Atrial Fibrillation Genetic Risk and Ischemic Stroke Mechanisms

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and on behalf of the WTCCC2, International Stroke Genetics Consortium, and AFGen Consortia

Abstract

Background and Purpose—Atrial fibrillation (AF) is a leading cause of cardioembolic stroke, but the relationship between AF and noncardioembolic stroke subtypes are unclear. Because AF may be unrecognized, and because AF has a substantial genetic basis, we assessed for predisposition to AF across ischemic stroke subtypes.

Methods—We examined associations between AF genetic risk and Trial of Org 10172 in Acute Stroke Treatment stroke subtypes in 2374 ambulatory individuals with ischemic stroke and 5175 without from the Wellcome Trust Case-Control Consortium 2 using logistic regression. We calculated AF genetic risk scores using single-nucleotide polymorphisms associated with AF in a previous independent analysis across a range of preselected significance thresholds.

Results—There were 460 (19.4%) individuals with cardioembolic stroke, 498 (21.0%) with large vessel, 474 (20.0%) with small vessel, and 814 (32.3%) individuals with strokes of undetermined cause. Most AF genetic risk scores were associated with stroke, with the strongest association ($P=6\times10^{-4}$) attributed to scores of 944 single-nucleotide polymorphisms (each associated with AF at $P<1\times10^{-3}$ in a previous analysis). Associations between AF genetic risk and stroke were enriched in the cardioembolic stroke subset (strongest $P=1.2\times10^{-9}$, 944 single-nucleotide polymorphism score). In contrast, AF genetic risk was not significantly associated with noncardioembolic stroke subtypes.

Conclusions—Comprehensive AF genetic risk scores were specific for cardioembolic stroke. Incomplete workups and subtype misclassification may have limited the power to detect associations with strokes of undetermined pathogenesis. Future studies are warranted to determine whether AF genetic risk is a useful biomarker to enhance clinical discrimination of stroke pathogeneses.

- atrial fibrillation
- genetics
- risk factors
- single-nucleotide polymorphism
- stroke

Introduction

Whereas one in 5 ischemic strokes can be attributed to cardioembolism in the setting of atrial fibrillation (AF),[1,2] a prevalent and heritable[3–8] arrhythmia, a substantial proportion of additional strokes may arise in association with AF. For example, a cause for stroke is not identified in up to one third of patients,[9–11] and unrecognized AF has been identified in about 30% of such individuals during long-term follow-up.[12–16] However, AF may be challenging to identify given the occasionally paroxysmal and asymptomatic nature of the arrhythmia. Moreover, AF confers a markedly increased risk of recurrent stroke,[17] and treatment with anticoagulation reduces the risk of stroke in patients with identified AF.[18] As such, there is a critical need to understand the extent to which AF contributes to strokes which may be attributed to other pathogeneses, and strokes in which no obvious pathogenesis is identified.

Ischemic stroke is heritable,[19] and recent discoveries indicate that genetic variants associated with AF are also associated with stroke.[20] The two most significant susceptibility loci for cardioembolism are also the two loci most strongly associated with AF.[21–26] We recently observed that comprehensive genome-wide genetic risk scores for AF have greater power for predicting AF than more limited scores and were significantly associated with cardioembolic stroke.[27] Therefore, to assess the contribution of AF to different clinically determined stroke mechanisms, we examined the relationship between genome-wide measures of AF genetic risk and ischemic stroke subtypes.

Methods

Study Participants

Participants in the study included 2374 ambulatory individuals with ischemic strokes and 5175 population-based controls (1958 Birth Cohort and National Blood Service Donors) from the WTCCC2 (Wellcome Trust Case-Control Consortium 2) ischemic stroke study.[24] Descriptions of the individual studies comprising the WTCCC2 sample are provided in the online-only Data Supplement. All individuals were of self-reported European ancestry. Participating studies were approved by relevant institutional review boards, and all participants gave written or oral consent for study participation, including genetic research, as approved by the local institutional body.

Stroke Ascertainment

Cases with ischemic stroke were ascertained from 3 sites across the UK—Edinburgh, Oxford, and St. George's (SGUL). The University of Edinburgh collection comprised 727 cases with ischemic stroke, consecutively collected as part of the Edinburgh Stroke Study. The University of Oxford collection comprised 896 cases with ischemic stroke, consecutively collected as part of the OXVASC (Oxford Vascular Study). The SGUL collection comprised 1224 ischemic stroke samples from a hospital-based setting. All patients underwent recording with continuous telemetry as inpatients and had electrocardiograms. Ischemic stroke subtypes were determined according to Trial of Org 10172 in Acute Stroke Treatment criteria based on relevant clinical imaging.[28] Strokes of other determined pathogenesis, using the Trial of Org 10172 in Acute Stroke Treatment criteria, were excluded from the case–control populations before genotyping. Full details about stroke ascertainment, neuroimaging, and other clinical work-up are provided in the online-only Data Supplement.

Genotyping and Imputation

All WTCCC2 cases were genotyped as part of the WTCCC2 ischemic stroke study using the Illumina Human660W-Quad array. Controls were genotyped using the Illumina Human1.2M-Duo. Quality control procedures involved excluding single-nucleotide polymorphisms (SNPs) not genotyped on all case and control collections and SNPs with Fisher information measure <0.98, genotype call rate <0.95, minor allele frequency <0.01, or Hardy–Weinberg $P<1\times10^{-20}$ in either the case or control collections. Samples were excluded if identified as outliers on call rate, heterozygosity, ancestry, and average probe intensity based on a Bayesian clustering algorithm. Samples were also removed if they exhibited discrepancies between inferred and recorded sex or cryptic relatedness with other WTCCC2 samples (pairwise identity-by-descent >0.05). Imputation was performed to the 1000 Genomes Phase 1 Integrated variant set. Phasing was perform using SHAPEIT[29] v2.778 and imputation was performed using IMPUTE v2.3.0.[30]

AF Genetic Risk

We selected SNPs in approximate linkage equilibrium by pruning[31] 2.2 million HapMap variants included in a previous independent meta-analysis of genome-wide association studies for AF from the AFGen consortium (6707 individuals with and 53 436 without AF).[32] Specifically, we recursively extracted SNPs within a sliding 250-kb window that were uncorrelated on the basis of an r^2 value of 0.3 using PLINK v1.90b3.32.[28]

For each individual in the WTCCC2 sample, we calculated AF genetic risk scores by summing the dosage of each AF risk allele (which can range from 0 to 2), weighted by the natural logarithm of the relative risk for each SNP determined from the previous independent AFGen meta-analysis.[32] For example, if a score is composed of 3 SNPs and the log-relative risks of the 3 SNPs are 0.3, 0.4, and 0.5, respectively, then if the individual was heterozygous for each of the 3 SNPs the score would be ([0.3×1]+[0.4×1]+[0.5×1]=1.2). If the individual was homozygous for risk alleles at all 3 SNPs, the score would be ([0.3×2]+[0.4×2]+[0.5×2]=2.4). Thus, genetic risk scores for each individual were single linear predictors which we treated as continuous variables.

As inclusion of SNPs liberally associated with a trait in genetic risk scores may increase the proportion of variance in the trait explained by the score,[33–36] we created scores based on SNPs associated with AF in the previous analysis[32] at 9 different significance thresholds, which we selected a priori (P<0.0001, <0.001, <0.01, <0.05, <0.1, <0.2, <0.3, <0.4, and <0.5).

Statistical Analysis

We examined the associations between AF genetic risk scores and stroke subtypes using multivariable logistic regression with adjustment for 2 ancestry-informative principal components. AF genetic risk was entered into models as a continuous variable. We specifically examined the associations between scores and all ischemic, cardioembolic, large vessel, small vessel, and unknown stroke subtypes. We used the same set of referents for all analyses.

The a priori significance threshold for all analyses was P<0.05 using 2-sided tests. Analyses were conducted using PLINK v1.90b3.32[31] and R 3.2.2.[37]

Results

Participant characteristics are summarized in Table 1. Among the 2374 cases with ischemic stroke, there were 460 (19.4%) individuals with cardioembolic stroke, 498 (21.0%) with large vessel, 474 (20.0%) with small vessel stroke subtypes, and 814 (34.2%) with strokes of undetermined cause. A further 128 cases (5.4%) had stroke of tandem pathogenesis and were not considered in the subtype analyses.

Table 1.

Characteristics of Wellcome Trust Case-Control Consortium 2 Participants Included in the Analysis

	n (%)	Age, y	Men, %	History of AF, n (%)	History of IHD, n (%)	MRI, n (%)	Echocardiogram, n (%)	Extracranial Imaging, n (%)
All ischemic stroke	2374	72.2±12.5	53.8	479 (20.1)	552 (23.3)	881 (37.1)	847 (35.7)	2176 (91.7)
Cardioembolic	460 (19.4)	75.4±12.5	62.1	362 (78.7)	141 (30.7)	113 (24.6)	259 (56.3)	393 (85.4)
Large vessel disease	498 (20.1)	68.2±10.8	66.2	2 (0.4)	136 (27.3)	196 (39.4)	133 (26.7)	487 (98.2)
Small vessel disease	474 (20.0%)	69.6±11.7	52.3	10 (2.1)	76 (16.0)	285 (60.1)	139 (29.1)	455 (96.0)
Unknown	814 (34.3)	70.8±13.8	45.7	26 (3.2)	153 (18.8)	248 (30.5)	248 (30.5)	726 (89.2)
Referents	5175	…	49.5	…	…	…	…	…

- Data presented as mean±SD or n (%) unless otherwise specified. A further 128 (5.4%) individuals had stroke of tandem pathogenesis and were not included in any subgroup analyses. All patients underwent computed tomographic imaging and an ECG. Extracranial cerebral arterial imaging includes carotid and vertebral artery ultrasound, or computed tomographic angiography, or MRI. AF indicates atrial fibrillation; IHD, ischemic heart disease; and MRI, magnetic resonance imaging.

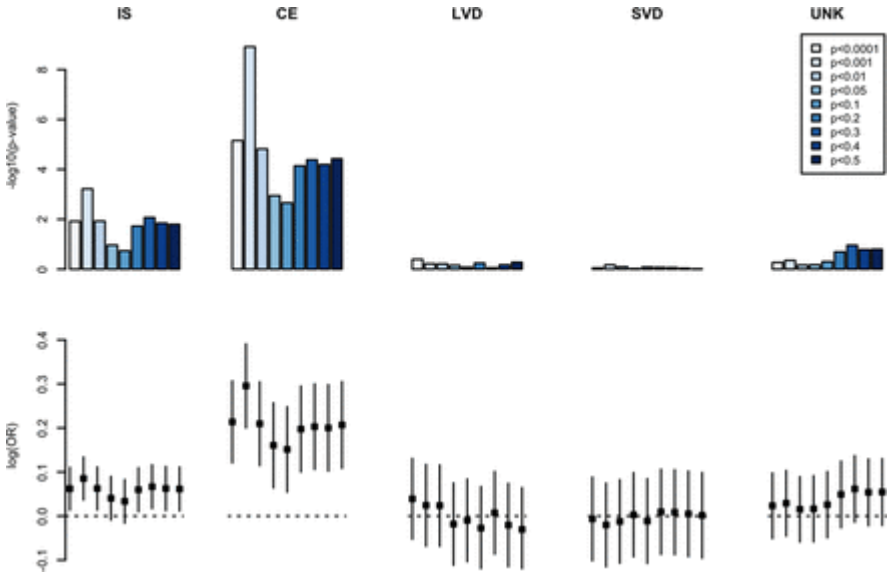
AF genetic risk scores were comprised between 172 and 162 456 SNPs across the 9 different preselected SNP significance thresholds (Table 2). AF genetic risk scores were associated with all ischemic stroke, with *P* values ranging from 6.0×10^{-4} (944 SNP score) to 0.18 (44 127 SNP score).

Table 2.

Number of SNPs Included in Each Atrial Fibrillation Genetic Risk Score

Discovery sample *P* value for association with AF	$<1\times10^{-4}$	$<1\times10^{-3}$	<0.01	<0.05	<0.1	<0.2	<0.3	<0.4	<0.5
n SNPs in genetic risk score	172	944	6182	24 599	44 127	78 329	109 124	137 122	162 456

- AF indicates atrial fibrillation; and SNP, single-nucleotide polymorphism.



Association between atrial fibrillation genetic risk and ischemic stroke subtypes. **Top**, The strength of association between genetic risk scores comprised atrial fibrillation genetic markers and ischemic stroke subtypes are displayed. Separate scores were calculated corresponding to differences in the strength of association between each variant and atrial fibrillation in a prior independent analysis.[32] **Bottom**, The magnitude of association per 1-U change in each genetic risk score is displayed. CE indicates cardioembolic stroke; IS, all ischemic stroke; LVD, large vessel disease stroke; OR, odds ratio; SVD, small vessel disease stroke; and UNK, stroke of unknown pathogenesis.

Among the stroke subtypes, AF genetic risk was enriched among the subset of individuals with cardioembolic stroke. We observed significant associations between AF genetic risk and cardioembolic stroke across all SNP scores, with the strongest association ($P=1.2\times10^{-9}$) accounted for by a score composed of SNPs associated with AF at $P<1\times10^{-3}$ in the previous AFGen analysis.[32] AF genetic risk scores were not significantly associated with large vessel disease, small vessel disease, or unknown stroke subtypes.

Discussion

In our analysis of 2374 individuals with ischemic stroke and 5175 population-based referents of European ancestry, we observed that comprehensive AF genetic risk scores were

significantly associated with stroke. The association was almost entirely explained by an association with cardioembolic stroke, whereas scores were not significantly associated with noncardioembolic stroke pathogeneses. In aggregate, these findings indicate that the associations between AF genetic risk and ischemic stroke are specific for cardioembolic stroke.

Our findings support and extend previous analyses examining the relationship between AF and ischemic stroke. AF is a well-recognized risk factor for stroke.[13] Genome-wide association studies of ischemic stroke, in which a subset of individuals from the present analysis were included, identified variants at the top 2 AF susceptibility loci on chromosomes 4q25 and 16q22 among the subset with cardioembolic strokes.[23–25] A genetic risk score comprised top genome-wide significant variants for clinical traits known to be associated with ischemic stroke, including 14 variants associated with AF, was associated with ischemic stroke in a previous analysis.[38] Our study extends previous literature by relating comprehensive genome-wide estimates of AF genetic risk to specific stroke subtypes in a large and well-characterized sample.

Our findings have 3 major implications. First, by testing scores composed of SNPs associated with AF at different significance thresholds in a previous independent analysis, our findings indicate that common genetic variants associated with AF at more liberal thresholds than the stringent genome-wide significance threshold typically used are associated with ischemic stroke. We observed similar findings in a separate analysis in which we assessed associations between AF genetic risk and incident AF.[27] Our analysis identified an informative subset of variants that may be relevant for assessing AF genetic risk in future studies. Discovery efforts in larger samples and using improved imputation reference panels may improve our understanding of genetic risk associated with both AF and stroke.

Second, our observation that AF genetic risk is associated nearly exclusively with cardioembolic stroke highlights the possibility that AF genetic risk may serve as a discriminating marker for strokes caused by thromboembolism rather than other mechanisms. The fact that the AF genetic risk score most significantly associated with cardioembolic stroke had no discernible association with other stroke classifications highlights the relative effectiveness of Trial of Org 10172 in Acute Stroke Treatment classification in distinguishing cardioembolic from other stroke pathogeneses. Identification of quantitative thresholds of AF genetic risk that maximize discrimination between cardioembolic and noncardioembolic stroke subtypes may inform prospective efforts to test the clinical use of AF genetic risk. Future consideration of both the clinical use and cost-effectiveness of genetic risk stratification to distinguish stroke mechanisms may be warranted.

Third, we did not observe a significant association between AF genetic risk and stroke of unknown pathogenesis. However, we only had sufficient power to identify an association if AF and stroke of unknown pathogenesis were moderately highly genetically correlated (r^2>0.5), meaning we cannot rule out a moderate association between the 2 traits, particularly if only a fraction of the strokes of unknown pathogenesis were due to AF. Moreover, the WTCCC2 data set is a heavily curated research tool, which may not mirror the imperfect standard community practice of stroke subtyping. Future larger studies using genetic risk of AF and other stroke risk factors may yield insights into the contribution of heritable risk factors to cryptogenic stroke.

Our study should be interpreted in the context of the observational study design. Individuals included in the analysis were of European ancestry, and therefore the results may not be generalizable to other ancestral groups. We had limited power to assess the relationship between AF genetic risk and noncardioembolic stroke subtypes. We were unable to adjust for clinical risk factors associated with ischemic stroke and AF, and therefore cannot exclude confounding between genetic risk and ischemic stroke. Nevertheless, we have separately observed significant associations between genetic markers and incident AF independent of clinical AF risk factors, which are highly correlated with stroke risk factors.[39] Individuals with strokes of unknown pathogenesis had clinical workups at the discretion of their treating providers, some of which may have been incomplete. Incomplete workups may have resulted in misclassification because further workup may have attributed strokes to an pathogenic subgroup, and thereby biased our analyses examining associations between AF genetic risk scores and stroke of undetermined pathogenesis toward the null if strokes were caused by other noncardioembolic pathogeneses. Moreover, the absence of systematic long-term cardiac rhythm monitoring results does not enable assessment of incident AF in patients with ischemic strokes. Future analyses with more complete phenotyping in the undetermined subset, and with a larger number of individuals with undetermined stroke, are warranted. It is also possible that more precise scores of AF genetic risk may be more specific for cardioembolic stroke subtypes and yield associations with strokes of undetermined pathogenesis. Large genome-wide association studies of AF are ongoing and are expected to yield more precise estimates of AF risk associated with each SNP marker.

Conclusions

In our analysis of 2374 individuals with stroke and 5175 population-based referents, we observed that AF genetic risk was strongly associated with ischemic stroke. Genetic risk scores composed of variants liberally associated with AF were associated specifically with the cardioembolic stroke subtype, indicating that the Trial of Org 10172 in Acute Stroke Treatment classification system effectively distinguishes cardioembolic from noncardioembolic stroke subtypes. Our observations suggest that polygenic AF risk is an important determinant of stroke risk. Future analyses are warranted to determine whether using information AF genetic risk can help distinguish between stroke subtypes.

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Footnotes

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References

1. 1.↵
    1. Hart RG,
    2. Halperin JL

    . *Atrial fibrillation and stroke: concepts and controversies. Stroke. 2001;32:803–808.*

    FREE Full TextGoogle Scholar

2. 2.↵
    1. Marini C,
    2. De Santis F,
    3. Sacco S,
    4. Russo T,
    5. Olivieri L,
    6. Totaro R,
    7. et al

    . *Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36:1115–1119. doi: 10.1161/01.STR.0000166053.83476.4a.*

Abstract/FREE Full TextGoogle Scholar

3. 3.↵
    1. Fox CS,
    2. Parise H,
    3. D'Agostino RB Sr,
    4. Lloyd-Jones DM,
    5. Vasan RS,
    6. Wang TJ,
    7. et al

. *Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004;291:2851–2855. doi: 10.1001/jama.291.23.2851.*

CrossRefPubMedGoogle Scholar

4. 4.↵
    1. Ellinor PT,
    2. Yoerger DM,
    3. Ruskin JN,
    4. MacRae CA

. *Familial aggregation in lone atrial fibrillation. Hum Genet. 2005;118:179–184. doi: 10.1007/s00439-005-0034-8.*

CrossRefPubMedGoogle Scholar

5. 5.↵
    1. Arnar DO,
    2. Thorvaldsson S,
    3. Manolio TA,
    4. Thorgeirsson G,
    5. Kristjansson K,
    6. Hakonarson H,
    7. et al

. *Familial aggregation of atrial fibrillation in Iceland. Eur Heart J. 2006;27:708–712. doi: 10.1093/eurheartj/ehi727.*

Abstract/FREE Full TextGoogle Scholar

6. 6.↵
    1. Christophersen IE,
    2. Ravn LS,
    3. Budtz-Joergensen E,
    4. Skytthe A,
    5. Haunsoe S,
    6. Svendsen JH,
    7. et al

. *Familial aggregation of atrial fibrillation: a study in Danish twins. Circ Arrhythm Electrophysiol. 2009;2:378–383. doi: 10.1161/CIRCEP.108.786665.*

Abstract/FREE Full TextGoogle Scholar

7. 7.↲
    1. Marcus GM,
    2. Smith LM,
    3. Vittinghoff E,
    4. Tseng ZH,
    5. Badhwar N,
    6. Lee BK,
    7. et al

. *A first-degree family history in lone atrial fibrillation patients. Heart Rhythm. 2008;5:826–830. doi: 10.1016/j.hrthm.2008.02.016.*

CrossRefPubMedGoogle Scholar

8. 8.↲
    1. Lubitz SA,
    2. Yin X,
    3. Fontes JD,
    4. Magnani JW,
    5. Rienstra M,
    6. Pai M,
    7. et al

. *Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. JAMA. 2010;304:2263–2269. doi: 10.1001/jama.2010.1690.*

CrossRefPubMedGoogle Scholar

9. 9.↲
    1. Petty GW,
    2. Brown RD Jr,
    3. Whisnant JP,
    4. Sicks JD,
    5. O'Fallon WM,
    6. Wiebers DO

. *Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke. 1999;30:2513–2516.*

Abstract/FREE Full TextGoogle Scholar

10. 10.↲
    1. Kolominsky-Rabas PL,
    2. Weber M,
    3. Gefeller O,

4. Neundoerfer B,
5. Heuschmann PU

. *Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32:2735–2740.*

Abstract/FREE Full TextGoogle Scholar

11. 11.↲
    1. Hajat C,
    2. Heuschmann PU,
    3. Coshall C,
    4. Padayachee S,
    5. Chambers J,
    6. Rudd AG,
    7. et al

. *Incidence of aetiological subtypes of stroke in a multi-ethnic population based study: the South London Stroke Register. J Neurol Neurosurg Psychiatry. 2011;82:527–533. doi: 10.1136/jnnp.2010.222919.*

Abstract/FREE Full TextGoogle Scholar

12. 12.↲
    1. Seet RC,
    2. Friedman PA,
    3. Rabinstein AA

. *Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation. 2011;124:477–486. doi: 10.1161/CIRCULATIONAHA.111.029801.*

FREE Full TextGoogle Scholar

13. 13.↲
    1. Healey JS,
    2. Connolly SJ,
    3. Gold MR,
    4. Israel CW,
    5. Van Gelder IC,
    6. Capucci A,
    7. et al

; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120–129. doi: 10.1056/NEJMoa1105575.

CrossRefPubMedGoogle Scholar

14. 14.↲

1. Kishore A,
2. Vail A,
3. Majid A,
4. Dawson J,
5. Lees KR,
6. Tyrrell PJ,
7. et al

. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Stroke. 2014;45:520–526. doi: 10.1161/STROKEAHA.113.003433.

Abstract/FREE Full TextGoogle Scholar

15. 15.↲
    1. Sanna T,
    2. Diener HC,
    3. Passman RS,
    4. Di Lazzaro V,
    5. Bernstein RA,
    6. Morillo CA,
    7. et al

    ; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478–2486. doi: 10.1056/NEJMoa1313600.

    CrossRefPubMedGoogle Scholar

16. 16.↲
    1. Gladstone DJ,
    2. Spring M,
    3. Dorian P,
    4. Panzov V,
    5. Thorpe KE,
    6. Hall J,
    7. et al

    ; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467–2477. doi: 10.1056/NEJMoa1311376.

    CrossRefPubMedGoogle Scholar

17. 17.↲
    1. Penado S,
    2. Cano M,
    3. Acha O,
    4. Hernández JL,
    5. Riancho JA

. *Atrial fibrillation as a risk factor for stroke recurrence. Am J Med. 2003;114:206–210.*

CrossRefPubMedGoogle Scholar

18. 18.↲
    1. Hart RG,
    2. Pearce LA,
    3. Aguilar MI

. *Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–867.*

CrossRefPubMedGoogle Scholar

19. 19.↲
    1. Seshadri S,
    2. Beiser A,
    3. Pikula A,
    4. Himali JJ,
    5. Kelly-Hayes M,
    6. Debette S,
    7. et al

. *Parental occurrence of stroke and risk of stroke in their children: the Framingham study. Circulation. 2010;121:1304–1312. doi: 10.1161/CIRCULATIONAHA.109.854240.*

Abstract/FREE Full TextGoogle Scholar

20. 20.↲
    1. Tada H,
    2. Shiffman D,
    3. Smith JG,
    4. Sjögren M,
    5. Lubitz SA,
    6. Ellinor PT,
    7. et al

. *Twelve-single nucleotide polymorphism genetic risk score identifies individuals at increased risk for future atrial fibrillation and stroke. Stroke. 2014;45:2856–2862. doi: 10.1161/STROKEAHA.114.006072.*

Abstract/FREE Full TextGoogle Scholar

21. 21.↲
    1. Gretarsdottir S,
    2. Thorleifsson G,
    3. Manolescu A,
    4. Styrkarsdottir U,

5. Helgadottir A,
6. Gschwendtner A,
7. et al

. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. Ann Neurol. 2008;64:402–409. doi: 10.1002/ana.21480.

CrossRefPubMedGoogle Scholar

22. 22.↲
    1. Gudbjartsson DF,
    2. Holm H,
    3. Gretarsdottir S,
    4. Thorleifsson G,
    5. Walters GB,
    6. Thorgeirsson G,
    7. et al

. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. Nat Genet. 2009;41:876–878. doi: 10.1038/ng.417.

CrossRefPubMedGoogle Scholar

23. 23.↲
    1. Lemmens R,
    2. Buysschaert I,
    3. Geelen V,
    4. Fernandez-Cadenas I,
    5. Montaner J,
    6. Schmidt H,
    7. et al

; International Stroke Genetics Consortium. The association of the 4q25 susceptibility variant for atrial fibrillation with stroke is limited to stroke of cardioembolic etiology. Stroke. 2010;41:1850–1857. doi: 10.1161/STROKEAHA.110.587980.

Abstract/FREE Full TextGoogle Scholar

24. 24.↲
    1. Bellenguez C,
    2. Bevan S,
    3. Gschwendtner A,
    4. Spencer CC,
    5. et al

; International Stroke Genetics C, Wellcome Trust Case Control C. Genome-wide association study identifies a variant in hdac9 associated with large vessel ischemic stroke. Nat Genet. 2012;44:328–333.

CrossRefPubMedGoogle Scholar

25. 25.↵
    1. Traylor M,
    2. Farrall M,
    3. Holliday EG,
    4. Sudlow C,
    5. Hopewell JC,
    6. Cheng YC,
    7. et al

    ; Australian Stroke Genetics Collaborative, Wellcome Trust Case Control Consortium 2 (WTCCC2); International Stroke Genetics Consortium. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet Neurol. 2012;11:951–962. doi: 10.1016/S1474-4422(12)70234-X.

    CrossRefPubMedGoogle Scholar

26. 26.↵

    Neurology Working Group of the Cohorts for H, Aging Research in Genomic Epidemiology C, Stroke Genetics N, International Stroke Genetics C. Identification of additional risk loci for stroke and small vessel disease: A meta-analysis of genome-wide association studies. Lancet Neurol. 2016;15:695–707. doi: 10.1016/S1474-4422(16)00102-2.

    CrossRefPubMedGoogle Scholar

27. 27.↵
    1. Lubitz SA,
    2. Yin X,
    3. Lin HJ,
    4. Kolek M,
    5. Smith JG,
    6. Trompet S,
    7. et al

    ; AFGen Consortium. Genetic Risk Prediction of Atrial Fibrillation. Circulation. 2017;135:1311–1320. doi: 10.1161/CIRCULATIONAHA.116.024143.

    Abstract/FREE Full TextGoogle Scholar

28. 28.↵
    1. Adams HP Jr,
    2. Bendixen BH,
    3. Kappelle LJ,
    4. Biller J,
    5. Love BB,
    6. Gordon DL,
    7. et al

. *Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.*

Abstract/FREE Full TextGoogle Scholar

29. 29.↵
    1. O'Connell J,
    2. Gurdasani D,
    3. Delaneau O,
    4. Pirastu N,
    5. Ulivi S,
    6. Cocca M,
    7. et al

. *A general approach for haplotype phasing across the full spectrum of relatedness. PLoS Genet. 2014;10:e1004234. doi: 10.1371/journal.pgen.1004234.*

CrossRefPubMedGoogle Scholar

30. 30.↵
    1. Howie BN,
    2. Donnelly P,
    3. Marchini J

. *A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 2009;5:e1000529. doi: 10.1371/journal.pgen.1000529.*

CrossRefPubMedGoogle Scholar

31. 31.↵
    1. Purcell S,
    2. Neale B,
    3. Todd-Brown K,
    4. Thomas L,
    5. Ferreira MA,
    6. Bender D,
    7. et al

. *PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81:559–575. doi: 10.1086/519795.*

CrossRefPubMedGoogle Scholar

32. 32.↵
    1. Ellinor PT,
    2. Lunetta KL,
    3. Albert CM,
    4. Glazer NL,

5. Ritchie MD,
6. Smith AV,
7. et al

. *Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet. 2012;44:670–675. doi: 10.1038/ng.2261.*

CrossRefPubMedGoogle Scholar

33. 33.↲
    1. Evans DM,
    2. Visscher PM,
    3. Wray NR

. *Harnessing the information contained within genome-wide association studies to improve individual prediction of complex disease risk. Hum Mol Genet. 2009;18:3525–3531. doi: 10.1093/hmg/ddp295.*

Abstract/FREE Full TextGoogle Scholar

34. 34.↲
    1. Purcell SM,
    2. Wray NR,
    3. Stone JL,
    4. Visscher PM,
    5. O'Donovan MC,
    6. Sullivan PF,
    7. et al

. *Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460:748–752*

CrossRefPubMedGoogle Scholar

35. 35.↲
    1. Lango Allen H,
    2. Estrada K,
    3. Lettre G,
    4. Berndt SI,
    5. Weedon MN,
    6. Rivadeneira F,
    7. et al

. *Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010;467:832–838. doi: 10.1038/nature09410.*

CrossRefPubMedGoogle Scholar

36. 36.↲
    1. Ehret GB,

2. Lamparter D,
3. Hoggart CJ,
4. Whittaker JC,
5. Beckmann JS,
6. Kutalik Z

; Genetic Investigation of Anthropometric Traits Consortium. A multi-SNP locus-association method reveals a substantial fraction of the missing heritability. Am J Hum Genet. 2012;91:863–871. doi: 10.1016/j.ajhg.2012.09.013.

CrossRefPubMedGoogle Scholar

37. 37.↲

R Core Team. R: A language and environment for statistical computing. https://www.r-project.org/. Accessed March 22, 2017.

Google Scholar

38. 38.↲
1. Malik R,
2. Bevan S,
3. Nalls MA,
4. Holliday EG,
5. Devan WJ,
6. Cheng YC,
7. et al

; Wellcome Trust Case Control Consortium 2. Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies. Stroke. 2014;45:394–402. doi: 10.1161/STROKEAHA.113.002938.

Abstract/FREE Full TextGoogle Scholar

39. 39.↲
1. Christophersen IE,
2. Yin X,
3. Larson MG,
4. Lubitz SA,
5. Magnani JW,
6. McManus DD,
7. et al

. A comparison of the CHARGE-AF and the CHA2DS2-VASc risk scores for prediction of atrial fibrillation in the Framingham Heart Study. Am Heart J. 2016;178:45–54. doi: 10.1016/j.ahj.2016.05.004.

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