Vilkki J, Savontaus M-L, Nikoskelainen EK (1990) Segregation of mitochondrial genomes in a heteroplasmic lineage with Leber hereditary optic neuroretinopathy. Am J Hum Genet 47:95–100

Vilkki J, Ott J, Savontaus M-L, Aula P, Nikoskelainen EK (1991) Optic atrophy in Leber hereditary optic neuroretinopathy is probably determined by an X-chromosomal gene closely linked to DXS7. Am J Hum Genet 48:486–491

Wallace DC, Singh G, Lott MT, Hodge JA, Schurr TG, Lezza AMS, Elsas LJ II, et al (1988) Mitochondrial DNA mutation associated with Leber's hereditary optic neuroretinopathy. Science 242:1427–1430

0002-9297/93/5301-0032$02.00

Am. J. Hum. Genet. 53:292–293, 1993

Compound Heterozygosity for the ΔF508 and F508C Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutations in a Patient with Congenital Bilateral Aplasia of the Vas Deferens

To the Editor:

In the November 1992 issue of the *Journal* Macek et al. (1992) describe a peculiar pattern of heteroduplex formation in a case of compound heterozygosity for the ΔF508 and F508C mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator gene). The individual carrying these mutations was the clinically normal father of a cystic fibrosis (CF) patient. We would like to report a similar molecular finding, observed in a completely different clinical setting.

There is increasing evidence that congenital bilateral aplasia of the vas deferens (CBAVD) is a primarily genital form of CF. Simple or compound heterozygosity for mutations in the CFTR gene has been found in up to 64% of individuals affected by this condition (Dumur et al. 1990; Anguiano et al. 1992). These patients can now be effectively treated with the technique of microsurgical sperm aspiration from the epididymis and consecutive in vitro fertilization (Silber et al. 1990). On the basis of the high prevalence of mutations in the CFTR gene, we have recently established a pretherapeutic genetic screening program for couples where the male partner is affected by CBAVD. DNA from both partners is screened for ΔF508 (by heteroduplex analysis) and other mutations in CFTR exons 7, 10, 11, and 21 (by direct sequencing after PCR amplification).

In a patient with surgically proved CBAVD we observed the same slightly shifted heteroduplex bands for ΔF508 as were described by Macek et al. Apart from a pneumonia in early infancy, the patient had never had any CF-typical symptoms. Sweat electrolytes were within the normal range. Direct sequencing showed heterozygosity for the ΔF508 and F508C mutations and the amino acid polymorphism M470V (Kerem et al. 1990). DNA from the patient's parents, both of whom were free of CF symptoms, was then analyzed with the same techniques. Results are summarized in table 1. The father was found to be heterozygous for the ΔF508 mutation. In the mother, heterozygosity for the F508C mutation and the M470V polymorphism was detected. In the patient and his mother, F508C and M470V were present on the same chromosome (*cis* configuration), as can be deduced from the segregation pattern (table 1).

Table 1

CFTR Gene Haplotypes in the Patient and His Parents

Mutation or Polymorphism	CFTR Gene Haplotype[a]		
	Patient	Father of Patient	Mother of Patient
ΔF508	ΔF508/+	ΔF508/+	+/+
F508C	+/F508C	+/+	+/F508C
M470C	+/M470V	+/+	+/M470V

[a] A plus sign (+) denotes presence of the wild-type allele.

Compound heterozygosity for ΔF508 and F508C has been reported in clinically normal individuals (Kobayashi et al. 1990; Macek et al. 1992), in patients with typical CF symptoms (Kerem et al. 1990), and now, for the first time, in a case of CBAVD. The basis for this wide clinical variability is unclear, as is the functional significance of the F508C mutation. The M470V mutation detected in our patient is considered a benign sequence variation without clinical consequences. It cannot be excluded, however, that this mutation contributes to the clinical phenotype of CBAVD if it is inherited together with ΔF508 and F508C. To further clarify this issue, we are currently screening a larger number of patients with congenital anomalies of the Wolffian-duct derivatives, for M470V and F508C mutations.

DIETER MESCHEDE,*,† ANTONIN EIGEL,†
JÜRGEN HORST,† AND EBERHARD NIESCHLAG*
**Institute of Reproductive Medicine and †Institute of Human Genetics, University of Münster, Münster*

Acknowledgment

This work was supported in part by Deutsche Forschungsgemeinschaft grants DFG Me 1086/1-1 and DFG Ni 130/11.

References

Anguiano A, Oates RD, Amos JA, Dean M, Gerrard B, Stewart C, Maher TA, et al (1992) Congenital bilateral absence of the vas deferens: a primarily genital form of cystic fibrosis. JAMA 267:1794–1797

Dumur V, Gervais R, Rigot J-M, Lafitte J-J, Manouvrier S, Bisserte J, Mazeman E, et al (1990) Abnormal distribution of CF ΔF508 allele in azoospermic men with congenital aplasia of epididymis and vas deferens. Lancet 336:512

Kerem B-S, Zielenski J, Markiewicz D, Bozon D, Gazit E, Yahav J, Kennedy D, et al (1990) Identification of mutations in regions corresponding to the two putative nucleotide (ATP)-binding folds of the cystic fibrosis gene. Proc Natl Acad Sci USA 87:8447–8451

Kobayashi K, Knowles MR, Boucher RC, O'Brien WE, Beaudet AL (1990) Benign missense variations in the cystic fibrosis gene. Am J Hum Genet 47:611–615

Macek M Jr, Ladanyi L, Bürger J, Reis A (1992) Missense variations in the cystic fibrosis gene: heteroduplex formation in the F508C mutation. Am J Hum Genet 51:1173–1174

Silber SJ, Ord T, Balmaceda J, Patrizio P, Asch RH (1990) Congenital absence of the vas deferens: the fertilizing capacity of human epididymal sperm. N Engl J Med 323:1788–1792

0002-9297/93/5301-0033$02.00