

therefore potentially preventing the cerebellar degeneration and ataxia which characterise AT. The identification of this gene makes it possible to confirm a diagnosis of AT, offer prenatal diagnosis to affected families, and identify heterozygotes. It should also now be possible to establish whether AT heterozygotes really do account for as many as 8% of all breast cancers, to quantify their risks more accurately, and to determine whether mammography should not be used on these patients because of their sensitivity to radiation.

JOHN C K BARBER

Gene transfer to primary chronic granulomatous disease monocytes

Thrasher AJ, Casimir CM, Kinnon C, Morgan G, Segal AW, Levinsky RJ. *Lancet* 1995; 346:92-3.

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

Allingham-Hawkins DJ, Ray PN. *Am J Hum Genet* 1995;57:72-6.

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

Kaplan P, Levinson M, Kaplan BS. *J Pediatr* 1995;126:943-5.

Ischaemic stroke and cerebral arteriopathy in Williams syndrome

Soper R, Chaloupka JC, Fayad PB, *et al.* *J Pediatr* 1995;126:945-8.

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 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 has 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 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

Gan KH, Veeze HJ, van den Ouweland AMW, *et al.* *N Engl J Med* 1995;333:95-9.

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 Saguenay-Lac St Jean region in northern Quebec, proves to be the second most common mutation causing cystic fibrosis in The Netherlands (3.0%). 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 ΔF508 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 ΔF508.

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