Effect of trinucleotide repeat length and parental sex on phenotypic variation in spinocerebellar ataxia 1

The autosomal dominant cerebellar ataxias (ADCA) are a group of late onset neurodegenerative disorders which primarily affect the cerebellum, but which are associated with other neurological abnormalities as well. ADCA type 1 (ADCA1) is characterised by progressive ataxia, ophthalmoplegia, extrapyramidal features, and peripheral neuropathies. There is genetic heterogeneity with at least three genes implicated: one on chromosome 6p (spinocerebellar ataxia, SCA1), one on 12q (SCA2), and one on 14q (SCA3 or Machado-Joseph disease). A repeated CAG trinucleotide sequence on 6p is selectively expanded in SCA1 patients; 98% of normal chromosomes contain <22 repeats, and one or more CAG trinucleotides in the repeat stretch. However, expanded genes invariably have uninterrupted CAG repeated sequences, a structure found only in normal chromosomes with <22 repeats (2% of chromosomes). This group reports DNA analysis in 64 subjects from 19 families with SCA1, 57 patients with SCA1, and seven subjects diagnosed post-symptomatically. In addition, 456 persons from 34 normal families from the CEPH reference panel were also studied. The authors report that the distributions of triplet repeat number on normal and SCA1 chromosomes are widely separated, with a gap of nine units, making predictive testing easier. The upper end of the normal range was 37 repeats, and the lower end of the abnormal range was 46 repeats. The data showed an unbalanced transmission of expanded alleles, according to the sex of the affected parent. Alleles with >54 repeats (17% of sample) were only transmitted by males. A small proportion of females, however, transmitted alleles which contracted slightly, by ≤6 repeats. Detailed clinical follow up of a subset of patients showed a significant correlation between increasing repeat number and an earlier age at onset, faster progression of the disease, and an earlier age at death. Finally, the authors conclude that the repeat number on the expanded chromosome could explain approximately two-thirds of the variation in age at onset in their series.

A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe Stb12.3: the first 2,233 cases

Fragile X mutations consist of longer expansion of this fragment, resulting from higher numbers of CGG repeats. Fragile X mutations are divided into premutations and full mutations. Premutations are unmethylated on the active X, generally <500 bp, and have no clinical effect. When a premutation is transmitted by a female, it has a high probability of being transformed into a full mutation, the risk of transition being proportional to the size of the premutation. Fragile X full mutations generally have >600 bp, and are associated with abnormal methylation of the surrounding CpG dinucleotides. Approximately 15% of those carrying a full mutation also have some premutations, and these persons have been called mosaics. Fragile X results from 318 families seen at 14 different centres have been compiled, but this number of cases was only slightly increased from 2253 persons was analysed with the probe Stb12.3, producing 909 normal results and 1344 with a fragile X mutation (693 full mutations and 651 premutations) in a total of 37 abnormal families, for example, non-methylated full mutations). The mental state of premutated persons did not differ from normal controls. Both the abnormal methylation of the FMR-1 Eagl site and the size of the expansion were highly correlated with cytogenetic findings, facial dysmorphism, macro-orchidism, and mental retardation. Mentally retarded female carriers of a full mutation had a significantly larger expansion than intellectually normal female carriers of a full mutation. Among the atypical cases were some non-methylated large mutations (<500 bp), and some abnormally methylated small mutations. Persons with non-methylated mutations had a normal phenotype, and those with abnormal methylation were affected, suggesting that the abnormal phenotype is more strongly associated with the presence of abnormal Eagl methylation at this locus than with the exact size of the expansion. Most of these cases are associated with mutations in the 500 to 1000 bp range, and may indicate the existence of a critical size range for the establishment of abnormal methylation which would, in turn, cut off FMR-1 gene expression. This critical size may vary from one person to another, or even from one cell type to another. There was a significantly higher proportion of mosaic cases among males with the full mutation (12%) than among females with the full mutation (6%). The mosaic males also had a larger expansion than the mosaic females. Finally, among 164 independent couples, three unrelated husbands carried a premutation, suggesting that the prevalence of fragile X premutations in the general population is approximately 0.9% of the X chromosomes, but with a large confidence interval (including 0%).