

## CLINICAL RESEARCH STUDIES

# Familial abdominal aortic aneurysms: Collection of 233 multiplex families

Helena Kuivaniemi, MD, PhD,<sup>a,b</sup> Hidenori Shibamura, MD, PhD,<sup>a</sup> Claudette Arthur, BN, MBA,<sup>c</sup> Ramon Berguer, MD, PhD,<sup>b</sup> C. William Cole, MD,<sup>c</sup> Tatu Juvonen, MD, PhD,<sup>d</sup> Ronald A. Kline, MD,<sup>b</sup> Raymond Limet, MD, PhD,<sup>c</sup> Gerry MacKean, MD,<sup>c</sup> Örjan Norrgård, MD, PhD,<sup>f</sup> Gerard Pals, PhD,<sup>g</sup> Janet T. Powell, MD,<sup>h</sup> Pekka Rainio, MD,<sup>d</sup> Natzi Sakalihan, MD, PhD,<sup>e</sup> Clarissa van Vlijmen-van Keulen, MD,<sup>i</sup> Alain Verloes, MD,<sup>j</sup> and Gerard Tromp, PhD,<sup>a</sup> *Detroit, Mich; Halifax, Canada; Oulu, Finland; Liège, Belgium; Umeå, Sweden; Amsterdam, The Netherlands; and Coventry, United Kingdom*

**Objective:** This study investigated a large number of families in which at least two individuals were diagnosed with abdominal aortic aneurysms to identify the relationship of the affected relatives to the proband.

**Subjects and Methods:** Families for the study were recruited through various vascular surgery centers in the United States, Finland, Belgium, Canada, the Netherlands, Sweden, and the United Kingdom and through our patient recruitment website ([www.genetics.wayne.edu/ags](http://www.genetics.wayne.edu/ags)).

**Results:** We identified 233 families with at least two individuals diagnosed with abdominal aortic aneurysms. The families originated from nine different nationalities, but all were white. There were 653 aneurysm patients in these families, with an average of 2.8 cases per family. Most of the families were small, with only two affected individuals. There were, however, six families with six, three with seven, and one with eight affected individuals. Most of the probands (82%) and the affected relatives (77%) were male, and the most common relationship to the proband was brother. Most of the families (72%) appeared to show autosomal recessive inheritance pattern, whereas in 58 families (25%), abdominal aortic aneurysms were inherited in autosomal dominant manner, and in eight families, the familial aggregation could be explained by autosomal dominant inheritance with incomplete penetrance. In the 66 families where abdominal aortic aneurysms were inherited in a dominant manner, 141 transmissions of the disease from one generation to another were identified, and the male-to-male, male-to-female, female-to-male, and female-to-female transmissions occurred in 46%, 11%, 32%, and 11%, respectively.

**Conclusion:** Our study supports previous studies about familial aggregation of abdominal aortic aneurysms and suggests that first-degree family members, male relatives, in particular, are at increased risk. No single inheritance mode could explain the occurrence of abdominal aortic aneurysms in the 233 families studied here, suggesting that abdominal aortic aneurysms are a multifactorial disorder with multiple genetic and environmental risk factors. (*J Vasc Surg* 2003;37:340-5.)

Abdominal aortic aneurysms (AAAs) are frequently familial.<sup>1-4</sup> The first family with three brothers who were all

diagnosed with AAA was reported by Clifton in 1977.<sup>5</sup> Four case reports on twins with AAA have also been published.<sup>2</sup> Tilson and Seashore<sup>6,7</sup> reported on two collections of families with AAA with 16 and 50 multiplex families, respectively, with at least two members with AAA. Interviews and ultrasonographic screening studies among relatives of patients with AAA have clearly shown the increased prevalence of AAA among first-degree relatives, with up to 18% of brothers and 5% of sisters having AAA.<sup>2,8</sup> Population-based ultrasonographic screening studies have also emphasized family history as an important risk factor for AAA.<sup>9,10</sup> Formal segregation studies have shown that AAAs are likely to be a genetic disease with autosomal, either dominant or recessive, inheritance pattern.<sup>3,4</sup>

The challenging question then is how to dissect the genetic components of AAA. The approaches used to date include analysis of candidate genes for mutations, genetic association studies, and development of animal models for AAA.<sup>11-23</sup> Such approaches revealed that about 2% of pa-

From the Center for Molecular Medicine and Genetics<sup>a</sup> and Department of Surgery,<sup>b</sup> Wayne State University School of Medicine; the Department of Surgery, Dalhousie University<sup>c</sup>; the Department of Surgery, University of Oulu<sup>d</sup>; the Departments of Cardiovascular Surgery<sup>e</sup> and Human Genetics,<sup>j</sup> University Hospital of Liège; General Surgery, Norrlands Universitetssjukhus<sup>f</sup>; the Departments of Clinical Genetics and Human Genetics<sup>g</sup> and Vascular Surgery,<sup>i</sup> Vrije University Medical Center; and University Hospitals of Coventry and Warwickshire.<sup>h</sup>

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Reprint requests: Helena Kuivaniemi, MD, PhD, 3106 Gordon H. Scott Hall of Basic Medical Sciences, Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, 540 E Canfield Ave, Detroit, MI 48201 (e-mail: [kuivan@sanger.med.wayne.edu](mailto:kuivan@sanger.med.wayne.edu)).

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tients with AAA have mutations in the gene for type III procollagen<sup>14,15</sup> and that one of the human leukocyte antigen alleles carries a susceptibility for AAAs.<sup>11,12</sup> In addition, it was found that mice lacking the gene for matrix metalloproteinase-9 had AAAs develop at a much lower frequency in the elastase-induced surgical aneurysm model than the wild-type mice.<sup>16</sup> Another mutant mouse model, namely the apolipoprotein deficient mice, had aneurysms develop with angiotensin II infusion.<sup>17</sup> These approaches, however, require that the investigators come up with one or more biologically plausible candidate genes to be tested with patient samples or in animal models, and the genes chosen for the study may or may not be the genes involved in the pathophysiology of the disease.

We are attempting to identify the genetic risk factors for AAA with families and an unbiased, comprehensive, genome-wide screen with highly variable repeat markers in a DNA linkage study. Here we report the first step of this approach to collect a large number of families with at least two affected individuals and suitable for genetic studies.

## METHODS

Families with at least two members with AAAs were identified for the study at the following sites: the Department of Surgery, Wayne State University School of Medicine, Detroit, Mich; the Department of Surgery, Dalhousie University, Halifax, Canada; the Department of Surgery, University of Oulu, Oulu, Finland; the Department of Cardiovascular Surgery, University of Liège, Liège, Belgium; the Department of Vascular Surgery, Vrije University Medical Center, Amsterdam, The Netherlands; the Department of Surgery, Charing Cross and Westminster Medical School, University of London, The United Kingdom; and the Department of General Surgery, University of Umeå, Umeå, Sweden; and through our website at <http://www.genetics.wayne.edu/ags>.<sup>24</sup> The study was approved by the Institutional Review Board of Wayne State University School of Medicine and by the patient recruiting centers.

An arterial aneurysm definition by Johnston et al<sup>25</sup> was used. These standards have also been used by other investigators.<sup>26-28</sup> In the participating vascular surgery units, medical records were searched for AAA operations. These patients then were contacted, consent was obtained, and family histories were collected. There were slight variations in the methods used to obtain the records by the different units, but in all units, a certified vascular surgeon was leading the efforts to identify patients with AAA and affected family members. Family histories of any new patients for surgical repair of AAAs at these sites were obtained in interviews conducted by a research nurse specifically trained for this work.

Those individuals who responded to our website were asked to complete a family history questionnaire. The patients who indicated that they had at least one other family member diagnosed with AAA were included into the study; a detailed family history and life-style questionnaire was

**Table I.** Nationalities of families with AAA

	<i>No. of families</i>
Canadian	80 (34%)
Belgian	59 (25%)
Dutch	47 (20%)
US American	37 (16%)
Finnish	5 (2.1%)
British	3 (1.3%)
Spanish	1 (0.4%)
Swedish	1 (0.4%)
Italian	1 (0.4%)
Total	233

All patients with AAA were white.

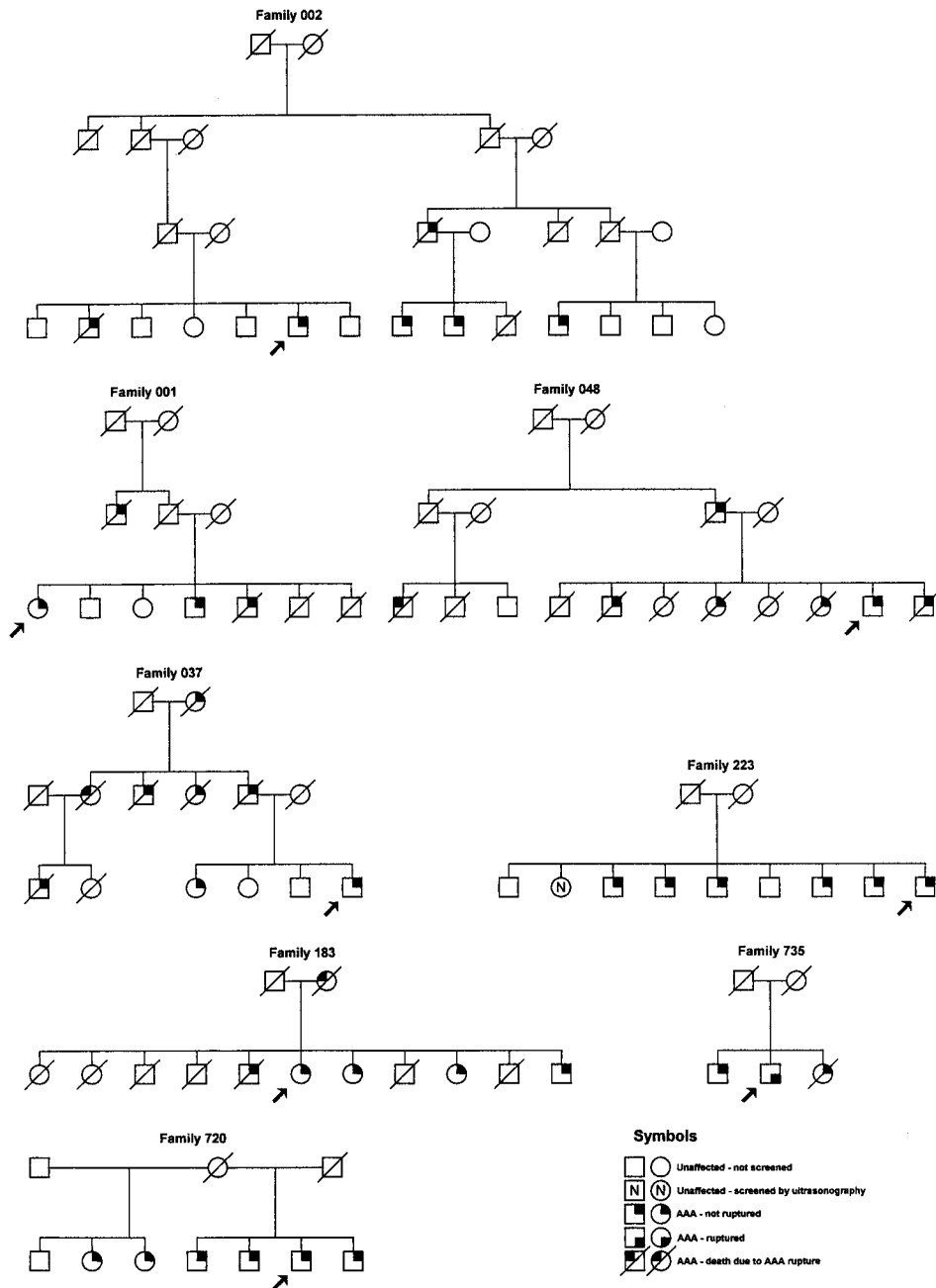
sent to them, and they were subsequently interviewed by a genetic counselor.

In most cases, only a limited amount of information was available from family members who were second-degree or more distant relatives. We did not contact estranged family members. To identify individuals with heritable connective tissue disorders, such as Ehlers-Danlos syndrome type IV or Marfan's syndrome, a specific questionnaire was used assessing skin and skeletal manifestations characteristic for these disorders. Families with these disorders were excluded from the study. The family trees were drawn with Cyrillic software (Cherwell Scientific Publishing Limited, Oxford, Great Britain). Whenever possible, the AAA diagnosis of a deceased family member was verified by requesting the autopsy or medical records. Some family members, if 50 years old or more, had been examined with ultrasonography and were identified as affected if the infrarenal aortic diameter was 3.0 cm or greater, a cutoff point used by other investigators previously.<sup>28</sup> If the patient had isolated iliac artery aneurysm, it was noted; likewise, other aneurysms such as thoracic or thoracoabdominal aneurysms were noted but not included into the study.

## RESULTS

We identified 233 families in which at least two members had an AAA (Table I; Fig). The families originated from nine different nationalities, but all were white (Table I). In 192 of the families (82%), the first person known to us to have an AAA (proband) was male, and in 41 of the families (18%), the proband was female. In addition to the probands, there were altogether 420 relatives with AAA, bringing the total number of AAA cases in the 233 families to 653, with an average of 2.8 AAA cases in each family. Although most of the families were small and had only two members with AAA, we identified six families with six affected individuals, three with seven, and one with eight (Table II). Tables II and III show the breakdown of different categories of relatives with an AAA. Most often the relative with an AAA was the proband's brother, and 74% of the families had at least one affected male sibling (Table III). Most (77%) of the affected relatives were male (Table IV).

Most of the families (72%) appeared to show autosomal recessive inheritance pattern on the basis of the fact that



Representative AAA families from our collection of 233 families. Proband in each family is indicated with *arrow*. *Slash* across symbol means death. Other symbols used are explained in insert to figure.

affected individuals had no affected parents, whereas in 58 families (25%), AAAs occurred in one parent of the affected individual and the inheritance mode was, therefore, consistent with autosomal dominant inheritance. In the remaining eight families (for example, families 002, and 048 in Fig), the familial aggregation could be explained by autosomal dominant inheritance with incomplete penetrance because some affected individuals in these families had an

affected parent and others did not. Alternatively, these eight families could have autosomal recessive inheritance with a common disease allele.

In the 66 families where AAAs appeared to be inherited in a dominant manner and it was, therefore, possible to follow the transmission of the disease, 141 transmissions of the disease from one generation to another were identified and the male-to-male, male-to-female, female-to-male, and

female-to-female transmissions occurred in 46%, 11%, 32%, and 11% of the cases, respectively. In 57% of the transmissions, the disease came from the father, and in 43%, from the mother. In 111 of the 141 transmissions (79%), the disease was transmitted from a mother or a father to a son, and in only 21% of the transmissions, it was transmitted to a daughter in the family.

## DISCUSSION

A large number of previous studies have identified family history of AAA as a significant risk factor for AAA development.<sup>2-4,8</sup> The specific genetic factors contributing to the susceptibility for AAA have, however, been difficult to identify because of the problems in obtaining large families for genetic studies. It is almost impossible to collect blood samples from family members in two or three consecutive generations because of the late age at onset and the high mortality rates associated with aneurysm rupture. Many of the pedigrees in our collection of 233 families with AAA (Fig) also show these features. Furthermore, it is not possible to predict the true phenotype of apparently unaffected individuals who might be completely asymptomatic today and show a development of AAA 5 to 10 years later, making it risky to use any genetic information from the unaffected person. In addition, AAAs do not consistently show any one mode of inheritance in the families, suggesting that they are a multifactorial disease with heterogenous etiology. Most of these characteristics are shared by many other adult-onset common diseases. The approach to study them must, therefore, take into consideration these factors. First, a large collection of families is necessary for initial and subsequent follow-up studies. Second, statistical methodology must be chosen carefully to take into consideration the fact that genetic information from currently unaffected individuals might be misleading because the person's phenotype could change over the years to come.

Our collection of 233 families with AAA had patients from nine different nationalities, but all of them were white. The underrepresentation of other ethnic groups has been noted by other investigators previously<sup>29</sup> and is in agreement with the hypothesis that genetic factors contribute to the disease.

Previous studies had suggested that although the prevalence of AAAs is lower in women than in men, AAAs might be more aggressive and perhaps more likely to be from accumulation of genetic susceptibility factors if present in women.<sup>30-32</sup> We therefore investigated the transmission of AAA from one generation to another to see whether females were more likely to pass on the disease to their offspring. To our surprise, we did not find a significant difference in the transmission of the disease between the father and the mother, and both genders seemed to transmit the disease at approximately equal frequency to their offspring. It was, however, noteworthy that in 79% of the observed transmissions, AAAs were transmitted from one

**Table II.** Number of affected relatives in families with AAA

No. of affected individuals	Families (%)	Relationship to proband*			
		M	F	B	S
2	131 (56)	8	14	89	14
3	56 (24)	7	10	69	16
4	25 (11)	5	6	43	8
5	11 (4.7)	2	3	27	5
6	6 (2.6)	2	3	12	4
7	3 (1.3)	1	1	12	3
8	1 (0.4)	0	1	0	1

\*Number of relatives in categories indicated.

Other relationships found were child, cousin, aunt, uncle, nephew, niece, grandparent, and great grandparent (see Table III).

M, Mother; F, Father; B, Brother; S, sister.

**Table III.** Relationship of affected relative to proband

Relationship	No. of families (n = 233) (%)
Brother	172 (74)
Sister	46 (20)
Father	37 (16)
Mother	25 (11)
Child	2 (0.9)
Uncle	16 (7)
Cousin	14 (6)
Aunt	8 (3.4)
Grandparent	5 (2.1)
Niece	1 (0.4)
Nephew	2 (0.9)

**Table IV.** Gender of affected relatives\*

Affected male relatives		Affected female relatives	
Relationship	No.	Relationship	No.
Brother	249	Sister	51
Father	38	Mother	25
Uncle	16	Aunt	10
Nephew	2	Niece	1
Male cousin	16	Female cousin	2
Grandfather	0	Grandmother	5
Total	321 (77%)		94 (23%)

\*Only affected relatives of probands are shown here. Probands were not taken into account. Total number of affected relatives was 420. Relationships shown account for 99% of all affected relatives.

of the parents to a son, and in only 21% of the cases, to a daughter.

The goal of our study was to collect as many families with AAA as possible to be later used in genome-wide DNA linkage studies. Many vascular surgery centers in the United States and abroad contributed to the study by identifying families, collecting family information, and drawing blood samples for future studies. We attempted to gather as much information about the affected family members as possible. There were, however, some limita-

tions in our study, including the uncertainty about second-degree and third-degree relatives of the proband, because in many cases it was difficult to obtain further information about relatives who were not part of the immediate family. It is, therefore, possible that we missed some of the affected second-degree and third-degree relatives. The second limitation was the uncertainty about currently unaffected individuals to determine whether they were truly unaffected or would have AAAs develop a few years later. In particular, this is a problem with individuals who are still relatively young, below the age of 60 years. The third limitation was that the exact cause of death is often not determined, meaning that no autopsy was performed and a sudden death from aneurysm rupture could have been listed as an apparent heart attack if no further investigations were carried out. This could be especially true with the older generations in the pedigrees and could lead to an interpretation of the inheritance mode to be autosomal recessive rather than dominant. The inheritance pattern in many families was also consistent with pseudodominant inheritance (ie, apparent dominance from one parent being homozygous and the other heterozygous for a recessive allele). Pseudodominance is not probable for AAA, however, because it requires a high population frequency of mutant alleles. Such a high frequency may be possible if alleles at all loci had equal and additive effects, but that is inconsistent with the conclusion of a major gene effect from segregation studies.<sup>3,4</sup> In the light of these limitations, the results presented here should be considered conservative estimates about the number of affected relatives in each family and the mode of inheritance.

Our study was not designed to compare the familial AAAs to sporadic ones or to identify differences in their risk factors. The data on the 233 multiplex families presented here emphasize the value of routinely obtaining family history from patients with AAA and considering ultrasonographic screening of unaffected siblings to detect AAAs before rupture. It is important that primary care physicians realize that AAAs do run in families even when no signs of Ehlers-Danlos syndrome or Marfan's syndrome are present, making familial AAAs (OMIM 100070; Online Mendelian Inheritance in Man at [www.ncbi.nlm.nih.gov/htbin-post/Omim](http://www.ncbi.nlm.nih.gov/htbin-post/Omim)) a separate disease entity deserving due attention.

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