On the Inheritance of Intracranial Aneurysms

Wouter I. Schievink, MD; Daniel J. Schaid, PhD; Harry M. Rogers, MD; David G. Piepgras, MD; Virginia V. Michels, MD

Background and Purpose The familial occurrence of intracranial aneurysms suggests the presence of a genetically determined underlying arteriopathy. The pattern of inheritance in these families usually is not known.

Methods A family with seven members with intracranial aneurysms is described, and, from the literature before 1994, a total of 238 families with 560 affected members (56% female and 44% male) with intracranial aneurysms not associated with a known heritable disease are reviewed. A segregation analysis was performed on 73 of these families.

Results Two members were affected in the great majority of families (79%); five or more members were reported in only eight families (3%). The most common affected kinship was among siblings. Angiographic screening in 12 families detected an intracranial aneurysm in 29% of 51 asymptomatic relatives. Segregation analysis revealed several patterns of inheritance that were consistent with the compiled pedigrees, but no single mendelian model was the overall best fitting, suggesting that genetic heterogeneity may be important. Twenty-two percent of siblings of male probands had an intracranial aneurysm compared with 9% of siblings of female probands (P = .003).

Conclusions Genetic heterogeneity may be important in the genetics of intracranial aneurysms. In families with intracranial aneurysms, siblings of an affected male proband may be at a higher risk of developing an aneurysm than siblings of an affected female proband. Screening for intracranial aneurysms in asymptomatic relatives should be considered in families with two or more affected members. In most families, the nature of the underlying arteriopathy remains obscure.

Key Words • cerebral aneurysm • subarachnoid hemorrhage • genetics

The etiology of intracranial aneurysms is not well understood and is likely to be multifactorial. Acquired factors are important because it has been shown that the incidence of aneurysmal subarachnoid hemorrhage (SAH) increases with age; various risk factors, such as hypertension and smoking, have been proposed. It is unlikely that hemodynamic stresses at intracranial arterial forks alone are sufficient to produce an aneurysm; rather, an underlying vessel wall abnormality is generally suspected. The familial occurrence of intracranial aneurysms and their association with certain heritable disorders suggest that the underlying defect of the arterial wall may, at least in part, be genetically determined.

It has been shown that familial intracranial aneurysms have characteristics that are different from those that occur sporadically. Familial intracranial aneurysms rupture at a lower age, occur less often at the anterior cerebral artery complex, and may rupture at a smaller size. In addition, among family members, intracranial aneurysms more often arise from the same arterial distribution and more often rupture within the same decade of life.

Since the initial report in 1954 by Chambers and colleagues, a multitude of families with documented intracranial aneurysms have been described, but the pattern of inheritance of familial intracranial aneurysms has not been established. To better delineate the pattern of inheritance of familial intracranial aneurysms, we present data on a large North American family with intracranial aneurysms and, in conjunction with this, analyze the data from all identified published pedigrees of familial intracranial aneurysms. Establishing a pattern of inheritance for familial intracranial aneurysms may shed some light on the nature of the putative underlying arteriopathy and would be of benefit in counseling individuals with a family history of intracranial aneurysms.

Family History

Description of Family

Seven patients in two generations of this family developed intracranial aneurysms. Their pedigree is shown in the Figure, and their clinical characteristics are summarized in Table 1. The family resides in North Dakota and is of Dutch and German descent. There is no evidence of a known heritable connective tissue disorder. None of the patients are the result of consanguineous mating.

Subject III 1, the propositus, presented to his neurosurgeon at age 38 years because of a family history of ruptured intracranial aneurysms. He had no history of unusual headaches. His father and mother were 19 and 18 years old, respectively, when he was born.

Subject II 9, his paternal uncle, had suddenly collapsed at work at age 36 years. Lumbar puncture revealed bloody cerebrospinal fluid, and angiography demonstrated a left posterior communicating artery aneurysm. He deteriorated after the angiogram and died. An autopsy was not performed.

Subject III 2, his brother, suffered his first SAH at age 28 years. Angiography demonstrated a left internal...
carotid artery aneurysm arising just distal to the ophtalmic artery. No aneurysms were demonstrated on the right carotid injection. A Silverstone clamp was applied to the left common carotid artery. He recovered but 2 years later again presented with an SAH. Angiography now demonstrated an aneurysm arising from the right internal carotid artery bifurcation. The left common carotid artery was occluded. He died shortly thereafter.

Subject I1, his paternal grandfather, suddenly developed a severe headache at age 51 years while fixing a chair and died. An autopsy was not performed.

Elective Angiographic Investigations

The propositus and his five remaining siblings underwent four-vessel cerebral angiography. Angiography revealed a right middle cerebral artery aneurysm in the propositus. A left ophtalmic artery aneurysm was demonstrated in his 35-year-old brother (subject III3). A left middle cerebral artery aneurysm was detected in his 26-year-old sister (subject III4). A left cavernous carotid artery aneurysm was detected in his 33-year-old sister (subject III5). His 29-year-old brother (subject III6) was found to have three intracranial aneurysms arising from the left posterior communicating artery, left internal carotid artery bifurcation, and distal left middle cerebral artery. Angiography was normal in his 32-year-old brother (subject III7).

All aneurysms, except the cavernous carotid aneurysm in subject III1, and the distal middle cerebral artery aneurysm in subject III5, were clipped. The size of the untreated aneurysms was stable on repeat angiography 1 year later. In the propositus, an additional minute middle cerebral artery aneurysm was identified at the time of surgery, which was wrapped in muslin gauze.

There was no morbidity or mortality associated with the radiographic or surgical procedures.

The current age of the propositus is 44 years. The parents were not studied.

Subjects and Methods

Review of the Literature

Reports on the familial aggregation of intracranial aneurysms in the world literature before 1994 were collected and reviewed by two of us (W.I.S. and D.J.S.). Familial aggregation of intracranial aneurysms was defined as the presence of at least two members of a family. Thus, pedigrees of familial SAH in which only a single member was proven to have an intracranial aneurysm were excluded. Families with a known heritable disorder that cosegregated with the presence of an intracranial aneurysm were also not included in the final analysis, although the number of such families was small.

In families in whom the proband was not clearly designated, the second affected relative (ie, the first individual who establishes the presence of familial intracranial aneurysms) was considered to be the proband.

Segregation Analyses

Inclusion Criteria for Nuclear Families

For segregation analyses, only the proband and his/her parents and siblings were included. This strategy resulted in some loss of information because, for some large pedigrees, only a single nuclear family was abstracted. However, we were concerned that the diagnosis of intracranial aneurysm may have been missed in the older generations and that the children of probands may not have been old enough to develop intracranial aneurysms. Our assumption is that the siblings of probands are at approximately the same age as the proband, at least in terms of being at similar risk to develop an intracranial aneurysm. Only these criteria were enforced for inclusion of pedigrees reported in the literature. No nuclear families were excluded based on the mode of inheritance apparent in the pedigree. Individuals were coded as affected when the presence of an intracranial aneurysm had been documented, and no distinction was made between ruptured and unruptured aneurysms or between persons with or without elective angiographic investigations.

Statistical Analysis

Complex segregation analysis was used to test a series of models that represent no genetic factors, as well as various modes of transmission, that can influence the distribution of the discrete trait of being affected with intracranial aneurysm versus normal. Under these models, the distribution of the affected individuals in the nuclear families could be a consequence of a nontransmitted environmental factor, a single major gene, or additive effects of a large number of independent polygenetic loci. The parameters of these models are as follows. Up to three general types (sometimes referred to as ossiotypes) of persons, labeled AA, AB, and BB, were allowed for in the analysis, where "type" describes an underlying
Results

Review of the Literature

Including the presently reported family, a total of 238 families with 563 affected relatives were reviewed. There were 246 men (44%) and 314 women (56%).

Of the 238 families, the great majority (79%) had two affected members; only 3% had five or more affected members (Table 2). First-degree relatives, ie, siblings, parents, or children, were affected in 203 families. The kinship among affected family members is shown in Table 3. Intracranial aneurysms occurred among siblings in 156 families and among a parent and child in 61 families.

Six pairs of twins with intracranial aneurysms have been reported. Angiographic screening for familial intracranial aneurysms has been performed in at least 51 asymptomatic first- or second-degree relatives in 12 families, with a detection rate of 29% (Table 4).

Familial Aggregation

A total of 73 nuclear families with 563 individuals (282 men and 281 women) were selected for analysis of familial aggregation. The remaining pedigrees could not be included because information on the total number of first-degree relatives was unavailable. Of the 282 men, 75 (27%) were affected compared with 104 (37%) of the 281 women. The number of offspring ranged from 2 to 12, with an average of 6. Among the 73 nuclear families, 28 sons were affected probands, 43 daughters were affected probands, 1 normal daughter was a proband, and 1 normal mother was a proband. The distribution of affection status among the children in these families, after excluding the child probands, is presented in Table 5. The percentage of affected sons did not significantly differ across the three categories of parental status \( P = .88 \), nor did the percentage of affected daughters \( P = .19 \). Furthermore, although there was a trend for daughters to be more frequently affected than sons, the overall percentage of daughters affected (31%) did not significantly differ from the percentage of sons affected (22%) \( P = .08 \). Also, when either parent was affected, more frequently it was the mother (61%).

To assess the risk to siblings of affected probands, we examined separately the percentage of affected brothers and affected sisters according to whether the affected child proband was a son or daughter. Crude percent-
TABLE 4. Results of Angiographic Screening for Intracranial Aneurysms in Asymptomatic Family Members

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>No. of Affected Family Members</th>
<th>No. of Screened Family Members</th>
<th>Closest Affected Relative</th>
<th>No. of Those Screened With Aneurysm</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edelsohn et al, 197225</td>
<td>4</td>
<td>5</td>
<td>Siblings</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Hashimoto, 197737</td>
<td>2</td>
<td>5</td>
<td>Siblings</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Stavenow, 197940</td>
<td>2</td>
<td>1</td>
<td>Sibling</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fox and Ko, 1980&quot;</td>
<td>3</td>
<td>8</td>
<td>Siblings</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>Evans etal, 198144</td>
<td>4</td>
<td>4</td>
<td>Siblings; daughter</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Halal etal, 198347</td>
<td>5</td>
<td>3</td>
<td>Siblings; daughter</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patrick and Appleby, 198349</td>
<td>4</td>
<td>6</td>
<td>Siblings</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Lozano and Leblanc, 1987'7</td>
<td>3</td>
<td>3</td>
<td>Sibling; niece</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mellergard et al, 198948</td>
<td>5</td>
<td>5</td>
<td>Siblings</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Leblanc et al, 1989'7</td>
<td>2</td>
<td>4</td>
<td>Siblings</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Elshunnar and Whittle, 1990'9</td>
<td>3</td>
<td>1</td>
<td>Siblings</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Present report</td>
<td>2</td>
<td>6</td>
<td>Siblings</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td></td>
<td></td>
<td>15</td>
<td>29 (95% CI, 17-44)</td>
</tr>
<tr>
<td>Siblings only</td>
<td>46</td>
<td></td>
<td></td>
<td>15</td>
<td>33 (95% CI, 20-48)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

ages, after exclusion of the proband, are presented in Table 6. For sons who are probands, the risks to brothers (30%) and sisters (34%) were similar, and for daughter probands, the risks to brothers (17%) and sisters (25%) were similar. Although these risk calculations were adjusted for ascertainment by excluding the proband from analyses, this adjustment is likely incomplete because at least two members of the pedigrees had to be affected for the nuclear family to be included. This will lead to oversampling of affected individuals and risk estimates that are too high. In an attempt to correct for this, we eliminated an additional affected child if both parents were normal. However, when estimating sex-specific risks, if both a brother and a sister of a proband were affected, then either of these siblings could have served as the second ascertained “proband,” so in this case neither sibling was excluded for the sex-specific risks. These results are presented in Table 7. As expected, the risks are lower than those in Table 6. If a son is a proband, the risk to his brothers (24%) is less than that for his sisters (30%) but not statistically significant (P=.45). If a daughter is a proband, the risk to her brothers (10%) is less than that for her sisters (14%) but not statistically significant (P=.32). Interestingly, the risk to all siblings of a male proband (26/117=22%) was significantly higher than the risk to all siblings of a female proband (17/179=9%) (P=.003).

Segregation Analyses

The likelihood models we fit were for (1) an environmental model with no major gene (NMG) determining the frequency of affected individuals, (2) autosomal dominant and recessive models, and (3) X-linked dominant and recessive models. We allowed for the frequency of aneurysms to differ between males and females but found no significant difference, and there-

TABLE 5. Distribution of Disease Among Offspring, Excluding Child Proband, in 73 Families Selected for Segregation Analysis

<table>
<thead>
<tr>
<th>Father</th>
<th>Mother</th>
<th>No. of Nuclear Families</th>
<th>Sons</th>
<th>Daughters</th>
<th>Total Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>55</td>
<td>32</td>
<td>23</td>
<td>109</td>
</tr>
<tr>
<td>N</td>
<td>A</td>
<td>11</td>
<td>6</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>A</td>
<td>N</td>
<td>7</td>
<td>2</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>73</td>
<td>40</td>
<td>22</td>
</tr>
</tbody>
</table>

A indicates affected; N, normal.
TABLE 6. Risk to Brothers and Sisters of Affected Proband Among 73 Families Selected for Segregation Analysis

| Affected Proband | Brothers | | | | | | | | | | Total |
|------------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                   | A        |      %  | No.      |          | N        |      %  | No.      |          | A        |      %  | No.      |          | N        |      %  | No.      |          |
| Son               | 22       | 30      | 51       | 70       | 21       | 34      | 40       | 66       | 43       | 32      | 91       | 68       |
| Daughter          | 18       | 17      | 88       | 83       | 25       | 25      | 74       | 75       | 43       | 21      | 162      | 79       |

A indicates affected; N, normal.

fore sex-specific penetrances are not reported here. Our strategy for model fitting was to begin with the most restricted model and then allow fewer restrictions. Results are presented in Table 8. Several genetic models fit the data significantly better than both the NMG model and the nontransmitted environmental model (ie, transmission probabilities are all equal to p). The best-fitting models were an autosomal dominant model with a very rare disease susceptibility allele and an autosomal recessive model with a not so rare susceptibility allele. For both of these models there was no evidence that the transmission parameter \( P(A/AB) \) differed from the mendelian probability of 1/2, and we did not detect a significant departure of the genotype frequencies from the Hardy-Weinberg proportions. In an attempt to distinguish autosomal dominant from autosomal recessive, we fit a more general codominant model allowing for three penetrances, one for each of the types AA, AB, and BB. The estimated penetrances were 0.80, 0.41, and 0.06, respectively, with allele frequency \( p = 0.001 \). However, this model did not fit significantly better than the dominant model \( (P = .65) \) or the recessive model \( (P = .14) \). Furthermore, an X-linked dominant model fit significantly better than the NMG model, although not as well as the autosomal models. Hence, for these data there is strong evidence for familial aggregation compatible with autosomal inheritance, but we do not have sufficient power to precisely resolve the mode of inheritance. A polygenic model, without a major gene, was also fit. However, the estimate of population incidence from this model was 0.009 with heritability of 100%, which seems an overestimate of heritability if polygenic inheritance were the only genetic etiology; this large an estimate of heritability would be expected if a major gene were contributing to the disorder, in which case polygenic heritability would not be the correct model to fit. Therefore, we did not include polygenic heritability in any other models.

Discussion

The presently described family is unique in that 6 of 7 siblings were found to have an intracranial aneurysm. The family described by Fox\(^{41,45} \) in whom 7 of 13 siblings were affected, and the family described by ter Berg et al\(^{16,59,71} \) in whom 5 of 9 siblings were affected, had a similarly high percentage and number of affected siblings.

The familial occurrence of intracranial aneurysms could argue for either genetic or common environmental influences in the development of these aneurysms. However, since there is no evidence directly relating possible environmental factors, eg, diet or pollution, to the development of intracranial aneurysms in humans, whereas aneurysms have been associated with several heritable connective tissue disorders, it is quite reasonable to conclude that there probably is a primary hereditary basis for many of these familial aneurysms. This, of course, does not negate the possible importance of certain external risk factors, such as smoking or hypertension.

Epidemiology

Recent investigations have shown that a family history of intracranial aneurysms is more common in patients with aneurysmal SAH than was previously appreciated. Norrgard et al\(^{61} \) detected one or more relatives with an intracranial aneurysm in 5.1% of Swedish patients with aneurysmal SAH. Ronkainen et al\(^{77} \) reported a somewhat higher percentage (8.8%) of familial intracranial aneurysms in a Finnish population.

The majority of families described in these epidemiological studies as well as those described in the literature consisted of only two affected relatives, and it is possible that in some of the families the aggregation of intracranial aneurysms was entirely fortuitous.

Pattern of Inheritance

A pattern of inheritance of familial intracranial aneurysms has not been established. Autosomal dominant or multifactorial inheritance has been suggested by most authors, whereas recessive inheritance is suggested by the occurrence of intracranial aneurysms in families with known consanguinity. McKusick\(^{48} \) categorizes intracranial aneurysms as an autosomal dominant disor-
by guest on November 11, 2017 http://stroke.ahajournals.org/ Downloaded from

Inheritance of Intracranial Aneurysms

TABLE 8. Maximum Likelihood Parameter Estimates and $\chi^2$ Statistics for Various Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Sex</th>
<th>AA</th>
<th>AB</th>
<th>BB</th>
<th>$-2\ln L$</th>
<th>$\chi^2$</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMG</td>
<td>1</td>
<td>.16</td>
<td></td>
<td></td>
<td>221.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontransmitted</td>
<td>.12</td>
<td>.15</td>
<td>.16</td>
<td>.16</td>
<td>221.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>.006</td>
<td>.57</td>
<td>.57</td>
<td>.003</td>
<td>203.38</td>
<td>18.22</td>
<td>2</td>
<td>.001</td>
</tr>
<tr>
<td>Recessive</td>
<td>.05</td>
<td>.75</td>
<td>.02</td>
<td>.02</td>
<td>205.76</td>
<td>15.80</td>
<td>2</td>
<td>.004</td>
</tr>
<tr>
<td>X-linked</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMG</td>
<td>1</td>
<td>M</td>
<td>.16</td>
<td></td>
<td>221.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>.006</td>
<td>M</td>
<td>.88</td>
<td>.05</td>
<td>205.93</td>
<td>15.63</td>
<td>3</td>
<td>.001</td>
</tr>
<tr>
<td>Recessive</td>
<td>.143</td>
<td>M</td>
<td>.34</td>
<td>.02</td>
<td>214.94</td>
<td>6.62</td>
<td>3</td>
<td>.09</td>
</tr>
</tbody>
</table>

NMG indicates no major gene.

*For X-linked models, penetrance for males with genotypes A and B are listed under genotypes AA and BB, respectively.

†Compared with the NMG models.

der (Mendelian Inheritance in Man [MIM] No. 105800). Some of the difficulties in establishing the inheritance pattern of familial intracranial aneurysms include the observation that these aneurysms are acquired lesions and the fact that an unknown percentage of intracranial aneurysms remain asymptomatic. Screening of asymptomatic family members overcomes only part of these uncertainties. Keeping these caveats in mind, we attempted to determine the pattern of inheritance of familial intracranial aneurysms from aggregate case reports from the literature using a segregation analysis. The results of our segregation analysis revealed several mendelian patterns of inheritance that were compatible with our collection of pedigrees, with autosomal dominant and recessive the best-fitting models. However, one needs to cautiously interpret some of the model parameter estimates. The most difficult, yet critical, component of our segregation analysis was to correctly account for how the pedigrees were ascertainment. Because most families with a single affected member are not reported in the literature, we could not include the reported pedigrees with a single affected person. Rather, we attempted to correct for ascertainment by requiring two or more affected members. This implies that each pedigree must have two probands. We randomly defined a second affected member to be the second proband. This may be a close approximation for some pedigrees but may not accurately account for how all pedigrees were reported in the literature. Furthermore, all inferences regarding the fit of genetic models pertain only to families with two or more affected persons and not to the much larger percentage of families with only a single affected member. Another limitation of these analyses is that we did not have information on age at onset and current age for unaffected members. This limits our segregation analysis by not being able to consider penetrance as it depends on age. For some complex disorders, earlier age at onset is a strong indication of genetic susceptibility, and hence age can help to resolve genetic from sporadic cases. Other limitations of our collection of pedigrees include treating all unaffected individuals as normal; i.e., we did not have angiographic results in all family members to determine if some unaffected subjects actually had an asymptomatic aneurysm. If we did and if we treated these subjects as affected, we would expect that our estimates of penetrance would increase, assuming that the genetic models do not change. Finally, we did not have data available on risk factors, such as smoking and hypertension. All of the above limitations make it difficult to accurately conclude the precise role of genetics in the etiology of intracranial aneurysms. However, our results suggest that the familial aggregation of aneurysms is not a chance occurrence and that genetic factors may play an important role in its etiology. A possible explanation of the observed familial aggregation is that there is much genetic heterogeneity, so that some families have a genetic etiology due to autosomal dominant genes, other families due to autosomal recessive or X-linked genes, perhaps others due to polygenes, and still others due to nongenetic factors. Genetic heterogeneity for a disease is not unusual and, for example, has been observed in retinitis pigmentosa.

Some of the limitations of our study could be overcome by conducting a prospective study on the familial occurrence of intracranial aneurysms in a defined population. However, the length of time such a study would require to ascertain an adequate number of affected families is considerable.

Associated Heritable Disorders

Intracranial aneurysms have been associated with various heritable disorders (Table 9). Of these disorders, only patients with polycystic kidney disease, Ehlers-Danlos syndrome, Marfan's syndrome, neurofibromatosis, and pseudoxanthoma elasticum are generally considered to be at an increased risk of developing an intracranial aneurysm, although this has only been firmly established for polycystic kidney disease. In autosomal dominant polycystic kidney disease, approximately 10% of asymptomatic patients are found to have...
an intracranial aneurysm.\textsuperscript{116,117} With the exception of autosomal dominant polycystic kidney disease, there is a paucity of reports of documented familial intracranial aneurysms associated with any of these aforementioned heritable disorders.\textsuperscript{118} Nevertheless, it may be prudent to consider the disorders listed in Table 9 when confronted with a case of familial intracranial aneurysms. A careful history and physical examination are mandatory and may direct one to the diagnosis. However, intracranial aneurysms may be the first manifestation of any of the heritable connective tissue disorders, and the external signs may be subtle. Ancillary diagnostic tests should be considered, such as ultrasound examination of the kidneys to exclude polycystic kidney disease and echocardiography to search for cardiac valvular abnormalities or aortic root dilatation indicating a systemic connective tissue disorder. With recent developments in cell biology and molecular genetics, the diagnosis of some of these disorders, such as Ehlers-Danlos syndrome type IV and Marfan's syndrome, can now be established at a molecular level, and this may be useful in a clinical setting when the diagnosis is uncertain.\textsuperscript{115}

**Screening**

The mortality rate of intracranial aneurysm rupture exceeds 50%, and the morbidity in survivors is a significant public health problem.\textsuperscript{1} Therefore, screening for intracranial aneurysms in asymptomatic individuals followed by surgical or endovascular obliteration of the unruptured aneurysm is an attractive alternative. However, much controversy exists regarding the management of asymptomatic unruptured intracranial aneurysms because the rate of rupture is uncertain and surgical or endovascular treatment is not without risk.\textsuperscript{119-121} Nevertheless, screening for intracranial aneurysms in asymptomatic relatives should be considered when there are two or more members with an intracranial aneurysm in the immediate family, although the benefits of such screening procedures have not been quantified. The yield of angiographic screening as reported in the literature is fairly high (29%), but the publication bias is likely to be significant. In a less selected population and using magnetic resonance angiography, Hernesniemi et al.\textsuperscript{122} detected intracranial aneurysms in 10% of 110 asymptomatic relatives of patients with familial intracranial aneurysms. Using intra-arterial digital subtraction angiography, Nakagawa and Hashi\textsuperscript{123} found intracranial aneurysms in 18% of 39 individuals with a family history of SAH. Our study was not able to determine which relatives are at the highest risk for developing an aneurysm but did suggest that siblings of affected males may be at a higher risk than siblings of affected females.

Decision-analytical methods have suggested that screening is advisable for all relatives between 35 and 60 years of age, when "the physician thinks that the risk of an intracranial aneurysm is increased."\textsuperscript{124} Decision analysis has also suggested that the risk of the radiographic procedure that is selected for screening virtually has no influence on the ultimate benefits from screening.\textsuperscript{125} Nevertheless, for most individuals with a family history of intracranial aneurysms, magnetic resonance angiography is the more practical alternative, even if the patient is aware of the uncertainties that exist regarding the sensitivity and specificity of magnetic resonance angiography at the present time in comparison with conventional angiography. Magnetic resonance angiography is especially attractive if screening is to be repeated when no aneurysm is detected initially. Aneurysms have been shown to appear de novo, and this may be more common in those with a family history of intracranial aneurysms (as was also seen in one of the

### Table 9. Heritable Disorders That Have Been Associated With Intracranial Aneurysms

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase deficiency*</td>
<td>AR</td>
<td>100, 102</td>
</tr>
<tr>
<td>α-Antitrypsin deficiency†</td>
<td>AR</td>
<td>114</td>
</tr>
<tr>
<td>Alkaptonuria</td>
<td>AR</td>
<td>105</td>
</tr>
<tr>
<td>Anderson-Fabry disease*‡</td>
<td>XLR</td>
<td>91, 112</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>AD</td>
<td>103, 104, 107, 108, 110</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome type IV</td>
<td>AD</td>
<td>92, 115</td>
</tr>
<tr>
<td>Familial idiopathic nonarteriosclerotic cerebral calcification syndrome</td>
<td>?</td>
<td>101</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>AD</td>
<td>85, 86, 89, 93, 106, 113</td>
</tr>
<tr>
<td>Marfan's syndrome</td>
<td>AD</td>
<td>115</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>AD</td>
<td>115</td>
</tr>
<tr>
<td>Noonan's syndrome</td>
<td>AD</td>
<td>96</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>AD, AR</td>
<td>115</td>
</tr>
<tr>
<td>Tuberous sclerosis*</td>
<td>AD</td>
<td>87, 88, 90, 94, 95, 97-99</td>
</tr>
<tr>
<td>Wermer's syndrome (multiple endocrine neoplasia type 1)</td>
<td>AD</td>
<td>111</td>
</tr>
<tr>
<td>3M syndrome</td>
<td>?</td>
<td>109</td>
</tr>
</tbody>
</table>

AR indicates autosomal recessive; XLR, X-linked recessive; and AD, autosomal dominant.

* Aneurysms are often fusiform. †Heterozygotes may be affected. ‡Carriers may be affected.
References


80. Hasstedt SJ. Pedigree Analysis Package, Rev. 3.0. Technical report, Department of Human Genetics, University of Utah Medical Center, 1989.  


On the inheritance of intracranial aneurysms.
W I Schievink, D J Schaid, H M Rogers, D G Piepgras and V V Michels

Stroke. 1994;25:2028-2037
doi: 10.1161/01.STR.25.10.2028

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/10/2028