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Genome Screen to Detect Linkage to Common Susceptibility Genes for Intracranial and Aortic Aneurysms

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Abstract

Background and Purpose—Risk for both intracranial aneurysms (IAs) and aortic aneurysms (AAs) is thought to be heritable with mounting evidence for genetic predisposition. The concept of shared risk for these conditions is challenged by differences in age of diagnosis and demographic characteristics. We performed a genomewide linkage analysis in multiplex families with both IA and AA from the Familial Intracranial Aneurysm study.

Methods—Available medical records of subjects who reported IA or abdominal/thoracic AA were reviewed with adjudication as definite/probable, possible, or not a case. To identify genes contributing to the susceptibility for IA and AA, genomewide linkage analysis was performed in the 26 multiplex IA families who had members who also had thoracic or abdominal AA. Individuals (n=91) were defined as affected if they had an IA (definite/probable) or an aortic or thoracic AA (definite/probable).

Results—Maximum logarithm of odds (LOD) scores were found on chromosomes 11 (144 cM; LOD=3.0) and 6 (33 cM; LOD=2.3). In both chromosomal regions, analyses of these same 26 families considering only IA as the disease phenotype produced LOD scores of 1.8 and 1.6, respectively.

Conclusions—Our linkage analysis in these 26 families using the broadest disease phenotype, including IA, abdominal AA, and thoracic AA, supports the concept of shared genetic risk. The chromosome 11 locus appears to confirm earlier independent associations in IA and AA. The chromosome 6 finding is novel. Both warrant further investigation.

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Disclosures

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Keywords

aortic aneurysms; genetic linkage; genetic susceptibility; intracranial aneurysm; single nucleotide polymorphism

Risk for both intracranial aneurysms (IAs) and aortic aneurysms (AAs) is thought to be heritable with mounting evidence in both for genetic predisposition.^{1,2} Both conditions share a number of associated risk factors such as smoking and hypertension. Co-occurrence of IAs and AAs within pedigrees is estimated to be 10.5%.³ Differences in age of diagnosis and demographic characteristics between the 2 conditions have led some to assume that such co-occurrence within a single pedigree was simply due to chance. However, familial aggregation studies suggest that shared genetic risk factors may contribute to IA and AA susceptibility.³ To test this hypothesis, we performed linkage analysis in a subset of the multiplex IA families collected as part of the international Familial Intracranial Aneurysm study that segregated both IA and AA aneurysms in extracerebral vessels, including the thoracic and abdominal aorta.

Methods

Subjects

The Familial Intracranial Aneurysm (FIA) study protocol⁴ and the initial genomewide linkage scan⁵ have been previously published. Briefly, probands were recruited through 41 experienced sites throughout North America, New Zealand, and Australia. Eligible families included those with either 2 or more siblings with an IA, at least one of whom is living and the other whose genotype could be reconstructed, or 3 or more affected family members with at least one of whom is living and at least one other affected relative whose genotype could be reconstructed. The FIA study was approved by the Institutional Review Boards/ethics committees at all clinical and analytic centers and recruitment sites.

Phenotyping

Intracranial aneurysm status was determined by 2 neurologists who independently reviewed the subjects' records and determined if the subject met all the inclusion and exclusion criteria. In cases of disagreement, a third neurologist was used to resolve the case diagnosis. Each potential affected family member was ranked as definite, probable, possible, or not a case (Table 1). Questionnaire data regarding demographics, environmental risk factors, and family history of IA were obtained from persons with an IA and their unaffected family members. This included information on aneurysms in other vascular beds.

All medical records and a phone screen of the proband and family members reporting an aortic, abdominal, or thoracic aneurysm were examined by 2 neurologists who independently reviewed the records to determine if the subject had an abdominal or thoracic AA and recorded location, size, and rupture status. In cases of disagreement, a third physician was used as a tiebreaker. Each subject was ranked as definite/probable, possible, or not a case (no mention of aneurysm in records or aneurysm located outside abdominal or thoracic region) as outlined in Table 1.

Genotyping

Blood was obtained from all participants for the isolation of DNA. The Center for Inherited Disease Research operated by National Human Genome Research Institute (NHGRI) genotyped 2317 individuals from 394 families using the 6K Illumina array. The error rate, based on paired genotypes from 107 duplicate samples, was 0.0022%. The percentage of missing genotypic data was 0.24%.

Statistical Analysis

Demographic and risk factor data were compared between those with IA and those with AA. Due to the anticipated difference in age at diagnosis for IA and AA, values were age-adjusted. For continuous risk factors, age was treated as a continuous covariate. For categorical risk factors, age at diagnosis was dichotomized as ≤ 65 versus ≥ 66 years. Analysis of covariance was used for continuous risk factors and Cochran-Mantel-Haenszel χ^2 tests with 2 age strata were used for categorical risk factors.

Detailed quality assessment was performed in genotypic data received from The Center for Inherited Disease Research before initiating analyses. All family relationships were verified⁶ and pedigree structures were altered as necessary. All markers with fewer than 90% of the individuals genotyped and all samples with fewer than 90% of the markers genotyped were removed from further analyses. Markers violating Hardy-Weinberg equilibrium at $P < 0.001$ or with very low informativeness (minor allele frequency < 0.05) were removed from further analysis. Mendelian errors in each family were reviewed and genotypes were removed as needed to eliminate inconsistencies. Final genotypic quality control focused on removing any remaining genotypes that were likely to be erroneous as determined by evidence of recombination with adjacent markers (22). Before performing any linkage analyses, the linkage disequilibrium between single nucleotide polymorphisms was evaluated and in all cases where D' exceeded 0.70, the single nucleotide polymorphism with the highest minor allele frequency (ie, the most informative marker) was preferentially retained. The final sample consisted of 333 multiplex IA families consisting of 1895 samples.

To evaluate the evidence that common genes affect both IA and AA, multipoint, model-independent linkage analyses were performed using 2 models of disease. The first and broadest disease definition classified as affected only those individuals who met the definite or probable criteria for either IA or AA in abdominal or thoracic locations. It has been suggested that thoracic AAs (TAA) may be more heritable and are more strongly linked to known genetic conditions such as Marfan's syndrome than abdominal aortic aneurysms (AAA)⁷; therefore, a second, narrower disease definition that classified as affected only those individuals who met criteria for definite IA and/or those who met criteria for definite or probable thoracic AA was used.

Results

As of September 1, 2007, 2847 individuals from 546 families were in the database. Both definite/probable IA and AA were found in 11 individuals; 19 had definite/probable AA but no history of IA. In addition, 2 subjects had definite/probable AA and a possible IA, 2 subjects had definite/probable IA and possible AA, and 3 had possible AA but no IA. Of the 11 individuals with both conditions, 2 had their AA diagnosed first, 4 their IA diagnosed first, 4 were diagnosed made within the same year, and the age of AA diagnosis was not available for one subject.

Comparison of baseline characteristics of subjects with IA and those with AA are presented in Table 2. As expected, the average age of diagnosis for IA was substantially younger than for AA. Age adjustment had a substantial effect on pack-years and duration of hypertension.

A total of 28 families had members with AA as well as IA. However, 2 families were not informative for linkage; therefore, they could not be included in the analysis. Thus, linkage analyses were performed in the 26 multiplex IA families who were informative for linkage and who had also had members with thoracic or abdominal AA. Individuals from these 26 families ($n=91$) were defined as affected in the analysis if they had an IA (definite or probable), a TAA (definite or probable), or an AAA (definite or probable; Table 3). Of those with IA, 33 of 70

(47.1%) had a history of subarachnoid hemorrhage, whereas 5 of 30 (16.7%) with AA had a history of rupture. None of the 9 individuals with both IA and AA had a history of AA rupture, but 4 of 9 had a history of subarachnoid hemorrhage.

Maximal logarithm of odds (LOD) scores were obtained on chromosome 11 (144 cM; LOD=3.0; Figure A) and chromosome 6 (33 cM; LOD=2.3; Figure B). In both chromosomal regions, analyses of only these same 26 families using only IA as the phenotype produced LOD scores of 1.8 and 1.6, respectively. Restricting the phenotype to thoracic AA or IA resulted in similar, albeit more modest, values (Figure C). Fine mapping of chromosomes 11 and 6 can be found online (Supplemental Figure I, A—B, available online at <http://stroke.ahajournals.org>).

Discussion

Although common genetic risk factors for both IA and AA disease have long been speculated,⁸ the data have been sparse and inconsistent. A pedigree analysis conducted in the Utah Pedigree Database, which links genealogical data to demographic and medical information, including death certificates, found cosegregation of AAs and other aneurysms, although not IAs.⁹ A very small series of individuals with coronary ectasia were screened with thoracic/abdominal and intracranial MR angiography and 3 were found to have aneurysms.¹⁰ A recent treatment-based case-series reported co-occurrence of AA within pedigrees in 10.5% of probands with IA, lending support to the theory of shared genetic risk.³ There are data suggesting that TAA and AAA may have different pathophysiological mechanisms. A recent analysis of risk factor profiles among those with AAA and TAA underscores the importance of considering differences between these disorders.¹¹ However, other data suggest potential shared genetic susceptibility, including a recent analysis of shared loci for TAA, AAA, and IA.¹² The fact that there are undoubtedly differences in these 3 disorders does not preclude the potential for shared genetic susceptibility.

In this analysis from the FIA study population, we found a substantial minority of families that reported members with AA. As has been noted in other series, those with AA tend to be older at diagnosis, more likely to be men, and have longstanding hypertension, dyslipidemia, and evidence of heart disease than those with IA. In a genomewide linkage analysis on 26 white families with the co-occurrence of IA and AA, we found 2 peaks on chromosome 11 and chromosome 6 for the broad phenotype of IA or any AA. In the narrow phenotype analysis, we did not see new peaks emerging or evidence that the overall association was driven by thoracic aneurysms. Furthermore, the results of our analysis differ from other recent studies focusing on thoracic disease.¹³

Our identification of the chromosome 11 locus adds to mounting evidence for a susceptibility gene in this region. This region (11q24-25) has been previously found linked in other studies to aneurysmal disease.^{14,15} In one study of 2 large pedigrees with IAs, 2 individuals known to harbor AAAs inherited the haplotype linked to IA on chromosome 11. The inclusion of these 2 AAA cases in the linkage analysis increased the LOD score from 3.6 to 4.3.¹⁵ The authors interpreted their linkage as confirming a finding from an earlier Japanese sibpair analysis.¹⁶ Another study of familial AAs described the FAA1 gene on 11q23–24 between D11S1341 and AFMB031WC9.¹⁴ This FAA1 locus has been associated with a more widespread vasculopathic process than other candidates,⁷ although none of the genes in the region are currently viewed as strong mechanistic candidates for aneurysmal disease.¹⁴

Our finding is between 137.3 and 149.3 cM (decode), which is between 128.2 Mbp and 132.5 Mbp. It is in the range of Ozturk et al (125.6 Mbp to 131.4 Mbp). It is approximately 10 Mbp from Vaughan et al (117 Mbp to 120 Mbp); however, key recombinants resulted in a very

narrow confidence interval (1.1 cM). This same region was associated with the IA phenotype in a meta-analysis with a probability value of 0.012.¹⁷ As outlined in a recent analysis of loci identified in IA, AAA, and TAA, the 11q24 locus is a relatively large block with many genes, none of which are currently implicated in disease pathophysiology.¹² The next step in the pursuit of these results will be to perform dense single nucleotide polymorphism genotyping and perform association analyses to narrow the critical interval and identify specific candidate genes.

The chromosome 6p23 region has not previously been linked to IA, AA, or other aneurysmal disease. There are relatively few genes described in this region, although they include the jumonji AT-rich interactive domain 2 associated with cardiovascular abnormalities in mouse models and dystrobrevin binding protein (DTNBP1) associated with a subtype of albinism. The evidence for linkage here is merely suggestive; until confirmed in an independent study, this result should be viewed as preliminary and hypothesis-generating.

The chromosome 9p21 locus that has previously been associated with coronary disease and type 2 diabetes was recently associated with both IAs and AAAs with a population-attributable risk of approximately 26% in those of European descent for each condition.¹⁸ These findings, validated in several populations, certainly support the idea of shared genetic risk, although these analyses looked at IA and AAA as separate phenotypes. Similarly, other candidates related to smooth muscle contractility and function have been identified in individuals with familial TAAs^{13,19} and therefore might be plausible candidates in the broader phenotype. We did not find evidence of linkage to these loci in the current analysis nor was there evidence of linkage in the genomewide linkage analysis of the FIA population overall⁵ or in a recent meta-analysis of other genomewide linkage studies in IA¹⁷ supporting heterogeneity in genetic determinants of these complex disorders. Further specific investigations into these candidate genes may be warranted in this population.

Teasing out shared and distinct genetic risk for IA and AA may have significance for therapeutics as well as risk stratification. In a recent analysis of the role of matrix metalloproteinases in the pathophysiology of aortic and intracranial aneurysm leading to progressive expansion, mRNA and protein expression data pointed to opposite effects of the renin angiotensin system in these 2 diseases.²⁰ Animal data suggest that blockade of matrix metalloproteinases ameliorates expansion but cannot reduce IA formation. They propose different pathological evolution and distinct responses to drug intervention.

The current analysis has several strengths and limitations. The FIA study represents the largest collection of IA pedigrees and data were systematically collected on all aneurysm types. Despite these strengths, the number of pedigrees with both IAs and AAs is relatively small limiting our ability to explore the role of known risk factors such as hypertension and smoking.

Summary

Although the FIA study is the largest study to date of multiplex IA pedigrees, in this report, we have analyzed only a subset of the families defined as those having members with AA. In analyses in the 26 families meeting this criterion, we detected evidence of possible linkage to chromosomes 11 and 6. Analyses of these same families, when limiting the phenotype to only IA, produces some possible evidence of linkage to both regions, but the LOD score on both chromosomes is substantially reduced. We interpret these data to suggest that in these 2 chromosomal regions, gene(s) are located that increase the risk for IA as well as AA. Analyses are underway to evaluate the role of potential candidate genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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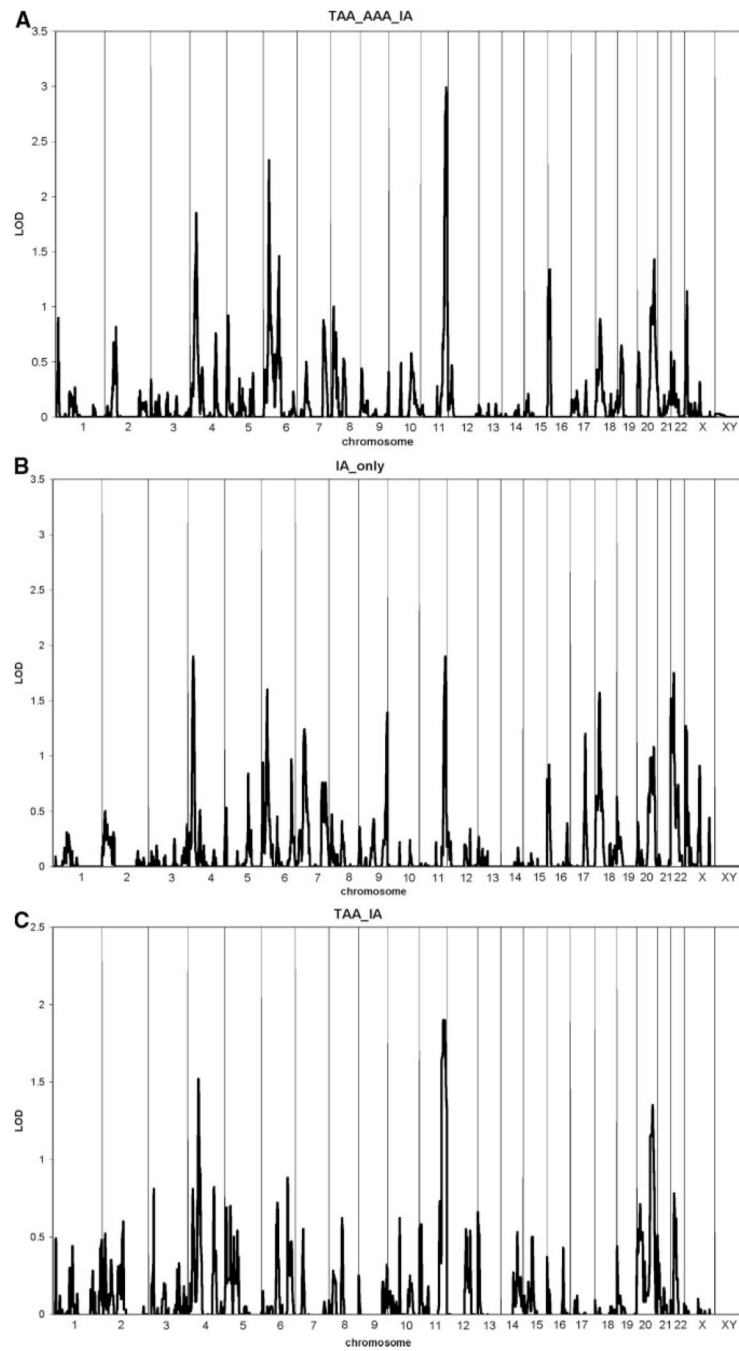


Figure.
Results of multipoint, model independent linkage analysis. A, Broadest disease definition: IA, AAA, or TAA. B, IA alone in the same families. C, Restricted disease definition: IA or TAA.

Table 1

Phenotype Definitions

	IA	AA
Definite	<ul style="list-style-type: none"> Medical records document IA on angiogram, operative report, autopsy, <u>or</u> A noninvasive imaging report (MR angiography, CT angiography) demonstrates an IA measuring 7 mm or greater 	<ul style="list-style-type: none"> Medical records document TAA or AAA diagnosed by CT, arteriogram, ultrasound, or visualized during operation or autopsy
Probable	<ul style="list-style-type: none"> Death certificate mentions intracranial aneurysm without supporting documentation or autopsy <u>or</u> Death certificate mentions subarachnoid hemorrhage (SAH) without mention of IA <u>and</u> a phone screen is consistent with ruptured IA (severe headache or altered level of consciousness) rapidly leading to death <u>or</u> An MR angiography documents an IA that is <7 mm but >3 mm 	<ul style="list-style-type: none"> TAA or AAA referenced in medical records with specific details
Possible	<ul style="list-style-type: none"> Noninvasive imaging report documents an aneurysm measuring between 2 and 3 mm <u>or</u> SAH was noted on death certificate, without any supporting documentation, autopsy, or recording of headache or altered level of consciousness on phone screen <u>or</u> Death certificate lists "aneurysm" without specifying cerebral location or accompanying SAH 	<ul style="list-style-type: none"> TAA or AAA diagnosed on chest or abdominal x-ray <u>only or</u> reported on medical history questionnaire or yearly follow-up without supporting documentation
Not case	<ul style="list-style-type: none"> There is no supporting information for a possible IA 	<ul style="list-style-type: none"> There is no supporting information for a possible AA; no mention of aneurysm in medical records or aneurysm located outside abdominal/thoracic region (for example, splenic aneurysm)

Table 2

Demographic and Risk Factor Characteristic Comparison of Subjects With Diagnosed IA to Diagnosed TAA/AAA*

Variable	IA (n = 1119)	TAA/AAA (N = 19)	P Value	Age-Adjusted P Value
Race, white	91.2%	100%	0.399	N/A
Sex, male	23.9%	52.6%	0.012	0.001
Smoking				
Current	50.3%	36.8%	0.382	0.601
Former	27.8%	42.1%		
Never	21.9%	21.1%		
Hypertensive	46.4%	73.7%	0.021	0.017
Frequent alcohol	39.3%	50.0%	0.648	0.557
Diabetes	7.6%	15.8%	0.176	0.399
High cholesterol	34.5%	88.2%	<.001	<0.001
Myocardial infarction or atrial fibrillation	7.5%	31.6%	0.002	0.007
Age at diagnosis, years	49.8 (SD, 12.1)	67.2 (SD, 11.3)	<.001	N/A
Cigarettes/day	16.7 (SD, 13.6)	18.3 (SD, 9.6)	0.667	0.656
	16.7 [†]	18.3 [†]		
Pack-years of cigarettes	23.9 (SD, 21.8)	33.3 (SD, 15.5)	0.095	0.759
	24.0 [†]	25.7 [†]		
Daily alcohol, drinks/day	0.96 (SD, 2.86)	0.38 (SD, 0.84)	0.010	0.768
	0.96 [†]	0.76 [†]		
Duration of hypertension	5.84 (SD, 11.4)	16.6 (SD, 13.8)	<.001	<0.001
	3.41 [†]	9.23 [†]		

NA indicates not applicable.

* Does not include the 11 individuals with both IA and AA.

[†] Denotes age-adjusted means for continuous variables.

Table 3
Distribution of Aneurysm Types Within the 26 Analyzed Families

IA	TAA	AAA	No. of Subjects (n = 91)
+	-	-	61
+	+	-	3
+	-	+	6
+	+	+	0
.	+	-	3
.	+	+	2
.	-	+	16