Medical genetics: advances in brief

Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM1 loci

Kajwara K, Berson EL, Dryja TP. *Science* 1994;264:1604-8.

Retinitis pigmentosa (RP) has a prevalence of 1 in 5000 in the UK and is a significant cause of blindness by middle age. RP is highly heterogeneous with autosomal recessive, multiple autosomal dominant, and at least two X linked forms of inheritance. These authors began with a missense mutation of the peripherin/RDS photoreceptor gene in three RP families. As the mutation did not consistently co-segregate with the disease, the authors chose to screen the ROM1 gene whose homodimer protein products complex with those of the peripherin/RDS gene. By means of single strand conformational polymorphism two different ROM1 mutations were found in the three families. Affected persons could be clearly distinguished from unaffected patients by their electroretinograms and were each found to have heterozygous mutations of both genes. Evidence of RP was not found in heterozygotes for the ROM1 mutations only. The peripherin/RDS gene has already been mapped to chromosome 6 and the ROM1 gene to chromosome 11. Thus these families provide evidence of RP resulting from the failure of two unlinked mutations to complement each other. It will be fascinating to discover how often such a digenic model can account for unusual patterns of inheritance in RP and other diseases.

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Association of idiopathic venous thromboembolism with single point-mutation at Arg⁵⁰⁶ of factor V

Voorberg J, Roelse J, Koopman R, *et al.* *Lancet* 1994;343:1535-6.

Linkage between inherited resistance to

activated protein C and factor V gene mutation in venous thrombosis

Zoller B, Dahlback B. *Lancet* 1994;343:1536-8.

Resistance to activated protein C (APC) is associated with thrombophilia, APC resistance in the population being approximately 5% as compared to a prevalence of 30-40% in patients with a history of idiopathic thrombosis. Similarly, more than 50% of families with thrombophilia show APC resistance. Preliminary evidence had suggested that the abnormal response might be a function of coagulation factor V. These two reports strengthen this association and expand on the relationship between APC resistance and factor V. Zoller and Dahlback investigated a pedigree with familial thrombophilia to see whether APC resistance might be caused by mutations in the factor V gene resulting in loss of anticoagulant activity of factor V or in increased resistance to APC. No recombinants were observed between 14 APC resistant persons in the pedigree and the factor V locus on 1q21, resulting in a lod score of 3.9. Voorberg *et al* investigated 27 consecutive, unrelated patients with idiopathic thromboembolism. The factor V gene was amplified from peripheral lymphocyte derived DNA and direct sequencing undertaken. Ten of the 27 were found to have the same heterozygous point mutation resulting in a Gln to Arg⁵⁰⁶ substitution. Eight of these 10 patients were APC resistant, while only one case with the wild type genotype had APC indices in the resistant range. The suggestion from Voorberg *et al* that APC resistance reflects failure to activate factor V anticoagulant activity is enhanced further by Zoller and Dahlback's finding of the same point mutation in their familial cases. However, molecular heterogeneity for APC resistance also emerges in their report as a result of APC resistance in "married in" patients who are phenotypically APC resistant but do not show the same point mutation.

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Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome

Reardon W, Winter RM, Rutland P, *et al.* *Nature Genet* 1994;8:98-103.

The molecular defects underlying the autosomal dominant craniosynostoses until recently have remained largely undefined. Mutations have been reported in only one type, the Boston type. Saethre-Chotzen has been localised to chromosome 7p by linkage and cytogenetic studies. Crouzon syndrome is one of the most distinctive of the dominant forms of craniosynostosis and has previously been mapped to chromosome 10q25-q26. In this study of Crouzon syndrome patients mutations have been defined in the fibroblast growth factor receptor 2 gene (FGFR2). Initially transcription factor genes such as PAX 2, mapping to the same region 10q, have topped the list of candidate loci. The authors however noted that the human FGFR2 gene has two alternate gene products; one of these, Bek (Bacterially expressed kinase), is known in murine models to be preferentially expressed in osteogenesis. In humans Bek differs from its other isoform by only a 49 amino acid sequence spanning the second half of the third Ig loop in the extracellular region. The authors detected sequence alterations using SSCP in nine out of 20 familial and sporadic cases of Crouzon syndrome but in none of the 178 controls. Seven of the nine mutations alter amino acids (usually a cysteine) in the third Ig domain. The other two mutations are silent nucleotide changes which are postulated to affect gene splicing. No evidence is seen for heterogeneity and it is being suggested that mutations elsewhere in the FGFR2 gene are responsible for the outstanding cases. The authors point out that the significance of the fibroblast growth factor receptor gene family is emphasised by the involvement of FGFR2 in Crouzon syndrome and also by recent reported mutations in the trans-membrane domain of FGFR3 causing achondroplasia.

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