High incidence of Δ507 mutation of the CFTR gene in a limited area of the north west of France

Since the discovery of the CFTR gene, more than 400 different mutations have been found to be responsible for cystic fibrosis, the most common of them by far being ΔF508. 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 west part of France (Basse Normandie, an area with 1,400,000 inhabitants), we recently found the Δ507 mutation to account for 12.3% of the non-ΔF508 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) and sequencing of PCR products. We also found the Δ507 to be constantly associated, as already reported by others, with the D haplotype (XYcc/TaqI allele 2, KM19/Pdx 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 Δ507 was therefore the second most frequent mutation after ΔF508 (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. According to that study, the observed mean relative frequency of the Δ507 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 Δ507 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.


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

Dentatorubral and pallidolysian 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. This rare autosomal dominant disorder, almost unknown in Europe, has been described in Japanese pedigrees with prevalence of one per million people. DRPLA has clinical and neurological 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. 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.

Patients with DRPLA may have a variety of symptoms overlapping with HD and 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, ataxia, or chorea 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. The number of CAG repeats in the SCA1 and HD genes were determined as precise...
length determinations using the Genesan software on an ABI 373A automatic sequencer. Southern blotting contains a PCR with one primer labelled with fluorescence dye.

For the statistical comparison of the distributions of CAG copies for the three samples, the p value from the exact procedure for contingency table was calculated using StatXact’s Monte Carlo approach with 1,000,000 replications. Thus the width of the 99% confidence interval for the p value could be reduced to 0.001 indicating that the p value given is at least to the second decimal.

The distribution of repeat sizes in the DRPLA gene in 47 male and female controls (94 chromosomes) was determined by subtracting seven and 25 CAG copies with a maximum for [CAG]_12 in 29% of the chromosomes. In two cases (4%) homozygosity has been observed.

In 35 patients with questionable diagnoses of SCA1 without expansions in the ataxin gene, seven to 21 CAG copies in the DRPLA gene have been found, including 26 of 70 alleles with [CAG]_12 (37%). No significant differences in trinucleotide repeat frequency of the DRPLA gene between controls and patients with ataxia could be ascertained. For seven patients only one allele could be amplified, indicating 20% homozygosity. This limited number of cases insufﬁcient to analyse the small number of cases. Insufﬁcient amplification of an expanded repeat appears improbable since DNA analyses of two affected persons, kindly provided by Dr T Warner and A Harding, London, have been successful.

Investigating the DNA of 73 patients suspected of having HD but negative for the mutation in the IT15 gene, alleles ranging from [CAG]_12 to [CAG]_19 in the DRPLA gene were identified. Two homozygous DNA samples (3%) were present. Surprisingly, in this collection the second most frequent allele was [CAG]_12, the most frequent being [CAG]_18 (30% of chromosomes). Twenty-six of the 146 chromosomes investigated (18%) contain 10 CAG copies representing about 36% of the patients with symptoms of HD. Controls and patients shared a common ethnic background and, therefore, differences between populations 4 cannot account for this result. Furthermore, the allele distribution in our controls corresponds to data of the white population, and, therefore, any difference between populations 5 cannot account for this result. 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