Medical genetics: advances in brief

CAG repeats in SCA6. Anticipating new clues

Zoghbi HY. *Neurology* 1997;49:1196-9.

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

Matsumura R, Futamura N, Fujimoto Y, et al. *Neurology* 1997;49:1238-43.

Clinical and molecular features of spinocerebellar ataxia type 6

Stevanin G, Dürr A, David GS, et al. *Neurology* 1997;49:1243-6.

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

Geschwind DH, Perlman S, Figueroa KP, et al. *Neurology* 1997;49:1247-51.

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 to this 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 asymptomatic 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 α_1 -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 homozygous 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 function causing episodic ataxia-like features, and later neurodegeneration caused by a novel or toxic mechanism.

EVAN REID

Is lifespan determined in utero?

Aihie Sayer A, Cooper C, Barker DJB. *Arch Dis Child (Fetal and Neonatal Edition)* 1997;77:F162-4.

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 Hertfordshire 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 lifestyle, not limited to cardiovascular disease, and 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 nutrition, and poor fetal growth is associated with impaired glucose tolerance, obstructive pulmonary disease, and reduced bone mineral content, poor nutrition in utero and 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 B cell mass, are also produced by diet restriction shortly after 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 collagens) 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 nephronophthisis type 1

Hildebrandt F, Otto E, Rensing C, et al. *Nat Genet* 1997;17:149-53.

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

Saunier S, Calado J, Heilig R, et al. *Hum Mol Genet* 1997;6:2317-23.

Juvenile nephronophthisis (NPH), otherwise known as autosomal recessive medullary cystic kidney disease, 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 sequence homology to src homology domain 3 (SH3). These domains regulate guanine nucleotide exchange factors of ras-like GTPases. The gene has at least 20 exons and was expressed weakly in kidney, heart, and pancreas but strongly in skeletal muscle in the first report. In NPH patients with hemizygous deletions, screening by SSCP was undertaken for mutations on the remaining allele. Point mutations predicted to be deleterious were detected in three patients by the first group on screening 18 of the 20 exons and two patients by the second group on screening 14 exons. The mutations segregated with the disease, were not found in the controls, and provide good evidence 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.

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