CAG repeats in SCA6. Anticipating new clues

Spinocerebellar ataxia type 6. Molecular and clinical features of 35 Japanese patients including one homozygous for the CAG repeat expansion

Clinical and molecular features of spinocerebellar ataxia type 6

Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations

Spinocerebellar ataxia type 6 (SCA6) is the most recent addition to the growing range of conditions associated with CAG trinucleotide repeat expansions, and the four papers above put some clinical flesh onto the bones of what is becoming a very interesting story. These reports and others indicate that, in most populations, SCA6 mutations are responsible for a significant minority of autosomal dominant cerebellar ataxia. The clinical syndrome associated with SCA6 mutations is of a relatively pure, late onset, slowly progressive, autosomal dominant cerebellar ataxia. It is not usually associated with the additional features characteristic of other cerebellar ataxias, although exceptions (3) make diagnosis by clinical means alone uncertain. The abnormal expansion has been detected in apparently sporadic cases of spinocerebellar ataxia and it is likely that such cases are the offspring of symptomatic parents. The SCA6 trinucleotide repeat is unique in its relatively small size and range, from 21 to 27 repeats. Like the other cerebellar ataxias, there is a striking correlation between trinucleotide repeat expansion size and age of onset of disease and, given the small range of abnormal alleles, this means that small increments in expansion size have very significant clinical effects. Perhaps because of the relatively small size of the expansion it appears to be relatively stable, with few instances of size increase recorded within families. The SCA6 expansion is located within a gene which codes for the α1 subunit of the voltage-dependent calcium channel gene. Point mutations in this gene are responsible for two other conditions, familial hemiplegic migraine (FHM) and episodic ataxia type 2 (EA2). FHM appears to be associated with missense mutations, while EA2 is associated with truncating mutations. Two clinical observations may be important in elucidating the molecular pathology of SCA6. Firstly, patients with homozgyous or compound heterozygous for the expanded allele tend to have an early age of onset or more severe disease, suggesting that a loss of function mechanism is more likely than a dominant negative effect. Secondly, early on in the clinical course of SCA6, some patients have features similar to EA2 which are superseded by the progressive ataxia. A tentative hypothesis to explain this is that the SCA6 expansion may have two separate effects, an initial interference with normal protein by function causing episodic ataxia-like features, and later neurodegeneration caused by a novel or toxic mechanism.

Evan reed

Is lifespan determined in utero?

The purpose of this review article is to explore the question of whether lifespan is determined in utero. Follow up studies of babies born in Herefordshire between 1911 and 1948 show that low birth weight in males (≤5.5 lbs) is associated with a threefold risk of NIDDM or impaired glucose tolerance at the age of 64, compared with those of high birth weight (≥9.5 lbs). This association is independent of current body mass index. The molecular etiology of such a correlation is uncertain, but it has been supported by similar studies carried out elsewhere in the world. The authors look further at the relationship between fetal growth, nutritional factors, and aging. As the major determinant of fetal growth is maternal nutritional status and poor fetal growth is associated with impaired glucose tolerance, obstructive pulmonary disease, and reduced bone mineral content, poor neonatal growth in the postnatal period may have a direct effect on lifespan. This has been called the “fetal origins hypothesis”. In animal studies of diet restriction during pregnancy, a growing body of evidence suggests that maternal undernutrition is associated with a range of adverse physiological effects in the offspring. These effects, such as reduced haemoglobin, raised blood pressure, and reduced pancreatic β cell mass, are also present in children who were born small for birth in the preweaning period. By contrast, studies of adult rodents and primates have shown that calorie restriction and other specific dietary interventions can prolong median and maximum lifespan and delay aging processes. The mechanism of this is unknown but alteration in metabolic rate, free radical production, and protein turnover have all been proposed. Thus, diet restriction seems to have opposite effects when operating in fetal or early postnatal life compared with later life. The authors review theories of aging which essentially condense into two groups; firstly that aging is genetically predetermined and secondly that it results from cumulative response to events over time. The “soma” theory combines these two and suggests that aging is the result of accumulation of defects in macromolecules (including DNA and tissue proteins such as collagen) and these occur because of limited capacity for maintenance and repair. There is less investment of nutritional resources in repair than is required for perfect maintenance and the result is aging. In the summary the authors suggest that inadequate nutrition in fetal life or infancy may impair the development of these repair processes and that this is a sustained effect. Obviously further work is needed and one way to begin could be to measure DNA repair capacity in terms of mutation rates of specific genes, telomere length, and DNA strand breaks. However, it is unlikely that one single approach will be able to answer this complex question and further epidemiological studies are likely to be important.

Sarah Slaney

A novel gene encoding an SH3 domain protein is mutated in nephropathies of juvenile type 1

A novel gene that encodes a protein with a putative src homology 3 domain is a candidate gene for familial juvenile nephropathies

Juvenile nephropathies (NPH), otherwise known as autosomal dominant kidney diseases, is a major cause of inherited chronic renal failure in childhood. The pathological hallmarks are small kidneys with disruption of the tubular basement membrane, interstitial lymphohistiocytic cell infiltrates, and the formation of cysts at the corticomedullary junction generally leading to end stage renal disease in adolescence. NPH may be associated with extrarenal abnormalities, including retinal dysplasia, hepatic fibrosis, cerebellar ataxia, and cone shaped epiphyses of bone, and this appears to reflect underlying genetic heterogeneity. Previous linkage studies have suggested that around 85% of the purely renal form is caused by a gene, NPH1, mapping to chromosome 2q13. Homozygous deletions of around 250 kb, involving a 100 kb inverted duplication within the region, have been detected in 80% of patients from NPH1 linked families and 65% of sporadic patients. These groups both report a novel candidate gene mapping within the deleted region, unrelated to any known gene families but exhibiting toxic effects. However, it is unlikely that this is the NPH disease gene. Both groups identified only one other gene within the deleted region. This has homology to the MAL gene which encodes a T lymphocyte maturation associated protein. Screening of all four exons by SSCP in the same patient group did not show any sequence changes (first report) and its potential contribution to the causation of NPH, if any, is not yet clear.

Louise Wilson