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HUMAN DISEASE

Rare disease mapped from just three cases

A remarkable study has pinpointed the gene involved in a rare form of epilepsy using data from only three affected individuals.

Action myoclonus-renal failure syndrome (AMRF) is a very rare, recessively inherited form of epilepsy that is accompanied by kidney failure. Berkovic and colleagues began their investigation with three cases of AMRF in unrelated families. In one case (case A), the parents of the affected individual were first cousins, whereas the other two families (of cases B and C) were not known to be consanguineous.

The authors reasoned that the gene responsible for AMRF would be expected to lie in a region of extended homozygosity in the consanguineous family. Using a 50K SNP array, they identified 21 regions for which genotyping of the affected family member suggested homozygosity by descent (HBD). These candidate regions were then narrowed down by looking at pairs of affected and unaffected siblings in all three families and eliminating or trimming down regions for which any sibling pair were likely to be identical by descent (IBD) on both chromosomes. This left 12 regions, with an average length of 6.2 cM.

If a single causal mutation had arisen in a particular population (which is possible, given the rarity of AMRF), inbreeding must have occurred at some point in the family history of cases B and C to result in homozygosity. This scenario gave the authors two approaches to narrow down candidate regions. First, they assumed that the parents were second cousins, redrew the pedigree accordingly, and looked for regions with evidence of HBD. Second, they assumed that for the region surrounding the mutation, affected individuals should be homozygous for all SNPs in the relevant haplotypes. Only 2 of the 12 candidate regions fulfilled these criteria. Finally, the critical region was narrowed down to one region on chromosome 4, ruling out the other chromosome using microsatellite markers to disprove HBD.

Berkovic and colleagues now had 66 candidate genes in a region of 6.6 Mb. Because AMRF is recessive, they hypothesized that the disease might be caused by reduced levels of mRNA, and therefore used expression microarrays to look for transcripts that are downregulated in lymphoblastoid cell lines of cases as compared with unaffected siblings. The most promising candidate was the gene *SCARB2* (scavenger receptor B2), and sequencing revealed *SCARB2* mutations that are predicted to result in a truncated protein in all three affected individuals. Further evidence that the casual gene had been identified came from the finding of *SCARB2* mutations in unrelated AMRF families.

Serendipitously, mice that are deficient for *Limp2*, the homologue of *SCARB2*, were already available. These mice show some overlap in phenotype with AMRF, and should provide a useful system to further investigate the role of *SCARB2*, which encodes an abundant lysosomal membrane protein, in the pathology of the disease.

The success of this study highlights how combining a range of genetic tools with clever detective work can be put to use for diseases that might otherwise remain obscure at the molecular level. Similar strategies should prove useful for mapping the genes underlying other rare monogenic disorders.

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ORIGINAL RESEARCH PAPER Berkovic, S. F. *et al.* Array based gene discovery with 3 unrelated subjects shows SCARB2/LIMP-2 deficiency causes myoclonus epilepsy and glomerulosclerosis. *Am. J. Hum. Genet.* 28 Feb 2008 (doi:10.1016/j.ajhg.2007.12.019)