Stroke

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Multiomic approaches to stroke: the beginning of a journey

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Using integrative multiomics, a new study has shed light on the aetiology of ischaemic stroke. By probing the mechanisms underlying stroke, such approaches could aid the development of therapies and improve risk prediction and stratification, with the ultimate aim of developing personalized preventive and therapeutic strategies.

Refers to Jung, J., Lu, Z., de Smith, A. & Mancuso, N. Novel insight into the aetiology of ischaemic stroke gained by integrative multiome-wide association study. *Hum. Mol. Genet.* https://doi.org/10.1093/hmg/ddad174 (2023).

Stroke is a leading cause of death worldwide and is also a major source of disability, cognitive decline and dementia, imposing a heavy burden on individuals and society. It is also an extremely heterogeneous condition, with numerous common and rare subtypes, and specific mechanism-based therapies are currently lacking for many of these subtypes. As for other complex diseases, researchers are increasingly leveraging genomics, in the form of genome-wide association studies (GWASs), to decipher the mechanisms underlying stroke and its subtypes, accelerate therapeutic developments and improve risk prediction and stratification, with the ultimate aim of developing personalized preventive and therapeutic strategies. In a new paper published in *Human Molecular Genetics*, Jung et al.[1] shed new light on the aetiology of ischaemic stroke by conducting integrative multiome-wide association studies.

> "researchers are increasingly leveraging genomics ... to decipher the mechanisms underlying stroke"

Retrospective studies have estimated that genetic evidence for drug effects is likely to increase the success rate of clinical trials greater than twofold and provides support for nearly two-thirds of the new drugs approved by the US Food and Drug Administration in the past decade[2]. The ability to link genomics to other affordable omics technologies, including epigenomics, transcriptomics, proteomics and metabolomics, using integrative multiomic analytical approaches is creating new opportunities to enhance the discovery of relevant genes, prognostic biomarkers, molecular mechanisms and tissue-specific and cell-specific causal pathways that underlie genetic associations with stroke[3].

Jung et al.'s journey began with publicly available summary statistics of the largest published GWAS of stroke, GIGASTROKE[4], which they integrated with a combination of molecular quantitative trait loci (QTL), including various types of transcriptomics in up to 50 different tissues, as well as blood-based proteomics[1]. Within the stroke GWAS, they focused on the subset of individuals who were incorporated into analysis of any ischaemic stroke (62,100 patients and 1,234,808 controls) and who were of European ancestry, so as to match the ancestry background of the QTL resources.

Using a suite of state-of-the-art analytical tools, including transcriptome-wide association studies (TWASs), phenome-wide association studies, colocalization analyses, Mendelian randomization and genetic correlation, the researchers identified 136 genes, non-coding enhancer RNAs or proteins associated with ischaemic stroke risk across 60 independent genomic regions. Nine genes expressed in stroke-relevant tissues were prioritized using probabilistic fine-mapping[5]. Application of the Trans-Phar tool[6], which integrates TWAS data with a database of pharmacological perturbations of gene expression, highlighted deoxycholic acid as a potential therapeutic agent for ischaemic stroke. Moreover, the study provided evidence for shared genetic contributions to reticulocyte counts and ischaemic stroke, whereas Mendelian randomization did not reveal a causal relationship.

Although several of these approaches were previously implemented in GIGASTROKE[4], Jung et al. updated and augmented the existing molecular QTL resources while also introducing complementary methodologies[1]. For TWASs and proteome-wide association studies (PWASs), they used expression QTL (eQTL) and splicing QTL (sQTL) from a more recent version than in GIGASTROKE, together with brain enhancer eQTL and blood protein QTL (pQTL) data from several large cohorts to boost power. Moreover, the researchers analysed aggregated gene expression across all tissues, whereas GIGASTROKE focused solely on vascular and brain tissues. The new approach produced a larger number of TWAS and PWAS associations, especially between ischaemic stroke risk and eQTLs in arterial and brain-related tissues. Extending the TWAS framework from gene expression to other transcriptomic data types (sQTL and enhancer eQTL) is an important and original contribution.

The emphasis that the authors put on the convergence of findings from different omics sources and methodologies is a conservative choice, prioritizing robustness of results. Overall, 71% of genes and proteins identified in GIGASTROKE were also found by Jung et al., and the TWAS effect sizes correlated strongly between the two studies. Among the nine genes that emerged from the TWAS fine-mapping, several, including *F11*, *MMP12* and *FOXF2* (refs. 4,7), had previously been highlighted as targets to pursue for stroke prevention and treatment. It is

tempting to speculate that a link exists between reticulocyte function and thrombosis in stroke, although the magnitude of genetic correlation is small and the potential underlying biology remains unknown.

Despite advancing the analysis of common variant susceptibility in stroke by introducing new multiomic data types, Jung et al.'s report[1] represents only a preliminary new step towards understanding mechanisms that might inform future preventive or therapeutic strategies. The restriction of analyses to participants with European ancestry illustrates the even greater lack of diversity for multiomics than for genomic approaches, calling for concerted efforts to generate and share more GWAS and molecular QTL resources from other ancestry groups. Although novel transcriptomic dimensions were included, several layers of multiomics, for example, epigenomics and metabolomics, were not considered. Epigenomic data could potentially address cell type-specific and temporal (for example, developmental) mechanisms and aid fine mapping[8]. Deoxycholic acid, which was presented as a possible therapeutic lead for ischaemic stroke, is a bile acid metabolite and could be investigated further using metabolomic approaches.

"The study ... illustrates how multiomics might be used to inform the prevention of and the clinical care of people with stroke"

The new study[1] did not advance the identification of cell-specific gene expression pathways for stroke risk, for example in vascular or liver cells, which might reflect arterial or metabolic functions, even though such analyses had been initiated in GIGASTROKE[4]. Moreover, the study could have attempted integration across implicated loci through formal pathway analysis with statistical support rather than solely through overlap of evidence from the separate multiomic modalities[9]. Ultimately, these omissions are relatively minor detractions from the wealth of findings. However, it is perhaps surprising that the authors did not compare and contrast their multiomic approach across subtypes of stroke, given the substantial mechanistic heterogeneity of this condition, especially as subtype analysis was explicitly emphasized in the GIGASTROKE study[4].

With the ever-increasing number and size of genomic and multiomic resources, combined with the development of novel artificial intelligence-based methods, we need guidance on where to direct research investment most efficiently. The work by Jung et al.[1] provides a glimpse into the staggering combinatorics that we can expect in the near future. However, one might argue that instead of introducing more multiomic approaches, the science should start to be driven by hypotheses, including in silico and experimental follow-up of the most robust leads that are being discovered. Without hindering unbiased approaches, disciplined reconciliation of big data findings with clinical expertise is also warranted.

The study by Jung et al.[1] illustrates how multiomics might be used to inform the prevention of and the clinical care of people with stroke. Given converging evidence that multiple co-existing pathologies, including neurovascular pathologies, contribute to other common and disabling age-related brain diseases such as dementia, combining multiomics of stroke and vascular brain disease with multiomics of neurodegenerative and neuroinflammatory conditions will also provide unprecedented opportunities to derive more comprehensive disease signatures and enable multitargeted personalized therapies[10]. To harness this huge potential, an urgent need exists to develop interdisciplinary expert guidance, possibly overcoming boundaries between academia and industry, in order to optimize resources, accelerate experimental validation of the most robust findings and, ultimately, enable the uptake of these findings in drug development pipelines. Jung et al. have taken an important step on the journey towards deeper mechanistic insights that could help to relieve the burden of stroke.

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Competing interests

The authors declare no competing interests.