J Med Genet 1992; 29: 138–139

MEDICAL GENETICS: ADVANCES IN BRIEF

Comments on important genetic topics from papers in other journals

The molecular basis of the undulated/Pax-1 mutation

Chalepakis G, Fritsch R, Fickenscher H, Deutsch U, Goulding M, Gruss P. *Cell* 1991;**66**:873–84.

The mouse Pax gene family all code for a protein domain, the paired box, originally identified in the *Drosophila* mutation Paired. It is a DNA binding element important in gene regulation and embryonic pattern formation, similar in many ways to the homeobox. Pax-1 is expressed in the segmented prevertebral column from day 9 in the mouse embryo, and later in the thymus and sternum. Pax-1 maps to mouse chromosome 2, near to the *un* (undulated) locus. Undulated mutants show abnormal development of the vertebral column and sternum, and have alterations in Pax-1. In this paper the authors show that the DNA sequence change in one *un* mutant, which results in a glycine→serine replacement in a highly conserved region of the molecule, changes the DNA binding activity of the Pax-1 protein. Affinity for normal receptor sequences is greatly reduced, consistent with a recessive loss-of-function mutation. In addition, the affinity for certain other sequences is much increased, suggesting there may also be dominant gain-of-function effects. Since human counterparts are known for this and some other Pax genes, it is clear that this represents an important avenue of investigation into human dysmorphic syndromes.

ANDREW READ

Obstructive sleep apnoea in children with Down syndrome

Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Davidson Ward SL. *Pediatrics* 1991;**88**:132–9.

Pulmonary hypertension in the absence of congenital heart disease is a well recognised complication in children with Down's syndrome. Obstructive sleep apnoea syndrome (OSAS) has been suggested by several authors as a cause for this phenomenon. In an attempt to estimate the frequency of OSAS in Down's syndrome, Marcus *et al* have used non-invasive recording of chest wall movements, heart rate, end tidal PO_2/PCO_2 and arterial saturation during sleep in 53 subjects. The results showed almost half of the subjects had obstructive apnoea during daytime naps and 32% had periods of arterial desaturation. Only 16 children had overnight studies but these were found to be abnormal in every case (63% had obstructive apnoea and 56% became arterially desaturated). Tonsillectomy and adenoidectomy were performed on eight of the children during the study period. Most showed a significant postoperative improvement although only three had completely normal recordings. Although the aetiological link between OSAS and unexplained pulmonary hypertension in Down's syndrome has still to be made, OSAS does seem to be a significant and potentially treatable complication of Down's syndrome.

DAVID FITZPATRICK

Prospects for homologous recombination in human gene therapy

Vega MA. *Hum Genet* 1991;**87**:245–53.

There will always be the new mutant, the sporadic, and the index case and therefore a role for gene therapy. In this review, Manuel Vega explores the possibility of using recombination between endogenous chromosomal DNA and artificially introduced homologous sequences. This approach has already been used for the correction of mutations in the HPRT gene in mice, but is in general hampered by the low frequency with which homologous recombination occurs. The greater efficiency of a retrovirus as vector for sequences that are integrated into the genome to complement existing deficiencies has therefore received greater support. However, Vega illustrates the advantages of the homologous recombination approach. For instance, an affected gene should be corrected at its exact chromosomal locus with all its upstream regulating machinery in place. Ideally this should confer normal levels of expression, tissue specificity, and genetic stability. He nevertheless acknowledges the difficulties in delivering any sequence of choice to the appropriate tissue in vivo, but ends with the suggestion that reimplantation of corrected bone marrow stem cells from subjects with adenosine deaminase deficiency may provide a promising starting point. Neither of these approaches can reverse development that has already taken place, but this does not mean that some improvement in the condition of those suffering from genetic diseases may not be possible in the future.

J C K BARBER

Review of neonatal screening programme for phenylketonuria

Smith I, Cook B, Beasley M. *BMJ* 1991;**303**:333–5.

An attempt was made to review data from screening laboratories and paediatricians on all live births in the UK during 1984 to 1988. The proportion of infants tested approached 100%. The incidence of PKU was 11·7/100 000 births (445 subjects): 273 had classic PKU and three had defects of cofactor metabolism. One child with PKU was missed in the study period compared with three in 1979 to 1983 and six in 1974 to 1978. Seven of these subjects had been missed because of negative test results. All seven had been tested with the bacterial inhibition assay, although only 53% of all infants had been so tested ($p = 0{\cdot}017$). Eleven infants with classic PKU were not tested by 14 days of age and 23 (8%) did not start treatment until after 20 days. This is important because IQ falls linearly by one point for each week's delay in starting treatment. There were wide regional variations. Although the screening programme achieves high coverage and effectiveness, some children are still missed. A national or supraregional practice for screening may help. This review may have important organisational lessons for other neonatal screening programmes, such as that proposed for Duchenne muscular dystrophy.

A M NORMAN

GLI3 zinc-finger gene interrupted by translocations in Greig syndrome families

Vortkamp A, Gessler M, Grzeschik K-H. *Nature* 1991;**352**:539–40.

Little is known about the molecular basis of dysmorphic syndromes, except those associated with biochemical abnormalities. This paper identifies the gene disrupted in Greig syndrome, a disorder comprising craniofacial malformations and polydactyly; the gene, *GLI3*, may be a transcriptional regulator. Greig syndrome has been localised to chromosome band 7p13 both by linkage analysis and its association with microdeletions and translocations of this band. Vortkamp *et al* showed that the breakpoints of three balanced translocations fell within a 630 kb *Not*I fragment; as a short cut to the laborious task of 'walking' towards the breakpoints, the authors tried a 'candidate gene approach' using *GLI3*, a zinc-finger gene of the *GLI-Kruppel* family recently mapped to 7p13. Amazingly, two of the three translocations break within this gene, while the third breakpoint lies 10 kb downstream, and may disrupt expression by a *cis* acting effect. *GLI3* is expressed in many tissues, so how can disruption of this gene explain the localised (craniofacial, digits) abnormalities of Greig syndrome? The mutations only reduce *GLI3* expression by 50%, and it may be that some tissues respond to *GLI3* in a graded fashion (developing a morphogen gradient), others as an 'on-off' switch. Functional studies on the limb bud, a well developed experimental system, will be interesting.

ANDREW WILKIE