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ORIGINAL RESEARCH

# Unraveling Mechanisms of Cryptogenic Stroke at the Genetic Level: A Systematic Literature Review

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**BACKGROUND:** A substantial proportion of ischemic strokes remain cryptogenic, which has important implications for secondary prevention. Identifying genetic variants related to mechanisms of stroke causes may provide a chance to clarify the actual causes of cryptogenic strokes.

**METHODS AND RESULTS:** In a 2-step process, 2 investigators independently and systematically screened studies that reported genetic variants in regard to stroke causes that were published between January 1991 and April 2021. Studies on monogenetic disorders, investigation of vascular risk factors as the primary end point, reviews, meta-analyses, and studies not written in English were excluded. We extracted information on study types, ancestries, corresponding single nucleotide polymorphisms, and sample and effect sizes. There were 937 studies screened, and 233 were eligible. We identified 35 single nucleotide polymorphisms and allele variants that were associated with an overlap between cryptogenic strokes and another defined cause.

**CONCLUSIONS:** Associations of single variants with an overlap between cryptogenic stroke and another defined cause were limited to a few polymorphisms. A limitation of all studies is a low granularity of clinical data, which is of major importance in a complex disease such as stroke. Deep phenotyping is in supposed contradiction with large sample sizes but needed for genome-wide analyses. Future studies should attempt to address this restriction to advance the promising approach of elucidating the cause of stroke at the genetic level. Especially in a highly heterogenous disease such as ischemic stroke, genetics are promising to establish a personalized approach in diagnostics and treatment in the sense of precision medicine.

**Key Words:** cryptogenic stroke ■ genetics ■ overlap ■ single nucleotide polymorphism ■ stroke cause

In up to 30% of all cases, the cause of ischemic stroke remains undetermined despite comprehensive diagnostic investigations.[1] This has important implications for secondary prevention, because the lack of insight into the mechanism results in uncertainty in the choice of the appropriate secondary preventive therapy.[2] Approaches such as a general anticoagulation in patients with cryptogenic stroke (CRY) with embolic pattern upon imaging (ie, embolic stroke of unknown source) have not been successful,[3] which underlines the importance of an individualized diagnosis and treatment.[4]

Stroke genetics has increasingly come into focus in recent years and has meanwhile gained a prominent role in cerebrovascular disease research.[5] Initially, targeted genetic analyses were done in smaller cohorts, which were prone to overestimation of the effect of detected risk loci. To date, more and more genome-wide association studies (GWAS) have been performed in large and sometimes extremely large cohorts thanks to recently developed high throughput technologies. This has enabled the identification of common variants associated with the risk of ischemic stroke.

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## RESEARCH PERSPECTIVE

### What Is New?

- A substantial proportion of strokes remain cryptogenic, which has important implications for secondary prevention.
- Identifying genetic variants related to mechanisms of stroke causes may provide a chance to unravel the actual mechanism of cryptogenic strokes.
- We systematically screened 937 studies reporting genetic variants related to stroke causes published over a 30-year period, and we identified 35 single nucleotide polymorphisms and allele variants that were associated with an overlap between cryptogenic strokes and another defined cause. A major limitation of these studies is a relatively low granularity of clinical data.

### What Question Should Be Addressed Next?

- Although deep phenotyping is in putative conflict with the large sample sizes required for genome-wide analyses, we suggest that future studies should attempt to overcome this limitation to advance the promising approach of elucidating the causes of stroke at the genetic level toward clinical application in the sense of precision medicine.
- One possible approach to resolve this dilemma could be to perform deep phenotyping in so-called phenotype-based genetic association studies.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| ***ADBR2*** | β-2 adrenergic receptor |
| ***ALOX5AP*** | arachidonate 5-lipoxygenase activating protein |
| **CRY** | cryptogenic stroke |
| ***eNOS*** | endothelial nitric oxide synthase |
| **GWAS** | genome-wide association study |
| ***KCNK17*** | potassium channel subfamily K member 17 |
| **LAA** | large artery atherosclerosis |
| **MR** | Mendelian randomization |
| **PDE4D** | phosphodiesterase 4D |
| **SVD** | small vessel disease |

Moreover, Mendelian randomization (MR) studies have recently contributed to the understanding of causal mechanisms of stroke.[5] Importantly, the identification of distinct genetic variants that are associated with specific mechanisms of stroke causes may provide a chance to clarify the actual origin in CRYs.

In this systematic literature review, we thus aimed to provide an overview on the current evidence of genetic risk factors of stroke causes. In particular, we were interested in the number and types of studies that have been conducted on this topic to date and whether specific genetic variants show overlaps between distinct causes of stroke and CRYs. These overlapping variants might be of particular interest in elucidating the respective cause of CRYs. More specifically, it is hypothesized that CRYs are due to hidden mechanisms that are shared with other causes of stroke. Unraveling these overlapping mechanisms at the level of genetics would support specifying the individual secondary preventive approach in terms of personalized medicine.

## METHODS

This systematic review has been registered at International Prospective Register of Systematic Reviews (ID: CRD42022335010). We screened studies in PubMed according to the following search keywords: ischemic stroke, GWAS, polymorphism, single nucleotide polymorphism (SNP), MR, cause, atrial fibrillation, small-vessel disease (SVD), carotid plaque, embolic stroke of undetermined source, and CRY. The full-scale search strategy is provided in Data S1. Studies published between January 1991 and April 2021 have been considered. For this systematic review, an approval by an ethics committee was waived. Informed consent was not required.

The following inclusion criteria were applied: studies that investigate common genetic variants, such as, candidate gene analyses, GWAS, MR studies, and studies that address major causes of ischemic stroke (ie, large artery atherosclerosis [LAA], SVD, cardioembolism, CRY including embolic stroke of unknown source, as well as other rare stroke causes including vasculitis or artery dissection). Exclusion criteria were defined as investigation of monogenetic disorders or a molecular genetic focus other than stroke, investigation of vascular risk factors as the primary end point, reviews, meta-analyses, and studies not written in English.

Two investigators (J.E. and G.M.G.) independently screened studies, first for eligibility considering the abstracts of all studies and second to retrieve the following data from the full texts of all eligible works: PubMed identification, study type (candidate gene analysis, GWAS, MR study, other), investigated stroke cause (LAA, cardioembolism, SVD, CRY, other rare stroke causes), outcome sample (stroke versus no stroke),

control sample (stroke versus no stroke), total sample size, outcome sample size, control sample size, ancestry of study participants, consortium (yes versus no), consortium name (if applicable), association of SNPs or other described genetic variant and stroke cause (yes versus no), relevant cause, corresponding sample sizes, types of control, relevant SNPs (including reference SNP cluster identification), or distinct label of genetic position and effect sizes including confidence limits (if applicable). Genetic variants were sorted according to the appropriate gene to find overlaps with the help of extensive literature research and genetic databases (https://www.ncbi.nlm.nih.gov/gene/; https://www.ncbi.nlm.nih.gov/snp). In this context, overlaps were defined as SNPs that were shown to be associated with CRY and at least another cause of stroke.

After both investigators independently assessed the eligibility of the studies in the first step, a consensus was reached in regular meetings after appropriate discussion in cases with disagreement. The same procedure was applied in the extraction of the data in the second step.

Figures were created using Biorender.com.

## RESULTS

Figure 1 presents an overview on the screened and included studies. Overall, 233 studies were eligible for analysis after applying inclusion and exclusion criteria.

Most of the studies (n=198) investigated single genetic targets. We identified 17 GWAS and 18 MR studies. In addition, 1 study was conducted as a combined GWAS and MR study. The majority of the studies investigated patients with White (n=135) or Asian ancestry (n=112), with possibly >1 ancestry analyzed in 1 study. In 188 out of 233 eligible studies, we found SNPs that were associated with a distinct stroke cause. The studies could deal with ≥1 cause. See Table 1 for general information of the analyzed studies.

### Genetic Variants of Interest in Stroke Causes

We identified 30 SNPs associated with distinct stroke causes in at least 2 studies. SNPs and corresponding genes are presented in Table 2. In addition to these, the following genes were shown to be associated with a distinct stroke cause in at least 2 studies: *ACE* (*angiotensin 1-converting enzyme*), *COL4A2* (*collagen type IV-α 2 chain*), *HABP2* (*hyaluronan-binding protein 2*), *IL1RN* (*interleukin 1 receptor antagonist*), *IL-1A* (*interleukin 1-α*), *IL6R* (*interleukin-6 receptor*), *MMP2* (*matrix metalloprotease 2*), *PITX2* (*paired like homeodomain 2*), *PPARG* (*peroxisome proliferator-activated receptor gamma*), *RGS7* (*regulator of G protein signaling 7*), *SH3PXD2A* (*SH3 and PX domains 2A*), *TTN* (*titin*), *TLR4* (*toll-like receptor 4*), *TNFRSF11B* (*tumor necrosis factor-α RSF11B*), *OLR1* (*oxidized low-density lipoprotein receptor 1*), and *PTGIS* (*prostaglandin I2 synthase*).

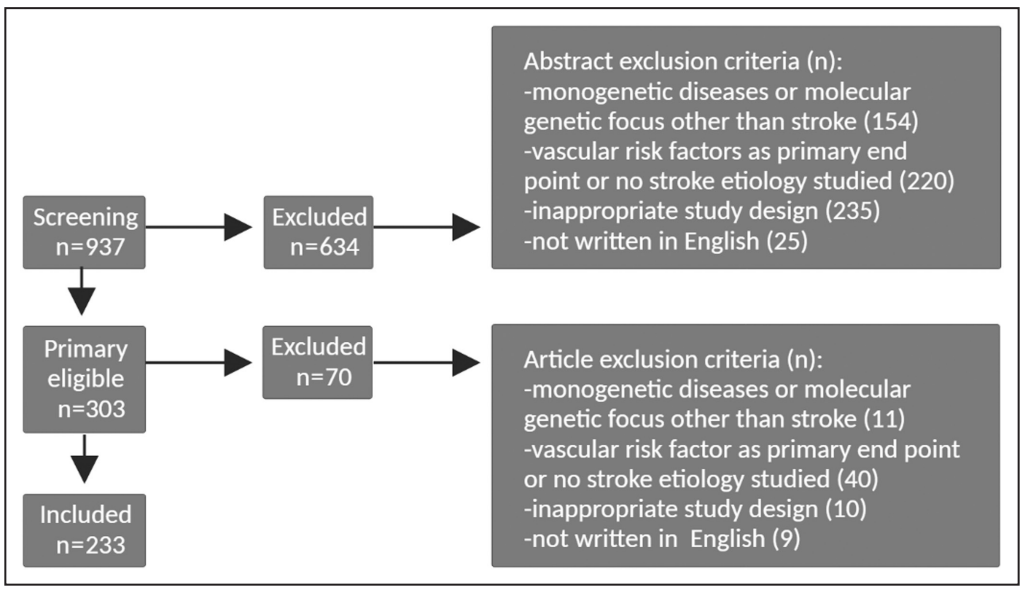


**Figure 1. Study flowchart.**
After systematic literature search, 937 studies were screened. There were 634 studies excluded according to the exclusion criteria after considering the abstract. There were 70 studies excluded due to above-mentioned exclusion criteria after a second review process in which the full text was studied. Finally, 233 studies were eligible for analysis.

**Table 1. Study Type, Studied Ancestry, and Summary of SNPs of the 233 Eligible Studies**

| General information | Value |
|---|---|
| Study type | |
| GWAS | 18 |
| Candidate gene analysis | 196 |
| Mendelian randomization | 19 |
| Other | 1 |
| Studied ancestry | |
| White | 135 |
| Black | 32 |
| Hispanic | 22 |
| Asian | 112 |
| Native American | 1 |
| Other | 4 |
| Differences in causes of SNPs | 188 |
| Relevant cause | Prevalence |
| LAA | 164 |
| Cardioembolism | 115 |
| SVD | 110 |
| CRY | 54 |
| OTH | 41 |
| Relevant SNPs | Prevalence |
| LAA | 110 |
| Cardioembolism | 48 |
| SVD | 51 |
| CRY | 19 |
| OTH | 4 |

Each study could cover ≥1 study type, ancestry, and cause. LAA, cardioembolism, and SVD were the most analyzed causes. CRY indicates cryptogenic stroke; GWAS, genome-wide association study; LAA, large artery atherosclerosis; OTH, other rare stroke causes; SNPs, single nucleotide polymorphisms; and SVD, small vessel disease.

## Overlaps of Genetic Variants Among Stroke Causes

Of note, there were some overlaps of genetic variants between cryptogenic and known stroke causes. This applied to 10 distinct SNPs. Figure 2 presents an overview on genetic variants that show an association with diverse stroke causes.

Interestingly, 6 risk genes with different SNPs had an agreement between LAA and CRY. Information on the SNPs, sample size, and effect size is provided in Table 3.

Information on genes and SNPs with an overlap between cardioembolism and CRY is provided in Table 4. Three of the 5 genes shared association with other causes as well, whereas TNF-α (tumor necrosis factor-α) and KCNK17 (potassium channel subfamily K member 17) were specifically associated with CRY and cardioembolism.

We identified variants in 5 genes, which show an overlap between SVD and CRY. Of these, eNOS (endothelial NO synthase) and TAFI (thrombin activatable fibrinolysis inhibitor) were associated only with SVD and CRY; the other relevant genes share overlap with ≥1 of the other causes (Table 5).

A particular variant in the *PDE4D* (*phosphodiesterase 4D*) gene was the only one that was associated with CRY and other rare stroke causes. However, other variants in the *PDE4D* gene shared significant SNPs with every stroke cause versus no strokes (Table 6).

# DISCUSSION

In this systematic review, we detected 937 studies that investigated common genetic variants in regard to stroke causes. Of note, the number of publications on this topic has increased exponentially in the past years. The types of studies have increasingly evolved from single-gene analyses to GWAS, just as the sample sizes of studies conducted as part of consortia have increased enormously. Over time, measures have been applied to overcome limitations of early GWAS, which were occasionally subject to winner's curse bias. A relevant proportion of SNPs, which were associated with CRYs, were derived from studies with small sample sizes as well as single-gene analyses. Thus, it was in the scope of this review to present an overview of the multitude of analyzed SNPs, with the known limitation that this field has gone through a remarkable technical development and is rapidly growing.

Far more studies have even been conducted on the question of the risk of stroke due to genetic variants per se.[6] In this context, work from the MEGASTROKE consortium stands out.[7] Malik et al identified 32 loci that are associated with stroke and described a subset of variants that relate to stroke subtypes, including overlaps between different vascular traits.[7] Georgakis et al recently described distinct genetic overlaps between CRY and known causes of stroke, especially LAA.[8] This would argue for a shared pathophysiology of embolic stroke of unknown source and atherosclerotic diseases, which would also be in line with current findings from clinical studies.[4,9]

Despite the extensive search for variants of interest on differences in causes in large data sets, we were able to identify only a few potential genetic risk factors in our study that provided evidence of an association with ≥1 specific stroke cause and CRYs. These variants are of interest in investigating potential hidden mechanisms in CRYs.

We identified several studies that revealed an association between apoE (apolipoprotein E) polymorphisms with atherosclerosis-related ischemic stroke (ie, LAA and SVD compared with CRYs). Interestingly, 2 studies also showed a higher risk for cardioembolism compared with CRYs in carriers of apoE polymorphisms.

**Table 2. SNPs With Association to a Distinct Stroke Cause in at Least 2 Included Studies**

| Gene abbreviation | Gene | SNP identified in >1 study | Associated cause |
|---|---|---|---|
| *ADBR2* | β-2 adrenergic receptor | rs1042714 | LAA, CRY |
| *ALOX5AP* | *5-lipoxygenase-activating protein* | rs10507391 | LAA, cardioembolism |
| *apoE* | *apolipoprotein E* | rs429358 | LAA, cardioembolism, SVD, CRY |
| | | rs7412 | |
| *CDKN2B-AS1* | *Antisense noncoding RNA in the INK4 locus* | rs2383207 | LAA, SVD |
| | | rs7857345 | LAA |
| *CRP* | *C-reactive protein* | rs1800947 | SVD |
| *CX3CR1* | *Fractalkine receptor* | rs3732378 | LAA |
| *CYP2C8* | *Cytochrome P450 2C8* | rs17110453 | LAA |
| *CYP4A11* | *Cytochrome P450 4A11* | rs9333025 | LAA |
| *ENOS* | *Endothelial NO synthase* | VNTR | SVD, CRY |
| *EPHX2* | *Epoxide hydrolase 2* | rs751141 | LAA |
| *FBG* | *Fibrinogen β* | rs1800787 | Cardioembolism, SVD |
| *HDAC9* | *Histone deacetylase 9* | rs2107595 | LAA |
| | | rs28688791 | LAA, SVD |
| *IL6* | *Interleukin-6* | rs1800795 | LAA, SVD |
| | | rs1800796 | |
| *ITAG2* | *Integrina-α 2* | rs1991013 | LAA |
| *LOC729065* | *Chromosome 4q25* | rs2200733 | Cardioembolism |
| *MMP3* | *Matrix metalloprotease 3* | rs35068180 | LAA |
| *MTHFR* | *Methylenetetrahydrofolate reductase* | rs1801133 | LAA, SVD, OTH |
| *PACERR/PTGS2* | *PTGS2 antisense NFKB1 complex-mediated expression regulator RNA* | rs20417 | LAA |
| *PDE4D* | *Phosphodiesterase 4D* | rs966221 | LAA |
| *PON1* | *Paraoxonase 1* | rs854560 | LAA, SVD |
| *SIRT6* | *Sirtuin 6* | rs107251 | LAA |
| *TBXAS1* | *Thromboxan A synthase 1* | rs41708 | LAA |
| *TNFSF4* | *Tumor necrosis factor superfamily member 4* | rs1234313 | LAA, cardioembolism |
| | | rs45454293 | |
| *TXA2R* | *Thromboxane A2 receptor* | rs1131882 | LAA |
| *ZFHX3* | *Zinc finger homeobox 3* | rs7193343 | Cardioembolism |

CRY indicates cryptogenic stroke; LAA, large artery atherosclerosis; OTH, other rare stroke causes; SNP, single nucleotide polymorphism; SVD, small vessel disease; and VNTR, various number tandem repeat.

There is a broad body of evidence that apoE polymorphisms come along with an increased risk for ischemic strokes per se.[10] By alterations of the structure and function of apoE, these polymorphisms have important implications on the lipoprotein metabolism, inflammation, and thus cardio- and cerebrovascular disease.[11] In carriers of such apoE polymorphisms who had a stroke, an atherosclerosis-related mechanism is thus more likely; however, atherosclerosis and atrial fibrillation, as the major embolic source in cardioembolism, often overlap and are pathophysiologically associated with each other.[9,12] Accordingly, it would be interesting to explore whether it is possible to distinguish individual mechanisms by apoE polymorphisms in studies with a higher granularity of clinical data. Of note, apoE is also implicated in Alzheimer pathology[13] and cerebral amyloid angiopathy, and recent experimental advances indicate a potential role of apoE-targeted immunotherapy in these pathologies.[14] Whether apoE-targeted therapy could also be of potential relevance in stroke prevention remains to be elucidated.

We found 1 study that showed a higher risk in patients with a polymorphism in the *TNF-α* gene for LAA and cardioembolism as compared with CRY. In accordance, a recent meta-analysis confirmed a link between TNF-α polymorphism as well as circulating TNF-α levels with ischemic stroke.[15] Although this finding seems plausible in light of the overwhelming evidence on inflammation and atherosclerosis,[16] further confirmatory studies are certainly needed before clinical relevance can be considered in regard to diagnosis of ischemic stroke causes.

Three studies reported an association between polymorphisms of ADBR2 (β-2 adrenergic receptor)

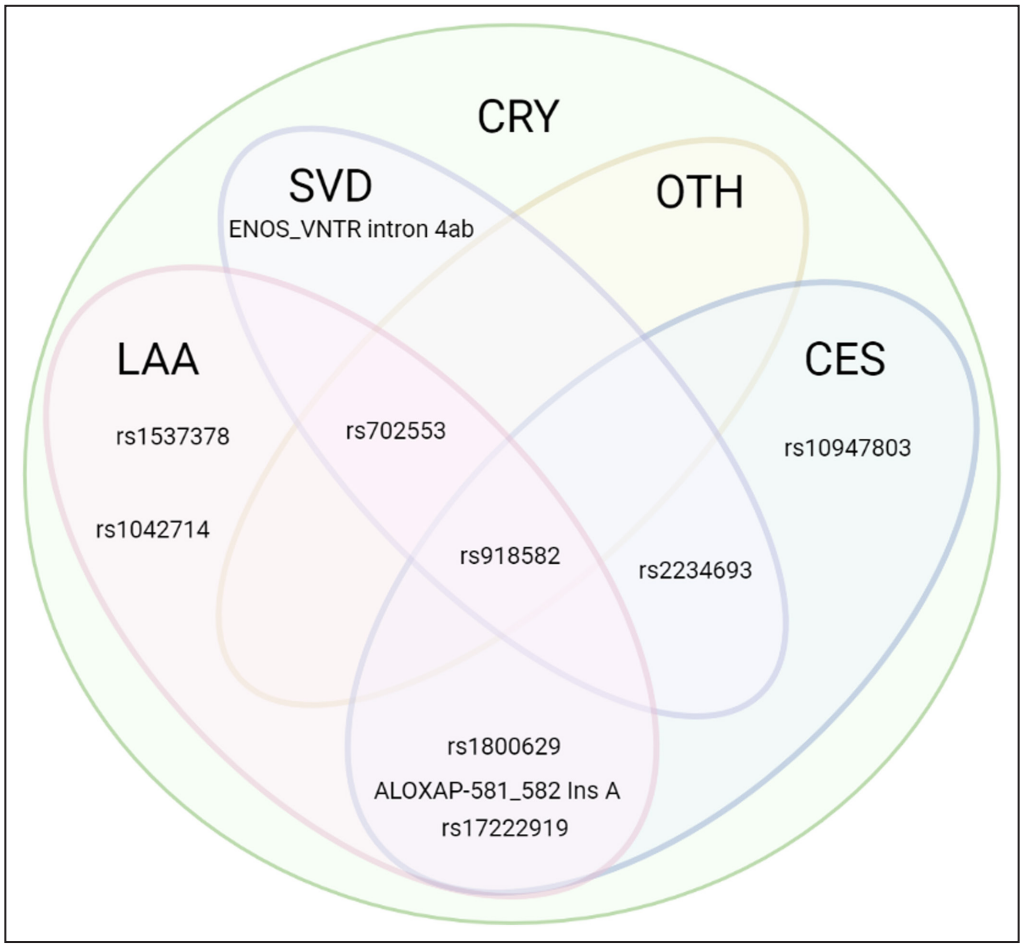


**Figure 2. Overlapping SNPs between CRY and the other causes.**
Ten SNPs had an overlap with CRY and another stroke cause. The position of the SNPs on the overlapping circles provides information about which causes are associated with CRY in every distinct SNP. For example, rs1537378 had an association with LAA and CRY, whereas rs702553 was associated with LAA, SVD, OTH, and CRY. ALOXAP indicates arachidonate 5-lipoxygenase activating protein; CES, cardioembolism; CRY, cryptogenic stroke; ENOS_VNTR, endothelial nitric oxide synthase various number tandem repeats; LAA, large artery atherosclerosis; OTH, other rare stroke causes; SNP, single nucleotide polymorphism; and SVD, small vessel disease.

with LAA and CRY. These polymorphisms may have substantial impact on cAMP generation and thus atherosclerosis.[17] The actual mechanisms explaining the effects of ADBR2 polymorphisms, however, need to be elucidated as well as any potential clinical applicability.

Polymorphisms in the *PDE4D* gene have been reported when comparing the various stroke causes with CRYs. Of note, the *PDE4D* gene is of pathophysiological interest in cerebrovascular disease, because its alterations may impact vascular cells, including cAMP signaling in vascular smooth muscle cells.[18] Interestingly, alteration in the *PDE4D* gene was predominantly observed in patients with stroke of distinct ancestry backgrounds.[19–21] However, our review revealed studies reporting differences in causes across different ancestries. Of note, the studies summarized in the present work consistently provided evidence for an association with LAA, cardioembolism, SVD, or strokes of other cause, respectively. Given this evidence, the *PDE4D* gene does not appear to specifically elucidate mechanisms of cryptogenic infarcts, but rather indicates its potential pathophysiological importance in stroke as a whole.[22]

Four studies revealed an association between LAA, cardioembolism, and CRY with variants of the *ALOX5AP* (*arachidonate 5-lipoxygenase-activating protein*) gene. The *ALOX5AP* gene encodes a cofactor of the leukotriene biosynthetic pathway in a variety of inflammatory responses.[21,23] Two variants, 581_582 insertion A and rs17222919, are localized in the promoter region,[21,24] whereas rs10507391 is an intronic variant.[25–27] Higher *ALOX5AP* gene expression levels were described in patients with myocardial infarction and ischemic stroke,[28,29] which emphasizes the probably

**Table 3. Genes With Overlap Between LAA and Cardioembolism**

| Gene | SNP/genetic variation | PMID | Cause | Outcome, n | Control, n | Effect size (95% CI) |
|---|---|---|---|---|---|---|
| *ADRB2* (β-2 adrenergic receptor) | rs1042714 | 19028820 | CRY | 200 | 459 | OR, 0.58 (0.35–0.96) |
| | | 17531924 | LAA+SVD | 215 | 236 | aOR, 1.33 (1.05–1.69) |
| | | 24966013 | LAA | 224 | 224 | OR, 3.9 (1.3–11) |
| *TNF-α* (*tumor necrosis factor-α*) | rs1800629 | 21219546 | LAA | 228 (EC 176, IC 52) | 500 | EC OR, 1.87 (1.068–3.302); IC, OR 2.67 (1.241–5.756) |
| | | | CRY | 105 | 500 | OR, 3.18 (1.68–6.027) |
| *ALOX5AP* (*arachidonate 5-lipoxygenase activating protein*) | 581_582 Ins A | 21893978 | LAA | 150 | 500 | OR, 3.50 (1.93–6.36) |
| | | | CRY | 129 | 500 | OR, 3.66 (1.92–6.94) |
| | rs17222919 | 25815512 | LAA | 704 | 925 | OR, 0.815 (0.687–0.967) |
| | | | CRY | 116 | 925 | OR, 0.661 (0.459–0.951) |
| | rs10507391 | 23076369 | LAA | 682 | 598 | Not specified |
| | | 23746795 | LAA | 237 | 610 | OR, 2.04 (1.279–3.275) |
| *ANRIL/CDKN2B-AS* (*antisense noncoding RNA in the INK4 locus*) | rs1537378 | 19475673 | LAA | 961 | 4202 | OR, 1.21 (1.09–1.35) |
| | | | CRY | 1266 | 4202 | OR, 1.11 (1.01–1.22) |
| | rs2383207 | | LAA | 731 | 3360 | OR, 1.15 (1.02–1.29) |
| | rs496892 | | LAA | 964 | 4190 | OR, 1.19 (1.07–1.33) |
| | rs564398 | | LAA | 970 | 4256 | OR, 1.10 (0.99–1.22) |
| | rs7044859 | | LAA | 962 | 4272 | OR, 1.19 (1.07–1.32) |
| | rs7865618 | | LAA | 962 | 4272 | OR, 1.19 (1.07–1.32) |
| *PDE4D* (*phosphodiesterase 4D*) | rs702553 | 22771915 | LAA | 230 (EC 82, IC 148) | 513 | EC OR, 3.11 (1.587–6.11); IC OR, 3.11 (1.754–5.53) |
| | | | CRY | 107 | 513 | OR, 3.78 (2.155–6.652) |
| | rs918582 | 16835261 | LAA | 27 | 207 | OR, 2,35 (1,22-4,53) |
| | | | CRY | 125 | 207 | OR, 1,50 (1,07-2,12) |
| | rs12153798 | 22771915 | LAA | 230 (EC 82, IC 148) | 513 | EC OR, 2.63 (1.366–5.069); IC OR, 3.10 (1.894–5.08) |
| | rs4133470 | 15802632 | LAA | 223 | 933 | Not specified |
| | rs2910829 | | | | | |
| | rs6450512 | 23076369 | LAA | 682 | 598 | Not specified |
| | rs966221 | 22045424 | LAA | 148 | 188 | OR, 3.38 (1.61–7.11) |
| | | 23076369 | LAA | 682 | 598 | Not specified |
| *apoE* (*apolipoprotein E*) | rs429358+rs7412 | 21296594 | LAA | 141 (EC 58, IC 83) | 167 | OR, 2.55 (1.07–6.05) |
| | | 29074556 | CRY | 23 | 64 | OR, 1.806 (1.049–3.111) |
| | | | LAA | 3 | 1 | OR, 16.525 (1.657–164.773) |
| | | 17095737 | LAA | 71 | 5785* | aOR, 2.12 (1.27–3.53) |
| | ε4 Allele | 21296594 | LAA | 141 (EC 58, IC 83) | 167 | OR, 2.85 (1.35–5.99) |
| | | 29074556 | CRY | 27 | 74 | OR, 1.694 (1.059–2.712) |
| | | | LAA | 27 | 74 | OR, 1.614 (1.007–2.587) |
| | ε2 Allele | 29074556 | LAA | 10 | 88 | OR, 0.5 (0.254–0.983) |
| | Apo E4-carrying + ACE Del/Del | 18027070 | LAA | 53 | 323 | OR, 2.26 (1.11–4.48) |

In 6 genes, an overlap between LAA and CRY was revealed. Outcome samples contained patients with stroke, and control samples contained no patients with stroke. OR or aOR was given for relevant outcome per copy of minor allele.

ACE indicates angiotensin-converting enzyme; aOR, adjusted odds ratio; CRY, cryptogenic stroke; EC, extracranial stenosis; IC, intracranial stenosis; LAA, large artery atherosclerosis; OR, odds ratio; PMID, PubMed identification; and SNP, single nucleotide polymorphism.

*A study with patients with and without stroke in the control and outcome group.

**Table 4. Genes With an Overlap Between Cardioembolism and CRY**

| Gene | SNP/genetic variation | PMID | Cause | Outcome, n | Control, n | Effect size (95% CI) |
|---|---|---|---|---|---|---|
| *ER-α* (*estrogen receptor-α*) | rs2234693 | 20699091 | Cardioembolism | 48 | 380 | OR, 3.792 |
| | | | CRY | 56 | 380 | OR, 3 |
| *TNF-α* (*tumor necrosis factor-α*) | rs1800629 | 21219546 | Cardioembolism | 74 | 500 | OR, 2.54 (1.244–5.217) |
| | | | CRY | 105 | 500 | OR, 3.18 (1.68–6.027) |
| *KCNK17* (*potassium channel subfamily K member 17*) | rs10947803 | 19647252 | Cardioembolism | 208 | 259 | OR, 1.47 (1.10–1.97) |
| | | | CRY | 118 | 259 | OR, 1.52 (1.01–2.27) |
| *ALOX5AP* (*arachidonate 5-lipoxygenase activating protein*) | rs10507391 | 23746795 | Cardioembolism | 91 | 610 | OR, 4.73 (2.661–8.439) |
| | 581_582 Ins A | 21893978 | CRY | 129 | 500 | OR, 3.66 (1.92–6.94) |
| | rs17222919 | 25815512 | CRY | 116 | 925 | OR, 0.661 (0.459–0.951) |
| *PDE4D* (*phosphodiesterase 4D*) | rs12153798 | 22771915 | Cardioembolism | 71 | 513 | OR, 0.38 (0.146–1.008) |
| | rs152312 | 21989204 | Cardioembolism | 24 | 30 | aOR, 3.85 (1.43–10.13) |
| | rs152341 | 15802632 | Cardioembolism | 80 | 933 | Not specified |
| | rs26949 | | | | | |
| | rs26950 | | | | | |
| | rs35382 | | | | | |
| | rs40512 | | | | | |
| | rs702553 | 22771915 | CRY | 107 | 513 | OR, 3.78 (2.155–6.652) |
| | rs918582 | 16835261 | CRY | 125 | 207 | OR, 1.50 (1.07-2.12) |

Five genes revealed an overlap between cardioembolism and CRY. Outcome samples contained patients with stroke, and control samples contained no patients with stroke. OR or aOR were given for relevant outcome per copy of minor allele.

aOR indicates adjusted odds ratio; CRY, cryptogenic stroke; OR, odds ratio; PMID, PubMed identification; and SNP, single nucleotide polymorphism.

underscored potential of variants in regulatory regions. A meta-analysis showed a high heterogeneity in studies about *ALOX5AP* gene variants and all ischemic strokes,[25] whereas its role in stroke causes needs to be further elucidated.

Sequence variants on chromosome 9p21.3 at the antisense noncoding RNA in the INK4 locus were identified as risk factors for atherosclerotic heart diseases due to GWAS.[30,31] Some studies revealed an impact of these variants on ischemic stroke,[32] but their impact, especially on stroke causes, is not well characterized. Gschwendtner et al published a multicenter analysis that revealed 1 genetic variant associated with LAA and CRY and 5 additional variants involved in LAA.[33] Chromosome 9p21.3 seems to be a heterogeneous risk locus for atherosclerotic diseases as well as other large artery diseases, such as aneurysms.[8] Its role in stroke causes and underlying pathomechanisms is not well established, whereas it is an interesting locus to further investigate.

We identified 1 study that showed an association between the *estrogen receptor-α* gene (*ER-α*) polymorphism PvuII (rs2234693) and cardioembolism, SVD and CRY. There is a large body of evidence that ER-α gene variation plays an important role in cardio- and cerebrovascular diseases, whereas its pathophysiological role is still unrevealed.[34–36] Munshi et al described an increased stroke risk in postmenopausal women in South India due to the PvuII polymorphism and in association with low estradiol levels.[37] It seems worthwhile investigating the effect of this polymorphism in other ethnic groups.

Another study revealed an association of the *KCNK17* gene polymorphism (rs10947803) and cardioembolism as well as CRY.[38] Polymorphisms in the *KCNK17* gene could lead to an increased extracellular potassium concentration via abnormal channel opening, which could result in a dilatation of cerebral blood vessels.[39] The respective pathomechanisms require deep exploration and should be experimentally addressed in future studies.

Two studies discovered aberrations in intron 4 (insertion/deletion/tandem repeat) of the *eNOS* gene as a risk factor for small vessel and CRYs. *eNOS* is a well-known player in NO metabolism and therefore in atherosclerosis. The insertion/deletion genotype was associated with a risk reduction of lacunar stroke,[40] whereas tandem repeat polymorphisms are accompanied by an increased risk of CRYs. Both studies had small sample sizes, requiring replication and deeper investigation.

An important limitation of the results of large genetic studies is the low granularity at the level of clinical patient characteristics. Therefore, potentially embolic sources, which are often coexistent, are usually not considered, and the cause classification only allows categorization, usually based on the traditionally used Trial of ORG 10172 in Acute Stroke Treatment classification. This

**Table 5. Genes With Overlap Between SVD and CRY**

| Gene | SNP/genetic variation | PMID | Cause | Outcome, n | Control, n | Effect size (95% CI) |
|---|---|---|---|---|---|---|
| *ER-α* (*estrogen receptor-α*) | rs2234693 | 20699091 | SVD | 54 | 380 | OR, 4.667 |
| | | | CRY | 56 | 380 | OR, 3 |
| *eNOS* (*endothelial nitric oxide synthase*) | Intron 4b/a (27-bpTR) variable number tandem repeat | 14963277 | SVD | 300 | 600 | OR, 0.55 (0.35–0.86) |
| | | 30997974 | CRY | 112 | 160 | OR, 2.715 (1.73–4.26) |
| *TAFI* (*thrombin activatable fibrinolysis inhibitor*) | H1B | 17272741 | SVD | 124 | 600 | aOR, 0.55 (0.35–0.87) |
| | H2D | | CRY | 162 | 600 | aOR, 1.99 (1.16–3.40) |
| | H2E | | | | | aOR, 2.48 (1.38–4.44) |
| | H2B | | | | | aOR, 1.57 (1.03–2.40) |
| *PDE4D* (*phosphodiesterase 4D*) | rs702553 | 22771915 | SVD | 22 | 513 | OR, 4.54 (2.359–8.767) |
| | | | CRY | 107 | 513 | OR, 3.78 (2.155–6.652) |
| | rs918582 | 16835261 | SVD | 45 | 207 | OR, 1,85 (1.12–3.05) |
| | | | CRY | 125 | 207 | OR, 1,50 (1.07–2.12) |
| | rs12153798 | 22771915 | SVD | 22 | 513 | OR, 2.20 (1.069–4.541) |
| *apoE* (*apolipoprotein E*) | rs429358 + rs7412 | 29074556 | SVD | 5 | 1 | OR, 11.298 (1.306–97.72) |
| | ε3/ε4 Allele | | CRY | 23 | 64 | OR, 1.806 (1.049–3.111) |
| | ε4 Allele | | | 27 | 74 | OR, 1.694 (1.059–2.712) |

We found 5 genes with an overlap between SVD and CRY. Outcome samples contained patients with stroke and control samples contained no patients with stroke. OR or aOR was given for relevant outcome per copy of minor allele.

aOR indicates adjusted odds ratio; CRY, cryptogenic stroke; OR, odds ratio; PMID, PubMed identification; SNP, single nucleotide polymorphism; and SVD, small vessel disease.

classification, however, only incompletely represents the actual biological spectrum of cerebrovascular disease. Moreover, overlaps between different causes of stroke may also be due to shared risk factors of distinct causes.

As a general limitation, it is noteworthy that only 1 of the 18 GWAS included patients with CRY, and thus to date, these patients are understudied in GWAS.

In our study, we performed mapping via reference SNP cluster identification, which may generally lead to a bias in that SNPs are potentially omitted in case of a high linkage disequilibrium in GWAS. However, the risk of such bias should be considered irrelevant in our study, because only 1 GWAS reported a hit for CRYs, whereas all other hits were detected in candidate gene analysis.

In consideration of the high burden of CRY, these patients should be more frequently addressed in future GWAS.

Moreover, further studies investigating different stroke mechanisms at once are necessary to identify polymorphisms that are distinctly associated with a particular cause of ischemic stroke.

Of note, we did not perform a meta-analysis or meta-regression, because we aimed to provide a systematic state of the art overview of the current literature.

It is noteworthy that potential associations of distinct SNPs with stroke causes may be missed due to low statistical power of the respective studies. When studying rare variants, the effect estimates from regression models may also be biased, and corresponding correction methods, such as Firth correction, are only infrequently used. In GWAS, sample sizes needed for providing evidence for the association of defined SNPs with certain stroke risks moreover conflict with the need of high granularity of clinical data. One possible approach to overcome these shortcomings could be the application of deep phenotyping in so-called phenotype-based genetic association studies, which have already been successfully applied in other highly heterogenous multifactorial conditions.[41,42] Due to higher granularity of clinical data, phenotype-based genetic association studies

**Table 6. Genes With Overlap Between OTH and CRY**

| Gene | SNP/genetic variation | PMID | Cause | Outcome, n | Control, n | Effect size (95% CI) |
|---|---|---|---|---|---|---|
| PDE4D (phosphodiesterase 4D) | rs702553 | 22771915 | OTH | 28 | 513 | OR, 6.64 (2.869–15.38) |
| | | | CRY | 107 | 513 | OR, 3.78 (2.155–6.652) |
| | rs918582 | 16835261 | CRY | 125 | 207 | OR, 1.50 (1.07–2.12) |

One gene showed an overlap between OTH and CRY. Outcome samples contained patients with stroke, and control samples contained no patients with stroke. OR was given for relevant outcome per copy of minor allele.

CRY indicates cryptogenic stroke; OR, odds ratio; OTH, other rare stroke causes; PMID, PubMed identification; and SNP, single nucleotide polymorphism.

would enable stratification by diverse risk factors and thus contribute to a better understanding of the link between specific genetic variants with stroke mechanisms. Phenotype-based genetic association studies could thus be a promising methodology to elucidate cryptogenic causes of ischemic stroke.

## CONCLUSIONS

In recent years, the number of studies on genetic risk factors of stroke causes has increased rapidly. Nevertheless, evidence for associations of single variants with stroke causes is currently limited to a few polymorphisms. A major limitation of genetic studies on this topic is the relatively low granularity of clinical data. Future studies should attempt to address this restriction to advance the promising approach of elucidating the cause of stroke at the genetic level toward clinical application in the sense of precision medicine.

## ARTICLE INFORMATION

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### Disclosures

None.

### Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the published article.

### Supplemental Material

Data S1.

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# SUPPLEMENTAL MATERIAL

**Data S1.**

## Supplemental Methods

### Full-scale search strategy:

("STROKE" OR "ISCHEMIC STROKE" OR "ISCHAEMIC STROKE" OR "CEREBROVASCULAR DISEASE") AND ("GWAS" OR "POLYMORPHISMS" OR "SNPS" OR "SINGLE NUCLEOTIDE POLYMORPHISM" OR "GENOME WIDE ASSOCIATION STUDY" OR "MENDELIAN RANDOMIZATION" OR "MENDELIAN RANDOMISATION") AND ("ETIOLOGY" OR "AETIOLOGY" OR "ATRIAL FIBRILLATION" OR "ATRIAL CARDIOPATHY" OR "SMALL VESSEL DISEASE" OR "CAROTID DISEASE" OR "CAROTID STENOSIS" OR "CAROTID PLAQUE" OR "MACROANGIOPATHY" OR "MICROANGIOPATHY" OR "EMBOLIC STROKE OF UNDETERMINED SOURCE" OR "ESUS" OR "CRYPTOGENIC STROKE").