Medical genetics: advances in brief

Identification of mutations in the duplicated region of the polycystic kidney disease 1 gene (PKD1) by a novel approach

Autosomal dominant polycystic kidney disease (ADPKD) has an incidence of 1 in 1000 and frequently leads to chronic renal failure by late middle age. It is genetically heterogeneous, with about 85% of families linked to the PKD1 gene on chromosome 16, which was cloned in 1994. The gene covers 52 kb of genomic DNA in 16p13.3 and contains 46 exons. The protein product, polycystin, is thought to be an integral membrane protein with a large extracellular region and multiple transmembrane domains. Mutation detection in PKD1 has proved difficult because most of the PKD1 gene lies in an intron of DNA which is repeated several times elsewhere on the same chromosome. The technique of denaturing gradient gel electrophoresis also encodes three genes (the HGL occipital) which show about 97% homology with the first 32 exons of PKD1. The degree of homology between PKD1 and the HGL regions means that both are visualised simultaneously when analysed by hybridisation, PCR, or reverse transcription PCR (RT-PCR) methods. As a result, the first 16 mutations characterised in PKD1 were clustered in the 14 exons at the 3' end encoded by single copy DNA. The authors have developed a novel anchored reverse transcription PCR (RT-PCR) approach to amplify specifically duplicated regions of PKD1, using a primer situated within the silent copy region and one within the reiterated area. They have screened 100 patients for more than half of the PKD1 exons (exons 22-46=57% of the coding region), including 11 (exons 22-32) within the duplicated gene region by use of the protein truncation test (PTT). Sixty of the patients were also screened for missense changes by use of the non-isotopic RNase cleavage method in exons 23-36. Eleven mutations were identified, six within the duplicated region, and there were three stop mutations, three frameshift deletions of a single nucleotide, two splicing defects, and three possible missense mutations. One mutation had previously been described elsewhere, but no mutation hot spot was identified. The authors suggest that the nature and distribution of the mutations, plus the lack of a clear phenotype-genotype correlation, suggest that they may inactivate the molecule. Certainly the method described is likely to prove very useful for mutation detection, and it may not be long before the whole gene can be screened efficiently and effectively.

FRANCES FLINTNER

Extensive DNA deletion associated with severe disease alleles on spinal muscular atrophy homologues

Significant steps towards understanding the molecular pathology of spinal muscular atrophy were taken in 1995, with the recognition that deletions of two genes, survival motor neurone (SMN) and neuronal apoptosis sensitive protein (NASSP), were associated with the condition. Both genes exist in multiple copies on chromosome 5q. The observation that the telomeric copy of SMN (SMN-T) is homozygously deleted in 90% of all cases of SMA, whereas deletions of NASSP and a third gene, basal transcription factor 44 (BTF2p44), are preferentially homozygously deleted in the most severe form of SMA, have led to the hypothesis that deletion of SMN-T is the primary cause of SMA, but that deletions of other nearby genes may influence disease severity. This paper tests that hypothesis by determining the extent of gene deletions in three unrelated, multigenerational families, each with one mildly and one severely affected member. Deletion assays for SMN, NASSP, BTF2p44, and a partially characterised cDNA clone which maps to the same region, C21, were carried out, and in each family the more severely affected member had more extensive homozygous deletions. Haplotyping was carried out, to identify firmly maternal and paternal homologues. In each family, both affected members shared one haplotype, so any variation in disease severity was likely to be determined by the other unshared haplotype. The hypothesis that one particular mildly affected subject had a “severe” disease homologue, with an extensive deletion, and a second “mild” disease homologue, with a small deletion, was confirmed using human-hamster somatic cell hybrids haploid for that subject’s chromosome 5q. This person transmitted the “severe” homologue to her severely affected son, whose paternally derived homologue also contained an extensive deletion. Thus, results in this small series of families support the notion that SMA disease severity is associated with the extent of homozygous deletion. The mechanism of this apparent relationship between three separate genes is as yet obscure and is discussed by the authors, as is the sensible suggestion that these results be confirmed in other families.

EVAN REID

High frequency of apolipoprotein E ε2 allele in haemorrhage due to cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is responsible for 10-15% of spontaneous cerebral haemorrhages in the elderly and CAA related haemorrhage appears not to share the avoidable risk factors associated with other types of stroke. Haemorrhage in CAA is caused by rupture of blood vessels whose walls are laden with a type of amyloid β-protein which is very similar in structure to that found in Alzheimer’s disease (AD). It is not surprising that relationships have been found between CAA and ApoE genotype, with ApoE ε4, the ApoE allele associated with AD, also being associated with CAA. Nicoll et al examined ApoE genotypes in 36 subjects with pathologically confirmed CAA related haemorrhage, 17 of whom had concomitant AD, and 104 controls, comprising 61 patients with AD and 43 elderly with no history of dementia and no AD pathology. Patients with CAA related haemorrhage and AD had a similar frequency of ApoE ε4 to AD controls. However, the ApoE ε4 frequency in patients with CAA related haemorrhage without AD pathology was lower than in controls lacking both AD and haemorrhage, suggesting that ApoE ε4 is not an independent risk factor for CAA related haemorrhage. On the other hand, the ApoE ε2 frequency in patients with CAA related haemorrhage was increased, whether they had concomitant AD or not. These data suggest that ApoE ε4 is not directly associated with CAA related haemorrhage, but that ApoE ε2 is. The authors suggest a potential model to explain these findings, taking into account the previously described association between ApoE ε4 and CAA. They postulate that the ApoE ε4 allele may be associated with deposition of vascular amyloid, but that ApoE ε2 is associated with vascular rupture and CAA related haemorrhage.

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