MEDICAL GENETICS: ADVANCES IN BRIEF

Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis

Zabner J, Coutre LA, Gregory RJ, Graham SM, Smith AE, Welsh MJ. *Cell* 1993;75:207-16.

The feasibility of transfer of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and correction of the chloride ion (Cl^-) transport defect has previously been shown both in vitro and in CF transgenic mice. This paper reports transfer of the CFTR gene to the nasal epithelia of three CF patients using an adenovirus vector in which the early region 1 (E1A) genes were replaced by CFTR cDNA. The application of virus using a plastic applicator resulted in transient inflammation but these changes appeared to be related to the procedure rather than because of the virus. Although CFTR transcripts could not be detected by RT-PCR, measurement of the voltage across the nasal epithelium showed a functional correction of the Cl^- transport defect with a decrease in the basal voltage and restoration of normal response to cAMP agonists. With regard to safety, virus replication was not observed and there was no clinical evidence of adenovirus infection. However, restoration of replication potential could occur by acquisition of E1A DNA through coinfection or recombination with E1A containing adenovirus. The patients in this study were assessed before the study and were shown to lack endogenous E1A DNA and nasal swab cultures were negative for adenovirus. Whether similar criteria have to be fulfilled for future patients remains to be elucidated. Although further questions about vectors, delivery systems, and safety need to be addressed, this study is an important step in the development of gene therapy for cystic fibrosis.

N S THAKKER

Molecular analysis and clinical correlations of the Huntington's disease mutation

MacMillan JC, Snell RG, Tyler A, *et al.* *Lancet* 1993;342:954-8.

Huntington's disease (HD) has now been positively correlated with a CAG expansion in the IT15 gene on chromosome 4 in most affected subjects. MacMillan *et al* now present data from 449 patients with a clinical diagnosis of HD and 1160 normal chromosomes and confirm the specificity of this procedure as a positive test. In fact, on the data presented, false positive results are more likely to be the result of procedural error or sample mix up. The data also confirm the sensitivity of the expansion test for the diagnosis of HD, both in the familial form and the clinically more difficult sporadic case situation. As with other studies, a poor correlation emerges between the clinical phenotype and the degree of molecular abnormality. Neither does age at onset correlate closely with repeat size. This is a paper which clinical geneticists and all other professionals charged with responsibility for the management of HD will warmly welcome, as it emphasises the benefits and some possible pitfalls of this diagnostic test. Data on such a large, well defined, and meticulously

documented patient cohort should help avoid the learning curve which might otherwise attend the use of this diagnostic test in clinical practice.

W REARDON

Normal phenotype with paternal uniparental isodisomy for chromosome 21

Blouin JL, Avramopoulos D, Pangalos C, Antonarakis SE. *Am J Hum Genet* 1993;53:1074-8.

Uniparental disomy (UPD) occurs when a person inherits two homologous chromosomes (or chromosome segments) from the same parent. In uniparental isodisomy, the two chromosomes are genetically identical because they are derived from a single, parental chromosome. The most likely mechanisms for UPD include fertilisation of a nullisomic gamete by a disomic gamete; postzygotic loss of a chromosome in a conceptus which was originally trisomic; or compensatory duplication in a monosomic cell. Several genetic diseases have been associated with UPD for different chromosomes because of homozygosity of recessive alleles, parentally imprinted genes, or a combination of both mechanisms. For example, UPD of chromosome 7 has led to cystic fibrosis, and parental imprinting on chromosome 15 is responsible for abnormal phenotypes in Prader-Willi and Angelman syndromes. Blouin *et al* report their study of a family which was ascertained when a child presented with features of Down's syndrome and was found to have a Robertsonian translocation t(21q;21q). The child's parents were karyotyped and the father (who was phenotypically normal) was found to have a de novo dup(21q). (The paternal grandparents had normal chromosomes.) The genotypes of 17 polymorphic loci on chromosome 21q were studied in DNA from the child's father and paternal grandparents. The father was homozygous for one paternal allele with all the markers typed, and additional data showed the absence of maternal alleles. These results suggest paternal uniparental isodisomy. The absence of any unusual clinical features owing to parentally imprinted genes on human chromosome 21 suggests that UPD for other human chromosomes might also not be associated with human disease.

F FLINTER

Inversions disrupting the factor VIII gene are a common cause of severe haemophilia A

Lekich D, Kazazian HH, Antonarakis SE, Gitschier J. *Nature Genet* 1993;5:236-41.

This paper solves very elegantly a puzzling conundrum. Whereas factor VIII (F8) mutations could be identified in virtually all cases of mild or moderate haemophilia A, in severe disease only about half were accounted for after careful scanning of the complete exon sequence and the intron-exon boundaries. This led to suggestions that the "missing" mutations might lie in promoter or intron sequences, or even that

a tightly linked F8 control factor was involved. Lakich *et al* integrated two seemingly disparate observations to reach the correct answer. First, the largest F8 intron, between exons 22 and 23, contains two other genes, F8A and F8B: two additional copies of F8A exist (in inverted orientation) about 500 kb telomeric of the F8 gene. Second, Gianelli's group had shown that in some severe haemophilia A patients it was impossible to amplify cDNA using primers between exons 22 and 23, even though all the F8 exons appeared structurally intact. The explanation seems to be that an intrachromosomal recombination between the intron 22 F8A gene and one of the inverted extragenic F8A sequences generates a rearrangement in which no genetic material is gained or lost, but the F8 gene is split into two and is non-functional. Such inversions may account for around 40% of severe haemophilia, and paradoxically are easily demonstrated by Southern blotting: their detection is therefore likely to become a first line screen during F8 gene mutation analysis. Similar mechanisms should be considered in other genes with a high mutation rate and "missing" mutations, such as the neurofibromin gene.

ANDREW WILKIE

A mutation in the homeodomain of the human MSX2 gene in a family affected with autosomal dominant craniosynostosis

Jabs EW, Müller U, Li X, *et al.* *Cell* 1993;75:443-50.

Craniosynostosis, premature fusion of calvarial sutures and consequent skull shape abnormality, commonly occurs as a sporadic isolated anomaly. However, syndromal craniosynostosis also occurs and is often seen in autosomal dominant conditions such as Crouzon syndrome, Apert syndrome, etc. This paper reports the cloning and characterisation of the human homeobox gene MSX2 on chromosome 5qter and detection of a missense mutation in a highly conserved region of the gene in a family with craniosynostosis Boston type. This autosomal dominant condition is characterised by high penetrance and variable expression with anomalies ranging from frontal orbital recession to trilobular shaped skull. Expression of MSX2 during skeletogenesis in embryonic mice was shown to be consistent with an aetiological role in craniosynostosis; transcripts were detected in membranous bone of calvaria and in adjacent mesenchymal cells in the regions of the sutures. Secondary abnormalities in the craniosynostosis family, for example, shortened metatarsals and cleft of the soft palate, were also consistent with the known expression of MSX2. Linkage and mutation analysis failed to show association of MSX2 with Crouzon, Jackson-Weiss, Pfeiffer, and Apert syndromes. Function of MSX2 is unknown. Previous tissue expression and tissue recombination studies suggest MSX2 expression may be associated with inductive tissue interactions. Investigation of interaction of MSX2 with other genes involved in calvarial morphogenesis may help identify candidate genes for other conditions with craniosynostosis.

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