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Report

Mapping a Mendelian Form of Intracranial Aneurysm to 1p34.3-p36.13

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The identification of pathways that underlie common disease has been greatly impacted by the study of rare families that segregate single genes with large effect. Intracranial aneurysm is a common neurological problem; the rupture of these aneurysms constitutes a frequently catastrophic neurologic event. The pathogenesis of these aneurysms is largely unknown, although genetic and environmental factors are believed to play a role. Previous genomewide studies in affected relative pairs have suggested linkage to several loci, but underlying genes have not been identified. We have identified a large kindred that segregates nonsyndromic intracranial aneurysm as a dominant trait with high penetrance. Genomewide analysis of linkage was performed using a two-stage approach: an analysis of ~10,000 single-nucleotide polymorphisms in the 6 living affected subjects, followed by the genotyping of simple tandem repeats across resulting candidate intervals in all 23 kindred members. Analysis revealed significant linkage to a single locus, with a LOD score of 4.2 at 1p34.3-p36.13 under a dominant model with high penetrance. These findings identify a Mendelian form of intracranial aneurysm and map the location of the underlying disease locus.

Intracranial aneurysms (IAs [MIM %105800 and MIM %608542]) represent a major public health problem. The incidence of subarachnoid hemorrhage (SAH) due to aneurysm rupture is 6 in 100,000, with ~28,000 aneurysmal ruptures per year; it is estimated that up to 2.3% of the general population have undetected aneurysms (Juvela 2002*b*). The consequences of SAH are catastrophic, with approximately half of IA ruptures resulting in immediate death. Those individuals who survive the initial hemorrhage experience a 40% mortality rate during the first month, and only 25% of those who live past the first month recover completely (King 1997).

Given the poor prognosis of SAH due to aneurysm rupture, surgical or endovascular intervention prior to rupture is considered to be of paramount importance. There is, however, no practical means for reliable early diagnosis, except through screening studies of high-risk individuals with tests such as magnetic resonance angiography (MRA) or computerized tomography angiography (CTA). Moreover, there currently are no widely accepted guidelines to identify these high-risk individuals (Wermer et al. 2003).

Neither the conditions that lead to aneurysm formation nor the aneurysm ruptures are well understood. Recent studies suggest that both environmental and genetic factors contribute to the pathogenesis of IA. Risk factors for the formation, growth, and rupture of IA include hypertension, atherosclerosis, diabetes, and vascular anatomical differences (Juvela 2002*a*; Ohkuma et al. 2003). In addition, social factors such as smoking and diet have also been suggested to play a role in the disease (Juvela 2002*b*; Anderson et al. 2004).

Several lines of evidence demonstrate that genetic factors play an important role in IA pathogenesis. First, a number of genetic diseases, such as adult polycystic kidney disease (MIM #173900) (Chapman et al. 1992), Marfan syndrome (MIM #154700) (ter Berg et al. 1986), glucocorticoid remediable aldosteronism (MIM #103900) (Litchfield et al. 1998), and Ehlers-Danlos syndrome type IV (MIM #130050) (de Paepe et al. 1988), appear to increase the risk of IA formation. Second, familial recurrence of nonsyndromic IA has been well described (Fox

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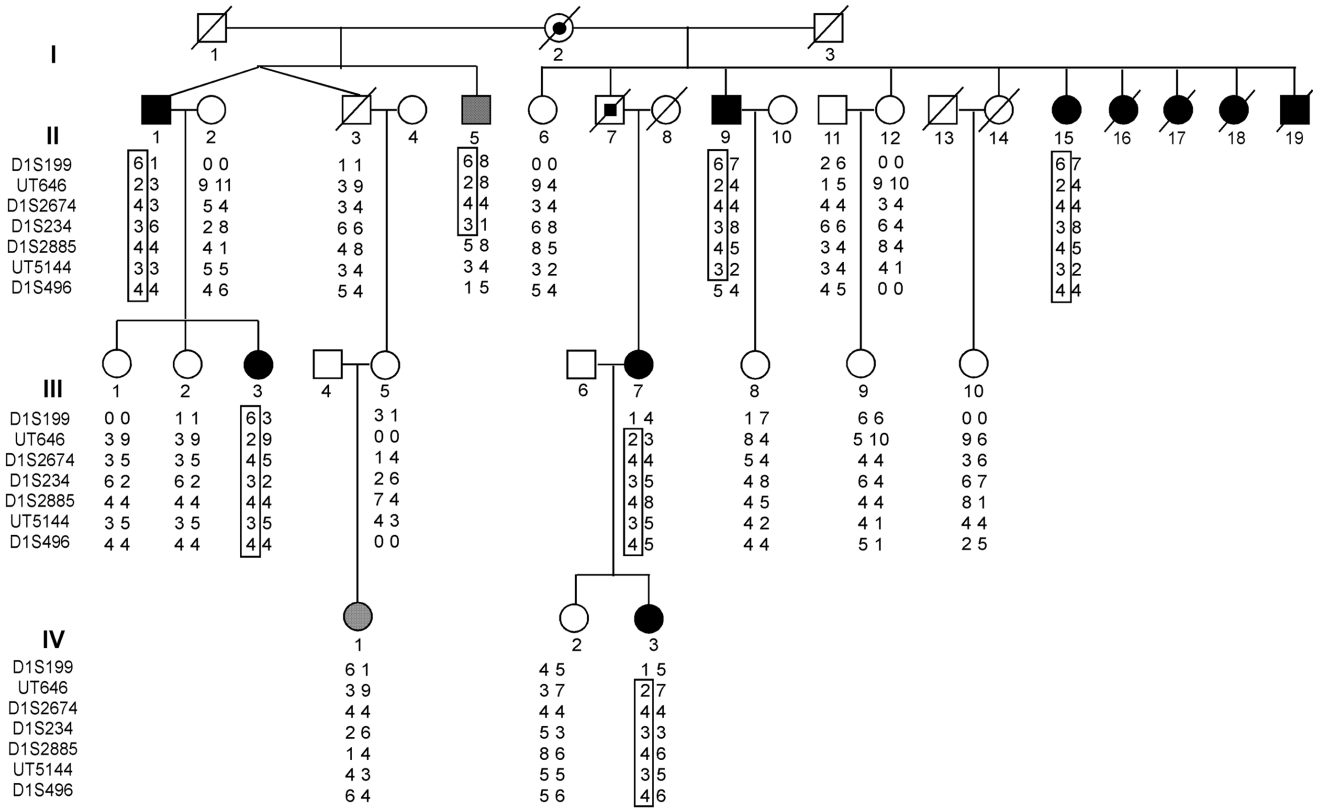


Figure 1 IA 20 kindred. Affected and unaffected individuals are shown as blackened and unblackened symbols, respectively. Obligate carriers are shown as partially blackened symbols. Individuals II-5 and IV-1 were assigned an affection status of "unknown" prior to linkage analysis and are shown as gray symbols. The genotypes of STR marker loci that span 14 cM at 1p34.3-p36.13 are shown, and segments of the haplotype linked to the disease phenotype are enclosed in a box. An allele designated "0" indicates a failed reaction.

and Ko 1980; Morooka and Waga 1983; Maroun et al. 1986; Elshunnar and Whittle 1990). Indeed, there is a three- to fivefold increase in risk for first-degree relatives of affected individuals, compared with the general population (Stehbens 1998; Ronkainen et al. 1999).

Among familial IAs, the varied pattern of recurrence has typically suggested complex causation. Several genomewide linkage studies that used affected sibling and/or relative pairs have identified various loci throughout the human genome that link to IA (Onda et al. 2001; Olson et al. 2002; Farnham et al. 2004; van der Voet et al. 2004). The results of these studies, however, have been inconsistent, and no specific disease-related genes have yet been identified. In addition, candidate-gene studies have not yet shown a robust association with IA (Onda et al. 2001; Hofer et al. 2003; Farnham et al. 2004; van der Voet et al. 2004).

In the context of substantial locus heterogeneity, the power of affected sibling pair studies or affected relative pair studies is markedly diminished (Risch and Merikangas 1996). Alternatively, the identification of rare Mendelian forms of disease can lead to the identification of genes and pathways that might play a key role in the pathogenesis of common, as well as rare, forms of the disease (Lifton et al. 2001). A limitation to this approach is that it is difficult to completely characterize and collect extended kindreds. In the present study, we have investigated what we believe is the largest-yet-reported kindred with IA; genomewide analysis of linkage provides significant evidence that the disease in this family is attributable to inheritance of a single locus at 1p34.3-p36.13.

Since 1994, we have screened >3,000 patients with IAs and identified 142 kindreds with two or more affected members. The family investigated in this study (IA 20) is the largest in our database and has been described elsewhere (Fox and Ko 1980). At that time, there were six members with proven IA, all in generation II (fig. 1). The pedigree has since been extended and further characterized. In total, there are now 10 documented subjects with IAs, 1 subject with distinctive multiple intracranial vessel occlusions and extensive collateral vessel formation of unknown etiology (subject III-3), and 1 subject with abdominal aortic aneurysm (AAA) at a young age (age 32 years) (individual II-5); this latter trait is sometimes as-

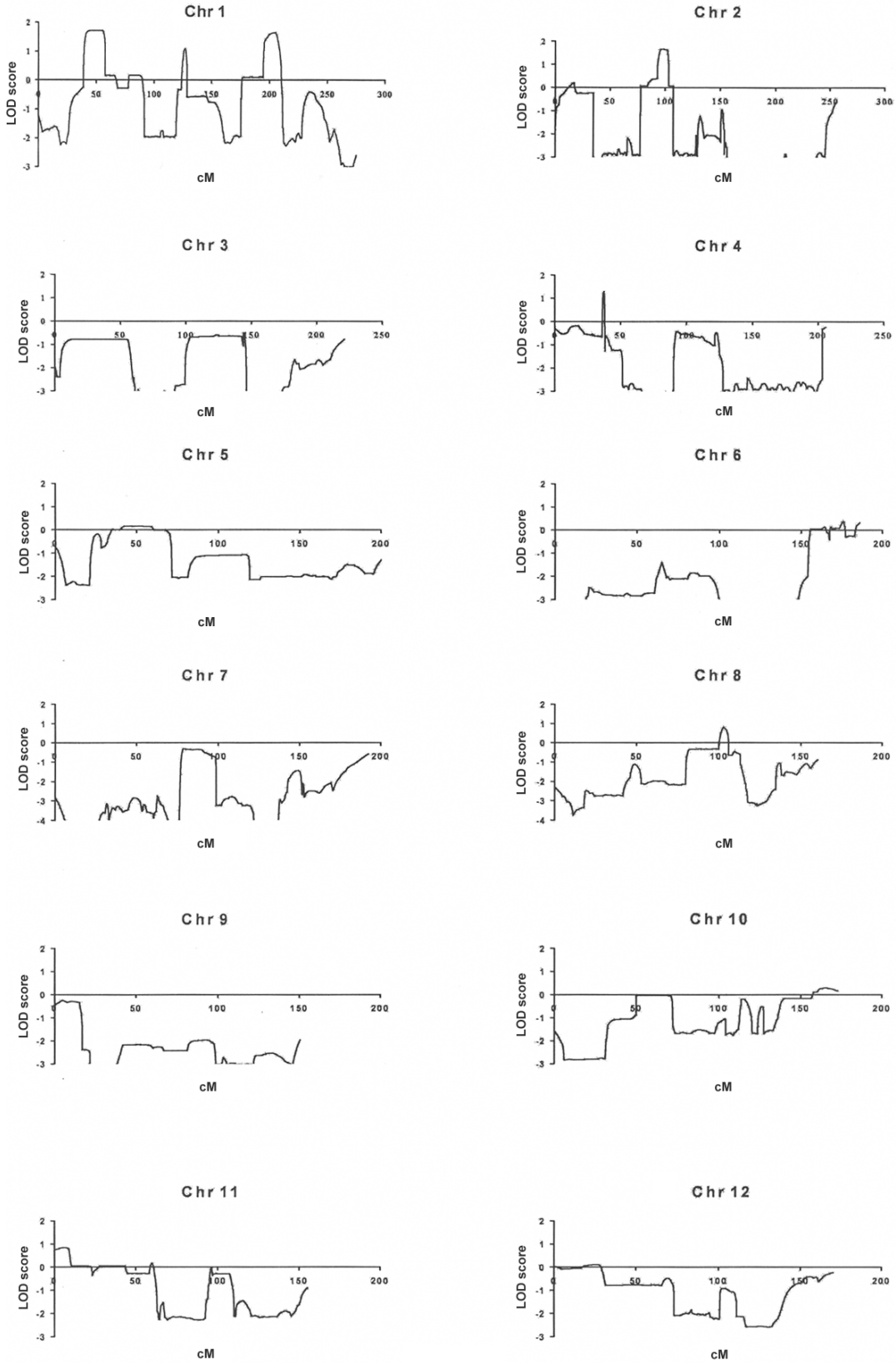
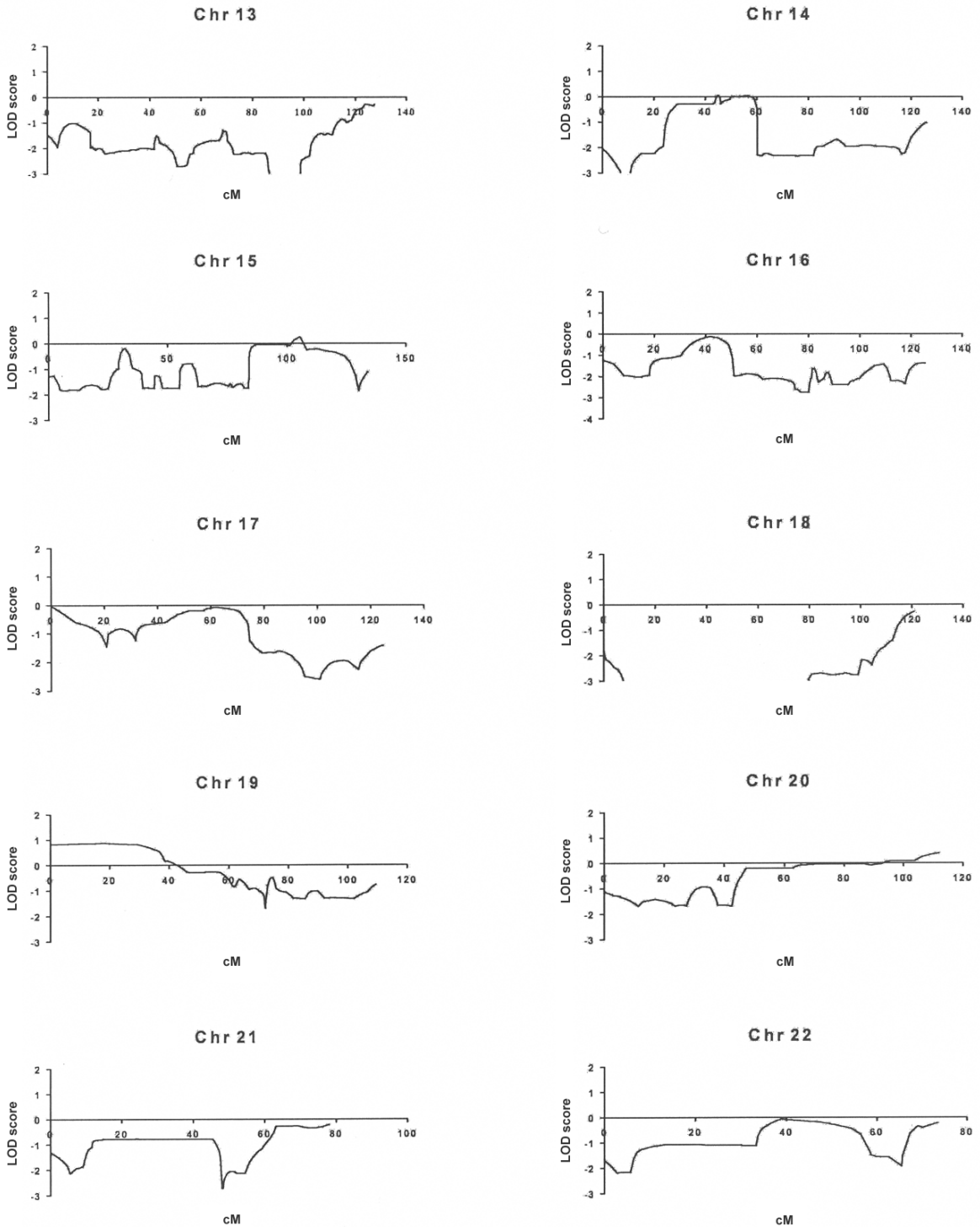


Figure 2 Analysis of linkage in the IA 20 kindred from GeneChip data of affected individuals. Linkage graphs for all chromosomes are shown; the *X*-axis corresponds to genetic distance (in cM), and the *Y*-axis shows LOD scores.



sociated with IA (Cannon Albright et al. 2003). For the purpose of linkage analysis, the patients with documented IAs and the patient with multiple intracranial vascular occlusions were classified as "affected," and the patient with AAA was prospectively classified as "phenotype unknown." There are also 12 unaffected descendents of subject I-2. Of these, 8 were asymptomatic at >30 years of age and had negative screening results for magnetic resonance imaging, MRA, CTA, and/or catheter angiogram (individuals II-3, II-6, II-12, II-14, III-1, III-2, III-8, and IV-2); 3 offspring of unaffected subjects were asymptomatic at >30 years of age and did not have screening studies (individuals III-5, III-9, and III-10); and 1 individual was asymptomatic at <30 years of age, without screening stud-

Table 1

Clinical Features of Affected Members of Kindred IA 20

ID	Aneurysm Location	Age at Diagnosis (years)
II-1	ACoA	38
II-7	ACA, left MCA	53
II-9	ACoA	40
II-15	Left MCA	29
II-16	Left MCA (SAH)	32
II-17	OphtA (SAH)	57
II-18	Right MCA, ACoA (SAH)	32
II-19	Left ICA (SAH)	29
III-3	Bilateral MCA occlusion	30
III-7	Left MCA	36
IV-3	Basilar, right MCA × 2	21

NOTE.—ACA = anterior cerebral; ACoA = anterior communicating; ICA = internal carotid; MCA = middle cerebral; OphtA = ophthalmic arteries.

ies (individual IV-1). For linkage studies, this latter subject was classified as "phenotype unknown," and the others were classified as "unaffected."

The clinical features of the affected members are presented in table 1. Age at diagnosis of IA ranged from 21 years to 53 years by MRA or CTA prior to SAH (n = 7) and from 29 years to 57 years for patients who presented with SAH (n = 4). There are scant risk factors for IA among kindred members; specifically, there is a history of hypertension in only one individual, and, although smoking was prevalent among both affected and unaffected family members, there was no significant difference between the two groups (8 of 10 affected individuals were smokers, and 10 of 12 unaffected individuals were smokers). Specifically, there is no history of polycystic kidney disease (no history of end-stage renal disease and no serum creatinine level >1.5 mg/dl), no history of Marfan syndrome (no history of aortic dissection, ectopia lentis, etc.), and no history of Ehlers-Danlos syndrome (no history of hypermobile joints, hyperextensible skin, or easy scarring). Finally, in neither the affected-only genomewide linkage analysis nor the affected-plus-unaffected analysis (see below) was there evidence of linkage to known loci for any of these syndromes. Members of both sexes are affected, the trait is present in consecutive generations, all affected members are the offspring of either known or suspected IA cases, and approximately half the offspring of such subjects have IA (fig. 1). These findings are consistent with autosomal dominant transmission of IA with high penetrance.

Blood samples were collected from all available family members after the obtainment of their informed consent; the study protocol was approved by the Yale Human Investigations Committee. Genomic DNA was prepared as described elsewhere (Bell et al. 1981).

We used a two-stage design in linkage analysis (Elston et al. 1996). We first genotyped all available affected individuals (n = 6) by use of Affymetrix 10K GeneChips. The SNPs genotyped on these chips provide an estimated information content equivalent to a microsatellite screen density of 1 marker/1–2.5 cM (Kruglyak 1997). SNP genotypes were obtained by following the Affymetrix protocol for the GeneChip Mapping 10K Xba Array. Briefly, genomic DNA was digested with *Xba*I; adapters were ligated to the product and an adapter-specific primer was used to amplify the product by PCR. The products were purified, fragmented, and labeled with biotin-ddnTP. Biotin-labeled DNA fragments were hybridized to the Mapping 10K Array chip. After hybridization, arrays were washed, stained, and scanned. Affymetrix MicroArray Suite 5.0 software was used to obtain raw microarray feature intensities, which were processed using the Affymetrix Genotyping Tools software package to derive SNP genotypes.

An average of 9,468 genotypes was scored per subject (SNP call-rate range, 91%–97%). To analyze the GeneChip data for linkage, we created a UNIX-based program (Chunky) that parses the data sheet into individual files per chromosome in linkage format. The information captured includes chromosome number, SNP markers, map distances, genotype calls, and allele frequencies.

For the multipoint analysis of linkage, we specified the disease locus as autosomal dominant, with penetrance that varied from 70% to 99%, a mutant disease-gene frequency of 0.001, and a phenocopy rate of 0.001. SNP allele-frequency data for the white population, as supplied by Affymetrix, were used for the analysis of linkage, which was performed using the Allegro program (deCODE). This analysis identified three intervals with LOD scores near the theoretical maximum of 1.8 (1p34.3-p36.13, 1q31-q41, and 2p11-p14), with LOD scores of <0 for nearly all of the remainder of the genome (fig. 2). The LOD scores were confirmed using the GENEHUNTER program. In an additional analysis, we specified the trait locus as X-linked dominant, with otherwise similar estimates of the trait locus; no interval on the X chromosome achieved a LOD score >-0.2. Additional genotyping with GeneChip of four unaffected individuals yielded only these same three intervals with LOD scores of $\geqslant$1.0. Changing the phenocopy rate had small effects on the LOD scores and did not identify additional candidate intervals.

Using data from the University of California–Santa Cruz (UCSC) Genome Browser (May 2004) (UCSC Genome Bioinformatics Web site), we identified and genotyped from five to nine highly polymorphic di- and tetranucleotide microsatellite markers across each of the three candidate intervals in all available kindred members (n = 23). Genotyping for microsatellite analysis was performed by PCR, with detection of fluorescent products

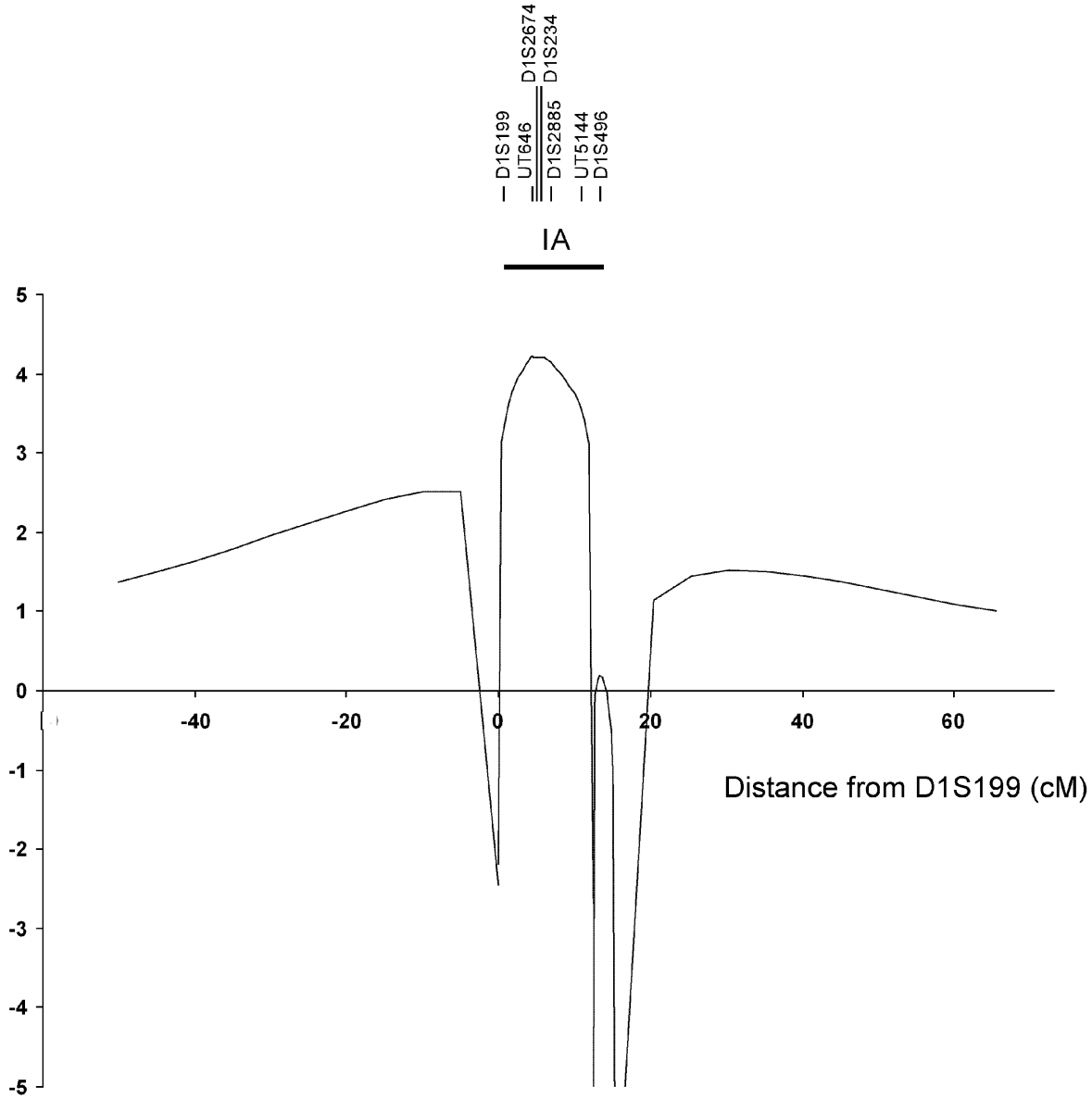


Figure 3 Analysis of linkage with STR markers on 1p34.3-p36.13. An IA gene is localized to a 12.5-cM region between markers *D1S199* and *D1S496*, with a maximum LOD score of 4.2. Multipoint analysis of linkage, for comparison of segregation of IA with marker loci, was performed. The location of marker loci used is indicated at the top of the diagram. The *Y*-axis shows LOD scores. The horizontal bar indicates the extent of the LOD-1 interval.

on an ABI 3700 sequencer (Applied Biosystems) equipped with GeneScan and Genotyper software (Applied Biosystems). The results were analyzed using the Simwalk program (we specified marker heterozygosities of 75% and the same autosomal dominant model of the trait locus used above, with penetrance of 70%–99%).

Our analysis diminished the evidence of linkage to 1q31-q41 and 2p11-p14 (table 2). In contrast, it demonstrated that all affected members inherit the same haplotype at 1p34.3-p36.13, whereas this haplotype was transmitted to none of the unaffected members (fig. 1). Parametric linkage analysis (with 99% penetrance specified) yielded a maximum LOD score of 4.2 at 1p34.3-p36.13 (table 2 and fig. 3); changing estimates of marker-allele frequencies had negligible effects on the LOD score. The likelihood of linkage to 1p34.3-p36.13 was nearly 1,000-fold more likely than the next-most-likely interval at 1q31-q41 (table 2).

The LOD score peak occurs at *UT646*; the LOD-1 interval is flanked by loci *D1S199* and *D1S496* (fig. 3),

Table 2

Maximum LOD Scores for Linkage of STRs and IA

Interval	Maximum LOD Score, for Penetrance of		
	70%	90%	99%
1p34-1p36	3.4	3.9	4.2
1q31-1q41	1.3	−.1	−5.6
2p11-2p14	−.3	−2.3	−6.6

Note.—Maximum LOD scores are reported for 1p34-1p36, 1q31-1q41, and 2p11-2p14 for STR markers in all family members, with varying estimates of penetrance.

which define a 12.5-cM interval that corresponds to a 15-Mb segment (from 19.3 million bp to 34.9 million bp). This is the same interval defined by the GeneChip analysis, which indicated a LOD-1 interval flanked by *rs950922* and *rs514262* that corresponded to a 15.4 million–bp interval (from 21.3 million bp to 36.7 million bp on 1p34.3-p36.13).

Analysis of critical recombinants supports localization of the IA locus within the specified interval. Affected subject II-9 is recombinant at the distal border, and subject III-7 is recombinant at the proximal border (fig. 1). Nearly identical borders define the linked interval by SNP analysis.

Examination of the LOD-1 interval identified ~240 genes. Among these, a number of genes have been identified as plausible candidate genes, including polycystic kidney disease–like 1, brain-specific angiogenesis inhibitor 2, fibronectin type III domain–containing gene, and collagen type XVI α1.

To our knowledge, the present kindred is the largest yet reported with IA, with 10 definitively affected subjects and one likely affected subject. Genomewide analysis of linkage in this kindred demonstrates complete linkage of IA to a 12.5-cM segment of chromosome 1, with evidence of linkage that substantially exceeds thresholds for significance. The phenotyping in the kindred was clear-cut; reclassification of the patient with multivessel occlusions and extensive collateral growth as "phenotype unknown" would reduce the maximum LOD score to 3.9. Moreover, the LOD score was substantially increased by inclusion of unaffected family members, which supports high penetrance of the trait locus. It is also of note that the subject with the early AAA inherited a segment of the linked haplotype, which suggests that this vascular aneurysm might be attributable to inheritance at this same locus. It would be of interest to obtain abdominal ultrasounds in kindred members to determine whether this phenotype commonly cosegregates with IAs and/or linked haplotypes. The pattern of segregation and the linkage data indicate that this family defines a new Mendelian form of IA that is transmitted as an autosomal dominant trait with high penetrance. Similar to reported cases of familial IAs, members of IA 20 presented with SAH or symptomatic findings at an earlier age than is typically found in sporadic cases (Lozano and Leblanc 1987).

These findings represent a first step in the identification of a susceptibility gene for IA. Other than young age, there are no obvious clinical features that separate IA in members of this family from typical cases in the general population. It is presently unknown whether the locus implicated in this study might play a role in other common forms of IA. In principle, it is possible that this might be a one-of-a-kind family with a rare mutation that results in a highly penetrant form of IA. It is also possible that other less-penetrant mutations in the same gene or pathway play a role in more-common forms of IA. To date, a number of studies have used linkage approaches to attempt to identify loci that contribute to IA risk (de Paepe et al. 1988; Pope et al. 1990; Kuivaniemi et al. 1993; Takenaka et al. 1999; Onda et al. 2001; Olson et al. 2002; Yoneyama et al. 2003; Farnham et al. 2004). Sib pair studies from Japanese and Finnish populations, as well as a recent study of a consanguineous Dutch family, have identified candidate intervals (Onda et al. 2001; Olson et al. 2002; Roos et al. 2004). The only intervals from such studies that meet genomewide evidence of significant linkage are 19q13.3 in the Finnish population (van der Voet et al. 2004) and 2p13 in the Dutch family (Roos et al. 2004).

The identification of the causative gene in IA 20 will shed light on the pathways that lead to disease. Whether this locus or pathway will play a role in more-common forms of disease remains to be determined. However, once genes that lead to IAs are identified, they may better define the pathophysiology and natural history of aneurysm formation and rupture. Finally, these findings may contribute to improved diagnostic and therapeutic approaches to this disease.

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Electronic-Database Information

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www

.ncbi.nlm.nih.gov/Omim/ (for IA, adult polycystic kidney disease, Marfan syndrome, glucocorticoid remediable aldosteronism, and Ehlers-Danlos syndrome type IV)
UCSC Genome Bioinformatics, http://genome.ucsc.edu/

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