Clinical Proteomics

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Identification of novel proteomic biomarkers for hypertension: a targeted approach for precision medicine

Rana S. Aldisi[1,2], Alsamman M. Alsamman[3,4], Peter Krawitz[1], Carlo Maj[5] and Hatem Zayed[6*]

Abstract

Background Hypertension is a critical public health issue worldwide. The identification of specific proteomic biomarkers in the Qatari population aims to advance personalized treatment strategies.

Methods We conducted proteomic profiling on 778 Qatari individuals using an aptamer-based SOMAscan platform to analyze 1,305 biomarkers. Statistical analysis involved two-way ANOVA and association analyses with FDR correction, alongside pathway and gene-set enrichment analyses using Reactome and DisGeNET databases.

Results The study identified 26 significant protein biomarkers associated with hypertension. Notably, QORL1 and BMP1 were identified as novel protein biomarkers. Enrichment analysis linked these biomarkers to critical pathways involved in vascular biology, immune system responses, and pathologies like arteriosclerosis and coronary artery disease. Correlation analyses highlighted robust interactions, particularly between QORL1 and various Apolipoprotein E isoforms, suggesting these biomarkers play pivotal roles in the molecular mechanisms underlying hypertension.

Conclusions This research enhances our understanding of the molecular basis of hypertension in the Qatari population and supports the development of precision medicine approaches for treatment.

Keywords Hypertension, Qatar Precision Health Institute-Qatar Biobank, Proteomic/macromolecular biomarkers, QORL1, BMP1, SOMAscan technology, Enrichment analysis, Cardiovascular diseases, Mean arterial pressure, Macromolecules

Introduction

Hypertension stands as the primary modifiable contributor to both cardiovascular disease and overall mortality on a global scale. According to the 2017 ACC/AHA guidelines, hypertension is now defined as a persistent elevation in blood pressure at or above 130/80 mmHg, marking a paradigm shift in the diagnosis and management of this prevalent condition. This updated threshold emphasizes the critical need for early detection and intervention, aiming to mitigate the global burden of hypertension and its associated complications through more proactive measures [1]. The global prevalence of hypertension continues to rise, underscoring its status as a leading public health challenge. In 2010, approximately 1.39 billion adults, representing 31.1% of the

*Correspondence:
Hatem Zayed
hatem.zayed@qu.edu.qa
[1] Institute for Genomics Statistics and Bioinformatics, University of Bonn, Bonn, Germany
[2] Institute for Human Genetics, University of Bonn, Bonn, Germany
[3] International Center for Agriculture Research in the Dry Areas (ICARDA), Giza, Egypt
[4] Department of Genome Mapping, Agricultural Genetic Engineering Research Institute (AGERI), Agricultural Research Center (ARC), Giza, Egypt
[5] Centre for Human Genetics, University of Marburg, Marburg, Germany
[6] Department of Biomedical Sciences College of Health Sciences, QU Health, Qatar University, Doha, Qatar

world's adult population, were diagnosed with hypertension. This alarming statistic is driven by demographic shifts, particularly the aging global population, and an increased exposure to modifiable lifestyle risk factors. Dietary habits characterized by excessive sodium intake and insufficient potassium consumption, alongside sedentary lifestyles, have significantly contributed to this trend. Additionally, rising obesity rates and high alcohol consumption further exacerbate the burden of hypertension. These findings highlight the urgent need for comprehensive strategies aimed at early detection, lifestyle modification, and targeted interventions to combat this growing epidemic [2]. Hypertension is a complex and multifaceted condition influenced by a polygenic basis and shaped by a dynamic interplay of genetic, demographic, and environmental factors. Heritability studies estimate that up to 60% of the variability in blood pressure is attributable to genetic factors, yet the precise genetic architecture remains elusive. Its manifestation is further modulated by sex, age, race, and lifestyle factors, reflecting its intricate and multifactorial nature [3]. In a recent study of the Qatari population, findings indicate that hypertension affects one in every three individuals [4]. Furthermore, we have previously identified a unique genetic susceptibility profile for hypertension in Qatari patients, revealing population-specific genetic associations [5]. Understanding the etiology underlying hypertension is critical for developing effective prevention and management strategies, particularly in populations with unique genetic and environmental characteristics [6, 7].

Proteomics has revolutionized the study of complex diseases, including hypertension, by enabling large-scale analysis of proteins and their functions. This approach facilitates the identification of specific biomarkers and signaling pathways central to disease pathogenesis. By uncovering these molecular players, proteomics enhances our understanding of disease mechanisms and highlights potential therapeutic targets. As a result, proteomics has become an indispensable tool for advancing diagnostics, guiding targeted therapies, and driving precision medicine strategies to improve patient outcomes [8]. In this study, we used proteomic data from the Qatar Biobank cohort to explore the association between proteomic biomarkers and the development of high hypertension, thereby assessing their potential role in hypertension risk.

Methods

This study used a cohort of 778 de-identified samples collected from the Qatar Biobank, a comprehensive biorepository initiative in Qatar [9]. Ethical approval (QF-QBB-RES-ACC-00095) was obtained and the proteomic data were provided by the Qatar Precision Health Institute—Qatar Biobank (QPHI-QBB) [10].

Data collection and analytical workflow

This study employed a comprehensive approach, integrating clinical data and proteomic profiling to investigate hypertension within the studied cohort.

Clinical data collection

Clinical data, including blood pressure measurements, medical history, and demographic information, were meticulously curated. Blood pressure readings were obtained using standardized protocols, with multiple readings taken at different time points to ensure accuracy. Participants' medical histories were reviewed to identify diagnosed cases of hypertension, and additional clinical data, such as medication usage and comorbidities, were also considered. Individuals with comorbidities or those using pharmacological treatments for hypertension were excluded from the analysis to minimize confounding factors [9]. Hypertension was defined based on systolic blood pressure (SBP) $\geq$ 130 mmHg and/or diastolic blood pressure (DBP) $\geq$ 80 mmHg, following hypertension stage 1 criteria [1]. This process resulted in the identification of 224 cases and 554 controls.

Proteomic data acquisition

Proteomic profiling was conducted using the SOMAscan v3.1 platform (Somalogic, Boulder, CO, USA). This innovative aptamer-based technology measures over 1,000 proteins simultaneously using specialized SOMAmers. The assay involved incubating EDTA-plasma samples with SOMAmers specific to protein epitopes, followed by binding the complexes to beads. Biotinylated proteins were isolated, photocleaved, and hybridized onto custom arrays of SOMAmer-complementary oligonucleotides for quantification. Standards were employed to process raw intensity data, resulting in measurements for 1305 aptamers without exclusions. Protein annotations were based on aptamer IDs linked to their respective target proteins using UniProt and Entrez Gene identifiers [11].

Mean arterial pressure (MAP), a quantitative measure for blood pressure, was calculated using the equation below:

$$MAP = DBP + 1/3(SBP - DBP)$$

Statistical analysis

Two-way ANOVA analysis was performed on Gender, age, and BMI using MAP as a target, to assess significant determinants. To find proteins associated with

hypertension, we performed a linear regression with MAP as the quantitative target, and a logistic regression with hypertension cases and controls, grouped as previously described. To account for multiple testing, we applied the FDR correction. The results were visualized in a volcano plot, effect sizes were calculated using the coefficients and standard errors extracted from the regression models.

Protein enrichment analysis

To gain deeper insights into the biological significance of our findings, we performed pathway and protein-enrichment analyses. The top significant proteins identified in the association analysis were analyzed using the Enrichr-KG web server, which integrates data from publicly available databases to explore gene-set associations. Specifically, we investigated associations between our protein set and functional pathways from the Reactome database, as well as gene-disease connections from the DisGeNET database.

To enhance the analysis, we expanded our protein set using gene co-expression data and protein–protein interaction networks from the STRING database. Results were visualized using Cytoscape to map interaction networks. Additionally, gene-enrichment analysis results were depicted using the R ggplot2 package, which visualized the frequency of genes across various Gene Ontology (GO) terms.

Correlation analysis

Investigating protein expression clustering involved conducting correlation analysis to explore potential associations among protein expressions in the Qatari individuals under study. The 'cor' function in R was employed to the expression matrix, with correlations having a p-value 0.01 removed. The correlation network and matrix were plotted using the corrplot R Package. Additionally, the 'corrr' R package was utilized to visualize protein–protein correlation networks, facilitating the identification of protein clusters based on their expression levels.

Results

Baseline characteristics

Our cohort contained 778 Qatari individuals of both genders between the ages of 30 and 60, of which 44.8% were women (n = 349) and 55.2% were men (n = 429). To be able to investigate blood pressure as a quantitative measure, MAP was calculated using systolic and diastolic blood pressure (see methods). The MAP for the cohort ranged between 68 and 145 mmHg with an average of 85.5 mmHg (normal MAP ranges between 70 and 100 mmHg). Table 1 displays the baseline parameters of the cohort. We also examined the distribution of MAP across genders and different age groups, which is visualized in Fig. 1. We performed a two-way ANOVA analysis to explore the statistical significance of age and sex on blood pressure. Gender emerged as a significant determinant of MAP ($F = 29.8$, $p = 6.60 \times 10^{-8}$), with distinctive patterns observed between men and women. Additionally, age displayed a substantial impact on MAP ($F = 9.2$, $p = 3.69 \times 10^{-34}$). Moreover, the interaction between gender and age did not significantly

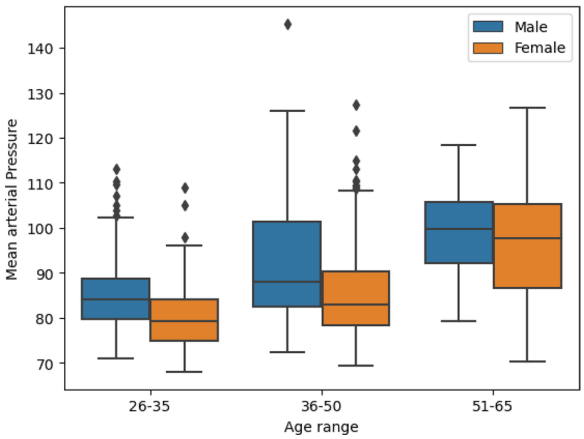

Fig. 1 Distribution of MAP values based on age group and gender across the studied population using boxplot analysis for both male and female subjects

Table 1 Baseline characteristics for hypertension case and control groups

	Hypertension cases (n = 224)	Controls (n = 554)
Age	30–60 (mean = 47.4)	30–60 (mean = 38.4)
Male (%)	59.3	53.4
BMI	21–32 (mean = 28.2)	15–32 (mean = 26.2)
Mean arterial pressure	83–145 (mean = 104.5)	68–93 (mean = 82.2)
Systolic blood pressure (mmHg)	114–198 (mean = 138.4)	84–120 (mean = 106.8)
Diastolic blood pressure (mmHg)	58–121 (mean = 87.5)	60–80 (mean = 69.8)
Triglycerides (mmol/L)	0.4–8.2 (mean = 1.9)	0.4–6.6 (mean = 1.3)
Total cholesterol (mmol/L)	2.3–7.9 (mean = 5.3)	2.5–8.1 (mean = 4.9)

influence MAP ($F = 1.1$, $p = 0.334$). We further performed a multivariate linear regression on MAP using age, sex, BMI, triglycerides and total cholesterol as independent variables. The regression analysis revealed that gender, age, BMI, total cholesterol, and triglyceride levels are all statistically significant predictors of mean arterial pressure ($p < 0.001$), with a model R^2 of 0.308.

Proteomics

An association analysis on a total of 778 individuals with available proteomic data was performed, employing linear regression as the statistical methodology to identify proteins that are significantly associated with the mean arterial pressure. Among a total of 1,305 circulating protein biomarkers scrutinized in our analysis, we identified 25 significant associations subsequent to FDR correction. A logistic regression was also performed to identify proteins associated with hypertension, in which 13 proteins were found to be significantly associated after FDR correction. Figures 2 and 3 present volcano plots showing all proteins with statistically significant associations after FDR correction for MAP and hypertension, respectively. Effect sizes are also presented in the figures where as for the MAP association analysis, negative effect size indicates that an increase in the respective protein leads to a decrease in MAP, while a positive effect size indicates that an increase in the respective protein leads to an increase in MAP. For the hypertension association analysis, a negative effect size indicates that a decrease in the respective protein leads to a lower likelihood of having

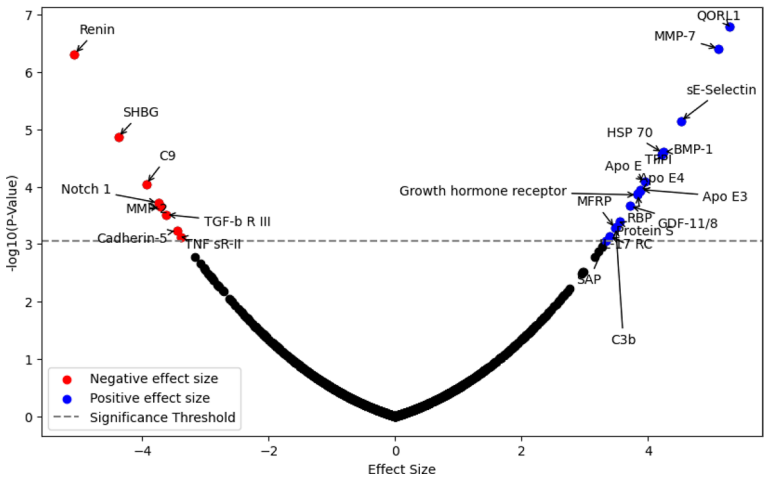

Fig. 2 Volcano plot showing the relationship between the – log10 p-value and effect sizes (z-score) from the MAP association analysis results. Proteins exhibiting significant associations are visually highlighted based on their negative or positive effects

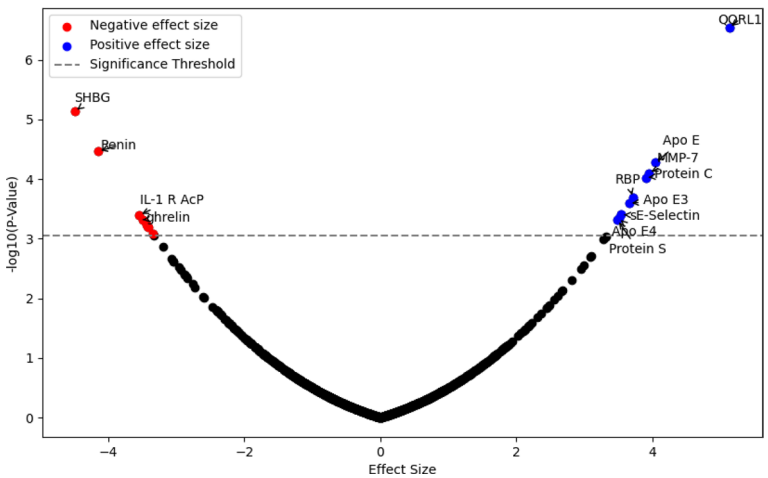

Fig. 3 Volcano plot showing the relationship between the – log10 p-value and effect sizes (z-score) from the hypertension association analysis results. Proteins exhibiting significant associations are visually highlighted based on their negative or positive effects

hypertension, while a positive effect size indicates that an increase in the respective protein leads to a higher likelihood of having hypertension.

Correlation analysis

We conducted correlation analysis to explore potential associations among protein expressions in the Qatari individuals under study (Fig. 4). The analysis revealed significant interactions among a group of proteins, several of which were found to be linked with hypertension. Notably, QORL1, which was emerged as a potentially novel candidate protein associated with development of hypertension in our study, displaying a positive correlation with several isoforms of the Apolipoprotein E (Apo E) protein including Apo E2, Apo E, Apo E3, and Apo-E4 (Fig. 4A). A distinct cluster of 21 interconnected proteins, including MMP-2, PAPP-A, VCAM-1, Notch 1, and SDF-1, exhibited positive correlations among each other (Fig. 4A). Interestingly, a cluster of 21 proteins exhibits mainly negative correlations with the expression levels of UBC9 and NAGK proteins. This suggests a potential interaction between the expression of this group of proteins and the two mentioned proteins. This correlation pattern demonstrates a prevailing trend with a slightly greater number of negative correlations than positive ones (Fig. 4B).

Pathway enrichment

The results of pathway and gene-disease enrichment analyses highlight several key pathways and processes involved in the pathogenesis of hypertension (Figs. 5, 6 and 7). We identified associations of the significant proteins with coronary artery disease and atherosclerosis. Firstly, a notable enrichment of genes associated with blood vessel maturation, morphogenesis, development, and the regulation of blood circulation underscores the pivotal role of vascular biology in hypertensive conditions, with observed gene percentages ranging from 1.49 to 25% (Fig. 5A). The enrichment analysis yielded valuable insights into gene functions and their potential impact on disease pathogenesis. The biological pathway category was mostly linked with blood vessel maturation, while the tissue category was related to blood vessel cells (Fig. 5A). Additionally, our findings reveal substantial involvement of complement pathways, including activation cascades and regulatory mechanisms, with observed gene percentages ranging from 6.67 to 21.05%, suggesting a complex interplay between immune responses

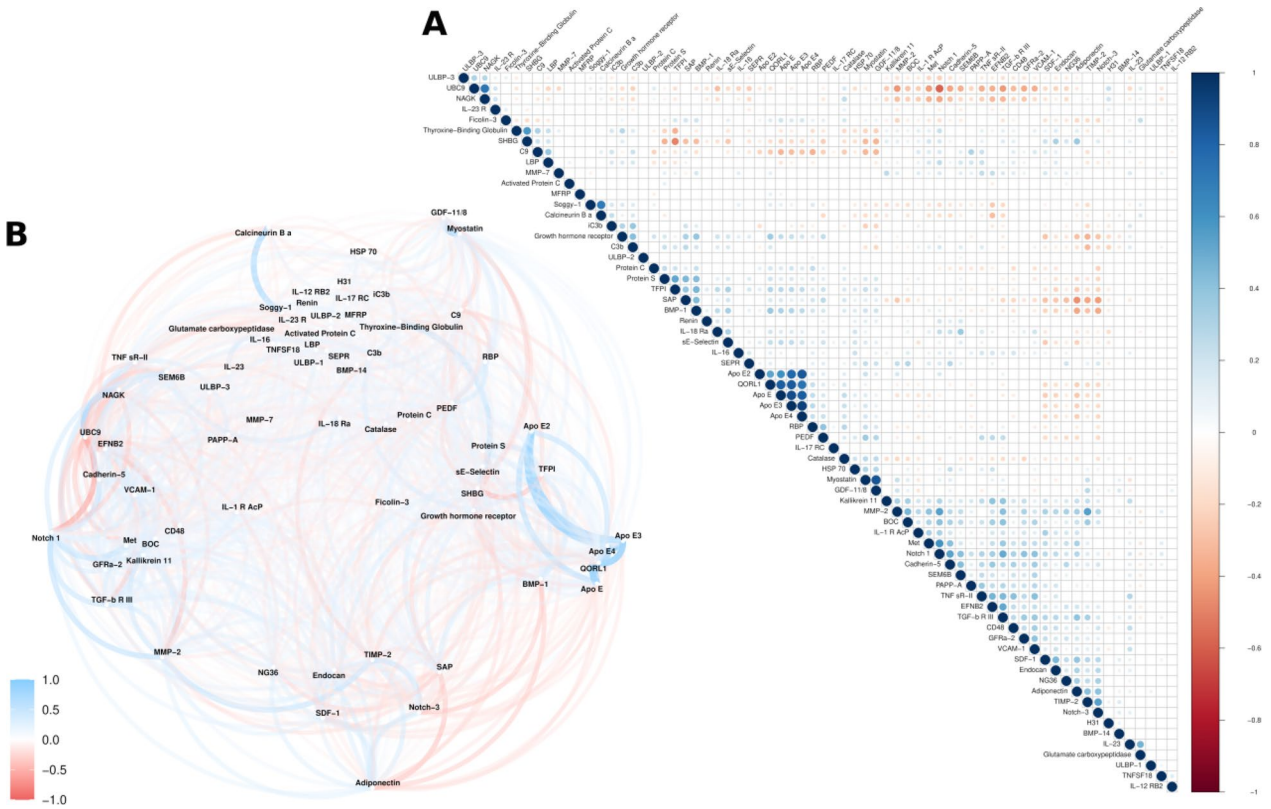

Fig. 4 Correlation analysis of protein biomarker based on their expression in the studied Qatari population depicted through two visualizations: **A** a correlation heat map and **B** a correlation network. The green and red stripes highlight positive and negative correlations

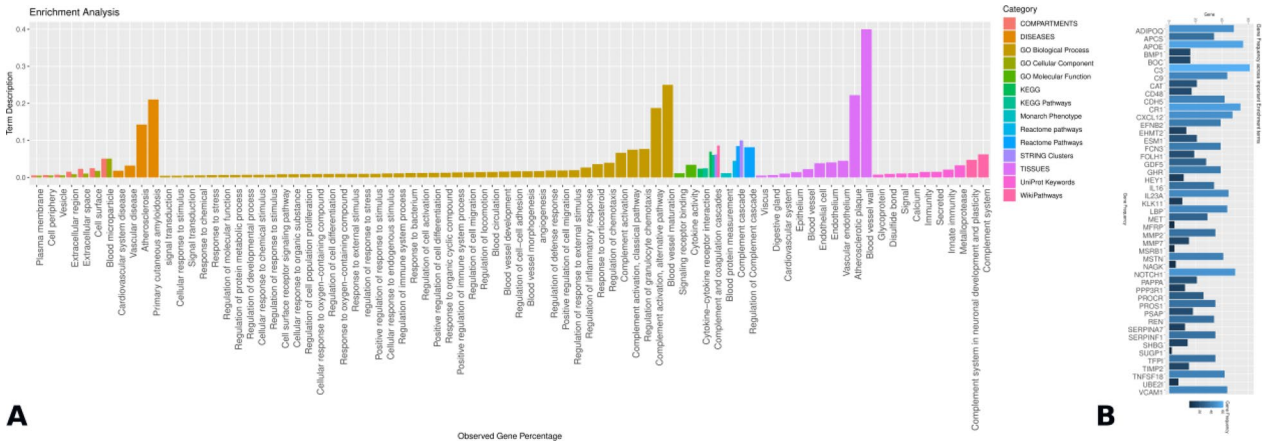

Fig. 5 Enrichment analysis of proteins associated with hypertension was conducted, revealing significant findings in two aspects: **A** Biological pathways and gene ontology categories along with their corresponding gene frequencies, and **B** The inclusion frequency of genes in various biological pathways

and hypertension (Fig. 5A). A close association between hypertension and atherosclerosis, as evidenced by the presence of genes linked to atherosclerotic plaque formation and cardiovascular diseases was found (Fig. 5A). Moreover, our analysis highlights the intricate involvement of immune response and inflammation pathways in hypertension.

The gene frequency observed across various biological pathways provides insights into genes that have been extensively studied and exhibit multifunctionality across different levels of biological pathways (Fig. 5B). Many of these genes, such as *C3, ADIPOQ, Notch1*, and *VCAM1*, are well-known for their established functions and roles in hypertension and related diseases (Fig. 6). This validation indicates that the current dataset offers a valuable network of genes. If thoroughly studied, these genes could potentially serve as a blueprint for understanding hypertension.

Discussion

Our study highlights the role of gender and age in hypertension within the Qatari population. We found that men generally had higher MAP than women, and MAP increased with age as shown in Fig. 1. These findings, consistent with global hypertension trends, emphasize the importance of demographic factors in understanding and managing hypertension [12]. However, it's essential to note that individual variations and other factors can influence this trend, so it's a general observation and not a rule for every individual. Notably, the interaction between gender and age did not significantly affect blood pressure. The regression model suggests that sex, age, BMI, total cholesterol, and triglyceride levels are all statistically significant predictors for MAP. Gender has a negative relationship with MAP, while age, BMI, total cholesterol, and triglyceride levels have positive relationships with MAP. However, it's important to note that the model only explains a portion of the variance in MAP, which is about 30.8%, and there may be other factors not included in the model that also influence MAP.

We further investigated the correlation between 1,305 circulating protein biomarkers and blood pressure regulation within 778 Qatari participants. Among these proteins, we have identified 25 significant protein associations with mean arterial pressure in the Qatari cohort: The analysis identified the following significant proteins: QORL1, MMP-7, Renin, E-Selectin, SHBG, BMP-1, HSP70, TFPI, ApoE, C9, ApoE3, ApoE4, RBP4, Growth Hormone Receptor, Notch 1, GDF-11/8, MMP-2, TGF-β Receptor III, Protein S, C3b, MFRP, Cadherin-5, IL-17 RC, TNF sR-II, and Serum Amyloid P Component (Fig. 2).

Additionally, 13 proteins were significantly associated with hypertension: QORL1, SHBG, Renin, ApoE, MMP-7, Protein C, RBP4, ApoE3, E-Selectin, IL1RAP, ApoE4, Ghrelin, and Protein S (Fig. 3). Notably, ten of these proteins overlapped with those identified in the initial analysis, emphasizing their potential relevance.

From both analyses, QORL1 and BMP1 emerged as novel candidate biomarkers for further investigation in the context of hypertension. Detailed summary statistics, along with the full names and gene symbols of these proteins, are provided in Supplementary Tables 1 and 2.

Our findings not only corroborate six previously known associations in hypertension research but also introduce new potential genes that might be involved in its pathogenesis. These macromolecular interactions, particularly those involving complex protein assemblies, underscore

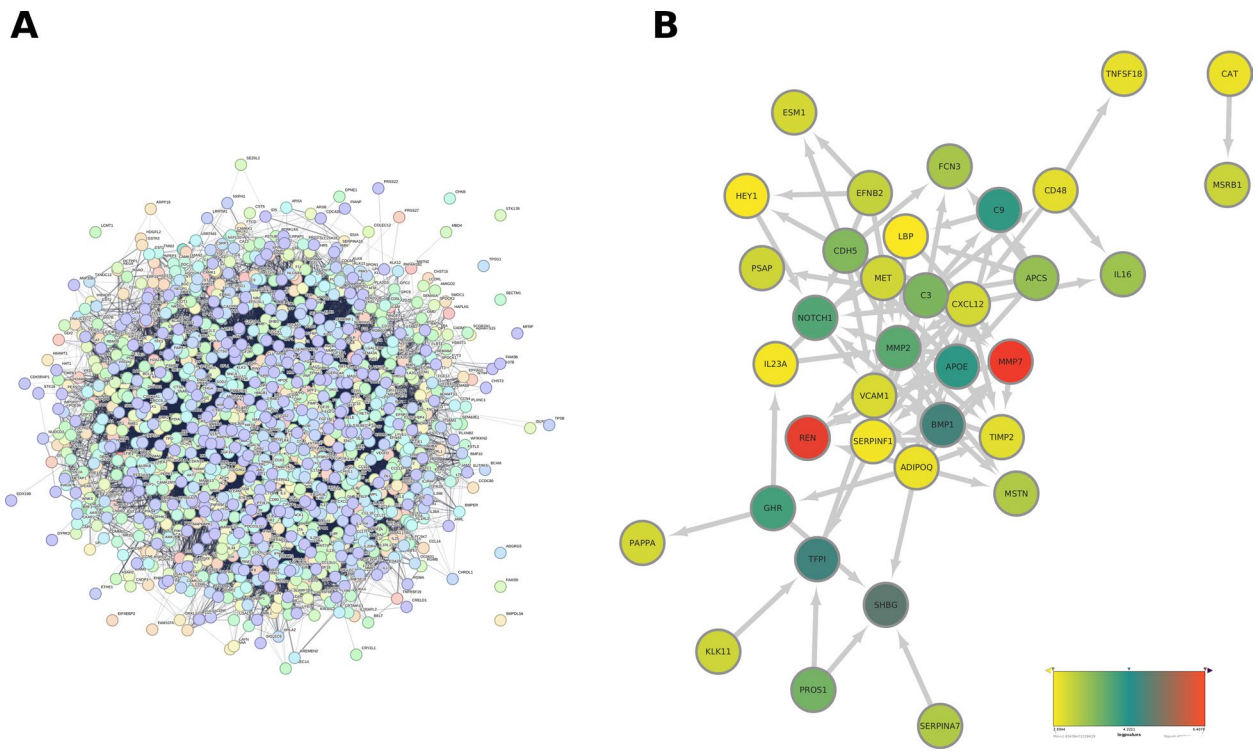

Fig. 6 Protein–Protein Interaction (PPI) Network. (**A**) The PPI network of all proteins studied as potential proteomic biomarkers for hypertension. (**B**) Highly associated proteins with hypertension, color-coded based on the significance of their association

the proteins' roles in pathways linked to conditions like coronary artery disease and arteriosclerosis, highlighting their potential as targets in the broader clinical spectrum of hypertension.

One of the top associations found in our analysis is Renin, a well-known blood pressure regulator due to its crucial role in the renin–angiotensin–aldosterone system (RAAS), which is implicated in hypertension and kidney disease. Renin's primary function is to catalyze the

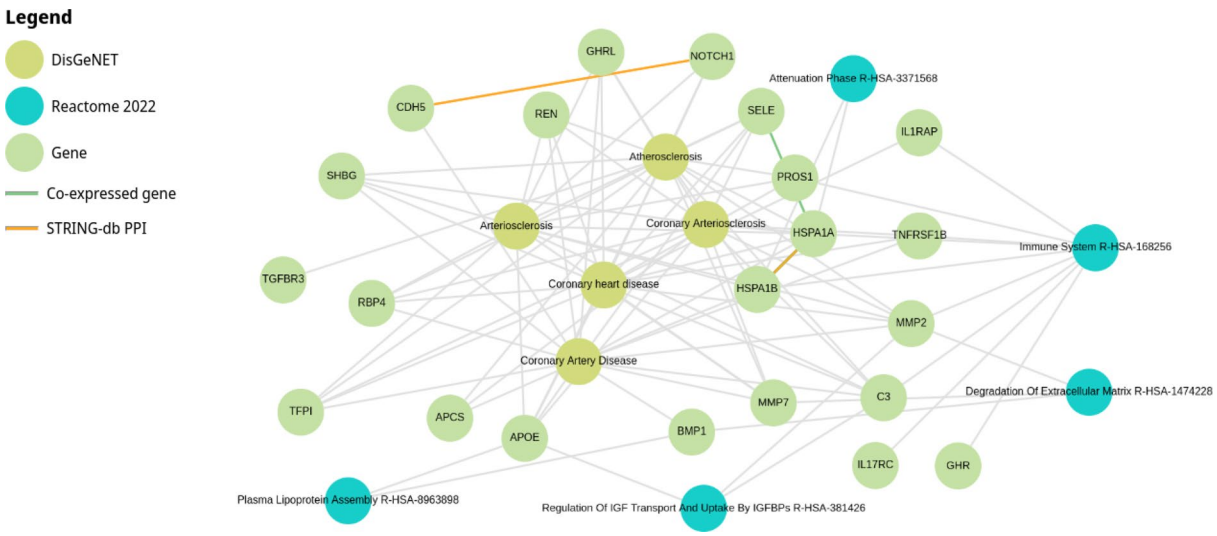

Fig. 7 Pathway and disease associations with top significant genes. Pathways were extracted from the Reactome database, and disease-gene links were extracted from the DisGeNET database. Orange lines show the protein–protein interactions taken from the STRING-db database while green lines present gene co-expression

conversion of angiotensinogen into angiotensin I, which subsequently leads to the production of angiotensin II—a potent vasoconstrictor that increases blood pressure. Dysregulation of the RAAS, including overactivity of renin, can result in elevated angiotensin II levels, leading to hypertension [13].

Many of the other significant proteins have gained attention in hypertension research, each shedding light on its unique role in this complex condition. For example, MMP2 (Matrix Metalloproteinase 2) and MMP7 (Matrix Metalloproteinase 7), are recognized for their involvement in hypertension due to their potent extracellular matrix-degrading capabilities, which can impact blood vessel architecture. MMPs regulatory influence extends to cardiovascular diseases like coronary artery disease and atherosclerosis, closely intertwined with hypertension. Genetic investigations have pinpointed a specific variation in the *MMP7* gene promoter strongly associated with hypertension; individuals carrying the AG genotype exhibit elevated blood pressure levels [14]. Interestingly, we observed that BMP1 is also involved in the degradation of the extracellular matrix pathway (Fig. 7). Another notable protein, E-selectin, a cell adhesion molecule expressed in endothelial cells lining blood vessels, has emerged as a correlate of hypertension. Studies reveal elevated E-selectin levels in hypertensive individuals compared to controls, possibly a consequence of chronic blood pressure elevation that subjects the endothelial lining to sustained mechanical stress, thereby triggering molecular responses, including E-selectin upregulation [15]. Furthermore, HSP70, an essential member of the heat shock protein family, has piqued interest. While a clear causal relationship has not been established, increased levels of HSP70 in people with hypertension was observed in multiple studies, suggesting its potential involvement as a protective response to vascular stress [16].

The correlation analysis revealed significant information about potential protein interaction networks (Fig. 4). Our newly identified key factor, QORL1, has emerged as a novel candidate gene associated with hypertension. Notably, it exhibits a positive correlation with various isoforms of the Apo E protein, such as Apo E2, Apo E, Apo E3, and Apo-E4 (Fig. 4A). The proteins listed represent distinct isoforms of the Apo E gene, a key player in lipid metabolism in the body. The clinical significance of Apo E in patients with hypertension has been the focus of numerous studies. These investigations have consistently demonstrated an association between Apo E and hypertension. The findings strongly support the hypothesis that Apo E serves as a susceptibility locus for systolic hypertension and carotid artery atherosclerosis [17]. Apo E2, Apo E3, and Apo E4 are variations of this gene, each characterized by slightly different amino acid sequences, leading to varied effects on lipid metabolism and associated health outcomes. Specifically, Apo E4 stands out as a contributing factor to neurodegeneration. It plays crucial roles in redistributing lipids among central nervous system cells to maintain normal lipid homeostasis, repair injured neurons, sustain synapto-dendritic connections, and scavenge toxins [18]. These Apo E isoforms, recognized as crucial players in lipid metabolism, have established correlations with QORL1 and are clinically significant in patients with hypertension.

A unique cluster of 21 interconnected proteins, comprising MMP-2, PAPP-A, VCAM-1, Notch 1, and SDF-1, displayed positive relationships with each other (Fig. 4A). Many of these genes are recognized for their relevance to hypertension and have been proposed as potential biomarkers for cardiovascular diseases. For example, MMP-2 has been implicated in the progression of cardiac and vascular hypertrophy, accompanied by elevated formation of reactive oxygen species [19]. The significance of Pregnancy-Associated Plasma Protein-A (PAPP-A) is underscored by its inclusion in a risk model for predicting hypertensive disorders of pregnancy (HDP). The risk model combines first-trimester maternal MAP, placental growth factor, and PAPP-A. The predictive value of these factors collectively in anticipating HDP is currently uncertain and warrants further investigation [20]. Their relevance to hypertension have been proposed as potential biomarkers for cardiovascular diseases. The correlation network revealed a common pattern with slightly more negative correlations than positive ones. A group of 21 proteins shows predominantly negative correlations with the frequencies of UBC9 and NAGK proteins. A recent investigation aimed to uncover the relationship between UBC9 expression and its potential impact on cardiac hypertrophy and heart failure [21]. UBC9 expression increased in the hearts of individuals with hypertrophic cardiomyopathy and pressure overload-induced mice. Moreover, Neonatal Mouse Cardiomyocytes treated with phenylephrine exhibited elevated UBC9 expression, suggesting its potential as a target for intervention in cardiac hypertrophy. A distinct clustering of proteins with both positive and negative correlations underscores the intricate interplay and potential regulatory relationships among them. This observation suggests that there might be a delicate balance in the regulatory relationships between these proteins. Such correlation profile could be indicative of a sophisticated regulatory mechanism, where subtle shifts in one protein's expression influence the others. Furthermore, the network distinctly delineates a cluster of proteins characterized by both positive and negative correlations. This distinct

clustering underscores the intricate interplay and potential regulatory relationships.

The enrichment analysis validated the importance of associated genes in hypertension. It highlighted genetic pathways and group functions linked to the cardiovascular system. Notable associations: biological pathway with blood vessel maturation, tissue category with blood vessel cells (Fig. 5A). Such information could give us a hint that these blood cell maturation and differentiation processes play a pivotal role in hypertension. Research indicates that an expedited biological maturation is linked to elevated blood pressure, the onset of arterial hypertension, and the emergence of cardiovascular disease in later stages of adulthood [22]. This is a current focal point of discussion in the context of children diagnosed with primary hypertension. Additionally, the gene enrichment analysis provided insights into extensively studied genes with versatility across biological pathways (Fig. 5B), including Well-known genes (*C3, ADIPOQ, Notch1, VCAM1*) associated with hypertension. For example, the famous Endothelial Notch1, which is known to be crucial in vascular development, appears to be prominent in the gene frequency distribution across diverse biological pathways. In a 2019 article by Babicheva and Yuan, the significance of Notch1 was thoroughly examined. It was revealed that *Notch1* is overexpressed in both humans and animals affected by pulmonary hypertension, with a specific emphasis on its crucial role in hyperproliferative and apoptotic-resistant endothelial cells [23]. Furthermore, the gene frequency analysis highlighted the *ADIPOQ* gene, which is also an important and well-studied factor for hypertension [24], obesity [25], and diabetes [26]. The *ADIPOQ* gene is linked to plasma adiponectin levels, and reduced adiponectin levels are associated with an increased risk of essential hypertension. Numerous studies have explored the connection between the *ADIPOQ* gene polymorphisms and factors like insulin resistance, adiponectin levels, and metabolic disorders, such as diabetes [27].

Our subsequent pathway and gene-disease enrichment analyses revealed interesting links between these proteins and cardiovascular health. As illustrated in Fig. 7, many of the identified proteins were further associated with coronary artery disease and atherosclerosis. These findings indicate that these proteins may serve not only as markers of blood pressure regulation but also as key players in the pathophysiology of cardiovascular diseases, potentially elucidating underlying mechanisms.

For example, NOTCH1 is critical for cardiovascular development. Although its direct link to hypertension is unclear, NOTCH1 may influence blood vessel structure and function, thereby contributing to hypertension through vascular abnormalities [23]. Similarly, CDH5, or Cadherin-5, is a protein localized in the endothelial cells lining blood vessels, playing an essential role in maintaining endothelial integrity. Dysfunction or variations in CDH5 may lead to endothelial dysfunction, a recognized risk factor for hypertension and other cardiovascular conditions [28, 29]. Interestingly, we also observed that APOE and BMP1 are intricately linked to the plasma lipoprotein pathway, which can exacerbate hypertension and vascular deterioration [30]. While several members of the peptidase M12A family of bone morphogenetic proteins (BMPs)—such as BMP2, BMP4, and BMP9—have established roles in pulmonary hypertension [31], the specific involvement of the BMP1 protein in this condition remains unclear.

Conclusion

Our study identified 28 proteomic biomarkers associated with blood pressure regulation in the Qatari population, including novel candidates QORL1 and BMP1. These biomarkers reveal critical pathways in vascular biology, endothelial integrity, and lipid metabolism, linking hypertension to broader cardiovascular conditions such as coronary artery disease and atherosclerosis.

Enrichment analyses underscored pathways related to blood vessel maturation and immune modulation, while protein interaction networks identified Notch1, CDH5, and APOE as pivotal players in hypertension pathogenesis. These findings not only validate established mechanisms but also provide new insights into the molecular complexity of blood pressure regulation.

Despite the study's strengths, including the application of advanced proteomic profiling, the findings require validation in larger, more diverse populations to enhance their translational potential. This work lays the foundation for biomarker-driven approaches to risk assessment and precision therapeutics, offering new pathways to address the global burden of hypertension.

Abbreviations

Apo E	Apolipoprotein E
BMI	Body mass index
BMP	Bone morphogenetic proteins
BP	Blood pressure
EH	Essential hypertension
HDP	Hypertensive disorders of pregnancy
MAP	Mean arterial pressure
MMP2	Matrix metalloproteinase 2
MMP7	Matrix metalloproteinase 7
PAPP-A	Pregnancy-associated plasma protein-A
RAAS	Renin–angiotensin–aldosterone system

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12014-024-09519-z.

Supplementary Material 1. Qatar biobank proteomics association analysis summary statistics (TSV).

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Author contributions
The study was designed and supervised by H.Z., C.M. and P.K., the methodology, data processing and data analysis was performed by R.S.A. and A.M.A. The manuscript was written by R.S.A. and A.M.A., and revised by H.Z., C.M. and P.K. Final critical editing and communication with the Editor was done by HZ.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Institutional Review Board of the Qatar Biobank (QF-QBB-RES-ACC-00095) and carried out according to the Declaration of Helsinki. A written consent was obtained for all participants to share their data.

Competing interests
The authors declare no competing interests.

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