

[P150] Genomewide Screen for Intracranial Aneurysm Susceptibility Genes

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Background: As compared with the general population, individuals with first degree relatives harboring an intracranial aneurysm (IA) are at an increased risk of IA. These data suggest that genetic variation is an important risk factor for IA susceptibility.

Methods: The Familial Intracranial Aneurysm study is a multi-national study which seeks to identify the genes underlying the risk of IA. Families with multiple individuals having either ruptured or unruptured IA are ascertained. All IA cases are classified as 'definite', 'probable', 'possible' and 'not a case'. To identify asymptomatic individuals with IA, relatives meeting criteria are offered screening with brain magnetic resonance angiography (MRA). A 10 cM microsatellite genome screen was completed by the Center for Inherited Disease Research in an initial sample of 109 families, including 743 individuals. Both parametric and nonparametric linkage analysis methods were performed. Two models of affection were employed in the analyses. The 'narrow' definition included as affected only subjects with definite IA while the 'broad' definition included both definite and probable IA.

Results: Initial analyses performed using nonparametric methods and the narrow disease definition found suggestive evidence of linkage to regions chromosomes 2q, 8 (including the centromere), and 15q (LOD ~1.4-1.5). Broadening the disease definition resulted in evidence of linkage to chromosomes 8 and 1p. To exploit the large informative families collected as part of this study, analyses were also performed using an autosomal dominant, reduced penetrance model of IA inheritance. Further evidence of linkage to chromosomes 1p and 15q were obtained using the broad definition (LOD~1.5-1.6). Evidence of linkage was also obtained to chromosome 7p (LOD~1.5).

Conclusions: Our study provides modest evidence of linkage to several chromosomes in familial IA. Further analyses using a larger sample of families and incorporating important covariates, such as smoking and hypertension, are underway.

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