MEDICAL GENETICS: ADVANCES IN BRIEF

Comments on important genetic topics from papers in other journals

The molecular basis of the undulated/Pax-1 mutation

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 other Pax genes and is a candidate for certain other conditions, including aortic arch hypoplasia and congenital heart disease. It is involved in neural crest development and plays a role in the differentiation of the neural tube and the development of the vertebral column and sternum. Pax-1 maps to mouse chromosome 2, near to the X(a) (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 Pax-1 mutation 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

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 PO2/PCO2 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 arteriole desaturatated). Tonsillotomy and adenoidectomy were performed on eight of the children during the study period and 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 seems to be a significant and potentially treatable complication of Down’s syndrome.

DAVID FITZPATRICK

Prospects for homologous recombination in human gene therapy

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 would 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 be possible in the future.

J C K BARBER

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

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 7p14 by linkage analysis in this study. Vortkamp et al showed that the breakpoints of three balanced translocations fell within a 630 kb NorI fragment, with 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. Interestingly, 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 tissue responses 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