Published in final edited form as:

Eur J Neurol. 2015 November ; 22(11): 1488–1491. doi:10.1111/ene.12827.

Heritability of young- and old-onset ischemic stroke

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Disclosures

None

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Abstract

Background and Purpose—Although the genetic contribution to stroke risk is well known, it remains unclear if young-onset stroke has a stronger genetic contribution than old-onset stroke. This study aims to compare heritability of ischemic stroke risk between young and old, using common genetic variants from whole-genome array data in population-based samples.

Methods—This analysis included 4,050 ischemic stroke cases and 5,765 controls from 6 study populations of European ancestry; 47% of cases were young-onset stroke (age <55 years). To quantify the heritability for stroke risk in these unrelated individuals, we estimated the pairwise genetic relatedness between individuals based on their whole-genome array data using a mixed linear model. Heritability was estimated separately for young-onset stroke and old-onset stroke (age ≥ 55 years).

Results—Heritabilities for young- stroke and old-onset stroke were estimated at 42% ($\pm$ 8%, $P < 0.001$) and 34% ($\pm$ 10%, $P < 0.001$), respectively.

Conclusions—Our data suggest that the genetic contribution to the risk of stroke may be higher in young-onset ischemic stroke, although the difference was not statistically significant.

Introduction

Ischemic stroke (IS) is a complex genetic disorder caused by multiple genetic and environmental factors. The heritability of IS has been estimated at 38~39%, varying across stroke subtypes [1, 2]. Stronger familial aggregation of IS has been reported in younger vs older onset cases [3–5], implicating a stronger genetic component for the young-onset form of stroke, although familial aggregation studies are inherently limited by their potential for recall bias and inability to distinguish between shared environment and shared genes [6, 7]. In this study, we estimate the heritability of IS in younger vs older onset IS cases via estimating the similarity among individuals based on the actual genotypes across the genome using data from 6 population-based case-control studies of IS.

Materials and Methods

This study includes 4,050 IS cases and 5,765 controls from 6 studies: Australia Stroke Genetic Collaborative (ASGC), Genes Affecting Stroke Risk and Outcomes Study (GASROS), Genetics of Early-onset Stroke Study (GEOS), Ischemic Stroke Genetics Study (ISGS), Besta Cerebrovascular Diseases Registry (CEDIR), and Stroke in Young Fabry Patients (SIFAP). Stroke cases in each study were adjudicated by neurologists, with controls

free of stroke selected based on study-specific criteria (Supplemental Methods). Young-onset IS cases were defined as having an age of onset <55 years and old-onset stroke cases 55 years. GEOS and SIFAP by design included stroke cases < 50 and <55 years, respectively. Thresholds < 55 years would not have allowed a large enough sample size of young onset cases for analysis in the other studies.

All participating studies were conducted with the consent of study subjects and were approved by the Institutional Review Board at each institution.

All studies were genotyped by Illumina genome-wide single nucleotide polymorphism (SNP) arrays (see Table S1). Samples with unexpected duplicates, gender mismatch, genotyping call rate < 99% and outliers in population structure were excluded. SNPs with minor allele frequency < 1%, missing genotype calls > 5% and Hardy-Weinberg equilibrium p-value < 0.05 were removed prior to analyses. SNPs that passed quality control criteria were used to construct the genomic relationship matrix for each study using the Genome-wide Complex Trait Analysis (GCTA) tool [8]. Individuals with cryptic relatedness (relatedness value > 0.025 estimated using GCTA) were also removed from analysis.

Heritability, defined as proportion of phenotypic variance explained by genome-wide SNPs, was estimated using mixed model analysis that models the phenotypic covariance between any two individuals as a function of their degree of genomic relatedness conditioned upon other covariates (estimated as fixed effects). Covariates in the model included age, sex, and population substructure, where population structure was estimated within each study using principal component (PC) analysis. We tested models adjusting for 0, 2, 10 and 20 PCs and selected the best fitting model using the log likelihood ratio test, with the exception of ASGC study in which population substructure was evaluated but revealed no evidence for genomic inflation as previously published [2]. Heritability was estimated for IS cases <55 years and in cases 55 years separately. For each study, the heritability of the dichotomous trait was estimated as a continuous trait using the linear mixed model software MMAP [9], and then transformed to account for ascertainment bias as previously described by Lee et al [10]. Individual-study estimates were then meta-analysed using an inverse variance weighted approach implemented in the *metan* function implemented in STATA 10.1 (College Station, TX).

Results

Among the 4,050 cases, 1,917 were <55 years old and the remaining 2,133 were 55 yrs. (Online Supplemental Table I.) All study participants were of European ancestry.

To estimate the heritability of stroke liability, we assume a population prevalence of 1.11% for young-onset stroke and 5.76% for old-onset stroke based on data from the 2012 *Behavioral Risk Factor Surveillance System (BRFSS)*, Center of Diseases Control and Prevention, US (personal communication with Dr. Kurt Greenlund at Centers of Disease Control and Prevention). The heritability of IS was estimated at 42% ($P<0.001$) and 34% ($P<0.001$) in young- and older- onset IS cases, respectively (Table 1). In neither group was there evidence for heterogeneity among studies (Heterogeneity $I^2=0\%$). There was overlap

in the 95% confidence intervals surrounding these estimates. Results were virtually identical when the ISGC study, in which genotyping was performed on two arrays, was excluded from the meta-analysis (data not shown).

Because the disease prevalence may vary between populations, sensitivity analyses of heritability were performed by assuming various different population disease prevalence and results were summarized in Online Supplemental Table II. Results from sensitivity analyses also suggested a slightly higher heritability in young-onset stroke cases.

Discussion

Our approach of using genetic markers/SNP arrays to estimate heritability and contrasting relatedness between cases and controls provides a more direct contrast of the genetic component of younger vs older onset IS than can be obtained through familial aggregation studies. Compared to familial aggregation studies, marker-based estimates of heritability are also less prone to recall bias and to the confounding potential effects of shared environment. Because the marker-based approach is also based on unrelated individuals, ours is by far the largest study to contrast the genetic contribution to IS between young vs. old onset cases. Our results are consistent with a higher heritability of younger- vs older- onset IS (42% vs. 34%), although it should be noted that the 95% confidence intervals for these two estimates overlap. A direct statistical comparison of these estimates is not possible because they utilize the same set of controls.

Our study is subject to several limitations. First, the small numbers of specific stroke subtypes precluded our ability to address the very interesting question as to whether differences in heritability can be attributable to differences in the distribution of stroke subtypes between young vs. old cases. It has been reported that heritability estimates differ among stroke subtypes [1] and there are differences in the distribution of subtypes between subjects with young and old onset stroke (e.g., less large and small artery stroke in younger onset, see Supplemental Table III). Second, our analyses were based on a meta-analysis of studies that included subjects from different regions with different ascertainment methods, which may introduce additional variability to the estimates. Moreover, although early onset stroke is very uncommon, it is possible that some of the population-based controls may have had stroke. Lastly, the genotype-based heritability estimates rely on genotypes of common variants across the genome. The potential genetic contribution of rare variants on young-onset vs. old-onset stroke was not investigated.

In summary, our data suggests a slightly higher heritability of young-onset stroke, albeit not statistically significant. Further studies in larger samples investigating the genetic contribution to young-onset stroke controlling for stroke subtype are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources

This work was supported in part by funding from the U.S. Department of Veterans Affairs (1IK2BX001823 to Y.C. and a Merit Review Award to S.J.K), U.S. National Institute Health (grants U01 HG004436, U01 NS069208, and P30 DK072488, 5U01NS069208, NIA intramural project Z01 AG-000954-06), the Australian National Health and Medical Research Council (NHMRC; project grant 569257), the Australian National Heart Foundation (NHF; project grant G 04S 1623), the Cariplo Foundation (grant n. 2010/0253) and Italian Ministry of Health (grant n. RC 2007/LR6, RC 2008/LR6; RC 2009/LR8; RC 2010/LR8). The PROCARDIS control samples was funded by FP6 LSHM-CT-2007-037273. E.G.H. is supported by a fellowship (100071) from the Australian Heart Foundation and National Stroke Foundation.

References

1. Bevan S, Traylor M, Adib-Samii P, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations. *Stroke; a journal of cerebral circulation*. 2012; 43:3161–3167.
2. Holliday EG, Maguire JM, Evans TJ, et al. Common variants at 6p21.1 are associated with large artery atherosclerotic stroke. *Nat Genet*. 2012; 44:1147–1151. [PubMed: 22941190]
3. MacClellan LR, Mitchell BD, Cole JW, et al. Familial aggregation of ischemic stroke in young women: the Stroke Prevention in Young Women Study. *Genet Epidemiol*. 2006; 30:602–608. [PubMed: 16868965]
4. Jousilahti P, Rastenyte D, Tuomilehto J, Sarti C, Vartiainen E. Parental history of cardiovascular disease and risk of stroke. A prospective follow-up of 14371 middle-aged men and women in Finland. *Stroke; a journal of cerebral circulation*. 1997; 28:1361–1366.
5. Seshadri S, Beiser A, Pikula A, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. *Circulation*. 2010; 121:1304–1312. [PubMed: 20212282]
6. Jerrard-Dunne P, Cloud G, Hassan A, Markus HS. Evaluating the genetic component of ischemic stroke subtypes: a family history study. *Stroke; a journal of cerebral circulation*. 2003; 34:1364–1369.
7. Cheng YC, Cole JW, Kittner SJ, Mitchell BD. Genetics of ischemic stroke in young adults. *Circ Cardiovasc Genet*. 2014; 7:383–392. [PubMed: 24951665]
8. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet*. 2011; 88:76–82. [PubMed: 21167468]
9. Sun C, VanRaden PM, Cole JB, O'Connell JR. Improvement of prediction ability for genomic selection of dairy cattle by including dominance effects. *PLoS ONE*. 2014; 9:e103934. [PubMed: 25084281]
10. Lee SH, Wray NR, Goddard ME, Visscher PM. Estimating missing heritability for disease from genome-wide association studies. *Am J Hum Genet*. 2011; 88:294–305. [PubMed: 21376301]

Table 1

Heritability for young-onset versus old-onset IS.*

	Heritability (SE)	P
Young-onset Stroke (< 55 years)	0.42 (0.08)	<0.00001
Old-onset Stroke (≥55 years)	0.34 (0.10)	0.0008

* Estimated using population prevalence of disease = 1.11% for young-onset stroke and 5.76% for late-onset stroke based on 2012 US BRFSS data.