Medical genetics: advances in brief

Effect of trinucleotide repeat length and parental sex on phenotypic variation in spirocerebellar 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 (spirocerebellar ataxia, SCAl), 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 CAT trinucleotide(s) in tertiaries of 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 presymptomatically. 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.

FRANCES FLINTER

Acquisition of Pseudomonas cepacia at summer camps for cystic fibrosis

Pseudomonas cepacia is a multi-drug resistant gram negative bacillus which has been associated with chronic colonisation of the respiratory tract in patients with CF, sometimes leading to a rapid decline in pulmonary function, increased hospitalisation, and earlier death. The risk of acquiring this organism from attending summer camps organised specifically for CF patients in the US has been studied by analysis of sputum samples taken before and after camp to check for the presence of the organism. Three different camps were involved in the study. Accommodation facilities were similar in each camp and there were no restrictions on mingling with other campers. No special hygiene precautions were taken, but there was no sharing of respiratory devices; 65% of campers contracted P. cepacia as a result of attending the camp. The ribotypes of the newly acquired cases corresponded to those of known infected campers in all but one case. The risk of contracting P. cepacia increased with the duration of the camp and the prevalence of known P. cepacia carriers. There was a positive correlation with sleeping in the same cabin, sharing of personal items, and dancing with an infected partner. The results indicated a significant risk of acquisition of P. cepacia from summer camps, a phenomenon which has not been observed with P. aeruginosa, the other CF pathogen linked with a poor prognosis. Possible ways of overcoming this problem include the introduction of contact isolation precautions, and prohibition of CF patients known to be infected with P. cepacia. Measures such as these will undoubtedly be detrimental to the social and interactive purpose of such gatherings. The US CF foundation has recently issued a recommendation to discontinue summer camps. Other implications of this study include the sequence of segregation of patients in clinic waiting rooms and CF conferences. There will undoubtedly be much debate over the social and medical aspects of the P. cepacia problem.

JILL CLAYTON-SMITH

A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe STB123: the first 2,233 cases

Fragile X mutations consist of an increase in the size of a target fragment containing a trinucleotide CGG repeat located in the 5′ end of the FMR-1 gene. The CGG trinucleotide repeat is highly polymorphic in the normal population (range 6 to approximately 50 repeats), but becomes unstable as its length reaches >45 repeats. 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 Δ>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. This multicentered study involved A>2253 persons was analysed with the probe STB123, producing 909 normal results and 1344 with a fragile X mutation (693 full mutations and 651 premutations). 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 widely 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 (Δ>700 bp), and some abnormally methylated small mutations (Δ<500 bp). 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 (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).

FRANCES FLINTER