Familial Intracranial Aneurysms
Is Anatomic Vulnerability Heritable?

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Background and Purpose—Previous studies have suggested that family members with intracranial aneurysms (IAs) often harbor IAs in similar anatomic locations. IA location is important because of its association with rupture. We tested the hypothesis that anatomic susceptibility to IA location exists using a family-based IA study.

Methods—We identified all affected probands and first-degree relatives (FDRs) with a definite or probable phenotype in each family. We stratified each IA of the probands by major arterial territory and calculated each family’s proband-FDR territory concordance and overall contribution to the concordance analysis. We then matched each family unit to an unrelated family unit selected randomly with replacement and performed 1001 simulations. The median concordance proportions, odds ratios (ORs), and $P$ values from the 1001 logistic regression analyses were used to represent the final results of the analysis.

Results—There were 323 family units available for analysis, including 323 probands and 448 FDRs, with a total of 1176 IAs. IA territorial concordance was higher in the internal carotid artery (55.4% versus 45.6%; OR, 1.54 [1.04–2.27]; $P=0.032$), middle cerebral artery (45.8% versus 30.5%; OR, 1.99 [1.22–3.22]; $P=0.006$), and vertebrobasilar system (26.6% versus 11.3%; OR, 2.90 [1.05–8.24], $P=0.04$) distributions in the true family compared with the comparison family. Concordance was also higher when any location was considered (53.0% versus 40.7%; OR, 1.82 [1.34–2.46]; $P<0.001$).

Conclusions—In a highly enriched sample with familial predisposition to IA development, we found that IA territorial concordance was higher when probands were compared with their own affected FDRs than with comparison FDRs, which suggests that anatomic vulnerability to IA formation exists. Future studies of IA genetics should consider stratifying cases by IA location. (Stroke. 2013;44:38-42.)

Key Words: concordance ■ epidemiology ■ familial ■ genetics in stroke ■ heritability ■ intracranial aneurysm

Intracranial aneurysm (IA) location is important because of its association with rupture risk.$^{1,2}$ Previous reports noted family members with IAs in similar locations and twins with IAs in identical locations.$^{3-8}$ These data suggest that there may be heritable susceptibility to IA location. We tested the hypothesis that anatomic susceptibility to IA location exists using a large multicenter family-based IA study.

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The abstract of this study was the winner of the 2011 Mordecai Y.T. Globus New Investigator in Stroke award and was presented at a plenary session of the International Stroke Conference on February 10, 2011 in Los Angeles, CA.

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Enrollment for Phase I of the FIA Study took place from October 2002 through October 2008.

Data for 547 families who reported multiple members affected with IA were collected. A family could span several generations, and participants who enrolled in the study included both affected and nonaffected subjects. For each potentially affected subject, an IA screening interview was performed, which included symptoms, the specialty of the physician who treated the subject, diagnostic tests, and treatment (if any) for each IA. Subjects who at study entry reported having had an IA completed more detailed interviews that included items on medical history and risk factors for IA, such as smoking use. After medical record review was performed to verify cases of IA, the structures of enrolled families were examined to determine whether they met criteria for FIA: (1) ≥2 living affected siblings, (2) ≥2 affected siblings, 1 living and another whose genotype could be reconstructed through the collection of closely related, living family members, (3) ≥3 affected family members, not necessarily siblings (e.g., parents or grandparents, children, uncles, aunts, cousins), with at least 2 living family members with living connecting relatives, (4) ≥3 affected family members, 1 living and at least 1 whose genotype could be reconstructed through the collection of closely related, living family members. Families did not meet FIA status if informed consent or medical records could not be obtained from sufficient family members to satisfy 1 of the 4 criteria listed above. Subjects with fusiform-shaped unruptured IA of a major intracranial trunk artery, or IA that is part of an arteriovenous malformation, as well as families with a family history of polycystic kidney disease, Ehlers Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, moyamoya disease, or sickle cell disease were excluded.

Medical record review was performed by a verification committee consisting of study neurologists from the University of Cincinnati and the Mayo Clinic to determine whether IAs were present in subjects reported to be affected. Each subject was phenotyped with regard to IA as definite, probable, possible, or not a case, per strictly defined criteria. The location of all IAs, if known, was recorded. Two study neurologists independently reviewed the records, and any disagreement was arbitrated independently by a third neurologist who was blinded as to the determinations of the 2 prior neurologists. Forsubmit a detailed report; a death certificate, notes a subarachnoid hemorrhage. Not included in the analysis were IAs with insufficient supporting documentation or autopsy, or notes a subarachnoid hemorrhage without mention of IA and symptoms recorded on the IA screen are consistent with ruptured IA (severe headache or altered level of consciousness rapidly leading to death). Possible: IA between 2 and 3 mm per noninvasive imaging report; a death certificate that notes a subarachnoid hemorrhage without supporting documentation, autopsy, or IA screen verification of headache or altered level of consciousness; or a death certificate that lists aneurysmal subarachnoid hemorrhage or IA but does not indicate the location of the IA, are excluded from the analysis.

IAs that occurred in the posterior communicating artery, ophthalmic artery, anterior choroidal artery, cavernous ICA, and distal ICA were subsumed under the ICA territory. The ACA territory included the anterior communicating and pericallosal arteries. The VB territory included the basilar tip as well as arteries such as the anterior inferior cerebellar artery, posterior inferior cerebellar artery, superior cerebellar artery, and posterior cerebral artery.

Statistical Methods

The statistical analysis used a logistic events/trials model with family as the unit of analysis. For each family unit, the total number of affected FDRs represented the trials, and the number of affected FDRs who had IAs in the same territory as the proband represented the events. For example, in a hypothetical family unit with a proband and 3 affected FDRs, the proband, FDR1, and FDR2 all had IAs in the ICA territory; the number of events was 2 out of 3 trials. The resulting proportion, 0.667, was considered a measure of concordance for the ICA territory. Events, trials, and proportions of concordance were determined separately for the ICA, MCA, ACA, and VB territories. In addition, a total concordance for each family unit was calculated based on the proportion of FDRs who had IAs in any of the same territories as the proband. For example, in a hypothetical family unit with a proband and 4 FDRs, the arterial territories were ICA and MCA for the proband, VB for FDR1, ICA and ACA for FDR2, ACA for FDR3, and MCA for FDR4; 2 of the FDRs had IAs in the same territory as the proband (FDR2’s ICA and FDR4’s MCA), and thus the total concordance proportion for that family unit was 0.5, that is, 2 events out of 4 trials.

Each family unit was matched to an unrelated family selected randomly with replacement from the set of families whose proband did not have IAs in the same territories as that of the index proband. This sampling strategy was necessary to avoid biased comparison estimates attributable to dilution of the comparison effect that would occur if index probands were matched to randomly selected probands who had an IA in the same location. Territory-specific and total concordance proportions between the index proband and the randomly selected family were calculated as the number of FDRs in the randomly selected family who had an IA in the same territory as the index proband divided by the total number of FDRs in the randomly selected family. This process is demonstrated in the Figure. Because the numbers of affected FDRs (not including the proband) ranged from 1 to 5, the events/trials model was used to properly weight the analysis based on the size of the family unit. The method of analysis was conditional logistic regression, with the matched pairs used as strata. To assure a robust analysis, the matched-pairs logistic models were simulated 1001 times. The median concordance proportions, odds ratios, and P values from the 1001 logistic regression analyses were used to represent the final results of the analysis.

Results

Among the 401 families that met FIA criteria, 5 families that met the criterion of ≥3 affected family members (which did not require FDRs) could not be included in the analysis because of lack of affected FDRs. Families were also excluded if only the proband remained after applying exclusion criteria; 30 were excluded because of possible phenotypes, 29 because of deceased affected FDRs with unknown IA location, and 18 because of living affected FDRs with unknown IA location. One family could not be used in the analysis because its proband had IAs in all 4 arterial territories, which rendered it impossible to find a matching family unit. The 19 families with 2 affected members but who did not meet the FIA strict inclusion criteria for FIA yielded 5 additional affected FDR pairs for inclusion, yielding a total of 323 family units available for the analysis.
Among the 323 probands, 228 had 1 affected FDR, 70 had 2 FDRs, 21 had 3 FDRs, 3 had 4 FDRs, and 1 had 5 FDRs. With regard to race, 288 probands were white non-Hispanic, 11 were white Hispanic, 12 were black, 4 were Asian, 1 was Asian Hispanic, 1 was Native American Hispanic, 2 were Pacific Islander, and 3 were of >1 race. The 323 probands had a total of 486 IAs and the 448 FDRs had a total of 690 IAs in known locations. Some subjects had multiple IAs in the same arterial territory and some had IAs in more than 1 territory. Among the probands, 161 (49.8%) had at least 1 IA in the ICA territory, 120 (37.2%) in the MCA, 80 (24.8%) in the ACA, and 47 (14.6%) in the VB. Among the FDRs, 222 (49.6%) had at least 1 ICA IA, 170 (39.6%) had at least 1 MCA IA, 119 (26.6%) had at least 1 ACA IA, and 61 (13.6%) had at least 1 VB IA.

The breakdown of proband and FDR IAs by location and rupture status is shown in Table 1. The distribution of IAs in the 4 major arterial distributions was not different between probands and FDRs for all IAs (χ²; P=0.89) or for ruptured IAs (χ²; P=0.85). At the time of study ascertainment, ruptured IAs had occurred in 111 probands (34.4%) and 207 FDRs (46.2%). IA risk factors and rupture location for probands and FDRs are shown in Table 2. Affected FDRs are dichotomized into those with an IA in the same territory as the proband versus those whose IAs were in a different territory. More probands than FDRs were women, whereas rupture was more common in FDRs.

The results of the logistic regression analysis are shown in Table 3. Concordance between the index proband and FDRs was higher in the ICA, MCA, and VB territories compared with the ACA, which was not different between the groups. When any location was considered, concordance was higher in the true family than in the comparison family.

**Discussion**

In a highly enriched sample with familial predisposition to IA development, we found that IA territorial concordance was higher when probands were compared with their own affected FDRs than with comparison family FDRs, which suggests that anatomic vulnerability to IA formation is heritable.

The MCA, ICA, and VB territories demonstrated significantly higher concordance proportions, whereas the ACA

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**Table 1. IA Location and Rupture Status in Probands and FDRs**

<table>
<thead>
<tr>
<th>Territory</th>
<th>Probands</th>
<th>FDRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ICA</td>
<td>206 (42.4%)</td>
<td>292 (42.3%)</td>
</tr>
<tr>
<td>ICA</td>
<td>10 (9.0%)</td>
<td>74 (16.4%)</td>
</tr>
<tr>
<td>PComm</td>
<td>64 (13.2%)</td>
<td>79 (15.5%)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>35 (7.2%)</td>
<td>47 (6.8%)</td>
</tr>
<tr>
<td>Anterior choroidal</td>
<td>7 (1.4%)</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Cerebral</td>
<td>5 (0.9%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Cavernous/ Hypophyseal</td>
<td>2 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Distal ICA</td>
<td>0</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Total MCA</td>
<td>149 (30.7%)</td>
<td>212 (30.7%)</td>
</tr>
<tr>
<td>Total ACA</td>
<td>81 (16.7%)</td>
<td>123 (17.8%)</td>
</tr>
<tr>
<td>AComm</td>
<td>62 (12.8%)</td>
<td>91 (13.2%)</td>
</tr>
<tr>
<td>ACA</td>
<td>15 (3.1%)</td>
<td>29 (4.2%)</td>
</tr>
<tr>
<td>Pericallosal</td>
<td>4 (0.8%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Total VB</td>
<td>50 (10.3%)</td>
<td>63 (9.1%)</td>
</tr>
<tr>
<td>Basilar tip</td>
<td>30 (6.2%)</td>
<td>40 (5.8%)</td>
</tr>
<tr>
<td>Other basilar and VB</td>
<td>12 (2.5%)</td>
<td>14 (2.0%)</td>
</tr>
<tr>
<td>Cerebral</td>
<td>2 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>PICA</td>
<td>3 (0.6%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>PCA</td>
<td>2 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>SCA</td>
<td>1 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; AComm, anterior communicating artery; FDR, first-degree relative; IA, intracranial aneurysm; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PComm, posterior communicating artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; and VB, vertebrobasilar.
Studies that examine IA location among affected FDRs are scarce and are typically case reports.3–9 One study investigated the association of single nucleotide polymorphisms on 9p21 with IA location and found that posterior communicating artery and posterior circulation IAs had stronger associations than the anterior circulation group.11 Recent genomewide association studies have identified loci associated with IA,12–14 but these studies did not stratify by IA territory. A related limitation is that, because we have limited imaging data, we are unable to comment on whether specific anatomic or hemodynamic variations have an impact on IA location. Because of the nature of the analysis, IAs for which the report did not document location were necessarily excluded. Additional data would have increased our power, but it is unclear how this would have affected our findings. To stratify the analysis by arterial location, it was necessary to group by major arterial distribution rather than by individual artery to have sufficient sample size. Because not all family members were included in the analysis, and how their inclusion would have affected the concordance proportions is unclear. The inclusion of additional data would have increased our power, but it is unclear how this would have affected our findings. To stratify the analysis by arterial location, it was necessary to group by major arterial distribution rather than by individual artery to have sufficient sample size. Because not all family members were included in the analysis, and how their inclusion would have affected the concordance proportions is unclear. Because the data represent a snapshot in time, we do not know whether affected subjects later developed additional IAs, whether unaffected family members later developed IAs, whether or not IAs later ruptured, or how any subsequent changes in IA status would affect our findings. A further limitation is that with the family unit as the unit of analysis, we were unable to incorporate risk factors for IA formation into the model. Finally, only affected subjects were included, which limits the interpretation of our findings because we can cite concordance proportions and odds ratios for FDRs only if they are already affected. We cannot predict whether an unaffected
did not. Both the odds ratios and the concordance proportions are of some interest. For instance, although the odds ratio was highest for the VB distribution, the proportion of affected FDRs with VB IAs was only about 1 in 4. Thus, although the odds ratio suggests a strong heritable component, the concordance proportion suggests that 3 out of 4 affected FDRs will not have VB IAs. The concordance proportions were higher for the ICA and MCA distributions, but the corresponding odds ratios were lower for the VB distribution. The reasons for the lack of signal in the ACA distribution are unclear. Previous work has suggested that risk factors vary according to IA site.10 One possibility is that genetic variation confers biologic vulnerability by location differentially in response to environmental risk factors.
FDR will become affected or predict the arterial distribution of a future IA based on the present analysis.

IA formation and rupture are complex processes associated with various environmental and genetic factors. This study supports the hypothesis that heritable predisposition for IAs in the same arterial territory within families exists. Future studies of IA genetics should consider adding location of IAs into their analyses.

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Disclosures
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References
家族性脳動脈瘤は解剖学的な脆弱性の遺伝か
Familial Intracranial Aneurysms Is Anatomic Vulnerability Heritable?

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背景および目的: 脳動脈瘤 (IA) を有する家族間では、解剖学的に同じ部位に IA を有する場合が多いことが先行研究において示唆されてきた。IA の発症部位は破裂のリスクがあることから重要である。家族ベースの IA 研究を用いて、IA 部位に解剖学的な脆弱性が存在するという仮説を検証した。

方法: 各家族において、めまいやめまいを伴う表現型を有する発端者および第 1 度近親者 (FDR) をすべて特定した。主要な動脈領域ごとに発端者の IA を層別化し、各家族における発端者・FDR 間の領域の一致度および一致度解析への全体寄与率を算定した。次に、無作為に抽出した無関係の家族と入れ替えて、各家族とマッチさせ、シミュレーションを 1,001 回実施した。1,001 回のロジスティック回帰分析から得た一致度、オッズ比 (OR)、および p 値の中央値を用いて、解析の最終結果を示した。

結果: 解析に使用可能であったのは、発端者 323 例および FDR 448 例を含む 323 家族で、IA の総発症数は 1,176 件であった。対照家族と比較して、真の家族における IA 領域の分布の一致度は、内頸動脈 [55.4% 対 45.6%, OR = 1.54, 95% CI: 1.04 ~ 2.27, p = 0.032], 中大脳動脈 [45.8% 対 30.5%, OR = 1.99, 95% CI: 1.22 ~ 3.22, p = 0.006], および椎骨脳底動脈系 [26.6% 対 11.3%, OR = 2.90, 95% CI: 1.05 ~ 8.24, p = 0.04] において高かった。あらゆる部位を検討した場合も、一致度は高かった (53.0% 対 40.7%, OR = 1.82, 95% CI: 1.34 ~ 2.46, p < 0.001)。

結論: IA 発症の家族性素因を有する極めて多くのサンプルから、発端者をその家族の罹患 FDR と比較した場合の方が、対照 FDR を比較した場合よりも、IA 領域の一致度が高くなることが示され、IA 形成に関する解剖学的な脆弱性の存在が示唆された。IA に関する今後の遺伝学的研究においては、IA の発症部位による症例の層別化を検討するべきである。

Stroke 2013; 44: 38-42

表3 IA 発症部位の一致度に関するロジスティック回帰分析

<table>
<thead>
<tr>
<th>助突動脈領域</th>
<th>対照家族</th>
<th>研究家族</th>
<th>OR (95% CI)</th>
<th>p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA (n = 161)</td>
<td>55.4%</td>
<td>45.6%</td>
<td>1.54 (1.04 ~ 2.27)</td>
<td>0.032</td>
</tr>
<tr>
<td>MCA (n = 120)</td>
<td>45.8%</td>
<td>30.5%</td>
<td>1.99 (1.22 ~ 3.22)</td>
<td>0.006</td>
</tr>
<tr>
<td>ACA (n = 80)</td>
<td>27.3%</td>
<td>26.9%</td>
<td>1.00 (0.54 ~ 1.85)</td>
<td>0.662</td>
</tr>
<tr>
<td>VB (n = 47)</td>
<td>26.6%</td>
<td>11.3%</td>
<td>2.90 (1.05 ~ 8.24)</td>
<td>0.040</td>
</tr>
<tr>
<td>あらゆる部位 (n = 323)</td>
<td>53.0%</td>
<td>40.7%</td>
<td>1.82 (1.34 ~ 2.46)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

ACA: 前大脳動脈。FDR: 第 1 度近親者。IA: 脳動脈瘤。ICA: 内頸動脈。MCA: 中大脳動脈。VB: 椎骨脳底動脈。

* 数値は、1,001 回反復シミュレーションの中央値を示す。