

LETTERS TO THE EDITOR

High incidence of $\Delta I507$ mutation of the CFTR gene in a limited area of the north west of France

Since the discovery of the CFTR gene,¹⁻³ more than 400 different mutations have been found to be responsible for cystic fibrosis, the most common of them by far being $\Delta F508$. Because the spectrum of mutations in the gene varies with ethnicity of populations, its identification for a given geographical area has major implications in prenatal diagnosis and genetic counselling. In screening for CF mutations in a limited area of the north western part of France (Basse Normandie, an area with 1 400 000 inhabitants), we recently found the $\Delta I507$ mutation to account for 12.3% of the non- $\Delta F508$ chromosomes or 4.2% of the CF chromosomes (seven out of 168 unrelated CF chromosomes). This mutation was identified by detection of heteroduplex molecules obtained after PCR on polyacrylamide gel electrophoresis (PAGE)⁴ and sequencing of PCR products. We also found the $\Delta I507$ to be constantly associated, as already reported by others,⁴⁻⁶ with the D haplotype (XV2c/TaqI allele 2, KM19/PstI allele 2). The other most common mutations observed in our study with a frequency higher than 1% were: G551D (2.4%), G542X (2.4%), 574delA (1.2%), 3659delC (1.2%), and N1303K (1.2%). The $\Delta I507$ was therefore the second most frequent mutation after $\Delta F508$ (66.3% of CF chromosomes) in the population under study.

Recently, the Cystic Fibrosis Genetic Analysis Consortium has published the population variation throughout the world of common cystic fibrosis mutations.⁷ According to that study, the observed mean relative frequency of the $\Delta I507$ mutation in the world is 0.2% and France is the country where the highest frequency is found (a mean of 0.6%, significantly different from the rest of the world). The frequency of $\Delta I507$ observed in the population of Basse Normandie

is again significantly higher than in rest of the country ($p < 0.05$). This high frequency and the constant association with haplotype D suggest the possible existence of a founder effect in the population under study.

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Allele distribution of a highly polymorphic repeat on chromosome 12 in patients with symptoms of chorea and ataxia

Dentatorubral and pallidolusian atrophy (DRPLA) is a progressive neurodegenerative disorder characterised by ataxia, chorea, epilepsy, and dementia. Recently, an unstable expanded CAG repeat in a gene located on chromosome 12 has been identified as causing DRPLA. The repeat size varied from 7 to 23 in normal subjects and one allele is expanded to 49 to 75 in patients.^{1,2} This rare autosomal

dominant disorder, almost unknown in Europe, has been described in Japanese pedigrees with a prevalence of one per million people. DRPLA has clinical and neuropathological similarities to Huntington's disease (HD) and spinocerebellar ataxia type 1 (SCA1). As in HD and SCA1, variable age of onset, anticipation of symptoms, and cases with juvenile onset following paternal transmission have been observed in DRPLA families.

HD is an autosomal dominant condition resulting in chorea, cognitive loss, and psychiatric manifestations. A tract of CAG repeats has been identified close to the 5' end of the HD transcript. The nucleotide stretch in the gene IT15 on chromosome 4 varies from 11 to 34 copies on normal chromosomes, whereas patients with HD have repeat units larger than 38 within the mutated gene.³

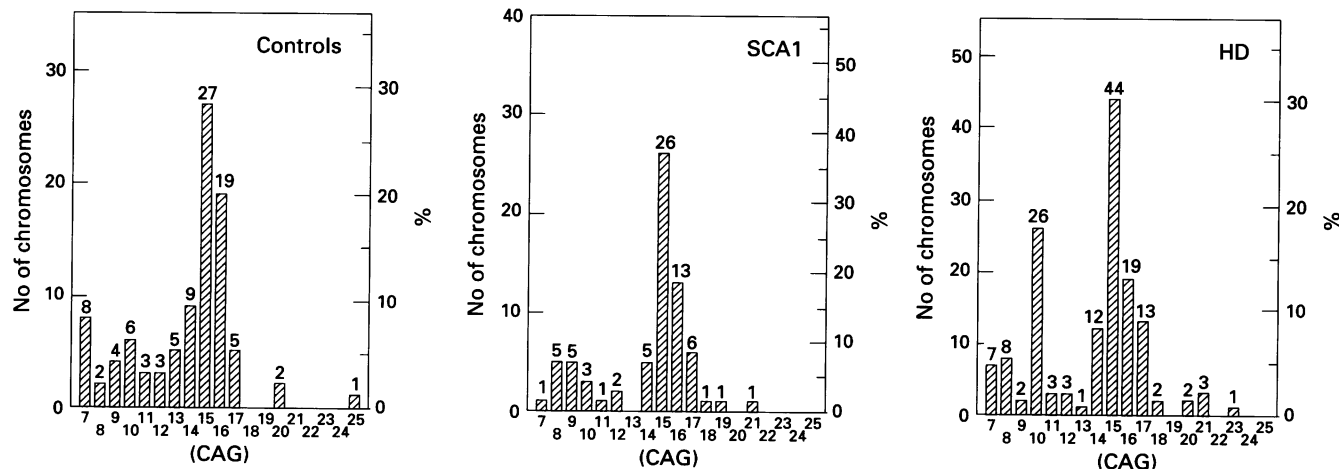
SCA1, another of the numerous autosomal dominantly inherited neurodegenerative disorders, is characterised by ataxia, dysarthria, and variable degree of motor weakness. The neurological findings include selective loss of neurons in the cerebellum, spinal cord, and brain stem. The underlying mutation is an expansion of a CAG trinucleotide repeat in the ataxin gene on chromosome 6. Normal repeat numbers span from 19 to 36 CAG copies, while in SCA1 patients the aberrant repeat is elongated to more than 40 trinucleotides.⁴

Patients with DRPLA may have a variety of symptoms overlapping with HD and SCA1. Therefore, we investigated 73 patients with signs of HD and 35 patients with signs of SCA1 but lacking the appropriate mutations on chromosomes 4 and 6 for length of a CAG repeat on chromosome 12. Normal allele distribution has been confirmed by analyses of 94 control chromosomes.

Blood samples from affected and control persons with a common geographical origin (Germany) were obtained by numerous neurologists asking for direct mutation analyses to confirm or exclude the potential diagnosis. In this study, the neurological criteria, containing the characteristic symptoms of progressive neurodegeneration, chorea, or ataxia or both, were of limited stringency to avoid preselection of the test collective.

DNA from blood lymphocytes was examined for the CAG repeat expansion in the DRPLA gene using the PCR assay as previously described.^{1,2}

The number of CAG repeats in the SCA1 and HD genes were determined as precise



Allele distribution in the DRPLA gene in the three groups.