**Medical genetics: advances in brief**

Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients

Williams syndrome (WS) is recognised clinically when patients present with a variety of features including a characteristic dysmorphic appearance, supravalvar aortic stenosis (SVAS), mental deficiency, gregarious personality with "cocktail party" conversation, and idopathic infantile hypercalcaemia. Patients with WS have a submicroscopic deletion at 7q11.23, detectable by FISH, which causes allelic loss of elastin (ELN). The authors used a weighted scoring system to classify patients:

<table>
<thead>
<tr>
<th>Phenotypic feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical facial features</td>
<td>3</td>
</tr>
<tr>
<td>Mental retardation/developmental delay</td>
<td>1</td>
</tr>
<tr>
<td>SVAS</td>
<td>2</td>
</tr>
<tr>
<td>Non-SVAS congenital heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>2</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
</tr>
</tbody>
</table>

Patients with 4 to 10 points were classified as "classical" cases of WS, and patients with 0 to 3 points as "uncertain". Ninety-six percent of patients with "classical" WS (n = 114) had molecular cytogenetic deletions, whereas only 8% (9/114) of "uncertain" WS had a deletion. A further 42 cases analysed were not classified phenotypically, and 60% of these had a deletion. The final 40 cases studied were referred to the clinical cytogenetics laboratory to "rule out WS", and 38% of these had an ELN deletion, but no cytogenetic deletion on banded analysis. These results suggest that FISH can be very useful in providing confirmation of a clinical diagnosis, but the clinical scoring system used seems to have been very effective. The absence of a deletion on FISH analysis might indicate the need for clinical re-evaluation. One unresolved question at the moment is the question of whether or not the parental chromosomes should be routinely studied once a 7q deletion has been detected in a child. The recurrence risk for WS is very small, but experience from other microdeletion syndromes would suggest that parents can occasionally carry a translocation, or even be asymptomatic carriers of the same deletion. Perhaps with WS any sub pairs which do occur are more likely to be the result of germinal mosaicism.

FRANCES FLINTER

Multiple sites of anterior neural tube closure in humans: evidence from anterior neural tube defects (anecephaly)

This study of anterior neural tube defects tested the hypothesis that humans, like mice and experimental animals, have multiple sites of neural tube closure rather than the continuous "zipper-like" model of neural tube closure described in most embryology textbooks. Twenty fetuses and neonates with partial anencephaly (complete anencephaly would not provide the necessary information about closure sites) were ascertained and the rostral and caudal extents of the open neural tube defect were mapped onto a model cranium. The location of frequent closure defects was not the usual malformations that result in open neural tube defects. Four closure sites for the anterior neural tube were identified and these corresponded closely to the four sites which have been described in the mouse. Mouse studies suggest that the time period during which these multiple closures can be observed in mouse embryos is very short. This may be why the observations have not been made previously in humans although Van Allen et al. (*Am J Med Genet* 1993; 47: 723–43) have also reported on this phenomenon. Neural tube defects are common malformations and studies suggest that they may have multifactorial origin, having both a genetic and an environmental contribution. Known environmental agents which can influence neural tube closure include folic acid and valproic acid. This study suggests that two or more different mechanisms could give rise to neural tube defects, the first being failure of two closures to meet and the second failure of a single closure. There is certainly genetic variation in the pattern of neural tube closure as evidenced by inbred strains of mice with differing susceptibilities and the particular type of neural tube defect seen in single gene disorders such as the Walker-Warburg syndrome. Some environmental factors also influence one closure site preferentially, for example, infants with fetal valproate syndrome tend to have very low lumbar or spinal defects. Correlation of the site of neural tube defects with particular aetiology in this way, and clarification of the underlying mechanisms, could significantly influence counselling for recurrence risks and further our knowledge of possible modes of prevention.

JILL CLAYTON-SMITH

A single ataxia telangiectasia gene with a product similar to PI-3 kinase

It may at first seem surprising that the isolation of the gene for an obscure recessive disorder with an incidence of as little as 1 in 100 000 is the cause of enormous interest. Ataxia telangiectasia (AT) is, however, a severe condition with cerebellar degeneration, immune deficiency, and death frequently before the age of 20. In addition, sensitivity to radiation and increased risk of cancer are found not only in homozygotes but also among heterozygotes who constitute about 1% of the population and may therefore be one of the most numerous groups with an inherited predisposition to cancer. For instance, female heterozygotes have five times the risk of cancer than their normal counterparts. Having mapped the AT gene to a single contig from 11q, this consortium have gone on to use cosmids and YAC clones for exon amplification of possible coding sequences and hybrid selection of complementary DNA sequences from cDNA libraries. From these, a transcription map of the area was produced and a single cDNA clone containing half the gene sequenced. This clone identified a major 12 kb evolutionarily conserved transcript in all tissues examined. Frameshift mutations have subsequently been identified in 14 patients, eight of whom are homozygous and six compound heterozygotes. The protein sequence is a module of homology to the src-related protein tyrosine kinases with several characteristic features including cell cycle control, DNA repair, and the coupling of the two. Strongest similarity is to the mammalian phosphatidylinositol-3' kinase (PI-3 kinase) gene which is part of a pathway thought to be involved in maintaining brain cells and nuclearosomes arising from cleavage of chromatin before cell death. Both methods showed widespread apoptosis in both cystic and non-cystic nephrons of kidneys from people with autosomal recessive and autosomal dominant polycystic kidney disease as well as in the kidneys of pcy and cpc mice. In contrast, no evidence of apoptosis was detected in tissues of normal and abnormal kidneys from patients with non-cystic renal diseases. The capacity of polycystic kidney cells to undergo apoptosis was retained in vitro. This study shows for the first time that apoptosis is an important mechanism in the pathogenesis of polycystic diseases. In his commentary, Grantham discusses this previously unsuspected process in inherited renal cystic diseases and points out that its recognition opens up another avenue of exploration for potential therapeutic opportunities. It is a new and interesting path for genetic disorders that cause significant morbidity and premature mortality in the population. It also comes at a time when, after many years of searching, the PKD1 gene and its product polycystin have finally been fully characterised.

DAVID RAVINE
Gene transfer to primary chronic granulomatous disease monocytes


Chronic granulomatous disease is caused by mutations in the genes that encode the phagocyte specific enzyme system NADPH oxidase. This is composed of a number of subunits mostly coded for by autosomal recessive genes, except for gp91phox which is coded for by an X linked gene. Mutations in gp91phox account for about 60% of chronic granulomatous disease cases. Thrasher et al describe a method using an adenoviral vector to restore function to patient monocytes deficient in one particular subunit of the NADPH oxidase system (p47phox). The efficacy of the system was measured by the ability of the cells to reduce nitroblue-tetrazolium to blue staining formazan after stimulation with phorbol myristate acetate when they had been infected with the adenoviral vectors. The reaction occurs within about 24 hours. Cells from three patients were studied, one known to be deficient in the p47phox, the other two with unidentified molecular defects. The known p47phox deficient patient and one of the others showed restored activity in a proportion of the cells after the adenoviral infection. The normal controls showed full activity, and sham infected cells showed no correction. Western blotting of crude protein extracts from the two unclassified patients confirmed the absence of immunoreactive p47phox in one. The potential for such a technique in gene therapy is discussed. Adenoviral transduction cannot produce stable correction of dividing cells in contrast to retroviral vectors. However, such an adenoviral vector could be of value in the management of acute infections. More immediately this system could be developed to aid in the accurate diagnosis of the site of the molecular defect in chronic granulomatous disease. The requirement for only a small quantity of patient sample, and the specificity and speed of the assay ensure that there is much to recommend such an approach.

ANGELA BARNICOAT

FRAXE expansion is not a common etiological factor among developmentally delayed males


Expansion of a (CGG)n triplet repeat at FRAXE, a site at Xq28 distal to FRAXA, is reported to be associated with mild mental retardation. Three hundred developmentally delayed males who were negative for the FRAXA triplet expansion were screened for the FRAXE expansion. These patients had a wide range of intellectual or behavioural problems (including developmental delay, attention deficit disorder, and autism), but none was severely mentally retarded; 19/300 had low level fragile site expression cytogenetically at Xq27-q28. None of the 300 patients tested positive for the FRAXE expansion, suggesting that FRAXE is not a common cause of developmental delay. These data support the hypothesis that FRAXE is either very rare, or a benign fragile site which is not associated with a clinical phenotype, similar to the FRAXF and FRA16A sites.

FRANCES FLINTER

Cerebral artery stenoses in Williams syndrome


Ischaemic stroke and cerebral arterioopathy in Williams syndrome


Williams syndrome is a multisystem disorder in which the main clinical features are developmental delay, dysmorphic facial features, infantile hypercalcaemia, and a vasculopathy. It is caused by a microdeletion of chromosome 7q11.2 and affected patients have been shown to be hemizygous for the elastin gene locus within this region. Although supravalvular aortic stenosis is the most commonly described cardiovascular problem, many other areas of the arterial system including the pulmonary arteries and ascending and descending aorta may also be involved. The abnormalities usually consist of diffuse or localised arterial stenoses with vessel wall thickening. The microscopic appearance, termed medial fibroelastic dysplasia, shows marked medial wall thickening, hypertrophied smooth muscle cells, and variable disorganisation of elastin fibres in an ex cessive, loose collagenous stroma. These two reports confirm previous evidence of involvement of the cerebral arteries in Williams syndrome. They describe three Williams syndrome patients aged 22, 5, and 2 years who suffered strokes and chronic hemipareses owing to narrowing of the lumen of the cerebral arteries. In the two older patients an extensive collateral circulation had developed and there was arterial “blushing” as seen in Moyamoya disease. These abnormalities were well shown by magnetic resonance angiography. The onset of the cerebral infarction was heralded by increased irritability, lowered level of consciousness, and a prolonged focal seizure in one case. The oldest patient had chronic hypertension and had multiple episodes of cerebral infarction. All patients showed some improvement in their hemiparesis following the infarcts, one receiving treatment with aspirin. Stroke-like episodes owing to cerebral artery insufficiency have been described previously in patients with Williams syndrome but cerebral artery stenoses may be more prevalent than initially thought. They should be considered in Williams syndrome patients who suddenly develop an altered conscious level or instability. This observation may also have implications for dominant supravalvular aortic stenosis patients where the genetic defect has been shown to map to the same locus. Magnetic resonance angiography is a relatively safe diagnostic procedure which will prove useful for detection of cerebrovascular abnormalities. Perhaps it is also worth considering a diagnosis of Williams syndrome in subjects who present with Moyamoya disease. Mental retardation is sometimes associated with Moyamoya disease and hitherto has always been presumed to be the result of the cerebral infarction. This may not always be the case.

JILL CLAYTON-SMITH

A cystic fibrosis mutation associated with mild lung disease


While a number of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) have been associated with pancreatic sufficiency (R117H, R334W, R347P, A455E, and P547H), until now no particular mutation has been associated with mild pulmonary disease. The generally rare mutation A455E, first found in patients from the Saguennay-Lac St Jean region in northern Quebec, proves to be the second most common mutation causing cystic fibrosis in The Netherlands (3%). In addition to an association with exocrine pancreatic sufficiency, this mutation is associated with residual secretion of chloride in electrophysiological studies of rectal biopsy specimens. When compared with those homozygous for the AF508 mutation, those patients with the A455E mutation had an older mean age at diagnosis (15·0 ± 3·1 years). Forced expiratory volume in one second and forced vital capacity were significantly higher in the patients with the A455E mutation, and fewer were colonised with Pseudomonas aeruginosa (33·3% v 60·6%, p = 0·02). Because survival in cystic fibrosis is strongly correlated with the progression of pulmonary disease, the authors conclude that patients with cystic fibrosis who have the A455E mutation will have a better prognosis than patients homozygous for AF508.

DAVID RAVINE