Xp22.2 Chromosomal Duplication in Familial Intracranial Arachnoid Cyst

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Introduction

Arachnoid cysts (AC) are congenital fluid-filled malformations that account for approximately 1% of all intracranial, space-occupying lesions in the central nervous system [1]. Despite an estimated prevalence of 1.4%, little is known about the pathogenesis of these presumed developmental anomalies of the arachnoid [2]. Co-incidence of arachnoid cysts in known Mendelian cystic disorders such as autosomal dominant polycystic kidney disease [3, 4], along with rare clinical reports of familial AC occurrence [5, 6], suggests a genetic basis for the disorder. However, to date, no gene or chromosomal abnormalities have been detected in familial intracranial AC. Here, we present a familial form of isolated intracranial AC showing autosomal dominant inheritance pattern and characterized by the presence of large, bilateral middle fossa arachnoid cysts [Figure 1] in four different family members of a nuclear kindred [Figure 2].

Methods

To investigate genetic determinants for this phenotype, we performed whole-exome sequencing and a SNP microarray on DNA obtained from all individuals with known bilateral, intracranial arachnoid cysts, as well their unaffected family members.

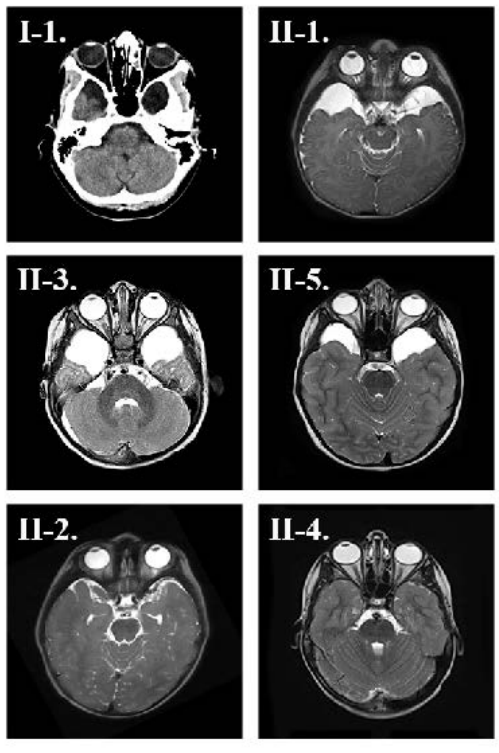
Conclusions

These results present the first evidence that a genetic mutation underlies the pathogenesis of intracranial AC. Further investigation of the genes in the duplicated Xp22.2 region may help elucidate the factors that contribute to intracranial arachnoid cystogenesis, with diagnostic and potentially therapeutic implications for more common forms of sporadic intracranial AC.

Results

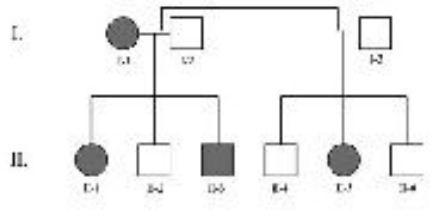
Array Comparitive Genomic Hybridization (aCGH) revealed a maternally-inherited 720kb duplication of Xp22.2 that segregated with the disease phenotype in all affected individuals (I-1, II-1, II-3, II-5) and was not present in any of the unaffected family members (I-2, II-2, II-4, II-6). The duplicated region (chrX:10,605,711-11,325,964) included the genes MID1, HCCS, AMELX, ARHGAP6. Breakpoints for the duplication were found within the intron following the first of nine coding exons of MID1, and within the intron following the first of thirteen coding exons of ARHGAP6, thus potentially interrupting the reading frame of these genes which could result in LOF. The entire coding sequence and 5'UTR of HCCS and AMELX were duplicated, suggesting increased dosage at these two loci. Interestingly, deletions and loss of function mutations of MID1 result in Opitz/BBB syndrome, which presents with ocular telorism similar to those with the duplication in this large kindred.

Figure 1



Radiological imaging fromaffected individuals depicting nearlyidentical presentations of large,bilateral, middle fossa arachnoidcysts. (I-1) Axial CT of the headwithout contrast. (II-1) Axial T2Magnetic resonance imaging withoutFLAIR. (II-3) Axial T2 Magneticresonance imaging without FLAIR. (II-5)Axial T2 Magnetic resonance imagingwithout FLAIR. (II-2) Axial T2 Magneticresonance imaging without FLAIR. (II-4)Axial T2 Magnetic resonance imagingwithout FLAIR.

Figure 2



Familial intracranial arachnoid cyst pedigree

Learning Objectives

By the conclusion of this session, participants should be able to:
1) Describe the epidemiology and genetic basis of Arachnoid Cyst,
2) Discuss, in small groups, potential causal mechanisms of AC in the context of genes contained within the Xp22.2 region and recognize the potential of genetic study of rare disorders (familial intracranial AC) to elucidate disease-causing pathways underlying more common disease (sporadic intracranial AC).

References

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