

MEDICAL GENETICS: ADVANCES IN BRIEF

Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction

Cambien F, Poirier O, Lecerf L, *et al.*
Nature 1992;359:641-4

Angiotensin converting enzyme (ACE) plays a key part in the renin-angiotensin and kallikrein-kinin systems and is widely distributed in vascular endothelial cells: the efficacy of ACE inhibitors in treatment of cardiovascular disease suggests that genetic variation in ACE might be a factor in disease susceptibility. Although genetic linkage of ACE to hypertension susceptibility in the rat was recently shown, similar studies in humans have been negative. Cambien *et al* have now found a significant relationship between an insertion/deletion (I/D) polymorphism in the ACE gene and occurrence of myocardial infarction (MI) in a multi-centre case-control study. The DD genotype (previously shown to be associated with raised ACE levels) carried a 1.34 fold increased risk of MI, compared with the ID and II genotypes; in a 'low risk' subgroup (non-obese, low apo B level), the relative risk rose to 3.2. These preliminary results imply a substantial (8%) overall contribution of genetic variation in ACE to MI susceptibility, raising many important questions. Is the I/D polymorphism itself responsible for the susceptibility, or simply in linkage disequilibrium with another determinant? Does the DD genotype define a subgroup responsive to ACE inhibitor therapy? If so, should population based genetic screening be contemplated? Much further careful groundwork will be required before the last question can be properly addressed.

ANDREW WILKIE

The genetic basis of epidermolytic hyperkeratosis: a disorder of differentiation-specific epidermal keratin genes

Cheng J, Syder AJ, Qian-Chun Y, Letai A, Paller AS, Fuchs E. *Cell* 1992;70:811-19.

A leucine proline mutation in the H1 subdomain of keratin 1 causes epidermolytic hyperkeratosis

Chipev CC, Korge BP, Markova N, *et al.*
Cell 1992;70:821-8.

Epidermolysis bullosa simplex (EBS), an autosomal dominant condition characterised by tonofilament clumping and disruption of basal cell integrity, has recently been shown to result from mutations in the rod domain of keratin 5 (K5) or keratin 14 (K14) genes. Epidermolytic hyperkeratosis (EH) is another autosomal dominant condition that is characterised by ultrastructural changes similar to EBS and disruption of spinous and granular cell layers of epithelium. These two papers report the identification of EH patient specific mutations in genes coding for the

terminal differentiation keratins 1 (K1) and 10 (K10). Interestingly, two of the mutations reported by Cheng *et al* affected a highly conserved arginine residue in the rod domain; this same residue has been previously shown to be mutated in K14 in three EBS patients. Furthermore, the keratin network in keratinocytes transfected with a vector carrying a fragment encompassing this mutation showed a pattern characteristic of both EBS and EH. The identification of the same K14 mutation in five out of nine EBS and EH patients suggests that this amino acid is critical for structural integrity. The K1 mutation identified by Chipev *et al* was also shown to affect the structural integrity of the keratin filaments. Further characterisation of the molecular pathology of these disorders should yield interesting and vital information about the function of the keratins.

N S THAKKER

Omission of exon 12 in cystic fibrosis transmembrane conductance regulator (CFTR) gene transcripts

Slomski R, Schloesser M, Berg LP, *et al.*
Hum Genet 1992;89:615-9.

The phenomenon of exon skipping and aberrant differential splicing of gene transcripts has previously been reported for a number of genes, including the cystic fibrosis gene. This paper describes the characterisation of CFTR mRNA transcripts isolated from both expressing and 'non-expressing' cell types in normal subjects using PCR rounds of nested primer sets. The investigators found that in nearly half the healthy controls a surprisingly high proportion of the CFTR mRNA transcripts (79 to 87%) lack exon 12, which encodes part of the first nucleotide binding fold domain of the CFTR polypeptide. The total lack of normal transcript in one healthy control would suggest, as the authors indicate, that caution is needed when interpreting such quantitative PCR data. However, on repeated analysis, the proportions of aberrant to normal transcripts remained constant for given subjects. It appears that at least for cystic fibrosis the normal clinical phenotype can be maintained by minimal amounts of correctly expressed CFTR, an encouraging finding for the future success of corrective gene therapy.

JOHN F HARVEY

Incidence and expression of the N1303K mutation of the cystic fibrosis (CFTR) gene

Osborne L, Santis G, Schwarz M, *et al.*
Hum Genet 1992;89:653-8.

In this paper 56 authors from 30 institutions have combined to present data on 216 CF

patients with one or more N1303K mutations. They establish N1303K as the fifth most common CF mutation accounting for 1.5% of all CF chromosomes. However, the frequency is significantly lower in northern Europe in contrast with southern Europe where the frequency is above 5% in southern Italy and Turkey. In the 53/58 patients so far investigated, the mutation has occurred against a single haplotype background but three other haplotypes have already been identified. The pancreatic phenotype is severe with insufficiency recorded in 97/102 patients on whom the information was available. By contrast, the severity of pulmonary disease was highly variable and presence of N1303K does not predict the severity of the pulmonary phenotype even among the 10 homozygotes. It is interesting that despite the fact that the N1303K and ΔF508 mutations probably occur in different nucleotide binding folds, the phenotype of the ΔF508/N1303K patients was similar as a group to that of the N1303K/N1303K homozygotes. The authors recommend the inclusion of this mutation in heterozygote screening programmes even in northern Europe where the mutation is less frequent.

JOHN C K BARBER

Deletions within chromosome 22q11 in familial congenital heart disease

Wilson DI, Goodship JA, Burn J, Cross IE, Scambler PJ, *Lancet* 1992;340:573-5.

The fortuitous observation of an interstitial deletion within 22q11 in three members of a sibship, all of whom had different forms of congenital heart disease, led Dr Wilson and colleagues to investigate whether this principle might apply to families with recurrence of this group of disorders. Analysis of 22q11 in nine families where more than one member have documented structural heart disease is reported in this paper. The clinical and echographic documentation of the nature of the heart lesions is outstanding, representing an example to which all workers in the area should aspire. Chromosome 22q deletions were found in five of the nine families. In four of these five, one or other parent had a cardiac abnormality, but in the fifth family both parents were clinically normal, although the same deletion was found in the father as in his three affected children. Of particular note is the observation in the four non-deleted families that the parents were clinically normal while the children had identical heart defects. Compared with the phenotypic variability seen in clinical expression in the five deleted cases, this phenotypic stability is very striking. A possible explanation for these observations might be that the 22q11 locus mutation is stable in non-deleted families and unstable in deleted families, varying from generation to generation.

W REARDON