Medical genetics: advances in brief

Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome

Barrett and colleagues have undertaken a cross sectional case finding study of DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) or Wolfram syndrome in the UK. They describe the natural history, complications, prevalence, and inheritance of the condition. Cases were ascertained from various sources, and most were referred by more than one source. The authors estimate 1 in 770 000 of the population to be affected (about 70 patients in the UK). There were 29 index patients of whom three had consanguineous parents; 25% of sibs were affected. There was no maternal history of diabetes or deafness. Recessive inheritance is probable, although the gene encoded (recently mapped to 4p) may be for a mitochondrial protein. A carrier frequency of 1 in 354 is calculated. Fifty three per cent of patients had all four criteria for DIDMOAD. Most patients presented first with diabetes mellitus (around 6 years) and developed optic atrophy in their first decade. There was a low incidence of diabetic retinopathy and nephropathy in patients. Cranial diabetes insipidus and sensorineural deafness developed by about 20 years. Later complications included dilated renal outflow tracts and neurological abnormalities. Other complications included gastrointestinal dysmotility and primary gonadal atrophy in males with menstrual irregularity in females. Death was premature with a median age of 30 years, commonly from central respiratory failure with brain stem atrophy. The relationship of DIDMOAD to disorders of the mitochondrial genome is discussed. None of 18 patients tested in the study had the mitochondrial tRNA Leu (3243) mutation. It is suggested that carriers may be predisposed to maturity onset diabetes mellitus because of a family history in seven pedigrees. This is an excellent clinical review of DIDMOAD in the UK, clarifying the phenotype and natural history as well as confirming the mode of inheritance and providing a new estimate of prevalence.

ANGELA BARNICOAT

Mutations in the dystrophin-associated protein γ-sarcoglycan in chromosome 13 muscular dystrophy

That muscular dystrophy (MD) is heterogeneous is well established, but this paper is one of several which are beginning to pin down specific genetic defects underlying each particular type. Severe childhood autosomal recessive muscular dystrophy (SCARMD) is one progressive muscle wasting form which accounts for 10–50% of MD in North Africa and which members of this team had already mapped to chromosome 13. As dystrophin is itself part of a multiprotein complex which forms a bridge between the internal cell skeleton and the extracellular matrix, the genes encoding other proteins in the complex have become key candidates for other forms of MD. One of these, γ-sarcoglycan, turned out not only to map to 13q12 but also to contain a homozygous single base pair deletion in three familial and one sporadic case of SCARMD. This deletion creates a premature stop codon and immunostaining indicates that all three (α, β, and γ) sarcoglycan members of the dystrophin-glycoprotein complex are deficient as a result. In an accompanying perspective, Worton summarises the present position with mutation in six genes now implicated in MD. Apart from dystrophin itself, all are autosomal and include the three sarcoglycans, α-2 laminin which is associated with severe congenital MD, and calpain-3 which accounts for at least one form of limb girdle MD. In general, frameshift mutations in the sarcoglycan genes lead to autosomal recessive MD and non-frameshift mutations in the same genes result in the milder limb girdle MD. These results are naturally of immediate significance to MD families but are also an elegant illustration of the power of combining good biochemistry and genetics.

JOHN C K BARBER

Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence

The majority of families in which there are multiple cases of breast and ovarian cancer segregating in an autosomal dominant fashion have mutations in the BRCA1 gene on chromosome 17q. This paper attempts to calculate the gene frequency of BRCA1 and its contribution to overall breast and ovarian cancer incidence. The assumption is made that the excess risk of ovarian cancer in first degree relatives of breast cancer patients, and vice versa, are both entirely accounted for by BRCA1, and the BRCA1 frequency is calculated as 0.006. The proportion of breast cancer cases in the general population as a result of BRCA1 is calculated as 5–3% below 40 years, 2–2% between 40 and 49 years, and 1–1% between 50 and 70 years. The corresponding figures for ovarian cancer are 5–7%, 4–6%, and 2–1%, respectively. The authors conclude that the majority of breast cancer families with fewer than four cases, and no ovarian cancer, are not the result of highly penetrant genes such as BRCA1, which are rare, but either the result of chance or of more common genes which have a lower penetrance.

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