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On the Inheritance of Abdominal Aortic Aneurysm

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Summary

To determine the mode of inheritance of abdominal aortic aneurysm, data on first-degree relatives of 91 probands were collected. Results of segregation analysis performed on these data are reported. Many models, including nongenetic and genetic models, were compared using likelihood methods. The nongenetic model was rejected; statistically significant evidence in favor of a genetic model was found. Among the many genetic models compared, the most parsimonious genetic model was that susceptibility to abdominal aortic aneurysm is determined by a recessive gene at an autosomal diallelic major locus. A multifactorial component in addition to the major locus does not increase the likelihood of the data significantly.

Introduction

Aortic aneurysm is a pathological condition characterized by dilatation of the aorta and involves the expansion and thinning of all the layers of the arterial wall. Aortic aneurysms are the thirteenth leading cause of death in the United States (Silverberg and Lubera 1983). In 1984, 1.2% of all men and 0.6% of all women over the age of 65 years died of aortic aneurysm in the United States (National Center for Health Statistics 1987). Abdominal aortic aneurysm (AAA) most commonly occurs in the infrarenal segment of the abdominal aorta, and most patients with AAA do not have aneurysms in other portions of the aorta (Roberts 1982). The major complication of an untreated AAA is rupture. Most patients who rupture an AAA die before they can be admitted to a hospital (Ingoldby et al. 1986). Infrarenal AAA is the predominant cause of aortic aneurysm mortality in the United States (Lilienfeld et al. 1987). There are several reports (Melton et al. 1984; Fowkes et al. 1989) indicating that the incidence of AAA may be increasing both in the United States and in England and Wales.

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AAA is a late-onset disease and most commonly occurs in the fifth to seventh decades of life. It has been estimated that 3% of those over 50 years of age harbor AAA (Allen et al. 1987). There are, however, several reports of AAA occurring in young individuals (Sterpetti et al. 1988). AAA is often asymptomatic. However, with the introduction of ultrasonography and computed tomography, detection of asymptomatic AAA is extremely accurate (Graeve et al. 1982). If this condition is found prior to rupture, death from AAA can be prevented. Elective repair of AAA is now a relatively safe surgical procedure, with an operative mortality of 1%–5% (Campbell et al. 1986; Jenkins et al. 1986). Successful aneurysm repair results in a near normal subsequent life expectancy (Soreide et al. 1982). The etiology of AAA is still unknown. Hypertension, smoking, and atherosclerosis have been attributed to be risk factors for development of AAA (Auerbach and Garfinkel 1980; Spittell 1983). These risk factors are very nonspecific, so population screening for AAA has not been found to be cost effective (Allen et al. 1987).

Familial clustering of AAA has been noted in many studies (Clifton 1977; Norrgard et al. 1984; Tilson and Seashore 1984*a*, 1984*b*; Victor et al. 1985; Johansen and Koepsell 1986; Powell and Greenhalgh 1987; Loosemore et al. 1988; Cole et al. 1989; Collin and Walton 1989; Webster et al., submitted). There are also reports of identical twin pairs in which both members are affected with AAA (Thayer 1984; Tilson and Seashore

1984*a*; Borkett-Jones et al. 1988). The majority of previous reports on the familiality of AAA have been in the form of clinical case reports. There have, however, been some exceptions. In a well-conducted case-control study, Johansen and Koepsell (1986) found that the age- and sex-adjusted relative risk to a first-degree relative of an AAA patient was 11.6%. Further, they found that a history of AAA in a parent appeared to confer about the same excess risk as did a history of AAA in a sibling. Norrgard et al. (1983), Tilson and Seashore (1984*a*), Cole et al. (1989), and Webster et al. (in press), have reported data on many families each ascertained through an AAA proband. Summary statistics of these studies have been compared in a study by Webster et al. (in press), from which it was seen that 11%–15% of patients with AAA have at least one affected first-degree relative. However, no satisfactory formal genetic analysis of family data has been performed. By a visual examination of their family data, Tilson and Seashore (1984*b*) concluded that the mode of inheritance of AAA could be either X linked or autosomal dominant or both. They did not rule out a multifactorial etiology. Under the assumption that AAA is multifactorial, which they did not justify, Powell and Greenhalgh (1987) estimated the heritability to be 70%.

In view of the fact that familial clustering of AAA has been consistently noted and that no adequate genetic analyses of family data have been performed, we have undertaken a family study of AAA in Pittsburgh. We herein report the results of segregation analysis performed on data from 91 families.

Material and Methods

The Family Data

Each family was ascertained through a single proband. The probands were selected from a list of patients who underwent either elective or emergency AAA repair performed by Dr. Webster or Dr. Steed between 1985 and 1989 at the Presbyterian University Hospital, University of Pittsburgh. Probands were selected without regard to gender, family history of AAA, or whether the proband had undergone elective or emergency surgical repair of AAA. However, to ensure homogeneity of sampled families, only Caucasian patients were selected as probands. Data on first-degree relatives (i.e., parents, sibs, and offspring) and spouse(s) (if the proband had offspring) of each proband were collected primarily through telephone interviews. Each first-degree relative was contacted by phone, and the relevant data were gathered in respect not only of the relative under consideration but also of his/her pertinent first-degree relatives. The duplicate information thus collected was used for purposes of cross-verification. For deceased individuals, information was collected and cross-verified from all living first-degree relatives. In cases of ambiguity or discrepancy of information, copies of medical records and/or death certificates were obtained. (It may be stated that there was only one case of discrepancy, and in this case medical records were successfully obtained.) In all, data on first-degree relatives of 91 probands (79 male and 12 female) were collected.

Various descriptive statistics of the family data—including a comparison of these statistics with those obtained in three previous studies—have been presented by Webster et al. (in press). We recapitulate some pertinent statistics. Among the 91 families, five were two generational; the remaining 86 were three generational. The proband in each of the two generational families was an offspring. In all the three-generational families, the probands belonged to the middle generation. Of the 91 families, 13 families had at least one affected first-degree relative of the proband, one family had a proband with an affected spouse, and the remaining 77 families were simplex. Although the male:female sex ratio among probands is 6.58:1, no significant difference was observed in the proportions of male and female affected siblings of probands. The mean ± standard error (SE) ages at onset among male (n = 79) and female (n = 12) probands were 67.0 ± 6.51 years and 68.5 ± 4.90 years, respectively. Among all affected individuals, the mean ± SE ages at onset were 67.1 ± 6.51 years and 69.2 ± 5.73 years for males (n = 89) and females (n = 19), respectively. None of these differences in ages at onset is statistically significant at the 5% level. The mean ± SD relative risks of affection, calculated according to the method of Weiss et al. (1982), for first-degree relatives of probands are as follows: father, 3.97 ± 1.40, mother, 4.03 ± 2.00, brother, 9.92 ± 1.11, and sister, 22.93 ± 1.95. Except for mothers of probands, the remaining relative risks are all significantly greater than 1 at the 5% level. Among families in which there was at least one affected first-degree relative of the proband, in three families one parent of the proband was affected, in three families two sibs of the proband were affected, and in seven families one sib of the proband was affected.

Cumulative Incidence

Bickerstaff et al. (1984) have obtained estimates of incidence of AAA that are based on records of diag-

noses made and surgical procedures performed on all patients with AAA during a 30-year period (1951–80) in a stable, predominantly white, population of Rochester, MN. Although Bickerstaff et al. (1984) have acknowledged that these age- and gender-specific incidence values may be underestimates of true values because no population screening for AAA by ultrasound was performed, these estimates may not be inappropriate for use in the present study, because we have also not included any ultrasound information and have scored individuals as being "affected" solely on the basis of medical records of diagnoses/surgery and death certificates. Further, since the population of Rochester, MN, is predominantly white, these estimates are particularly appropriate for our Caucasian families. The per-person-year incidence estimates given by Bickerstaff et al. (1984) were converted by us to per-person estimates. Bickerstaff et al. (1984) provided the per-person-year estimates of cumulative incidence not for individual ages but only for six age groups—<40 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years. For converting the per-person-year estimates to per-person estimates we had to make two simplifying assumptions: (1) that the age of an individual belonging to a particular age group was equal to the midpoint of the age group and (2) that the sex ratio in the <40-year age group in the general population was 1:1. From the demographic and incidence data given by Bickerstaff et al. (1984) and by making use of the assumptions stated above, we recomputed, by simple arithmetical techniques, the per-person cumulative incidence values. The recalculated cumulative incidence estimates, by gender and age groups, are presented in table 1.

Segregation Analysis

To determine the most parsimonious genetic model for AAA, we have performed segregation analysis of the family data under various genetic models. The general model and parametrization for segregation analysis used in the present study is the unified model formulated by Lalouel et al. (1983), which is an extension of the mixed model (Morton and MacLean 1974). For a dichotomous trait the model assumes that every individual has a certain value on an unobservable liability scale. An individual is affected if his or her liability exceeds a threshold. The thresholds may be gender specific. The value of liability X for an individual is assumed to be equal to $G + C + E$, where G is a major transmissible effect, C is a multifactorial transmissible effect, and E is a nontransmitted random effect. It is also assumed that G, C, and E are mutually uncorrelated. Further, C and E are assumed to follow normal distributions, each with a mean of zero and with variance σ_C^2 or σ_E^2, respectively. Since only affection-status data are used, the mean and variance of X are arbitrary and were taken to be equal to 0 and 1, respectively. Under a genetic hypothesis, the major transmissible effect corresponds to segregation at a major locus assumed to have two alleles, A and a, with population proportions p and q $(= 1-p)$, respectively. Possessing the a allele increases, on average, an individual's liability value. The population is assumed to be in Hardy-Weinberg equilibrium at the major locus. The effect, G, of the major locus is assumed to be equal to z if the genotype of an individual at the major locus is AA, to be equal to $z + t$ if the genotype is aa, and to be equal to $z + td$ if the genotype is Aa. The difference between the means of the two homozygous major-locus genotypes, t, is called the "displacement." The degree of dominance is d $(0 \leq d \leq 1)$. If $d = 0$, then the a allele is recessive; if $d = 1$, then the a allele is dominant; and, if $d = 1/2$, then the alleles A and a are additive. If the total phenotypic variance is denoted by V, then the polygenic heritability H is defined as σ_C^2/V, which reflects the proportion of the total phenotypic variance due to polygenic effects. The parameters of this model are, therefore, d, t, q, and H. Unlike the mixed model, which assumes Mendelian transmission of alleles from parent to offspring, the unified model parametrizes transmission in terms of three additional parameters—τ_1, τ_2, and τ_3—which denote, respectively, the probabilities of transmitting the A allele for genotypes AA, Aa, and aa. Under Mendelian transmission $\tau_1 = 1$, $\tau_2 = 1/2$, and $\tau_3 = 0$.

Various nested submodels can be constructed from the unified model. The sporadic model assumes that liability variance is due solely to random environmen-

Table 1

Cumulative Incidence of AAA, by Gender and Age Group

Age Group (years)	Male	Female
≤49	.00015	0
50–59	.00152	.00009
60–69	.00482	.00094
70–79	.00773	.00232
≥80	.00893	.00434

[a] Data are recomputed from Bickerstaff et al. (1984).

tal effects; therefore, q and H are set to zero. No transmission of major effect is obtained by imposing the constraint $\tau_1 = \tau_2 = \tau_3$. The multifactorial model, postulating no major transmissible effect, can be obtained by setting $d = t = q = 0$. The major-locus model assumes that liability is determined by a major gene that segregates in a Mendelian fashion (i.e., $\tau_1 = 1$; $\tau_2 = 1/2$; $\tau_3 = 0$) and random nontransmissible effects, but no polygenic effect. This model is obtained by setting $H = 0$. For the dominant, additive, and recessive major-locus models, d is fixed at 1, 1/2, or 0, respectively, and t and q are treated as parameters.

Comparison of models is performed by a likelihood-ratio χ^2 test. Specifically, a general model (with m independent parameters) and a nested submodel (with k independent parameters and with the remaining $m - k$ parameters being held constant) are compared by determining the difference between the maximum value of the log-likelihood function (a) under the general model and (b) under the submodel. The difference follows a χ^2 distribution with $m - k$ df.

Segregation analysis of the family data was performed using the computer program POINTER (Lalouel and Yee 1980). Pedigrees were broken into component nuclear families by using the pointer strategy (Lalouel and Morton 1981). Since the cumulative estimates of incidence vary with age and gender (table 1), 10 liability classes were defined; liability classes 1–5 comprised males, and liability classes 6–10 comprised females. Thus, an individual belonged to liability class 1 if he was a male <49 years of age and belonged to liability class 10 if she was a female aged ≥80 years. For each liability class, the risk represents the corresponding cumulative incidence.

Finally, we note that probands were selected from a list of patients who were surgically treated by two vascular surgeons at one (Presbyterian University Hospital) of the many hospitals in Pittsburgh and that there were no multiple probands in any of the ascertained families. These facts are supportive of single ascertainment, i.e., the probability of ascertainment, $\pi \approx 0$. In the present study, π was set equal to .001.

Results

The results of segregation analyses are presented in table 2. In comparison with the multifactorial model, a sporadic model not providing for family resemblance is strongly rejected ($\chi^2 = 921.39 - 870.20 = 51.19$; df = 1; $P < 10^{-6}$). Under the unified model the estimated values of the parameters and a comparison of

Table 2

Results of Segregation Analysis of AAA

Model	No. of Parameters	Parameter[a]							$-2\ln L + C$
		d	t	q	H	τ_1	τ_2	τ_3	
Unified	7	.2455 (.1114)	3.084 (.190)	.0558 (.0085)	.0107 (.0801)	<1.0>	.5028 (.0394)	.5598 (.4823)	−929.97
No transmission of major effect (equal τ's)	5	.7984 (.2613)	3.124 (.172)	.0960 (.0078)	.0020 (.0739)	.6840 (.2421)	.6840 (.2421)	.6840 (.2421)	−920.28
Mixed with Medelian transmission of major effect ($\tau_1 = 1$; $\tau_2 = 1/2$; $\tau_3 = 0$)	4	.2043 (.1317)	2.957 (.178)	.0522 (.0074)	.0041 (.0692)	[1.0]	[.5]	[0]	−929.14
Major locus ($H = 0$):	3	.1984 (.143)	2.952 (.344)	.0530 (.015)	[0]	[1.0]	[.5]	[0]	−929.13
Dominant ($d = 1$)	2	[1]	2.000 (.202)	.0034 (.002)	[0]	[1.0]	[.5]	[0]	−923.52
Additive ($d = .5$)	2	[.5]	4.002 (.443)	.0033 (.002)	[0]	[1.0]	[.5]	[0]	−923.34
Recessive ($d = 0$)	2	[0]	2.824 (.314)	.0590 (.015)	[0]	[1.0]	[.5]	[0]	−928.72
Multifactorial ($d = t = q = 0$)	1	[0]	[0]	[0]	.7200 (.078)	[1.0]	[.5]	[0]	−921.39
Sporadic ($d = t = q = H = 0$)	0	[0]	[0]	[0]	[0]	[1.0]	[.5]	[0]	−870.20

[a] Values in () are SEs; values in [] are fixed values of noniterated parameters; and value in <> is boundary value attained during likelihood maximization.

the estimates with their SEs indicate the existence of a major locus. Multifactorial effect is found to be minimal; in fact, the SE (.0801) of the maximum-likelihood estimate of H is much higher than the estimate (.0107) itself. Further, on maximization of the likelihood function, the parameter τ_1 reaches the boundary value of 1, and the estimate of τ_2 is practically 1/2. The estimate of τ_3 (.5598) is much greater than 0, but the associated SE of the estimate (.4823) is also very large. In fact, it was observed that the value of $-2\ln L + C$ was rather insensitive to the value of τ_3. The value of $-2\ln L + C$ at the maximum-likelihood estimates of the parameters is -929.97. To test whether the major effect was transmissible, we reestimated the parameters d, t, q, H, and τ, under the constraint $\tau = \tau_1 = \tau_2 = \tau_3$. The mean $\pm$ SE maximum-likelihood estimate of τ was .6840 $\pm$ .2421. The value of $-2\ln L + C$ under the no-transmission-of-major-effect model was -920.28, which, therefore, provides a significantly worse fit ($\chi^2 = 929.97 - 920.28 = 9.69$; df = 2; $.005 < P < .01$).

Having inferred the presence of a transmissible major effect, we then tested whether the major effect was transmitted in a Mendelian fashion. This was done by maximizing the likelihood with respect to the parameters d, t, q, and H, under the constraint $\tau_1 = 1$, $\tau_2 = 1/2$, $\tau_3 = 0$. The value of $-2\ln L + C$ of the data under this model turned out to be -929.14. Compared with the mixed model with Mendelian transmission of the major gene, the unified model does not provide a significantly better fit to the data ($\chi^2 = 929.97 - 929.14 = .83$; df = 3; $.75 < P < .9$).

As is seen, the estimated value of H is virtually zero under either the unified model or the mixed model with Mendelian transmission. To test formally the hypothesis that there is no transmissible multifactorial component, we maximized the likelihood under the constraint $H = 0$. It was found that a multifactorial component in addition to the major gene is not necessary ($\chi^2 = 929.14 - 929.13 = .01$; df = 1; $P > .9$).

Our analysis thus far has, therefore, revealed that susceptibility to AAA can be accounted for by the presence of a major gene without any multifactorial component. We then sought to determine whether the major gene behaved as a dominant or recessive or whether the effects of the alleles at the major locus were additive. This was done by setting d equal to 1, 0, and .5, respectively. It is seen from table 2 that the recessive major-gene model yields an acceptable fit to the data ($\chi^2 = 929.13 - 928.72 = .41$; df = 1; $.5 < P < .75$). The dominant and additive models yield χ^2 values (with 1 df) of 5.61 (i.e., 929.13 – 923.52) and 5.79 (i.e., 929.13 – 923.34), respectively, both of which are significant at the 5% level.

Discussion

The results of the segregation analyses presented above clearly show that there is a significant genetic component in the etiology of AAA. Further, among the models considered, the most parsimonious one is that AAA is controlled by a major autosomal diallelic locus, with the disease-causing allele being recessive. A multifactorial component in addition to the major locus does not lead to a significant increase in the likelihood of the data.

Even though the familiality of AAA has been consistently noted in many studies, until now the genetic component in the etiology of AAA has not been clearly specified. Almost all possible genetic models have been invoked: X-linked (Tilson and Seashore 1984*b*), autosomal dominant (Tilson and Seashore 1984*b*), autosomal recessive (Bowers and Cave 1985), and multifactorial (Tilson and Seashore 1984*b*; Powell and Greenhalgh 1987). However, no systematic formal genetic analysis of family data has, to the best of our knowledge, been attempted before.

Many risk factors, both environmental and biological, have been implicated in AAA. Traditionally, smoking, hypertension, and atherosclerosis have been considered to be risk factors for the development of AAA. However, in the age group in which AAA most commonly occurs, these risk factors are very nonspecific. Further, a substantial number of AAA patients have been found to be nonsmokers and normotensives (O'Kelly and Heather 1989; Reilly and Tilson 1989). Various biochemical parameters have also been implicated in the causation of AAA disease. These include defects in the structural components of the aortic wall and deficiencies in the protease inhibitor system. Both decreased levels of collagen and elastin (Sumner et al. 1970) and increased activities of collagenase and elastase (Busuttil et al. 1980; Busuttil and Cardenas 1982) have been noted in the aneurysmal aortic wall. Cannon and Read (1982) demonstrated both an increased serum elastolytic activity and a decreased antiproteolytic activity in AAA. Further, Cohen et al. (1987, 1988) demonstrated that aortic elastase activity is due to a serine protease which is inhibited by alpha-1-antitrypsin. Tilson (1988) has reported that 10% of AAA patients are carriers of the PI deficiency allele, Pi^Z; this is significantly higher than the Caucasian population frequency (2%) of the Pi^Z allele. It is, however, unclear

whether these environmental and biological correlates are direct causal factors or are promoters of aneurysms in genetically susceptible individuals.

Our analysis clearly reveals that AAA should not be viewed as a multifactorial disease. There is clear evidence of the involvement of a single autosomal recessive gene. It is interesting to note that our estimate of H (72%) under the multifactorial model nearly coincides with the estimate of 70% obtained by Powell and Greenhalgh (1987). We have not been able to test for genetic heterogeneity because of our limited sample size.

Another point that warrants discussion is the possible effect that noninclusion of asymptomatic cases has on the analysis. Although many AAAs go undetected until they rupture, at present such rupture occurs in a substantial proportion of affected subjects (Cole 1989). Detection of asymptomatic cases is generally accomplished by the use of ultrasonography. The present study deals with AAA cases which are either ruptured or reconstructed (which implies that the aneurysm diameter is $\geq$5 cm, since reconstruction is generally not recommended for smaller diameters). While this definition of AAA is unambiguous and well accepted, definition of AAA on the basis of ultrasound results is debated. In a recent international workshop on AAA, it was recommended that research strategies should be directed toward providing a clear definition of AAA (Cole 1989). Of relevance to the present study is the consideration of possible impact on inferences if results of ultrasound scans are incorporated. Apart from the problem of defining AAA on the basis of results of an ultrasound scan, another pertinent problem is the lack of AAA prevalence data that incorporate results of ultrasound performed across all ages and genders. In the present study we were, therefore, unable to utilize the ultrasound data (albeit limited) that are available with us. However, a description of the ultrasound data will provide clues to the possible effects that their noninclusion will have on the inferences regarding mode of inheritance of AAA.

We have performed abdominal ultrasound scans on 104 unaffected relatives of 41 probands included in the present study. Only relatives $\geq$40 years of age who agreed to undergo an abdominal scan were included. Of the 104 relatives scanned, six turned out to be "positive," in the sense that their infrarenal aortic diameters were >2 cm. (We wish to point out that, although it is unclear whether an individual with an infrarenal aortic diameter just exceeding 2 cm should be scored as being "positive," to be conservative we base our discussion on this low cut-off diameter.) These six individuals were distributed in five families, one of which was multiplex. In this multiplex family, comprising unaffected parents, there were 14 offspring, three of whom were affected. On ultrasound examination, one more offspring was found to have an aortic diameter of 3.2 cm, raising the total number of "affected" offspring to four (in a total of 14). In three other families each with unaffected parents, among the total of 21 unaffected offspring excluding the three probands, ultrasound examinations found three enlarged aortic diameters: 2.8 cm, 2.7 cm, and 4.4 cm. The above figures indicate that segregation ratios from the inferred recessive model are not grossly altered by inclusion of the ultrasound results. The other family in which "positive" cases were detected by ultrasound is interesting. In this family the wife of the proband, on ultrasound, was found to have an aortic diameter of 3.3 cm. This affected (proband) $\times$ "affected" (proband's wife) mating had two offspring, ages 53 years and 51 years. Ultrasound scan revealed an aortic diameter of 2.7 cm in the older offspring. The younger offspring had a normal aorta. Under the recessive mode of inheritance that has been inferred in the present study, although it is expected that both offspring in this family should be affected, given the age (51 years) of the younger offspring there is a substantial probability of his not being affected by this age. A careful consideration of the above description of findings from our ultrasound results indicates that the inferences of the segregation analysis presented in the present paper are likely to remain unaltered even when data on asymptomatic AAAs are included. We are continuing the ultrasound investigations among relatives of our probands, and we plan to undertake an analysis incorporating the ultrasound information as soon as these investigations are completed.

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