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Pairing Neuropathology with Genetics: A New Tool for Parsing Cerebrovascular Disease

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In this issue of *Cerebrovascular Diseases*, Chou et al. [1] report the findings from their review of genetic data from a unique resource, the combination of the complementary Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP). The authors leveraged these databases to investigate genetic susceptibility for microscopic infarctions (clinically, leukoaraiosis), macroscopic infarctions (clinically, discrete ischemic infarcts) and small-vessel arteriosclerosis. In terms of the advancement of the study of stroke genetics, this is very exciting. To have neuropathologic data paired 1:1 with genomic data is to open a vast expanse of future research possibilities, especially given that the ROS and MAP continue to accrue data [2].

The preliminary data presented in this publication provide a glimpse at the kind of information that we may glean from future iterations. However, in their current form they are somewhat limited in their opportunity to be translated into clinically meaningful information regarding genetic susceptibility for both the neuropathologic outcomes studied as well as for ischemic stroke more broadly. Most concretely, we must recognize that, after correction for multiple variables, none of the primary or secondary outcomes reached statistical significance. Previous work discovering and replicating susceptibility loci for ischemic stroke required data sets of multiple thousands of patients [3–5], indicating that the current study lacks sufficient power to home in on established genetic risk for stroke or its myriad risk factors. As the database expands, further prospective studies will undoubtedly yield better-powered results.

Given the relatively small sample size, the authors were unable to stratify results by the presence or absence of cervical arterial atherosclerosis, intracranial large vessel atherosclerosis and/or atrial fibrillation. While the ROS and MAP both have data pertaining to the two former criteria, allowing the potential for later investigation when the sample size permits, data regarding clinical history of atrial fibrillation is lacking in both, which limits the abil-

ity to gain novel understanding of genetic susceptibility for cardio-embolic stroke (and in that vein, it is not surprising that the authors did not replicate the finding of PITX2 or ZFHX3 as susceptibility loci for ischemic stroke or atrial fibrillation). We remain optimistic that further study of genetic susceptibility for strokes of large-vessel atherosclerotic as well as lacunar subtypes can yield important insights.

Further stratification of those grouped as ‘macroscopic infarcts’ into cortical and subcortical location may allow better understanding of genetic risk as it pertains to strokes of differing subtypes. We know, for example, that the clinical risk factors for lacunar strokes are different than those for thromboembolic strokes [6, 7] and, as such, one might expect the genetic susceptibility to vary similarly. Only with a much larger sample size, particularly inclusive of a greater number of patients with clinical history of stroke, will we gain the ability to investigate these groups with sufficient power.

Overall, this is very promising work. The pairing of genomic and neuropathologic data represents a novel avenue of stroke genetics research, one that has the potential to teach us a great deal regarding genetic susceptibility for specific ischemic stroke subtypes. Though the study as presented is limited by a relatively small sample size, further investigation in the arena should be pursued with zeal in the search for genetic data that could herald a meaningful change in the clinical practice of ischemic stroke.

References

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