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Cystic fibrosis mutations ΔF508 and G542X in Jewish patients

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Abstract

We have screened our CF patients for mutations in exons 10 and 11 of the CFTR gene. Two mutations, ΔF508 and G542X, have been found in 66 Jewish CF patients. The average frequency of the ΔF508 mutation in the Jewish population is 33·8%. The G542X mutation accounts for 13% of the Ashkenazi CF mutations and has been found in three out of seven chromosomes of Jewish patients from Turkey (probably descended from Ashkenazi immigrants). The G542X mutation was not found in any of the other non-Ashkenazi patients. All the G542X bearing chromosomes have the same haplotype. Based on these observations it is concluded that the G542X mutation was introduced into the Jewish people after the split into Ashkenazi and non-Ashkenazi.

Since the cloning of the CFTR gene[1] and the identification of a major mutation, ΔF508, in cystic fibrosis (CF) patients,[2] additional mutations (more than 60) have been identified. The majority of these are rare mutations observed in single families but some mutations are relatively frequent.[3]

We have screened CF patients for the ΔF508 mutation and for G542X, G551D, R553X, and S549N or I, all within exon 11, and for the splice mutation 1717-1G→A. Two mutations have been found among the Jewish patients, ΔF508 and G542X. The distribution of these mutations and their haplotypes in the Jewish communities are the subject of the present report.

Materials and methods

Genomic DNA was extracted from peripheral blood samples by standard procedures. The ΔF508 mutation was tested for by PCR amplification and allele specific oligonucleotide (ASO) hybridisation[2] of dot blots.

Exon 11 was amplified by PCR using 11i-5 and 11i-3 as primers.[3] The mutations G542X and 1717-1G→A were analysed by ASO hybridisation. For other exon 11 mutations the PCR products were subjected to restriction enzymes *Hinc*II and *Dde*I and electrophoresed on 2% agarose gel. G551D and R553X eliminate a *Hinc*II site. S549N or I eliminates a *Dde*I site.[4]

RFLPs were analysed by either Southern blot hybridisation or by PCR.[5,6] The DNA primers for the amplification of the DNA segment flanking XV2c were: 5′-TGAGTCTCTGCTGCCAGT-3′ and 5′-GTTCAAACTATGTCAAAG-3′ (Beaudet, personal communication).

Patients

Sixty-six Jewish families with at least one living affected child were studied: 40 families of Ashkenazi origin, 19 non-Ashkenazi families, and seven families of mixed origin. The non-Ashkenazi families included Sephardic Jews from European countries, North Africa, and Iran and Iraq. None of our patients was of Yemenite or Ethiopian origin.

The parents were first cousins in two non-Ashkenazi families and in one Ashkenazi family. In cases of consanguinity one CF chromosome per family was counted. Among the Ashkenazi families, the mother was not Jewish in one family (and had the R553X mutation) and in one family the patient was the result of uniparental disomy.[7] Therefore, the total number of CF chromosomes was 127, of which 84 chromosomes were of Ashkenazi origin and 43 of non-Ashkenazi origin.

Results

The ΔF508 mutation was found in 43 of 127 (33·8%) CF chromosomes. In the Ashkenazi CF chromosomes the ΔF508 mutation accounted for 29·7% (25 out of 84) of the CF mutations and in the non-Ashkenazi chromosomes it accounted for 41·8% (18 out of 43) CF mutations ($\chi^2 = 1{\cdot}8$, $0{\cdot}25 > p > 0{\cdot}10$, NS).

The haplotype of the ΔF508 bearing chromosomes always included allele 1 of T6/20-*Msp*I[2] and was in strong linkage disequilibrium with haplotype B at the *D7S23* locus (KM19/*Pst*I allele 2, XV2c/*Taq*I allele 1) and with allele 2 of J3.11/*Msp*I (tables 1 and 2).

The G542X mutation was found in 14 CF chromosomes, in 11 (13%) chromosomes of Ashkenazi origin and in three out of a total of seven (43%) chromosomes of Turkish origin. None of the other Sephardic CF chromosomes had the G542X mutation. We did not find any patients homozygous for the G542X mutation.

The haplotype of the G542X bearing chromosomes was allele 1 of T6/20-*Msp*I, haplotype B at the *D7S23* locus, allele 1 of J3.11/*Msp*I, allele 2 of both MetH/*Taq*I and MetD/*Ban*I, and allele 1 of MetD/*Taq*I. None of the other exon 11 mutations, G551D, R553X, S549 N or I, and 1717-1G→A, was found in our patients.

The majority (73%) of the rest of the CF chromosomes had haplotype B, 18% had haplotype C, and a small minority had either

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Table 1 Allelic distribution of closely linked RFLPs in CF and normal chromosomes of Jewish patients.

Locus	*Met*			*D7S23*				*CFTR*	*D7S8*
DNA probe	MetH	MetD	MetD	KM19	–		XV2c	T6/20	J3.11
Enzyme	*Taq*I	*Taq*I	*Ban*I	*Pst*I			*Taq*I	*Msp*I	*Msp*I
Allele haplotype	1 2	1 2	1 2	1-1 A	2-1 B	1-2 C	2-2 D	1 2	1 2
Normal chromosomes									
Ashkenazi (n=52)	25 24	34 4	17 33	15	8	27	2	19 3	26 25
Non-Ashkenazi (n=30)	14 9	15 7	12 17	6	4	16	4	12 3	14 16
ΔF508 chromosomes (n=43)									
Ashkenazi (n=25)	13 4	13 0	13 5	0	22	0	3	18 0	2 21
Non-Ashkenazi (n=18)	8 3	8 3	7 7	1	17	0	0	12 0	2 13
G542X chromosomes (n=14)									
Ashkenazi (n=11)									
Turkish origin (n=3)	1 6	7 0	0 9	0	14	0	0	12 0	11 0
CF chromosomes, unknown mutations (n=70)									
Ashkenazi (n=48)	28 2	22 1	24 6	0	43	4	1	6 17	3 40
Non-Ashkenazi (n=22)	11 7	15 1	12 8	1	8	9	1	7 2	7 11

Table 2 Allelic association coefficient (A) of closely linked RFLPs and the ΔF508 mutation.*

DNA probe	Enzyme	A*
MetH	*Taq*I	0·32
MetD	*Taq*I	0·08
MetD	*Ban*I	0·44
KM19	*Pst*I	0·98
XV2c	*Taq*I	0·89
J3.11	*Msp*I	0·78

* A was computed according to Kerem *et al.*[2]

haplotype D or A. The B haplotype chromosomes were associated with either allele 1 or 2 of T6/20-*Msp*I and the C haplotype chromosomes were associated exclusively with allele 1.

Discussion

It is already known that the ΔF508 mutation accounts for about one-third of the CF mutations in Jewish patients.[8 9] The similarity of the closely linked RFLPs of the ΔF508 chromosomes in our patients to those found elsewhere in the world[10] support the view of a single origin of this mutation. However, in the Jewish patients the ΔF508 chromosomes are in strong linkage disequilibrium (A=0·78) with allele 2 of J3.11/*Msp*I. In Canada[2] the majority of ΔF508 chromosomes are associated with allele 1 of J3.11/*Msp*I. In other populations, such as in Italy,[11] Scotland,[12] and England,[13] allele 2 exists in higher proportions but not to the degree we observed in our population. In Greece,[14] however, 29 out of 37 ΔF508 chromosomes had allele 2 of J3.11/*Msp*I, which is comparable to the frequency we observed in our Jewish patients. It is likely that the ΔF508 chromosomes in the Jewish population represent a subgroup in which allele 2 of J3.11/*Msp*I has not yet reached equilibrium owing to the small size and the relative isolation of the Jewish people.

G542X is a termination mutation in codon 542 of the putative CFTR protein gene. It is quite common,[3] being found in 10 to 15% of CF bearing chromosomes in Europe (European Concerted Action on CF, Newsletter, November 1990). In our sample, this mutation was confined to Ashkenazi patients and patients of Turkish origin. Since we know Ashkenazi Jews migrated from central Europe to Turkey in the 14th century, we assume that these patients are descended from Ashkenazi immigrants. This argument is strengthened by the fact that one of the families from Turkey with G542X has the surname Ashkenazi, which was given to the Ashkenazi immigrants. The high proportion of G542X in the patients from Turkey indicates a possible founder effect.

The haplotype of the G542X chromosome is unique, even when one examines the distant RFLPs at the Met and J3.11 loci. This in itself indicates that the mutation is relatively young in the Jewish people and was probably introduced by admixture after the split into Ashkenazi and non-Ashkenazi. It would be interesting to compare the haplotypes of those G542X chromosomes to those from other sources in Europe.

The mutations ΔF508 and G542X together account for less than 50% of the CF mutations in the Jewish patients. Haplotype analysis of CF chromosomes with unknown mutations predicts at least two more mutations in Ashkenazi Jews, one of them probably common. In non-Ashkenazi Jews several more mutations are expected.

Addendum

Since this manuscript was submitted we have found that the nonsense mutation, W1282X at exon 20,[3 15] is the most frequent mutation in Ashkenazi CF chromosomes accounting for 49% (41/84) of the CF mutations. The W1282X mutation was found in one CF chromosome of Turkish origin and in one of North African origin. The mutations of seven CF chromosomes of Ashkenazi origin and 22 non-Ashkenazi CF chromosomes are still unknown.

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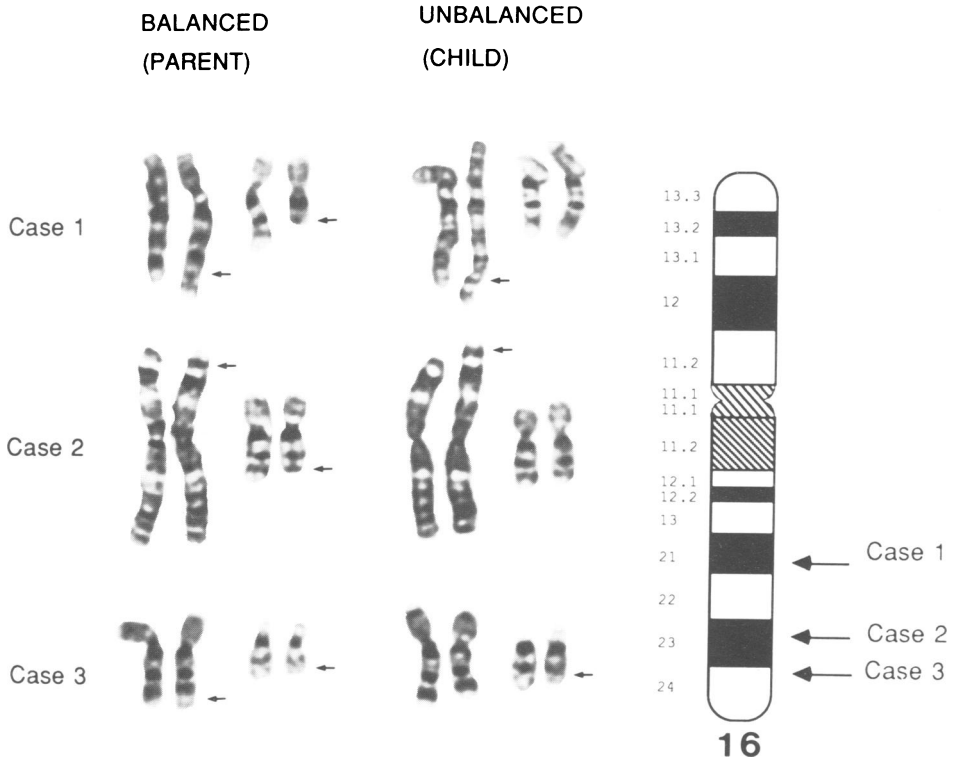
Correction

In the paper by Maher *et al* in the November 1991 issue of the Journal (*J Med Genet* 1991;**28**:801–2), we regret that two chromosomes were missing from the partial karyotype. The correct figure is reproduced below.



GTG banded partial karyotypes observed in cases 1, 2, and 3 for balanced translocation carrier parent and unbalanced translocation child. Full details of karyotypes are in the text. The ideogram of chromosome 16 shows the breakpoint on chromosome 16q for each case.