Novel Insights Into the Genetics of Intracerebral Hemorrhage

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Isolated observations suggest a role for genetic risk factors in intracerebral hemorrhage (ICH). However, no systematic evaluation on the role of DNA variation in ICH has been attempted to date. We performed a large-scale genetic association study of 2189 ICH cases and 4041 controls. We included 1104 ICH cases attributable to cerebral amyloid angiopathy (CAA-ICH) and 1085 hypertensive ICH cases (H-ICH). Recently developed methods were used to determine heritability from unrelated ICH cases and controls. We also analyzed clinical ICH phenotypes: these included admission ICH volume (quantified on computed tomography scan), hematoma expansion (on follow-up computed tomography scan), and functional independence and mortality at 90 days post-ICH. We tested single variants across the entire genome (at genome-wide significance threshold of $P<5.0\times10^{-8}$). We also tested 2 genetic risk scores, summarizing the effect of known hypertension and Alzheimer disease risk loci. We estimated heritability of 45% for ICH, 70% for the CAA-ICH subset, and 35% for the H-ICH subset. *Apolipoprotein E* ε2/ε4 were associated with CAA-ICH at genome-wide significance levels (odds ratio [OR]=1.82; $P=6.6\times10^{-10}$ and OR=2.20; $P=2.4\times10^{-11}$, respectively). ε2 was also associated with larger admission CAA-ICH volume (hematoma size increase=5.3 cc per allele copy; $P=0.004$) and with CAA-ICH hematoma expansion (OR=2.72; $P=0.009$). We also found associations between *apolipoprotein E* ε2 and functional independence (OR=0.68; $P=0.009$) and mortality (OR=1.57; $P=0.021$) after CAA-ICH. A genetic risk score summarizing the effects of all known Alzheimer disease loci was associated with CAA-ICH (OR=1.22 for each of the 11 incorporated variants; $P=2.2\times10^{-5}$). This was largely mediated by one variant in the *CR1* gene (OR=1.61; $P=8.0\times10^{-4}$), which was also associated with CAA-ICH recurrence (hazard ratio=1.35; $P=0.024$). A genetic risk score summarizing the effects of all known hypertension loci was associated with the risk of H-ICH (OR=1.18 of each of 40 incorporated variants; $P=0.001$) but not CAA-ICH ($P=0.34$). We provided the first quantitative assessment of ICH heritability. We also identified aolipoprotein E ε2/ε4 as risk factors for CAA-ICH at genome-wide level. ε2 is also associated with CAA-ICH volume and outcome. Another Alzheimer disease–related locus, *CR1*, also influences CAA-ICH incidence and recurrence. Conversely, hypertension loci play a role in H-ICH risk but not in CAA-ICH. Our results confirm the suspected clinical and etiopathogenetic heterogeneity of ICH: amyloid-related processes influence incidence and clinical course of CAA-ICH, whereas hypertension genetics play a major role in H-ICH.

Disclosures

None.

Key Words: ApoE ■ Cerebral Amyloid Angiopathy ■ hypertension ■ intracerebral hemorrhage ■ population genetics

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