Letters to the Editor

Am. J. Hum. Genet. 54:384–385, 1994

A Healthy Male with Compound and Double Heterozygosities for ΔF508, F508C, and M47OV in Exon 10 of the Cystic Fibrosis Gene

To the Editor:

In the August 1993 issue of the *Journal,* Meschede et al. (1993) describe a patient with congenital bilateral aplasia of the vas deferens (CBAVD), who is heterozygous for the mutation ΔF508, and presents a compound heterozygosity for the variations F508C and M470V. The authors postulate that the M470V allele could contribute to the clinical phenotype of CBAVD if it is inherited together with ΔF508 and F508C.

However, we found the same genotype in a healthy, nonsterile male individual from southern France. This man is the uncle of a cystic fibrosis (CF) patient homozygous for the ΔF508; he requested a carrier diagnosis because his wife was pregnant. On ΔF508 mutation screening by visualization of the 3-bp deletion, we discovered an unusual pattern of heteroduplexes that was slightly different from the usual heteroduplex in ΔI507 mutation carriers, as shown in figure 1. Subsequent direct DNA sequencing allowed the identification of three nucleotide changes: ΔF508, F508C, and M47OV. From the familial segregation pattern, it could be deduced that F508C and M47OV were present on the same chromosome (*cis* configuration) and that ΔF508 was present on the other chromosome.

Since the identification of the ΔF508 deletion in the CF transmembrane regulator (CFTR) gene (Kerem et al. 1989), several nucleotide changes have been described in exon 10 (Tsui 1992; Cystic Fibrosis Genetic Analysis Consortium, unpublished results). Among them, the substitution of cysteine for phenylalanine 508, named "F508C" (Kobayashi et al. 1990) or 1655 T or G (Cystic Fibrosis Genetic Analysis Consortium, unpublished results), is of particular interest both because of its physiological significance and because it can cause pitfalls in molecular diagnosis. Four other compound heterozygous persons ΔF508/F508C have been reported in this *Journal* (Kobayashi et al. 1990; Macek et al. 1992; Meschede et al. 1993). The change M470V (named "1540 A or G" by the Cystic Fibrosis Genetic Analysis Consortium) is frequent and has been found associated with ΔF508 as well as with non-ΔF508 mutations or normal alleles (authors' unpublished observations).

The case described here makes it unlikely that, as concluded by Meschede et al. (1993), the combined *trans* and *cis* configuration of ΔF508, F508C, and M470V could contribute to the CBAVD phenotype.

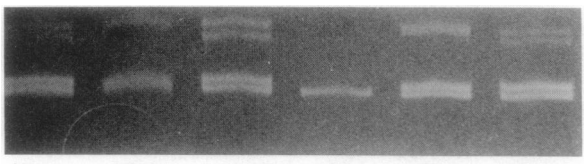

Figure 1

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mtDNA: Pathogenic or Nonpathogenic Sequence Changes

To the Editor:

Tatuch et al. (1992) have reviewed the literature on the 8993 mtDNA mutation in a recent case report in this *Journal*. Their evidence that this point mutation causes Leigh disease is strong, even though it has not yet been possible to document the predicted biochemical defect. Their case does not need the spurious support they infer from our data (Poulton et al. 1988). We reported a patient with Kearn-Sayre syndrome (KSS; see Petty et al. [1986]), which we described as group I mitochondrial myopathy, in whom we found two restriction-site losses in the region of the 8993 mutation. Unlike the family they described, our patient was homoplasmic for the point mutation, as were his asymptomatic maternal relatives. Sequence analysis now confirms that there is a G-to-A transition at bp 8994 that does not cause an amino acid substitution. We conclude that this mutation is not pathogenic. Furthermore, this boy has an mtDNA deletion (fig. 1) that is sufficient to explain his clinical syndrome.

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TACCACCTACCTCCCTCACCAAA  ATPase 8
          **********
TACCACCTACCTCCCTGACAAGC  Patient
          **********
TCATCGCTACCTCCCTGACAAGC  ND5
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Figure 1 Exact homology between bp 8468–8477 (*top strand*) and bp 13580–13589 (*bottom strand*). Asterisks (*) indicate the homologous region.

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