hg	130 (118–143)	135 (120–148)	0.001
Diastolic blood pressure, mm Hg	74 (68–80)	72 (68–80)	0.41

Continuous measures are presented as median (interquartile range); categorical measures are presented as n (%) of the column total. BMI indicates body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; and LDL, low-density lipoprotein cholesterol.

Soul and HUNT3 (Helseundersøkelsen i Nord-Trøndelag).[9] As the present analysis included only data from the Heart and Soul cohort, the applicable number of prognostic biomarkers proteins is 196, rather than 200. The Ingenuity Pathway Analysis (IPA) tool,[9,25] was used to evaluate common functional groups related to cardiovascular and renal disease. IPA recognized 1045 of the 1054 proteins measured, and 217 of the 218 proteins whose plasma level correlated with estimated glomerular filtration rates at $\rho \geq 0.2$.

Statistical Analysis

For population characteristics, we divided the cohort according to eGFR ≥60 mL/min per 1.73 m^2 (non-CKD group) and eGFR<60 mL/min per 1.73 m^2 (CKD group). Differences among continuous variables were tested using the Wilcoxon Rank Sum Test. Comparisons of categorial measures were made using Chi-squared analysis. Levels of plasma proteins were correlated with eGFR by Spearman rank correlation coefficients. Associations that were statistically significant at $P<0.05$ were defined as weak for absolute (ie, positive or negative) value of $\rho<0.2$, moderate for absolute ρ 0.2 to <0.5 and strong for absolute $\rho \geq 0.5$. Absolute values of rho are referred to as "rho". The primary outcome (referred to as the cardiovascular outcome) in this study was defined as the first event among MI, stroke/transient ischemic attack (referred to as stroke), heart failure hospitalization, or all-cause death.[9] Cox proportional hazard models were used to estimate the association between individual protein levels and risk of the primary outcome. In single-variable analysis of the associations between individual proteins and the primary outcome, Bonferroni-corrected significance levels were reported (p_{adj}) adjusting for all 1054 proteins measured. This resulted in a nominal significance level of $P_{adj}=4.74\times10^{-5}$. To find proteins prognostic of the primary outcome separately in patients without or with CKD, we divided the cohort according to the non-CKD group and CKD group, respectively.[21,22] Percentages reported are of the total 1054 proteins unless otherwise stated.

RESULTS

Population Characteristics

The baseline characteristics of the study participants, divided according to non-CKD (n=679) or CKD (n=258) populations are summarized in Table 1. One patient was excluded because of incomplete data. Median (interquartile range) eGFR was 80.9 (71.1–93.1) mL/min per 1.73 m^2 for non-CKD participants and 50.0 (40.1–55.4) mL/min per 1.73 m^2 for CKD participants ($P=2.0\times10^{-16}$). As expected, participants with CKD were older, more frequently diabetic, and had higher systolic blood pressures. They also had lower rates of current smoking. Also expected, time to events were shorter and the cardiovascular event rates (MI, stroke, heart failure, and death) were nearly twice as high in participants with CKD.

Impact of eGFR on the Circulating Plasma Proteome

Table S2 displays the Spearman rho correlations between eGFR and plasma levels for all 1054 proteins. Plasma levels of 709 proteins (67.3%) correlated with eGFR significantly ($P<0.05$). Of these, 24 proteins (2.3%), correlated with eGFR strongly ($\rho \geq 0.5$), 194 proteins (18.4%) moderately (ρ 0.2 to <0.5) and 491 proteins (46.6%) weakly (ρ 0.06 to <0.2). The histogram in

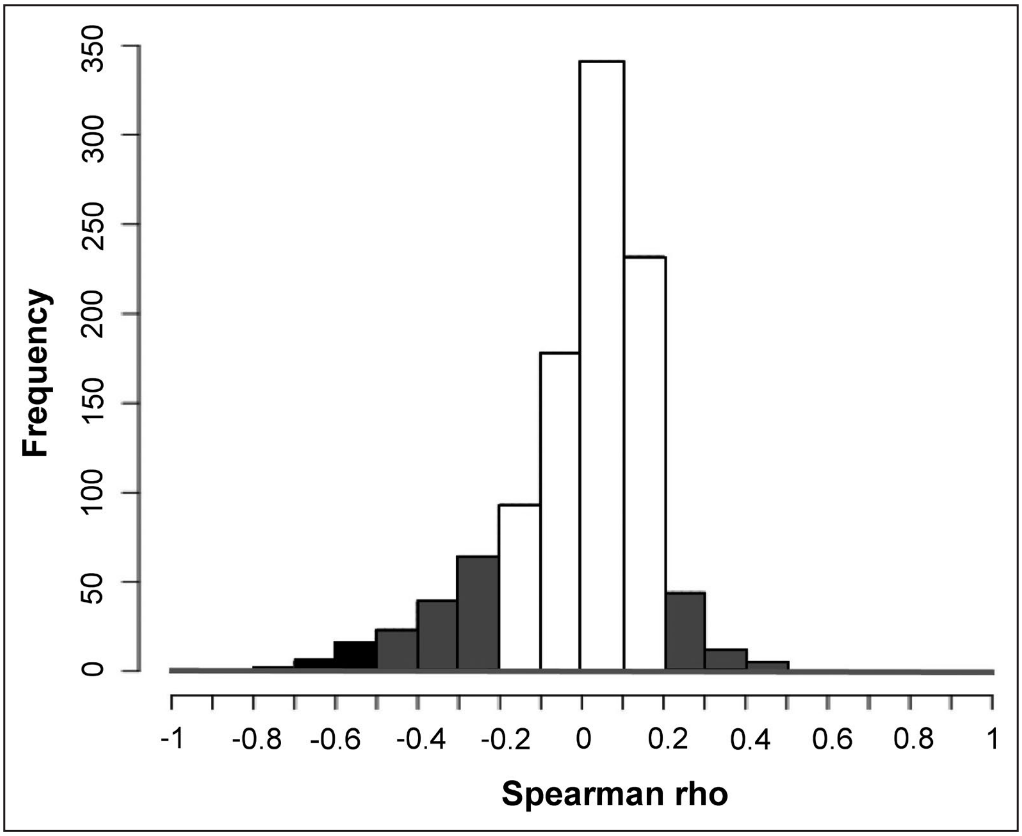

Figure 2. Distribution of Spearman rho correlations between the 1054 proteins measured and estimated glomerular filtration rate.
Strong correlation (black bars), moderate correlation (gray bars), weak correlation (white bars). The Spearman rho correlations for each of the 1054 proteins are shown in Table S2.

Figure 2 depicts the distribution of these correlations. Notably, for the 24 proteins that correlated with eGFR strongly, all the rho correlations were negative (ie, in each case, lower eGFR was associated with higher plasma protein levels). For the 194 proteins that correlated eGFR moderately, levels of 131 (12.4%) proteins correlated with eGFR negatively and 63 (6.0%) positively.

Figure 3 displays the number of proteins within 12 cardiovascular and renal disease-related biological functions whose plasma level is impacted by eGFR at $\rho \geq 0.2$. The top 3 functional groups based on the largest number of proteins affected by eGFR relate to angiogenesis (n=34 proteins), hypertension (n=21 proteins), and cardiac fibrosis (n=15 proteins).

Contribution of Kidney Function to Prognostic Information Contained Within 196 Cardiovascular Risk Biomarkers and Biomarkers Independent of Kidney Function

From the Heart and Soul cohort, we previously identified 196 proteins that are prognostic of cardiovascular risk.[9] By adjusting the hazard ratios of these biomarkers for eGFR, we discerned how much of the prognostic information they carry is attributable to kidney function. Only 87 of 196 proteins (44%) survived this adjustment (at a Bonferroni corrected *P* value<0.05), as shown in Table S3 with the hazard ratios and levels of statistical significance for all 196 proteins, before and after the eGFR correction.

Cardiovascular Risk Biomarkers in Chronic Kidney Disease Versus Normal Kidney Function

To discover biomarkers that are prognostic of cardiovascular risk in patients with CKD as compared with those with normal kidney function, we divided the cohort according to eGFR (Table 1). There were 679 non-CKD participants who had 285 cardiovascular events (MI, stroke, heart failure events, and death) and 258 participants with CKD who had 180 events.

At a Bonferroni corrected *P* value<P_{adj}, there were 84 proteins prognostic of cardiovascular risk in non-CKD patients (Table S3) and 21 proteins that were prognostic of cardiovascular risk in CKD patients

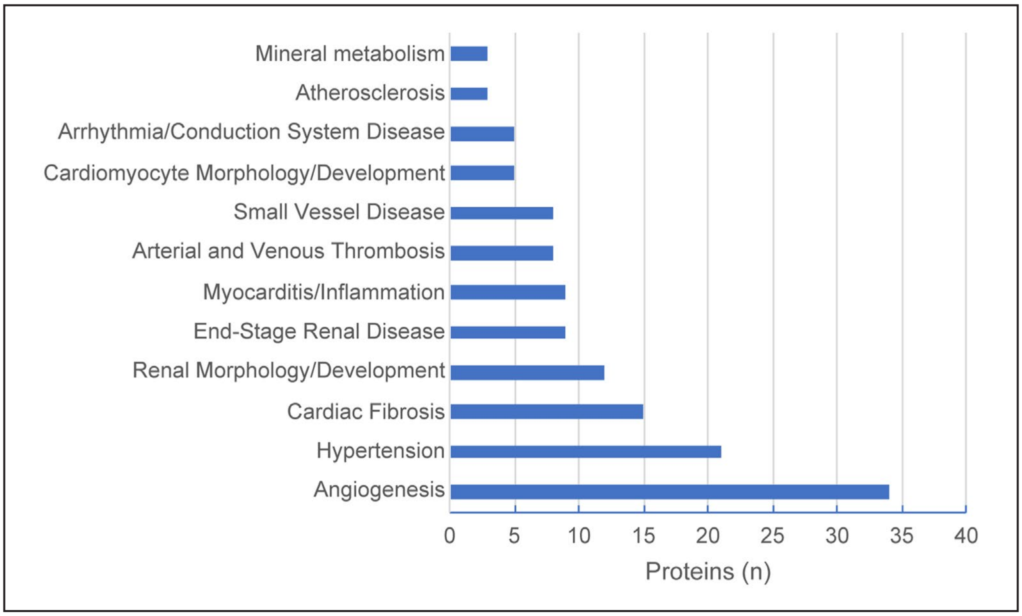

Figure 3. The number of plasma proteins whose level is impacted by estimated glomerular filtration rate at ρ≥0.2 for 12 cardiovascular and renal disease-related biological functions, derived from Ingenuity Pathway Analysis.

(Table 2). Among these 21 proteins, 8 proteins were unique to CKD (highlighted in grey color in Table 2). The plasma levels of these 8 proteins correlated significantly with eGFR, for one protein positively: dual 3’,5’-cyclic-AMP and -GMP phosphodiesterase 11A (ie, lower eGFR was associated with lower concentration of this protein) and for 7 proteins negatively (Table 2). The molecular weights and key biological functions derived from the literature and IPA annotations for these 21 protein cardiovascular risk biomarkers, including those 8 that are unique to CKD, are provided in Table 2.

Dividing the Heart and Soul cohort based on eGFR created 2 smaller groups, each with fewer outcome events. This likely reduced the statistical power to detect prognostic proteins within each smaller group by widening the CIs around each hazard ratio point estimate. To shed light on this issue, Figure S1 shows the point estimates and CIs of hazard ratios for each of the 196 proteins that were prognostic of cardiovascular risk in the full cohort and for the smaller groups of non-CKD and CKD participants.

DISCUSSION

Among patients with CKD, increased cardiovascular risk is a well-recognized cause of mortality and morbidity.[2,3] As this risk is not fully accounted for by traditional risk factors,[3] identification of new cardiovascular risk biomarkers has been a high priority in CKD research. Prior studies have suggested that reduced GFR and the biochemical changes associated with “uremic milieu” can impact the concentration of some circulating proteins[4–6] but the extent to which this occurs in patients with coronary heart disease, many of whom also have CKD,[16,17] has not been previously defined. The present study reached a new milestone by measuring a far greater number of plasma proteins than has otherwise been possible with targeted approaches. We used the Heart and Soul cohort to successfully accomplish 3 aims: (1) We conducted the largest survey to date of the impact of glomerular filtration rates on the composition of the plasma proteome in patients with coronary heart disease, making a total of nearly 1 million individual protein measurements. We found that reductions in eGFR broadly impact the circulating proteome and affect biological functions involved in cardiovascular and renal diseases. (2) We determined how much of the information among previously identified 196 cardiovascular biomarkers,[9] relates specifically to kidney function by adjusting their hazard ratios for eGFR. We found that kidney function contributes prominently to the prognostic information carried by cardiovascular protein biomarkers—fewer than half of these biomarkers survived the adjustment for eGFR. In this process, we identified 87 protein biomarkers that remained prognostic of cardiovascular risk, and that can contribute to cardiovascular risk modeling independently of kidney function. (3) We conducted a de novo proteomic discovery in the Heart and Soul cohort that informed 21 biomarkers of cardiovascular risk specifically in patients with CKD. From this analysis, we identified 8 cardiovascular biomarkers that are unique to patients with CKD.

Table 2. Twenty-One Proteins Prognostic of Cardiovascular Risk in Patients With CKD

Protein	UniProt ID	Molecular Weight (kDa)	HR	*P* value	Spearman ρ	*P* value ρ	Biological Function
Tumor necrosis factor receptor superfamily member 1A	P19438	50.5	1.31	1.63×10^{-05}	−0.65	8.84×10^{-112}	Soluble form of TNF-alpha receptor. Antagonizes activity of TNF-alpha
Beta-2-microglobulin	P61769	14	1.34	1.10×10^{-05}	−0.63	2.33×10^{-100}	Part of major histocompatibility complex. Involved in inflammatory response
Tumor necrosis factor receptor superfamily member 27	Q9HAV5	32.8	1.32	4.44×10^{-06}	−0.53	9.33×10^{-66}	Involved in ectodermal and epidermal development
Metalloproteinase inhibitor 1	P01033	23	1.51	7.23×10^{-08}	−0.43	1.32×10^{-42}	Extracellular matrix remodeling and turnover.
Hepatitis A virus cellular receptor 2	Q8TDQ0	33.4	1.39	4.05×10^{-05}	−0.41	3.04×10^{-37}	Co-inhibitory molecule that regulates T-cell activation or tolerance
Platelet-activating factor acetylhydrolase IB subunit beta	P68402	30	1.36	7.98×10^{-07}	−0.38	1.91×10^{-32}	Degrades platelet-activating factor. Mediator of inflammation
Tumor necrosis factor receptor superfamily member 9	Q07011	27.9	1.35	1.47×10^{-05}	−0.33	1.57×10^{-23}	Co-stimulator of T-cells
Phosphatidylethanolamine-binding protein 1	P30086	21.1	1.33	4.55×10^{-05}	−0.28	7.64×10^{-17}	Tumor suppressor gene
Fibroblast growth factor 7	P21781	36	1.39	1.84×10^{-06}	−0.25	4.18×10^{-14}	Tissue repair. Tumor growth and survival
Troponin I, cardiac muscle	P19429	24.0	1.31	1.67×10^{-05}	−0.23	1.08×10^{-11}	Marker of myocardial damage
Tyrosine-protein kinase, yes	P07947	60.8	1.39	1.25×10^{-05}	−0.21	8.46×10^{-10}	Src family of oncogenes. Regulates cell growth and survival
Angiopoietin-2	O15123	56.9	1.66	5.62×10^{-12}	−0.14	2.85×10^{-05}	Modulates vascular development and remodeling during angiogenesis and inflammation
PSA:alpha-1-antichymotrypsin complex	P07288, P01011	76.4	1.42	5.12×10^{-06}	−0.13	0.00011	Acute phase reactant protein. Expressed in several malignancies
Complement component C7	P10643	110	1.57	1.79×10^{-09}	−0.12	0.00065	Involved in innate immunity.
Ubiquitin+1, truncated mutation for UbB	P62979	18	1.32	2.92×10^{-05}	−0.12	0.00048	Frameshift mutation of Ubiquitin. Associated with neurodegenerative disorders
Interleukin-8	P10145	11.1	1.3	2.12×10^{-05}	0.03	0.36	Chemoattractant that promotes activation of monocytes and neutrophils
Cadherin-3	P22223	91.4	0.71	3.37×10^{-06}	0.26	1.60×10^{-14}	Calcium-dependent cell adhesion molecule. Tumor suppressor role
Growth hormone receptor	P10912	71.5	0.69	6.45×10^{-07}	0.26	3.70×10^{-15}	Activates JAK-STAT signaling pathways that alter calcium signaling in contractile and cytoskeletal proteins.
Proto-oncogene tyrosine-protein kinase receptor Ret	P07949	124.3	0.7	2.65×10^{-05}	0.31	3.04×10^{-21}	Gain of function mutation results in cancer syndromes
Dual 3′,5′-cyclic-AMP and -GMP phosphodiesterase 11A	Q9HCR9	104.8	0.71	2.98×10^{-05}	0.37	3.29×10^{-30}	Binds cAMP and cGMP. Similar to PDE-5
Epidermal growth factor receptor	P00533	134.3	0.71	1.41×10^{-05}	0.44	5.89×10^{-45}	Regulates epithelial tissue development and homeostasis

Proteins unique to patients with chronic kidney disease are shown in gray color. CKD indicates chronic kidney disease; HR, hazard ratio; and TNF, tumor necrosis factor.

Notably, levels of approximately of the 1054 proteins measured (67.3%) were significantly correlated with eGFR demonstrating that a large portion of the circulating proteome is impacted to some degree by a decline in kidney function (rho coefficients ranged from 0.06–0.74, Table S2). For one fifth of the circulating proteome (20.7%) levels of proteins were moderately or strongly correlated with eGFR ($\rho \geq 0.2$). As many of the proteins we measured are cytokines, chemokines, adipokines, growth factors and hormones that orchestrate biological functions,[12] any changes in their circulating concentrations have implications for the risk of cardiovascular and other diseases. Concretely, Figure 3 displays cardiovascular and renal disease-related pathways derived from IPA for the 217 proteins recognized by the IPA, whose circulating levels are associated with eGFR at $\rho \geq 0.2$. The observed shift in the proteome as eGFR declines involves critical functions in cardiovascular and renal diseases, such as angiogenesis, control of blood pressure (hypertension) and cardiac fibrosis (Figure 3), providing a plausible biological underpinning to the host of cardiovascular and non-cardiovascular co-morbidities reported in patients with CKD. Interestingly, in addition to the cardiovascular and renal disease pathways shown in Figure 3, there was a substantial number of proteins involved in pathways leading to the development of gastrointestinal tract tumors (not shown). Notably, increased risk of gastrointestinal, urinary tract, and endocrine tumors has been reported in patients with end-stage renal disease.[26]

Our findings of the impact of reduced eGFR on the circulating proteome is supported by a recent report from Lund, Sweden.[5] In their study, 389 participants whose kidney function ranged from stage I to stage V CKD had their glomerular filtration assessed directly with iohexol and a total of 2893 circulating proteins were measured with modified aptamers. Despite major differences between their and our studies (eg. the Lund cohort consisted of patients referred for evaluation of suspected kidney disease, regardless of their cardiovascular status which was not reported;[5] their samples consisted of LiHeparin plasma whereas ours were EDTA plasma; 2 different versions of the modified aptamer SOMAscan platform were used; the Lund cohort had greater representation of patients with advanced CKD), our findings and those from Lund[5] are remarkably consistent, providing important external validation to our findings. This is illustrated in Table S4 which compares the rho coefficients for the top 100 proteins from our Heart and Soul cohort to the same proteins assessed in the Lund cohort (98 proteins in common to the 2 cohorts are shown). The scatterplot of these 98 rho coefficients shows generally good agreement between findings in our Heart and Soul and the Lund cohorts (Figure S2).

The observed changes in the plasma proteome across eGFR can be explained through several potential mechanisms. (1) Concentration of specific proteins may vary by the function of the kidney which filters, potentially reabsorbs, and catabolizes many low molecular weight proteins. As filtration by glomeruli occurs freely for proteins <15 kDa and relatively rapidly for proteins 15 to 45 kDa,[6] any plasma accumulation of proteins of that size can be at least partly attributable to their reduced glomerular filtration. To inform this issue, Table S2 also lists the molecular weights for all 1054 proteins that we measured along with their rho correlations with eGFR. (2) Additionally, healthy kidneys serve as a rich source of circulating proteins.[27,28] Accordingly, the loss of renal parenchyma in CKD can reduce the plasma levels of some proteins, with circulating erythropoietin in CKD as a well-known clinical example.[29] (3) Lastly, kidney function is susceptible to damage from many of the same risk factors that lead to atherosclerotic cardiovascular disease, with diabetes mellitus or hypertension as familiar examples.[7] Changes in the circulating proteome in patients with CKD can thus reflect the effect of shared cardiovascular and renal risk factors.[7]

Determining disease-based risk through identification of novel biomarkers, as well as development of individualized risk prediction models are the key objectives of the field of precision (personalized) medicine.[30] We previously constructed a proteomic cardiovascular risk model based on a discovery program for new biomarkers using a large-scale, agnostic proteomics approach.[9] Likewise, the current study relied on the same large-scale methodology to identify protein biomarkers that are prognostic of cardiovascular risk in patients with CKD. We first focused on the 196 cardiovascular risk biomarkers that we had identified[9] that did not previously account for kidney function in their discovery. After correcting for eGFR, the number of prognostic proteins fell from 196 to just 87, signifying that kidney function contributes prominently to cardiovascular risk information contained in many circulating proteins. The hazard ratios for all 196 protein cardiovascular biomarkers before and after correction for eGFR are listed in Table S3. Conversely, the 87 proteins that survived the eGFR correction (shown in Table S3) are able to serve as cardiovascular risk biomarkers independently of eGFR.[9]

In our second approach to elucidating cardiovascular risk protein biomarkers in CKD, we conducted de novo discovery for such biomarkers, separately for individuals with CKD and those with normal kidney function. At a Bonferroni corrected *P* value$<P_{\text{adj}}$, among the 1054 proteins measured, we identified 84 proteins that were prognostic of cardiovascular risk in participants with normal kidney function (eGFR≥60 mL/min per 1.73 m^2, shown in Table S5) and 21 proteins that were

prognostic of cardiovascular risk specifically in participants with CKD (Table 2). As summarized in Table 2, based on literature review and IPA annotations, these 21 proteins are involved in a number of pathobiological processes including angiogenesis, inflammation, cell signaling with extracellular matrix interactions, tissue repair, and malignant transformation of cells. These cardiovascular risk biomarkers in patients with CKD should be investigated in future studies as potential causal mediators in this setting. Of particular interest, among these 21 proteins are 8 proteins that are prognostic of cardiovascular risk only among individuals with CKD but not among those with normal kidney function (highlighted in grey color in Table 2). The molecular weights of these 21 protein biomarkers in CKD and their rho correlations with eGFR are described in Table 2. Notably, only 2 of these 21 prognostic proteins were strongly associated with eGFR ($\rho \geq 0.5$) while, conversely, 22 of 24 proteins strongly associated with eGFR (Table S2) were not prognostic of cardiovascular risk in the setting of CKD (Table S2). These results suggest that these 21 proteins carry prognostic information that extends beyond glomerular filtration.

The high fidelity of the SOMAscan proteomic assay has been previously established in several ways. The effect of cis-genetic variants on protein expression measured by the modified aptamer (SOMAscan) assay has been published for 552[12] and 1046[13] variants and confirmed that the assay was measuring the intended protein target. Furthermore, orthogonal validation of the target protein by mass spectrometry has been performed for ~1000 aptamer reagents.[13] Overall, these data have suggested that the large majority of modified aptamers are highly specific for their cognate protein targets.[12] Notably, the specificity of the modified aptamers for their target proteins has been verified for 19 of the 21 protein cardiovascular risk biomarkers in CKD that we have discovered in the present analysis (tumor necrosis factor receptor superfamily member 9 and phosphatidylethanol-amine-binding protein 1 were not evaluated), as part of a larger study to confirm the specificity of 920 aptamers by mass spectometry.[12] In addition, for 16 of these 19 aptamers tested, there was no cross-reactivity with proteins closely related to the target proteins (defined as proteins with >40% sequence identity with the target protein or members of the same protein family), while for 3 proteins (angiopoeitin-2, tyrosine kinase YES, and epidermal growth factor receptor), weak cross-reactivity with closely related proteins was noted.[12] Other methods for orthogonal correlations such as ELISA, are not readily available for a wide range of proteins that we measured and have their own challenges with respect to target specificity and cross-reactivity.

Among the 8 prognostic proteins unique to CKD, shown in Table 2, platelet-activating factor acetylhydrolase IB subunit beta (also known as lipoprotein-associated phospholipase A2) degrades platelet-activating factor and regulates inflammation.[31] FGF-7 (fibroblast growth factor) is an epithelial specific growth factor involved in tissue repair as well as tumor growth and survival.[32,33] Tyrosine kinase YES is a member of the Src family of oncogenes and regulates cell growth and survival.[34,35] Tumor necrosis factor receptor superfamily member 9 is a member of the TNF-receptor family and functions a co-stimulator of T-cells.[36] Tumor necrosis factor receptor superfamily member 1A is a soluble form of the TNF-alpha receptor and antagonizes its activity.[37–39] Tumor necrosis factor receptor superfamily member 1A has been established as a predictor of cardiovascular outcomes in advanced CKD and may play a role in heart failure.[37–40] Ubiquitin+1 is a frameshift mutation of Ubiquitin, affecting the proteasome degradation system.[41–44] Ubiqutin+1 has been associated with neurodegenerative disorders. Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase-11 binds both cAMP and cGMP and bears similarity to PDE-5.[45,46] Phosphatidylethanolamine-binding protein 1 acts as a tumor suppressor gene and also activates the beta-adrenergic receptor, playing an adaptive role in heart failure.[47–49] From the cardiovascular risk standpoint, among these 8 proteins, platelet-activating factor acetylhydrolase IB subunit beta (lipoprotein-associated phospholipase A2) has been suspected of being involved in the pathogenesis of atherosclerosis. Although clinical trials of lipoprotein-associated phospholipase A2 inhibition with darapladib did not demonstrate a clinical benefit,[50,51] given our findings of a strong association of this biomarker with cardiovascular risk in patients with CKD, one might plausibly ask if the result may have been different in a trial that specifically targeted the CKD population. Admittedly, we do not yet know if our lipoprotein-associated phospholipase A2 aptamer assay measures protein abundance (as expected of a binding assay) or whether it also informs its enzymatic activity. In the subgroup analysis of cardiovascular biomarkers in CKD or no CKD, the total number of participants and cardiovascular outcome events in each group was smaller than in the total cohort, likely leading to fewer prognostic biomarkers in each group. Notably, among the 196 prognostic proteins, there were additional proteins that trended towards statistical significance threshold within the CKD or no CKD smaller groups (shown in Figure S1).

In conclusion, by scanning the plasma proteome for 1054 distinct proteins, we have shown in patients with coronary heart disease that kidney function has a broad impact on the circulating proteome and specifically on biological functions relevant to cardiovascular and renal diseases. We have described protein biomarkers that predict cardiovascular risk in CKD independently of glomerular filtration and biomarkers that were newly discovered specifically to predict cardiovascular risk in CKD. The impact of eGFR on the plasma levels of 1054 individual proteins shown in Table S2, the hazard ratios for the associations of proteins with cardiovascular risk in the 1054 proteins before and after eGFR correction also shown here in Table S2 as well as the discovery of 21 proteins that specifically predict cardiovascular risk in CKD shown in Table 2, will provide a wealth of new leads for future academic investigations and drug discovery in the field of CKD. Future studies, for example using Mendelian randomization, will determine which of the cardiovascular risk biomarkers in CKD that we have described are also causal cardiovascular disease mediators and thus desirable new therapeutic targets to reduce this risk in patients with CKD.

Our study had many strengths but also some limitations. The present study from the Heart and Soul cohort focuses on patients with kidney function ranging from normal to moderately reduced. Future studies with greater representation of patients with CKD stages 4 and 5 are needed. Furthermore, in the present study, our rigorous statistical approach that adjusted for multiplicity of testing during biomarker discovery led to a statistical significance threshold of $P_{adj}=4.74\times10^{-5}$. This stringent threshold excluded some familiar cardiovascular risk biomarkers in CKD, notably fibroblast growth factor 23 (which had hazard ratio, 1.18; $P=0.0039$), whereas the 21 aforementioned protein biomarkers had stronger associations with cardiovascular risk (Table 2). Lastly, we present convincing external validation for the impact of eGFR on the composition of the circulating proteome (ie, the Lund cohort) but further validation in external cohorts will be needed for the 21 cardiovascular risk biomarkers that we report in patients with CKD.

ARTICLE INFORMATION

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Disclosures

Dr. Ganz serves on a medical advisory board to SomaLogic, Inc., for which he accepts no salary, honoraria, or any other financial incentives. Drs. Brody, Mehler, Weiss, DeLisle, Ostroff, and Williams are employees of SomaLogic, Inc. SomaLogic had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the article. Dr Ganz had the ultimate responsibility for all aspects of this study. SomaLogic, Inc., had no veto rights concerning the decision to submit the article for publication. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Summary of the average total-run (i.e. intra-run plus inter-run) % coefficients of variation (%CVs) for 1129 proteins measured by modified aptamers in EDTA plasma across 3 runs, each run performed by a different laboratory technician.

Percentile of protein targets	Total-Run %CV
5%	≤ 2.4%
25%	≤ 3.1%
50%	≤ 3.9%
75%	≤ 5.0%
95%	≤ 10.5%

The average was computed from three individual samples performed in triplicate on each run.

Table S2. Spearman rho correlations between eGFR (CKD-EPI 2009) and plasma concentrations of 1054 proteins measured.

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Cystatin-C	P01034	-0.74	$1.12x10^{-163}$	15.799
Insulin-like growth factor-binding protein 6	P24592	-0.7	$2.86x10^{-138}$	25.322
Tumor necrosis factor receptor superfamily member 1A	P19438	-0.65	$2.51x10^{-114}$	50.495
Neuroblastoma suppressor of tumorigenicity 1	P41271	-0.64	$2.29x10^{-109}$	23.169
Beta-2-microglobulin	P61769	-0.63	$1.11x10^{-102}$	13.715
Tumor necrosis factor receptor superfamily member 19L	Q969Z4	-0.62	$1.01x10^{-100}$	46.092
Cathepsin H	P09668	-0.61	$1.51x10^{-95}$	37.394
Follistatin-related protein 3	O95633	-0.58	$7.07x10^{-87}$	27.663
Endothelial cell-selective adhesion molecule	Q96AP7	-0.58	$4.98x10^{-86}$	15.170
Adapter molecule crk	P46108	-0.58	$2.86x10^{-85}$	33.831
Cerebral dopamine neurotrophic factor	Q49AH0	-0.57	$3.10x10^{-81}$	20.964
RGM domain family member B	Q6NW40	-0.54	$1.43x10^{-73}$	47.547
Ephrin-A5	P52803	-0.53	$3.39x10^{-70}$	26.297
Trefoil factor 3	Q07654	-0.53	$6.07x10^{-69}$	8.641
Tumor necrosis factor receptor superfamily member 27	Q9HAV5	-0.53	$1.33x10^{-67}$	32.759
Endostatin	P39060	-0.52	$1.03x10^{-66}$	178.188
Ephrin-A4	P52798	-0.52	$3.27x10^{-66}$	22.386
Netrin receptor UNC5C	O95185	-0.51	$1.43x10^{-64}$	103.146
Ephrin type-B receptor 6	O15197	-0.51	$3.98x10^{-64}$	110.700
Tumor necrosis factor receptor superfamily member 1B	P20333	-0.51	$1.40x10^{-63}$	48.291
Glutathione S-transferase P	P09211	-0.51	$5.89x10^{-62}$	23.356
C-C motif chemokine 14	Q16627	-0.5	$3.76x10^{-61}$	10.678

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Macrophage-capping protein	P40121	-0.5	6.26×10^{-61}	38.499
Junctional adhesion molecule B	P57087	-0.5	2.76×10^{-59}	33.207
Layilin	Q6UX15	-0.49	1.56×10^{-57}	43.108
Ephrin type-A receptor 2	P29317	-0.49	2.11×10^{-57}	54.305
Tyrosine-protein kinase transmembrane receptor ROR1	Q01973	-0.48	2.10×10^{-56}	104.283
Scavenger receptor class F member 1	Q14162	-0.47	1.69×10^{-53}	87.387
Fatty acid-binding protein, heart	P05413	-0.47	2.37×10^{-52}	14.858
Testican-2	Q92563	0.46	2.58×10^{-51}	46.779
Netrin receptor UNC5D	Q6UXZ4	-0.46	3.25×10^{-49}	105.880
Myoglobin	P02144	-0.45	4.71×10^{-49}	17.184
Tumor necrosis factor receptor superfamily member 19	Q9NS68	-0.45	3.70×10^{-47}	46.015
Elafin	P19957	-0.45	6.13×10^{-47}	12.270
Epidermal growth factor receptor	P00533	0.44	1.96×10^{-46}	134.277
Interleukin-15 receptor subunit alpha	Q13261	-0.44	8.60×10^{-46}	28.233
Receptor tyrosine-protein kinase erbB-3	P21860	0.43	4.03×10^{-44}	148.098
Metalloproteinase inhibitor 1	P01033	-0.43	4.76×10^{-44}	23.171
Antileukoproteinase	P03973	-0.43	1.81×10^{-42}	14.326
Cystatin-M	Q15828	-0.42	3.97×10^{-41}	16.511
Cathepsin L2	O60911	0.42	1.66×10^{-40}	37.329
Chordin-like protein 1	Q9BU40	-0.41	7.30×10^{-40}	51.168
Complement factor D	P00746	-0.41	8.38×10^{-40}	27.033
Coiled-coil domain-containing protein 80	Q76M96	-0.41	9.08×10^{-40}	10.174

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Delta-like protein 1	O00548	-0.41	1.12x10^{-39}	78.056
Complement decay-accelerating factor	P08174	-0.41	2.69x10^{-39}	41.400
Hepatitis A virus cellular receptor 2	Q8TDQ0	-0.41	1.35x10^{-38}	33.394
Alpha-2-antiplasmin	P08697	0.41	1.42x10^{-38}	54.566
Tumor necrosis factor ligand superfamily member 15	O95150	-0.4	3.90x10^{-38}	28.087
Neurexin-1-beta	P58400	-0.4	4.40x10^{-3}8	50.424
Tumor necrosis factor receptor superfamily member 21	O75509	-0.4	1.62x10^{-37}	71.845
Ck-beta-8-1	P55773	-0.4	1.80x10^{-36}	13.411
Neurexin-3-beta	Q9HDB5	-0.39	5.94x10^{-36}	69.305
Cystatin-SA	P09228	-0.38	2.99x10^{-34}	16.455
Bone morphogenetic protein 1	P13497	0.38	6.44x10^{-34}	111.249
Kallikrein-11	Q9UBX7	-0.38	6.96x10^{-34}	31.059
Platelet-activating factor acetylhydrolase IB subunit beta	P68402	-0.38	1.05x10^{-33}	25.569
C-C motif chemokine 23	P55773	-0.38	1.05x10^{-33}	13.411
Macrophage metalloelastase	P39900	-0.38	1.22x10^{-33}	54.002
Endoplasmic reticulum resident protein 29	P30040	-0.38	1.61x10^{-33}	28.993
SLIT and NTRK-like protein 5	O94991	-0.38	4.63x10^{-33}	107.486
Transforming growth factor beta receptor type 3	Q03167	-0.38	7.66x10^{-33}	93.499
Insulin-like growth factor-binding protein 2	P18065	-0.37	2.00x10^{-32}	34.814
Vascular endothelial growth factor receptor 2	P35968	0.37	1.48x10^{-31}	151.527
Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A	Q9HCR9	0.37	2.03x10^{-31}	104.752
Matrilysin	P09237	-0.37	4.55x10^{-31}	29.677

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Dual specificity mitogen-activated protein kinase kinase 2	P36507	-0.36	1.00×10^{-30}	44.424
Retinoic acid receptor responder protein 2	Q99969	-0.36	1.12×10^{-30}	18.618
Cell adhesion molecule 3	Q8N126	-0.36	1.70×10^{-30}	43.300
A disintegrin and metalloproteinase with thrombospondin motifs 13	Q76LX8	0.36	5.02×10^{-30}	153.604
Pappalysin-1	Q13219	-0.36	8.10×10^{-30}	180.973
Resistin	Q9HD89	-0.36	9.52×10^{-30}	11.419
Tissue Factor	P13726	-0.36	1.18×10^{-29}	33.068
Cystatin-D	P28325	-0.36	1.91×10^{-29}	16.080
Cell adhesion molecule-related/down-regulated by oncogenes	Q4KMG0	0.35	5.31×10^{-29}	139.147
Interleukin-17 receptor C	Q8NAC3	-0.35	1.30×10^{-28}	86.240
Cystatin-SN	P01037	-0.35	4.37×10^{-28}	16.388
Carbonic anhydrase 3	P07451	-0.35	6.17×10^{-28}	39.557
Kallikrein-8	O60259	-0.35	8.80×10^{-28}	28.048
Fibroblast growth factor 20	Q9NP95	0.35	1.17×10^{-27}	23.499
Melanoma-derived growth regulatory protein	Q16674	-0.34	2.30×10^{-26}	14.509
Ciliary neurotrophic factor receptor subunit alpha	P26992	-0.33	5.32×10^{-26}	40.633
Urokinase plasminogen activator surface receptor	Q03405	-0.33	1.17×10^{-25}	36.978
Tumor necrosis factor receptor superfamily member EDAR	Q9UNE0	-0.33	3.60×10^{-25}	48.582
Interleukin-19	Q9UHD0	0.33	5.40×10^{-25}	20.452
Interleukin-16	Q14005	-0.33	1.23×10^{-24}	141.752
Tumor necrosis factor receptor superfamily member 9	Q07011	-0.33	1.29×10^{-24}	27.899

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
gp41 C34 peptide, HIV	Q70626	-0.32	2.84×10^{-24}	96.938
Ficolin-3	O75636	0.32	4.56×10^{-24}	32903
Angiostatin	P00747	0.32	5.15×10^{-24}	90.569
Vascular endothelial growth factor A	P15692	-0.32	1.72×10^{-23}	27.042
Matrilin-2	O00339	-0.32	2.73×10^{-23}	106.837
NudC domain-containing protein 3	Q8IVD9	-0.31	7.58×10^{-23}	40.822
Pancreatic hormone	P01298	-0.31	1.44×10^{-22}	10.445
6-phosphogluconate dehydrogenase, decarboxylating	P52209	0.31	1.86×10^{-22}	53.140
SHC-transforming protein 1	P29353	-0.31	2.68×10^{-22}	62.822
Proto-oncogene tyrosine-protein kinase receptor Ret	P07949	0.31	2.80×10^{-22}	124.319
OX-2 membrane glycoprotein	P41217	-0.31	3.21×10^{-22}	31.264
Ephrin type-A receptor 1	P21709	-0.31	8.34×10^{-22}	108.127
Agouti-related protein	O00253	-0.31	1.16×10^{-21}	14.440
Ubiquitin-fold modifier-conjugating enzyme 1	Q9Y3C8	-0.3	1.88×10^{-21}	19.458
Neurexophilin-1	P58417	0.3	3.94×10^{-21}	31.082
Interleukin-18-binding protein	O95998	-0.3	9.17×10^{-21}	21.099
Trypsin-2	P07478	-0.3	1.04×10^{-20}	26.488
Platelet glycoprotein VI	Q9HCN6	-0.3	1.19×10^{-20}	36.866
Fibroblast growth factor receptor 1	P11362	-0.3	1.39×10^{-20}	91.868
Cryptic protein	P0CG37	-0.29	5.14×10^{-20}	24.612
Superoxide dismutase [Mn], mitochondrial	P04179	0.29	1.74×10^{-19}	24.750
Creatine kinase M-type:Creatine kinase B-type heterodimer	P12277 P06732	0.29	2.83×10^{-19}	42.644

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
C-C motif chemokine 18	P55774	-0.29	$5.46x10^{-19}$	9.849
Junctional adhesion molecule C	Q9BX67	-0.28	$8.00x10-^{19}$	35.020
Follistatin	P19883	-0.28	$2.04x10^{-18}$	38.007
Ephrin type-B receptor 2	P29323	-0.28	$2.58x10^{-18}$	117.493
Metalloproteinase inhibitor 3	P35625	0.28	$3.55x10^{-18}$	24.145
Malate dehydrogenase, cytoplasmic	P40925	0.28	$5.64x10-^{18}$	36.426
Vascular endothelial growth factor C	P49767	-0.28	$5.67x10^{-18}$	46.883
Lysozyme C	P61626	-0.28	$6.48x10^{-18}$	16.537
Alcohol dehydrogenase [NADP(+)]	P14550	-0.28	$7.46x10^{-18}$	36.573
Aminoacylase-1	Q03154	0.28	$7.65x10^{-18}$	45.885
Phosphatidylethanolamine-binding protein 1	P30086	-0.28	$8.69x10^{-18}$	21.057
Thrombospondin-4	P35443	-0.28	$8.85x10^{-18}$	105.869
Neurogenic locus notch homolog protein 3	Q9UM47	-0.27	$1.30x10^{-17}$	243.631
Mitogen-activated protein kinase 11	Q15759	-0.27	$1.41x10^{-17}$	41.357
SLAM family member 5	Q9UIB8	-0.27	$1.77x10^{-17}$	38.782
Plasminogen	P00747	0.27	$4.34x10^{-17}$	90.569
Complement factor B	P00751	0.27	$4.61x10^{-17}$	85.533
Cathepsin Z	Q9UBR2	-0.27	$6.60x10^{-17}$	33.868
Stromelysin-1	P08254	-0.27	$9.69x10^{-17}$	53.977
Dickkopf-related protein 3	Q9UBP4	-0.27	$1.52x10^{-16}$	38.390
14-3-3 protein sigma	P31947	-0.26	$2.39x10^{-16}$	27.774
Mitogen-activated protein kinase 12	P53778	-0.26	$3.64x10^{-16}$	41.940
C-type lectin domain family 4 member M	Q9H2X3	0.26	$3.75x10^{-16}$	45.350

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Growth hormone receptor	P10912	0.26	4.67×10^{-16}	30.120
Tumor necrosis factor receptor superfamily member 4	P43489	-0.26	5.87×10^{-16}	29.341
Reticulon-4 receptor	Q9BZR6	-0.26	6.17×10^{-16}	50.708
Legumain	Q99538	0.26	1.15×10^{-15}	49.411
Brain-specific serine protease 4	Q9GZN4	-0.26	1.17×10^{-15}	33.732
Glypican-3	P51654	0.26	1.54×10^{-15}	65.563
Interleukin-17F	Q96PD4	-0.26	1.97×10^{-15}	18.045
Cadherin-3	P22223	0.26	2.13×10^{-15}	86.552
Fibroblast growth factor 7	P21781	-0.25	5.59×10^{-15}	22.509
Trypsin-1	P07477	-0.25	5.71×10^{-15}	26.558
Annexin A1	P04083	-0.25	6.34×10^{-15}	38.714
Low affinity immunoglobulin epsilon Fc receptor	P06734	-0.25	7.51×10^{-15}	36.469
T-cell surface glycoprotein CD4	P01730	-0.25	1.33×10^{-14}	51.111
Ectonucleoside triphosphate diphosphohydrolase 5	O75356	0.25	1.80×10^{-14}	47.517
Tumor necrosis factor receptor superfamily member 14	Q92956	-0.25	2.02×10^{-14}	30.392
Complement component 1 Q subcomponent-binding protein, mitochondrial	Q07021	0.24	4.71×10^{-14}	31.362
Afamin	P43652	0.24	6.25×10^{-14}	69.069
Mannan-binding lectin serine protease 1	P48740	0.24	6.32×10^{-14}	79.247
Periostin	Q15063	-0.24	7.65×10^{-14}	93.314
Ficolin-2	Q15485	0.24	8.52×10^{-14}	34.001
Repulsive guidance molecule A	Q96B86	-0.24	8.79×10^{-14}	49.347
Beta-Ala-His dipeptidase	Q96KN2	0.24	9.70×10^{-14}	56.706

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Mast/stem cell growth factor receptor Kit	P10721	0.24	1.34×10^{-13}	109.865
Gelsolin	P06396	-0.24	1.35×10^{-13}	85.698
Stanniocalcin-1	P52823	-0.24	1.47×10^{-13}	27.621
Netrin-4	Q9HB63	0.24	1.66×10^{-13}	70.071
Spondin-1	Q9HCB6	-0.24	1.81×10^{-13}	90.973
Serine/threonine-protein kinase 17B	O94768	0.24	2.66×10^{-13}	42.344
Prothrombin	P00734	0.24	3.02×10^{-13}	70.037
Testican-1	Q08629	0.23	3.67×10^{-13}	49.124
Protein DJ-1	Q99497	-0.23	4.90×10^{-13}	19.891
Cell adhesion molecule 1	Q9BY67	-0.23	4.93×10^{-13}	48.509
NSFL1 cofactor p47	Q9UNZ2	-0.23	5.11×10^{-13}	40.573
C-C motif chemokine 3	P10147	-0.23	8.05×10^{-13}	10.085
Glyceraldehyde-3-phosphate dehydrogenase	P04406	0.23	1.21×10^{-12}	36.053
Vascular endothelial growth factor receptor 3	P35916	0.23	1.34×10^{-12}	152.757
Natural cytotoxicity triggering receptor 1	O76036	-0.23	1.46×10^{-12}	34.481
Troponin I, cardiac muscle	P19429	-0.23	1.75×10^{-12}	24.008
Endothelial monocyte-activating polypeptide 2	Q12904	0.23	2.59×10^{-12}	34.353
Neuroligin-4, X-linked	Q8N0W4	-0.23	2.66×10^{-12}	91.915
Ubiquitin-fold modifier 1	P61960	-0.22	3.72×10^{-12}	9.118
Delta-like protein 4	Q9NR61	-0.22	4.38×10^{-12}	74.605
Interleukin-20 receptor subunit alpha	Q9UHF4	-0.22	4.70×10^{-12}	62.485
Dickkopf-related protein 4	Q9UBT3	-0.22	6.45×10^{-12}	24.876
WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2	Q8TEU8	-0.22	6.68×10^{-12}	63.941

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Pyruvate kinase PKM	P14618	0.22	8.91×10^{-12}	57.937
Translationally-controlled tumor protein	P13693	-0.22	1.36×10^{-11}	19.595
Peptide YY	P10082	-0.22	1.86×10^{-11}	11.145
C-C motif chemokine 27	Q9Y4X3	-0.22	2.12×10^{-11}	12.618
Cadherin-2	P19022	-0.22	2.33×10^{-11}	99.809
Aflatoxin B1 aldehyde reductase member 2	O43488	0.22	2.63×10^{-11}	39.589
15-hydroxyprostaglandin dehydrogenase [NAD(+)]	P15428	0.21	3.09×10^{-11}	28.977
Parathyroid hormone-related protein	P12272	-0.21	3.40×10^{-11}	20.194
Acid sphingomyelinase-like phosphodiesterase 3a	Q92484	0.21	3.50×10^{-11}	51.260
Plasma kallikrein	P03952	0.21	3.64×10^{-11}	71.370
Cyclin-dependent kinase 8:Cyclin-C complex	P49336 P24863	0.21	4.12×10^{-11}	53.284
Inosine-5'-monophosphate dehydrogenase 2	P12268	0.21	5.67×10^{-11}	55.805
Glucagon	P01275	-0.21	6.32×10^{-11}	20.909
Ephrin type-A receptor 5	P54756	-0.21	6.50×10^{-11}	114.803
Hemojuvelin	Q6ZVN8	-0.21	6.54×10^{-11}	45.080
Dipeptidyl peptidase 2	Q9UHL4	0.21	6.57×10^{-11}	54.341
Drebrin-like protein	Q9UJU6	0.21	6.58×10^{-11}	48.207
A disintegrin and metalloproteinase with thrombospondin motifs 5	Q9UNA0	-0.21	7.24×10^{-11}	101.718
Eukaryotic translation initiation factor 4 gamma 2	P78344	-0.21	1.03×10^{-10}	102.362
NADPH--cytochrome P450 reductase	P16435	0.21	1.16×10^{-10}	76.690
Carbonic anhydrase-related protein 10	Q9NS85	0.21	1.38×10^{-10}	37.563

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Tyrosine-protein phosphatase non-receptor type 1	P18031	0.21	1.39×10^{-10}	49.967
Programmed cell death 1 ligand 2	Q9BQ51	-0.21	1.44×10^{-10}	30.957
Tyrosine-protein kinase Yes	P07947	-0.21	1.61×10^{-10}	60.801
CD48 antigen	P09326	-0.21	2.28×10^{-10}	19.429
Alpha-2-HS-glycoprotein	P02765	0.21	2.30×10^{-10}	39.325
C-C motif chemokine 16	O15467	-0.2	2.40×10^{-10}	13.600
Coagulation factor Xa	P00742	0.2	2.52×10^{-10}	54.732
Creatine kinase M-type	P06732	0.2	2.94×10^{-10}	43.101
SPARC	P09486	0.2	3.00×10^{-10}	34.632
Lymphotoxin alpha2:beta1	P01374, Q06643	0.2	3.24×10^{-10}	22.297
Sialic acid-binding Ig-like lectin 14	Q08ET2	-0.2	3.43×10^{-10}	43.970
C-X-C motif chemokine 5	P42830	0.2	6.05×10^{-10}	11.972
Thrombospondin-2	P35442	-0.2	1.01×10^{-09}	129.991
Complement factor I	P05156	0.2	1.10×10^{-09}	65.750
Insulin-like growth factor-binding protein 1	P08833	-0.2	1.13×10^{-09}	27.904
Adenylate kinase isoenzyme 1	P00568	0.2	1.18×10^{-09}	21.635
Thyroid Stimulating Hormone	P01215 P01222	-0.2	1.40×10^{-09}	13.075
Ras-related C3 botulinum toxin substrate 1	P63000	0.2	1.73×10^{-09}	21.450
Vitamin K-dependent protein C	P04070	0.2	1.74×10^{-09}	52.071
Dickkopf-like protein 1	Q9UK85	0.19	2.19×10^{-09}	27.007
Protein kinase B alpha/beta/gamma	Family	0.19	2.62×10^{-09}	55.059
cGMP-dependent 3',5'-cyclic phosphodiesterase	O00408	0.19	2.90×10^{-09}	105.717
Collectin-11	Q9BWP8	0.19	3.13×10^{-09}	28.665

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Serine/threonine-protein kinase PAK 7	Q9P286	0.19	3.43×10^{-09}	80.745
Complement factor H	P08603	0.19	3.69×10^{-09}	1.231
Cytochrome P450 3A4	P08684	0.19	3.70×10^{-09}	57.343
Neurogenic locus notch homolog protein 1	P46531	0.19	4.83×10^{-09}	272.505
Transketolase	P29401	0.19	4.85×10^{-09}	67.878
Calcium/calmodulin-dependent protein kinase type 1D	Q8IU85	0.19	5.09×10^{-09}	42.914
alpha-2-macroglobulin receptor-associated protein	P30533	0.19	5.41×10^{-09}	41.466
Angiopoietin-related protein 4	Q9BY76	-0.19	5.66×10^{-09}	45.214
Plexin-C1	O60486	0.19	5.73×10^{-09}	175.742
Serine protease HTRA2, mitochondrial	O43464	-0.19	7.39×10^{-09}	48.841
Glycylpeptide N-tetradecanoyltransferase 1	P30419	0.19	7.56×10^{-09}	56.806
Stress-induced-phosphoprotein 1	P31948	0.19	7.87×10^{-09}	62.639
14-3-3 protein family	P31946, P62258, P61981, Q04917, P27348, P63104, P31947	-0.19	8.18×10^{-09}	28.082
Limbic system-associated membrane protein	Q13449	-0.19	1.02×10^{-08}	37.393
Probable G-protein coupled receptor 114	Q8IZF4	0.19	1.04×10^{-08}	59.000
Protein disulfide-isomerase A3	P30101	0.19	1.16×10^{-08}	56.782
Tartrate-resistant acid phosphatase type 5	P13686	0.18	1.19×10^{-08}	36.599
E-Selectin	P16581	0.18	1.30×10^{-08}	66.655
Triosephosphate isomerase	P60174	0.18	1.31×10^{-08}	30.791

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Ectonucleotide pyrophosphatase/phosphodiesterase family member 7	Q6UWV6	0.18	1.42x10^{-08}	51.494
Chymase	P23946	0.18	1.60x10^{-08}	27.325
Sialic acid-binding Ig-like lectin 7	Q9Y286	0.18	1.84x10^{-08}	51.143
Alanine aminotransferase 1	P24298	0.18	2.56x10^{-08}	54.637
Thrombin	00734	0.18	3.30x10^{-08}	70.300
Kin of IRRE-like protein 3	Q8IZU9	-0.18	3.44x10^{-08}	85.255
Casein kinase II subunit alpha	P68400	0.18	3.84x10^{-08}	45.144
NKG2-D type II integral membrane protein	P26718	-0.18	4.09x10^{-08}	25.274
B-cell receptor CD22	P20273	0.18	4.41x10^{-08}	95.348
Fibroblast growth factor 19	O95750	-0.18	4.56x10^{-08}	24.003
Platelet endothelial cell adhesion molecule	P16284	0.18	4.91x10^{-08}	82.522
Proliferation-associated protein 2G4	Q9UQ80	0.18	4.99x10^{-08}	43.787
Aurora kinase B	Q96GD4	0.18	5.37x10-^{08}	39.311
Hepatoma-derived growth factor-related protein 2	Q7Z4V5	-0.18	5.83x10^{-08}	74.317
AH receptor-interacting protein	O00170	0.17	7.26x10^{-08}	37.636
Cytokine receptor common subunit gamma	P31785	0.17	7.61x10^{-08}	42.287
Intercellular adhesion molecule 1	P05362	0.17	7.98x10^{-08}	57.825
Stabilin-2	Q8WWQ8	0.17	8.57x10^{-08}	276.988
Corticosteroid-binding globulin	P08185	0.17	9.70x10^{-08}	45.141
Kallikrein-14	Q9P0G3	0.17	1.01x10^{-07}	29.122
Advanced glycosylation end product-specific receptor, soluble	Q15109	-0.17	1.02x10^{-07}	42.803
Fibroblast growth factor 9	P31371	0.17	1.04x10^{-07}	23.441

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Rab GDP dissociation inhibitor beta	P50395	0.17	$1.04x10^{-07}$	50.663
Interleukin-4	P05112	0.17	$1.13x10^{-07}$	17.492
Natural cytotoxicity triggering receptor 3	O14931	-0.17	$1.15x10^{-07}$	21.593
GTP-binding nuclear protein Ran	P62826	0.17	$1.23x10^{-07}$	24.423
C-C motif chemokine 3-like 1	P16619	-0.17	$1.37x10^{-07}$	10.161
Kunitz-type protease inhibitor 2	O43291	-0.17	$1.39x10^{-07}$	28.228
Fetuin-B	Q9UGM5	0.17	$1.96x10^{-07}$	42.055
Galectin-3-binding protein	Q08380	0.17	$2.13x10^{-07}$	65.331
Seprase	Q12884	0.17	$2.16x10^{-07}$	87.713
Complement component C9	P02748	-0.17	$2.25x10^{-07}$	63.173
Eotaxin	P51671	-0.17	$2.36\ x10^{-07}$	10.732
C-X-C motif chemokine 13	O43927	-0.17	$2.67x10^{-07}$	12.664
Insulin-like growth factor-binding protein 5	P24593	-0.17	$3.06x10^{-07}$	30.570
dCTP pyrophosphatase 1	Q9H773	-0.17	$3.38x10^{-07}$	18.681
Renin	P00797	-0.17	$3.39x10^{-07}$	45.057
Interleukin-27	Q8NEV9 Q14213	-0.16	$3.97x10^{-07}$	27.493
UMP-CMP kinase	P30085	0.16	$4.13x10^{-07}$	22.222
C-X-C motif chemokine 10	P02778	-0.16	$4.52x10^{-07}$	10.881
Mammaglobin-B	O75556	0.16	$5.01x10^{-07}$	10.884
Serine/threonine-protein kinase Chk1	O14757	0.16	$5.05x10^{-07}$	54.434
DNA topoisomerase 1	P11387	0.16	$5.06x10^{-07}$	90.726
Prostaglandin G/H synthase 2	P35354	0.16	$5.20x10^{-07}$	68.996
Cyclin-dependent kinase 2:Cyclin-A2 complex	P24941 P20248	0.16	$5.31x10^{-07}$	33.930

Protein	**UniProt ID**	**Spearman rho**	**p-value**	**Molecular Weight (kDa)**
Heat shock 70 kDa protein 1A/1B	P08107	-0.16	$5.46\text{x}10^{-07}$	70.052
Peptidyl-prolyl cis-trans isomerase D	Q08752	0.16	$5.64\text{x}10^{-07}$	40.764
C-C motif chemokine 7	P80098	-0.16	$6.47\text{x}10^{-07}$	11.200
Proto-oncogene tyrosine-protein kinase Src	P12931	0.16	$6.75\text{x}10^{-07}$	59.835
Cytoskeleton-associated protein 2	Q8WWK9	0.16	$6.83\text{x}10^{-07}$	76.897
Muellerian-inhibiting factor	P03971	0.16	$7.04\text{x}10^{-07}$	59.195
Interleukin-37	Q9NZH6	0.16	$7.17\text{x}10^{-07}$	24.126
Brain natriuretic peptide 32	P16860	-0.16	$7.75\text{x}10^{-07}$	14.726
Polymeric immunoglobulin receptor	P01833	0.16	$8.71\text{x}10^{-07}$	83.284
Plasminogen activator inhibitor 1	P05121	0.16	$9.10\text{x}10^{-07}$	45.060
Fibroblast growth factor 8 isoform B	P55075	0.16	$9.30\text{x}10^{-07}$	26.525
Tyrosine-protein kinase BTK	Q06187	0.16	$9.64\text{x}10^{-07}$	76.281
Vascular cell adhesion protein 1	P19320	-0.16	$9.90\text{x}10^{-07}$	81.276
COMM domain-containing protein 7	Q86VX2	0.16	$1.02\text{x}10^{-06}$	22.540
Coagulation Factor V	P12259	0.16	$1.22\text{x}10^{-06}$	251.703
Tryptase beta-2	P20231	-0.16	$1.24\text{x}10^{-06}$	30.515
Small glutamine-rich tetratricopeptide repeat-containing protein alpha	O43765	0.16	$1.31\text{x}10^{-06}$	34.063
Stromal cell-derived factor 1	P48061	-0.16	$1.34\text{x}10^{-06}$	10.666
Prolactin receptor	P16471	-0.16	$1.40\text{x}10^{-06}$	69.506
Antithrombin-III	P01008	0.16	$1.41\text{x}10^{-06}$	52.602
1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-1	P19174	0.16	$1.55\text{x}10^{-06}$	148.532

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Interleukin-12	P29459, P29460	0.16	1.73x10^{-06}	24.874
Lymphocyte activation gene 3 protein	P18627	-0.16	1.81x10^{-06}	57.449
Heterogeneous nuclear ribonucleoprotein Q	O60506	0.15	1.99x10^{-06}	69.603
Transcription factor IIIB 90 kDa subunit	Q92994	0.15	2.02x10^{-06}	73.840
Calcineurin subunit B type 1	P63098	0.15	2.12x10^{-06}	19.300
Interferon gamma	P01579	0.15	2.21x10^{-06}	19.348
Matrix metalloproteinase-9	P14780	0.15	2.36x10^{-06}	78.458
C-C motif chemokine 5	P13501	0.15	2.64x10^{-06}	9.990
Kynureninase	Q16719	0.15	2.70x10^{-06}	52.325
Contactin-4	Q8IWV2	0.15	2.87x10^{-06}	113.454
Serine/threonine-protein kinase 16	O75716	0.15	2.93x10^{-06}	34.656
CD5 antigen-like	O43866	-0.15	2.98x10^{-06}	38.088
Tumor necrosis factor ligand superfamily member 11	O14788	0.15	3.03x10^{-06}	35.478
Arginase-1	P05089	0.15	3.14x10^{-06}	34.735
Neutral ceramidase	Q9NR71	0.15	3.55x10^{-06}	85.516
Nucleoside diphosphate kinase B	P22392	0.15	3.71x10^{-06}	17.298
Cardiotrophin-1	Q16619	-0.15	3.78x10^{-06}	21.227
Interleukin-13 receptor subunit alpha-1	P78552	-0.15	3.85x10-^{06}	48.760
Tyrosine-protein kinase receptor Tie-1, soluble	P35590	0.15	3.87x10^{-06}	125.090
Bone sialoprotein 2	P21815	-0.15	4.03x10^{-06}	35.148
beta-adrenergic receptor kinase 1	P25098	0.15	4.03x10^{-06}	79.574
Copine-1	Q99829	0.15	4.08x10^{-06}	59.059

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Tyrosine-protein phosphatase non-receptor type 11	Q06124	-0.15	4.27×10^{-06}	68.436
RNA-binding protein 39	Q14498	-0.15	4.45×10^{-06}	59.380
Kininogen-1	P01042	0.15	4.66×10^{-06}	71.957
Prostate-specific antigen	P07288	-0.15	4.81×10^{-06}	28.741
Cytokine receptor-like factor 2	Q9HC73	0.15	5.20×10^{-06}	42.013
Mitogen-activated protein kinase 14	Q16539	0.15	5.27×10^{-06}	41.293
Extracellular matrix protein 1	Q16610	0.15	5.69×10^{-06}	60.674
Casein kinase II 2-alpha:2-beta heterotetramer	P68400 P67870	0.15	6.07×10^{-06}	45.144
Protein FAM107B	Q9H098	0.15	6.17×10^{-06}	15.558
Calpastatin	P20810	0.15	6.67×10^{-06}	76.573
Tyrosine-protein kinase CSK	P41240	0.15	6.67×10^{-06}	50.704
Endothelial cell-specific molecule 1	Q9NQ30	-0.15	6.79×10^{-06}	20.095
Heat shock protein HSP 90-alpha/beta	P07900 P08238	0.15	6.81×10^{-06}	84.660
Complement C1s subcomponent	P09871	0.15	7.05×10^{-06}	76.684
Cyclin-dependent kinase 5:Cyclin-dependent kinase 5 activator 1 complex	Q00535 Q15078	0.15	7.23×10^{-06}	33.304
Glutamate carboxypeptidase 2	Q04609	0.15	8.15×10^{-06}	84.331
Mitochondrial import inner membrane translocase subunit TIM14	Q96DA6	0.14	8.51×10^{-06}	12.499
Angiopoietin-2	O15123	-0.14	9.37×10^{-06}	56.919
Complement component C6	P13671	0.14	1.13×10^{-05}	104.786
High mobility group protein B1	P09429	0.14	1.14×10^{-05}	24.894
Importin subunit beta-1	Q14974	0.14	1.16×10^{-05}	97.170
Ubiquitin-conjugating enzyme E2 N	P61088	0.14	1.20×10^{-05}	17.138

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Calpain I	P07384 P04632	0.14	$1.22x10^{-05}$	81.890
Dual specificity mitogen-activated protein kinase kinase 1	Q02750	-0.14	$1.33x10^{-05}$	43.439
Tumor necrosis factor receptor superfamily member 17	Q02223	-0.14	$1.37x10^{-05}$	20.165
Artemin	Q5T4W7	0.14	$1.42x10^{-05}$	22.878
Amphiregulin	P15514	0.14	$1.46x10^{-05}$	27.895
Macrophage migration inhibitory factor	P14174	-0.14	$1.59x10^{-05}$	12.476
Serotransferrin	P02787	0.14	$1.62x10^{-05}$	77.064
Death-associated protein kinase 2	Q9UIK4	-0.14	$1.63x10^{-05}$	42.898
Cyclin-dependent kinase 1:G2/mitotic-specific cyclin-B1 complex	P06493 P14635	0.14	$1.65x10^{-05}$	34.095
Properdin	P27918	0.14	$1.70x10^{-05}$	51.276
C-C motif chemokine 24	O00175	0.14	$1.71x10^{-05}$	13.134
Tyrosine-protein kinase ZAP-70	P43403	0.14	$1.90x10^{-05}$	69.872
CD70 antigen	P32970	-0.14	$2.03x10^{-05}$	21.118
Chromobox protein homolog 5	P45973	0.14	$2.07x10^{-05}$	22.225
BDNF/NT-3 growth factors receptor	Q16620	0.14	$2.19x10^{-05}$	91.999
cAMP-specific 3',5'-cyclic phosphodiesterase 4D	Q08499	0.14	$2.27x10^{-05}$	91.115
Phospholipase A2	P04054	-0.14	$2.27x10^{-05}$	16.360
Methionine aminopeptidase 1	P53582	0.14	$2.28x10^{-05}$	43.215
Insulin-degrading enzyme	P14735	0.14	$2.28x10^{-05}$	117.968
S-formylglutathione hydrolase	P10768	0.14	$2.55x10^{-05}$	31.463
Macrophage colony-stimulating factor 1	P09603	-0.14	$2.75x10^{-05}$	60.179

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Protein NOV homolog	P48745	-0.14	2.88x10^{-05}	39.162
Keratin, type I cytoskeletal 18	P05783	-0.14	3.07x10^{-05}	48.058
Thyroxine-Binding Globulin	P05543	0.14	3.18x10-^{05}	46.325
Calcium/calmodulin-dependent protein kinase type II subunit delta	Q13557	0.14	3.34x10^{-05}	56.369
Leucine-rich repeats and immunoglobulin-like domains protein 3	Q6UXM1	0.13	3.42x10^{-05}	123.434
TATA-box-binding protein	P20226	0.13	3.43x10^{-05}	37.698
Kallikrein-5	Q9Y337	0.13	3.44x10^{-05}	32.020
Protein kinase C beta type (splice variant beta-II)	P05771	0.13	3.72x10^{-05}	76.869
PSA:alpha-1-antichymotrypsin complex	P07288, P01011	-0.13	4.06x10^{-05}	28.741
Calcium/calmodulin-dependent protein kinase type 1	Q14012	0.13	4.15x10^{-05}	41.337
Programmed cell death 1 ligand 1	Q9NZQ7	-0.13	4.20x10^{-05}	33.275
Platelet-derived growth factor subunit B	P01127	0.13	4.81x10^{-05}	27.283
Annexin A6	P08133	0.13	4.88x10^{-05}	75.873
von Willebrand factor	P04275	-0.13	5.62x10^{-05}	309.265
DNA repair protein RAD51 homolog 1	Q06609	0.13	5.65x10^{-05}	36.966
40S ribosomal protein S3	P23396	0.13	5.85x10^{-05}	26.688
Proteasome activator complex subunit 3	P61289	0.13	5.90x10^{-05}	29.506
Fibroblast growth factor 4	P08620	0.13	5.93x10^{-05}	22.048
Glycogen synthase kinase-3 alpha/beta	P49840 P49841	0.13	5.99x10^{-05}	50.981
Bone morphogenetic protein 7	P18075	-0.13	6.14x10^{-05}	49.313
Angiopoietin-1	Q15389	-0.13	6.18x10^{-05}	57.513

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Semaphorin-3E	O15041	-0.13	$6.22x10^{-05}$	89.228
Baculoviral IAP repeat-containing protein 5	O15392	0.13	$6.27x10^{-05}$	16.389
Tyrosine-protein kinase Lyn	P07948	0.13	$6.64x10^{-05}$	58.574
Semaphorin-3A	Q14563	0.13	$6.68x10^{-05}$	88.889
Peroxiredoxin-1	Q06830	0.13	$6.72x10^{-05}$	22.110
Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	P60484	-0.13	$6.82x10^{-05}$	47.166
Oxidized low-density lipoprotein receptor 1	P78380	-0.13	$6.85x10^{-05}$	30.959
Neuropilin-1	O14786	-0.13	$6.98x10^{-05}$	103.134
GDNF family receptor alpha-1	P56159	-0.13	$7.15x10^{-05}$	51.456
Estrogen receptor	P03372	0.13	$7.70x10^{-05}$	66.216
Galectin-2	P05162	-0.13	$7.81x10^{-05}$	14.644
Arylsulfatase B	P15848	0.13	$7.94x10^{-05}$	59.687
Retinoblastoma-associated protein	P06400	0.13	$8.08x10^{-05}$	106.159
Carbonic anhydrase 1	P00915	0.13	$8.77x10^{-05}$	28.870
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	P48736	0.13	$8.91x10^{-05}$	126.454
DnaJ homolog subfamily B member 1	P25685	0.13	$9.04x10^{-05}$	38.044
Thyroid peroxidase	P07202	0.13	$9.39x10^{-05}$	102.963
CD97 antigen	P48960	0.13	$9.91x10^{-05}$	91.869
Macrophage scavenger receptor types I and II	P21757	0.13	$9.98x10^{-05}$	49.762
Intercellular adhesion molecule 3	P32942	0.13	0.000102	59.541
Angiopoietin-related protein 3	Q9Y5C1	0.13	0.000107	53.637

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Proteasome activator complex subunit 1	Q06323	0.13	0.000120	28.723
Anterior gradient protein 2 homolog	O95994	0.13	0.000120	19.979
Pyridoxal phosphate phosphatase	Q96GD0	0.13	0.000121	31.698
Chitotriosidase-1	Q13231	-0.12	0.000128	51.681
Hepatocyte growth factor receptor	P08581	0.12	0.000130	1.390
Intercellular adhesion molecule 2	P13598	0.12	0.000130	30.654
Lactoperoxidase	P22079	0.12	0.000132	80.288
Leptin receptor	P48357	0.12	0.000133	132.494
Apoptosis regulator Bcl-2	P10415	0.12	0.000134	26.266
Heparan-sulfate 6-O-sulfotransferase 1	O60243	0.12	0.000141	48.226
Opioid-binding protein/cell adhesion molecule	Q14982	0.12	0.000146	38.008
Hepatocyte growth factor-like protein	P26927	0.12	0.000147	80.320
Cadherin-5	P33151	-0.12	0.000150	87.528
GTPase KRas	P01116	0.12	0.000157	21.656
Vascular endothelial growth factor A, isoform 121	P15692	0.12	0.000162	27.042
Ephrin-B3	Q15768	-0.12	0.000162	35.835
Cation-independent mannose-6-phosphate receptor	P11717	0.12	0.000163	274.375
Interleukin-1 receptor type 1	P14778	-0.12	0.000167	65.402
TGF-beta receptor type-2	P37173	0.12	0.000180	64.568
Tumor necrosis factor ligand superfamily member 12	O43508	0.12	0.000180	27.216
Protein jagged-1	P78504	-0.12	0.000181	133.799
Tyrosine-protein kinase Lck	P06239	0.12	0.000184	58.001

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Peptidoglycan recognition protein 1	O75594	-0.12	0.000184	21.731
Collagen alpha-1(XXIII) chain	Q86Y22	0.12	0.000191	51.944
3-phosphoinositide-dependent protein kinase 1	O15530	0.12	0.000193	63.152
Neural cell adhesion molecule L1	P32004	0.12	0.000197	140.003
Thyroglobulin	P01266	0.12	0.000202	304.790
Ubiquitin+1, truncated mutation for UbB	P62979	-0.12	0.000202	17.965
R-spondin-2	Q6UXX9	0.12	0.000204	28.315
Protein kinase C iota type	P41743	0.12	0.000216	68.262
Ficolin-1	O00602	-0.12	0.000217	35.078
High affinity cGMP-specific 3',5'-cyclic phosphodiesterase 9A	O76083	-0.12	0.000226	68.493
Peroxiredoxin-6	P30041	0.12	0.000231	25.035
Lymphatic vessel endothelial hyaluronic acid receptor 1	Q9Y5Y7	-0.12	0.000251	35.213
Interleukin-17A	Q16552	0.12	0.000261	17.504
C-C motif chemokine 21	O00585	0.12	0.000262	14.646
Adenylosuccinate lyase	P30566	0.12	0.000271	54.889
Growth arrest-specific protein 1	P54826	-0.12	0.000275	35.693
Immunoglobulin D	P01880	0.12	0.000276	42.353
Mitogen-activated protein kinase kinase kinase 7:TGF-beta-activated kinase 1 and MAP3K7-binding protein 1 fusion	O43318 Q15750	0.12	0.000278	67.196
Complement component C7	P10643	-0.12	0.000280	93.518
Calcium/calmodulin-dependent protein kinase type II subunit alpha	Q9UQM7	0.12	0.000280	54.088

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
AMP Kinase (alpha2beta2gamma1)	P54646 O43741 P54619	0.12	0.000281	62.320
Superoxide dismutase [Cu-Zn]	P00441	0.12	0.000302	15.936
Growth/differentiation factor 11	O95390	0.12	0.000314	45.091
interleukin-17 receptor B	Q9NRM6	-0.12	0.000323	55.885
Catalase	P04040	0.12	0.000330	59.756
Fibroblast growth factor 16	O43320	0.12	0.000354	23.759
Complement component C8	P07357,P07358,P07360	0.12	0.000354	65.163
Tyrosine-protein kinase Lyn, isoform B	P07948	0.12	0.000376	58.574
Fibroblast growth factor 23	Q9GZV9	-0.12	0.000377	27.954
Cytosolic non-specific dipeptidase	Q96KP4	0.12	0.000386	52.878
C-type lectin domain family 1 member B	Q9P126	-0.12	0.000393	26.596
NAD-dependent protein deacetylase sirtuin-2	Q8IXJ6	0.12	0.000405	43.182
Ras GTPase-activating protein 1	P20936	0.12	0.000408	116.403
Proteasome subunit alpha type-6	P60900	0.12	0.000408	27.399
Dual specificity tyrosine-phosphorylation-regulated kinase 3	O43781	0.11	0.000435	65.714
Fibrinogen gamma chain	P02679	-0.11	0.000443	51.512
Calcium/calmodulin-dependent protein kinase kinase 1	Q8N5S9	0.11	0.000445	55.735
Baculoviral IAP repeat-containing protein 7 Isoform beta	Q96CA5	0.11	0.000458	32.798
Cadherin-6	P55285	0.11	0.000465	88.309
Platelet glycoprotein Ib alpha chain	P07359	-0.11	0.000480	71.540

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Cathepsin B	P07858	-0.11	0.000487	37.822
Importin subunit alpha-1	P52292	-0.11	0.000495	57.862
C-X-C motif chemokine 6	P80162	-0.11	0.000520	11.897
Vacuolar protein sorting-associated protein VTA1 homolog	Q9NP79	0.11	0.000541	33.879
Protein kinase C alpha type	P17252	0.11	0.000577	76.750
Receptor-type tyrosine-protein kinase FLT3	P36888	0.11	0.000586	112.903
Cytochrome c	P99999	0.11	0.000587	11.749
Asialoglycoprotein receptor 1	P07306	-0.11	0.000630	33.186
Ectonucleoside triphosphate diphosphohydrolase 1	P49961	0.11	0.000636	57.965
Serine/threonine-protein kinase TBK1	Q9UHD2	0.11	0.000663	83.642
Inhibin beta A chain	P08476	-0.11	0.000675	47.442
Decorin	P07585	0.11	0.000729	39.747
Mitochondrial glutamate carrier 2	Q9H1K4	0.11	0.000743	33.849
Serine/threonine-protein kinase receptor R3	P37023	0.11	0.000762	56.124
Calreticulin	P27797	-0.11	0.000773	48.142
Fibroblast growth factor 18	O76093	0.11	0.000788	23.989
Sphingosine kinase 1	Q9NYA1	0.11	0.000793	42.518
Tumor necrosis factor receptor superfamily member 13C	Q96RJ3	0.11	0.000793	18.864
Oncostatin-M	P13725	0.11	0.000818	28.484
GRB2-related adapter protein 2	O75791	0.11	0.000827	24.382
Interleukin-1 Receptor accessory protein	Q9NPH3	0.11	0.000841	65.418
Alpha-soluble NSF attachment protein	P54920	0.11	0.000852	33.233

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
3-hydroxyacyl-CoA dehydrogenase type-2	Q99714	0.11	0.000866	25.984
Leucine-rich repeat transmembrane neuronal protein 1	Q86UE6	0.11	0.000904	58.641
Proprotein convertase subtilisin/kexin type 9	Q8NBP7	0.11	0.000955	74.286
Protein E7_HPV18	P06788	0.11	0.00096	11.995
Pulmonary surfactant-associated protein D	P35247	0.11	0.00106	37.728
Ribosome maturation protein SBDS	Q9Y3A5	0.11	0.00109	28.764
Carbonic anhydrase 6	P23280	0.11	0.00111	35.367
Ubiquitin-conjugating enzyme E2 L3	P68036	0.11	0.00114	17.862
Heterogeneous nuclear ribonucleoproteins A2/B1	P22626	-0.11	0.00117	37.430
GDNF family receptor alpha-2	O00451	-0.11	0.00118	51.544
Interleukin-3 receptor subunit alpha	P26951	0.11	0.00121	43.330
Transforming growth factor-beta-induced protein ig-h3	Q15582	0.1	0.00129	74.681
Macrophage-stimulating protein receptor	Q04912	0.1	0.00129	152.241
Histone acetyltransferase KAT6A	Q92794	0.1	0.00133	225.028
Kremen protein 2	Q8NCW0	0.1	0.00135	48.849
Leukotriene A-4 hydrolase	P09960	-0.1	0.00138	69.285
Low affinity immunoglobulin gamma Fc region receptor III-B	O75015	-0.1	0.00140	26.216
Interferon alpha-2	P01563	0.1	0.00153	21.550
Insulin-like growth factor-binding protein 7	Q16270	0.1	0.00155	29.130
Metalloproteinase inhibitor 2	P16035	0.1	0.00158	24.399

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Kallistatin	P29622	0.1	0.00165	48.542
C-X-C motif chemokine 16	Q9H2A7	-0.1	0.00168	27.579
Interleukin-20	Q9NYY1	0.1	0.00170	20.072
Cytokine receptor-like factor 1:Cardiotrophin-like cytokine factor 1 Complex	O75462 Q9UBD9	-0.1	0.00171	46.302
Toll-like receptor 4:Lymphocyte antigen 96 complex	O00206 Q9Y6Y9	0.1	0.00176	95.680
Endoplasmic reticulum aminopeptidase 1	Q9NZ08	0.1	0.00178	107.235
C-C motif chemokine 28	Q9NRJ3	-0.1	0.00181	14.280
3-hydroxy-3-methylglutaryl-coenzyme A reductase	P04035	0.1	0.00183	97.476
C-C motif chemokine 25	O15444	0.1	0.00189	16.609
Bone morphogenetic protein receptor type-1A	P36894	-0.1	0.00193	60.198
Alpha-(1,3)-fucosyltransferase 5	Q11128	-0.1	0.00193	43.008
Complement C5b-C6 complex	P01031,P13671	0.1	0.00209	188.305
Serum albumin	P02768	-0.1	0.00209	69.367
Killer cell immunoglobulin-like receptor 3DL2	P43630	0.1	0.00209	50.230
cAMP-regulated phosphoprotein 19	P56211	0.1	0.00212	12.323
A disintegrin and metalloproteinase with thrombospondin motifs 4	O75173	0.1	0.00212	90.197
Ribosomal protein S6 kinase alpha-3	P51812	0.1	0.00212	83.736
Tropomyosin alpha-1 chain	P09493	0.1	0.00215	32.709
Cytoplasmic tyrosine-protein kinase BMX	P51813	0.1	0.00227	78.011
Creatine kinase B-type	P12277	-0.1	0.00229	42.644

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Transforming growth factor beta-3	P10600	0.1	0.00231	47.328
[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 1, mitochondrial	Q15118	0.1	0.00242	49.244
Protein FAM107A	O95990	0.1	0.00249	17.455
Tropomyosin beta chain	P07951	0.1	0.00254	32.851
T-lymphocyte surface antigen Ly-9	Q9HBG7	-0.1	0.00271	72.139
Collectin-12	Q5KU26	0.1	0.00275	81.515
Calcium-dependent phospholipase A2	P39877	0.1	0.00280	15.674
Cyclin-dependent kinase inhibitor 1B	P46527	0.1	0.00284	22.073
cGMP-specific 3',5'-cyclic phosphodiesterase	O76074	0.1	0.00300	99.985
OCIA domain-containing protein 1	Q9NX40	-0.1	0.00306	27.626
Breast cancer anti-estrogen resistance protein 3	O75815	0.1	0.00310	92.566
Platelet-derived growth factor subunit A	P04085	0.1	0.00317	24.043
Calcium/calmodulin-dependent protein kinase type II subunit beta	Q13554	0.1	0.00332	72.678
Interleukin-22	Q9GZX6	-0.1	0.00334	20.011
Neural cell adhesion molecule L1-like protein	O00533	0.1	0.00338	135.071
Growth/differentiation factor 9	O60383	0.1	0.00339	51.444
Fibroblast growth factor 10	O15520	0.1	0.00340	23.436
Tyrosine-protein kinase receptor TYRO3	Q06418	-0.09	0.00363	96.905
SLAM family member 6	Q96DU3	-0.09	0.00363	37.345
Syntaxin-1A	Q16623	0.09	0.00371	33.023

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Cadherin-15	P55291	0.09	0.00378	88.916
Baculoviral IAP repeat-containing protein 3	Q13489	0.09	0.00390	68.372
Interleukin-18 receptor accessory protein	O95256	0.09	0.00397	68.310
S-phase kinase-associated protein 1	P63208	0.09	0.00413	18.658
Secretin	P09683	-0.09	0.00441	13.016
Granzyme B	P10144	0.09	0.00464	27.716
Prokineticin-1	P58294	0.09	0.00468	11.715
Heparin cofactor 2	P05546	0.09	0.00482	57.071
Caspase-3	P42574	0.09	0.00546	31.608
ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2	Q10588	0.09	0.00554	35.724
Abelson tyrosine-protein kinase 2	P42684	0.09	0.00557	128.343
C-type mannose receptor 2	Q9UBG0	0.09	0.00558	166.674
Ectodysplasin-A, secreted form	Q92838	0.09	0.00563	41.294
Alpha-1-antitrypsin	P01009	-0.09	0.00593	46.737
Mitogen-activated protein kinase 13	O15264	0.09	0.00601	42.090
Galectin-8	O00214	0.09	0.00607	35.808
Contactin-5	O94779	0.09	0.00625	120.686
Neuronal cell adhesion molecule	Q92823	-0.09	0.00634	14..890
Tumor necrosis factor ligand superfamily member 9	P41273	0.09	0.00651	26.625
Protein Wnt-7a	O00755	0.09	0.00661	39.005
CD40 ligand	P29965	0.09	0.00673	29.274
alpha-S1-casein	P47710	0.09	0.00680	21.671
Glucokinase regulatory protein	Q14397	-0.09	0.00716	68.685

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Fibroblast growth factor 2	P09038	0.09	0.00720	30.770
Serine/threonine-protein kinase MRCK beta	Q9Y5S2	0.09	0.00781	194.315
T-lymphocyte activation antigen CD86	P42081	0.09	0.00836	37.682
Interleukin-1 alpha	P01583	-0.09	0.00850	30.607
Ectonucleoside triphosphate diphosphohydrolase 3	O75355	0.09	0.00865	59.105
NT-3 growth factor receptor	Q16288	-0.09	0.00880	94.428
CD226 antigen	Q15762	0.09	0.00900	38.614
Phospholipase A2, membrane associated	P14555	-0.08	0.00929	16.083
Methionine aminopeptidase 2	P50579	0.08	0.00933	52.892
Receptor tyrosine-protein kinase erbB-2	P04626	0.08	0.00964	137.910
Cathepsin D	P07339	0.08	0.00969	44.552
Tumor necrosis factor receptor superfamily member 8	P28908	-0.08	0.00991	63.747
Plasmin	P00747	0.08	0.0101	90.569
Lipopolysaccharide-binding protein	P18428	-0.08	0.0101	53.384
Group 10 secretory phospholipase A2	O15496	0.08	0.0105	18.153
Ciliary Neurotrophic Factor	P26441	0.08	0.0106	22.931
Lysosome membrane protein 2	Q14108	0.08	0.0108	54.290
Matrilin-3	O15232	0.08	0.0109	52.817
Annexin A2	P07355	-0.08	0.0111	38.604
Osteomodulin	Q99983	-0.08	0.0111	49.492
Killer cell lectin-like receptor subfamily F member 1	Q9NZS2	0.08	0.0116	26.666
Tumor necrosis factor ligand superfamily member 18	Q9UNG2	0.08	0.0116	22.724

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Mesothelin	Q13421	0.08	0.0120	68.986
Fibroblast growth factor receptor 4	P22455	0.08	0.0125	87.954
Lysosomal protective protein	P10619	0.08	0.0126	54.466
72 kDa type IV collagenase	P08253	0.08	0.0126	73.882
Neurotrophin-3	P20783	0.08	0.0133	29.355
Interleukin-13	P35225	0.08	0.0135	15.816
AMP Kinase (alpha1beta1gamma1)	Q13131 Q9Y478 P54619	0.08	0.0138	64.009
Granzyme H	P20718	0.08	0.0138	27.315
Somatostatin-28	P61278	0.08	0.0140	12.736
Kinesin-like protein KIF23	Q02241	0.08	0.0142	110.059
Bone morphogenetic protein 6	P22004	-0.08	0.0144	57.226
Serine/threonine-protein kinase Chk2	O96017	0.08	0.0145	60.915
Persephin	O60542	-0.08	0.0146	16.600
Leptin	P41159	-0.08	0.0148	18.641
Interleukin-7 receptor subunit alpha	P16871	0.08	0.0150	51.581
Discoidin domain-containing receptor 2	Q16832	-0.08	0.0151	96.736
Prefoldin subunit 5	Q99471	-0.08	0.0153	17.328
Apolipoprotein E (isoform E3)	P02649	0.08	0.0153	36.154
Apolipoprotein E (isoform E2)	P02649	0.08	0.0157	36.154
Interleukin-17B	Q9UHF5	0.08	0.0158	20.437
Tyrosine-protein kinase Fgr	P09769	0.08	0.0159	59.479
Fibroblast growth factor 1	P05230	0.08	0.0160	17.460
Glutathione S-transferase A3	Q16772	0.08	0.0166	25.302
C-C motif chemokine 13	Q99616	0.08	0.0169	10.986

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Dual specificity protein phosphatase 3	P51452	0.08	0.0170	20.478
Proliferating cell nuclear antigen	P12004	-0.08	0.0172	28.769
L-Selectin	P14151	0.08	0.0173	42.187
C-C motif chemokine 17	Q92583	-0.08	0.0174	10.507
Carboxypeptidase B2	Q96IY4	0.08	0.0175	48.424
Cysteine-rich secretory protein 3	P54108	0.08	0.0175	27.630
Kallikrein-4	Q9Y5K2	0.08	0.0175	27.032
Coactosin-like protein	Q14019	-0.08	0.0177	15.945
Angiotensin-converting enzyme 2	Q9BYF1	0.08	0.0180	92.463
C-C motif chemokine 20	P78556	0.08	0.0183	10.762
Protein kinase C theta type	Q04759	0.08	0.0192	81.865
AT-rich interactive domain-containing protein 3A	Q99856	0.08	0.0194	62.889
Activated Protein C	P04070	-0.08	0.0207	52.071
Macrophage colony-stimulating factor 1 receptor	P07333	-0.08	0.0207	107.984
Fibroblast growth factor 6	P10767	0.08	0.0211	22.905
Prolactin	P01236	-0.08	0.0214	25.876
Eukaryotic initiation factor 4A-III	P38919	0.08	0.0216	46.871
Cell surface glycoprotein CD200 receptor 1	Q8TD46	0.08	0.0216	36.620
Carboxypeptidase E	P16870	0.07	0.0220	53.151
Interleukin-27 receptor subunit alpha	Q6UWB1	0.07	0.0220	69.474
A disintegrin and metalloproteinase with thrombospondin motifs 1	Q9UHI8	0.07	0.0220	105.358
Thymidylate synthase	P04818	-0.07	0.0225	35.716

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Macrophage mannose receptor 1	P22897	-0.07	0.0232	166.012
C-C motif chemokine 8	P80075	-0.07	0.0232	11.246
Serum paraoxonase/arylesterase 1	P27169	0.07	0.0252	39.731
Transmembrane glycoprotein NMB	Q14956	-0.07	0.0252	63.923
P-Selectin	P16109	0.07	0.0257	90.834
Estradiol 17-beta-dehydrogenase 1	P14061	0.07	0.0260	34.950
Interferon lambda-1	Q8IU54	0.07	0.0262	21.898
Tyrosine-protein phosphatase non-receptor type 2	P17706	0.07	0.0263	48.473
Interstitial collagenase	P03956	-0.07	0.0266	54.007
Platelet-activating factor acetylhydrolase	Q13093	-0.07	0.0270	50.077
Tumor necrosis factor receptor superfamily member 3	P36941	0.07	0.0277	46.709
Scavenger receptor class F member 2	Q96GP6	0.07	0.0278	92.479
C3a anaphylatoxin des Arginine	P01024	0.07	0.0282	187.148
Elongation factor 1-beta	P24534	0.07	0.0284	24.764
Tissue-type plasminogen activator	P00750	0.07	0.0284	62.917
Leukemia inhibitory factor receptor	P42702	-0.07	0.0303	123.743
Complement C3b	P01024	0.07	0.0316	187.148
Cytotoxic and regulatory T-cell molecule	O95727	0.07	0.0324	44.641
alpha-L-iduronidase	P35475	0.07	0.0327	72.670
Tryptase gamma	Q9NRR2	0.07	0.0330	33.815
Luteinizing hormone	P01215, P01229	-0.07	0.0331	13.075

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Leucine carboxyl methyltransferase 1	Q9UIC8	0.07	0.0334	38.379
MAP kinase-activated protein kinase 2	P49137	0.07	0.0342	45.568
Aromatic-L-amino-acid decarboxylase	P20711	0.07	0.0342	53.926
Scavenger receptor cysteine-rich type 1 protein M130	Q86VB7	0.07	0.0343	125.451
Neurotrophin-4	P34130	0.07	0.0343	22.427
Pituitary adenylate cyclase-activating polypeptide 38	P18509	0.07	0.0357	18.835
MHC class I polypeptide-related sequence B	Q29980	-0.07	0.0361	42.646
Cystatin-S	P01036	-0.07	0.0361	16.214
Fibroblast growth factor 12	P61328	0.07	0.0365	27.399
Neutrophil collagenase	P22894	0.07	0.0367	53.412
Granulocyte-macrophage colony-stimulating factor	P04141	-0.07	0.0369	16.295
beta-nerve growth factor	P01138	-0.07	0.0374	26.959
SPARC-like protein 1	Q14515	-0.07	0.0378	75.208
Cystatin-F	O76096	-0.07	0.0380	16.454
Interleukin-34	Q6ZMJ4	0.07	0.0384	27.482
Tyrosine-protein kinase JAK2	O60674	0.07	0.0385	130.674
C-X-C motif chemokine 11	O14625	-0.07	0.0386	10.365
Bcl-2-related protein A1	Q16548	0.07	0.0390	20.132
C-C motif chemokine 2	P13500	0.07	0.0395	11.025
Interleukin-22 receptor subunit alpha-2	Q969J5	0.07	0.0399	30.550
Bcl-2-like protein 1	Q07817	0.07	0.0405	26.049
Tumor necrosis factor receptor superfamily member 18	Q9Y5U5	0.07	0.0407	26.000

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Low affinity immunoglobulin gamma Fc region receptor II-a/b	P12318 P31994	-0.07	0.0407	35.001
Toll-like receptor 2	O60603	-0.07	0.0414	89.838
Ligand-dependent nuclear receptor corepressor-like protein	Q8N3X6	0.07	0.0416	66.964
3-hydroxyisobutyrate dehydrogenase, mitochondrial	P31937	0.07	0.0416	35.329
Receptor tyrosine-protein kinase erbB-4	Q15303	0.07	0.0422	146.808
Secreted frizzled-related protein 3	Q92765	-0.07	0.0422	36.254
Tumor necrosis factor receptor superfamily member 10A	O00220	0.07	0.0426	50.089
Hsp90 co-chaperone Cdc37	Q16543	-0.07	0.0435	44.468
Thymidine kinase, cytosolic	P04183	0.07	0.0435	25.469
Matrix metalloproteinase-17	Q9ULZ9	0.07	0.0442	66.653
Cathepsin E	P14091	0.07	0.0442	42.794
Carbonic anhydrase 7	P43166	0.07	0.0447	29.658
Insulin-like growth factor I	P05019	-0.07	0.0453	21.841
Mitogen-activated protein kinase 1	P28482	0.07	0.0455	41.390
Complement C5	P01031	0.06	0.0470	188.305
Plasma protease C1 inhibitor	P05155	0.06	0.0480	55.154
Glypican-2	Q8N158	0.06	0.0489	62.830
Platelet glycoprotein 4	P16671	0.06	0.0510	53.053
Persulfide dioxygenase ETHE1, mitochondrial	O95571	0.06	0.0519	27.873
Roundabout homolog 3	Q96MS0	0.06	0.0521	148.209
Interleukin-10	P22301	0.06	0.0522	20.517
ATP-dependent RNA helicase DDX19B	Q9UMR2	0.06	0.0528	53.927

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Enteropeptidase	P98073	0.06	0.0540	112.935
Amyloid beta A4 protein	P05067	-0.06	0.0555	86.943
Proteasome subunit alpha type-1	P25786	0.06	0.0561	29.556
Bone morphogenetic protein receptor type-2	Q13873	-0.06	0.0563	115.201
Angiopoietin-1 receptor, soluble	Q02763	0.06	0.0570	125.830
40S ribosomal protein S7	P62081	0.06	0.0576	22.127
Protein disulfide-isomerase	P07237	0.06	0.0576	57.116
NKG2D ligand 1	Q9BZM6	0.06	0.0581	27.997
Arylsulfatase A	P15289	0.06	0.0583	53.588
Dynactin subunit 2	Q13561	0.06	0.0597	44.231
Human Chorionic Gonadotropin	P01215,P01233	-0.06	0.0613	13.075
Acidic leucine-rich nuclear phosphoprotein 32 family member B	Q92688	-0.06	0.0622	28.788
cGMP-inhibited 3',5'-cyclic phosphodiesterase A	Q14432	0.06	0.0633	124.979
Sex hormone-binding globulin	P04278	-0.06	0.0658	43.779
Protein jagged-2	Q9Y219	0.06	0.0692	133.367
Interleukin-23	P29460, Q9NPF7	0.06	0.0697	37.169
E3 ubiquitin-protein ligase Mdm2	Q00987	0.06	0.0698	55.233
Immunoglobulin alpha Fc receptor	P24071	0.06	0.0701	32.265
Cadherin-1	P12830	0.06	0.0702	97.456
Interleukin-12 receptor subunit beta-1	P42701	-0.06	0.0712	73.109
Tenascin	P24821	0.06	0.0718	240.853
Lactadherin	Q08431	-0.06	0.0733	43.123

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Fibronectin Fragment 4	P02751	0.06	0.0739	262.625
Roundabout homolog 2	Q9HCK4	0.06	0.0758	151.200
Serum amyloid A-1 protein	P0DJI8	-0.06	0.0759	13.532
Focal adhesion kinase 1	Q05397	0.06	0.0778	119.233
Interleukin-17D	Q8TAD2	0.06	0.0799	21.893
Kunitz-type protease inhibitor 1	O43278	0.06	0.0801	58.398
Proprotein convertase subtilisin/kexin type 7	Q16549	0.06	0.0808	86.247
Vasoactive Intestinal Peptide	P01282	0.06	0.0809	19.169
Coagulation factor IXab	P00740	0.06	0.0810	51.778
L-lactate dehydrogenase B chain	P07195	-0.06	0.0816	36.638
ICOS ligand	O75144	0.06	0.0817	33.349
Disintegrin and metalloproteinase domain-containing protein 9	Q13443	-0.06	0.0819	90.556
Complement C2	P06681	0.06	0.0828	83.268
Seizure 6-like protein 2	Q6UXD5	0.06	0.0862	97.560
60 kDa heat shock protein, mitochondrial	P10809	0.06	0.0867	61.055
Tyrosine-protein kinase Tec	P42680	0.06	0.0870	73.581
Lymphocyte antigen 86	O95711	-0.06	0.0885	17.906
Interleukin-24	Q13007	0.06	0.0890	23.825
Interleukin-11 receptor subunit alpha	Q14626	-0.06	0.0892	45.222
Interleukin-6	P05231	-0.06	0.0894	23.718
Fibroblast growth factor 8 isoform A	P55075	0.06	0.0912	26.525
Fms-related tyrosine kinase 3 ligand	P49771	0.06	0.0915	26.416
Fibronectin	P02751	0.05	0.0950	262.625

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Iduronate 2-sulfatase	P22304	0.05	0.0969	61.873
Insulin receptor	P06213	-0.05	0.0969	156.333
Epiregulin	O14944	0.05	0.0973	19.044
Interleukin-6 receptor subunit beta	P40189	0.05	0.0979	103.537
Hepcidin	P81172	-0.05	0.102	9.408
Brother of CDO	Q9BWV1	0.05	0.102	121.509
Thioredoxin domain-containing protein 12	O95881	0.05	0.103	19.206
Ubiquitin carboxyl-terminal hydrolase isozyme L1	P09936	0.05	0.104	24.824
Myeloid cell surface antigen CD33	P20138	-0.05	0.105	39.825
C-type lectin domain family 7 member A	Q9BXN2	-0.05	0.106	27.627
Protein Rev_HV2BE	P18093	0.05	0.106	11.792
Galectin-4	P56470	0.05	0.107	35.941
Cytotoxic T-lymphocyte protein 4	P16410	0.05	0.111	24.656
Nuclear receptor subfamily 1 group D member 1	P20393	0.05	0.112	66.805
VPS10 domain-containing receptor SorCS2	Q96PQ0	0.05	0.113	128.152
Inducible T-cell costimulator	Q9Y6W8	0.05	0.113	22.625
Interleukin-3	P08700	0.05	0.113	17.233
Complement C3d fragment	P01024	0.05	0.114	187.148
NKG2D ligand 2	Q9BZM5	0.05	0.115	27.368
Erythropoietin	P01588	-0.05	0.115	21.307
Ephrin type-A receptor 10	Q5JZY3	-0.05	0.116	109.716
Histone H2A.z	P0C0S5	-0.05	0.116	13.553
Desert hedgehog protein N-product	O43323	0.05	0.122	43.577

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Immunoglobulin G	P01857	-0.05	0.122	36.106
Caspase-2	P42575	0.05	0.127	50.685
Killer cell immunoglobulin-like receptor 3DS1	Q14943	0.05	0.128	42.475
CD109 antigen	Q6YHK3	-0.05	0.133	161.689
Interleukin-23 receptor	Q5VWK5	0.05	0.134	71.722
C-C motif chemokine 4-like	Q8NHW4	-0.05	0.134	10.166
Coagulation factor IX	P00740	0.05	0.134	51.778
Gro-beta/gamma	P19876 P19875	0.05	0.134	11.342
Dynein light chain roadblock-type 1	Q9NP97	0.05	0.135	10.922
Protein kinase C delta type	Q05655	-0.05	0.136	77.505
Methyl-CpG-binding domain protein 4	O95243	0.05	0.137	66.051
Kallikrein-12	Q9UKR0	0.05	0.139	26.734
Dynein light chain 1, cytoplasmic	P63167	0.05	0.139	10.366
C-C motif chemokine 22	O00626	0.05	0.141	10.625
Interleukin-12 receptor subunit beta-2	Q99665	-0.05	0.142	97.135
Corticotropin	P01189	-0.05	0.143	29.424
Carbohydrate sulfotransferase 6	Q9GZX3	0.05	0.145	44.099
Proteasome subunit alpha type-2	P25787	-0.05	0.148	25.899
Midkine	P21741	-0.05	0.150	15.585
Interleukin-7	P13232	0.05	0.150	20.187
A disintegrin and metalloproteinase with thrombospondin motifs 15	Q8TE58	-0.05	0.151	103.287
GDNF family receptor alpha-3	O60609	0.05	0.153	44.511

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Matrix extracellular phosphoglycoprotein	Q9NQ76	0.05	0.156	58.419
Dual specificity mitogen-activated protein kinase kinase 4	P45985	0.05	0.157	44.288
Complement C4b	P0C0L4 P0C0L5	0.05	0.160	192.785
Low-density lipoprotein receptor-related protein 8	Q14114	-0.05	0.163	105.634
Growth/differentiation factor 2	Q9UK05	0.05	0.166	47.320
Pescadillo homolog	O00541	0.05	0.166	68.003
Haptoglobin	P00738	-0.05	0.168	45.205
WAP, kazal, immunoglobulin, kunitz and NTR domain-containing protein 1	Q96NZ8	0.04	0.170	58.798
Eukaryotic translation initiation factor 5	P55010	-0.04	0.174	49.223
Disintegrin and metalloproteinase domain-containing protein 12	O43184	0.04	0.175	99.542
Hemopexin	P02790	-0.04	0.176	51.676
Neutrophil-activating peptide 2	P02775	0.04	0.177	13.894
Transforming growth factor beta-2	P61812	0.04	0.177	47.748
Interleukin-5 receptor subunit alpha	Q01344	-0.04	0.180	47.685
Interleukin-25	Q9H293	-0.04	0.182	20.330
Parathyroid hormone	P01270	-0.04	0.182	12.861
Calcineurin	Q08209 P63098	-0.04	0.183	58.688
Cytoplasmic protein NCK1	P16333	0.04	0.187	42.864
Serum amyloid P-component	P02743	0.04	0.187	25.387
Histone H1.2	P16403	0.04	0.187	21.365

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Leucine-rich repeat transmembrane protein FLRT1	Q9NZU1	0.04	0.188	71.358
Interleukin-2	P60568	0.04	0.188	17.628
Interleukin-6 receptor subunit alpha	P08887	-0.04	0.193	51.548
Carbohydrate sulfotransferase 2	Q9Y4C5	0.04	0.195	57.857
Interleukin-17 receptor D	Q8NFM7	0.04	0.196	82.411
Connective tissue growth factor	P29279	0.04	0.199	38.091
Carbonic anhydrase 13	Q8N1Q1	0.04	0.200	29.443
Sialic acid-binding Ig-like lectin 6	O43699	-0.04	0.204	49.913
Granzyme A	P12544	-0.04	0.205	28.999
Interleukin-1 receptor-like 2	Q9HB29	-0.04	0.205	65.405
Spectrin alpha chain, non-erythrocytic 1	Q13813	0.04	0.206	284.539
Matrix metalloproteinase-16	P51512	0.04	0.208	69.521
Histone acetyltransferase type B catalytic subunit	O14929	0.04	0.209	49.513
Interleukin-17 receptor A	Q96F46	0.04	0.209	96.122
Sialoadhesin	Q9BZZ2	-0.04	0.212	182.624
Urokinase-type plasminogen activator	P00749	0.04	0.212	48.507
Homeobox protein NANOG	Q9H9S0	0.04	0.216	34.620
Fibroblast growth factor receptor 2	P21802	0.04	0.217	92.025
Aurora kinase A	O14965	0.04	0.219	45.809
Tumor necrosis factor ligand superfamily member 4	P23510	0.04	0.221	21.050
Vitamin K-dependent protein S	P07225	0.04	0.228	75.123
Interleukin-4 receptor subunit alpha	P24394	0.04	0.229	89.658

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
SLAM family member 7	Q9NQ25	0.04	0.230	37.421
Serine/threonine-protein kinase PAK 6	Q9NQU5	0.04	0.234	74.869
Interleukin-22 receptor subunit alpha-1	Q8N6P7	0.04	0.236	63.077
Homeodomain-interacting protein kinase 3	Q9H422	0.04	0.238	133.743
Tyrosine-protein kinase Fyn	P06241	0.04	0.246	60.762
Brain-derived neurotrophic factor	P23560	0.04	0.247	27.818
Galactoside 3(4)-L-fucosyltransferase	P21217	0.04	0.250	42.117
MAP kinase-activated protein kinase 3	Q16644	0.04	0.254	42.987
Xaa-Pro aminopeptidase 1	Q9NQW7	0.04	0.255	69.918
Dentin matrix acidic phosphoprotein 1	Q13316	-0.04	0.256	55.782
Interleukin-11	P20809	0.04	0.257	21.429
G2/mitotic-specific cyclin-B1	P14635	0.04	0.267	48.337
40S ribosomal protein SA	P08865	-0.04	0.272	32.854
Epithelial discoidin domain-containing receptor 1	Q08345	-0.04	0.273	101.128
Reticulon-4	Q9NQC3	0.04	0.273	129.931
Tumor necrosis factor receptor superfamily member 11A	Q9Y6Q6	0.04	0.273	66.034
Heparin-binding EGF-like growth factor	Q99075	-0.04	0.275	23.067
Integrin alpha-V: beta-5 complex	P06756, P18084	0.04	0.276	116.038
Moesin	P26038	0.03	0.285	67.820
Contactin-2	Q02246	-0.03	0.286	113.393
Follicle stimulating hormone	P01215, P01225	-0.03	0.297	13.075

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Carbonic anhydrase 2	P00918	0.03	0.299	29.246
Interleukin-8	P10145	0.03	0.300	11.098
Intercellular adhesion molecule 5	Q9UMF0	-0.03	0.305	97.116
Complement C4	P0C0L4, P0C0L5	0.03	0.305	192.785
Thymic stromal lymphopoietin	Q969D9	-0.03	0.306	18.141
Protein-glutamine gamma-glutamyltransferase E	Q08188	-0.03	0.311	76.632
cAMP-dependent protein kinase catalytic subunit alpha	P17612	0.03	0.311	40.590
C-reactive protein	P02741	-0.03	0.313	25.039
C-C motif chemokine 19	Q99731	-0.03	0.313	10.993
Tumor necrosis factor	P01375	0.03	0.322	25.644
Angiotensinogen	P01019	0.03	0.325	53.154
Complement C1r subcomponent	P00736	0.03	0.326	80.119
Natural cytotoxicity triggering receptor 2	O95944	-0.03	0.337	30.677
Endoglin	P17813	-0.03	0.341	70.578
Immunoglobulin M	P01871	-0.03	0.343	49.440
Tumor necrosis factor-inducible gene 6 protein	P98066	0.03	0.345	31.203
Wnt inhibitory factor 1	Q9Y5W5	-0.03	0.346	41.528
Interleukin-10 receptor subunit beta	Q08334	-0.03	0.348	36.995
Tyrosine-protein phosphatase non-receptor type 6	P29350	-0.03	0.350	67.561
Lymphotoxin alpha1:beta2	P01374, Q06643	0.03	0.353	22.297
Tumor necrosis factor receptor superfamily member 6B	O95407	-0.03	0.355	32.680
Fc receptor-like protein 3	Q96P31	0.03	0.356	80.856

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Kallikrein-7	P49862	0.03	0.358	27.525
Ribosomal protein S6 kinase alpha-5	O75582	-0.03	0.358	89.865
Histone-lysine N-methyltransferase EHMT2	Q96KQ7	0.03	0.374	132.370
Azurocidin	P20160	0.03	0.375	26.886
Collagen alpha-1(VIII) chain	P27658	0.03	0.381	73.364
Leukocyte immunoglobulin-like receptor subfamily B member 1	Q8NHL6	0.03	0.385	70.819
Alpha-1-antichymotrypsin	P01011	-0.03	0.386	47.651
Killer cell immunoglobulin-like receptor 2DL4	Q99706	0.03	0.390	41.487
Tyrosine-protein kinase Fer	P16591	0.03	0.392	94.638
Protein-tyrosine kinase 6	Q13882	0.03	0.401	51.834
Transforming growth factor beta-1	P01137	0.03	0.406	44.341
Tyrosine-protein kinase HCK	P08631	0.03	0.407	59.600
Growth-regulated alpha protein	P09341	0.03	0.410	11.301
Mitogen-activated protein kinase 3	P27361	0.03	0.411	43.136
Matrix metalloproteinase-14	P50281	-0.03	0.413	65.894
Interleukin-18 receptor 1	Q13478	0.03	0.416	62.304
Interferon gamma receptor 1	P15260	-0.03	0.417	54.405
EGF-like module-containing mucin-like hormone receptor-like 2	Q9UHX3	-0.03	0.426	90.472
BMP-binding endothelial regulator protein	Q8N8U9	-0.03	0.427	75.997
NKG2D ligand 3	Q9BZM4	0.03	0.432	27.949
Gremlin-1	O60565	0.03	0.435	20.697
Protein E7_HPV16	P03129	-0.03	0.436	11.022

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Myeloperoxidase	P05164	-0.03	0.437	83.869
Inter-alpha-trypsin inhibitor heavy chain H4	Q14624	-0.03	0.439	103.357
T-lymphocyte activation antigen CD80	P33681	0.03	0.442	33.048
Collagenase 3	P45452	-0.02	0.447	53.820
Heme oxygenase 2	P30519	-0.02	0.448	36.033
Allograft inflammatory factor 1	P55008	0.02	0.451	16.703
Interferon lambda-2	Q8IZJ0	0.02	0.457	22.288
Membrane frizzled-related protein	Q9BY79	0.02	0.458	62.212
Carbonic anhydrase 9	Q16790	0.02	0.461	49.698
Mediator of RNA polymerase II transcription subunit 1	Q15648	-0.02	0.462	168.478
Group IIE secretory phospholipase A2	Q9NZK7	0.02	0.464	15.989
Glypican-5	P78333	0.02	0.466	63.707
Myeloblastin	P24158	0.02	0.468	27.807
Small nuclear ribonucleoprotein F	P62306	0.02	0.474	9.725
Trypsin-3	P35030	0.02	0.479	32.529
Biglycan	P21810	-0.02	0.484	41.654
Leukocyte immunoglobulin-like receptor subfamily B member 2	Q8N423	0.02	0.488	65.039
Glia-derived nexin	P07093	0.02	0.488	44.002
Epidermal growth factor receptor substrate 15-like 1	Q9UBC2	-0.02	0.492	94.255
Sialic acid-binding Ig-like lectin 9	Q9Y336	0.02	0.494	50.082
Connective tissue-activating peptide III	P02775	0.02	0.499	13.894
Caspase-10	Q92851	-0.02	0.503	58.951

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Teratocarcinoma-derived growth factor 1	P13385	-0.02	0.505	21.169
Insulin-like growth factor 1 receptor	P08069	-0.02	0.517	154.793
Tumor-associated calcium signal transducer 2	P09758	0.02	0.518	35.709
Granulysin	P22749	0.02	0.531	16.374
Aggrecan core protein	P16112	-0.02	0.539	261.329
Tumor necrosis factor ligand superfamily member 8	P32971	-0.02	0.539	26.017
CD166 antigen	Q13740	0.02	0.547	65.102
Neurogenic locus notch homolog protein 2	Q04721	-0.02	0.547	265.405
Complement factor H-related protein 5	Q9BXR6	-0.02	0.549	64.419
Ephrin type-A receptor 3	P29320	-0.02	0.555	110.131
Nidogen-1	P14543	-0.02	0.555	136.377
Alkaline phosphatase, tissue-nonspecific isozyme	P05186	0.02	0.559	57.305
Tumor necrosis factor ligand superfamily member 13B	Q9Y275	0.02	0.559	31.223
Immunoglobulin E	P01854	0.02	0.563	47.019
High affinity cAMP-specific 3',5'-cyclic phosphodiesterase 7A	Q13946	0.02	0.565	55.505
Desmocollin-3	Q14574	-0.02	0.566	99.969
Dickkopf-related protein 1	O94907	-0.02	0.570	28.672
FACT complex subunit SSRP1	Q08945	0.02	0.573	81.075
Platelet-derived growth factor C	Q9NRA1	0.02	0.573	39.029
Nidogen-2	Q14112	-0.02	0.575	151.254
Megakaryocyte-associated tyrosine-protein kinase	P42679	0.02	0.575	56.469

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Hyaluronan and proteoglycan link protein 1	P10915	0.02	0.575	40.166
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform:Phosphatidylinositol 3-kinase regulatory subunit alpha complex	P42336 P27986	0.02	0.576	124.284
MHC class I polypeptide-related sequence A	Q29983	-0.02	0.578	42.915
Heterogeneous nuclear ribonucleoprotein A/B	Q99729	0.02	0.582	36.225
Dipeptidyl peptidase 1	P53634	0.02	0.587	51.854
Nicotinamide phosphoribosyltransferase	P43490	-0.02	0.590	55.521
Anti-Muellerian hormone type-2 receptor	Q16671	-0.02	0.597	62.750
Pituitary adenylate cyclase-activating polypeptide 27	P18509	0.02	0.598	18.835
Peptidyl-prolyl cis-trans isomerase E	Q9UNP9	-0.02	0.598	33.341
Erythropoietin receptor	P19235	0.02	0.598	55.065
Granulins	P28799	0.02	0.603	63.544
Hepatocyte growth factor	P14210	0.02	0.621	83.134
Lamin-B1	P20700	0.02	0.622	66.408
Lactotransferrin	P02788	0.02	0.625	78.182
Platelet-derived growth factor receptor beta	P09619	-0.02	0.633	123.968
Angiopoietin-4	Q9Y264	-0.02	0.643	56.849
Junctional adhesion molecule-like	Q86YT9	0.02	0.645	44.339
Fibronectin Fragment 3	P02751	-0.01	0.650	262.625
Tyrosine-protein kinase ABL1	P00519	0.01	0.654	122.873
Fibroblast growth factor receptor 3	P22607	0.01	0.655	87.710

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Interleukin-1 receptor-like 1	Q01638	0.01	0.669	63.358
Phosphoglycerate kinase 1	P00558	-0.01	0.671	44.615
Leucine-rich repeat transmembrane neuronal protein 3	Q86VH5	-0.01	0.674	65.896
Neutrophil elastase	P08246	0.01	0.675	28.518
Hepatocyte growth factor activator	Q04756	0.01	0.676	70.682
Activin receptor type-1B	P36896	0.01	0.679	56.807
Membrane metallo-endopeptidase-like 1	Q495T6	0.01	0.681	89.367
Tumor necrosis factor ligand superfamily member 6, soluble form	P48023	0.01	0.693	31.485
Protein kinase C zeta type	Q05513	-0.01	0.694	67.660
C-type lectin domain family 4 member K	Q9UJ71	-0.01	0.701	36.725
Casein kinase II 2-alpha':2-beta heterotetramer	P19784 P67870	0.01	0.702	41.213
Histidine triad nucleotide-binding protein 1	P49773	0.01	0.715	13.802
Serine/threonine-protein kinase PLK1	P53350	-0.01	0.715	68.255
Kallikrein-13	Q9UKR3	-0.01	0.720	30.570
Brevican core protein	Q96GW7	-0.01	0.721	99.118
SUMO-conjugating enzyme UBC9	P63279	0.01	0.729	18.007
Tumor necrosis factor ligand superfamily member 14	O43557	-0.01	0.739	26.350
Cathepsin S	P25774	0.01	0.744	37.496
Eukaryotic translation initiation factor 5A-1	P63241	0.01	0.752	16.832
Thrombopoietin Receptor	P40238	-0.01	0.752	71.245

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Bactericidal permeability-increasing protein	P17213	0.01	0.752	53.900
N-acetyl-D-glucosamine kinase	Q9UJ70	0.01	0.752	37.376
26S proteasome non-ATPase regulatory subunit 7	P51665	-0.01	0.757	37.025
CD209 antigen	Q9NNX6	0.01	0.762	45.775
Granulocyte colony-stimulating factor receptor	Q99062	-0.01	0.770	92.156
Histone deacetylase 8	Q9BY41	-0.01	0.773	41.758
Tissue factor pathway inhibitor	P10646	0.01	0.774	35.015
Neural cell adhesion molecule 1, 120 kDa isoform	P13591	-0.01	0.777	94.574
Inosine-5'-monophosphate dehydrogenase 1	P20839	-0.01	0.785	55.406
Lymphotactin	P47992	-0.01	0.785	12.517
Immunoglobulin G	P01857	-0.01	0.789	36.106
Peroxiredoxin-5, mitochondrial	P30044	0.01	0.790	22.086
Cathepsin G	P08311	-0.01	0.799	28.837
Heterogeneous nuclear ribonucleoprotein K	P61978	0.01	0.805	50.976
Desmoglein-2	Q14126	0.01	0.807	122.294
Chloride intracellular channel protein 1	O00299	0.01	0.819	26.923
Stem Cell Growth Factor-alpha	Q9Y240	-0.01	0.823	35.695
Endothelin-converting enzyme 1	P42892	0.01	0.824	87.164
Lymphotoxin-alpha	P01374	0.01	0.826	22.297
Desmoglein-1	Q02413	-0.01	0.832	113.748
X-linked interleukin-1 receptor accessory protein-like 2	Q9NP60	-0.01	0.833	78.670
Kallikrein-6	Q92876	0.01	0.837	26.856

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Mitogen-activated protein kinase 8	P45983	-0.01	0.837	48.296
Fibrinogen	P02671 P02675 P02679	-0.01	0.838	94.973
Microtubule-associated protein tau	P10636	-0.01	0.848	78.928
Glial fibrillary acidic protein	P14136	-0.01	0.848	49.880
Interleukin-2 receptor subunit alpha	P01589	-0.01	0.852	30.819
Carbohydrate sulfotransferase 15	Q7LFX5	0.01	0.852	64.926
Sphingosine kinase 2	Q9NRA0	-0.01	0.869	69.217
Tumor necrosis factor receptor superfamily member 13B	O14836	-0.01	0.871	31.816
C-C motif chemokine 1	P22362	0.01	0.872	10.992
Insulin	P01308	-0.01	0.873	11.981
Coagulation Factor VII	P08709	0	0.892	51.594
Low molecular weight phosphotyrosine protein phosphatase	P24666	0	0.898	18.042
N-acylethanolamine-hydrolyzing acid amidase	Q02083	0	0.898	40.066
Fibroblast growth factor 5	P12034	0	0.899	29.551
X-ray repair cross-complementing protein 6	P12956	0	0.902	69.843
Serine/threonine-protein kinase pim-1	P11309	0	0.902	45.412
Cofilin-1	P23528	0	0.905	18.502
High affinity immunoglobulin gamma Fc receptor I	P12314	0	0.909	42.632
Eukaryotic translation initiation factor 4E-binding protein 2	Q13542	0	0.911	12.939
Glucose-6-phosphate isomerase	P06744	0	0.913	63.147

Protein	UniProt ID	Spearman rho	p-value	Molecular Weight (kDa)
Integrin alpha-I: beta-1 complex	P56199, P05556	0	0.914	130.848
Tumor necrosis factor receptor superfamily member 25	Q93038	0	0.915	45.385
Placenta growth factor	P49763	0	0.921	24.789
Contactin-1	Q12860	0	0.938	113.320
Inhibin beta A chain:Inhibin beta B chain heterodimer	P08476 P09529	0	0.939	47.442
Sonic hedgehog protein	Q15465	0	0.940	49.607
MAP kinase-activated protein kinase 5	Q8IW41	0	0.940	54.220
Stromelysin-2	P09238	0	0.943	54.151
Semaphorin-6A	Q9H2E6	0	0.944	114.395
Sorting nexin-4	O95219	0	0.945	51.909
Apolipoprotein B	P04114	0	0.946	515.605
Mannose-binding protein C	P11226	0	0.958	26.144
Tumor necrosis factor receptor superfamily member 12A	Q9NP84	0	0.960	13.911
High affinity nerve growth factor receptor	P04629	0	0.963	87.497
Protein lin-7 homolog B	Q9HAP6	0	0.964	22.896
Heat shock cognate 71 kDa protein	P11142	0	0.969	70.898
Stem Cell Growth Factor-beta	Q9Y240	0	0.981	35.695
Fibroblast growth factor 17	O60258	0	0.985	24.891
Cadherin-12	P55289	0	0.998	88.332

Protein	**UniProt ID**	**HR**	**p-value**	**Bonferroni corrected p-value**	**HR corrected for eGFR**	**p-value (HR corrected for eGFR)**	**p-value (HR corrected for eGFR and Bonferroni corrected)**
Metalloproteinase inhibitor 1	P01033	1.34	<2.2x10^{-16}	<2.2x10^{-16}	1.28	2.11x10^{-13}	2.22x10^{-10}
Insulin-like growth factor-binding protein 2	P18065	1.57	<2.2x10^{-16}	<2.2x10^{-16}	1.41	6.92x10^{-11}	7.30x10^{-08}
Angiopoietin-2	O15123	1.66	<2.2x10^{-16}	<2.2x10^{-16}	1.52	0	0
Cystatin-C	P01034	1.48	<2.2x10^{-16}	<2.2x10^{-16}	1.49	2.22x10^{-06}	0.00234
Ephrin-A4	P52798	1.43	<2.2x10^{-16}	<2.2x10^{-16}	1.25	0.000372	0.392
Cadherin-3	P22223	0.67	<2.2x10^{-16}	<2.2x10^{-16}	0.74	3.76x10^{-09}	3.96x10^{-06}
Tumor necrosis factor receptor superfamily member 1A	P19438	1.23	<2.2x10^{-16}	<2.2x10^{-16}	1.13	0.00177	1
Epidermal growth factor receptor	P00533	0.59	<2.2x10^{-16}	<2.2x10^{-16}	0.65	5.66x10^{-15}	5.97x10^{-12}
Matrilysin	P09237	1.52	<2.2x10^{-16}	<2.2x10^{-16}	1.37	1.16x10^{-11}	1.23x10^{-08}
Complement component C7	P10643	1.46	<2.2x10^{-16}	<2.2x10^{-16}	1.46	0	0
C-C motif chemokine 14	Q16627	1.54	<2.2x10^{-16}	<2.2x10^{-16}	1.33	2.80x10^{-06}	0.00295
Neuroblastoma suppressor of tumorigenicity 1	P41271	1.43	<2.2x10^{-16}	<2.2x10^{-16}	1.28	0.000461	0.4857
Growth hormone receptor	P10912	0.62	<2.2x10^{-16}	<2.2x10^{-16}	0.68	7.88x10^{-15}	8.31x10^{-12}
Alpha-2-antiplasmin	P08697	0.64	<2.2x10^{-16}	<2.2x10^{-16}	0.7	1.87x10^{-12}	1.97x10^{-09}
Tumor necrosis factor receptor superfamily member 27	Q9HAV5	1.26	<2.2x10^{-16}	<2.2x10^{-16}	1.17	1.51x10^{-05}	0.0159
Tumor necrosis factor receptor superfamily member 1B	P20333	1.56	<2.2x10^{-16}	<2.2x10^{-16}	1.41	9.41x10^{-09}	9.92x10^{-06}
Thrombospondin-2	P35442	1.53	<2.2x10^{-16}	<2.2x10^{-16}	1.47	0	0
Follistatin-related protein 3	O95633	1.55	<2.2x10^{-16}	<2.2x10^{-16}	1.4	6.14x10^{-08}	6.48x10^{-05}
Beta-2-microglobulin	P61769	1.53	<2.2x10^{-16}	<2.2x10^{-16}	1.5	1.77x10^{-09}	1.87x10^{-06}
Beta-Ala-His dipeptidase	Q96KN2	0.69	<2.2x10^{-16}	<2.2x10^{-16}	0.72	2.78x10^{-15}	2.93x10^{-12}
Cathepsin H	P09668	1.52	<2.2x10^{-16}	<2.2x10^{-16}	1.45	2.95x10^{-08}	3.11x10^{-05}
Spondin-1	Q9HCB6	1.4	<2.2x10^{-16}	<2.2x10^{-16}	1.33	3.35x10-^{12}	3.53x10^{-09}
Macrophage metalloelastase	P39900	1.65	<2.2x10^{-16}	<2.2x10^{-16}	1.5	8.88x10^{-16}	9.36x10^{-13}
Ephrin type-A receptor 2	P29317	1.42	<2.2x10^{-16}	<2.2x10^{-16}	1.26	3.77x10^{-06}	0.00397
Adapter molecule crk	P46108	1.37	<2.2x10^{-16}	<2.2x10^{-16}	1.17	0.007316	1
Tumor necrosis factor receptor superfamily member 19L	Q969Z4	1.45	<2.2x10^{-16}	<2.2x10^{-16}	1.26	0.000289	0.305
Scavenger receptor class F member 1	Q14162	1.38	<2.2x10^{-16}	<2.2x10^{-16}	1.2	0.000298	0.314
Hepatitis A virus cellular receptor 2	Q8TDQ0	1.59	<2.2x10^{-16}	<2.2x10^{-16}	1.42	1.77x10^{-10}	1.86x10^{-07}
Delta-like protein 1	O00548	1.31	<2.2x10^{-16}	<2.2x10^{-16}	1.21	6.03x10^{-07}	0.000635
Interleukin-18-binding protein	O95998	1.49	1.11x10^{-16}	1.17x10^{-13}	1.35	9.84x10^{-09}	1.04x10^{-05}
Macrophage-capping protein	P40121	1.35	2.22x10^{-16}	2.34x10^{-13}	1.22	7.91x10^{-06}	0.00834
Netrin receptor UNC5C	O95185	1.43	2.22x10^{-16}	2.34x10^{-13}	1.23	0.000264	0.278
Brain-specific serine protease 4	Q9GZN4	1.42	3.33x10^{-16}	3.51x10^{-13}	1.3	2.66x10^{-08}	2.80x10^{-05}
C-C motif chemokine 18	P55774	1.46	4.44x10^{-16}	4.68x10^{-13}	1.35	1.27x10^{-09}	1.34x10^{-06}
Chordin-like protein 1	Q9BU40	1.47	5.55x10^{-16}	5.85x10^{-13}	1.31	1.33x10^{-07}	0.000140

Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value	HR corrected for eGFR	p-value (HR corrected for eGFR)	p-value (HR corrected for eGFR and Bonferroni corrected)
Ephrin type-B receptor 2	P29323	1.49	5.55x10^{-16}	5.85x10^{-13}	1.33	4.61x10^{-08}	4.85x10^{-05}
Endostatin	P39060	1.5	6.66x10^{-16}	7.02x10^{-13}	1.26	0.000147	0.155
SLAM family member 5	Q9UIB8	1.29	1.24x10^{-14}	1.31x10^{-11}	1.23	1.59x10^{-07}	0.000167
Vitamin K-dependent protein C	P04070	0.74	1.44x10^{-14}	1.52x10^{-11}	0.76	1.06x10^{-10}	1.12x10^{-07}
Cell adhesion molecule-related/down-regulated by oncogenes	Q4KMG0	0.7	1.91x10^{-14}	2.01x10^{-11}	0.78	9.85x10^{-07}	0.00104
Bone morphogenetic protein 1	P13497	0.7	2.63x10^{-14}	2.77x10^{-11}	0.78	8.03x10^{-07}	0.000847
Ephrin-A5	P52803	1.36	3.03x10^{-14}	3.19x10^{-11}	1.1	0.113	1
Endothelial cell-selective adhesion molecule	Q96AP7	1.36	6.36x10^{-14}	6.71x10^{-11}	1.04	0.521	1
Protein jagged-1	P78504	1.42	9.56x10^{-14}	1.01x10^{-10}	1.36	1.54x10^{-10}	1.62x10^{-07}
PSA:alpha-1-antichymotrypsin complex	P07288, P01011	1.38	1.15x10^{-13}	1.21x10^{-10}	1.3	7.97x10^{-09}	8.40x10^{-06}
Proto-oncogene tyrosine-protein kinase receptor Ret	P07949	0.65	1.20x10^{-13}	1.27x10^{-10}	0.74	1.36x10^{-07}	0.000143
Platelet-activating factor acetylhydrolase IB subunit beta	P68402	1.29	2.41x10^{-13}	2.54x10^{-10}	1.13	0.0105	1
Creatine kinase M-type:Creatine kinase B-type heterodimer	P12277 P06732	0.68	2.80x10^{-13}	2.95x10^{-10}	0.75	1.38x10^{-07}	0.000146
Complement component C9	P02748	1.47	3.94x10^{-13}	4.16x10^{-10}	1.39	7.28x10^{-10}	7.67x10^{-07}
Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A	Q9HCR9	0.67	4.20x10^{-13}	4.43x10^{-10}	0.77	3.75x10^{-06}	0.00396
Trefoil factor 3	Q07654	1.3	7.64x10^{-13}	8.05x10^{-10}	1.11	0.0539	1
Urokinase plasminogen activator surface receptor	Q03405	1.28	1.87x10^{-12}	1.97x10^{-09}	1.21	1.23x10^{-05}	0.0129
Tissue Factor	P13726	1.22	2.74x10^{-12}	2.89x10^{-09}	1.15	0.000159	0.167
Tumor necrosis factor ligand superfamily member 15	O95150	1.27	2.88x10^{-12}	3.03x10^{-09}	1.13	0.00479	1
Troponin I, cardiac muscle	P19429	1.26	3.06x10^{-12}	3.23x10^{-09}	1.26	6.00x10^{-11}	6.33x10^{-08}
Glutathione S-transferase P	P09211	1.35	5.50x10^{-12}	5.80x10^{-09}	1.15	0.00686	1
Neuroligin-4, X-linked	Q8N0W4	1.28	7.06x10^{-12}	7.44x10^{-09}	1.18	5.16x10^{-05}	0.0544
Angiostatin	P00747	0.72	9.43x10^{-12}	9.94x10^{-09}	0.81	3.51x10^{-05}	0.0370
Vascular endothelial growth factor A	P15692	1.38	1.55x10^{-11}	1.64x10^{-08}	1.23	5.05x10^{-05}	0.0532
Creatine kinase M-type	P06732	0.69	1.83x10^{-11}	1.93x10^{-08}	0.74	9.15x10^{-08}	9.64x10^{-05}
Elafin	P19957	1.34	1.86x10^{-11}	1.96x10^{-08}	1.13	0.0215	1
Fibroblast growth factor 7	P21781	1.24	2.58x10^{-11}	2.72x10^{-08}	1.2	5.70x10^{-07}	0.000601
Vascular endothelial growth factor receptor 2	P35968	0.73	2.84x10^{-11}	2.99x10^{-08}	0.81	2.50x10^{-05}	0.0264
Receptor tyrosine-protein kinase erbB-3	P21860	0.71	3.57x10^{-11}	3.77x10^{-08}	0.81	0.000223	0.2355
C-X-C motif chemokine 13	O43927	1.28	3.70x10^{-11}	3.90x10^{-08}	1.24	4.05x10^{-08}	4.27x10^{-05}
Plasma kallikrein	P03952	0.75	4.33x10^{-11}	4.57x10^{-08}	0.8	7.56x10^{-07}	0.000796
Stanniocalcin-1	P52823	1.33	5.88x10^{-11}	6.20x10^{-08}	1.21	4.73x10^{-05}	0.0498
Kallikrein-11	Q9UBX7	1.3	6.26x10^{-11}	6.60x10^{-08}	1.11	0.0415	1

Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value	HR corrected for eGFR	p-value (HR corrected for eGFR)	p-value (HR corrected for eGFR and Bonferroni corrected)
Periostin	Q15063	1.38	6.61x10^{-11}	6.97x10^{-08}	1.28	1.04x10^{-06}	0.00110
Insulin-like growth factor-binding protein 6	P24592	1.26	1.14x10^{-10}	1.20x10^{-07}	0.92	0.237	1
Angiopoietin-related protein 4	Q9BY76	1.26	1.80x10^{-10}	1.89x10^{-07}	1.23	8.20x10^{-08}	8.64x10^{-05}
Pancreatic hormone	P01298	1.32	1.94x10^{-10}	2.04x10^{-07}	1.19	0.000248	0.261
Heat shock 70 kDa protein 1A/1B	P08107	1.33	4.37x10^{-10}	4.60x10^{-07}	1.28	1.60x10^{-07}	0.000168
Fatty acid-binding protein, heart	P05413	1.26	4.50x10^{-10}	4.75x10^{-07}	1.09	0.0923	1
Antileukoproteinase	P03973	1.32	5.57x10^{-10}	5.87x10^{-07}	1.15	0.00724	1
Low affinity immunoglobulin gamma Fc region receptor III-B	O75015	1.33	8.93x10^{-10}	9.42x10^{-07}	1.3	1.85x10^{-08}	1.95x10^{-05}
Tumor necrosis factor receptor superfamily member 21	O75509	1.34	1.07x10^{-09}	1.13x10^{-06}	1.11	0.0744	1
Coiled-coil domain-containing protein 80	Q76M96	1.33	1.11x10^{-09}	1.17x10^{-06}	1.17	0.00254	1
15-hydroxyprostaglandin dehydrogenase [NAD(+)]	P15428	0.72	1.15x10^{-09}	1.21x10^{-06}	0.79	6.43x10^{-06}	0.00678
A disintegrin and metalloproteinase with thrombospondin motifs 13	Q76LX8	0.77	1.22x10^{-09}	1.29x10^{-06}	0.87	0.00553	1
Lymphocyte activation gene 3 protein	P18627	1.34	1.30x10^{-09}	1.37x10^{-06}	1.28	5.88x10^{-07}	0.000619
Kallistatin	P29622	0.76	1.73x10^{-09}	1.83x10^{-06}	0.8	1.90x10^{-06}	0.00200
Stromelysin-1	P08254	1.33	1.74x10^{-09}	1.84x10^{-06}	1.19	0.000275	0.290
Interleukin-15 receptor subunit alpha	Q13261	1.19	1.81x10^{-09}	1.91x10^{-06}	1.09	0.0238	1
Afamin	P43652	0.8	1.89x10^{-09}	1.99x10^{-06}	0.87	0.00162	1
Cystatin-D	P28325	1.31	1.95x10^{-09}	2.05x10^{-06}	1.09	0.103	1
CD48 antigen	P09326	1.28	2.01x10^{-09}	2.12x10^{-06}	1.19	7.78x10^{-05}	0.082
Interleukin-1 receptor-like 1	Q01638	1.3	2.28x10^{-09}	2.40x10^{-06}	1.28	3.10x10^{-08}	3.27x10^{-05}
Cerebral dopamine neurotrophic factor	Q49AH0	1.31	2.37x10^{-09}	2.50x10^{-06}	1	0.965	1
Growth/differentiation factor 11	O95390	0.71	2.46x10^{-09}	2.59x10^{-06}	0.74	1.06x10^{-07}	0.000112
Brain natriuretic peptide 32	P16860	1.21	3.13x10^{-09}	3.30x10^{-06}	1.19	1.64x10^{-07}	0.000173
Cathepsin Z	Q9UBR2	1.3	3.51x10^{-09}	3.70x10^{-06}	1.18	0.000799	0.842
Neurexophilin-1	P58417	0.75	4.00x10^{-09}	4.21x10^{-06}	0.82	0.000218	0.230
C-type lectin domain family 4 member M	Q9H2X3	0.76	4.37x10^{-09}	4.61x10^{-06}	0.86	0.00177	1
Prothrombin	P00734	0.79	4.41x10^{-09}	4.65x10^{-06}	0.84	6.03x10^{-05}	0.0636
Platelet glycoprotein VI	Q9HCN6	1.31	4.68x10^{-09}	4.93x10^{-06}	1.13	0.0145	1
Immunoglobulin G	P01857	1.32	4.89x10^{-09}	5.16x10^{-06}	1.33	8.11x10^{-09}	8.55x10^{-06}
Layilin	Q6UX15	1.25	5.16x10^{-09}	5.44x10^{-06}	0.99	0.837	1
Coagulation factor Xa	P00742	0.79	6.57x10^{-09}	6.92x10^{-06}	0.82	2.71x10^{-06}	0.00285
C-C motif chemokine 23	P55773	1.3	6.65x10^{-09}	7.00x10^{-06}	1.12	0.0285	1
Tyrosine-protein kinase Yes	P07947	1.26	7.33x10^{-09}	7.72x10^{-06}	1.21	8.05x10^{-06}	0.00848

Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value	HR corrected for eGFR	p-value (HR corrected for eGFR)	p-value (HR corrected for eGFR and Bonferroni corrected)
Cathepsin L2	O60911	0.75	$7.94x10^{-09}$	$8.36x10^{-06}$	0.88	0.0170	1
Ficolin-3	O75636	0.78	$7.96x10^{-09}$	$8.38x10^{-06}$	0.85	0.000369	0.389
Dickkopf-like protein 1	Q9UK85	0.74	$8.48x10^{-09}$	$8.94x10^{-06}$	0.81	$9.78x10^{-05}$	0.103
Midkine	P21741	1.23	$9.16x10^{-09}$	$9.66x10^{-06}$	1.21	$4.29x10^{-07}$	0.000452
Interleukin-17 receptor C	Q8NAC3	1.22	$9.74x10^{-09}$	$1.03x10^{-05}$	1.1	0.0343	1
Phospholipase A2, membrane associated	P14555	1.27	$9.86x10^{-09}$	$1.04x10^{-05}$	1.23	$2.10x10^{-06}$	0.00221
Alpha-2-HS-glycoprotein	P02765	0.77	$1.56x10^{-08}$	$1.65x10^{-05}$	0.85	0.000885	0.933
Ephrin type-B receptor 6	O15197	1.24	$1.66x10^{-08}$	$1.75x10^{-05}$	1	0.990	1
Insulin-like growth factor-binding protein 1	P08833	1.29	$2.24x10^{-08}$	$2.36x10^{-05}$	1.23	$1.16x10^{-05}$	0.0122
Serine protease HTRA2, mitochondrial	O43464	1.27	$2.75x10^{-08}$	$2.90x10^{-05}$	1.16	0.00229	1
Ck-beta-8-1	P55773	1.34	$3.18x10^{-08}$	$3.35x10^{-05}$	1.15	0.0145	1
Renin	P00797	1.28	$3.24x10^{-08}$	$3.41x10^{-05}$	1.24	$1.52x10^{-06}$	0.00160
Resistin	Q9HD89	1.28	$3.56x10^{-08}$	$3.75x10^{-05}$	1.06	0.30305	1
Tyrosine-protein kinase transmembrane receptor ROR1	Q01973	1.23	$4.40x10^{-08}$	$4.63x10^{-05}$	1.08	0.149	1
Tumor necrosis factor receptor superfamily member 9	Q07011	1.18	$7.87x10^{-08}$	$8.30x10^{-05}$	1.1	0.0129	1
Pappalysin-1	Q13219	1.28	$8.52x10^{-08}$	$8.98x10^{-05}$	1.13	0.0146	1
Bone sialoprotein 2	P21815	1.26	$9.63x10^{-08}$	$1.01x10^{-04}$	1.14	0.00485	1
SHC-transforming protein 1	P29353	1.22	$1.26x10^{-07}$	$1.33x10^{-04}$	1.08	0.0939	1
Neuropilin-1	O14786	1.21	$1.32x10^{-07}$	$1.39x10^{-04}$	1.19	$4.05x10^{-06}$	0.00427
Fibroblast growth factor 23	Q9GZV9	1.18	$1.62x10^{-07}$	$1.70x10^{-04}$	1.1	0.00536	1
Fibroblast growth factor 20	Q9NP95	0.74	$2.03x10^{-07}$	$2.14x10^{-04}$	0.9	0.0768	1
Superoxide dismutase [Mn], mitochondrial	P04179	0.77	$2.07x10^{-07}$	$2.18x10^{-04}$	0.88	0.0158	1
Interleukin-8	P10145	1.18	$3.26x10^{-07}$	$3.43x10^{-04}$	1.2	$2.70x10^{-08}$	$2.85x10^{-05}$
Nidogen-1	P14543	1.27	$3.75x10^{-07}$	$3.95x10^{-04}$	1.23	$4.03x10^{-06}$	0.00425
Seprase	Q12884	0.73	$4.21x10^{-07}$	$4.44x10^{-04}$	0.79	0.000102	0.108
Tumor necrosis factor receptor superfamily member 19	Q9NS68	1.17	$4.51x10^{-07}$	$4.75x10^{-04}$	1.03	0.471	1
Oxidized low-density lipoprotein receptor 1	P78380	1.24	$5.23x10^{-07}$	$5.51x10^{-04}$	1.23	$2.03x10^{-06}$	0.00214
Cytochrome P450 3A4	P08684	0.78	$5.78x10^{-07}$	$6.09x10^{-04}$	0.84	0.000540	0.569
Tenascin	P24821	1.26	$6.31x10^{-07}$	$6.66x10^{-04}$	1.32	$2.55x10^{-09}$	$2.69x10^{-06}$
Malate dehydrogenase, cytoplasmic	P40925	0.79	$6.41x10^{-07}$	$6.76x10^{-04}$	0.88	0.00776	1
Insulin-like growth factor-binding protein 7	Q16270	1.26	$6.67x10^{-07}$	$7.03x10^{-04}$	1.33	$1.06x10^{-09}$	$1.11x10^{-06}$
Muellerian-inhibiting factor	P03971	0.83	$7.84x10^{-07}$	$8.27x10^{-04}$	0.88	0.00451	1
BDNF/NT-3 growth factors receptor	Q16620	0.77	$8.22x10^{-07}$	$8.66x10^{-04}$	0.86	0.00450	1
Stromal cell-derived factor 1	P48061	1.26	$8.71x10^{-07}$	$9.18x10^{-04}$	1.22	$5.91x10^{-05}$	0.0623

Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value	HR corrected for eGFR	p-value (HR corrected for eGFR)	p-value (HR corrected for eGFR and Bonferroni corrected)
Complement factor D	P00746	1.17	8.91x10^{-07}	9.39x10^{-04}	1.06	0.229	1
Ectonucleoside triphosphate diphosphohydrolase 5	O75356	0.79	9.33x10^{-07}	9.84x10^{-04}	0.85	0.000929	0.979
Carbonic anhydrase 3	P07451	1.25	9.48x10^{-07}	9.99x10-^{04}	1.09	0.0952	1
C-C motif chemokine 7	P80098	1.22	1.05x10^{-06}	1.10x10^{-03}	1.15	0.00125	1
Tumor necrosis factor ligand superfamily member 12	O43508	0.72	1.09x10^{-06}	1.14x10^{-03}	0.78	0.000134	0.142
cGMP-dependent 3',5'-cyclic phosphodiesterase	O00408	0.78	1.23x10^{-06}	1.29x10^{-03}	0.86	0.00303	1
Alpha-(1,3)-fucosyltransferase 5	Q11128	1.27	1.53x10^{-06}	1.61x10^{-03}	1.23	3.43x10^{-05}	0.0362
Plasminogen	P00747	0.79	1.64x10^{-06}	1.73x10^{-03}	0.85	0.00151	1
Neurogenic locus notch homolog protein 1	P46531	0.81	1.78x10^{-06}	1.88x10^{-03}	0.87	0.00225	1
Matrilin-2	O00339	1.25	1.98x10^{-06}	2.09x10^{-03}	1.03	0.510	1
Tyrosine-protein phosphatase non-receptor type 1	P18031	0.76	2.28x10^{-06}	2.41x10^{-03}	0.83	0.00149	1
C-X-C motif chemokine 10	P02778	1.23	2.33x10^{-06}	2.46x10^{-03}	1.21	2.59x10^{-05}	0.0273
Heparin cofactor 2	P05546	0.81	2.50x10^{-06}	2.64x10^{-03}	0.85	0.000310	0.326
Neurogenic locus notch homolog protein 3	Q9UM47	1.2	2.52x10^{-06}	2.66x10^{-03}	1.13	0.00582	1
Lipopolysaccharide-binding protein	P18428	1.27	2.56x10^{-06}	2.70x10^{-03}	1.23	5.02x10^{-05}	0.0529
Testican-1	Q08629	0.79	2.74x10^{-06}	2.89x10^{-03}	0.85	0.00197	1
Interleukin-1 receptor type 1	P14778	1.26	2.94x10^{-06}	3.10x10^{-03}	1.18	0.000661	0.696
C-C motif chemokine 3	P10147	1.17	3.03x10^{-06}	3.19x10^{-03}	1.1	0.0131	1
Tumor necrosis factor ligand superfamily member 8	P32971	1.21	3.11x10^{-06}	3.27x10^{-03}	1.22	7.46x10^{-07}	0.000787
Antithrombin-III	P01008	0.83	3.44x10^{-06}	3.62x10^{-03}	0.87	0.00130	1
6-phosphogluconate dehydrogenase, decarboxylating	P52209	0.8	3.44x10^{-06}	3.63x10^{-03}	0.92	0.0690	1
Alcohol dehydrogenase [NADP(+)]	P14550	1.24	3.45x10^{-06}	3.63x10^{-03}	1.13	0.0128	1
Opioid-binding protein/cell adhesion molecule	Q14982	0.79	3.68x10^{-06}	3.88x10^{-03}	0.81	5.88x10^{-05}	0.0620
Intercellular adhesion molecule 5	Q9UMF0	1.21	3.99x10^{-06}	4.21x10^{-03}	1.23	3.65x10^{-07}	0.000385
Cystatin-SA	P09228	1.24	4.61x10^{-06}	4.86x10^{-03}	1.01	0.831	1
Aminoacylase-1	Q03154	0.79	5.02x10^{-06}	5.29x10^{-03}	0.9	0.0468	1
Ficolin-2	Q15485	0.83	5.10x10^{-06}	5.37x10^{-03}	0.89	0.00662	1
Insulin-like growth factor 1 receptor	P08069	1.25	5.17x10^{-06}	5.45x10^{-03}	1.23	1.51x10^{-05}	0.0159
Serine/threonine-protein kinase 17B	O94768	0.79	5.45x10^{-06}	5.75x10^{-03}	0.88	0.0156	1
T-lymphocyte surface antigen Ly-9	Q9HBG7	1.24	6.00x10^{-06}	6.32x10^{-03}	1.19	0.000390	0.412
Programmed cell death 1 ligand 1	Q9NZQ7	1.19	6.04x10^{-06}	6.36x10^{-03}	1.15	0.000847	0.893
Carbonic anhydrase 6	P23280	0.81	6.89x10^{-06}	7.26x10^{-03}	0.84	0.000192	0.203

Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value	HR corrected for eGFR	p-value (HR corrected for eGFR)	p-value (HR corrected for eGFR and Bonferroni corrected)
Junctional adhesion molecule B	P57087	1.18	$7.15x10^{-06}$	$7.54x10^{-03}$	0.93	0.221	1
Dual specificity mitogen-activated protein kinase kinase 4	P45985	0.82	$7.19x10^{-06}$	$7.58x10^{-03}$	0.84	0.000168	0.177
gp41 C34 peptide, HIV	Q70626	1.2	$7.41x10^{-06}$	$7.81x10^{-03}$	1.08	0.119	1
Plasminogen activator inhibitor 1	P05121	0.8	$7.54x10^{-06}$	$7.95x10^{-03}$	0.88	0.00669	1
Transmembrane glycoprotein NMB	Q14956	1.22	$8.40x10^{-06}$	$8.85x10^{-03}$	1.18	0.000189	0.199
N-acetyl-D-glucosamine kinase	Q9UJ70	1.23	$9.26x10^{-06}$	$9.76x10^{-03}$	1.31	$3.54x10^{-09}$	$3.73x10^{-06}$
Low affinity immunoglobulin gamma Fc region receptor II-a/b	P12318 P31994	1.23	$1.04x10^{-05}$	$1.09x10^{-02}$	1.22	$4.20x10^{-05}$	0.0443
C-C motif chemokine 4-like	Q8NHW4	1.21	$1.18x10^{-05}$	$1.24x10^{-02}$	1.19	$8.30x10^{-05}$	0.0875
Cathepsin B	P07858	1.22	$1.27x10^{-05}$	$1.33x10^{-02}$	1.2	$3.76x10^{-05}$	0.0396
Kunitz-type protease inhibitor 2	O43291	1.17	$1.31x10^{-05}$	$1.38x10^{-02}$	1.1	0.0282	1
CD5 antigen-like	O43866	1.21	$1.52x10^{-05}$	$1.60x10^{-02}$	1.15	0.00110	1
Vascular endothelial growth factor C	P49767	1.15	$1.74x10^{-05}$	$1.83x10^{-02}$	1.08	0.0383	1
Endothelin-converting enzyme 1	P42892	0.82	$1.79x10^{-05}$	$1.89x10^{-02}$	0.83	$8.83x10^{-05}$	0.0931
dCTP pyrophosphatase 1	Q9H773	1.24	$1.80x10^{-05}$	$1.90x10^{-02}$	1.18	0.000937	0.988
Fibrinogen gamma chain	P02679	1.23	$1.81x10^{-05}$	$1.90x10^{-02}$	1.19	0.000237	0.250
Mannose-binding protein C	P11226	1.23	$2.01x10^{-05}$	$2.12x10^{-02}$	1.22	$6.49x10^{-05}$	0.0684
Complement component 1 Q subcomponent-binding protein, mitochondrial	Q07021	0.72	$2.33x10^{-05}$	$2.45x10^{-02}$	0.85	0.0247	1
Mammaglobin-B	O75556	0.79	$2.33x10^{-05}$	$2.46x10^{-02}$	0.86	0.00616	1
Neutral ceramidase	Q9NR71	0.82	$2.34x10^{-05}$	$2.46x10^{-02}$	0.88	0.00999	1
von Willebrand factor	P04275	1.22	$2.44x10^{-05}$	$2.57x10^{-02}$	1.18	0.000592	0.624
Dual specificity mitogen-activated protein kinase kinase 2	P36507	1.22	$2.61x10^{-05}$	$2.75x10^{-02}$	0.99	0.907	1
Calcium/calmodulin-dependent protein kinase type 1	Q14012	0.82	$2.64x10^{-05}$	$2.78x10^{-02}$	0.84	0.000198	0.209
Inosine-5'-monophosphate dehydrogenase 2	P12268	0.79	$2.94x10^{-05}$	$3.09x10^{-02}$	0.86	0.00667	1
Carboxypeptidase B2	Q96IY4	0.82	$3.06x10^{-05}$	$3.22x10^{-02}$	0.87	0.00291	1
Retinoic acid receptor responder protein 2	Q99969	1.21	$3.61x10^{-05}$	$3.81x10^{-02}$	1.01	0.815	1
Endothelial monocyte-activating polypeptide 2	Q12904	0.82	$3.82x10^{-05}$	$4.02x10^{-02}$	0.89	0.0202	1
C-C motif chemokine 28	Q9NRJ3	1.21	$4.03x10^{-05}$	$4.25x10^{-02}$	1.17	0.000951	1
Cell adhesion molecule 1	Q9BY67	1.2	$4.09x10^{-05}$	$4.31x10^{-02}$	1.12	0.0193	1
Macrophage mannose receptor 1	P22897	1.22	$4.44x10^{-05}$	$4.68x10^{-02}$	1.21	$3.15x10^{-05}$	0.0332

Below: Proteins that become prognostic of cardiovascular risk only after correction for eGFR

Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value	HR corrected for eGFR	p-value (corrected for eGFR)	p-value (HR corrected for eGFR and Bonferroni corrected)
Scavenger receptor cysteine-rich type 1 protein M130	Q86VB7	1.17	$6.93x10^{-04}$	$7.30x10^{-01}$	1.25	$4.13x10^{-06}$	$4.35x10^{-03}$
Insulin-like growth factor I	P05019	0.83	$2.94x10^{-04}$	$3.10x10^{-01}$	0.79	$7.50x10^{-06}$	$7.90x10^{-03}$
P-Selectin	P16109	1.2	$1.46x10^{-04}$	$1.54x10^{-01}$	1.22	$1.26x10^{-05}$	$1.33x10^{-02}$
Hemojuvelin	Q6ZVN8	0.92	$9.25x10^{-02}$	1	0.82	$2.57x10^{-05}$	$2.71x10^{-02}$
Interleukin-6 receptor subunit beta	P40189	1.17	$1.09x10^{-03}$	1	1.22	$3.56x10^{-05}$	$3.75x10^{-02}$
Sialic acid-binding Ig-like lectin 7	Q9Y286	1.1	$2.77x10^{-02}$	1	1.19	$4.64x10^{-05}$	$4.89x10^{-02}$
Interleukin-18 receptor 1	Q13478	1.2	$8.83x10^{-05}$	$9.31x10^{-02}$	1.21	$4.67x10^{-05}$	$4.92x10^{-02}$
Neurexin-1-beta	P58400	1.05	$3.06x10^{-01}$	1	0.81	$2.99x10^{-04}$	$3.15x10^{-01}$
Melanoma-derived growth regulatory protein	Q16674	0.99	$8.48x10^{-01}$	1	0.82	$1.48x10^{-04}$	$1.56x10^{-01}$
Lysosomal protective protein	P10619	1.15	$2.44x10^{-03}$	1	1.2	$4.87x10^{-05}$	$5.13x10^{-02}$
Gelsolin	P06396	0.93	$1.02x10^{-01}$	1	0.83	$5.14x10^{-05}$	$5.42x10^{-02}$
Cystatin-M	Q15828	1.13	$8.01x10^{-03}$	1	0.85	$4.24x10^{-03}$	$1.00x10^{+00}$

Table S3. Shown at the top of this supplemental table are 196 proteins associated with cardiovascular risk in the Heart and Soul cohort with unadjusted hazard ratios (HR) that were significant at Bonferroni corrected p-value < 0.05 (correction was based on all 1054 proteins measured). Also shown are HRs and their p-values after correction for eGFR. Also shown in the bottom portion of this supplemental table are 12 proteins that become prognostic of cardiovascular risk only after correction for eGFR

Table S4. Spearman rho correlations and p-values for the 100 proteins with the strongest rho coefficients in the Heart and Soul cohort, shown with rho correlations and p-values for the same proteins reported in the Lund cohort (98 of 100 proteins which were measured in both cohorts are shown in the Table). (Lund cohort data: DOI: 10.1002/prca.201700067)

Protein	UniProt ID	Heart and Soul rho	Heart and Soul p-value	Lund rho	Lund p-value
Cystatin-C	P01034	-0.74	$1.12\text{x}10^{-163}$	-0.85	$3.86\text{x}10^{-101}$
Insulin-like growth factor-binding protein 6	P24592	-0.7	$2.86\text{x}10^{-138}$	-0.81	$7.00\text{x}10^{-86}$
Tumor necrosis factor receptor superfamily member 1A	P19438	-0.65	$2.51\text{x}10^{-114}$	-0.6	$8.65\text{x}10^{-37}$
Neuroblastoma suppressor of tumorigenicity 1	P41271	-0.64	$2.29\text{x}10^{-109}$	-0.79	$9.95\text{x}10^{-79}$
Beta-2-microglobulin	P61769	-0.63	$1.11\text{x}10^{-102}$	-0.76	$6.18\text{x}10^{-69}$
Tumor necrosis factor receptor superfamily member 19L	Q969Z4	-0.62	$1.01\text{x}10^{-100}$	-0.56	$4.44\text{x}10^{-32}$
Cathepsin H	P09668	-0.61	$1.51\text{x}10^{-95}$	-0.31	$2.16\text{x}10^{-09}$
Follistatin-related protein 3	O95633	-0.58	$7.07\text{x}10^{-87}$	-0.79	$1.78\text{x}10^{-78}$
Endothelial cell-selective adhesion molecule	Q96AP7	-0.58	$4.98\text{x}10^{-86}$	-0.54	$1.76\text{x}10^{-28}$
Adapter molecule crk	P46108	-0.58	$2.86\text{x}10^{-85}$	-0.44	$2.20\text{x}10^{-18}$
Cerebral dopamine neurotrophic factor	Q49AH0	-0.57	$3.10\text{x}10^{-81}$	-0.71	$4.68\text{x}10^{-56}$
RGM domain family member B	Q6NW40	-0.54	$1.43\text{x}10^{-73}$	-0.51	$2.44\text{x}10^{-25}$
Ephrin-A5	P52803	-0.53	$3.39\text{x}10^{-70}$	-0.74	$1.65\text{x}10^{-64}$
Trefoil factor 3	Q07654	-0.53	$6.07\text{x}10^{-69}$	-0.76	$2.12\text{x}10^{-70}$
Tumor necrosis factor receptor superfamily member 27	Q9HAV5	-0.53	$1.33\text{x}10^{-67}$	-0.27	$1.56\text{x}10^{-07}$
Endostatin	P39060	-0.52	$1.03\text{x}10^{-66}$	-0.75	$1.09\text{x}10^{-66}$
Ephrin-A4	P52798	-0.52	$3.27\text{x}10^{-66}$	-0.6	$2.71\text{x}10^{-36}$
Netrin receptor UNC5C	O95185	-0.51	$1.43\text{x}10^{-64}$	-0.69	$1.36\text{x}10^{-53}$
Ephrin type-B receptor 6	O15197	-0.51	$3.98\text{x}10^{-64}$	-0.61	$4.16\text{x}10^{-38}$
Tumor necrosis factor receptor superfamily member 1B	P20333	-0.51	$1.40\text{x}10^{-63}$	-0.29	$1.19\text{x}10^{-08}$
Glutathione S-transferase P	P09211	-0.51	$5.89\text{x}10^{-62}$	-0.25	$1.33\text{x}10^{-06}$
C-C motif chemokine 14	Q16627	-0.5	$3.76\text{x}10^{-61}$	-0.65	$1.70\text{x}10^{-45}$
Macrophage-capping protein	P40121	-0.5	$6.26\text{x}10^{-61}$	-0.24	$2.49\text{x}10^{-06}$
Junctional adhesion molecule B	P57087	-0.5	$2.76\text{x}10^{-59}$	0.09	$9.19\text{x}10^{-02}$
Layilin	Q6UX15	-0.49	$1.56\text{x}10^{-57}$	-0.22	$2.78\text{x}10^{-05}$
Ephrin type-A receptor 2	P29317	-0.49	$2.11\text{x}10^{-57}$	-0.63	$8.37\text{x}10^{-42}$
Tyrosine-protein kinase transmembrane receptor ROR1	Q01973	-0.48	$2.10\text{x}10^{-56}$	-0.51	$3.67\text{x}10^{-25}$
Scavenger receptor class F member 1	Q14162	-0.47	$1.69\text{x}10^{-53}$	-0.12	$2.40\text{x}10^{-02}$
Fatty acid-binding protein, heart	P05413	-0.47	$2.37\text{x}10^{-52}$	-0.5	$1.08\text{x}10^{-24}$
Testican-2	Q92563	0.46	$2.58\text{x}10^{-51}$	0.42	$6.64\text{x}10^{-17}$
Netrin receptor UNC5D	Q6UXZ4	-0.46	$3.25\text{x}10^{-49}$	-0.55	$1.22\text{x}10^{-29}$

Protein	UniProt ID	Heart and Soul rho	Heart and Soul p-value	Lund rho	Lund p-value
Myoglobin	P02144	-0.45	4.71x10^{-49}	-0.42	1.17x10^{-16}
Tumor necrosis factor receptor superfamily member 19	Q9NS68	-0.45	3.70x10^{-47}	-0.57	1.93x10^{-32}
Elafin	P19957	-0.45	6.13x10^{-47}	-0.69	1.48x10^{-52}
Epidermal growth factor receptor	P00533	0.44	1.96x10^{-46}	0.25	1.70x10^{-06}
Interleukin-15 receptor subunit alpha	Q13261	-0.44	8.60x10-^{46}	-0.24	4.38x10^{-06}
Receptor tyrosine-protein kinase erbB-3	P21860	0.43	4.03x10^{-44}	0.1	5.10x10^{-02}
Metalloproteinase inhibitor 1	P01033	-0.43	4.76x10^{-44}	-0.25	8.89x10^{-07}
Antileukoproteinase	P03973	-0.43	1.81x10^{-42}	-0.64	9.83x10^{-44}
Cystatin-M	Q15828	-0.42	3.97x10^{-4}1	-0.65	8.24x10^{-45}
Cathepsin L2	O60911	0.42	1.66x10^{-40}	0.31	2.83x10^{-09}
Chordin-like protein 1	Q9BU40	-0.41	7.30x10^{-40}	-0.46	9.84x10^{-21}
Complement factor D	P00746	-0.41	8.38x10^{-40}	-0.08	1.31x10^{-01}
Coiled-coil domain-containing protein 80	Q76M96	-0.41	9.08x10^{-40}	-0.45	6.62x10^{-20}
Delta-like protein 1	O00548	-0.41	1.12x10^{-39}	-0.4	4.42x10^{-15}
Complement decay-accelerating factor	P08174	-0.41	2.69x10^{-39}	-0.64	7.85x10^{-43}
Hepatitis A virus cellular receptor 2	Q8TDQ0	-0.41	1.35x10^{-38}	-0.52	9.77x10^{-27}
Alpha-2-antiplasmin	P08697	0.41	1.42x10^{-38}	0.22	3.01x10^{-05}
Tumor necrosis factor ligand superfamily member 15	O95150	-0.4	3.90x10^{-38}	-0.47	3.16x10^{-21}
Neurexin-1-beta	P58400	-0.4	4.40x10^{-38}	-0.32	2.99x10^{-10}
Tumor necrosis factor receptor superfamily member 21	O75509	-0.4	1.62x10^{-37}	-0.53	3.75x10^{-28}
Ck-beta-8-1	P55773	-0.4	1.80x10^{-3}6	-0.34	2.43x10^{-11}
Neurexin-3-beta	Q9HDB5	-0.39	5.94x10^{-36}	-0.57	2.06x10^{-33}
Cystatin-SA	P09228	-0.38	2.99x10^{-34}	-0.53	9.21x10^{-28}
Bone morphogenetic protein 1	P13497	0.38	6.44x10^{-34}	0.1	6.40x10^{-02}
Kallikrein-11	Q9UBX7	-0.38	6.96x10^{-34}	-0.39	5.05x10^{-15}
Platelet-activating factor acetylhydrolase IB subunit beta	P68402	-0.38	1.05x10^{-33}	-0.26	3.55x10^{-07}
C-C motif chemokine 23	P55773	-0.38	1.05x10^{-33}	-0.35	9.05x10^{-12}
Macrophage metalloelastase	P39900	-0.38	1.22x10^{-33}	-0.27	2.53x10^{-07}
Endoplasmic reticulum resident protein 29	P30040	-0.38	1.61x10^{-33}	-0.52	4.72x10^{-26}
SLIT and NTRK-like protein 5	O94991	-0.38	4.63x10^{-33}	-0.35	1.00x10^{-11}
Transforming growth factor beta receptor type 3	Q03167	-0.38	7.66x10^{-33}	-0.6	5.17x10^{-37}
Insulin-like growth factor-binding protein 2	P18065	-0.37	2.00x10^{-32}	-0.48	1.42x10^{-22}
Vascular endothelial growth factor receptor 2	P35968	0.37	1.48x10^{-31}	0.16	1.92x10^{-0}3

Protein	UniProt ID	Heart and Soul rho	Heart and Soul p-value	Lund rho	Lund p-value
Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A	Q9HCR9	0.37	2.03x10^{-31}	0.21	5.51x10^{-05}
Matrilysin	P09237	-0.37	4.55x10^{-31}	-0.56	2.10x10^{-31}
Dual specificity mitogen-activated protein kinase kinase 2	P36507	-0.36	1.00x10^{-30}	-0.37	3.46x10^{-13}
Retinoic acid receptor responder protein 2	Q99969	-0.36	1.12x10^{-30}	-0.38	3.83x10^{-14}
Cell adhesion molecule 3	Q8N126	-0.36	1.70x10^{-30}	-0.27	2.78x10^{-07}
A disintegrin and metalloproteinase with thrombospondin motifs 13	Q76LX8	0.36	5.02x10^{-30}	0.2	9.67x10^{-05}
Pappalysin-1	Q13219	-0.36	8.10x10^{-30}	-0.37	2.29x10^{-13}
Resistin	Q9HD89	-0.36	9.52x10^{-30}	-0.32	2.59x10^{-10}
Tissue Factor	P13726	-0.36	1.18x10^{-29}	-0.48	1.81x10^{-22}
Cystatin-D	P28325	-0.36	1.91x10^{-29}	-0.48	5.92x10^{-22}
Cell adhesion molecule-related/down-regulated by oncogenes	Q4KMG0	0.35	5.31x10^{-29}	0.18	4.18x10^{-04}
Interleukin-17 receptor C	Q8NAC3	-0.35	1.30x10^{-28}	-0.38	6.16x10^{-14}
Cystatin-SN	P01037	-0.35	4.37x10^{-28}	-0.49	1.48x10^{-23}
Carbonic anhydrase 3	P07451	-0.35	6.17x10^{-28}	-0.48	9.33x10^{-23}
Kallikrein-8	O60259	-0.35	8.80x10^{-28}	-0.46	1.92x10^{-20}
Fibroblast growth factor 20	Q9NP95	0.35	1.17x10^{-27}	0.16	1.87x10^{-03}
Melanoma-derived growth regulatory protein	Q16674	-0.34	2.30x10^{-26}	-0.32	6.53x10^{-10}
Ciliary neurotrophic factor receptor subunit alpha	P26992	-0.33	5.32x10^{-26}	-0.64	5.07x10^{-44}
Urokinase plasminogen activator surface receptor	Q03405	-0.33	1.17x10^{-25}	-0.33	1.46x10^{-10}
Tumor necrosis factor receptor superfamily member EDAR	Q9UNE0	-0.33	3.60x10^{-25}	0.02	7.15x10^{-01}
Interleukin-19	Q9UHD0	0.33	5.40x10^{-25}	-0.11	4.34x10^{-02}
Interleukin-16	Q14005	-0.33	1.23x10^{-24}	-0.03	6.22x10^{-01}
Tumor necrosis factor receptor superfamily member 9	Q07011	-0.33	1.29x10^{-24}	-0.21	7.15x10^{-05}
Angiostatin	P00747	0.32	5.15x10^{-24}	0.01	9.12x10^{-01}
Vascular endothelial growth factor A	P15692	-0.32	1.72x10^{-23}	-0.35	9.34x10^{-12}
Matrilin-2	O00339	-0.32	2.73x10^{-23}	-0.59	1.81x10^{-35}
NudC domain-containing protein 3	Q8IVD9	-0.31	7.58x10^{-23}	-0.09	8.73x10^{-02}
Pancreatic hormone	P01298	-0.31	1.44x10^{-22}	-0.31	2.71x10^{-09}
6-phosphogluconate dehydrogenase, decarboxylating	P52209	0.31	1.86x10^{-22}	0.21	4.50x10^{-05}
SHC-transforming protein 1	P29353	-0.31	2.68x10^{-22}	0.01	8.98x10^{-01}
Proto-oncogene tyrosine-protein kinase receptor Ret	P07949	0.31	2.80x10^{-22}	0.18	6.59x10^{-04}
OX-2 membrane glycoprotein	P41217	-0.31	3.21x10^{-22}	-0.04	4.68x10^{-01}

Protein	UniProt ID	Heart and Soul rho	Heart and Soul p-value	Lund rho	Lund p-value
Ephrin type-A receptor 1	P21709	-0.31	8.34×10^{-22}	-0.51	4.20×10^{-25}
Agouti-related protein	O00253	-0.31	1.16×10^{-21}	-0.28	4.68×10^{-08}

Table S5. Eighty-four proteins associated with cardiovascular risk in the Heart and Soul cohort, in participants with eGFR ≥ 60 ml/min/1.73m^2 (non-CKD patients).

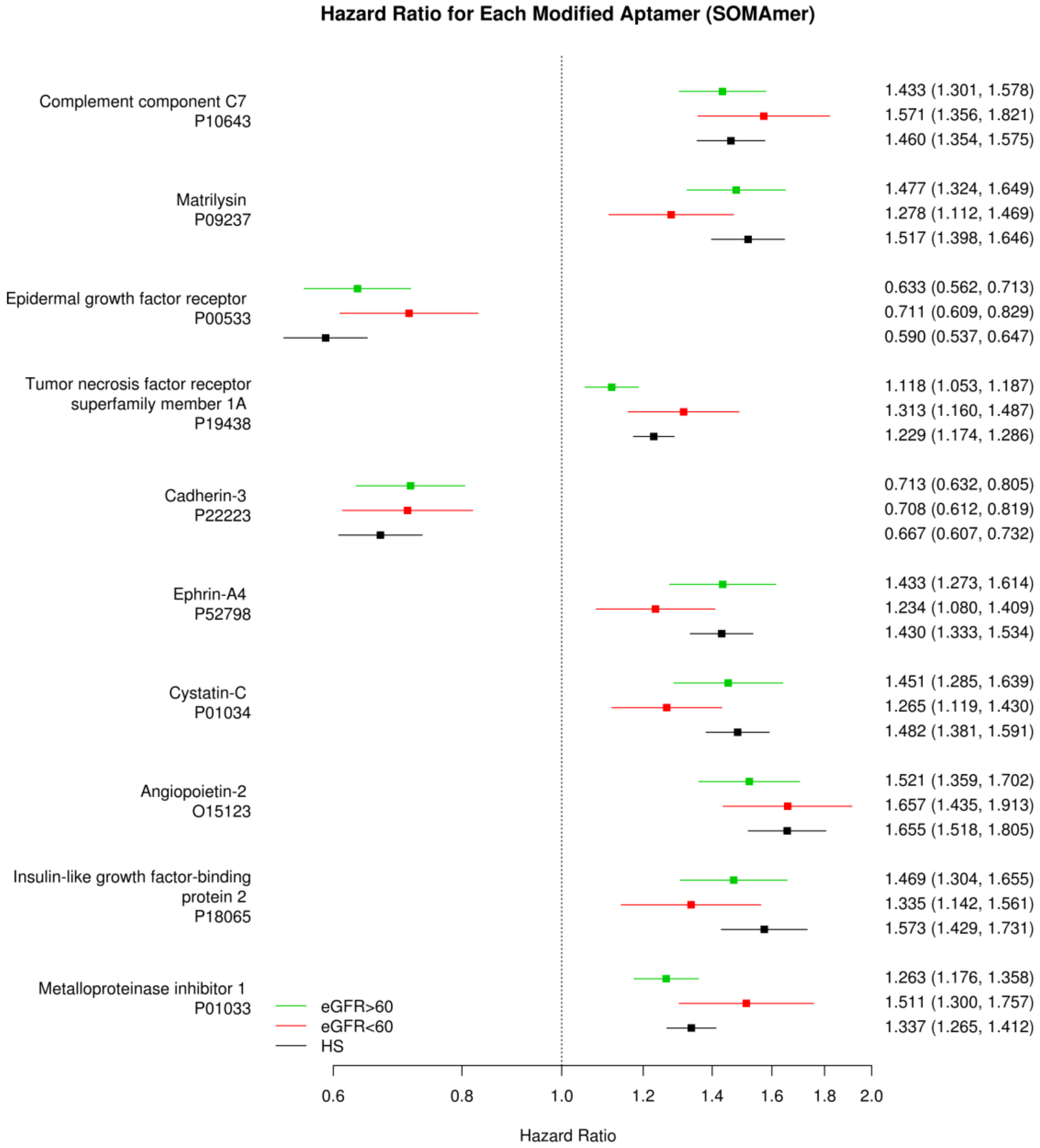
Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value
Thrombospondin-2	P35442	1.62	$<2.2\text{x}10^{-16}$	$<2.2\text{x}10^{-16}$
Macrophage metalloelastase	P39900	1.58	$4.22\text{x}10^{-15}$	$4.45\text{x}10^{-12}$
Epidermal growth factor receptor	P00533	0.63	$4.87\text{x}10^{-14}$	$5.14\text{x}10^{-11}$
Beta-Ala-His dipeptidase	Q96KN2	0.7	$2.26\text{x}10^{-13}$	$2.38\text{x}10^{-10}$
Angiopoietin-2	O15123	1.52	$3.00\text{x}10^{-13}$	$3.16\text{x}10^{-10}$
Complement component C7	P10643	1.43	$3.19\text{x}10^{-13}$	$3.36\text{x}10^{-10}$
Spondin-1	Q9HCB6	1.46	$8.46\text{x}10^{-13}$	$8.91\text{x}10^{-10}$
Matrilysin	P09237	1.48	$3.30\text{x}10^{-12}$	$3.47\text{x}10^{-09}$
Growth hormone receptor	P10912	0.66	$4.56\text{x}10^{-12}$	$4.81\text{x}10^{-09}$
Beta-2-microglobulin	P61769	1.46	$4.67\text{x}10^{-12}$	$4.92\text{x}10^{-09}$
Cathepsin H	P09668	1.48	$7.45\text{x}10^{-12}$	$7.85\text{x}10^{-09}$
Alpha-2-antiplasmin	P08697	0.68	$2.46\text{x}10^{-11}$	$2.59\text{x}10^{-08}$
Tumor necrosis factor receptor superfamily member 1B	P20333	1.46	$6.12\text{x}10^{-11}$	$6.45\text{x}10^{-08}$
Hepatitis A virus cellular receptor 2	Q8TDQ0	1.46	$7.50\text{x}10^{-11}$	$7.90\text{x}10^{-08}$
Follistatin-related protein 3	O95633	1.48	$7.65\text{x}10^{-11}$	$8.06\text{x}10^{-08}$
Brain-specific serine protease 4	Q9GZN4	1.4	$1.72\text{x}10^{-10}$	$1.81\text{x}10^{-07}$
Delta-like protein 1	O00548	1.36	$1.90\text{x}10^{-10}$	$2.01\text{x}10^{-07}$
Metalloproteinase inhibitor 1	P01033	1.26	$1.92\text{x}10^{-10}$	$2.02\text{x}10^{-07}$
Insulin-like growth factor-binding protein 2	P18065	1.47	$2.54\text{x}10^{-10}$	$2.68\text{x}10^{-07}$
Interleukin-18-binding protein	O95998	1.46	$2.96\text{x}10^{-10}$	$3.12\text{x}10^{-07}$
Ephrin type-B receptor 2	P29323	1.46	$4.51\text{x}10^{-10}$	$4.75\text{x}10^{-07}$
Vitamin K-dependent protein C	P04070	0.73	$5.39\text{x}10^{-10}$	$5.68\text{x}10^{-07}$

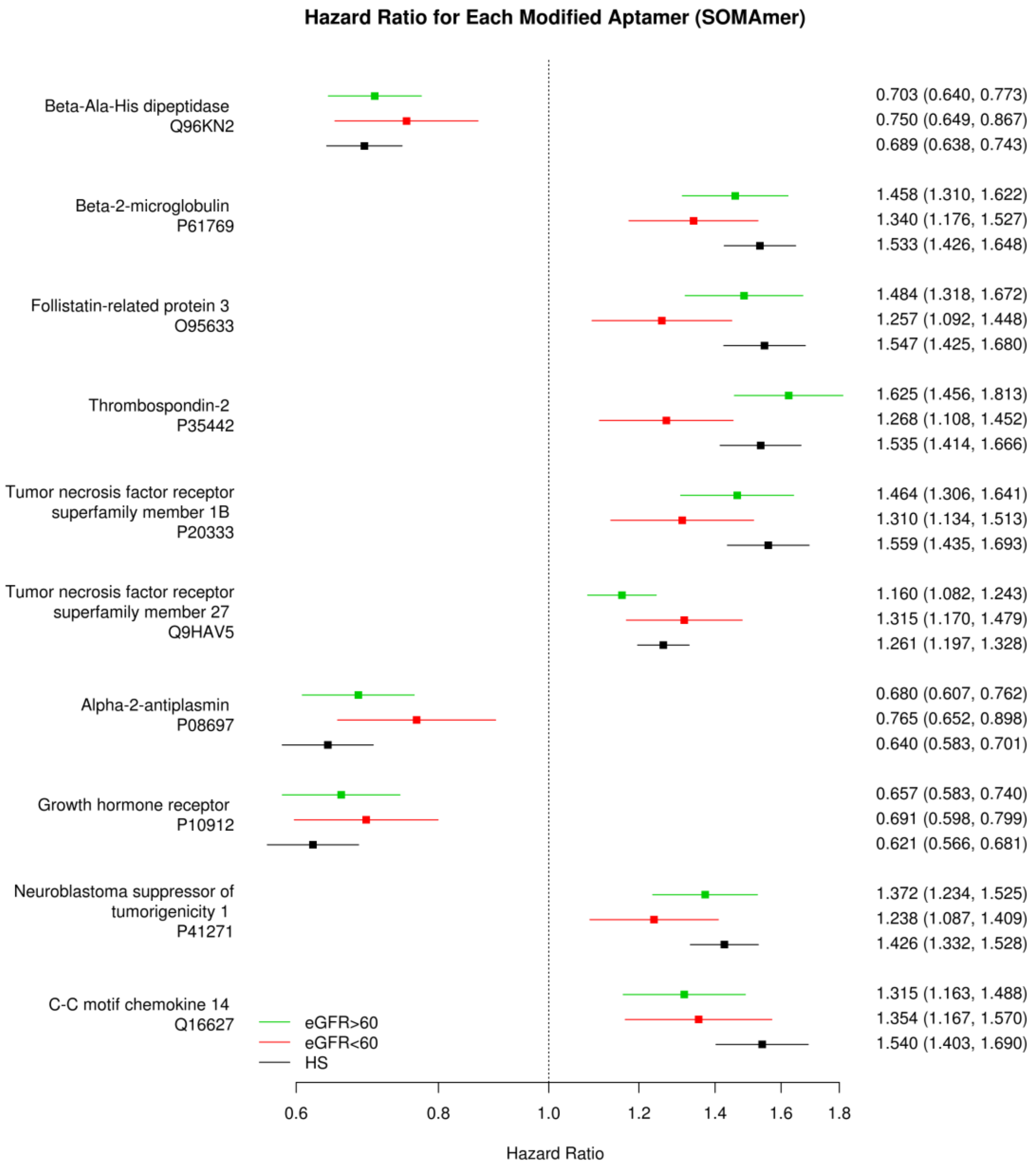
Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value
Protein jagged-1	P78504	1.43	1.71×10^{-09}	1.81×10^{-06}
Cystatin-C	P01034	1.45	2.02×10^{-09}	2.13×10^{-06}
Ephrin type-A receptor 2	P29317	1.37	2.23×10^{-09}	2.35×10^{-06}
Ephrin-A4	P52798	1.43	2.80×10^{-09}	2.95×10^{-06}
Neuroblastoma suppressor of tumorigenicity 1	P41271	1.37	4.73×10^{-09}	4.99×10^{-06}
Interleukin-1 receptor-like 1	Q01638	1.36	2.08×10^{-08}	2.20×10^{-05}
Midkine	P21741	1.26	3.21×10^{-08}	3.38×10^{-05}
Cadherin-3	P22223	0.71	4.87×10^{-08}	5.13×10^{-05}
Angiopoietin-related protein 4	Q9BY76	1.28	5.57×10^{-08}	5.87×10^{-05}
Scavenger receptor class F member 1	Q14162	1.28	6.09×10^{-08}	6.42×10^{-05}
Insulin-like growth factor-binding protein 7	Q16270	1.36	6.76×10^{-08}	7.13×10^{-05}
Creatine kinase M-type:Creatine kinase B-type heterodimer	P12277 P06732	0.7	8.24×10^{-08}	8.68×10^{-05}
Immunoglobulin G	P01857	1.38	9.07×10^{-08}	9.56×10^{-05}
Creatine kinase M-type	P06732	0.69	9.89×10^{-08}	1.04×10^{-04}
C-X-C motif chemokine 13	O43927	1.27	1.55×10^{-07}	1.64×10^{-04}
Complement component C9	P02748	1.42	1.78×10^{-07}	1.88×10^{-04}
Stanniocalcin-1	P52823	1.34	1.87×10^{-07}	1.97×10^{-04}
SLAM family member 5	Q9UIB8	1.24	2.82×10^{-07}	2.97×10^{-04}
C-C motif chemokine 18	P55774	1.35	3.15×10^{-07}	3.32×10^{-04}
Tumor necrosis factor receptor superfamily member 19L	Q969Z4	1.32	3.81×10^{-07}	4.01×10^{-04}
Troponin I, cardiac muscle	P19429	1.24	5.15×10^{-07}	5.43×10^{-04}
Heat shock 70 kDa protein 1A/1B	P08107	1.32	8.43×10^{-07}	8.88×10^{-04}
Chordin-like protein 1	Q9BU40	1.34	9.40×10^{-07}	9.90×10^{-04}
Netrin receptor UNC5C	O95185	1.32	1.09×10^{-06}	1.15×10^{-03}

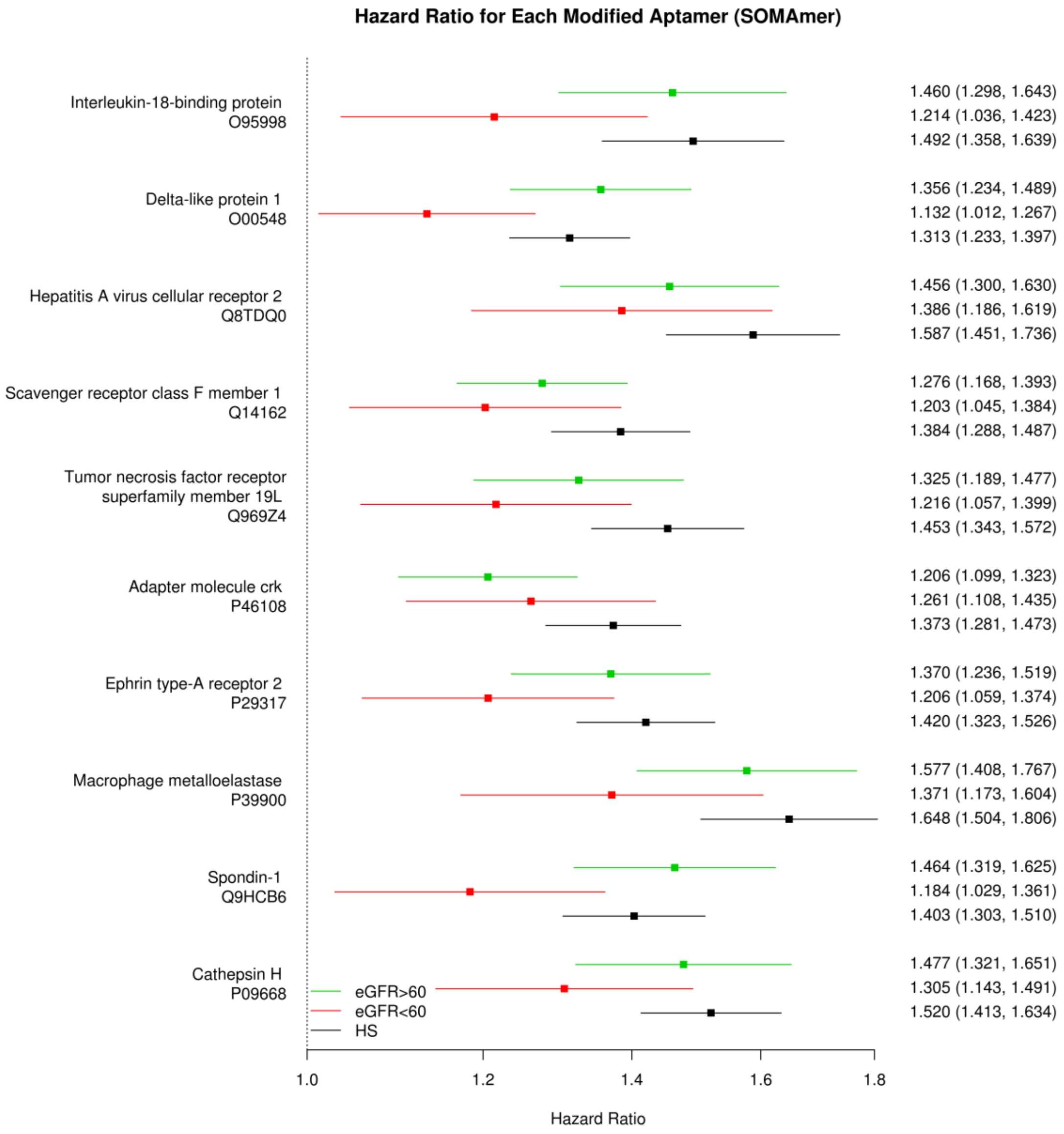
Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value
Low affinity immunoglobulin gamma Fc region receptor III-B	O75015	1.32	$1.12x10^{-06}$	$1.18x10^{-03}$
Tenascin	P24821	1.34	$1.14x10^{-06}$	$1.20x10^{-03}$
Vascular endothelial growth factor A	P15692	1.34	$1.28x10^{-06}$	$1.35x10^{-03}$
Growth/differentiation factor 11	O95390	0.69	$1.76x10^{-06}$	$1.85x10^{-03}$
Alpha-1-antichymotrypsin complex	P07288, P01011	1.3	$2.42x10^{-06}$	$2.55x10^{-03}$
Tissue Factor	P13726	1.19	$2.56x10^{-06}$	$2.70x10^{-03}$
Periostin	Q15063	1.33	$3.73x10^{-06}$	$3.93x10^{-03}$
Coagulation factor Xa	P00742	0.79	$3.88x10^{-06}$	$4.09x10^{-03}$
N-acetyl-D-glucosamine kinase	Q9UJ70	1.31	$4.24x10^{-06}$	$4.47x10^{-03}$
Macrophage-capping protein	P40121	1.23	$4.49x10^{-06}$	$4.73x10^{-03}$
Bone morphogenetic protein 1	P13497	0.77	$4.49x10^{-06}$	$4.73x10^{-03}$
Kallistatin	P29622	0.77	$5.95x10^{-06}$	$6.27x10^{-03}$
Lymphocyte activation gene 3 protein	P18627	1.31	$6.80x10^{-06}$	$7.16x10^{-03}$
Urokinase plasminogen activator surface receptor	Q03405	1.22	$6.86x10^{-06}$	$7.23x10^{-03}$
Programmed cell death 1 ligand 1	Q9NZQ7	1.25	$7.83x10^{-06}$	$8.25x10^{-03}$
Neuroligin-4, X-linked	Q8N0W4	1.23	$8.18x10^{-06}$	$8.62x10^{-03}$
C-C motif chemokine 4-like	Q8NHW4	1.27	$8.55x10^{-06}$	$9.01x10^{-03}$
Prothrombin	P00734	0.8	$1.02x10^{-05}$	$1.08x10^{-02}$
Cell adhesion molecule-related/down-regulated by oncogenes	Q4KMG0	0.77	$1.08x10^{-05}$	$1.14x10^{-02}$
Kallikrein-7	P49862	0.75	$1.11x10^{-05}$	$1.17x10^{-02}$
Fibroblast growth factor 20	Q9NP95	0.73	$1.31x10^{-05}$	$1.38x10^{-02}$

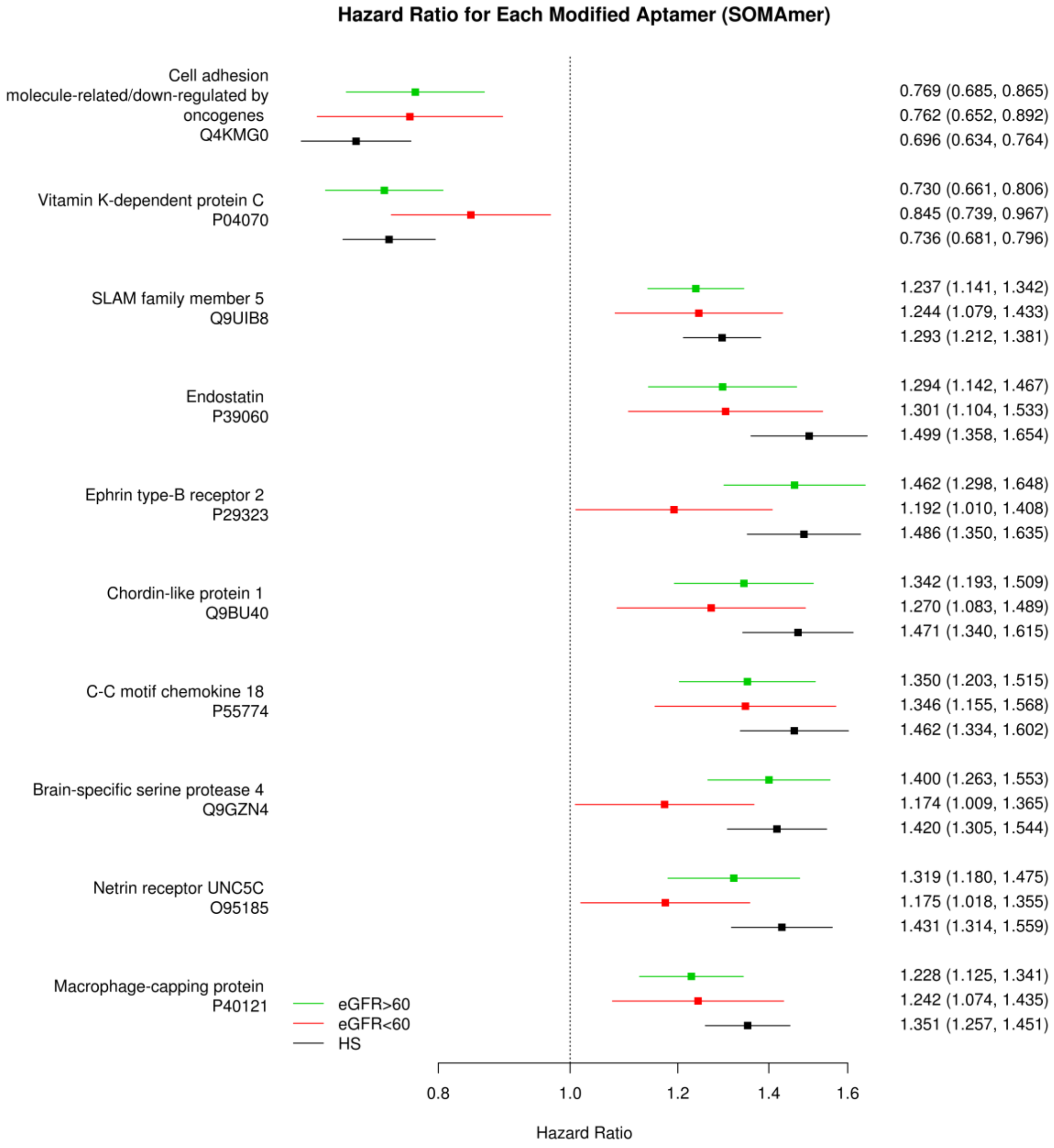
Protein	UniProt ID	HR	p-value	Bonferroni corrected p-value
C-C motif chemokine 14	Q16627	1.32	1.36×10^{-05}	1.44×10^{-02}
Leucine-rich repeat transmembrane protein FLRT1	Q9NZU1	0.67	1.59×10^{-05}	1.68×10^{-02}
Granzyme A	P12544	1.28	1.71×10^{-05}	1.80×10^{-02}
Proto-oncogene tyrosine-protein kinase receptor Ret	P07949	0.74	1.97×10^{-05}	2.07×10^{-02}
Neuropilin-1	O14786	1.21	2.02×10^{-05}	2.13×10^{-02}
P-Selectin	P16109	1.29	2.38×10^{-05}	2.51×10^{-02}
Plasma kallikrein	P03952	0.79	2.53×10^{-05}	2.67×10^{-02}
Angiostatin	P00747	0.77	2.80×10^{-05}	2.95×10^{-02}
Tumor necrosis factor receptor superfamily member 27	Q9HAV5	1.16	2.81×10^{-05}	2.96×10^{-02}
Insulin-like growth factor 1 receptor	P08069	1.3	2.84×10^{-05}	2.99×10^{-02}
Intercellular adhesion molecule 5	Q9UMF0	1.23	2.96×10^{-05}	3.11×10^{-02}
Brain natriuretic peptide 32	P16860	1.18	3.03×10^{-05}	3.20×10^{-02}
Lipopolysaccharide-binding protein	P18428	1.3	3.40×10^{-05}	3.59×10^{-02}
Alpha-(1,3)-fucosyltransferase 5	Q11128	1.3	3.69×10^{-05}	3.89×10^{-02}
Interleukin-8	P10145	1.18	3.74×10^{-05}	3.94×10^{-02}
Phospholipase A2, membrane associated	P14555	1.24	3.82×10^{-05}	4.02×10^{-02}
Renin	P00797	1.26	4.15×10^{-05}	4.37×10^{-02}

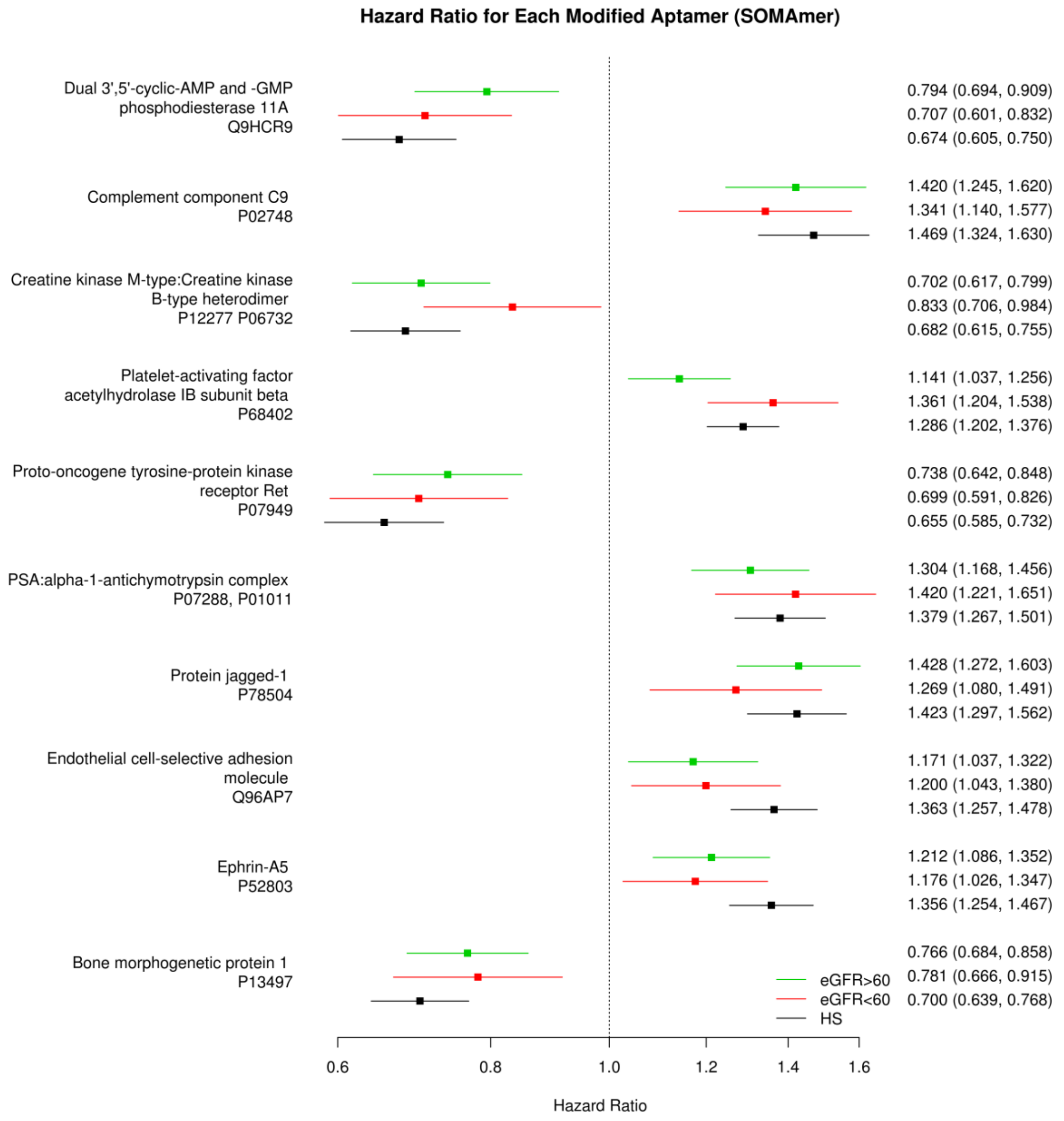
Figure S1. Hazard ratios and confidence intervals for proteins prognostic of cardiovascular risk in the settings of eGFR<60 ml/min/1.73m^2, eGFR≥60 ml/min/1.73m^2 and for all participants in Heart and Soul, regardless of eGFR (HS).

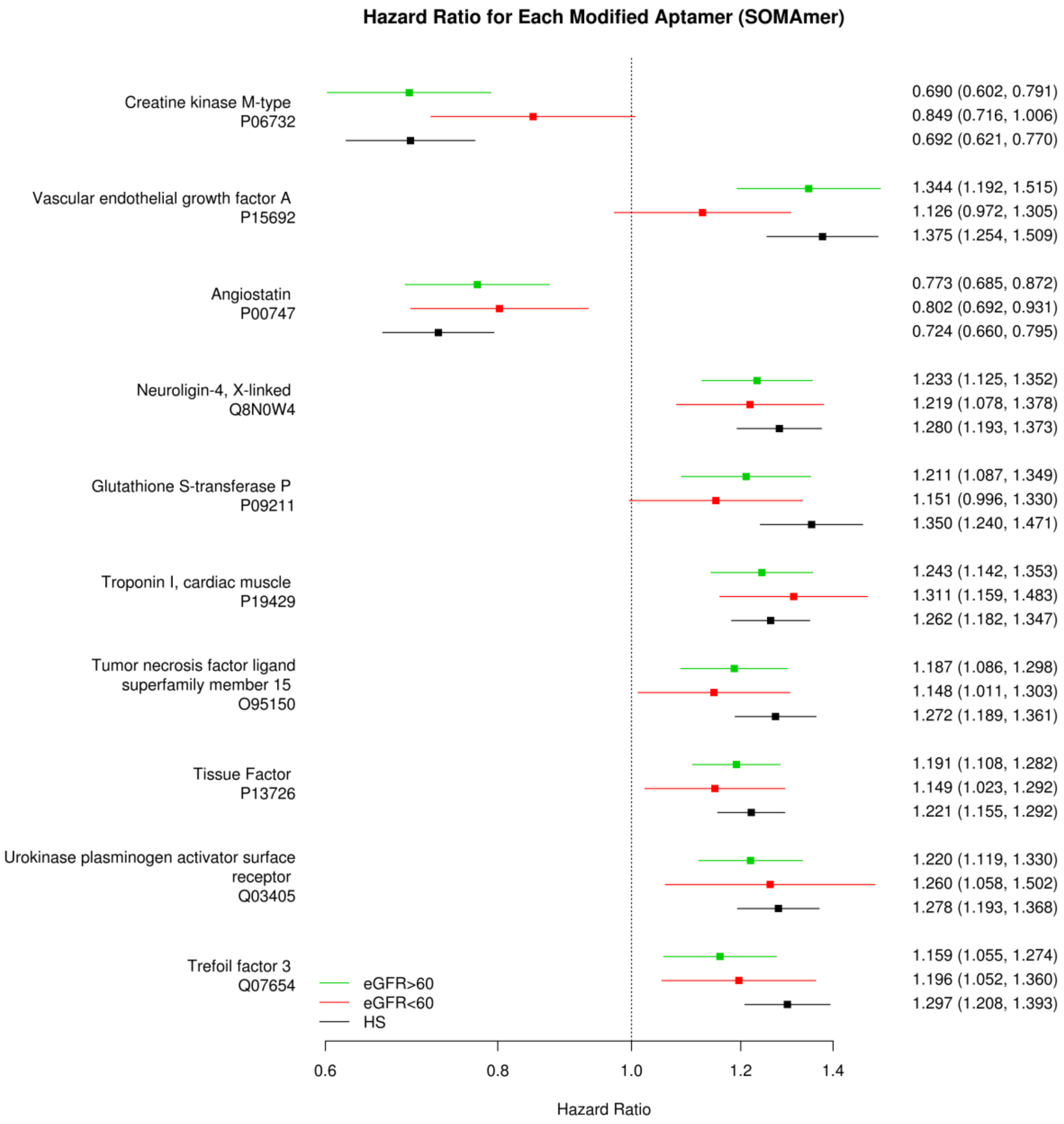



Hazard Ratio for Each Modified Aptamer (SOMAmer)
Beta-Ala-His dipeptidase
Q96KN2
0.703 (0.640, 0.773)
0.750 (0.649, 0.867)
0.689 (0.638, 0.743)
Beta-2-microglobulin
P61769
1.458 (1.310, 1.622)
1.340 (1.176, 1.527)
1.533 (1.426, 1.648)
Follistatin-related protein 3
O95633
1.484 (1.318, 1.672)
1.257 (1.092, 1.448)
1.547 (1.425, 1.680)
Thrombospondin-2
P35442
1.625 (1.456, 1.813)
1.268 (1.108, 1.452)
1.535 (1.414, 1.666)
Tumor necrosis factor receptor superfamily member 1B
P20333
1.464 (1.306, 1.641)
1.310 (1.134, 1.513)
1.559 (1.435, 1.693)
Tumor necrosis factor receptor superfamily member 27
Q9HAV5
1.160 (1.082, 1.243)
1.315 (1.170, 1.479)
1.261 (1.197, 1.328)
Alpha-2-antiplasmin
P08697
0.680 (0.607, 0.762)
0.765 (0.652, 0.898)
0.640 (0.583, 0.701)
Growth hormone receptor
P10912
0.657 (0.583, 0.740)
0.691 (0.598, 0.799)
0.621 (0.566, 0.681)
Neuroblastoma suppressor of tumorigenicity 1
P41271
1.372 (1.234, 1.525)
1.238 (1.087, 1.409)
1.426 (1.332, 1.528)
C-C motif chemokine 14
Q16627
1.315 (1.163, 1.488)
1.354 (1.167, 1.570)
1.540 (1.403, 1.690)
eGFR>60
eGFR<60
HS
0.6
0.8
1.0
1.2
1.4
1.6
1.8
Hazard Ratio

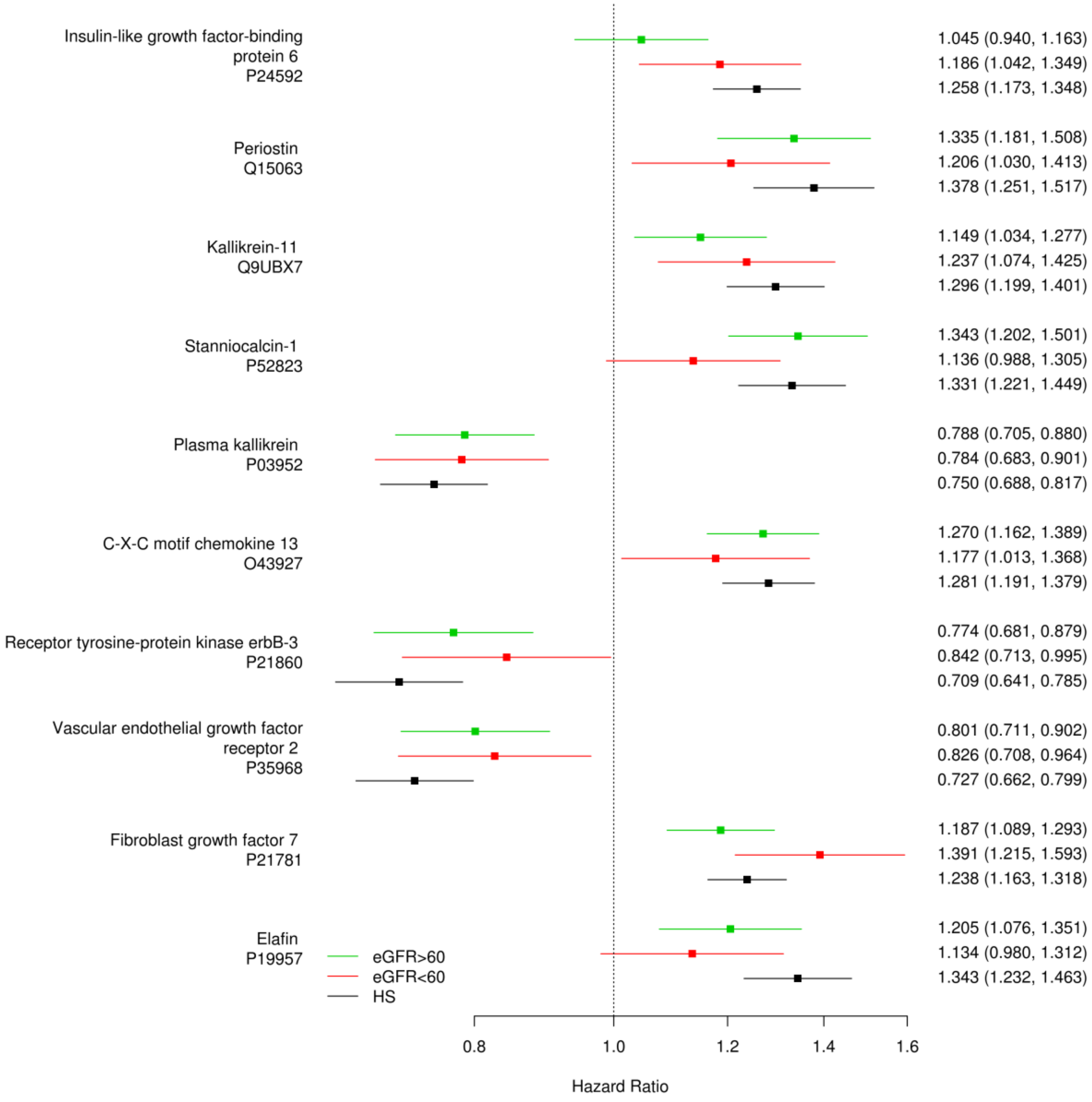

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Interleukin-18-binding protein
O95998
Delta-like protein 1
O00548
Hepatitis A virus cellular receptor 2
Q8TDQ0
Scavenger receptor class F member 1
Q14162
Tumor necrosis factor receptor
superfamily member 19L
Q969Z4
Adapter molecule crk
P46108
Ephrin type-A receptor 2
P29317
Macrophage metalloelastase
P39900
Spondin-1
Q9HCB6
Cathepsin H
P09668
eGFR>60
eGFR<60
HS
1.460 (1.298, 1.643)
1.214 (1.036, 1.423)
1.492 (1.358, 1.639)
1.356 (1.234, 1.489)
1.132 (1.012, 1.267)
1.313 (1.233, 1.397)
1.456 (1.300, 1.630)
1.386 (1.186, 1.619)
1.587 (1.451, 1.736)
1.276 (1.168, 1.393)
1.203 (1.045, 1.384)
1.384 (1.288, 1.487)
1.325 (1.189, 1.477)
1.216 (1.057, 1.399)
1.453 (1.343, 1.572)
1.206 (1.099, 1.323)
1.261 (1.108, 1.435)
1.373 (1.281, 1.473)
1.370 (1.236, 1.519)
1.206 (1.059, 1.374)
1.420 (1.323, 1.526)
1.577 (1.408, 1.767)
1.371 (1.173, 1.604)
1.648 (1.504, 1.806)
1.464 (1.319, 1.625)
1.184 (1.029, 1.361)
1.403 (1.303, 1.510)
1.477 (1.321, 1.651)
1.305 (1.143, 1.491)
1.520 (1.413, 1.634)
1.0
1.2
1.4
1.6
1.8
Hazard Ratio

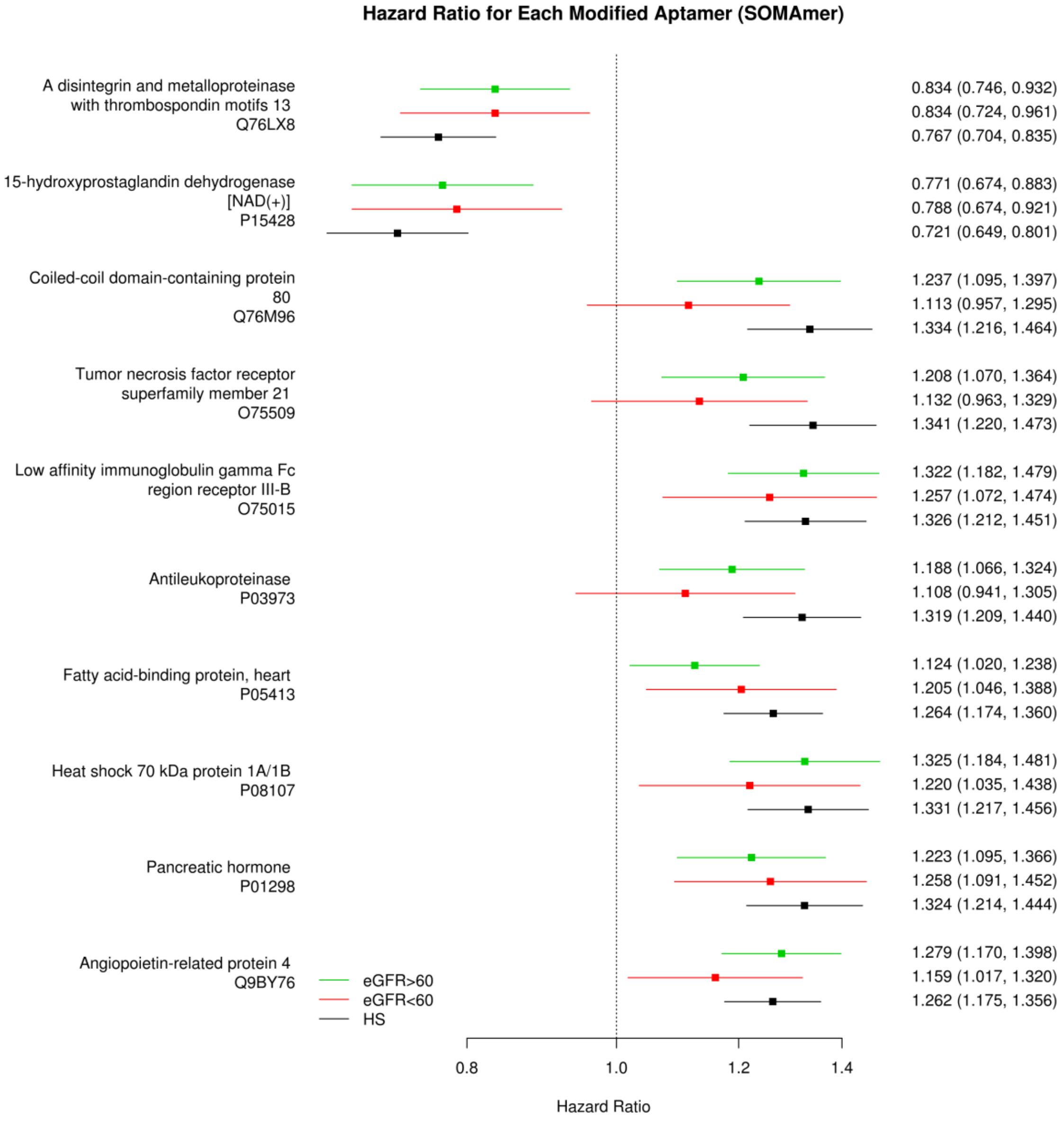

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Cell adhesion molecule-related/down-regulated by oncogenes
Q4KMG0
0.769 (0.685, 0.865)
0.762 (0.652, 0.892)
0.696 (0.634, 0.764)
Vitamin K-dependent protein C
P04070
0.730 (0.661, 0.806)
0.845 (0.739, 0.967)
0.736 (0.681, 0.796)
SLAM family member 5
Q9UIB8
1.237 (1.141, 1.342)
1.244 (1.079, 1.433)
1.293 (1.212, 1.381)
Endostatin
P39060
1.294 (1.142, 1.467)
1.301 (1.104, 1.533)
1.499 (1.358, 1.654)
Ephrin type-B receptor 2
P29323
1.462 (1.298, 1.648)
1.192 (1.010, 1.408)
1.486 (1.350, 1.635)
Chordin-like protein 1
Q9BU40
1.342 (1.193, 1.509)
1.270 (1.083, 1.489)
1.471 (1.340, 1.615)
C-C motif chemokine 18
P55774
1.350 (1.203, 1.515)
1.346 (1.155, 1.568)
1.462 (1.334, 1.602)
Brain-specific serine protease 4
Q9GZN4
1.400 (1.263, 1.553)
1.174 (1.009, 1.365)
1.420 (1.305, 1.544)
Netrin receptor UNC5C
O95185
1.319 (1.180, 1.475)
1.175 (1.018, 1.355)
1.431 (1.314, 1.559)
Macrophage-capping protein
P40121
1.228 (1.125, 1.341)
1.242 (1.074, 1.435)
1.351 (1.257, 1.451)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
1.6
Hazard Ratio

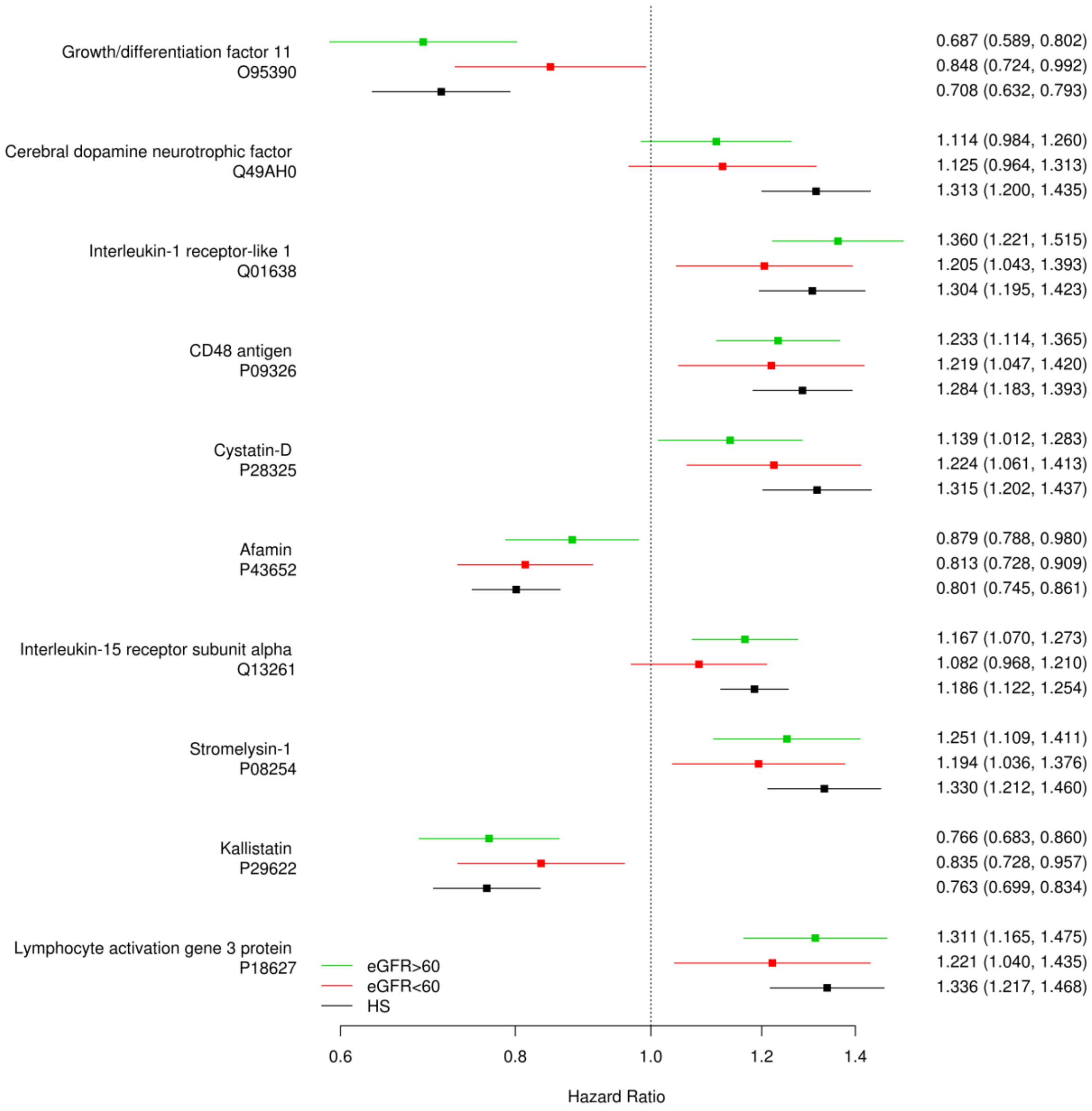

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A Q9HCR9
0.794 (0.694, 0.909)
0.707 (0.601, 0.832)
0.674 (0.605, 0.750)
Complement component C9 P02748
1.420 (1.245, 1.620)
1.341 (1.140, 1.577)
1.469 (1.324, 1.630)
Creatine kinase M-type:Creatine kinase B-type heterodimer P12277 P06732
0.702 (0.617, 0.799)
0.833 (0.706, 0.984)
0.682 (0.615, 0.755)
Platelet-activating factor acetylhydrolase IB subunit beta P68402
1.141 (1.037, 1.256)
1.361 (1.204, 1.538)
1.286 (1.202, 1.376)
Proto-oncogene tyrosine-protein kinase receptor Ret P07949
0.738 (0.642, 0.848)
0.699 (0.591, 0.826)
0.655 (0.585, 0.732)
PSA:alpha-1-antichymotrypsin complex P07288, P01011
1.304 (1.168, 1.456)
1.420 (1.221, 1.651)
1.379 (1.267, 1.501)
Protein jagged-1 P78504
1.428 (1.272, 1.603)
1.269 (1.080, 1.491)
1.423 (1.297, 1.562)
Endothelial cell-selective adhesion molecule Q96AP7
1.171 (1.037, 1.322)
1.200 (1.043, 1.380)
1.363 (1.257, 1.478)
Ephrin-A5 P52803
1.212 (1.086, 1.352)
1.176 (1.026, 1.347)
1.356 (1.254, 1.467)
Bone morphogenetic protein 1 P13497
0.766 (0.684, 0.858)
0.781 (0.666, 0.915)
0.700 (0.639, 0.768)
eGFR>60
eGFR<60
HS
0.6
0.8
1.0
1.2
1.4
1.6
Hazard Ratio


Hazard Ratio for Each Modified Aptamer (SOMAmer)
Creatine kinase M-type
P06732
0.690 (0.602, 0.791)
0.849 (0.716, 1.006)
0.692 (0.621, 0.770)
Vascular endothelial growth factor A
P15692
1.344 (1.192, 1.515)
1.126 (0.972, 1.305)
1.375 (1.254, 1.509)
Angiostatin
P00747
0.773 (0.685, 0.872)
0.802 (0.692, 0.931)
0.724 (0.660, 0.795)
Neuroligin-4, X-linked
Q8N0W4
1.233 (1.125, 1.352)
1.219 (1.078, 1.378)
1.280 (1.193, 1.373)
Glutathione S-transferase P
P09211
1.211 (1.087, 1.349)
1.151 (0.996, 1.330)
1.350 (1.240, 1.471)
Troponin I, cardiac muscle
P19429
1.243 (1.142, 1.353)
1.311 (1.159, 1.483)
1.262 (1.182, 1.347)
Tumor necrosis factor ligand superfamily member 15
O95150
1.187 (1.086, 1.298)
1.148 (1.011, 1.303)
1.272 (1.189, 1.361)
Tissue Factor
P13726
1.191 (1.108, 1.282)
1.149 (1.023, 1.292)
1.221 (1.155, 1.292)
Urokinase plasminogen activator surface receptor
Q03405
1.220 (1.119, 1.330)
1.260 (1.058, 1.502)
1.278 (1.193, 1.368)
Trefoil factor 3
Q07654
1.159 (1.055, 1.274)
1.196 (1.052, 1.360)
1.297 (1.208, 1.393)
eGFR>60
eGFR<60
HS
0.6
0.8
1.0
1.2
1.4
Hazard Ratio

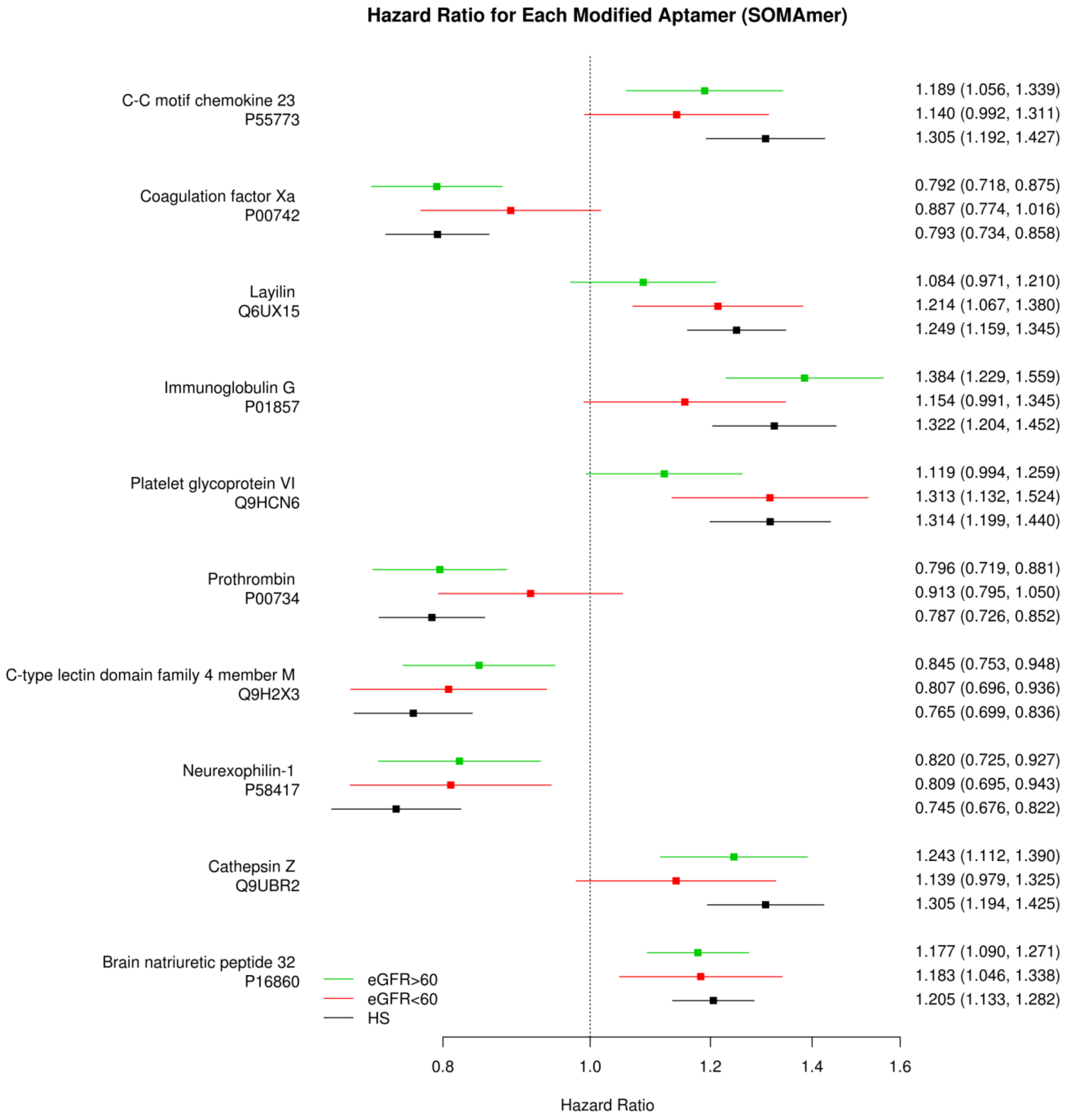
Hazard Ratio for Each Modified Aptamer (SOMAmer)

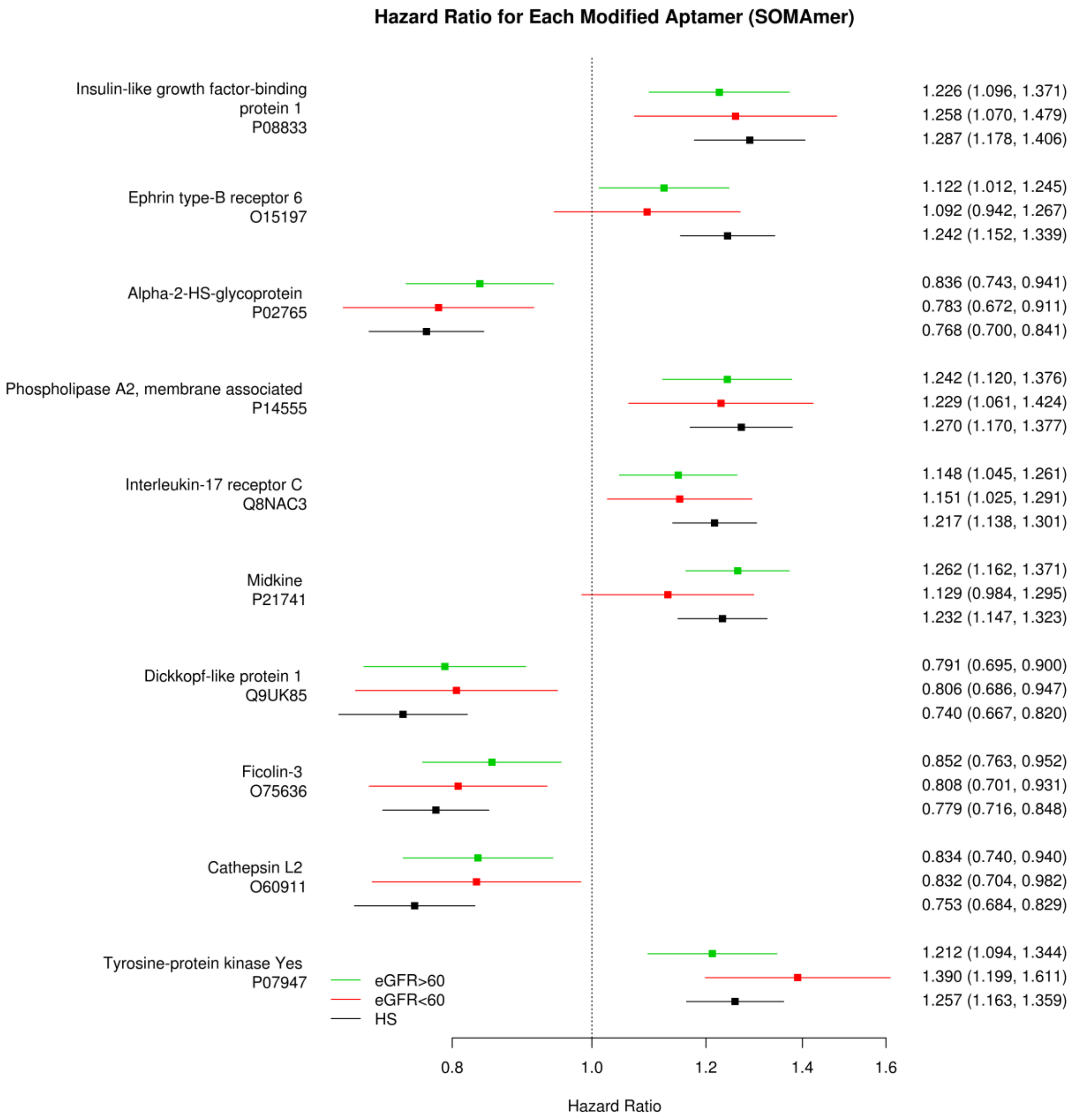


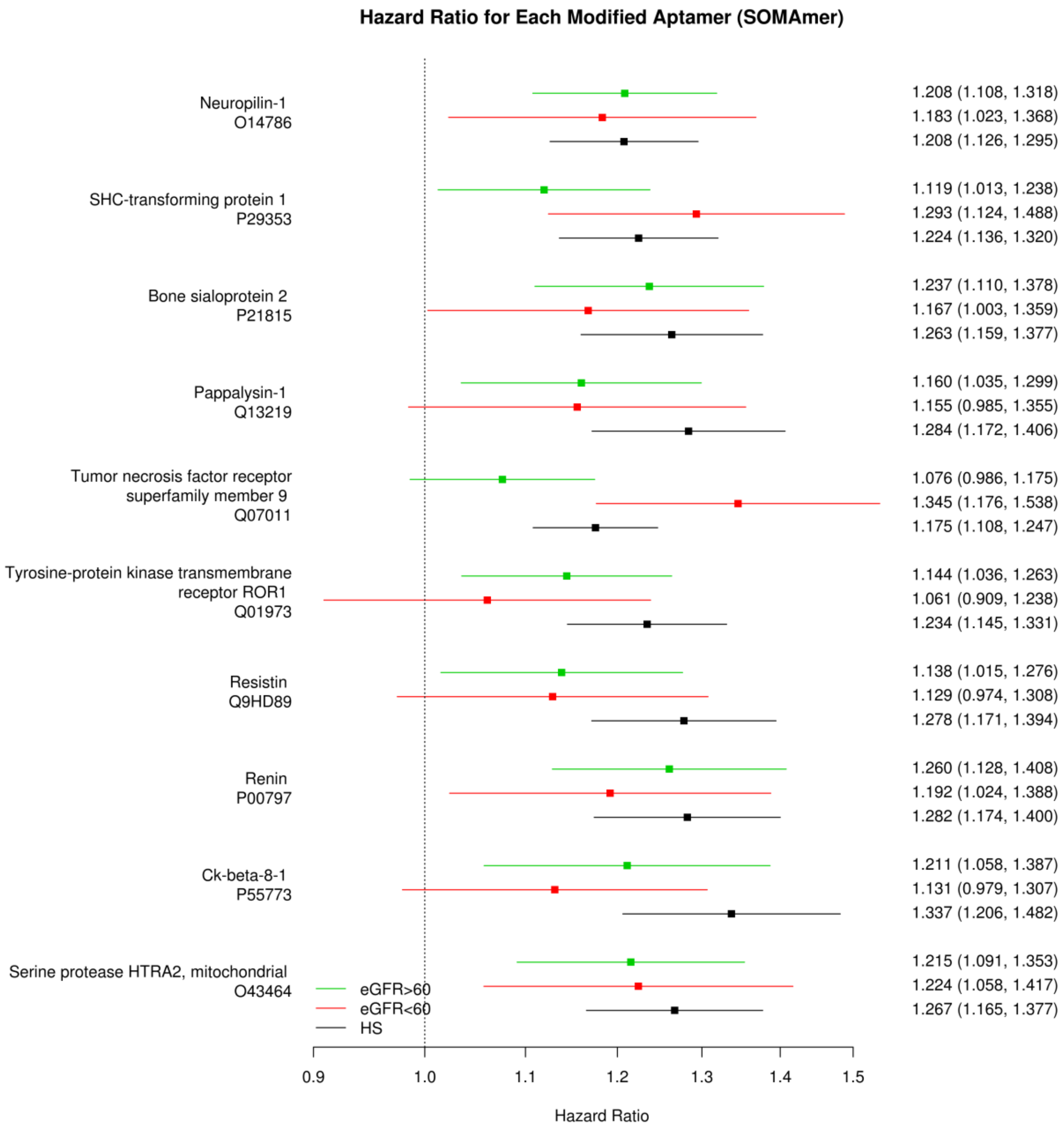

Hazard Ratio for Each Modified Aptamer (SOMAmer)
A disintegrin and metalloproteinase with thrombospondin motifs 13
Q76LX8
0.834 (0.746, 0.932)
0.834 (0.724, 0.961)
0.767 (0.704, 0.835)
15-hydroxyprostaglandin dehydrogenase [NAD(+)]
P15428
0.771 (0.674, 0.883)
0.788 (0.674, 0.921)
0.721 (0.649, 0.801)
Coiled-coil domain-containing protein 80
Q76M96
1.237 (1.095, 1.397)
1.113 (0.957, 1.295)
1.334 (1.216, 1.464)
Tumor necrosis factor receptor superfamily member 21
O75509
1.208 (1.070, 1.364)
1.132 (0.963, 1.329)
1.341 (1.220, 1.473)
Low affinity immunoglobulin gamma Fc region receptor III-B
O75015
1.322 (1.182, 1.479)
1.257 (1.072, 1.474)
1.326 (1.212, 1.451)
Antileukoproteinase
P03973
1.188 (1.066, 1.324)
1.108 (0.941, 1.305)
1.319 (1.209, 1.440)
Fatty acid-binding protein, heart
P05413
1.124 (1.020, 1.238)
1.205 (1.046, 1.388)
1.264 (1.174, 1.360)
Heat shock 70 kDa protein 1A/1B
P08107
1.325 (1.184, 1.481)
1.220 (1.035, 1.438)
1.331 (1.217, 1.456)
Pancreatic hormone
P01298
1.223 (1.095, 1.366)
1.258 (1.091, 1.452)
1.324 (1.214, 1.444)
Angiopoietin-related protein 4
Q9BY76
1.279 (1.170, 1.398)
1.159 (1.017, 1.320)
1.262 (1.175, 1.356)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
Hazard Ratio

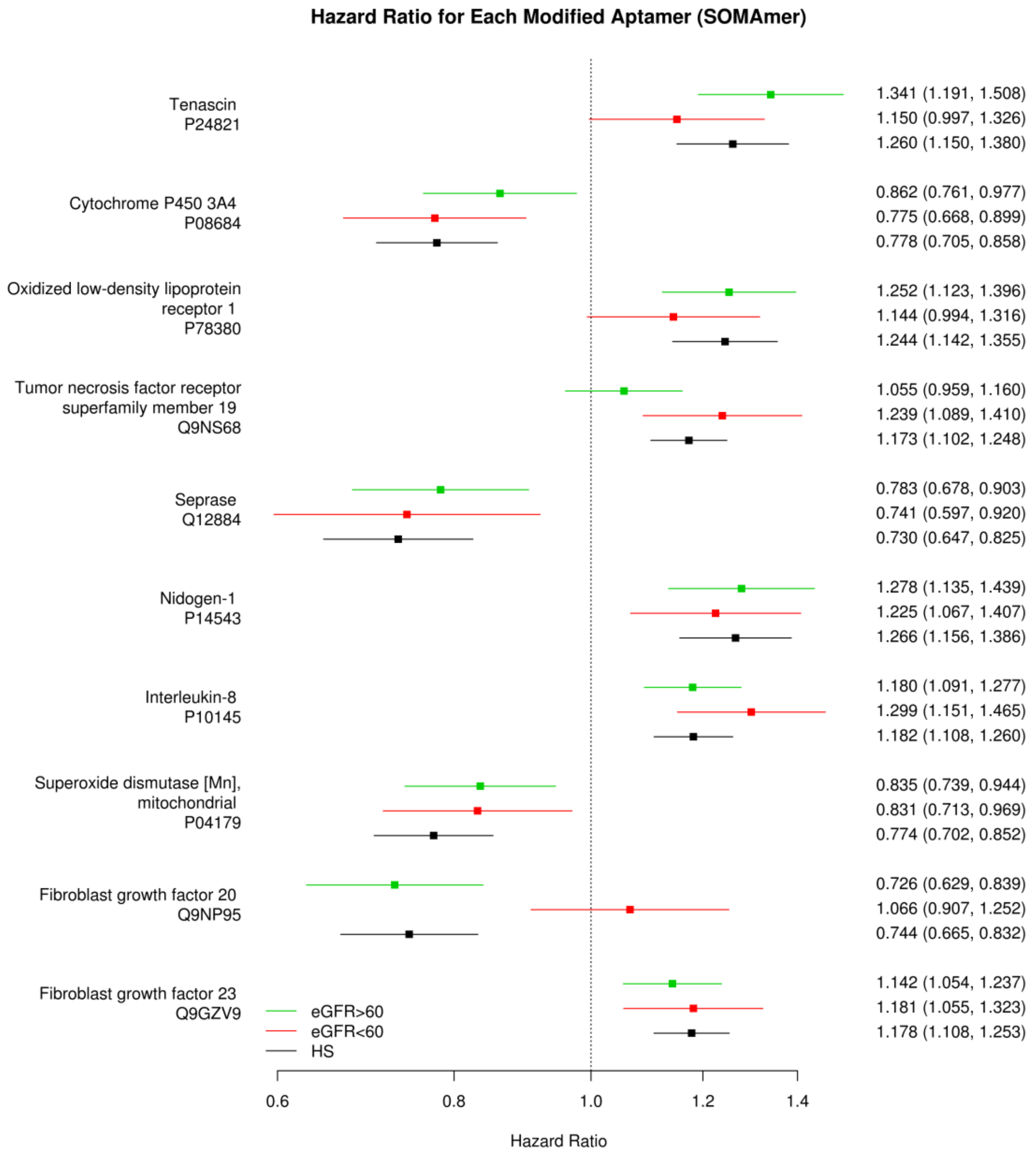


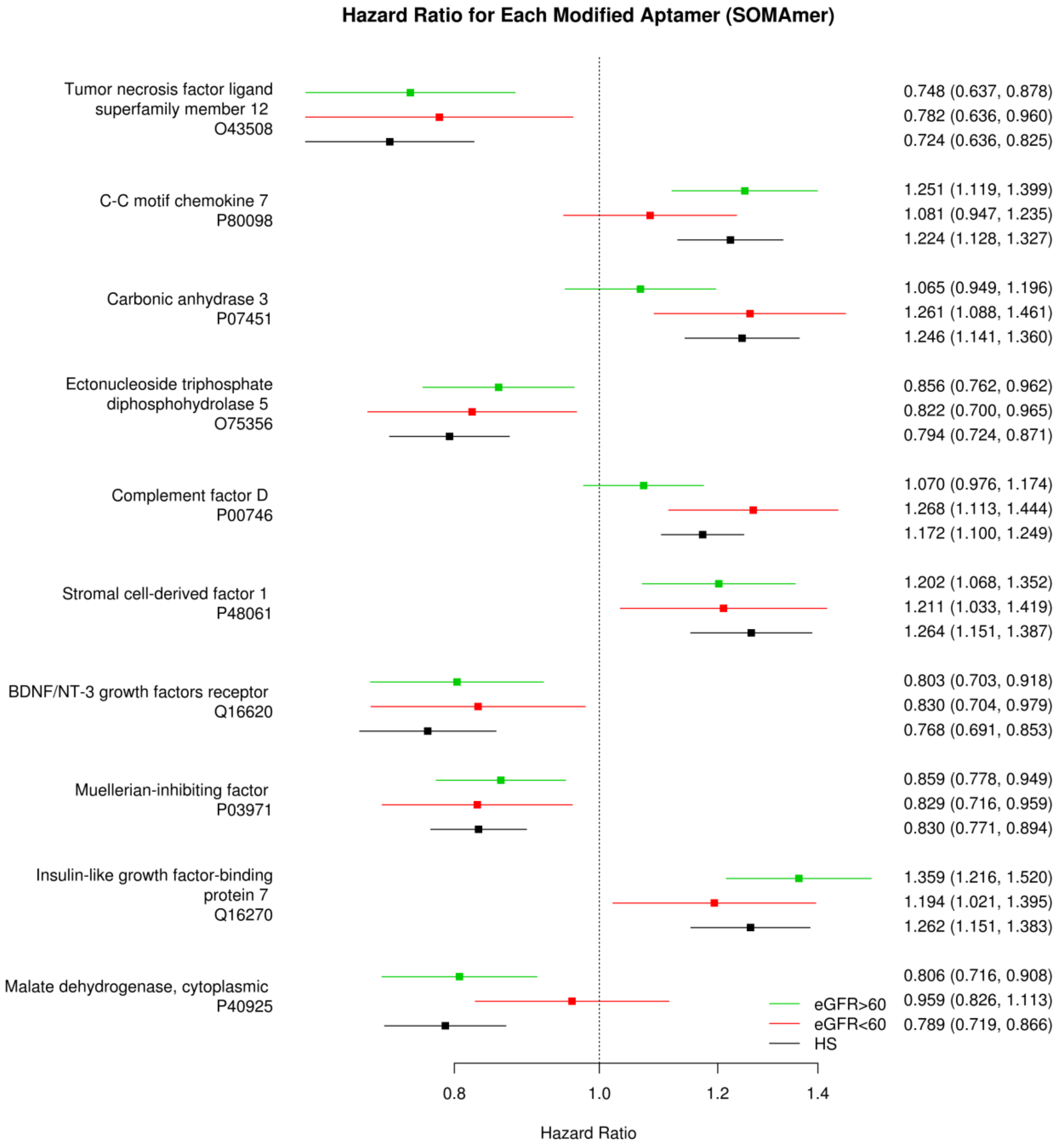
Hazard Ratio for Each Modified Aptamer (SOMAmer)

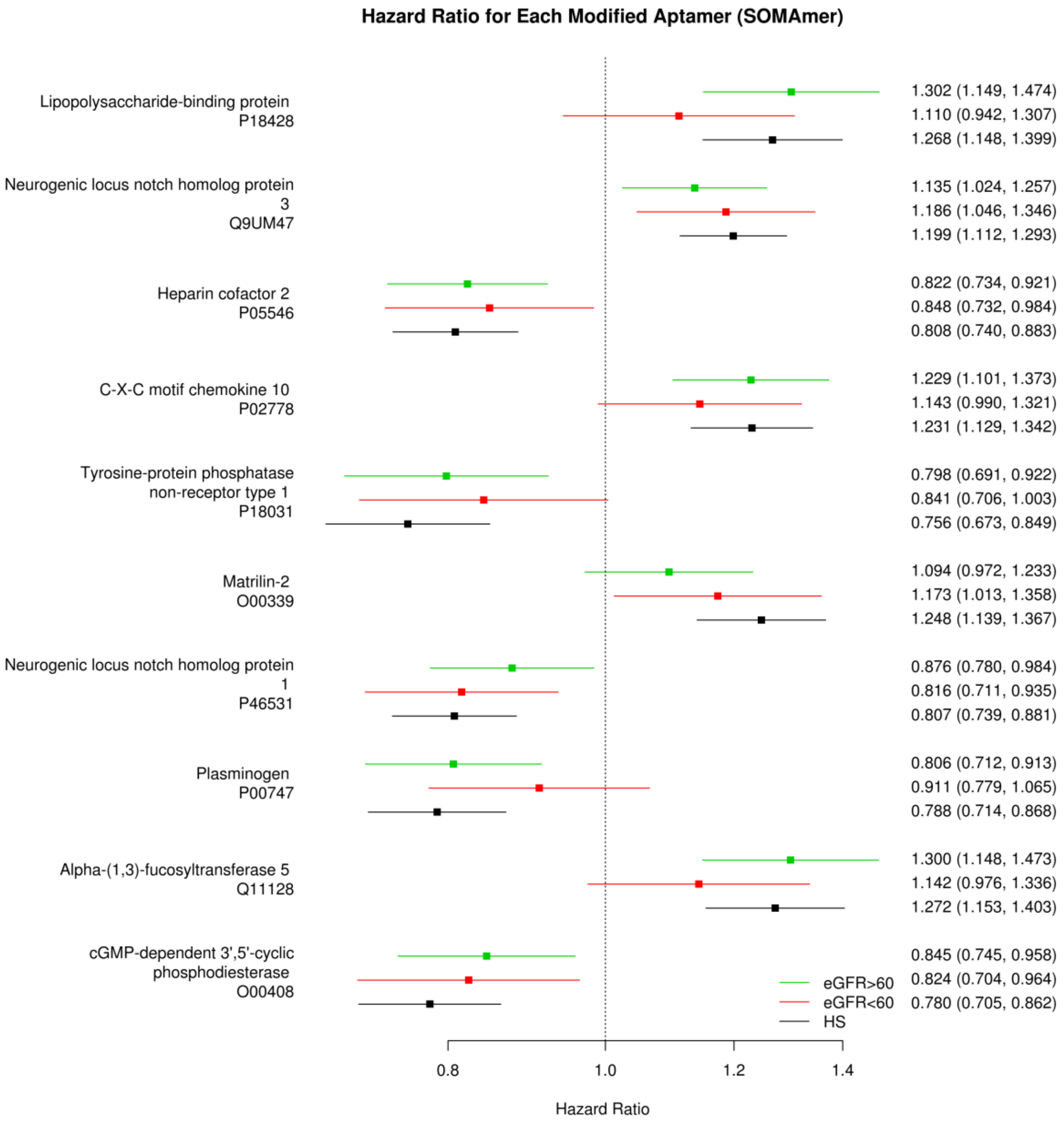

Hazard Ratio for Each Modified Aptamer (SOMAmer)
C-C motif chemokine 23
P55773
1.189 (1.056, 1.339)
1.140 (0.992, 1.311)
1.305 (1.192, 1.427)
Coagulation factor Xa
P00742
0.792 (0.718, 0.875)
0.887 (0.774, 1.016)
0.793 (0.734, 0.858)
Layilin
Q6UX15
1.084 (0.971, 1.210)
1.214 (1.067, 1.380)
1.249 (1.159, 1.345)
Immunoglobulin G
P01857
1.384 (1.229, 1.559)
1.154 (0.991, 1.345)
1.322 (1.204, 1.452)
Platelet glycoprotein VI
Q9HCN6
1.119 (0.994, 1.259)
1.313 (1.132, 1.524)
1.314 (1.199, 1.440)
Prothrombin
P00734
0.796 (0.719, 0.881)
0.913 (0.795, 1.050)
0.787 (0.726, 0.852)
C-type lectin domain family 4 member M
Q9H2X3
0.845 (0.753, 0.948)
0.807 (0.696, 0.936)
0.765 (0.699, 0.836)
Neurexophilin-1
P58417
0.820 (0.725, 0.927)
0.809 (0.695, 0.943)
0.745 (0.676, 0.822)
Cathepsin Z
Q9UBR2
1.243 (1.112, 1.390)
1.139 (0.979, 1.325)
1.305 (1.194, 1.425)
Brain natriuretic peptide 32
P16860
1.177 (1.090, 1.271)
1.183 (1.046, 1.338)
1.205 (1.133, 1.282)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
1.6
Hazard Ratio

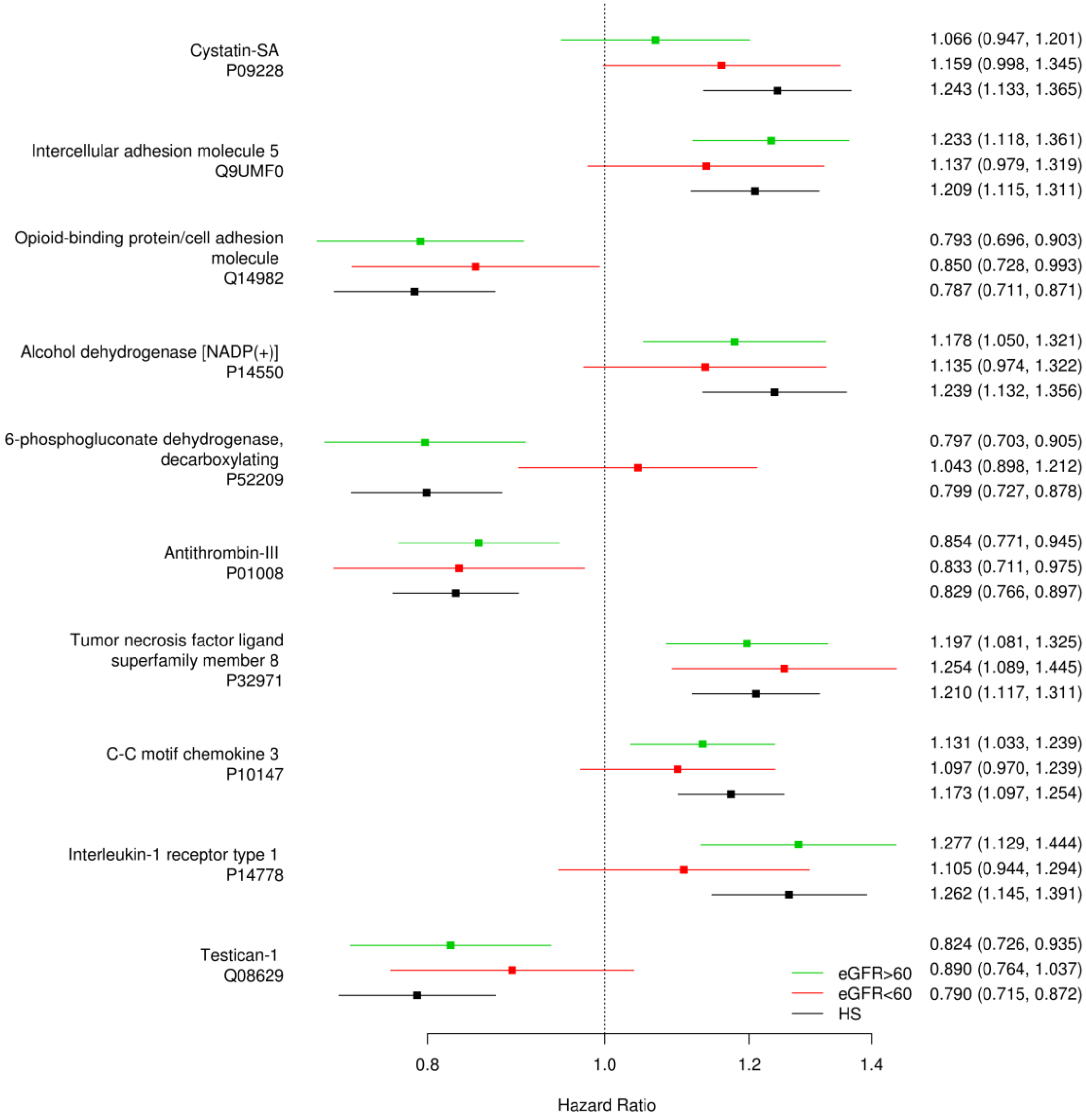

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Insulin-like growth factor-binding protein 1
P08833
1.226 (1.096, 1.371)
1.258 (1.070, 1.479)
1.287 (1.178, 1.406)
Ephrin type-B receptor 6
O15197
1.122 (1.012, 1.245)
1.092 (0.942, 1.267)
1.242 (1.152, 1.339)
Alpha-2-HS-glycoprotein
P02765
0.836 (0.743, 0.941)
0.783 (0.672, 0.911)
0.768 (0.700, 0.841)
Phospholipase A2, membrane associated
P14555
1.242 (1.120, 1.376)
1.229 (1.061, 1.424)
1.270 (1.170, 1.377)
Interleukin-17 receptor C
Q8NAC3
1.148 (1.045, 1.261)
1.151 (1.025, 1.291)
1.217 (1.138, 1.301)
Midkine
P21741
1.262 (1.162, 1.371)
1.129 (0.984, 1.295)
1.232 (1.147, 1.323)
Dickkopf-like protein 1
Q9UK85
0.791 (0.695, 0.900)
0.806 (0.686, 0.947)
0.740 (0.667, 0.820)
Ficolin-3
O75636
0.852 (0.763, 0.952)
0.808 (0.701, 0.931)
0.779 (0.716, 0.848)
Cathepsin L2
O60911
0.834 (0.740, 0.940)
0.832 (0.704, 0.982)
0.753 (0.684, 0.829)
Tyrosine-protein kinase Yes
P07947
1.212 (1.094, 1.344)
1.390 (1.199, 1.611)
1.257 (1.163, 1.359)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
1.6
Hazard Ratio

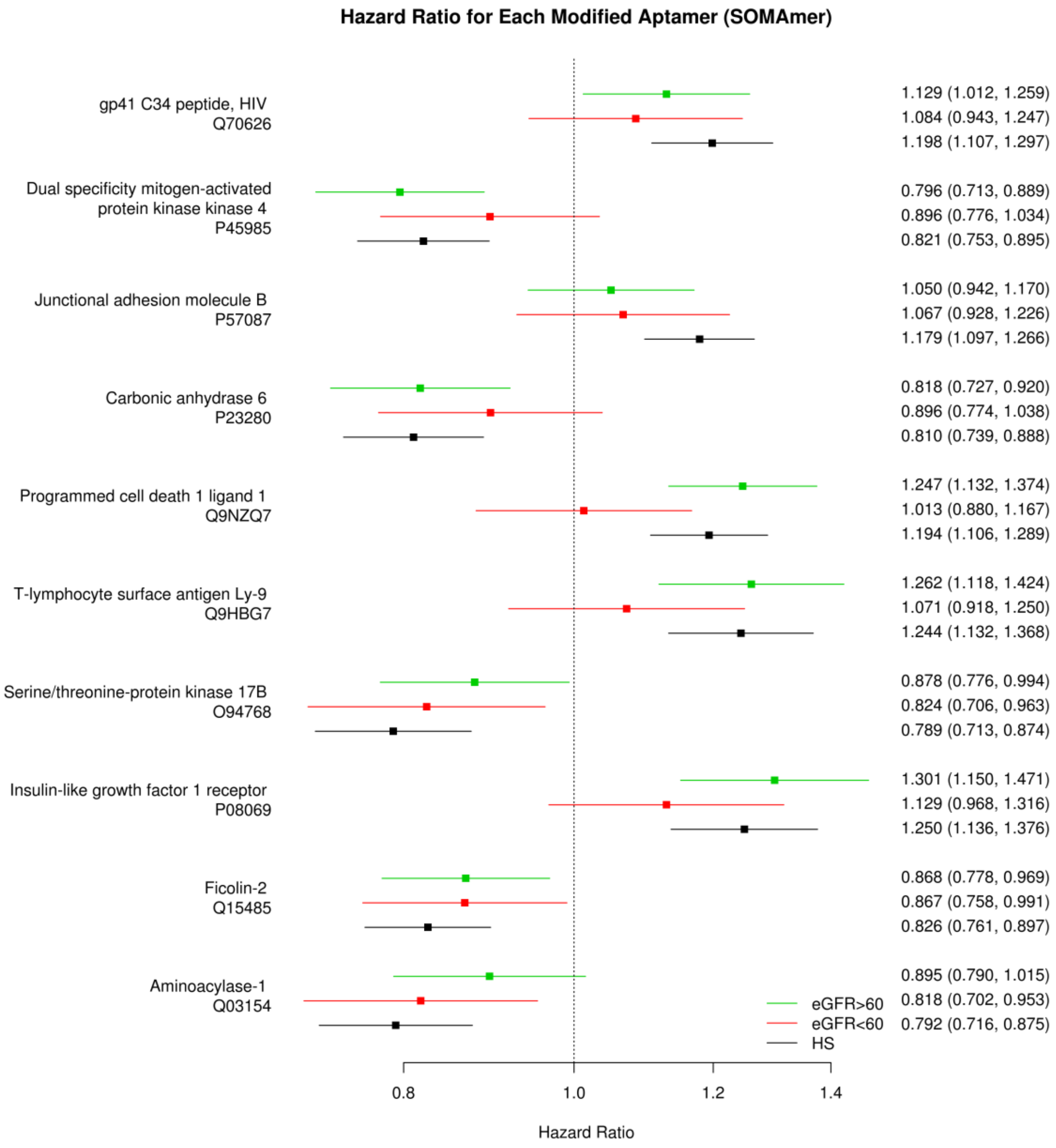

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Neuropilin-1
O14786
1.208 (1.108, 1.318)
1.183 (1.023, 1.368)
1.208 (1.126, 1.295)
SHC-transforming protein 1
P29353
1.119 (1.013, 1.238)
1.293 (1.124, 1.488)
1.224 (1.136, 1.320)
Bone sialoprotein 2
P21815
1.237 (1.110, 1.378)
1.167 (1.003, 1.359)
1.263 (1.159, 1.377)
Pappalysin-1
Q13219
1.160 (1.035, 1.299)
1.155 (0.985, 1.355)
1.284 (1.172, 1.406)
Tumor necrosis factor receptor
superfamily member 9
Q07011
1.076 (0.986, 1.175)
1.345 (1.176, 1.538)
1.175 (1.108, 1.247)
Tyrosine-protein kinase transmembrane
receptor ROR1
Q01973
1.144 (1.036, 1.263)
1.061 (0.909, 1.238)
1.234 (1.145, 1.331)
Resistin
Q9HD89
1.138 (1.015, 1.276)
1.129 (0.974, 1.308)
1.278 (1.171, 1.394)
Renin
P00797
1.260 (1.128, 1.408)
1.192 (1.024, 1.388)
1.282 (1.174, 1.400)
Ck-beta-8-1
P55773
1.211 (1.058, 1.387)
1.131 (0.979, 1.307)
1.337 (1.206, 1.482)
Serine protease HTRA2, mitochondrial
O43464
1.215 (1.091, 1.353)
1.224 (1.058, 1.417)
1.267 (1.165, 1.377)
eGFR>60
eGFR<60
HS
0.9
1.0
1.1
1.2
1.3
1.4
1.5
Hazard Ratio


Hazard Ratio for Each Modified Aptamer (SOMAmer)
Tenascin
P24821
1.341 (1.191, 1.508)
1.150 (0.997, 1.326)
1.260 (1.150, 1.380)
Cytochrome P450 3A4
P08684
0.862 (0.761, 0.977)
0.775 (0.668, 0.899)
0.778 (0.705, 0.858)
Oxidized low-density lipoprotein receptor 1
P78380
1.252 (1.123, 1.396)
1.144 (0.994, 1.316)
1.244 (1.142, 1.355)
Tumor necrosis factor receptor superfamily member 19
Q9NS68
1.055 (0.959, 1.160)
1.239 (1.089, 1.410)
1.173 (1.102, 1.248)
Seprase
Q12884
0.783 (0.678, 0.903)
0.741 (0.597, 0.920)
0.730 (0.647, 0.825)
Nidogen-1
P14543
1.278 (1.135, 1.439)
1.225 (1.067, 1.407)
1.266 (1.156, 1.386)
Interleukin-8
P10145
1.180 (1.091, 1.277)
1.299 (1.151, 1.465)
1.182 (1.108, 1.260)
Superoxide dismutase [Mn], mitochondrial
P04179
0.835 (0.739, 0.944)
0.831 (0.713, 0.969)
0.774 (0.702, 0.852)
Fibroblast growth factor 20
Q9NP95
0.726 (0.629, 0.839)
1.066 (0.907, 1.252)
0.744 (0.665, 0.832)
Fibroblast growth factor 23
Q9GZV9
1.142 (1.054, 1.237)
1.181 (1.055, 1.323)
1.178 (1.108, 1.253)
eGFR>60
eGFR<60
HS
0.6
0.8
1.0
1.2
1.4
Hazard Ratio

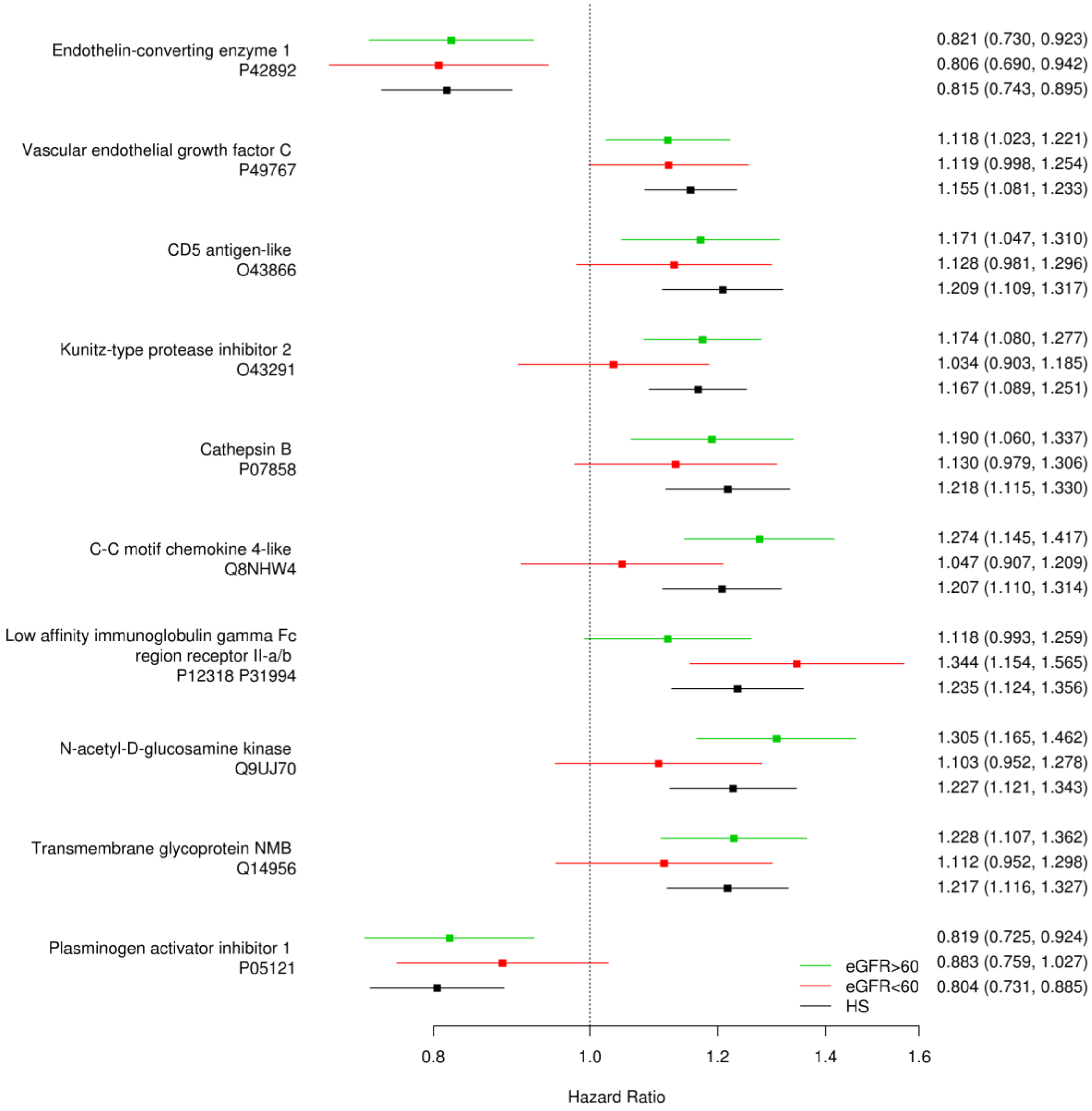

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Tumor necrosis factor ligand superfamily member 12
O43508
0.748 (0.637, 0.878)
0.782 (0.636, 0.960)
0.724 (0.636, 0.825)
C-C motif chemokine 7
P80098
1.251 (1.119, 1.399)
1.081 (0.947, 1.235)
1.224 (1.128, 1.327)
Carbonic anhydrase 3
P07451
1.065 (0.949, 1.196)
1.261 (1.088, 1.461)
1.246 (1.141, 1.360)
Ectonucleoside triphosphate diphosphohydrolase 5
O75356
0.856 (0.762, 0.962)
0.822 (0.700, 0.965)
0.794 (0.724, 0.871)
Complement factor D
P00746
1.070 (0.976, 1.174)
1.268 (1.113, 1.444)
1.172 (1.100, 1.249)
Stromal cell-derived factor 1
P48061
1.202 (1.068, 1.352)
1.211 (1.033, 1.419)
1.264 (1.151, 1.387)
BDNF/NT-3 growth factors receptor
Q16620
0.803 (0.703, 0.918)
0.830 (0.704, 0.979)
0.768 (0.691, 0.853)
Muellerian-inhibiting factor
P03971
0.859 (0.778, 0.949)
0.829 (0.716, 0.959)
0.830 (0.771, 0.894)
Insulin-like growth factor-binding protein 7
Q16270
1.359 (1.216, 1.520)
1.194 (1.021, 1.395)
1.262 (1.151, 1.383)
Malate dehydrogenase, cytoplasmic
P40925
0.806 (0.716, 0.908)
0.959 (0.826, 1.113)
0.789 (0.719, 0.866)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
Hazard Ratio

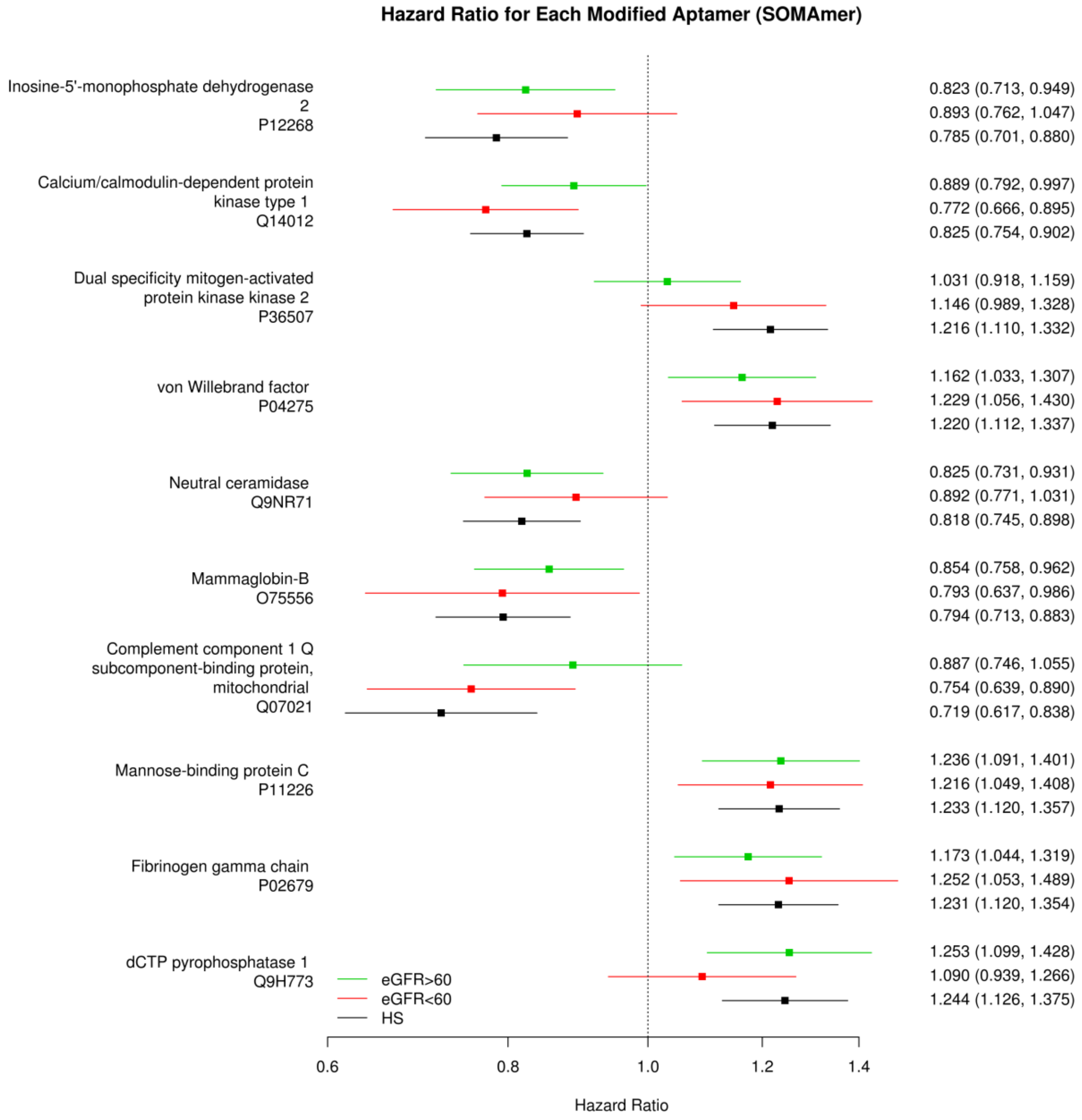

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Lipopolysaccharide-binding protein
P18428
1.302 (1.149, 1.474)
1.110 (0.942, 1.307)
1.268 (1.148, 1.399)
Neurogenic locus notch homolog protein
3
Q9UM47
1.135 (1.024, 1.257)
1.186 (1.046, 1.346)
1.199 (1.112, 1.293)
Heparin cofactor 2
P05546
0.822 (0.734, 0.921)
0.848 (0.732, 0.984)
0.808 (0.740, 0.883)
C-X-C motif chemokine 10
P02778
1.229 (1.101, 1.373)
1.143 (0.990, 1.321)
1.231 (1.129, 1.342)
Tyrosine-protein phosphatase
non-receptor type 1
P18031
0.798 (0.691, 0.922)
0.841 (0.706, 1.003)
0.756 (0.673, 0.849)
Matrilin-2
O00339
1.094 (0.972, 1.233)
1.173 (1.013, 1.358)
1.248 (1.139, 1.367)
Neurogenic locus notch homolog protein
1
P46531
0.876 (0.780, 0.984)
0.816 (0.711, 0.935)
0.807 (0.739, 0.881)
Plasminogen
P00747
0.806 (0.712, 0.913)
0.911 (0.779, 1.065)
0.788 (0.714, 0.868)
Alpha-(1,3)-fucosyltransferase 5
Q11128
1.300 (1.148, 1.473)
1.142 (0.976, 1.336)
1.272 (1.153, 1.403)
cGMP-dependent 3',5'-cyclic
phosphodiesterase
O00408
0.845 (0.745, 0.958)
0.824 (0.704, 0.964)
0.780 (0.705, 0.862)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
Hazard Ratio


Hazard Ratio for Each Modified Aptamer (SOMAmer)


Hazard Ratio for Each Modified Aptamer (SOMAmer)
gp41 C34 peptide, HIV
Q70626
1.129 (1.012, 1.259)
1.084 (0.943, 1.247)
1.198 (1.107, 1.297)
Dual specificity mitogen-activated
protein kinase kinase 4
P45985
0.796 (0.713, 0.889)
0.896 (0.776, 1.034)
0.821 (0.753, 0.895)
Junctional adhesion molecule B
P57087
1.050 (0.942, 1.170)
1.067 (0.928, 1.226)
1.179 (1.097, 1.266)
Carbonic anhydrase 6
P23280
0.818 (0.727, 0.920)
0.896 (0.774, 1.038)
0.810 (0.739, 0.888)
Programmed cell death 1 ligand 1
Q9NZQ7
1.247 (1.132, 1.374)
1.013 (0.880, 1.167)
1.194 (1.106, 1.289)
T-lymphocyte surface antigen Ly-9
Q9HBG7
1.262 (1.118, 1.424)
1.071 (0.918, 1.250)
1.244 (1.132, 1.368)
Serine/threonine-protein kinase 17B
O94768
0.878 (0.776, 0.994)
0.824 (0.706, 0.963)
0.789 (0.713, 0.874)
Insulin-like growth factor 1 receptor
P08069
1.301 (1.150, 1.471)
1.129 (0.968, 1.316)
1.250 (1.136, 1.376)
Ficolin-2
Q15485
0.868 (0.778, 0.969)
0.867 (0.758, 0.991)
0.826 (0.761, 0.897)
Aminoacylase-1
Q03154
0.895 (0.790, 1.015)
0.818 (0.702, 0.953)
0.792 (0.716, 0.875)
eGFR>60
eGFR<60
HS
0.8
1.0
1.2
1.4
Hazard Ratio

Hazard Ratio for Each Modified Aptamer (SOMAmer)




Hazard Ratio for Each Modified Aptamer (SOMAmer)
Inosine-5'-monophosphate dehydrogenase 2
P12268
0.823 (0.713, 0.949)
0.893 (0.762, 1.047)
0.785 (0.701, 0.880)
Calcium/calmodulin-dependent protein kinase type 1
Q14012
0.889 (0.792, 0.997)
0.772 (0.666, 0.895)
0.825 (0.754, 0.902)
Dual specificity mitogen-activated protein kinase kinase 2
P36507
1.031 (0.918, 1.159)
1.146 (0.989, 1.328)
1.216 (1.110, 1.332)
von Willebrand factor
P04275
1.162 (1.033, 1.307)
1.229 (1.056, 1.430)
1.220 (1.112, 1.337)
Neutral ceramidase
Q9NR71
0.825 (0.731, 0.931)
0.892 (0.771, 1.031)
0.818 (0.745, 0.898)
Mammaglobin-B
O75556
0.854 (0.758, 0.962)
0.793 (0.637, 0.986)
0.794 (0.713, 0.883)
Complement component 1 Q subcomponent-binding protein, mitochondrial
Q07021
0.887 (0.746, 1.055)
0.754 (0.639, 0.890)
0.719 (0.617, 0.838)
Mannose-binding protein C
P11226
1.236 (1.091, 1.401)
1.216 (1.049, 1.408)
1.233 (1.120, 1.357)
Fibrinogen gamma chain
P02679
1.173 (1.044, 1.319)
1.252 (1.053, 1.489)
1.231 (1.120, 1.354)
dCTP pyrophosphatase 1
Q9H773
1.253 (1.099, 1.428)
1.090 (0.939, 1.266)
1.244 (1.126, 1.375)
eGFR>60
eGFR<60
HS
0.6
0.8
1.0
1.2
1.4
Hazard Ratio

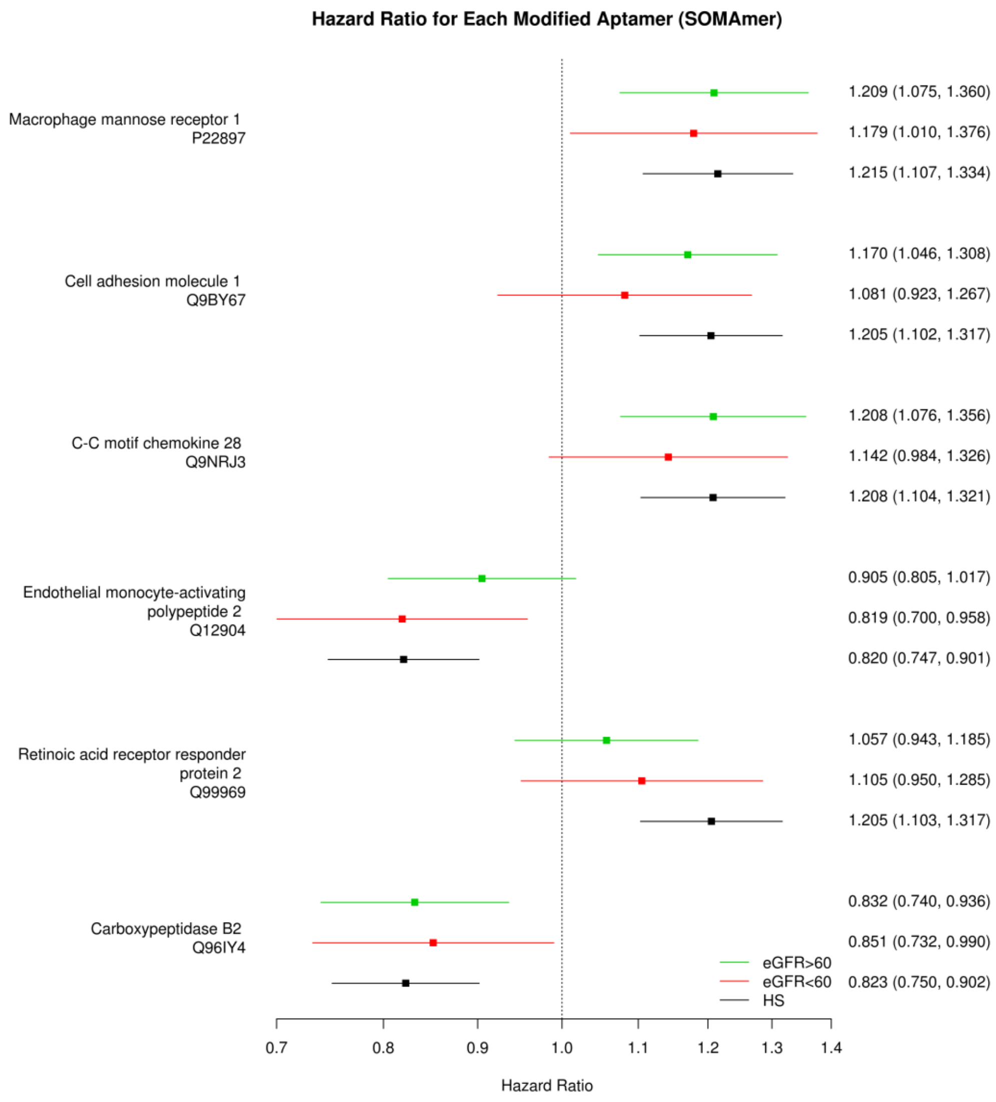

Hazard Ratio for Each Modified Aptamer (SOMAmer)
Macrophage mannose receptor 1
P22897
1.209 (1.075, 1.360)
1.179 (1.010, 1.376)
1.215 (1.107, 1.334)
Cell adhesion molecule 1
Q9BY67
1.170 (1.046, 1.308)
1.081 (0.923, 1.267)
1.205 (1.102, 1.317)
C-C motif chemokine 28
Q9NRJ3
1.208 (1.076, 1.356)
1.142 (0.984, 1.326)
1.208 (1.104, 1.321)
Endothelial monocyte-activating polypeptide 2
Q12904
0.905 (0.805, 1.017)
0.819 (0.700, 0.958)
0.820 (0.747, 0.901)
Retinoic acid receptor responder protein 2
Q99969
1.057 (0.943, 1.185)
1.105 (0.950, 1.285)
1.205 (1.103, 1.317)
Carboxypeptidase B2
Q96IY4
0.832 (0.740, 0.936)
0.851 (0.732, 0.990)
0.823 (0.750, 0.902)
eGFR>60
eGFR<60
HS
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
Hazard Ratio

Figure S2. Spearman rho coefficients among the top 100 proteins in the Heart and Soul cohort, which were also measured in the Lund cohort (shown are 98 of 100 proteins that were measured in both cohorts).