Novel Insights Into the Genetics of Intracerebral Hemorrhage

Alessandro Biffi, MD; Christopher D. Anderson, MD; Guido J. Falcone, MD; Brett Kissela, MD; Bo Norrving, MD; David L. Tirschwell, MD, MSc; Magdy Selim, MD; Devin L. Brown, MD, MS; Scott L. Silliman, MD; Bradford B. Worrall, MD, MSc; James F. Meschia, MD; Chelsea S. Kidwell, MD; Joseph P. Broderick, MD; Steven M. Greenberg, MD, PhD; Jaume Roquer, MD, PhD; Arne Lindgren, MD; Agnieszka Slowik, MD, PhD; Reinhold Schmidt, MD; Daniel Woo, MD, MSc; Jonathan Rosand, MD, MSc; on behalf of the International Stroke Genetics Consortium

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 \( \varepsilon2/\varepsilon4 \) 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). \( \varepsilon2 \) 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 \( \varepsilon2 \) 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 apolipoprotein E \( \varepsilon2/\varepsilon4 \) risk factors for CAA-ICH at genome-wide level. \( \varepsilon2 \) 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
Novel Insights Into the Genetics of Intracerebral Hemorrhage
on behalf of the International Stroke Genetics Consortium

Stroke. 2013;44:S137
doi: 10.1161/STROKEAHA.113.001912
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/6_suppl_1/S137

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/