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 \( \epsilon_2/\epsilon_4 \) was 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). \( \epsilon_2 \) 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 \( \text{apolipoprotein E} \ \epsilon_2 \) 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; \( P=2.2\times10^{-11} \)). This was largely mediated by one variant in the \( \text{CR1} \) 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 \( \text{apolipoprotein E} \ \epsilon_2/\epsilon_4 \) as risk factors for CAA-ICH at genome-wide level. \( \epsilon_2 \) is also associated with CAA-ICH volume and outcome. Another Alzheimer disease–related locus, \( \text{CR1} \), 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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