ONLINE MUTATION REPORT

Relationship between genotype and phenotype for the *CFTR* gene W846X mutation

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Cystic fibrosis (CF) is the most common inherited disorder in white populations. It occurs in approximately 1/2500 live births and is characterised by chronic and progressive obstructive lung disease, pancreatic insufficiency, and high sweat electrolyte levels. Western Brittany has one of the highest rates of CF in the world.[1 2] Over 98% of the CF mutations in the Celtic population of Brittany have been identified.[3 4] In this population, only five mutations account for 92.4% of the chromosomes: ΔF508 81.2%, 1078delT 4.9%, G551D 4.1%, 1717-1G→A 1.1%, and W846X2 1.1%.

Most of the genotyping laboratories do not distinguish W846X1[5] and W846X2[6] mutations, which are located in the second transmembrane domain (exon 14a) and involve the substitution of a tryptophan for a stop codon. W846X2 is the result of the change of a G to an A nucleotide at position 2670.

Because of its high frequency and evidence of founder effect in Brittany (all CF chromosomes carrying W846X2 share the same 16-32-13 microsatellites haplotype[7]), we decided to study the correlation between the genotype and phenotype for this mutation.

We extracted from the French CF Registry all the patients who attended a participating care centre at least once during 1999 and for whom the genotype was composed of the W846X and ΔF508 mutations. Each patient was matched to a patient of the same sex and age (±1 year), homozygous for the ΔF508 mutation, and having attended the same care unit during 1999. All the data were obtained from the 1999 enquiry, except for clinical events that were compiled during the last six years (1994-1999).

Categorical variables were compared using the χ^2 test or, for small samples, the Fisher exact test. Continuous variables were compared by a two tailed paired *t* test in the matched paired analysis. A significance level of 5% was used. Analyses were performed using Epi Info 6.04 FR.

Table 1 shows the phenotypic characteristics of the 10 CF patients compound heterozygous for the W846X and ΔF508 mutations and the 10 ΔF508 homozygous patients. No significant difference was found for the mean ages at the time of diagnosis despite wide variation owing to two late diagnoses in the W846X/ΔF508 group: a male was diagnosed at 29 years old and a female at 27.4 years old. All 20 patients had pancreatic insufficiency.

More ΔF508 homozygotes than W846X/ΔF508 patients were colonised with *Pseudomonas aeruginosa*, the difference being borderline significant (p=0.057). The mean FEV_1 and FCV values were much higher among the W846X/ΔF508 patients (73.5 and 80.9% of the predicted values) than among the ΔF508/ΔF508 patients (53.9 and 68.9%); however, the differences were not significant.

Usually nonsense mutations are linked with severe disease, when associated with ΔF508.[8–10] However, Hubert *et al*[11] found that some CF adults with ΔF508 and a nonsense mutation had severe pancreatic insufficiency but milder pulmonary disease.[11] They proposed two hypotheses: (1) the truncated protein may have a residual function, or (2) mRNA splicing may produce a small quantity of protein in some tissues, which would decrease the effect of the mutation.

Statistically, no distinction can be made between the compound heterozygotes and the ΔF508 homozygotes, except for a higher risk of diarrhoea at the time of diagnosis ($p<0.03$). However, a higher proportion of compound heterozygotes reached young adulthood and adulthood than ΔF508 homozygotes from the whole French CF registry (70% of 15 years old and over versus 40%).

The small size of the population under study may explain why some differences, although large, did not reach significance. It is particularly the case for the lung function tests for which W846W/ΔF508 patients have far better results than the ΔF508/ΔF508 patients. This has important clinical consequences: a FEV_1 close to 75% corresponds to milder obstruction and low morbidity, whereas a value close to 50% is disabling in everyday life.

The better anthropometric and lung function results combined with a higher probability of reaching adulthood lead us to conclude that, although the W846X mutation should be considered a severe allele, it is associated with less severe pulmonary manifestation and probably a better prognosis of the disease.

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Table 1 Characteristics of compound heterozygotes for the W846X mutation compared to homozygotes for the ΔF508 mutation

	W846X/ΔF508	ΔF508/ΔF508	p values
Sex (males/females)	4/6	4/6	
Age on 31.12.99 (y)			
Mean age (SD)	22.48 (9.92)	21.96 (9.31)	*
Median age	20.6	21	
Range	[11.5–41.2]	[10.3–39.4]	
Age at diagnosis (mth)			
Mean age (SD)	79.5 (137.08)	29 (41.15)	*
Median age	16.5	13	
Range	[2–348]	[1–138]	
Status at diagnosis			
Family history	1	0	*
Prenatal diagnosis	0	0	
Neonatal screening	0	1	*
Meconium ileus	0	1	*
Intestinal obstruction	1	2	*
Malnutrition	3	4	*
Diarrhoea	6	1	0.0223
Respiratory symptoms	4	6	*
Sweat chloride concentration (mEq/l)			
Mean value (SD)	126 (26)	113 (22)	*
Median value	124	111	
Range	[100–156]	[90–140]	
Microbiology (No of patients)			
Haemophilus influenzae	3	1	*
Staphylococcus aureus	5	6	*
Pseudomonas aeruginosa	5	9	0.0571
Stenotrophomonas maltophilia	0	0	
Burkholderia cepacia	0	0	
Aspergillus	3	0	0.067
Candida	4	3	*
Anthropometry			
Height (Z score) (SD)	–0.59 (1.06)	–0.31 (1.22)	*
Weight (Z score) (SD)	–0.39 (1.57)	–0.71 (1.66)	*
BMI (SD)	19.27 (3.87)	18.04 (3.28)	*
Pulmonary status (% of predicted value)			
FEV_1 (SD)	73.49 (33.37)	53.93 (37.19)	*
FCV (SD)	80.86 (28.05)	68.88 (30.35)	*
Clinical events (No of patients)			
Cirrhosis	0	1	*
Diabetes mellitus	1	3	*
Gallstones	2	0	*
Pancreatitis	0	0	
Intestinal obstruction	1	1	
Haemoptysis	0	1	*
Nasals polyps	4	3	*
Pneumothorax	0	1	*
Arthropathy	0	0	
Allergic bronchopulmonary aspergillosis	2	3	*
Pancreatic insufficiency	10	10	

*No significant difference at p=0.05.

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