

Exploring the Plasma Proteome Networks: Unravelling Insights into Ischemic Stroke Pathophysiology

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INTRODUCTION

Ischemic Stroke (IS), a devastating cerebrovascular event, remains a leading cause of death and disability worldwide. It occurs when a blood clot blocks an artery supplying blood to the brain, leading to a sudden loss of blood flow and oxygen deprivation. The resulting tissue death can cause a range of neurological impairments, impacting everything from movement and speech to cognitive function and emotional regulation.¹⁻³ The severity of the stroke and the individual's long-term prognosis depend on various factors, including the location and size of the blockage, the duration of blood flow interruption and pre-existing health conditions.^{4,5} Despite significant advancements in stroke management, early and accurate diagnosis is crucial for maximizing treatment efficacy and minimizing long-term complications.^{6,7} Traditionally, stroke diagnosis relies heavily on clinical assessment tools like the National Institutes of Health Stroke Scale (NIHSS) and neuroimaging techniques such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).^{6,7} However, these methods have limitations. Clinical assessment can be subjective and may be unreliable in patients with limited communication abilities. While neuroimaging provides valuable information about brain damage, it often takes time to acquire and interpret, delaying critical treatment decisions.^{8,9} This is where the concept of reliable biomarkers for IS risk emerges. Biomarkers are objectively measurable biological characteristics that can reflect underlying biological processes associated with a disease state.^{10,11} In the context of IS, reliable biomarkers have the potential to revolutionize stroke care by offering several distinct advantages, including early detection, improved diagnosis, objective IS Risk stratification, prognosis prediction, treatment monitoring and developing effective prevention strategies. Recent advancements in plasma proteomics offer a promising avenue to gain novel insights into the complex mechanisms involved in IS.

The quest for reliable biomarkers for IS risk has gained significant momentum in recent years. Researchers are exploring a vast array of potential candidates, encompassing various biological domains.¹⁰⁻¹² The genetic markers using the Genome-Wide Association Studies (GWAS) aim to identify specific gene variants that increase susceptibility to IS. While some promising associations have been found, the complex interplay of genes and environmental factors necessitates further investigation in this area. Blood-based biomarkers are most preferred options due to their agility and cost effectiveness.¹³ Several blood proteins, inflammatory markers and cellular components are being investigated for their association with IS risk and severity. Imaging biomarkers are also being explored using advanced neuroimaging techniques to identify subtle changes in brain structure or function that may precede or accompany IS.^{6,7} This research holds promise for identifying high-risk individuals even before they experience a stroke. Last but not the least, electrophysiological biomarkers have also been looked at using Electroencephalogram (EEG) or Evoked Potential (EP) abnormalities as indicators of increased stroke risk.¹⁴ These non-invasive tests could offer valuable insights into brain functionality. In a recent study conducted by Kalani *et al.*,¹⁵ the relationship between the plasma proteome and IS risk was investigated using data from the Cardiovascular Health Study (CHS). The findings shed light on significant associations between specific plasma proteins and IS risk, presenting an opportunity for future advancements in stroke prevention and management.

Unveiling Biomarkers: NTproBNP and MMP12

Among the extensive panel of plasma proteins evaluated, N-Terminal probrain natriuretic peptide (NTproBNP) and Macrophage Metalloelastase (MMP12) emerged as independent predictors of IS risk in this recent study. The association of NTproBNP with IS risk aligns with previous research that has established its role as a reliable biomarker for cardiac stress and dysfunction.¹⁶ NTproBNP is released by the heart in response to increased ventricular wall stress and elevated levels are indicative of underlying cardiovascular abnormalities. The findings of this study reinforce the significance of NTproBNP in predicting the occurrence of IS, highlighting the importance of incorporating cardiac evaluations into stroke risk assessments. Detecting



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elevated NTproBNP levels could prompt further investigation and interventions to mitigate the risk of stroke.

On the other hand, the identification of MMP12 as an independent biomarker for IS risk sheds light on the involvement of inflammatory processes in stroke pathogenesis. MMP12 is an enzyme produced by macrophages and is known to contribute to tissue remodelling and degradation.¹⁷⁻¹⁹ In the context of stroke, increased MMP12 levels indicate heightened inflammation and matrix remodelling in the vasculature. Chronic inflammation plays a crucial role in atherosclerosis, the main underlying cause of ischemic stroke. MMP12 has been implicated in the breakdown of extracellular matrix proteins within atherosclerotic plaques, potentially leading to plaque instability and subsequent stroke events.^{20,21} However, there is a need for research specifically focused to elucidate the precise mechanisms by which MMP12 contributes to stroke development. Understanding the intricate interplay between inflammation, matrix remodelling and the pathogenesis of IS could unveil novel therapeutic targets. Targeting MMP12 or modulating its activity might hold promise in preventing or attenuating the progression of atherosclerosis and reducing the risk of IS. However, extensive investigations, including preclinical and clinical studies, are necessary to fully comprehend the potential of MMP12 as a therapeutic target in stroke management.

Sex and Racial Disparities

The evaluation of associations in subgroups defined by sex and race is a crucial aspect of the study on plasma proteomics and ischemic stroke risk.¹⁵ The consistent associations of NTproBNP and MMP12 with IS risk across these subgroups underscore the robustness of these biomarkers in predicting stroke, irrespective of gender or race. The finding that NTproBNP and MMP12 are independently associated with IS risk in both men and women is significant. It demonstrates that these biomarkers have consistent predictive value for stroke in both sexes. This highlights the universal relevance of these biomarkers in stroke risk assessments, regardless of gender. Incorporating NTproBNP and MMP12 measurements into risk stratification models can aid in identifying individuals at higher risk of stroke, enabling targeted preventive interventions.

Similarly, the study's observation of consistent associations in black and non-black participants emphasizes the generalizability of these biomarkers across racial backgrounds. Stroke is known to exhibit disparities across different racial and ethnic groups, with variations in incidence, risk factors and outcomes.²²⁻²⁴ The consistent associations of NTproBNP and MMP12 with IS risk in both racial subgroups suggest that these biomarkers transcend racial differences and remain informative predictors of stroke risk.¹⁵ This finding highlights the potential of these biomarkers to contribute to inclusive stroke prevention strategies that are applicable to diverse populations. By demonstrating the consistent

associations of NTproBNP and MMP12 with IS risk across sex and race subgroups, this study emphasizes the importance of personalized approaches in stroke risk assessments. Stroke risk assessment tools that consider individual characteristics and biomarkers can enable tailored interventions to mitigate stroke risk based on an individual's unique profile. The robustness of NTproBNP and MMP12 in predicting stroke across diverse populations underscores their potential utility in developing personalized stroke prevention strategies. Furthermore, this finding underscores the need for inclusive approaches in stroke prevention. By identifying biomarkers that hold predictive value for stroke across sex and racial subgroups, the study highlights the importance of considering diverse populations in research and clinical practice. Inclusive approaches in stroke prevention can help address disparities and ensure that preventive interventions are effective and equitable for all individuals, regardless of gender or race.

Subtype-Specific Associations and Left Atrial Dysfunction

The analysis of subtype-specific associations in the study provided valuable insights into the distinct protein signatures associated with cardioembolic and noncardioembolic IS.¹⁵ By identifying these subtype-specific protein patterns, the study opens avenues for tailored preventive interventions and targeted therapies based on the underlying mechanisms of each stroke subtype. The identification of specific protein signatures associated with cardioembolic IS is particularly significant. Cardioembolic strokes are caused by blood clots that originate from the heart, often associated with conditions such as atrial fibrillation.^{25,26} The study found that NTproBNP was independently associated with incident cardioembolic IS. NTproBNP is a well-known biomarker for cardiac stress and dysfunction.¹⁶ Its association with cardioembolic stroke reinforces the importance of cardiac evaluations in stroke risk assessments, as elevated NTproBNP levels can indicate underlying heart conditions that may increase the risk of cardioembolic stroke. These findings suggest that monitoring NTproBNP levels could help identify individuals at higher risk of cardioembolic stroke, allowing for targeted preventive interventions such as anticoagulant therapy or interventions to manage atrial fibrillation.^{27,28}

In contrast, the identification of Secreted Frizzled-Related Protein 1 (SFRP1) as a protein associated with IS risk in individuals with left atrial dysfunction, even in the absence of atrial fibrillation, is intriguing.²⁹ Left atrial dysfunction refers to impaired functioning of the left atrium, which can be caused by various factors such as structural abnormalities or impaired contractility. The association of SFRP1 with IS risk in this specific subgroup suggests that this protein may serve as a potential biomarker for risk stratification in individuals with left atrial dysfunction. This finding highlights the importance of considering both clinical parameters (such as left atrial dysfunction) and proteomic markers (such as SFRP1)

in individualized stroke risk assessments. Incorporating such biomarkers into risk stratification models may enable more accurate identification of individuals at higher risk of stroke, allowing for targeted preventive interventions and closer monitoring.

Implications for Stroke Prevention and Future Directions

The study by Kalani *et al.*,¹⁵ marks a significant step forward in our understanding of the plasma proteomic landscape and its relevance to IS risk prediction. The identified biomarkers, NTproBNP and MMP12, hold promise as potential targets for therapeutic interventions and risk stratification in stroke. However, the search for reliable biomarkers for IS risk faces several challenges. IS is a complex and heterogeneous disease with diverse underlying causes and presentations.¹⁻³ A single biomarker may not capture the full spectrum of stroke risk across different populations. Biomarkers need to be highly specific for IS, as they should not be elevated in other neurological conditions. Additionally, they should be sensitive enough to detect even a slightly increased risk of stroke, allowing for risk stratification. Promising results from initial studies need to be rigorously validated in larger, multi-centre trials to ensure the biomarker's generalizability and robustness across different populations and clinical settings. The cost of implementing a new biomarker test needs to be weighed against its clinical utility. Cost-effective biomarkers are more likely to be widely adopted in real-world practice. Despite these challenges, the potential benefits of reliable biomarkers for IS risk are immense. Further investigations into the mechanisms of biomarker proteins in stroke pathophysiology are warranted, including elucidating their roles in inflammation, cardiac dysfunction and vascular remodelling. Continued research in this field holds the promise of revolutionizing stroke prevention, diagnosis and treatment, ultimately leading to improved patient care and a significant reduction in the burden of stroke on individuals, healthcare systems and society. Integrating proteomic approaches into clinical practice has the potential to revolutionize stroke risk assessment, enabling more accurate prediction and targeted interventions. Future studies should aim to validate these findings in larger cohorts and explore the utility of proteomic profiling in clinical decision-making, therapeutic development and monitoring treatment response.

CONCLUSION

In conclusion, the study by Kalani *et al.*,¹⁵ provides compelling evidence supporting the relationship between the plasma proteome and IS risk. The identification of NTproBNP, MMP12 and subtype-specific associations opens new avenues for personalized stroke prevention and management. By harnessing the power of plasma proteomics, we are one step closer to unravelling the complexities of IS pathophysiology and developing innovative strategies to combat this devastating disease.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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