A genealogical assessment of heritable predisposition to aneurysms

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Object. This study was conducted to investigate the familial and genetic contribution to intracranial, abdominal aortic, and other types of aneurysms, and to define familial relationships among patients who present with the different aneurysm types.

Methods. The authors used a unique Utah resource to perform population-based analysis of the familial nature of aneurysms. The Utah Population Data Base is a genealogy of the Utah population dating back eight generations, which is combined with death certificate data for the state of Utah dating back to 1904. Taking into account the genetic relationships among all aneurysm cases derived from this resource, the authors used a previously published method to estimate the familiality of different aneurysm types. Using internal, birth-cohort-specific rates of disease calculated from the database, they estimated relative risks by comparing observed to expected rates of aneurysm incidence in defined sets of relatives of probands.

Conclusions. Each of the three aneurysm types investigated showed significant evidence for a genetic component. Relatives of patients with intracranial aneurysms do not appear to be at increased risk for abdominal or other lesions, but relatives of patients with abdominal aortic aneurysms appear to be at increased risk for other types of these lesions.

KEY WORDS • familial aneurysm • relative risk

Although the familial nature of aneurysms has been recognized, it has been defined primarily based on studies of first-degree relatives of selected cases. The identification of associations among the different types of aneurysms (intracranial, abdominal aortic, and other) has rarely been a part of such studies. Family studies are usually limited both in genealogical data and knowledge of the complete health status of relatives outside the nuclear family. We have used a unique population-based resource in Utah to study the familial nature of aneurysms by using death certificate records, and to examine genetic relationships among patients with different aneurysm types from a population perspective. This type of population-based study, in which genealogical and death certificate data for the state are used, may represent a more complete assessment of the genetic contribution to disease than is typically available. Evidence of a very high degree of familiality for all three types of aneurysms was observed, indicating a familial/genetic component for each of these phenotypes. Associations among intracranial, aortic, and other arterial aneurysms have occasionally been reported in individuals with these lesions and their close relatives. Our analysis supports this finding, and we suggest that common predispositions for different aneurysm types exist.

An aneurysm is defined as a sac formed by the dilation of the wall of an artery or vein, or an abnormal, permanent, and irreversible localized dilation of a vessel to at least 1.5 times the size of the normal artery proximally. Aneurysms can affect any arterial segment. Intracranial aneurysms typically form berrylike sacs that develop at the bifurcation sites on medium-sized arteries, usually at a site of high turbulence. The origin of intracranial aneurysms is a matter of controversy but the evidence indicates that they are an acquired lesion rather than a congenital one. The majority of clinically detectable systemic aneurysms are found in the infrarenal abdominal aorta, often including the common iliac arteries, and are typically close to a bifurcation. These lesions are morphologically different from intracranial aneurysms in that they typically consist of a fusiform dilation. They result from circumferential failure of the vessel ultrastructure rather than focal failure at a vessel branch point. In this report we have examined intracranial, aortic, and other aneurysm types. These three categories of lesions are recognizable and can be distinctly identified using ICD codes (Table 1).

Clinical Material and Methods

The UPDB used for this analysis is a unique resource consisting of multiple computerized data sources, including a Utah genealogy and Utah death certificates. The UPDB genealogy represents approximately 1.3 million Utah pioneers and descendants in Utah. Previous familyuality analyses of the cancer records in the UPDB provided strong evidence for the familial nature of cancer of most sites.
Approval by the Institutional Review Board and officials at the Resource for Genetic Epidemiology (UPDB) was granted for this study.

The 297,002 records representing death certificates from the years 1904 to 1999 included in the UPDB were used for this analysis. The cause of death recorded on the Utah death certificates was coded using the ICD system (revisions 6–10). The death certificate record linking to genealogy data used the individual’s name and birthdate. A single matching individual genealogy record was identified for approximately 40 to 50% of death records, with linkage rates varying somewhat by sex and birth cohort. Studies of the Utah population have shown that it is genetically representative of Northern Europe and that there are normal levels of inbreeding. Utah has much lower death rates than the US as a whole, due to a younger population, but a comparison of rankings of cause of death and death rates indicates that the distribution of cause of death by frequency is not significantly different for the most common causes of death.

We have defined three different aneurysm phenotypes by using cause-of-death codes represented in the UPDB, including death certificates dating back to ICD Revision 6. The cause-of-death codes used to classify affected individuals by aneurysm type are shown in Table 1, along with the associated sample sizes.

### Genealogical Index of Familiality

The UPDB resource allows analysis of familial aggregation of disease. One method of quantifying familial aggregation that was developed for the UPDB is the GIF. The GIF is used to measure the mean degree of relatedness among a set of individuals who are usually chosen because they share a phenotype; they are called cases. The degree of relatedness between all possible pairs of cases is measured using the Malécot coefficient of kinship. The coefficient of kinship for each pair is defined as the probability that randomly selected homologous genes from the two individuals are identical by descent from a common ancestor (for siblings the coefficient is 0.25). The case GIF is defined as the mean of the coefficients of kinship between all possible pairs of cases ($\times 10^4$ for convenience). To evaluate whether excess relatedness exists among the case set, the case GIF can be compared with the same measurement obtained in a set of randomly selected controls that are matched to the cases by 5-year birth cohort, sex, and birthplace (in Utah or not). A control GIF can then be calculated in an analogous way to the case GIF. One thousand independent control sets are selected, GIF calculations are repeated, and an empirical distribution for the GIF statistic is created. An empirical probability value for assessment of significance is determined by placement of the observed case GIF in the empirically derived null distribution. Recent analysis of the Iceland genealogy/disease resource demonstrates the use of a kinship statistic very similar to the GIF to define the familiality of disease.

**Relative Risk**

A more commonly used measure of familial/genetic risk is the RR. In contrast to the GIF, which is used to evaluate all familial relationships among cases, the RR is limited to close relationships only. We estimated the RR of disease among family members by using internal rates of disease calculated for each aneurysm that caused a death. All individuals in the UPDB are assigned membership in one of 128 birth year-, sex-, and birthplace-specific cohorts. Populationwide internal cohort-specific rates of aneurysm presence are calculated for all 128 birth cohorts separately by summing the number of individuals with the selected cause of death in each cohort and dividing by the number of individuals with any cause-of-death code in the cohort. We include only individuals for whom there is a linked death certificate with cause-of-death information, such that the cause in all other individuals is considered unknown. Although these rates may not represent population rates for the selected cause of death, they are appropriate internal rates for comparative purposes. Expected numbers of cases are estimated by identifying all first-degree relatives of the set of probands with the disease by cohort, multiplying the number of relatives per cohort by the cohort-specific disease rate, then summing over all 128 cohorts. The observed counts for affected first-degree relatives are then compared with the expected counts. The formula $RR = observed/expected$ is an unbiased estimator of RR and can be calculated for multiple different relationships (for example, first- or second-degree family members). Exact one-sided Poisson probabilities are calculated under the null hypothesis that the RR was equal to unity, based on the assumption that the
Heritable predisposition to aneurysms

Results

Analysis of Familiality for Aneurysm Type

The results of the analysis of familiality for aneurysm types are shown in Table 2, which includes the lesion types, the number of individuals with this type, the GIF measurement in the cases, the mean GIF in the controls, and the empirical probability value for the sample of 1000 control individuals in whom the GIF was evaluated. The GIF familiality measures for the three types of aneurysm are all higher than we have previously estimated for any cancer site, including breast and prostate cancer, for which multiple predisposition loci have been identified. When compared with sets of control individuals, the familiality measure of mean relatedness for each aneurysm type is significantly in excess of that seen in controls.

Because early age at onset is a recognized characteristic of inherited forms of many diseases, we also estimated the familiality only for the individuals in each aneurysm class who died at an early age. For intracranial aneurysms, in which earlier deaths were observed, we considered patients with aneurysms in whom death occurred before the age of 60 years, and separately, those in whom death occurred before the age of 50 years, as early deaths. For aortic and other aneurysms we selected patients in whom death occurred before the age of 65 years as early deaths to allow adequate sample sizes. Table 3 shows the sample size, case and mean control GIF, and empirical probability values for these groups.

Familial RR

To test the hypothesis of increased RRs for aneurysm between different lesion types, we selected the set of deaths associated with each aneurysm type independently, and estimated the RR of each type in first-degree family members. The results are shown in Table 4. We found that, for each of the three aneurysm types, first-degree family members of the patients are at significantly increased risk for that same lesion type, with RRs ranging from 2.07 for abdominal aortic types to 13 for other aneurysms.

We have used the UPDB to examine RRs more fully for different degrees of relationship, by using the same methods to estimate expected numbers of family members (comparison of observed with expected internal rates). Table 5 shows RR estimates for various sets of family members and for spouses of patients with the three aneurysm types. Increased RRs for intracranial aneurysms are observed for first-degree, but not for second-degree family members, and sibling risk is increased over parent/offspring risk. For abdominal aortic aneurysms, the RR for second-degree family members is slightly lower than that for first-degree relatives, and sibling risk is very similar to parent/offspring risk. Sample sizes for other aneurysms are very small and many fewer deaths were observed for this category of lesion. The RR of 13 for other aneurysms in first-degree family members (Table 4) is inflated and entirely due to an excess sibling risk estimated to be 20.9, which was based on the observation of only two affected siblings. The RRs for spouses were not significantly elevated.

Table 3

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Relatedness (GIF)</th>
<th>Sample</th>
<th>Cases</th>
<th>Mean in Controls</th>
<th>Empirical p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic</td>
<td>Intracranial</td>
<td>no</td>
<td>287</td>
<td>4.77</td>
<td>2.69</td>
</tr>
<tr>
<td>An</td>
<td>intracranial</td>
<td>&lt;65 yrs</td>
<td>315</td>
<td>3.63</td>
<td>2.39</td>
</tr>
<tr>
<td>An</td>
<td>&lt;50 yrs</td>
<td>194</td>
<td>2.05</td>
<td>2.18</td>
<td>0.495</td>
</tr>
<tr>
<td>An</td>
<td>Other</td>
<td>&lt;65 yrs</td>
<td>30</td>
<td>3.59</td>
<td>2.99</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Aneurysm Type</th>
<th>Observed/ Expected</th>
<th>RR‡</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>2401</td>
<td>19/5.2</td>
<td>3.67</td>
</tr>
<tr>
<td>Abdominal aortic</td>
<td>6961</td>
<td>77/37.2</td>
<td>2.07</td>
</tr>
<tr>
<td>Other</td>
<td>482</td>
<td>20.2</td>
<td>13.0</td>
</tr>
</tbody>
</table>

* See Table 2 for an explanation of relatedness and the empirical probability value.

Table 5

<table>
<thead>
<tr>
<th>Probandi An</th>
<th>Relative risk for aneurysm classified by type of lesion and familial relationship*</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/ Same Type</td>
<td>Observed/ Expected</td>
</tr>
<tr>
<td>lesion</td>
<td>Proband</td>
</tr>
<tr>
<td>Intracranial</td>
<td>second degree</td>
</tr>
<tr>
<td></td>
<td>sibling</td>
</tr>
<tr>
<td></td>
<td>parent/offspring</td>
</tr>
<tr>
<td></td>
<td>spouse</td>
</tr>
<tr>
<td>Abdominal aortic</td>
<td>second degree</td>
</tr>
<tr>
<td></td>
<td>sibling</td>
</tr>
<tr>
<td></td>
<td>parent/offspring</td>
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<tr>
<td></td>
<td>spouse</td>
</tr>
<tr>
<td>Other</td>
<td>second degree</td>
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<td>sibling</td>
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<td></td>
<td>parent/offspring</td>
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<tr>
<td></td>
<td>spouse</td>
</tr>
</tbody>
</table>

* Aneurysm type in the proband and in relatives, with sample size and relationship, is shown. The number of cases observed among relatives of probands is compared with the expected number of cases by using internally calculated aneurysm rates. N.B.: Patients who are both a parent and a sibling of another patient are only counted once in Table 4, but will be counted separately as a sibling or as a parent in Table 5. See Table 4 for explanations of RR and probability value. Abbreviation: NA = not applicable.
TABLE 6

First-degree RRs among aneurysm types

<table>
<thead>
<tr>
<th>Aneurysm Type</th>
<th>RR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal aortic</td>
<td>1.59</td>
<td>0.056</td>
</tr>
<tr>
<td>Intracranial aortic</td>
<td>1.00</td>
<td>0.53</td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Aneurysm type in the proband and in first-degree relatives is shown. The number of cases observed among relatives of probands is compared with the expected number of cases by using internally calculated aneurysm rates. See Table 4 for explanations of RR and probability value.

Association Among Different Types of Aneurysms

We can also use the UPDB to test whether relatives of probands with one type of aneurysm are at increased risk for any other type. Table 6 shows RRs for first-degree family members estimated among the three different aneurysm types. First-degree family members of patients who died of abdominal aortic aneurysms are not at increased risk for intracranial aneurysms, and vice versa (RR = 1 and 0.96, respectively). Nevertheless, first-degree family members of patients who died of abdominal aortic aneurysms are at increased risk for other aneurysms (RR = 3.24, p = 0.0068), and vice versa (RR = 3.18, p = 0.004 for RR of abdominal aortic aneurysms in first-degree family members of patients who died of other aneurysms).

Aneurysm Clusters

Using the genealogical data in each case, we can identify all independent clusters, or pedigrees, of patients with aneurysms who are descended from a common ancestor in the genealogy. To determine the size of the resource we have for pedigree studies, we identified all clusters of two or more patients with aneurysms who were descended from the same ancestor in the UPDB for the three different aneurysm types. The cluster counts are shown by size in Table 7. A sample intracranial aneurysm high-risk pedigree (cluster) is shown in Fig. 1. Pedigree 1546699 is a high-risk cluster of 10 intracranial aneurysm cases (3.71 cases were expected, p = 0.005); four abdominal aortic aneurysm cases were also identified among the descendants of the pedigree founder (6.2 cases expected, p = 0.87).

Discussion

Previous analysis of the UPDB allowed the first population-level description of the familial nature of most cancer sites, and indicated that most cancers had a heritable subgroup, before such a hypothesis was commonly accepted. The subsequent identification of predisposing genes for many cancers has supported those early observations on the familial/genetic nature of cancer. These previous cancer studies were possible in Utah because the UPDB resource contains the Utah Cancer Registry records, which provide complete information on all cancer in the state for the last three decades. In addition to the cancer data, the UPDB resource also contains complete records of all deaths in Utah dating back to 1904. The UPDB genealogy and linked death certificate data have allowed us to perform a population-based, unbiased estimation of familiality and RR (based on death certificate data) for aneurysms, which is presented here. The confirmation of the UPDB cancer familiality estimates lends support to the accuracy of our preliminary findings for aneurysm.

Types of Aneurysms Evaluated

The familial aggregation of intracranial aneurysms was first described in 1942 by O’Brien,25 and other reports followed.1,8,20,34 Familial intracranial aneurysms are not rare, and may account for 7 to 20% of patients with aneurysmal subarachnoid hemorrhage.26,28 First-degree relatives of patients with aneurysmal subarachnoid hemorrhage have been reported to be at an approximately two- to fourfold increased risk of suffering ruptured intracranial aneurysms compared with the general population.27 Both the association of various heritable disorders with intracranial aneurysms (Ehlers–Danlos Types II and IV, Marfan syndrome, and polycystic kidney disease), and the familial aggregation of intracranial aneurysms in the absence of any known systemic disorder indicate that genetic factors may play a role in these lesions.

Abdominal aortic aneurysms affect 1.5% of the male population older than 50 years of age. Aggregation of abdominal aortic aneurysm in nuclear families was first reported by Clifton,2 and similar findings have been reported by others.15,24,33,35 The cumulative incidence of abdominal aortic aneurysms in one or more first-degree family members of probands is between 11 and 33%, with RR estimates in first-degree family members ranging from 11 to 18.7,15,35 Certain heritable diseases of connective tissue metabolism, such as the Marfan and Ehlers–Danlos syndromes, clearly cause aneurysms arising from degeneration of the aorta, but are responsible for relatively few abdominal aortic aneurysms overall. Aneurysms of the cerebral arteries have appeared with increased frequency in patients with abdominal aortic aneurysms or their relatives, indicating the existence of a complex relationship between all arterial aneurysms.23,35,36 Ward36 concluded that a general peripheral
artery dilation is noted in abdominal aortic aneurysm disease that may be unrelated to atherosclerosis.

Other aneurysms of the peripheral arteries (femoral, popliteal, and isolated iliac) are less common than abdominal aortic or intracranial aneurysms. Lawrence, et al., performed a pedigree study of first-degree relatives of patients who received a diagnosis of peripheral arterial aneurysm, arteriomegaly, or abdominal aortic aneurysm. In patients with peripheral arterial aneurysms there was a 10% familial incidence rate of a lesion, with abdominal aortic aneurysm being the lesion most commonly diagnosed among first-degree relatives.

The Genetic/Familial Nature of Aneurysms

The GIF measure of familiality in this analysis is used to classify the mean relatedness, and the associated hypothesis test is for the presence of excess familiality, or relatedness, in cases compared with matched controls. The excess familiality we have observed for each aneurysm type does not prove the existence of a genetic susceptibility, but, like the significant RRs observed, is indicative of such a factor. The further identification of extended, high-risk pedigrees containing multiple cases, rather than just small nuclear families, indicates a genetic rather than a familial or environmental component. The findings reported here provide support for earlier observations in the literature in which some heritable component was identified for each type of aneurysm.

We have performed validation simulations for the familiality analysis in which it was shown that neither incomplete ascertainment of cases nor inclusion of false positives biases the hypothesis test for excess familiality. Whereas the RR method only considers closely related individuals and might indicate familial rather than genetic effects, the GIF method considers both close and distant relatives and is much less sensitive to biases such as similar reporting of the cause of death in close relatives.

Each of the aneurysm types that we investigated showed significant evidence of increased familiality and significantly elevated RR. Additionally, family members of probands with abdominal aortic or other aneurysms were found to be at increased risk for both of these types of lesions. Finally, pedigree clusters identified for two or more cases of abdominal aortic aneurysm have been noted to include intracranial and other aneurysm cases among the descendants of the pedigree founders. Although all three aneurysm phenotypes have been reported to be associated within individuals and in their family members in some clinical and case studies, a common, inherited predisposition is not usually assumed. Our analysis of the Utah resource indicates the existence of inherited predisposition(s) that increase the risk for different types of arterial aneurysms in carriers. Abdominal aortic and other aneurysms may be related, based on our RR analysis, although intracranial aneurysms do not appear to be associated with increased risk for abdominal aortic or other aneurysms, based on small sample sizes. Pleiotropic mechanisms for genes re-
sponsible for both abdominal aortic and other aneurysm phenotypes might include genes responsible, for example, for high blood pressure or for vessel wall strength, which might be reasonably expected to manifest as different types of aneurysms in different pedigree members who inherit the same variant, but who differ in environmental risk factor exposure or who have different variants of other aneurysm-related genes.

Individuals who die of abdominal aortic aneurysms at an early age appeared to be even more closely related, on average, than all patients with this type of lesion, supporting a heritable component that is easier to observe in early-onset abdominal aortic aneurysm cases. This same effect was not observed for intracranial aneurysms in either early-onset group considered, nor for other aneurysms, for which the number of early deaths is quite small. This may support the hypothesis that intracranial aneurysms are acquired and are possibly degenerative and not congenital. The heritability of intracranial aneurysms may be a byproduct of a vascular tree phenotype rather than a specific structural defect of collagen. Although it is commonly assumed that earlier-onset cases of a disorder are more likely to have genetic origins, and this does appear to be true for abdominal aortic aneurysms, it does not appear to be the case for intracranial lesions and remains undetermined for other aneurysms.

Previously, the familial cancer risk estimates and the high-risk pedigrees identified in the UPDB resource were critical to the localization and identification of several major cancer predisposing genes (BRCA1, BRCA2, p16, and HPC2). We have identified hundreds of clusters of aneurysm-related deaths that can be similarly studied to search for aneurysm predisposing genes. As predisposing genes for aneurysms are identified in the future, the hypothesis that there are common predisposing genes for different types of aneurysms can be easily tested in these high-risk pedigrees in which more than one type of aneurysm is exhibited. A high-risk intracranial aneurysm pedigree study has been underway in Utah for 5 years.

A limitation of our analysis may be that the physician's assignment of a cause of death on a death certificate may not always reflect all, or any, of the true underlying disease(s) present in the deceased individual (false-negatives). The inclusion of false-positive aneurysm cases might also be a potential problem for this analysis, but it is unlikely because we have only used the ICD codes referring most specifically to aneurysms as causes of death. Our strict classifications of each type of lesion may result in incomplete ascertainment of the total aneurysm cases in the population in this study. In addition to missing individuals whose death might have been due to an aneurysm, but whose death certificate did not clearly indicate this, we were also unable to identify individuals in our resource who had an aneurysm, but were not yet deceased. In this resource, however, cases and controls are similarly censored. Because this analysis is population-based, and rate comparisons are internal, cases and controls have the same rates of incomplete ascertainment. Failure to identify all deaths caused by aneurysms in the population may result in an underestimate of the overall measures of familiality and RR for these lesions, but it does not affect the validity of the tests of the hypothesis. Our estimates of RR for aneurysms are similar to those in other populations. Although we would not extrapolate our estimates of familiality and RRs to the general population, we have provided a valid test of the hypothesis of excess familiality, and potentially conservative estimates of RR and RR.

This type of familiality analysis is possible in only one other population today. That is in Iceland, where similar genealogical data have been computerized and where medical diagnosis records are beginning to be linked. Similar limitations to those we have discussed for the UPDB apply to the Icelandic resource. Recently, analyses investigating the familiality of osteoarthritis, rheumatoid arthritis, and Parkinson disease, as well as human longevity, have been reported using very similar measures of familiality. Some of these findings have already led to gene localization in high-risk pedigrees identified in Iceland. The success of this genealogical approach in understanding familiality and identifying pedigrees to be used for genetic studies of cancer both in Iceland and in the UPDB indicates the power of such resources.

Conclusions

Most aneurysms are asymptomatic. Consequently, patients who die of a ruptured aneurysm were usually previously unaware of its presence. When symptoms do arise, catastrophic rupture is imminent or has occurred. The clinical significance of the ability to diagnose an aneurysm before rupture is clear, and the diagnosis of an aneurysm before rupture is straightforward. The cost of populationwide screening for aneurysms, however, is prohibitive. Several screening studies of the relatives of patients with intracranial aneurysms, including our own studies, have shown that 10 to 30% of first-degree relatives have a previously undetected intracranial aneurysm; studies of abdominal aortic aneurysms show similar frequencies. Screening directed toward those at highest risk has significant potential to reduce morbidity and mortality rates from ruptured aneurysms. In this study we suggest that the population of at-risk individuals may extend beyond the first-degree relatives of patients with aneurysms, and that increased risk of aneurysms in near and distant relatives may also include different types of lesions. Based on our findings, we suggest more thorough screening for all types of aneurysms in these high-risk populations. The importance of the identification of populations at increased risk, and the screening of selected, high-risk individuals for the purpose of early diagnosis is clear. Mechanisms for such early diagnosis, followed by appropriate treatment, could significantly alter morbidity and mortality rates in patients with this common disease.

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Disclaimer

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References

2. Bishop DT, Skolnick MH: Genetic epidemiology of cancer in
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