ELECTRONIC LETTER

A new locus for autosomal dominant intracranial aneurysm, *ANIB4*, maps to chromosome 5p15.2-14.3

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Background: Intracranial aneurysms (IA) are dilatations of intracranial arteries that occur most commonly at arterial bifurcations. Unruptured IA are present in approximately 1–2% of the population aged over 30 years of age. Aneurysms are only rarely symptomatic unless they rupture, which typically results in a subarachnoid haemorrhage associated with high morbidity and mortality.

Methods: A large French Canadian (FC) family (Aneu60) was identified which contained 12 affected individuals with intracranial aneurysms. Nine of the affected patients and three unaffected individuals were sent for an 8 cM genome-wide scan. Multipoint and two-point methods were used to analyse the scan data by using a dominant parametric model.

Results: We identified an IA susceptibility locus (*ANIB4*) located on chromosome 5p15.2-14.3. The locus was found by genome-wide linkage analysis and follow up analyses provided a maximum multipoint LOD score of 3.57 over the region. An identical haplotype segment of 7.2 Mb was found in a second FC pedigree and contributes to the refinement of the candidate gene interval.

Conclusions: Our results indicate that there is a major gene locus on chromosome 5p.

Intracranial aneurysms (IA) are dilatations of cerebral arteries that occur most commonly at arterial bifurcations (MIM 105800). The lifetime incidence of IA is in the order of 1–2%,¹ while the lifetime risk of rupture is between 0.5% and 1%, representing about 10% of all strokes.² Rupture of an IA causing a subarachnoid haemorrhage (SAH) occurs with a frequency of between 6 and 8 per 100 000 in most Western populations³; typically the incidence of SAH is higher among women than among men.⁴ IA usually occurs in adults where the incidence increases with increasing age. It is a serious condition because the first manifestation is almost always rupture, leading to death in 50% of cases and severe morbidity in an additional 30% of cases.^{5–6} Pathologically, IA are characterised by a very thin or absent tunica media and internal elastic lamina of the vascular wall. Because IA usually occur at the bifurcations of large intracranial arteries, which are exposed to the greatest pressures, premature weakening of the blood vessel is thought to predispose to IA.⁷ Environmental factors, such as cigarette smoking and alcohol consumption, have been identified as risk factors for SAH.⁸

Evidence suggests that genetics contribute to the development of IA.⁹ Among first degree relatives of patients with SAH, the risk of a ruptured IA is three to seven times higher than in the general population.^{10–12} In a study of 412 ruptured aneurysms in the Saguenay-Lac-Saint-Jean region of Quebec, Canada, 30% aggregated within families.¹³ In addition, multiple aneurysms occur in 20–30% of patients (often those

with a family history), suggesting that these individuals are particularly predisposed to the development of IA.¹⁴ Familial aneurysms tend to be smaller in size, may rupture at an earlier age, and are more often followed by the formation of a new aneurysm compared to sporadic aneurysms.^{4 15 16}

Several patterns, including both recessive and dominant models of inheritance, have been described, suggesting a level of genetic heterogeneity.^{16 17} In addition, several groups have studied familial IA by performing genome scan studies on sibships^{18 19} and on large families.^{20–22} Different possible susceptibility loci for familial IA have been described, but no gene has yet been identified. In this study, we performed a genome-wide linkage analysis in a large French Canadian (FC) pedigree affected with IA in order to identify a susceptibility locus for this disorder.

METHODS

Study inclusion

Twenty nine FC families, with at least two affected individuals, were enrolled in this study, which was approved by the Montreal General Hospital Research Ethics Committee. After informed consent, blood samples were taken from 231 subjects and DNA was extracted from peripheral blood by standard methods. The total number of affected individuals was 112, of whom 54 were enrolled in the study and 19 were genetically reconstructable. Subjects were considered affected if an IA was documented either by standard angiography or surgical ablation or if they had an infundibulum.^{23 24} Subjects were excluded if they had a personal diagnosis or family history of polycystic kidney disease (MIM 173900), Ehlers-Danlos syndrome type IV (MIM 130050), neurofibromatosis type 1 (MIM 162200), Marfan syndrome (MIM 154700),² a fusiform aneurysm of a major intracranial artery, or other intracranial vascular malformations. In all instances, a complete family and medical history was obtained, including cigarette consumption and history of hypertension. During the enrolment of these families, a large family (Aneu60) was identified, which contained 12 affected individuals, nine of whom were available for analysis (three are deceased).

Linkage analysis

Samples from nine affected and three unaffected individuals from the Aneu60 family were sent for an 8 cM genome-wide scan performed by the company deCODE (Reykjavik, Iceland). A panel of 531 highly polymorphic evenly spaced microsatellite markers was used and the genotyping success rate was more than 95%. The disease segregation within the family was compatible with Mendelian inheritance (fig 1), and a parametric LOD score approach was used to test for linkage. To analyse the genome scan markers, a test using an

Abbreviations: FC, French Canadian; HLOD, heterogeneity score; IA, intracranial aneurysms; MRA, magnetic resonance angiography; SAH, subarachnoid haemorrhage

Figure 1 Pedigree of the French Canadian Aneu60 kindred segregating intracranial aneurysm. Filled symbols indicate affected individuals, while empty symbols indicated individuals not known to be affected. A small dot within a symbol denotes an obligate carrier. Parentheses signify an inferred genotype. The disease haplotype is shown by a black bar. The upper recombinant can be found in individual III:8 and the lower recombinant in individual IV:5.

affecteds-only approach was conducted with an autosomal dominant model, a phenocopy frequency of 0.01, a penetrance of 0.8, and a disease allele frequency of 0.001. Multipoint linkage of the autosomes was performed using GENEHUNTER version 2.1_r5 beta²⁵ and two point linkage for the X chromosome was calculated using MLINK from the FASTLINK 3.0P package.²⁶ Analyses were performed using deCODE allele frequencies for the genome-wide analysis and were set to CEPH frequencies²⁷ for fine mapping linkage.

Fine mapping

Additional genotyping was performed using polymorphic markers obtained from the Marshfield genetic map²⁸ (<http://research.marshfieldclinic.org/genetics>). Each primer pair was amplified according to specific polymerase chain reaction (PCR) conditions and the product was labelled with nucleotide ³⁵S-dATP. The PCR products were separated on 6% denaturing polyacrylamide gels and detected by exposure to autoradiographic film. The alleles were assigned on the basis of their size in accordance with CEPH data and with

comparison to an M13mp18 sequence ladder. Marker location was obtained from the UCSC physical map (May 2004 assembly: <http://genome.ucsc.edu>).

Additional analysis of other FC families

Ten additional FC families (family trees are available from a supplemental figure at <http://www.jmedgenet.com/supplemental>) were tested for linkage on 5p15.2-14.3. All families were genotyped using markers spanning the critical region defined by the markers D5S2095 and D5S2031 using the markers D5S2095, D5S667, D5S1991, D5S1954, D5S1963, D5S1997, D5S268, D5S2096, and D5S2031. Haplotypes and heterogeneity scores (HLOD) were calculated using GENEHUNTER version 2.1_r5 beta.²⁵

RESULTS

Aneu60 is an FC family that contains 12 individuals affected with IA that seems to segregate according to a monogenic inheritance pattern (fig 1). Clinical information for the Aneu60 kindred indicated that aneurysm location was not

Table 1 Clinical features of affected members of the Aneu60 family

ID	Aneurysm location	Age at diagnosis (years)	Smoker	Ruptured	Clipped
II:2	NA (SAH)	55	Y	Y	N
II:4	NA (SAH)	42	S	Y	N
III:3	L infundibulum on posterior communicating artery	49	Y	N	N
III:5	R MCA	42	Y	N	Y
III:8	L superior cerebellar artery	48	Y	N	Y
	L posterior communicating artery			N	Y
III:10	R MCA	55	S	N	Y
III:11	NA (SAH)	56	NA	Y	N
III:13	L MCA bifurcation	41	Y	N	Y
	R paraophthalmic intercavernous			N	N
III:21	L intracavernous carotid artery	53	Y	N	N
IV:5	R infundibulum on posterior communicating artery	40	Y	N	N
IV:6	R ophthalmic artery	34	Y	N	Y
IV:14	L MCA	45	Y	N	N

L, left; MCA, middle cerebral artery; N, no; NA, not available; R, right; S, smokes on social occasions; SAH, died of subarachnoid haemorrhage; Y, yes.

Figure 2 Multipoint LOD score of Aneu60 on 5p15.2-14.3.

specific to a particular area, although four of the nine documented aneurysms were located at the middle cerebral artery (table 1). In addition, two of the patients had aneurysms in two different locations. The age at diagnosis varied between 34 and 56 and most of the affected individuals were smokers. Following the deaths of individuals II:2 and III:11, many aneurysms were discovered when descendants of II:2 underwent preventive screening by magnetic resonance angiography (MRA). However, as only a few descendants of II:7 have undergone MRA screening, other aneurysms have probably remained undiagnosed. This may explain why there seem to be only two affected individuals in that branch.

The genome-wide scan analysis revealed that the strongest evidence for linkage was found around microsatellite markers D5S1486 and D5S2081 on chromosome 5p with a multipoint LOD score of 2.69. Two other regions revealed LOD scores higher than 2, D12S2081 (LOD = 2.12) and D16S418 (LOD = 2.24). These three regions were further investigated by genotyping every individual from the family included unaffected members. For chromosome 5, segregation revealed a disease haplotype for every affected individual in the Aneu60 family (fig 1) and maximum multipoint LOD

score analysis gave 3.57 at marker D5S1954 (fig 2). For chromosomes 12 and 16, a disease haplotype did not segregate with every affected individual and multipoint LOD scores were reduced to 0.35 and 0.97, respectively.

We investigated the chromosome 5 region in 10 other FC families in the hope that they would be linked to this same region. Calculations for all families together, including the Aneu60 family, resulted in a maximum multipoint HLOD score of 3.42 and an α value of 0.40. Haplotype analysis was performed to determine if a common haplotype was being observed in the potentially linked families. The analysis revealed that one of the 10 families (Aneu57) shares a 7.2 Mb haplotype segment identical to the Aneu60 haplotype between D5S2095 and D5S1963 (table 2).

DISCUSSION

The identification of a large FC family (Aneu60) has helped us to identify a susceptibility locus using a monogenic approach for this disorder. The genome-wide scan revealed a susceptibility locus on chromosome 5p for this particular family with a multipoint LOD score of 3.57 (fig 2). Further fine mapping of the region allowed the identification of an upper (III:8) and lower (IV:5) recombinant, defining the locus as being from marker D5S2095 to D5S2031 and spanning 11.7 Mb at 5p15.2-14.3 (fig 1). There are at least two non-penetrant individuals in Aneu60 (II:7 and III:23) and it is interesting to note that they are both non-smokers. Individual III:6, a 52 year old non-smoking man, carries the upper part of the disease haplotype and although his last MRA was normal, reducing the linked region using this information would not be advisable as IA is not a fully penetrant disease.

The existence of a founder effect in the FC population has been confirmed by many studies.^{29–36} This population is particularly well suited for genetic studies due to the relatively small number of ancestors.³⁷ Many of these founders were related to each other directly or were from a limited number of regions in France further reducing the number of ancestral chromosomes in the FC compared to other outbreed populations. In addition, for socio-economic, religious, and linguistic reasons, the descendants of these founders did not mix with other immigrants for over three centuries. There was also significant sustained demographic growth of the population, which doubled every 25–30 years. Therefore, a large number of individuals now living in Quebec have inherited chromosomes almost exclusively from a relatively small pool of founders, thus facilitating the use of haplotypes for fine mapping. Haplotyping of 10 other FC families revealed that one family (Aneu57) shares a portion of the Aneu60 disease haplotype. Considering only the shared haplotype, the critical region is reduced from 11.7 to 7.2 Mb (table 2). Some smaller families, which could potentially be linked, do not share the Aneu60 haplotype at the marker resolution tested. These other haplotypes could represent other disease haplotypes or the families may not be linked.

Table 2 Haplotype analysis of families Aneu60 and Aneu57						
Markers	Mb	cM	Aneu60	Aneu57	Allele length (bp)	CEPH allele frequency
D5S2095	9.44	19.67	8*			
D5S2004	10.55	21.81	<i>1</i>	<i>1</i>	211	29%
D5S2081	13.53	24.48	<i>6</i>	<i>6</i>	197	50%
D5S1991	14.93	26.73	<i>5</i>	<i>5</i>	233	3.6%
D5S1954	15.87	28.30	<i>2</i>	<i>2</i>	225	52%
D5S1963	16.68	28.76	<i>4</i>	<i>1</i>		
D5S2031	21.15	36.25	5*			
*Alleles in bold indicate that a recombinant occurred within the family. Italics indicate haplotype that is shared by Aneu60 and Aneu57. Allele lengths were down-coded according to CEPH.						

There is no evident familial link between Aneu60 and Aneu57. Further genealogical studies will be needed to determine how and if they are related.

The markers D5S2095 and D5S1963 now define the critical region for the 5p locus. This large region of 7.2 Mb seems gene poor as it encompasses only about 25 known genes. Two good candidate genes found within this region, *CTNND2* and *TRIO*, seem to be involved in cell modelling. *CTNND2*, catenin delta-2 (delta-catenin), may be involved in neuronal cell adhesion and tissue morphogenesis and integrity by regulating adhesion molecules.³⁸ In vitro studies have shown that it can induce cell motility and cell scattering in response to hepatocyte growth factor treatment. *CTNND2* may also bind to E-cadherin at a juxtamembrane site within the cytoplasmic domain and/or bind to presenilin-1. Its subcellular location seems to be at the adherens junction and it is predominantly expressed in the brain. On the other hand, *TRIO* is a triple functional domain protein (PTPRF interacting protein) that promotes the exchange of GDP by GTP.³⁹ Together with leucocyte antigen related (LAR) protein, it could play a role in coordinating cell-matrix and cytoskeletal rearrangements necessary for cell migration and cell growth. It is highly expressed in heart, skeletal muscle, brain, pancreas, placenta, liver, kidney, and lung. Screening of these genes is currently underway.

In summary, our results indicate that there is a major gene locus on chromosome 5p, which was named *ANIB4* by the HUGO Gene Nomenclature Committee.⁴⁰ Two families were found to share a common ancestral haplotype, which allowed us to refine our candidate gene region to 7.2 Mb. Nonetheless, our data indicate that there must be other loci involved in the genetic determination of IA in the FC population.

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ELECTRONIC-DATABASE INFORMATION

The family trees are given in a supplemental figure at <http://www.jmedgenet.com/supplemental>. The Center for Medical Genetics web site is at <http://research.marshfieldclinic.org/genetics> and the UCSC Genome Bioinformatics web site is at <http://genome.ucsc.edu>.

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