Familial Intracranial Aneurysms
An Analysis of 346 Multiplex Finnish Families

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Background and Purpose—Genetic risk factors are considered important in the development, growth, and rupture of intracranial aneurysms; however, few have been identified. We analyzed intracranial aneurysm families with at least 2 affected persons and determined relationships between affected persons and assessed the inheritance patterns of aneurysms.

Methods—Families with ≥2 members with verified diagnoses of intracranial aneurysms were recruited from Kuopio and Helsinki, Finland. Families with a diagnosis of other heritable disorders that have associated intracranial aneurysms, such as autosomal dominant polycystic kidney disease, were excluded.

Results—We identified 346 Finnish multiplex families with 160 (46.2%) male and 186 (53.8%) female index cases. There were a total of 937 aneurysm cases, with an average of 2.7 cases per family. The majority of the families had only 2 affected relatives (n=206; 59.5%), although there were families with up to 6 (n=10), 7 (n=1), 8 (n=1), or 10 (n=2) affected persons. The affected relatives of the index cases included 108 sisters, 116 brothers, 105 parents, 30 children, 15 grandparents, 102 aunts or uncles, and 64 cousins. Of the 937 affected persons, 569 (60.7%) were alive and available for genetic analysis. Inheritance patterns consistent with autosomal recessiveness were observed in 198 (57.2%), autosomal dominance in 126 (36.4%), and autosomal dominance with incomplete penetrance in 19 (5.5%) of the families.

Conclusions—The collection is the most extensive published to date and extends previous observations of familial aggregation that are consistent with a major gene effect. (Stroke. 2003;34:1370-1374.)

Key Words: genetics ■ pedigree ■ risk factors ■ stroke ■ subarachnoid hemorrhage

Intracranial aneurysms (IAs) are moderately common in industrialized countries and have a substantial impact on society.1 Lifetime prevalence estimates from autopsy and angiography studies range from 0.2% to 9.9% (mean, 5.5%).2–8 Rupture of IA is the cause of >75% of all subarachnoid hemorrhage (SAH) cases. In some reports, >90% of SAH cases are due to ruptured IA, and most ruptured IAs present with SAH.1,2,7,9–11 SAH has high morbidity and mortality; approximately half of those who suffer from a ruptured IA will die within 30 days from the onset of SAH. Only one fifth to one third of SAH survivors will have a moderately good to good recovery.2,9,12,13 Since half the survivors remain permanently disabled as a result of cognitive dysfunction, economic and social ramifications are extensive.14 It has been estimated that 10 to 15 million persons in the United States already have or will develop an IA.15

The mean age at onset of rupture of IA in the Finnish population (49.3 years; SD 13 years)11 is similar to that in other industrialized countries1,7,15 and is approximately normally distributed.12 IA and SAH have been extensively studied in Finland,1,2,6,11,16–20 and the incidence is higher than in most other countries.6–8,11 A variety of factors may influence the development, growth, and rupture of IA and include factors that have behavioral components such as smoking,1,9,12,17,21–26 alcohol consumption,12,25,27,28 and use of contraceptives,26,29,30 as well as hypertension1,12,18,22,23,31–33 and stochastic factors. Reports of IA in some patients with rare mendelian disorders such as autosomal dominant polycystic kidney disease (ADPKD),1,10,34–37 Ehlers-Danlos syndrome type IV (EDS-IV),10 Marfan syndrome,13 and fibromuscular dysplasia38 suggested that it was more common in subjects with these diseases than in the general population. Recent careful and systematic studies on larger groups of patients with Marfan syndrome39,40 and fibromuscular dysplasia41 have, however, demonstrated that IAs are only infrequently part of the clinical manifestations in these rare conditions.
disorders and the prevalence is only moderately elevated in patients with EDS-IV.\textsuperscript{42} IAs are, however, more common in patients with ADPKD than in the general population.\textsuperscript{34,37} A number of studies on familial clustering of IAs in the absence of other predisposing disorders have suggested that family history should be considered a risk factor for IAs. We showed previously that approximately 10% of IA cases in the Finnish population have a family history.\textsuperscript{11,16} Studies in other populations have reported either 6.7%\textsuperscript{43} or 23.4%.\textsuperscript{23} Since these familial intracranial aneurysm (FIA) families show no signs of other disorders that may predispose them to IA, the aggregation supports the hypothesis that some IAs have a genetic component separate from previously defined diseases. The suggestion that genetic factors contribute to IA is further supported by 2 recent DNA linkage studies.\textsuperscript{44,45}

In this study we extended our previous collection of 85 families\textsuperscript{11,16} by 261 additional pedigrees in which at least 2 biologically related persons had been diagnosed with an IA. We identified familial relationships of individuals diagnosed with IA to the index case and assessed the nature of the transmission of IA.

**Subjects and Methods**

Patients treated for IA at either the University Hospital of Kuopio, Kuopio, Finland, or the University Hospital of Helsinki, Helsinki, Finland, were identified. After consent was obtained, the patients or their relatives were interviewed to determine whether there were other relatives who had IA. When additional affected persons were identified, they or their close relatives were also interviewed. Medical and autopsy records were reviewed by certified neurosurgeons or research nurses, specifically trained for the task, to verify that the reported diagnoses were indeed saccular IA. Some IAs were identified by screening with MR angiography and verified by digital subtraction angiography.\textsuperscript{11,46} We included only families with a familial intracranial aneurysm (FIA) families that show no signs of other disorders that may predispose them to IA, the aggregation supports the hypothesis that some IAs have a genetic component separate from previously defined diseases. The suggestion that genetic factors contribute to IA is further supported by 2 recent DNA linkage studies.\textsuperscript{44,45}

In this study we extended our previous collection of 85 families\textsuperscript{11,16} by 261 additional pedigrees in which at least 2 biologically related persons had been diagnosed with an IA. We identified familial relationships of individuals diagnosed with IA to the index case and assessed the nature of the transmission of IA.

**Results**

We identified 346 families in which at least 2 members had an IA. These families had first-, second-, and third-degree relatives affected with IA. All families originated from Finland. In 186 families (53.8%) the first person identified as having IA, the index case, was female, and in 160 families (46.2%) the index case was male. The difference between proportion of male and proportion of female probands was significant ($P=0.005$). There were 591 affected relatives in addition to the index cases, totaling 937 affected individuals, with an average of 2.7 cases per family. All index cases and >90% of all cases had symptomatic IAs. Among the entire collection of affected relatives, the proportion of males and females was almost equal: 476 females (50.8%) and 461 males (49.2%) (1.03:1 female-to-male ratio). The difference was not statistically significant ($P=0.33$). Although the majority of families had only 2 members affected ($n=206$; 59.5%), there were 10 families (2.9%) with 6 affected persons, 1 family each with 7 and 8 affected persons (0.3%), and 2 families with 10 affected persons (0.6%; Table 1).

The affected relatives of the index cases included 108 sisters, 116 brothers, 105 parents, 30 children, 15 grandparents, and 166 aunts, uncles, and cousins. One index case had both parents affected, 4 index cases had >1 child affected, 40 index cases had >1 sibling affected, 4 index cases had >1 avuncular relationship, 1 index case had a maternal and paternal grandparent affected, 9 index cases had >1 cousin affected, and 11 index cases had >1 affected relative in extended relationship categories not listed above or specified in Table 2 (category: other; since some index cases had relationships in >1 category, the percentages sum to >100%).

Of the 937 affected relatives, 569 (60.7%) were still alive and available for genetic analysis. The families demonstrated inheritance patterns consistent with autosomal recessiveness in 198 (57.2%), autosomal dominance in 126 (36.4%), and autosomal dominance with incomplete penetrance in 19 (5.5%) of the families. Of the 346 families, 3 (0.9%) were complex and were not consistent with any known pattern of inheritance (Figure).

**TABLE 1. Relationship of First-Degree Affected Relatives to the Index Case**

<table>
<thead>
<tr>
<th>Affecteds</th>
<th>Families</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>2</td>
<td>206</td>
<td>59.5</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>9.5</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>2.9</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>2.9</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

M indicates mother; F, father; Br, brother; Si, sister; D, daughter; S, son.

**TABLE 2. Relationships of All Affected Relatives to the Index Case**

<table>
<thead>
<tr>
<th>Relationship*</th>
<th>Degree</th>
<th>Kinship†</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>1</td>
<td>1/4</td>
<td>60</td>
<td>45</td>
<td>105</td>
<td>104</td>
<td>30.1</td>
</tr>
<tr>
<td>Sibling</td>
<td>1</td>
<td>1/4</td>
<td>108</td>
<td>116</td>
<td>224</td>
<td>186</td>
<td>53.8</td>
</tr>
<tr>
<td>Child</td>
<td>1</td>
<td>1/4</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td>26</td>
<td>7.5</td>
</tr>
<tr>
<td>Avuncular‡</td>
<td>2</td>
<td>1/8</td>
<td>45</td>
<td>57</td>
<td>102</td>
<td>94</td>
<td>27.2</td>
</tr>
<tr>
<td>Grandparent</td>
<td>2</td>
<td>1/8</td>
<td>10</td>
<td>5</td>
<td>15</td>
<td>13</td>
<td>3.8</td>
</tr>
<tr>
<td>First cousin</td>
<td>3</td>
<td>1/16</td>
<td>35</td>
<td>29</td>
<td>64</td>
<td>53</td>
<td>15.3</td>
</tr>
<tr>
<td>Other§</td>
<td>&gt;4</td>
<td>&gt;1/32</td>
<td>16</td>
<td>35</td>
<td>51</td>
<td>41</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*With respect to index case.
†The typical value of kinship is given and is calculated as $(1/2)^{k+1}$, where $k$ is degree of relationship.\textsuperscript{59}
‡Uncle to niece/nephew or aunt to niece/nephew.
§Relationships such as half sibs, half cousin, half niece/nephew, second- and third-degree cousin, half avuncular, grandsonie or granddaughter and greatgrandparental.
Table 3 summarizes the transmission of IA from parents to children in those families consistent with autosomal dominance inheritance. For families with IA cases in 2 consecutive generations, all affected children were counted as instances of disease transmission, and all unaffected children were counted as instances of nontransmission of disease. The overall percent transmission was 31.5%, less than the expected for classic autosomal dominance inheritance but consistent with a complex disease.

ANOVA of the transmission data did not detect a significant effect for the sex of the parent, ie, transmission was not more frequent from mothers than from fathers ($P=0.10$). There was no significant effect for sex of child ($P=0.31$) and no significant interaction, ie, neither parent transmitted the disease more frequently to either sons or daughters ($P=0.57$; Table 3).

<table>
<thead>
<tr>
<th>Family</th>
<th>Pedigree</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td><img src="image1" alt="Family 10 Pedigree" /></td>
<td>Autosomal recessive inheritance</td>
</tr>
<tr>
<td>105</td>
<td><img src="image2" alt="Family 105 Pedigree" /></td>
<td>Autosomal dominant inheritance</td>
</tr>
<tr>
<td>250</td>
<td><img src="image3" alt="Family 250 Pedigree" /></td>
<td>Autosomal dominant inheritance</td>
</tr>
<tr>
<td>49</td>
<td><img src="image4" alt="Family 49 Pedigree" /></td>
<td>Autosomal dominant inheritance with incomplete penetrance</td>
</tr>
<tr>
<td>225</td>
<td><img src="image5" alt="Family 225 Pedigree" /></td>
<td>Complex inheritance</td>
</tr>
<tr>
<td>124</td>
<td><img src="image6" alt="Family 124 Pedigree" /></td>
<td></td>
</tr>
<tr>
<td>151</td>
<td><img src="image7" alt="Family 151 Pedigree" /></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image8" alt="Family 6 Pedigree" /></td>
<td></td>
</tr>
</tbody>
</table>

Representative pedigrees from our collection of 346 multiplex Finnish FIA families. Families 10 and 250 were consistent with an autosomal recessive inheritance and families 151 and 6 with autosomal dominant inheritance. Families 105 and 49 were consistent with autosomal dominant inheritance with incomplete penetrance, and families 124 and 225 were considered to have complex inheritance. MRA indicates MR angiography; square, male; circle, female; diagonal slash through symbol, deceased individual; arrow (below and to the left of individual), index case of family; and diagonal descent lines, twins. Definitions of affection status are shown at the top right of the figure.

**TABLE 3. Transmission of IA With Families Consistent With Autosomal Dominant Inheritance**

<table>
<thead>
<tr>
<th>Mother to</th>
<th>Father to</th>
<th>Parent to</th>
</tr>
</thead>
<tbody>
<tr>
<td>S  D  C</td>
<td>S  D  C</td>
<td>S  D  C</td>
</tr>
<tr>
<td>T  54  68  122</td>
<td>33  41  74</td>
<td>196</td>
</tr>
<tr>
<td>NT 120 116 236</td>
<td>89 102 191</td>
<td>427</td>
</tr>
<tr>
<td>Total 174 184 358</td>
<td>122 143 265</td>
<td>623</td>
</tr>
<tr>
<td>% 31.0 37.0 34.1</td>
<td>27.0 28.7 27.9</td>
<td>31.5</td>
</tr>
</tbody>
</table>

S indicates son; D, daughter; C, child; T, IA transmitted; NT, IA not transmitted.

**Discussion**

The concept that IA has a genetic component is increasingly supported by studies demonstrating familial aggregation.\(^3,5,10,11,16,22,33,43,47-53\) It is a disease with incomplete penetrance and late age at onset, with associated censoring and truncation, environmental, and stochastic risk factors. Our population consisted of families in which ≥2 individuals were affected with IA. There were 85 families included in our population that were previously described\(^11,16\) and an additional 261 families. The collection is the most extensive published to date and extends previous observations of familial aggregation that are consistent with a major gene effect. Previous studies have indicated that a family history of IA is a risk factor for a person to develop IA.\(^1,3,5,11,16,23,43,47,48,50,52-54\) We excluded families that had a diagnosis of any other heritable disorder reported to have associated IAs but were unable to gather complete data on environmental and behavioral factors.

Although this study presents the largest collection of FIA to date, it has some limitations. It was not designed to address the differences between sporadic and familial IAs. In addition, since IA is a disease with a late age at onset, diagnosis in the absence of rupture is rare, and genetic testing is not yet available, it is nearly impossible to identify individuals who are currently asymptomatic but may develop IA in the future.\(^55,56\) Individuals may have died for reasons other than IA rupture or before the development of IA, and even though autopsy is common in Finland, it is possible that an IA may have been overlooked if death occurred for reasons other than rupture (Figure). IA may also have gone unnoticed if another
more obvious cause of death, such as myocardial infarction, was present. Some affected family members may have chosen not to participate, and it was difficult to obtain information on family members removed more than second degree; consequently, there may have been additional affected family members. Our estimates are therefore probably conservative.

Our study found evidence consistent with multiple modes of inheritance. As with previous studies of the Finnish population, we found little or no evidence for a preponderance of females. The finding that both parents transmit IA to either sons or daughters is consistent with autosomal inheritance. Previous studies demonstrated late age at onset, suggesting that IA, and in particular FIA, is a complex disorder. Other studies have demonstrated that environmental factors are important for IA. Consequently, IA is probably multifactorial.

Linkage analysis of complex disorders is best achieved by model-free, relative-pair, allele-sharing approaches. Two recent studies found suggestive linkage for IA. The studies used different populations, Finnish and Japanese, and found linkage at distinct locations. Both studies were based on small sample sizes, and the observations need to be verified with larger samples. We intend to follow up on the linkage findings with the collection presented here. The larger sample size should provide increased power to localize the gene or genes that predispose to IA.

Acknowledgments

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References

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