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 idiopathic 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>Inginal 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%/5% of those with “classical” 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 sib pairs which do occur are more likely to be the result of germline 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 other 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 same as those of nondisjunctional malformations in mice. 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 their 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 deficits. Correlation of the site of neural tube defects with particular aetiologies 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

Apoptosis and loss of renal tissue in polycystic kidney diseases

Polycystic kidney disease—there goes the neighbourhood

The inherited polycystic kidney diseases are characterised by the enlargement of renal cysts, interstitial fibrosis, and gradual loss of normal renal tissue. In autosomal dominant polycystic kidney disease, cysts originate in less than 1% to 2% of nephrons. David Woo, noting that renal insufficiency would be surprising if the many non-cystic nephrons remained functional despite the presence of neighbouring cysts, evaluated the possibility that non-cystic nephrons in polycystic kidneys may be lost by apoptosis. Specific labelling of nuclear DNA fragmentation, a modification of the homopolymer tailed method, would detect the apoptotic nuclei. Agarose gel electrophoresis was used to search for DNA ladders of oligonucleosomes 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 pck mice. In contrast, no evidence of apoptosis was detected in the non-cystic renal tissues 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 concept that might provide us with a new avenue that could significantly increase and premature mortality in the population. It also comes at a time when, after many years of searching, the PKD1 gene and its protein product have finally been fully characterised.

DAVID RAVINE

A single ataxia telangiectasia gene with a product similar to P1-3 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 homoyzogotes 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 cosmid 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. Framed mutations have subsequently been identified in 14 patients, eight of whom are homozygous and six compound heterozygotes. The protein sequence is a monomer of homology to a new ATP-dependent tyrosine kinase and auto- and non-ATP relevant functions 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...
FRAE expansion is not a common etiological factor among developmentally delayed males

Expansion of a (CGG)n triplet repeat at FRAE, a site at Xq28 distal to FRAA, is reported to be associated with mild mental retardation. Three hundred developmentally delayed males who were negative for the FRAA triplet expansion were screened for the FRAE 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 FRAE expansion, suggesting that FRAE is not a common cause of developmental delay. These data support the hypothesis that FRAE 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 arteriopathy in Williams syndrome

Williams syndrome is a multisystem disorder in which the main clinical features are developmental delay, dysmorphic facial appearance, infantile hypercalcemia, 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 supravalvar aortic stenosis is the most common 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 fibroelastosis, shows marked medial wall thickening, hypertrophied smooth muscle cells, and variable disorganisation of elastin fibres in an excessive, 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 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 irritability. This observation may also have implications for dominant supravalvar 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 P474T), until now no particular mutation has been associated with mild pulmonary disease. The generally rare mutation A455E, first found in patients from the Saguenay-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 v 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