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Polygenic Risk for Depression Increases Risk of Ischemic Stroke: from the Stroke Genetics Network (SiGN) Study

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Abstract

Background and Purpose—While depression is a risk factor for stroke in large prospective studies, it is unknown whether these conditions have a shared genetic basis.

Methods—We applied a polygenic risk score (PRS) for major depressive disorder (MDD) derived from European ancestry analyses by the Psychiatric Genomics Consortium (PGC) to a GWAS of ischemic stroke in the NINDS Stroke Genetics Network (SiGN). Included in separate analyses were 12,577 stroke cases and 25,643 controls of European ancestry and 1,353 cases and 2,383 controls of African ancestry. We examined the association between depression PRS and ischemic stroke overall and with etiologic subtypes using logistic regression analyses.

Results—The depression PRS was associated with higher risk of ischemic stroke overall in both European (p=.025) and African ancestry (p=.011) samples from SiGN. Ischemic stroke risk increased by 3.0% (OR=1.03, 95%CI: 1.00–1.05) for every one standard deviation increase in PRS

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for those of European ancestry and by 8% (OR=1.08, 95%CI: 1.04–1.13) for those of African ancestry. Among stroke subtypes, elevated risk of small artery occlusion was observed in both European and African ancestry samples. Depression PRS was also associated with higher risk of cardioembolic stroke in European ancestry and large artery atherosclerosis in African ancestry persons.

Conclusions—Higher polygenic risk for MDD is associated with increased risk of ischemic stroke overall and with small artery occlusion. Additional associations with ischemic stroke subtypes differed by ancestry.

Keywords

stroke; depression; genetic association; polygenic risk; NINDS stroke genetics network

INTRODUCTION/BACKGROUND

Major depressive disorder (MDD) is one of the most common psychiatric disorders worldwide, with a lifetime prevalence estimated to be 15%[1, 2]. The prevalence of mild, moderate or severe depressive symptoms was 20% in a national representative sample of U.S adults, with 7% reporting moderate or severe symptoms[3]. Numerous large-scale epidemiological studies have demonstrated that MDD or depressive symptoms prospectively predict increased risk of stroke in Caucasian, Asian and African-American populations [45678]

Despite the consistency of multiple large cohort studies showing that a history of depression prospectively predicts incident stroke, the mechanisms underlying this association have not been elucidated. Specifically, little is known about whether depression is a general risk factor for stroke or a more specific risk factor for hemorrhagic or ischemic stroke. Further, depression may be a cause of stroke or a prodromal symptom of an impending stroke, may influence behaviors that increase risk of stroke, or may relate indirectly to other unknown factors that increase both depression and stroke risk.

Genetic studies offer an important opportunity to evaluate shared etiologic contributions to depression and stroke. Recent genome wide association studies (GWAS) have enabled the estimation of common variant heritability for complex traits (SNP heritability or h^2_{SNP}). Significant h^2_{SNP} estimates have been reported for both depression (~5–20%) [910] and stroke and its subtypes (~20–40%)[11–15,16]. In the present study, we used polygenic risk scores (PRS) derived from genetic analyses of MDD from the Psychiatric Genomics Consortium (PGC)[17] to examine whether genetic risk for depression is associated with ischemic stroke and its subtypes. As an alternative to testing the effects of individual SNPs, PRS have been commonly used to evaluate whether genetic risk for one condition (e.g., depression) is associated with risk for a second condition (e.g., stroke). A PRS is the weighted sum of individual SNP effect sizes derived from a GWAS. An association of the PRS with the second trait is typically interpreted as evidence for pleiotropy – i.e. a common set of genetic variants that jointly influence risk of both conditions.

PRS for depression have been created for different phenotypic definitions of depression [18]. A PRS for the clinical phenotype of MDD has been constructed by PGC's MDD Working

Group[17] where a GWAS was performed on a discovery sample of 11,625 individuals (4,984 cases of depression and 6,641 controls). In the present report, we applied this PRS to participants in the Stroke Genetics Network (SiGN) to test whether genetic risk for MDD is associated with risk of stroke. SiGN also includes adjudicated cases of stroke subtypes by presumed mechanism, allowing us to examine whether genetic predisposition to depression is associated with etiologic subtypes of stroke.

METHODS

Population: SiGN

The National Institute of Neurological Disorders and Stroke (NINDS) Stroke Genetics Network (NINDS-SiGN) was launched in 2010 to identify genetic loci associated with ischemic stroke and its subtypes. The design, rationale and primary GWAS findings from SiGN have been described elsewhere [19–21]. The present report is based on 13,930 ischemic stroke cases and 28,026 controls of European and African ancestry for whom a PRS for MDD was generated. Ischemic stroke cases were accrued from 24 genetic research centers across the United States and Europe. Among the 24 individual cohorts, informed consent procedures may have varied, but each had its own Institutional Review Board (IRB) approval. To remain compliant with IRB approvals at some sites, only summary statistics are publicly available at http://www.cerebrovascularportal.org/. A subset of the SiGN individual level data that is IRB compliant is available at dbGaP (phs000615.v1.p1). Requests for analysis of the full set of individual level data can be made through the authors (BDM).

All SiGN GWAS were adjusted for sex and the top ten principal components[21], after matching cases and controls within multiple analytic strata based on ancestry and genotyping platform as previously described[22].

Subtypes for ischemic stroke were standardized using the web-based causative classification of stroke system (CCS) that employs a validated algorithm to assign stroke subtypes according to presumed mechanism based on clinical and ancillary test findings, and was developed to maximize inter-examiner reliability in stroke classification while utilizing the full diagnostic data set from a typical “stroke work-up”. There are two major versions: CCS phenotypic (CCSp) and CCS causative (CCSc). The CCSp algorithm is a documentation of abnormal test findings and does not require judgments on the part of the adjudicator. CCSc involves the integration of symptoms, vascular risk factors, diagnostic test results, response to treatment, and prognosis, and thus requires a decision-making process. We present CCSp in this paper, but also present the results for CCSc in the Supplement.

Data were entered by trained and certified adjudicators at participating genetic research centers. TOAST (Trial of Org 10 172 in Acute Stroke Treatment) stroke subtype classifications were also available and the comparison between the CCS and TOAST classifications has been published[20], indicating that the overall agreement was moderate and varied widely across study sites, ranging from 28% to 90%. Furthermore, the inter-rater reliability of TOAST is considerably lower than that of CCS, with kappas ranging between 0.42 and 0.54 while CCS kappas range between 0.8 and 0.9[23–29]. Thus, in this paper we use CCS because it is a uniform classification system using algorithms that are applied across

many different international cohorts; however we also present the TOAST results in the Supplement.

Genotyping was conducted at the Center for Inherited Diseases Research, (CIDR). Strokes were classified as being due to: large artery atherosclerosis (LAA), small artery occlusion (SAO), cardioembolic (CE), other type or mixed type (Other), or cryptogenic (Crypto) undetermined or unknown usually due to insufficient workup or imaging).

Depression PRS and its application to SiGN participants

The depression PRS was derived from GWAS results from the Major Depressive Disorder Working Group of the PGC[17]. The PGC GWAS analyzed more than 1.2 million SNPs in 18,759 cases and controls. The full set of PGC GWAS results can be found at https://www.med.unc.edu/pgc/results-and-downloads. The PGC association results were generated for 123,025 independent SNPs based on linkage disequilibrium structure. MDD risk alleles were designated as the allele for each SNP associated with higher MDD risk. Alleles were weighted by their beta coefficients from the MDD association analysis. In the PGC analysis, multiple p value thresholds for the association of individual SNPs with MDD were applied for inclusion in the depression PRS (from $P_T = 0.001$ to 0.5). The p-value threshold of 0.5 performed best in the PGC test sample and was highly significant in predicting MDD (with $p<10^{-6}$), but accounted for only a small proportion of the variance with R^2 of 0.6%. The SNP weights generated by the PGC were then used to generate PRS for subjects in the SiGN dataset.

We extracted data for the PGC polygenic score SNPs from the SiGN data. For each SNP we converted the genotype posterior probabilities into single allelic dosages according to formula (1) below.

$$Allelic\ Dosage\ (AD) = 2 * p(AA) + 1 * p(AB) + 0 * p(BB) \quad (1)$$

where p(AA), p(AB) and p(BB) = probabilities of having genotype AA, AB and BB, with allele A corresponding to the risk allele.

To obtain the weighted PRSs, we multiplied allelic dosage by the regression beta coefficient and summed this product across all loci in the SNP set (see formula 2):

$$Polygenic\ Risk\ Score\ (PRS) = \sum (\beta i * ADs) \quad (2)$$

where β_i = beta value for the i_{th} SNP from the PGC analysis and AD_s = allelic dosage for SiGN subjects

Logistic regression analyses were conducted to relate PRS to stroke and its subtypes, where Stroke (0,1) = $beta_s$ (PRS), adjusted for analytic strata and sex.

Statistical analysis

Logistic regression models were applied to test the association between the eight PRSs, generated by different inclusion probability criteria for the individual SNPs, with separate models for stroke and its subtypes. Analyses were conducted separately for SiGN subjects of European and African ancestry.

RESULTS

The analyses included 12,577 stroke cases and 25,643 controls of European ancestry and 1,353 stroke cases and 2,383 controls of African ancestry. Age of onset of stroke was: (mean, s.d.) 65.5 ± 15; in cases 53.9% were males and in controls 45.2% were males. Tables 1 and 2 show the beta coefficients for PRS in European and African ancestry groups, respectively, for different SNP inclusion criteria in the PRS.

The MDD PRS was associated with overall risk of ischemic stroke for P_T= 0.4 and P_T= 0.5 in both European and African ancestry samples. We present the primary results for P_T= 0.5 because this threshold was most closely related to depression in the PGC target sample, but the results for PT <0.4 which includes 71,315 SNPs, are also shown in the Supplement.

In the SNP set where the SNP inclusion criterion was p =0.5 with 83,890 SNPs used in the SiGN PRS, an additional 358 SNPs (0.42% of SNPs) available in the PGC depression PRS were unavailable in SiGN. Overall, for every one standard deviation difference in PRS ($P_{T=}$ 0.5) ischemic stroke risk increased by 3.0% (OR=1.03, 95%CI: 1.00–1.05) in those of European ancestry (Table 3) while those of African ancestry had an 8% risk increase (OR=1.08, 95%CI: 1.04–1.13), (Table 4). The corresponding figures for $P_{T=}$ 0.4 are similar (Supplemental Tables I and II).

For analyses of ischemic stroke subtypes, we limited PRS analyses to SNPs included based on P_T= 0.5. In those of European ancestry (Table 3), polygenic risk for MDD was associated with small artery occlusion (SAO) stroke (p<.001) and cardioembolic (CE) stroke (p<.042). In those of African ancestry (Table 4), the MDD PRS was associated with LAA, (p <.032) and SAO (p=<.029), despite the smaller sample of African ancestry cases. For each standard deviation increase in PRS, the risk of SAO increased by 8% (OR= 1.08, 95%CI: 1.03–1.13) for those of European ancestry and by 9%% (OR= 1.09, 95%CI: 1.01–1.19) for those of African ancestry. The results were similar when using the CCSc classification (Supplemental Tables III and IV). The TOAST classification also showed a significant increase in risk of SAO of 5% and 10% per 1 s.d. increase in PRS in European and African samples respectively, (p<0.03), but other subtypes generally did not reach statistical significance (Supplemental Tables V and VI).

DISCUSSION

Large epidemiological studies have demonstrated that depression is associated with increased risk of stroke, however it has been unclear whether this phenotypic association reflects a shared genetic basis. To our knowledge, this is the first report of an association

between genetic risk for depression and ischemic stroke subtypes, providing a potential mechanism underlying the link between these common conditions.

We used a PRS for MDD derived from a large European ancestry sample and applied it to GWAS results from the NINDS Stroke Genetics Network (SiGN) Study. We found that higher PRS for depression is associated with higher risk of ischemic stroke, particularly of the SAO subtype, in both European and African ancestry subsamples of SiGN. As the MDD PRS was derived from GWAS of European ancestry samples, these results suggest a transethnic association between polygenic risk for MDD and stroke. For every one standard deviation difference in the PRS for MDD, overall ischemic stroke risk increased by 2.6% and 7.0% for those of European and African ancestry, respectively. Further, in those of European ancestry, the PRS was additionally associated with CE strokes, while in the African ancestry group, it was associated with the LAA subtype. PRS was significantly associated with SAO in the CCS phenotypic (CCSp), the CCS causative (CCSc), and in the TOAST classification systems.

In contrast to our results, a recent large-scale analysis of genetic correlations among 24 psychiatric and neurological disorders conducted by the Brainstorm Consortium, which included 10,307 ischemic stroke cases and 19,326 population-matched controls from Metastroke, found no significant relationship between MDD and ischemic stroke.[30] There is some overlap of data with our SiGN cases and controls: 5,247 of the total 16,851 SiGN cases (31%) and 8,034 of the 32,473 SiGN controls (25%) were also part of Metastroke. The current report however, is based on a subset of the larger SiGN samples after excluding those of Hispanic ancestry, resulting in 13,930 cases of European or African ancestry and 28,026 controls. Based on the total SiGN sample, one can assume that less than one third of the cases and controls used in this SiGN paper overlap with those in the Brainstorm analysis. With regard to depression data, Brainstorm used a larger and more recent PGC-MDD dataset, not available at the time of our analyses.

In addition, our analyses differ from those done in the Brainstorm Consortium's in several important respects. First, we focused on the genetic relationship of MDD to subtypes of stroke that was not examined in the Brainstorm analysis. Second, we examined ischemic stroke subtypes defined by the Causative Classification System (CCS), a classification algorithm based on all relevant clinical and test information that has demonstrated improved reliability relative to the TOAST classification approach used in the Brainstorm analysis). Third, to examine cross-phenotype relationships, we use PRS whereas the Brainstorm analysis used LD score regression (LDSC). LDSC is used to estimate genetic correlation using only summary statistics and can be less powerful in some contexts compared to methods that utilize individual-level genotype data. In addition, LDSC can estimate the genetic correlation of traits using data across the entire genome; in PRS analyses, the scores examined are subsets of SNPs, typically restricted to those in the upper tails of the distribution of GWAS results (i.e. the p value thresholds are pre-specified for inclusion of SNPs in the PRS). Thus, if the genetic overlap is concentrated in loci that are within the selected p value threshold, PRS analyses may be more likely to show significant effects than might be seen with a genomewide LDSC; this may be relevant to our finding of a genetic relationship between MDD and stroke that was not seen in the Brainstorm analyses.

The underlying mechanism connecting the observed association between genetic predisposition to depression and ischemic stroke risk is unclear. Recent research on the stroke-depression relationship has focused on pathophysiologic mechanisms, including vascular dysfunction and neuroendocrine pathways as well as genetic predisposition. The vascular depression disconnection hypothesis is that focal ischemic white matter lesions can disrupt neural connections among regions regulating mood and cognition, contributing to the clinical symptomatology of depression[31, 32]. Since the disconnection hypothesis depends on the strategic location of such small vessel lesions, it is possible that the strength of the genetic association observed is limited by the randomness of where these small vessel lesions occured[33–35]. Interestingly, we found a consistent association between polygenic depression risk and the lacunar (small vessel) ischemic stroke mechanism across both ancestry groups.

A second possible mechanistic connection is a common pathway promoting inflammation, although prior evidence is limited. Several candidate gene studies have linked polymorphisms associated with pro-inflammatory responses in depression. Prior studies linked genetic polymorphisms that promote pro-inflammatory responses with depression. [36–38]. Atherothrombotic (large artery stroke) has also been linked to pro-inflammatory genes [39]. Thirdly, platelets and endothelial function may play a role in the association between depression and stroke risk. Studies of candidate genes in patients with depression and coronary disease have implicated platelet dysregulation and inflammation as causal mechanisms. Thus, increased stroke risk with depression may be mediated through excessive platelet activation[40, 41]. Endothelial dysfunction may be related as a study of young women with subclinical depression found a significant association between depression and abnormal endothelial function assessed by pulse-wave amplitude assessment[42]. We observed evidence of association between MDD and atherothrombotic ischemic stroke only for individuals of European ancestry. The lack of association among those of African ancestry might be due to limited power in that sample or transethnic differences in the genetic etiology of LAA. Of note, the atherothrombotic type is more common in European ancestry patients [43]. Finally, another possible common mechanism is cerebrovascular dysregulation and hypoperfusion[44].

An important strength of our study is the very large number of strokes in both European and African ancestry individuals that have been classified by subtype in a uniform manner, though we note several limitations of our study. Power to detect associations with certain subtypes was still limited by sample sizes. Power in African ancestry samples also may have been reduced by transethnic differences in the genetic basis of stroke. A PRS derived from an African ancestry GWAS might contain different SNPs and thus could show a stronger or different relationship to certain subtypes of stroke in African-ancestry samples. However, it is noteworthy that a European-derived MDD PRS was also associated with stroke in those of African ancestry. In addition, the relationship of the PRS derived in the PGC to MDD explained only a small proportion of the variance of depression.

In the very large NINDS-Strokes Genetics Network study of 13,930 ischemic strokes, we found that higher polygenic risk for MDD depression is associated with higher risk of ischemic stroke overall and with small artery occlusion, both for those of European and African ancestry, supporting a common genetic basis between depression and stroke risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Relationship between polygenic risk for depression and all ischemic stroke using 8 polygenic risk scores for different inclusion criteria (P_T) into the PRS European Ancestry adults (N = 12,577 Cases, 25,643 Controls)

P_T	# of SNPs included in PRS	# of SNPs (%) from PGC that were not present in SiGN	$Beta_s$	SE	P-values for $Beta_s$
.001	427	2 (0.47)	0.000298	0.00025	0.233
.01	3,348	11 (0.33)	0.000176	0.000092	0.055
.05	13,243	57 (0.43)	0.000073	0.000047	0.122
0.1	23,606	92 (0.39)	0.000053	0.000035	0.136
0.2	41,475	164 (0.39)	0.000046	0.000027	0.088
0.3	57,186	238 (0.41)	0.000043	0.000023	0.058
0.4	71,315	306 (.43)	0.000050	0.000021	0.016
0.5	83,890	358 (0.42)	0.000043	0.000019	0.025

P_T: p-value threshold for SNP inclusion into the PRS.

$Beta_S$ relates PRS to stroke subtype, per unit of PRS

Table 2

Relationship between polygenic risk for depression and all ischemic stroke using 8 polygenic risk scores for different inclusion criteria (P_T) into the PRS African Ancestry Adults (N = 1353 cases, 2383 controls)

P_T	# of SNPs included in PRS	# of SNPs (%) from PGC that were not present in SiGN	$Beta_s$	SE	P-values for $Beta_s$
.001	427	2 (0.47)	0.000110	0.000771	0.886
.01	3,348	11 (0.33)	0.000688	0.000284	0.016
.05	13,243	57 (0.43)	0.000105	0.000142	0.458
0.1	23,606	92 (0.39)	0.000181	0.000105	0.084
0.2	41,475	164 (0.39)	0.000098	0.000072	0.169
0.3	57,186	238 (0.41)	0.000102	0.000057	0.074
0.4	71,315	306 (0.43)	0.000132	0.000048	0.006
0.5	83,890	358 (0.42)	0.000108	0.000043	0.011

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Table 3

Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of p<.5, by CCSp stroke subtype for European Ancestry Adults

Phenotype (CCSp)	Total N cases	Total N Controls	$Beta_S$	SE	p for $beta_S$	OR (95%CI) for Stroke, Per 1 s.d. of PRS* = $e^{beta * s.d.}$
All stroke	12,577	25,643	0.000043	0.000019	.025	1.03 (1.00, 1.05)
LAA	2,229	25,643	0.000031	0.000038	0.406	1.02 (0.98, 1.07)
SAO	2,029	25,643	0.000132	0.000039	0.001	1.08 (1.03, 1.13)
CE	3,400	25,643	0.000065	0.000032	0.0419	1.04 (1.00, 1.08)
OTHER	612	25,643	0.000087	0.00007	0.205	1.05 (0.97, 1.14)
Crypto	963	25,643	0.000090	0.000056	0.106	1.06 (0.99, 1.13)

CCSp is the Causative Classification System - phenotypic

* 1 sd of PRS in SiGN is approximately 600 units

$Beta_S$ relates PRS to stroke subtype, per unit of PRS

Table 4

Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of p<.5, by CCSp stroke subtype for African Ancestry

Phenotype (CCSp)	Total N cases	Total N Controls	$Beta_s$	SE	p for $beta_s$	OR (95%CI) for Stroke, Per 1 s.d. of PRS* = $e^{beta^*s.d.}$
All stroke	1353	2383	0.000108	0.000039	0.001	1.08 (1.04, 1.13)
LAA	220	2383	0.000191	0.000089	0.032	1.12 (1.01, 1.25)
SAO	390	2383	0.000150	0.000069	0.029	1.09 (1.01, 1.19)
CE	208	2383	−0.00002	0.000089	0.816	0.99 (0.89, 1.10)
OTHER	106	2383	0.000155	0.000126	0.219	1.10 (0.95, 1.27)
Crypto	133	2383	0.00012	0.000110	0.285	1.07 (0.94, 1.22)

CCSp is the Causative Classification System - phenotypic

*1 sd of PRS in SiGN is approximately 600 units

$Beta_S$ relates PRS to stroke subtype, per unit of PRS