Invited Contribution

Advances in stroke genetics, genomics and precision medicine

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Non-standard Abbreviations and Acronyms

CSVD, cerebral small vessel disease

GWAS, genome-wide association studies

WMH, White matter hyperintensities

GRS, genomic risk score

BP, blood pressure

MR, Mendelian randomization

IA, intracranial aneurysm

IL-6, interleukin-6

TEXT

Ever more refined and statistically powerful genome-wide association studies (GWAS) continue to advance our understanding of the relationship between genetic variations and stroke risk. A study involving more than 7000 patients with MR-confirmed lacunar stroke found five loci that were associated with the lacunar stroke phenotype and an additional seven associated loci in a multi-trait analysis including cerebral white matter hyperintensities (WMH).[1] Two loci contained genes causing monogenic disorders (*COL42A* and *HTRA1*). Complementing these results, investigators have focused on the assessment of imaging phenotypes reflecting cerebral small vessel disease (CSVD). The first study found 34 genetic risk loci across three MRI traits (WMH volume and two diffusion-tensor imaging markers).[2] Some associations were confined to either WMH volume or diffusion-tensor imaging markers, while others were shared by all three traits. The nature of the loci support involvement of the cerebrovascular matrisome and inflammatory mechanisms. The second study found 27 genetic risk loci for WMH volume.[3] About 30 percent of the WMH volume variance was explained by common and low frequency variants. Over half of the loci are associated with higher blood pressure (BP) levels. The associations of genetically predicted BP remained significant after adjustment for hypertension, suggesting that higher BP levels remain a risk factor for larger WMH volume even below thresholds typically used to define hypertension.

Among the most important findings in 2020 is the identification of multiple risk loci for intracranial aneurysms (IA) through a GWAS in more than 10.000 IA cases and 300.000 controls (N=17 loci, 11 new).[4] This study further demonstrated a high genetic correlation between ruptured and unruptured IA. An assessment of potentially causative genes in combination with bioinformatic analyses highlighted the role of endothelial cells in the pathogenesis of IAs. The study also uncovered a genetic overlap of IA with abdominal aortic aneurysm and stroke, which was largely accounted for by genes implicated in BP regulation

and smoking.[4] Collectively, these findings emphasize avenues for prevention while also guiding future research into basic disease mechanisms.

Large-scale exome sequencing and targeted sequencing have allowed further investigation of the relationship of variants in genes related to single-gene disorders with sporadic stroke and cerebrovascular disease. Drawing on ~200.000 participants from the UK biobank, a recent study found that roughly one in 450 individuals harbored a cysteine-altering *NOTCH3* variant and that these variants, particularly those located in epidermal growth factor repeat domains one through six, are associated with stroke, vascular dementia and imaging markers of CSVD.[5] Homozygous and compound heterozygous mutations in the *HTRA1* gene have been identified as a cause of familial stroke and vascular dementia. Whole-exome gene-based burden testing applied to data from ~17.000 UK biobank participants found missense and loss-of-function variants in *HTRA1* to be associated with WMH burden.[6] Domain specific burden testing revealed that the association was limited to variants in the protease domain (amino acids 204-364) and that the majority of these variants result in markedly reduced protease activity. Rare mutations usually affecting glycine residues in Gly-Xaa-Yaa triplet repeats in collagen IV alpha chain 1 and 2 (COL4A1/A2) cause a Mendelian early onset stroke syndrome. Targeted sequencing of these genes in sporadic patients with intracerebral haemorrhage and in healthy controls identified two missense mutations that were associated with intracerebral haemorrhage.[7] Taken together, these findings highlight the importance of rare variants in sporadic stroke and cerebrovascular disease.

Progress has further been made on genomic risk scores (GRS). Such scores offer the potential to personalize risk prediction, surveillance programs and prevention strategies years or even decades before the typical age for manifestation of conventional risk factors. Among the latest developments is a meta-GRS derived from multiple GRS for individual traits including ischemic stroke, small vessel disease, and classical risk factors such as low density lipoprotein, atrial fibrillation and coronary artery disease.[8] The predictive power of the new

meta-GRS was twice as high than that of the prior best ischemic stroke GRS. It was comparable to BP, and higher than most other risk factors. Individuals in the top 0.25 percent of the meta-GRS had a 3-fold increase in ischemic stroke risk comparable to a monogenic level of risk (e.g. to carriers of a cysteine-altering *NOTCH3* variant[5]). Efforts to improve the prediction of venous thrombosis have likewise led to the development of GRS with improved predictive power,[9] a development that is expected to continue as additional genetic information accrues.

Natural sequence variation in genes encoding drug targets is increasingly being used to understand the efficacy and side effects of existing drugs and to prioritize drug targets for future drug development. Mendelian randomization (MR) applied to 7 genetic variants in the interleukin-6 (IL-6) receptor locus showed similar effects on up- and down-stream molecules in the IL-6 signaling pathway as IL-6 receptor inhibitors in clinical trials (e.g., tocilizumab).[10] Genetic downregulation of IL-6 signaling was associated with, among other aspects, lower risk of atherosclerotic phenotypes, lower glycated haemoglobin, and higher risk of neutropenia and infections. Directly translating these results to drug effects has limitations. The IL-6 cascade has a classical and trans-signaling component and disentangling the respective effects is beyond the limits of MR. Further, MR assesses lifelong effects, whereas drug therapies can be applied short-term. Genomic information can further be used to compare effects and side effects of categories of drugs. Using genetic proxies for angiotensin-converting enzyme inhibitors, beta blockers and calcium channel blockers, investigators confirmed differential effects of individual drug categories on risk of stroke and cardiovascular disease seen in trials.[11] Additionally, they identified a potential adverse effect of nondihydropyridine calcium channel blockers on the risk of diverticulosis.

In an effort to identify novel drug targets for stroke prevention, MR has further been applied to the circulating proteome. A study on 653 circulating biomarkers found seven proteins (five known; two novel) that significantly associated with at least one ischemic stroke subtype.[12]

These proteins were then tested for association with hemorrhagic stroke subtypes and results tested in an extended phenome-wide MR analysis. The multistage analysis identified scavenger receptor class A5 (SCARA5) as a candidate drug target for preventing cardioembolic stroke.[13] The field of stroke genets is moving at a rapid pace. The next challenge is to translate recent discoveries into clinical applications.

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DISCLOSURES

None.

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