dominating; this is not the ancestral type; in Holland (D. Halley, personal communication) as in all other populations described, the larger type 1 allele is by far the commonest.

Group 4: Pakistani children from Lancashire. There are 9 children from 6 families. The parents of all are consanguineous but are not related, to their knowledge, to the other families. All the affected children show a type B haplotype but 3 of the 6 have no ΔF508 gene. Their parental consanguinity makes it likely that they are homozygous for their (non-ΔF508) CF genes.

Group 5: Isolated families from elsewhere in Europe and England. Details of these have been incorporated in the overall report on European haplotype and ΔF508 findings.

Table 5 gives clinical details. We have not attempted to analyse clinical features by haplotype, although the B haplotype is associated with most severe forms of the disease. Haplotype B is also associated with the vast majority of ΔF508. The high proportion of this deletion makes it likely that the probable heterozygous advantage in CF follows mainly from ΔF508. On the other hand, the predominance of the B haplotype and its occurrence on non-ΔF CF genes raises the possibility of the advantage being related to the haplotype, with the CF carrier incidence rising as a hitch-hiker or epistatic event (Wagener and Cavalli-Sforza 1975).

There is a suggestion from our figures (Table 5) that meconium ileus is commoner among compound heterozygotes for ΔF than in homozygotes, with slight evidence of a similar trend in relation to liver disease. Subjects from all groups who present with meconium ileus are much more likely to be colonised earlier with *Pseudomonas,* pointing to an association with meconium ileus rather than with the status in relation to ΔF508.

The ΔF508 mutation in cystic fibrosis patients of Southern Italy

Gianfranco Sebastio, Ornella Castiglione, Barbara Incerti, Donatello Salvatore, and Francesca Santamaria

Department of Paediatrics, 2nd School of Medicine, University of Naples, Via Sergio Pansini, I-80131 Naples, Italy

Summary. Fifty one independent cystic fibrosis (CF) families originating from a restricted area of Southern Italy (Campania) have been analyzed for KM19 and XV2c haplotypes and the ΔF508 mutation: 54% of the total CF chromosomes show the ΔF508 mutation. No significative correlations were obtained when clinical score, radiological score, *Pseudomonas* colonization, or clinical symptoms at presentation were matched with the presence or absence of the ΔF508 mutation.

Introduction and methods

Preliminary data reveal significative differences of cystic fibrosis (CF) haplotypes frequencies between populations from the North, Center and South of Italy (Gasparini et al. 1990). These results are in agreement with the hypothesis that the genetic structure of Italy still shows the complex ethnic composition of the pre-Roman age (Piazza et al. 1988).

We report the genetic analysis of CF patients whose families originated from a restricted area of Southern Italy (Campania) for at least three generations. DNA was prepared from the peripheral blood of these 51 independent families. The methods used are reported in the Summary Table at the end of the study.

Evaluation of the standardized disequilibrium coefficient *(sdc)* and the approximate relative risk *(r)* were carried out according to Krawczak et al. (1988).

Results and discussion

The allele 2 of KM19 shows an *sdc* of −0.43, which is different from values found in North European populations and lower than the mean value observed in Italy (Estivill et al. 1988). Allele 1 of XV2c shows an *sdc* of 0.18, which is very low and undermines the diagnostic significance of haplotypes identified by KM19 and XV2c. Indeed, haplotype K2X1, which is very frequent in North European CF chromosomes (up to 85%), is associated with 65% of the CF chromosomes in Campania (*sdc* −0.41). In addition, the K2X2 haplotype, which is not frequent among North American and North European CF chromosomes, is the second "at risk" haplotype in Campania ($r = 4.3$).

The ΔF508 mutation has been found in 54% of the total CF chromosomes of patients from Campania (Table 1), a value lower than that found (68%) by Kerem et al. (1989b). In our survey, 25% of patients are homozygous for the ΔF508 mutation, 57% are heterozygous and 18% do not show the mutation (Table 2).

Table 1. Mutation ΔF508 frequencies on 102 CF chromosomes (%). + and − indicate the presence and absence of the ΔF508 mutation, respectively

	Haplotype				Total
KM19	1	1	2	2	
XV2c	1 A	2 B	1 C	2 D	
ΔF508 +	0	3 (0.05)	45 (0.82)	7 (0.13)	55 (0.54)
ΔF508 −	9 (0.19)	8 (0.17)	22 (0.47)	8 (0.17)	47 (0.46)
Normal	33 (0.32)	31 (0.30)	25 (0.25)	13 (0.13)	102

Table 2. Genotypes of 51 unrelated patients in the present study. + and − indicate the presence and absence of the ΔF508 mutation, respectively

Genotype		
ΔF508 +/+	ΔF508+/−	ΔF508−/−
13 (0.25)	29 (0.57)	9 (0.18)

Although not all the patients who entered this study were investigated for pancreatic sufficiency (PS), we know that 50/51 of them need pancreatic extract supplementation, thus suggesting that they suffer from pancreatic insufficiency (PI). The only patient with PS, as demonstrated by laboratory investigation, is heterozygous for the ΔF508 mutation; the haplotype carrying the unknown mutation is K1X2. Despite being based on a clinical evaluation of PI, the frequency of the other severe mutation(s) is 0.49, whereas the mild mutation(s) has a frequency of 0.01. These predicted frequencies are in agreement with the observed results. Only 67% of the K2X1 haplotypes carry the ΔF508 mutation.

Finally, no significative correlations were obtained when clinical score, radiological score, *Pseudomonas* colonization, or clinical symptoms at the presentation were matched with the presence or absence of ΔF508 mutation (data not shown).

The cystic fibrosis ΔF508 mutation in the French population

B. Simon-Bouy[1], E. Mornet[1], J. L. Serre[2], A. Taillandier[1], J. Boué[1], and A. Boué[1]

[1]Unité 73 and [2]Unité 155,
Institut National de la Santé et de la Recherche Médicale,
Château de Longchamp, F-75016 Paris, France

Summary. French families (n = 129) with at least one cystic fibrosis (CF) affected child and 44 unrelated subjects from the general population were tested for the presence of the ΔF508 mutation by the polymerase chain reaction. The ΔF508/CF mutation ratio (CF: uncharacterised CF mutations) was tested in the CF families with and without meconium ileus. The association between ΔF508 and CF mutations and restriction fragment length polymorphism haplotypes (XV2c and KM19) has been estimated; these data suggest that the CF chromosomes include a panel of independent and probably different mutations.

Introduction and methods

We report here the results of the screening of the ΔF508 mutation in a sample of the French population. DNA samples were obtained from 129 French cystic fibrosis (CF) families with at least one affected child, 40 of whom had a history of meconium ileus (MI) and 89 of whom had no history of MI. Parents of CF patients each of whom were supposed to carry an N and a CF chromosome were suitable for DNA analysis of normal chromosomes. Moreover, 44 unrelated subjects of the general population were tested.

The methods used for DNA analysis are described in the Summary Table at the end of the study.

Results and discussion

The ΔF508 mutation has been observed in 187 out of the 258 CF chromosomes (72.5%) and is more frequent (80%) within the CF chromosomes of index cases with MI than within the CF chromosomes of index cases without MI (69%), with a risk level of 7.5% (Table 1, χ^2 = 3.29, 1 *df*). In the general population, 2 out of the 44 subjects typed at the 508 position were heterozygotes for the ΔF508 mutation.

The frequencies of restriction fragment length polymorphism (RFLP) haplotypes (defined by the XV2c and KM19 probes) within the ΔF508, CFX and normal chromosomes are reported in Table 2. There is a strong association between the B RFLP haplotype and both the ΔF508 and CFX mutations, compared with the normal chromosomes (respectively, χ^2 = 197.1 and 21.01; $P < 10^{-4}$ and 5×10^{-3}).

The CFX mutation is significantly associated with the E2 allele of the KM19 RFLP (χ^2 = 25.55; $P < 5 \times 10^{-3}$; standard $\Delta = -0.34$), but there is no significant association with the D1 allele of the XV2c RFLP (χ^2 = 0.17; $P = 0.3$).

Among the 103 sibs studied, 32 were homozygous (15 females, 17 males) and 71 were heterozygous (35 females, 36 males). These proportions do not significantly differ from the expected normal/carrier ratio and do not corroborate the previous study of Kitzis et al. (1988). Moreover, the inheritance of the CF allele does not show any

Table 1. Number (and frequencies) of genotypes or alleles at the ΔF508 site in the CF locus in index cases with or without MI

Index cases	Alleles		Genotypes		
	ΔF508	CFX	ΔF508/ΔF508	ΔF508	X/X
With MI	64 (0.80)	16 (0.20)	27 (0.67)	10 (0.25)	3 (0.08)
Without MI	123 (0.69)	55 (0.31)	43 (0.48)	37 (0.41)	9 (0.10)

Table 2. Frequencies of RFLP haplotypes among normal and CF chromosomes with the ΔF508 mutation or an unknown CFX mutation

	RFLP haplotypes		CF chromosomes		Normal chromosomes
	XV2c	KM19	ΔF508	CFX	
A	−	−	1 (0.7)	4 (10.5)	82 (46.1)
B	−	+	129 (92.1)	17 (44.7)	23 (12.9)
C	+	−	1 (0.7)	8 (21.1)	50 (28.1)
D	+	+	9 (6.4)	9 (23.7)	23 (12.9)
	No. observed		140	38	178