The Genetics of Aicardi-Goutières Syndrome

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In 1984 two French paediatric neurologists, Jean Aicardi and Françoise Goutières, described 8 children with an early onset, progressive encephalopathy characterised by basal ganglia calcification, leukodystrophy, chronic cerebrospinal fluid lymphocytosis and negative serological investigations for common prenatal infections[1]. This clinical phenotype had previously only been associated with the sequelae of intrauterine infection. However, the observation of familial cases, affected females and parental consanguinity prompted these authors to propose that the condition they described was inherited as an autosomal recessive trait. Further reports have identified families with affected siblings separated in age by a number of years and in birth order by intervening normal children. These features provide strong evidence against a causative role for an unidentified congenital infective agent.

In order to localise the gene/genes involved in Aicardi-Goutières syndrome we recently performed a genome-wide linkage analysis of 23 children from 13 families with a clinical diagnosis of Aicardi-Goutières syndrome[2].

The use of linkage analysis in familial disorders represents a method for localising a disease causing gene to a particular chromosomal region. A locus can be defined as the unique chromosomal location of an individual gene or DNA sequence and the basis of linkage analysis is that recombination events occur between 2 genetic loci on the same chromosome at a rate related to the distance between them. The goal of linkage analysis in Mendelian diseases is to determine whether 2 loci (a disease gene and a marker) co-segregate more often than they would if they were not physically close together on the same chromosome. It was not possible to set out to map a disease with a reasonable hope of success until polymorphic markers spaced regularly throughout the genome became available. The development of such genetic maps has revolutionised gene localisation and subsequent gene cloning.

Our analysis relied heavily on the statsitical power derived by using consanguineous families in genome-wide linkage analysis. Alleles that are identical because they are 2 copies of the same single allele present in a common ancestor are defined as being autozygous or identical by descent. The increased risk of autosomal recessive disease in the offspring of consanguineous parents arises as a consequence of the associated autozygosity present in an affected individual due to inbreeding. That is, the most

parsimonious explanation for the presence of 2 mutated alleles in the offspring of a consanguineous couple is the passage of a single mutation, derived from a common ancestor, down both sides of the family. The exact size of the autozygous segment in an affected individual will vary depending on the occurrence of meiotic recombination between the common ancestor and the study individual. Within the autozygous region, all polymorphic markers will be homozygous and so a search can be made to find such autozygous segments by typing multiple polymorphic markers at regular intervals throughout the genome. The rarer the disease allele is in the population, the greater the likelihood that homozygosity represents autozygosity.

In choosing families for analysis, we stipulated that all affected singletons, and at least one sibling from every family where more than one child was affected, fulfilled the following inclusion criteria by showing: (1) A progressive neurological disorder with onset in the first year of life; (2) a normal head circumference at birth; (3) calcification involving the basal ganglia and sometimes extending to the white matter; (4) a CSF leucocytosis (> 5 white cells/mm^3) and/or a raised level of CSF IFN-α (> 2 IU/L); (5) negative TORCH studies (toxoplasmosis, rubella, cytomegalovirus and herpes simplex).

After publication of the linkage data from the group of Fauré and colleagues[3], we considered it likely that Aicardi-Goutières syndrome would demonstrate locus heterogeneity. Locus heterogeneity is recognised as a common genetic phenomenon and can occur in a number of ways. For example, disease may result from mutations in proteins involved at different stages in the same biochemical pathway. The fundamental point about locus heterogeneity is that, however it occurs, it is not possible to identify the genetic basis for the disease in any given family other than through linkage analysis and/or mutation detection. As a consequence of this fact, locus heterogeneity can present a major obstacle to gene localisation, especially where several disease loci exist. Strategies employed to overcome the difficulties associated with locus heterogeneity include the use of population isolates or single large families which are sufficiently powerful in themselves to detect linkage. In both cases it is assumed that within the sample a single gene will generate the phenotype. Unfortunately, no large families were available to us, in part due to the rarity of Aicardi-Goutières syndrome, partly as a consequence of the need for specialised tests for the diagnosis and also because of the likelihood of death in infancy. In the presence of locus heterogeneity, small families are harder to utilise since they lack sufficient power for confident assignment to any 1 locus. Because of this associated uncertainty of locus assignment, recombination events cannot be used to definitively narrow a critical region.

Despite these difficulties, linkage analysis of our 13 mapping families gave a maximum multipoint heterogeneity LOD score of 5.28 at D3S3563 with a value for α of 0.48

where α is the proportion of linked families. In addition to identifying the first locus for Aicardi-Goutières syndrome, AGS1, our data also indicated the existence of locus heterogeneity. We considered that this represented the most likely explanation for difficulties experienced in identifying genetic linkage in the study of Fauré et al.

Since our initial publication we have attempted to refine the AGS1 critical region by specifically searching for ancestral haplotypes in families sharing a common ethnicity. The power of such an approach in narrowing a critical region identified by linkage analysis has been well demonstrated in the Finnish disease heritage[4]. Pleasingly, such an approach has allowed us to identify an ancestral haplotype in a Pakistani subset of Aicardi-Goutières syndrome families (manuscript in preparation). This Pakistani ancestral haplotype has been determined on the basis of homozygosity and allele sharing across a set of more than 30 polymorphic markers covering a genetic distance of 2.2 cM.

Ultimately, the refinement possible by linkage analysis and haplotype identification is limited and at some point, in the absence of obvious candidates, systematic sequencing of genes in the critical region will be necessary.

It is worth remembering that our data suggest at least 1 other locus exists for Aicardi-Goutières syndrome. It is possible that, complementing any new linkage data, identification of the AGS1 gene may allow for the isolation of other responsible genes either by homology, involvement in a defined biochemical pathway or the demonstration of a protein-protein interaction using yeast-two hybrid technology.

The identification of genes involved in Aicardi-Goutières syndrome will allow us to assess the effects of particular types of mutation on phenotypic expression of the disease. Additionally, it may be possible to identify differences between patients with mutations in the AGS1 gene and those with disease due to mutations in other genes. We consider it possible that Aicardi-Goutières syndrome and pseudo-TORCH syndrome are allelic disorders. Identification of the AGS1 gene will allow us to explore this hypothesis further, and potentially provide a molecular basis for classifying these disorders. We will also work toward the development of a clinical service in an NHS diagnostic laboratory.

Our recent genetic mapping studies have significantly refined the AGS1 critical region to a small genomic interval. In view of the rapid advances in human genomics, this should readily permit cloning of the AGS1 gene. Our large cohort of patients will facilitate identification of pathogenic mutations and the exploration of potential phenotype-genotype correlations. Such studies should provide exciting insights into

IFN-α metabolism and the pathogenesis of a variety of genetic and non-genetic childhood encephalopathies.

References

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