

# Chapter 2

## Familial Occurrence and Heritability of Stroke

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### Introduction

Clustering of clinical strokes among related family members is an indication of the aggregate genetic, environmental, and lifestyle factors shared by these family members, all of which could increase susceptibility to stroke. A family history of stroke or of other atherosclerotic events, such as a myocardial infarction, is a moderate risk factor for stroke, as observed in twin, cohort, and case-control studies [1]. With the exception of some rare Mendelian disorders, most stroke occurring in a clinic or population sample has a complex inheritance pattern, but the relative importance of genetic factors can be estimated by studying the familial occurrence of stroke. Patterns of familial aggregation can also direct which subgroups to investigate further as more likely to share common underlying genetic variation; thus we could define subgroups by age, gender, ethnicity, presence of vascular risk factors, or stroke subtype [2, 3]. Focused investigations within these subgroups using modern genotyping techniques (phenotyping ‘splitting’) can increase the yield in identifying gene variants associated with stroke [4, 5]. As a predisposing risk factor, family history can be used clinically for risk prediction and to encourage primary disease prevention [6].

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Establishing the Heritability of Stroke

Heritability may be defined as the proportion of the observed phenotypic variation among individuals, in traits or in risk of disease, that is attributable to genetic variability. Family history and verified familial occurrence studies, particularly twin studies [7, 8], were instrumental in demonstrating that part of the variability recorded in the occurrence of stroke was attributable to genetic variation [9]. Familial aggregation of stroke risk factors, such as hypertension and smoking, could partially explain these associations. Studies that adjusted analyses for vascular risk factors showed an attenuated association. However, family history of stroke persists in these studies as an independent risk factor [1, 10].

New methods have used data from genome-wide association studies (GWAS) to confirm the heritability of stroke. Genome-wide complex trait analysis, using known genetic associations with stroke, estimates the heritability of ischemic stroke and intracerebral hemorrhage. [11, 12] Heritability of endophenotypes, such as MRI markers of subclinical disease or intermediate vascular risk factors, have also been investigated. The degree of white matter hyperintensities measured on brain MRI, for example, is estimated to have a heritability as high as 55–80% [13, 14]. Heritability estimates for these phenotypes and endophenotypes are shown in Table 2.1.

Given the wide range of phenotypes and endophenotypes that characterize a clinical stroke, it is evident that many genes are involved in contributing to stroke risk. Genes may interact with other genes, as well, causing epistatic modification, which can impact true heritability. The majority of family and genetic studies have been performed using populations of European descent. The distribution and heritability of stroke may differ by ethnicity [15].

**Table 2.1** Heritability of ischemic stroke, stroke subtypes, and endophenotypes

Any ischemic stroke [11]	38%
Ischemic stroke subtype [11]	
Large vessel ischemic stroke	40%
Cardioembolic stroke	33%
Small vessel ischemic stroke	16%
Endophenotypes	
White matter hyperintensities [13, 14]	55–80%
Carotid intima media thickness [16, 17]	21–38%
Carotid artery plaque [17–19]	23–78%
Mediating risk factors [20]	
Hypertension	40–60%
High-density lipoprotein	25–50%
Intracerebral hemorrhage (ICH) [12]	44%
Deep ICH	34%
Lobar ICH	73%

## **Twin Studies to Investigate the Genetic Epidemiology of Stroke**

Twin studies are important for differentiating the role of genetic factors from that of shared environmental or lifestyle influences for stroke. Up to a doubling of risk is observed in monozygotic twins compared to dizygotic twins or siblings [1, 7]. Monozygotic twins are also more likely to have comparable increased volume of white matter hyperintensities on brain MRI than dizygotic twins [13]. A challenge for this type of study is the recruitment of sufficient twin pairs to analyze by subgroups, such as by ethnicity or stroke subtype. Stroke is common at older ages, and twins may be more likely to die of unrelated diseases as they age, so capturing sufficient cases may be difficult. Similar challenges are seen in recruiting non-twin sibling pairs [21].

## **Parental Stroke and Risk of Stroke in Offspring**

The effects of familial relationship in family history of stroke have been investigated in prospective cohort and case-control studies [1, 10, 22–31]. In the Framingham Heart Study Original (parental) and Offspring cohorts, parental stroke by 65 years of age resulted in a nearly threefold increased risk of stroke in the offspring [10]. The risk of stroke was highest in those offspring who also had a stroke before 65 years of age [10, 27]. A family history of stroke in both parents can more than double the risk of stroke [23, 32]. Parental history of stroke was associated with subclinical (silent) cerebral infarct, after adjustment for vascular risk factors [31]. Studies to date have not found a clear association between parental history of stroke and TIA or recurrent stroke [33–35].

## **Risk of Stroke Between Siblings**

A history of ischemic stroke in a sibling is associated with an increased risk of ischemic stroke in a proband, and the same pattern is seen in concordance of hemorrhagic stroke between siblings [36]. Stroke in siblings may also be associated with risk of recurrent stroke and with stroke severity [37, 38]. Co-existence of stroke is higher in full, than in half siblings [39]. Environmental and genetic interactions may be even more pronounced among siblings, who share parents, common risk factor exposures, and lifestyle behaviors.

Siblings share similar cardiovascular risk factors [40, 41] but may not always develop similar stroke subtypes [36, 42–44]. Associations persist however, even after adjustment for known vascular risk factors, suggesting that genetic factors may have an independent mechanism and heritability apart from conventional risk factors [10, 37]. There may also be differences across ethnicities for how stroke and vascular risk factors aggregate between siblings [15].

## Age at Onset with Familial Aggregation of Stroke

The extent to which genetic factors increase stroke risk appears to be age dependent. Typically, family history of stroke is a stronger stroke risk factor when either the affected first-degree relative or the individual stroke patient with positive family history are younger at the time of the stroke [1, 45–47]. In meta-analysis, family history of stroke was shown to be more frequent in studies that restricted the age of either the proband or the relatives to <70 years [1]. Genetic factors increasing risk for stroke may be enriched in families with early-onset of the disease. The proband may develop stroke at a younger age due to influences from the shared environment, adoption of similar lifestyle behaviors, as well as shared genetics [45, 48, 49].

## Family History and Sex Differences

Differences in stroke risk associated with parental stroke are observed according to the sex of the proband and to whether there is a maternal or paternal history of stroke. Female stroke patients are more likely to have a first-degree relative with stroke, compared to male patients, and they are more likely to report a maternal history of stroke [10, 50–52]. An excess in affected sisters of female probands has also been observed [50]. In contrast, male probands are no more likely to have a paternal than a maternal history of stroke in many studies [53]. These observations suggest a sex-specific interaction [53, 54].

Sex differences, in female stroke patients overall and in younger cohorts, may be explained by genetic, developmental, and environmental pathways. Penetrance may be increased in females due to inheritance of mitochondrial DNA. Depending on the sex of the parent transmitting the gene, there may be differential imprinting of a disease susceptibility gene. Special imprinting may occur through sex chromosomes or mitochondrial inheritance [53]. In utero effects, stimulated by the immune system, tobacco, drugs, diet, or factors associated with socioeconomic status of the mother, for example, may cause specific epigenetic changes in the fetus. Fetal programming in certain environments may increase the risk of stroke as an adult. Potential differences between maternal and paternal transmission of stroke need further study [22, 28].

## Familial Aggregation by Stroke Phenotype

A few studies have related family history of stroke to ischemic stroke subtypes of small artery occlusion and large-artery atherosclerosis [10, 26, 27]. Other subtypes, including cardioembolism, rare causes such as dissection, and undetermined causes, may share less significant or no association with family history of stroke [27, 51].

Data from the Framingham Heart Study showed that increased risk of stroke in offspring with a parental history of stroke was most associated with atherosclerotic brain infarction. This category includes small-vessel occlusion, ‘lacunar’ infarctions, and large-artery atherosclerosis [10].

Underlying disorders for cerebral small vessel disease may be more heterogeneous than for large-artery atherosclerosis. This may partly explain why heritability of large vessel disease is observed to be higher [26, 27]. Heritability of carotid artery stenosis has been studied, showing a moderate association with family history of stroke [55]. Investigators were unable to correlate family history of stroke to stroke subtypes in an Asian population, specifically with risk of intracranial atherosclerotic disease [37]. Cardioembolic stroke may show less association with family history due to the heterogeneous etiology of the embolic sources, such as valve disease, myocardial infarction, patent foramen ovale, and cardiomyopathy [27]. There may be fewer overall cases of stroke due to cardioembolism, or these may be misclassified during hospitalization due to unrecognized factors, such as paroxysmal atrial fibrillation.

Intermediate phenotypes, such as neuroimaging biomarkers of cerebral small vessel disease, have also been studied in relation to family history of stroke. White matter hyperintensities seen on brain MRI are associated with stroke in first degree relatives [13, 56]. Familial aggregation is associated with asymptomatic lacunar infarcts in younger stroke patients age <65 years [46]. Further research is needed to confirm associations of family history of stroke with cerebral microbleeds, enlarged perivascular (‘Virchow-Robin’) spaces, and cortical cerebral microinfarcts [57–59]. Methods for phenotyping stroke and subclinical disease are important for genetic studies, as the genetics of stroke may be subtype dependent [4, 5, 60].

Table 2.2 displays associations of family history of stroke in first degree relatives, parents, or siblings, with ischemic stroke subtype. Familial aggregation of intracerebral hemorrhage and cerebral amyloid angiopathy are discussed in a subsequent chapter. Intracerebral and subarachnoid hemorrhage risk are associated with a positive family history, as summarized in Table 2.3.

## Challenges in Family History Studies of Stroke

The variability of results from family history studies may be partially attributed to misclassification of stroke cases or insufficient data regarding associated vascular risk factors. Inaccurate reporting of family history may underestimate the heritable component of stroke. Insufficient adjustment for confounding factors may overestimate heritability.

Recall bias may occur in case-control studies because stroke patients are more likely to recall or know of a family history of stroke than controls, who have not suffered the disease or inquired with family members [68]. The accuracy of offspring reports of parental history of stroke is highest where no stroke has occurred in the

**Table 2.2** Representative studies associating family history of stroke to increased stroke risk, adjusted for vascular risk factors

	All ischemic stroke [1, 10, 27, 39, 61]	Stroke recurrence [33]	Small-artery occlusion [26, 27, 45, 62]	Carotid artery stenosis [55]	Large-artery atherosclerosis [26, 27, 45]	Cardioembolic stroke [26, 27, 45]	Cryptogenic or undetermined stroke [26, 27, 45]
First degree relative	OR 1.3–1.8	HR NS-2.1 <sup>a</sup>	OR NS <sup>b</sup>	OR 1.4	OR 1.7 <sup>b</sup>	OR NS <sup>b,c</sup>	OR NS <sup>b</sup>
			OR 1.8 <sup>c</sup> –2.8		OR 1.9 <sup>c</sup> –2.1		OR 1.7 <sup>c</sup>
			RR 2.9				
Parental stroke	OR 1.9–2.2 <sup>d</sup>	HR NS	RR 4.5	OR NS	<sup>e</sup>	<sup>e</sup>	<sup>e</sup>
Sibling stroke	OR 1.7	HR 1.7	RR 2.1	OR 1.5	<sup>e</sup>	<sup>e</sup>	<sup>e</sup>
	RR 1.6						

OR odds ratio, RR relative risk, HR hazard ratio, NS non-significant association

<sup>a</sup>Relative’s age at stroke onset <50 years

<sup>b</sup>First degree relative stroke by ≤65 years of age

<sup>c</sup>Family history of stroke in patients with stroke <70 years of age

<sup>d</sup>Parental stroke by ≤65 years of age

<sup>e</sup>Unknown or data unavailable

**Table 2.3** Increased risk of intracranial hemorrhage in patients with family history of hemorrhagic stroke, adjusted for vascular risk factors

	Intracerebral hemorrhage [26, 47, 63, 64]	Subarachnoid hemorrhage [65–67]
Increased risk with positive family history of ICH/SAH	OR 2.1–6.3	OR 3.2 <sup>a</sup> –4.3
	Lobar ICH: OR 3.9	
	Non-lobar ICH: OR 5.4	

<sup>a</sup>First degree relative with subarachnoid hemorrhage or intracranial aneurysm

parent [69]. Family history of subarachnoid hemorrhage, a rare outcome, is particularly difficult to ascertain [70]. Research with family history data need to consider not only whether or not there is a positive family history but also the number of relatives affected [71].

Methods of ascertaining and recording the familial occurrence of stroke include recall by the proband in a structured interview or through use of a questionnaire. Concordance between reporting of stroke by parents and offspring is good when offspring are interviewed in a standardized manner by a health professional [72]. There are no differences between men and women in recall of family history when one examines data from community-based and hospital studies [69, 72]. Studies may also collect data on cerebrovascular disease within a family from their death certificates, although the accuracy of these data has been called into question [73]. Other sources include hospital and outpatient documentation, review of parental medical records, and data from medical registries. Hospital studies are susceptible

to inclusion bias. Multigenerational cohort or clinic-based studies have the advantage of directly interviewing both parents and all offspring for information regarding whether or not they ever developed symptoms suggestive of a stroke and examining them for any residual signs of an old stroke. This is arguably the most accurate way to ascertain familial co-occurrence of stroke. A final factor that may introduce bias would be misattributed paternity. Rates of non-paternity are very low and this would have little effect overall.

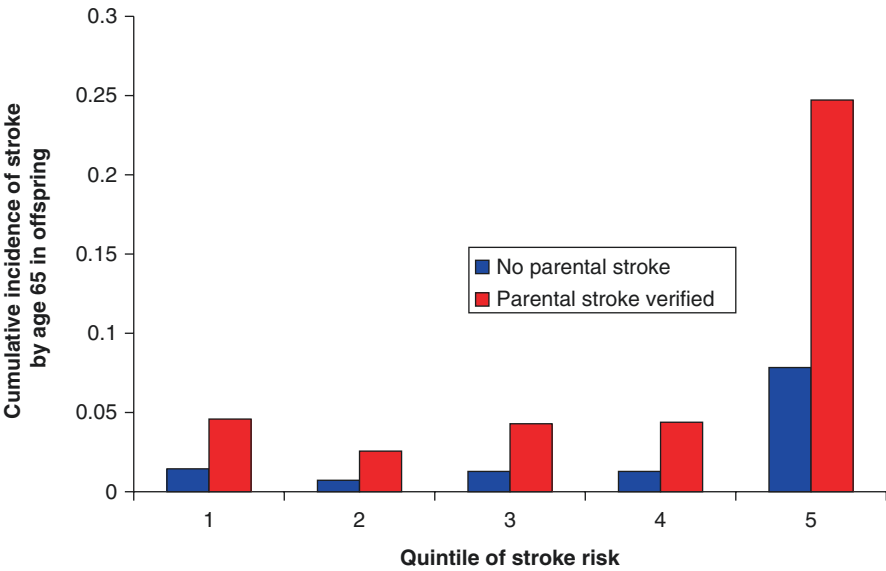
Hemorrhagic and ischemic stroke types are frequently analyzed together in older studies. Ascertainment bias can occur where these types are not distinguished or if there is no information on stroke subtype. This may occur especially in the parents' generation, as older patients may have worse recall of distant events. Also, with strokes that occurred prior to 1970, the diagnosis of stroke subtypes was only reliable for fatal events that came to autopsy, as the available technologies such as a carotid arteriogram were more dangerous, less routinely undertaken, and less capable of correctly classifying the stroke type. CT scans were not widely available before the late 1970s and modern neuroimaging with MRI came into clinical use only in the 1990s.

## Research Application in Genetic Studies

Family studies in stroke have provided strong evidence of familial aggregation, suggesting that research in stroke genetics can identify gene variants responsible for increasing disease risk. Candidate genes account for stroke in many monogenic disorders, such as the NOTCH3 gene in CADASIL (see Chap. 6), explaining the grouping of stroke in certain families. GWAS and next-generation sequencing studies have identified over a dozen gene variants associated with stroke. These studies could be enriched by findings exploring stroke heritability patterns using various designs of family history studies. Future research would benefit from differentiation of ischemic and hemorrhagic stroke types, classification of ischemic stroke subtypes, subgroup analyses by age and gender, and adjustment for intermediate phenotypes or mediators of increased stroke risk. Well-defined subtypes allow investigators to identify specific pathogenic pathways that can be targeted for preventive strategies and treatments.

## Clinical Application

One clinical application of family history studies is emphasizing the urgent need for, and benefits to, addressing environmental or lifestyle (modifiable) risk factors which predispose to disease in the person with a strong inherited (non-modifiable) risk profile. Data in Fig. 2.1, from the Framingham Heart Study, show that aggregation of vascular risk factors greatly amplifies the stroke risk associated with family history [10]. Thus, intense risk factor management can mitigate the increased



**Fig. 2.1** Cumulative incidence of all stroke in offspring by quintile of baseline Framingham Stroke Risk Profile (FSRP) score\* for offspring with and without parental occurrence of stroke before 65 years of age (Seshadri, et al. *Circulation*, 2010). \*FSRP: covariates include age, sex, systolic blood pressure, antihypertensive therapy, diabetes mellitus, smoking status, history of cardiovascular disease other than stroke, and the presence of atrial fibrillation or left ventricular hypertrophy on electrocardiogram

Born a twin? Yes (identical) Yes (fraternal) No		Were you adopted? Yes No	
First degree relative		Age at first diagnosis of stroke	Age at death
Biological mother			
Biological father			
Female siblings	Number:		
Male siblings	Number:		

**Fig. 2.2** Proforma for family history of stroke

risk from a positive family history. Separate research has shown associations between family history of stroke and specific modifiable risk factors, such as blood pressure [74].

In determining stroke risk, prediction algorithms may incorporate family history of stroke to improve clinical risk prediction. Used as a screening tool, practitioners can encourage behavioral modification or medications to prevent disease. Figure 2.2 is an example of a proforma that can be used in clinical practice to collect information about family history of stroke.



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