A Family History of Stroke Is Associated with Increased Intima-Media Thickness in Young Ischemic Stroke - The Norwegian Stroke in the Young Study (NOR-SYS)

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Abstract

Background and Purpose

Positive family history (FH+) of cardiovascular disease (CVD) is a risk factor for own CVD. We aimed to analyze the effect of different types of FH (stroke, coronary heart disease (CHD), peripheral artery disease (PAD) on carotid intima-media thickness (cIMT) in young and middle-aged ischemic stroke patients.

Methods

First-degree FH of CVD was assessed in ischemic stroke patients ≤ 60y using a standardized interview. Carotid ultrasound was performed and far wall cIMT in three carotid artery segments was registered, representing the common carotid (CCA-IMT), carotid bifurcation (BIF-IMT) and the internal carotid artery (ICA-IMT). Measurements were compared between FH+ and FH negative groups and stepwise backward regression analyses were performed to identify factors associated with increased cIMT.

Results

During the study period 382 patients were enrolled, of which 262 (68%) were males and 233 (61%) reported FH of CVD. Regression analyses adjusting for risk factors revealed age as the most important predictor of cIMT in all segments. The association between FH+ and cIMT was modified by age (p = 0.014) and was significant only regarding ICA-IMT. FH+ was associated with increased ICA-IMT in patients aged < 45y (p = 0.001), but not in patients ≥ 45y (p = 0.083). The association with ICA-IMT was present for a FH of stroke (p = 0.034), but not a FH+ of CHD or PAD.
Conclusions
FH of stroke is associated with higher ICA-IMT in young ischemic stroke patients. Subtyping of cardiovascular FH is important to investigate heredity in young ischemic stroke patients.

Trial Registration
ClinicalTrials.gov NCT01597453

Introduction
Family history (FH) of cardiovascular disease (CVD) is a risk factor for CVD.[1–3] Carotid intima media thickness (cIMT) is associated with CVD development, although the clinical value in predicting future vascular events is unclear.[4, 5] The 2013 update of the ACC/AHA guidelines on cardiovascular risk assessment withdrew the previous Class IIA recommendation to use cIMT measurements for cardiovascular risk stratification.[6] A recent meta-analysis found no association between cIMT progression measured by serial ultrasound measurements and future risk of CVD.[7] However, a recent study showed that increased cIMT is associated with risk factors for CVD and with first time stroke or myocardial infarction in patients < 45y.[8] Adding maximum internal carotid artery IMT (ICA-IMT) to a traditional risk stratification score has improved prediction of CVD events.[9] Increased cIMT is seen in children, adolescents and young adults with a history of premature parental coronary heart disease (CHD), suggesting an increased vulnerability to vascular risk factors.[10–13] A FH of premature CVD shows strong association with both CHD[14] and stroke[15] and the association between a FH of parental stroke <60y of age and increased ICA-IMT as a good marker of hereditary stroke risk.[16] Increased ICA-IMT in ischemic stroke patients compared with controls and higher ICA-IMT in subjects with a FH of CVD have been reported in young patients.[17] Atherosclerosis is an inflammatory process that starts early in life, with a complex genetic and environmental chain of causality.[18–20] Increased IMT during childhood correlates well with the risk factor burden, and is considered an early manifestation of atherosclerosis.[21] ICA-IMT may be an easily accessible proxy to assess genetic risk in young ischemic stroke patients. We aimed to analyze associations between a FH of different CVD events and standardized segment cIMT measurements in young and middle-aged ischemic stroke patients included in the Norwegian Stroke in the Young Study (NOR-SYS).

Materials and Methods
Study population
All patients ≤ 60y with suspected stroke in the Bergen area with approximately 360,000 inhabitants, are admitted to the Stroke Unit at Haukeland University Hospital. From 1st September 2010 to 31st August 2015, 391 consecutive patients aged 15 to 60y were prospectively included in NOR-SYS after documented acute ischemic stroke, 98.5% documented by magnetic resonance imaging (MRI) and the remaining by computed tomography (CT). The methods and rationale of NOR-SYS have been described in detail previously.[22] Three of the admitted patients died early from basilar occlusion and written consent with family members was not obtained. Four patients were adopted and had unknown biological parents and two patients were after inclusion found to have other disease than ischemic stroke, and were therefore
excluded from this study. Young adults were defined < 45y, whereas patients aged 45 to 60y were defined as middle-aged.

Family history
The FH of stroke, CHD and peripheral artery disease (PAD), was assessed in first-degree relatives (FDRs) using a face-to-face, standardized, questionnaire-based interview, as previously described.[23] The patient was interviewed within the first few days of admission and FH was considered positive (FH+) if the patient reported ≥ 1 FDR with CVD. The patient was designated FH negative (FH-) if no family members with CVD were reported. In 26 patients having aphasia or other communication difficulties a close relative was consulted as a secondary source of information during the interview, seven received help from one or both parents, 14 from a spouse, three from offspring and two from a sibling.

Risk factor definitions
Patients were interviewed regarding working status and education and grouped accordingly. Diabetes mellitus (DM), hypertension (HT) and hypercholesterolemia were considered present if diagnosed before hospital admission and treated either by lifestyle changes and or medication. Years of treatment were available and calculated for DM and HT. Blood pressure (BP) was measured in both arms using appropriate cuff size after 15–30 minutes rest in supine position. These measurements were used to calculate mean systolic and diastolic BP. Serum glucose; low density lipoprotein (LDL), high density lipoprotein (HDL) and total cholesterol were measured. Patients were grouped as active smoker, previous smoker if cessation for at least one year, or never smoker. Degree of tobacco exposure was defined by pack-years, i.e. number of cigarette packs (20cig/pack) per day multiplied by number of years of active smoking. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist-hip ratio (WHR) was calculated dividing waist circumference by hip circumference. Activity score was defined as an ordinal variable with range 0–5 and composed household activities, outdoor walks and active exercise. We defined inactivity/no physical activity of significance as 0, regular household activity and maintenance work as 1, outdoor walks 1–3h/week as 2, outdoor walks exceeding 3h/week as 3 and moderate to high intensity exercise 1–3h/week as 4, and moderate to high intensity exercise exceeding 3h/week as 5. Average weekly alcohol consumption of 0–3, 4–12, 13–20 or > 20 units per week was considered an ordinal variable defining never, low, moderate, high and excessive alcohol consumers, respectively.

Carotid intima-media thickness
Carotid ultrasound was performed with a 3–9 MHz linear array transducer (Philips Medical Systems iU22, Bothell, WA, USA) and far wall IMT and/or plaque was visualized using B-mode longitudinal plane scanning. The acquisition and measurement of cIMT have been described in detail previously.[22] Eight far-wall pictures were obtained at 4 standardized CCA angles, and four far-wall pictures were obtained at sites with maximum findings for the right and left BIF and ICA segments. We used Meijer’s Carotid Arc:® for images at 180, 150, 120 and 90 degrees at the right carotid artery, at 180, 210, 240 and 270 degrees at the left carotid artery and saved all images at the end diastole, using electrocardiogram gating. The mean cIMT was analyzed offline using the QLAB automated IMT measurement plug-in (Philips, Bothell, WA) incorporating plaques if present at the pre-defined angle of image acquisition. Mean cIMT values from 10 mm measurements were registered from three carotid artery segments, defined as 20–10 mm, 10–0 mm proximal and 0–10 mm distal to the tip of the flow divider, representing the common carotid (CCA), carotid bifurcation (BIF) and internal
carotid artery (ICA), respectively. All doctors involved in patient inclusion underwent an international training program with external accreditation before inclusion of patients. The highest cIMT values from either left or right side was used separately for CCA, BIF and ICA. The reliability of measurements within and between observers and equipment has been tested and reported previously.[17]

Statistics

Descriptive statistics are reported using the mean and standard deviation (SD), median and interquartile range (IQR) or proportions with 95% confidence interval (CI). The chi square test was used for categorical data. Continuous data were analyzed by Student’s t-test or Mann–Whitney’s U-test as appropriate. The cIMT-variables were highly skewed to the right and were therefore transformed. The transformation of cIMT by 1/(square root of cIMT) gave distributions and residual distributions resembling a normal distribution and was therefore chosen as the most appropriate conversion for linear regression analyses. Of note, this inverse square root transformation means apparent negative associations must be interpreted as positive.

Multiple linear regression analysis was performed to test associations with cIMT. Results were reported as regression coefficients (coef.) and standard errors (SE). All regression analyses were performed as stepwise backwards procedures to identify factors associated with increased or reduced cIMT. The first step regression model included age, sex, FH of CVD, WHR, BMI, smoking status, pack-years of smoking, activity score, alcohol consumption score, hypercholesterolemia, HT, years of HT treatment, DM, years of DM treatment, mean systolic BP, mean diastolic BP, number of siblings, educational category, working status, s-glucose, s-HDL-C, s-LDL-C and s-total cholesterol. The least significant variable was removed in each step of the procedure until only significant variables remained (p \leq 0.05). Age and sex were forced into all models. Finally, putative interactions with age and sex were added to the model and tested. If IMT measurements were missing due to severe atherosclerosis documented by autopsy, angiographic imaging or carotid surgery before ultrasound examinations the missing data points in regression analyses were treated with 90th percentile high value imputation, robustness of this approach was tested by repeating the regression analyses using list-wise deletion and imputation of low and mean values. Missing measurements due to anatomical variations were treated by mean imputation and robustness was tested with a similar approach. Robust standard errors were used for calculation.

The level of significance was set at 0.05. Stata 13.1 (StataCorp, College Station, TX) was used for all analyses.

Ethics

All patients or legal guardians signed a written informed consent. NOR-SYS is approved by the Regional Ethics Committee of Western Norway, and is conducted in accordance with the Declaration of Helsinki.

Results

Demographics

Over a period of 5 years 382 ischemic stroke patients were enrolled in this study, of which 262 (68%) were males and 233 (61%) reported FH of CVD in \geq 1 FDR. A FH of stroke was reported by 128 (33.5%), while 167 (43.7%) and 26 (6.8%) reported a FH of CHD and PAD, respectively. Cigarette smoking (p < 0.001) and HT (p = 0.001) were more common in the FH + group. The FH+ patients had lower mean activity score (p = 0.004) and were less educated...
with 33% graduating from college or university compared to 47% of FH- patients (p = 0.016). FH+ patients had higher WHR, BP, LDL-C and total cholesterol (all p ≤ 0.005). In 10 (2.6%) patients anamnestic values were used to calculate BMI. All seven patients with missing measurements due to atherosclerotic occlusions were middle-aged and six of them had FH+ (p = 0.859). The demographic data are presented stratified between young and middle-aged due to the age-related discrepancy in FH+ and FH- in these groups, respectively (p < 0.001 and p = 0.400; Table 1).

Table 1. Demographic data of 382 young and middle-aged patients included in—the Norwegian Stroke in the Young Study (NOR-SYS)—in Bergen, Norway 2010–2015.

| Variables                      | Age 15-44y (N = 94) | Age 45-60y (N = 288) | P    |
|--------------------------------|---------------------|----------------------|------|
| Age in years                   | FH+ (n = 25, 27%)   | FH- (n = 69, 73%)    | 0.001†|
| Male sex, n (%)                | 11 (44.0)           | 42 (60.9)            | 0.145*|
| Education, n (%)               |                     |                      | 0.017*|
| Basic school                   | 7 (28.0)            | 8 (11.8)             | 0.017*|
| High school                    | 11 (44.0)           | 19 (28.0)            | 0.217*|
| College/University             | 7 (28.0)            | 41 (60.3)            | 0.017*|
| Working status a, n (%)        |                     |                      | 0.513*|
| Full-time                      | 18 (72.0)           | 55 (82.1)            | 0.007*|
| Part-time                      | 3 (12.0)            | 4 (6.0)              | 0.007*|
| Unemployed                     | 4 (16.0)            | 8 (11.0)             | 0.007*|
| Cigarette smoking, n (%)       |                     |                      | 0.192*|
| Never                          | 5 (20.0)            | 39 (56.5)            | 0.192*|
| Former                         | 6 (24.0)            | 10 (14.5)            | 0.192*|
| Active                         | 14 (56.0)           | 20 (29.0)            | 0.192*|
| High/excessive alcohol, n (%)  |                     |                      | 0.537*|
| Activity score                 | 2.7 (1.4)           | 3.4 (1.6)            | 0.023†|
| CVD events, n (%)              | 1 (4.0)             | 6 (8.7)              | 0.444|
| BP-lowering therapy, n (%)     | 3 (12.0)            | 15 (21.7)            | 0.289*|
| DM therapy, n (%)              | 1 (4.0)             | 3 (4.4)              | 0.941*|
| Lipid-lowering therapy, n (%)  | 0 (0.0)             | 1 (1.4)              | 0.545*|
| Systolic BP, mmHg              | 131 (14)            | 131 (17)             | 0.563†|
| Diastolic BP, mmHg             | 81 (11)             | 81 (14)              | 0.615†|
| Body-mass index, kg/m²         | 27.8 (6.4)          | 26.9 (6.4)           | 0.317†|
| Waist-hip ratio                | 0.88 (0.07)         | 0.87 (0.1)           | 0.470†|
| Total cholesterol, mmol/L      | 5.49 (1.5)          | 4.97 (1.1)           | 0.101†|
| LDL-C, mmol/L                  | 3.67 (1.3)          | 3.08 (1.0)           | 0.028†|
| HDL-C, mmol/L                  | 1.34 (0.4)          | 1.51 (0.6)           | 0.309†|
| Glucose, mmol/L                | 5.4 (0.6)           | 5.7 (1.0)            | 0.139†|
| Number of siblings, median (IQR)| 1 (1–2)            | 2 (1–3)              | 0.197†|
| Number of children, median (IQR)| 1 (0–3)            | 1 (0–2)              | 0.452†|

Values are given as mean with standard deviation unless otherwise stated.

Abbreviations: n (%): absolute number of patients and percentage within group; CVD: cardiovascular disease; FH: Family history, i.e. FH+: at least one first-degree relative with CVD; DM: diabetes mellitus; BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range.

* Full-time working status, includes students/pupils; part-time, includes stay at home parents and part-time benefit recipients if also working; unemployed includes full benefit recipients and 3 young and 10 middle-aged patients on long term (> 6 months) sick-leave.

* Chi square test.
† Mann–Whitney U test.

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The young FH+ group had more deceased parents than the FH- with 9 (36%) deceased fathers and 3 (12.5%) mothers compared with 9 (13%) and 3 (4.4%) in the FH- group (p = 0.014 and 0.161). No difference in numbers of deceased parents was observed in the middle-aged group.

**IMT measurements and predictors of increased IMT**

One patient (0.2%) had unsuccessful BIF-IMT, whereas six (1.5%) had unsuccessful ICA-IMT measurements on both sides. One patient had no successful ultrasound IMT measurements due to technical difficulties. Due to the large impact of age on IMT and FH and the skewed age distribution, IMT data are shown stratified by FH and age (Table 2). In young patients the highest mean ICA-IMT was 0.265 mm (49%) higher and BIF-IMT measurements were 0.17 mm (24%) higher in FH+ compared with FH- patients (p < 0.001 and p = 0.002). No significant difference was found regarding CCA or in any segment in middle-aged patients.

The variables associated with increased CCA-IMT after backwards selection procedure were age, male sex, HT, mean systolic BP, pack-years of smoking and LDL-cholesterol (all p < 0.008). The variables associated with increased BIF-IMT were high age, previous CVD, mean systolic BP, years of DM, active smoking, increased LDL-cholesterol (all p < 0.004) and lower HDL-cholesterol (p < 0.001). The variables associated with increased ICA-IMT included FH, age, mean systolic BP, pack years of smoking, years of DM and the interaction term between FH and age (FH×age) (all p ≤ 0.013). The FH×age term showed effect modification of the association between FH and ICA-IMT by age with increasing age attenuating the effect of a positive FH on IMT (p = 0.006). No interactions between age and other risk factors were significant.

FH is associated with higher ICA-IMT in patients < 45y. The effect of FH+ on ICA-IMT attenuates with increasing age and after the age of 50y a converse association seems apparent, as shown in Fig 1.

Splitting the FH in subdomains to analyze if a FH of stroke, CHD or PAD differed with regard to impact on ICA-IMT showed only a FH of stroke was significantly associated with higher ICA-IMT in stroke patients (p = 0.011; Table 3). No imputation method for missing data altered the main results. However, imputing expected high ICA-IMT values in patients with documented ICA atherosclerosis strengthened the main association between FH of stroke and ICA-IMT, whereas imputing low values attenuated the association.

| Variables                | Age 15-44y | Age 45-60y |
|--------------------------|------------|------------|
| Mean IMT right CCA, mm   | 0.611 (0.13) | 0.587 (0.12) | 0.342 |
| Mean IMT right BIF, mm   | 0.781 (0.38) | 0.642 (0.26) | 0.021 |
| Mean IMT right ICA, mm   | 0.762 (0.44) | 0.519 (0.19) | 0.002 |
| Mean IMT left CCA, mm    | 0.871 (1.21) | 0.586 (0.12) | 0.033 |
| Mean IMT left BIF, mm    | 0.778 (0.27) | 0.622 (0.23) | < 0.001 |
| Mean IMT left ICA, mm    | 0.659 (0.35) | 0.475 (0.11) | < 0.001 |
| Highest mean IMT CCA, mm | 0.886 (1.21) | 0.623 (0.12) | 0.126 |
| Highest mean IMT BIF, mm | 0.864 (0.36) | 0.694 (0.29) | 0.002 |
| Highest mean IMT ICA, mm | 0.806 (0.42) | 0.541 (0.18) | < 0.001 |

Values are given as mean with standard deviation unless otherwise stated.

**Abbreviations**: FH: family history; IMT: intima-media thickness; CCA: common carotid artery; BIF: carotid bifurcation; ICA: internal carotid artery; SD: standard deviation; P: p-value of comparison between FH+ and FH- groups calculated by Mann–Whitney’s U test.

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Discussion

We found FH+ of CVD associated with increased ICA-IMT in young ischemic stroke patients. The association was present only for a FH of stroke, although a FH of CHD was borderline significant. This expands on the recent finding that common carotid IMT measurements in patients < 45y improves CVD event prediction.[8] The increased ICA-IMT in young FH+ patients indicate that genetic factors seem to have more impact on ICA-IMT and risk of CVD in young compared with middle-aged patients. Given the association between ICA-IMT and FH is driven by a FH of stroke, the hereditary factor for increased ICA-IMT seems to be stroke specific. We found a significant association between age and IMT in all carotid artery segments, and in addition we found the IMT of the BIF and the CCA are associated with traditional and modifiable risk factors such as smoking, DM, BP and cholesterol levels. These findings are in line with previous studies, although varying impact of risk factors on IMT has been reported.[24, 25] Several of these risk factors such as BP[26] and cholesterol levels[27] are shown to have a strong hereditary component themselves, and this may influence the impact of FH+ in our regression analyses. Regarding ICA-IMT in the middle-aged group, there was a pattern with increased impact of traditional risk factors whereas the impact of genetics represented by FH+ was lower as compared with the young group. This may contribute to explain why cIMT has less impact on risk prediction in older patients.[5–7] In addition, previous CVD was more common in the middle-aged FH+ patients with 26% vs. 15% in the FH- group. This
difference may be prone to bias by age, due to the large impact of age on both prior CVD in patients and FH status of patients. The lack of association between a FH of CVD and ICA-IMT in middle-aged patients may be explained by our definition of FH of CVD, with no age limit imposed on the FH. With this definition of FH we show the middle-aged patients have a much higher prevalence of FH+ than the young, probably to a large degree caused by the higher age of the relatives and thus the higher prevalence of CVD with progressing age. Increasing prevalence of FH+ with increasing age has recently been reported from another large European cohort of young ischemic stroke patients.[28] With no age-limits on the FH the increased FH of CVD prevalence in the middle-aged may be largely caused by parental events at high age thereby diluting the possible effect of a FH of premature CVD in the middle-aged.[1]

The Mannheim consensus recommends cIMT measurements in a distal CCA region free of plaque and with an easily discernable IMT double-line pattern, ensuring high reproducibility and comparable results between populations.[29] An approach using one of three carotid segments with the fastest progressing IMT, allowing incorporation of plaques in the measurement showed significant association with subsequent vascular events.[30] This supports the feasibility of a maximum pathology approach if cIMT is used for risk prediction. There is evidence that genetic factors explain a large part of phenotypic cIMT variation, with studies reporting 30–66% of CCA-IMT and even up to 75% of ICA-IMT variation accounted for by genes.[25, 31–33] This suggests ICA-IMT as an appropriate measure in investigations of genetic stroke risk.[15, 25] Our finding of a strong association between a FH of stroke and increased ICA-IMT supports this. Adjusting the strategy for future genetic analyses in stroke seems

| Variablea | Coef. | 95%CI | P-value |
|-----------|-------|-------|---------|
| Age       | -0.013| -0.017—0.010 | < 0.001 |
| Sex       | 0.432 | -0.032—0.074 | 0.432 |

FH of CVD

| FH of stroke | -0.528 | -0.936—0.121 | 0.011 |
| FH of CHD    | -0.383 | -0.760—0.197 | 0.062 |
| FH of PAD    | 1.897  | -0.608—4.403 | 0.137 |
| FH of several | -0.044 | -0.548—0.460 | 0.863 |

FH type X ageb

| FH of stroke | 0.0117 | 0.003—0.019 | 0.004 |
| FH of CHD    | 0.0075 | 0.000—0.015 | 0.065 |
| FH of PAD    | -0.0329 | -0.075—0.009 | 0.132 |
| FH of several | 0.0010 | -0.008—0.010 | 0.828 |

Body-mass index

-0.005 | -0.010—0.001 | 0.025

Mean blood pressure

-0.002 | -0.003—0.000 | 0.020

Years of diabetes mellitus

-0.009 | -0.015—0.004 | 0.001

Pack years of smoking

-0.003 | -0.004—0.001 | < 0.001

Abbreviations: Coef.: regression coefficient; 95% CI: 95% confidence interval; FH: Family history; CVD: cardio-vascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

a Remaining variables from backwards stepwise selection procedure with first step including age, sex, FH of CVD, waist-hip ratio, body mass index, smoking status, pack-years of smoking, activity score, alcohol consumption score, hypercholesterolemia, hypertension, years of hypertension treatment, diabetes mellitus, years of diabetes mellitus treatment, mean systolic blood pressure, mean diastolic blood pressure, number of siblings, working status, educational category, s-glucose, s-HDL-C, s-LDL-C and s-total cholesterol.

b Interaction term describing effect modification by age on the association between a FH of stroke and ICA-IMT.

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imperative given that even large genetic consortia have only uncovered a few genetic variants with low explanatory effect on ischemic stroke.[34] A thorough standardized clinical work-up and phenotypic stratification of stroke patients seems a promising approach to enable collaboration for future genetic studies.[35]

The main strengths of our study are the detailed and standardized multi-angle assessment of pre-defined carotid artery segments and the detailed FH divided in components of stroke, CHD and PAD. Further strengths include the prospective and consecutive inclusion of patients, the strict inclusion criteria with mandatory verification of acute cerebral infarction by a high rate of MRI and extensive risk factor evaluation. There are some limitations to our study. Firstly, parent age at CVD event was not systematically ascertained, using premature FH could potentially strengthen the associations between FH and cIMT.[12] Secondly, self-reported FH data carries a risk of recall bias. However, reliability of the patient-reported FH from this cohort has previously been tested against the reports from living parents resulting in adequate concordance.[36]

The present paper shows an association between a FH of stroke and increased ICA-IMT in young ischemic stroke patients. Most of the genetic risk in vascular disease is polygenic, with the exception of monogenic disorders such as CADASIL, identifying homogenous phenotypes allows a more targeted approach in the search for genetic variants associated with increased stroke risk.[35, 37] The use of ultrasound ICA-IMT measurements in young patients may assist in identification of individuals with a genetic CVD component, thereby allowing targeted advice on lifestyle alterations such as exercise, weight loss and smoking cessation to potentially reduce future CVD related disability and mortality. Our results suggest future guidelines for the assessment of stroke risk should consider recommendations of ICA-IMT measurements in young adults.

Conclusions

The present paper shows association between a family history of stroke and increased intima media thickness of the internal carotid artery in young ischemic stroke patients. This supports the influence of a genetic component in young stroke and suggests that measurements of intima media thickness can identify young patients with a hereditary risk for stroke. Genetic research regarding atherosclerosis in stroke should target young individuals with a high likelihood of genetic disease components. Additionally, identifying individuals with a hereditary risk enables targeted advice on lifestyle alterations such as exercise, weight loss and smoking cessation to reduce future disability and mortality caused by cardiovascular disease.

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Author Contributions

Conceived and designed the experiments: HØ UWA LT HN.
Performed the experiments: HØ AF KMS UWA.
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