**Table 1**

**Breast Ovary Families with Negative Lod Scores to BRCA1**

| Family | No. of Cancers: Breast, Female | Breast, Male | Ovarian | Lod Score to BRCA1[a] | BRCA1 Mutation?[b] | Lod Score to BRCA2[b,c] |
|---|---|---|---|---|---|---|
| IARC 2850 | 15 | 0 | 2 | −1.71 | Yes | ... |
| RUL 49 | 4 | 1 | 3 | −1.11 | Yes | ... |
| CRC 128 | 4 | 0 | 4 | −.91 | Yes | ... |
| CRC 186 | 16 | 1 | 1 | −2.61 | ... | 3.70 |
| RUL9 | 7 | 0 | 1 | −2.01 | ... | 1.64 |
| UTAH 107 | 32 | 3 | 6 | −2.45 | ... | 3.48 |
| UTAH 2044 | 7 | 1 | 4 | −1.32 | ... | 2.11 |
| ICELAND 6 | 15 | 1 | 1 | −.96 | ... | 2.92 |
| ICELAND 2204 | 3 | 4 | 1 | −.85 | ... | .93 |
| ICELAND 80004 | 8 | 0 | 1 | −1.89 | ... | 1.82 |

NOTE.—The linkage model is presented in the report by Narod et al. (1995).
[a] Based on the markers D17S250 and D17S579.
[b] An ellipsis indicates that the test was not done.
[c] Based on markers D13S260, D13SS289, and D13S267.

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## CFTR Gene Variant for Patients with Congenital Absence of Vas Deferens

*To the Editor:*

Obstructive azoospermia due to congenital absence of vas deferens is a prominent clinical feature among male patients with cystic fibrosis (CF) (Holsclaw et al. 1971). A similar autosomal recessive condition with no other CF manifestations is classified as congenital bilateral absence of vas deferens (CBAVD; McKusick 277180; Schellen and van Stratten 1980). Since 50%–64% of CBAVD patients have been found to be positive for at least one known CFTR mutation, it is believed that at least part of the CBAVD population represents an atypical form of CF affecting only the male reproductive system (Dumur et al. 1990; Anguiano et al. 1992; Gervais et al 1993; Osborne et al. 1993; Patrizio et al. 1993; Culard et al. 1994). This explanation is not completely satisfactory, however, because only ~10% of CBAVD patients are found to carry known CF mutations on both chromosomes, even after exhaustive screening of the entire CFTR coding region. Here we present data to show that a previously known sequence variant in intron 8 of the CFTR gene (Chu et al. 1993) is a specific and frequent mutation associated with CBAVD.

Varied lengths of a thymidine (T)–tract (5, 7, or 9T) have been noted in front of the splice-acceptor site of intron 8 (Chu et al. 1993). The length appears to correlate with the efficiency of exon 9 splicing, with the 5T variant that is present in 5% of the CFTR alleles among the Caucasian population producing almost exclusively (95%) exon 9-minus mRNA (Chu et al. 1993). The effect of this T-tract polymorphism in CFTR gene expression is also documented by its relationship with a known CF mutation R117H (Dean et al. 1990): While R117H(5T) is found in typical CF patients with pancreatic sufficiency, R117H(7T) is associated with CBAVD (Kiesewetter et al. 1993). More recently, CFTR alleles

**Table 1**

**CFTR Mutations Detected in the CBAVD Patients**

| Genotype | | Number of Patients | Percentage of Total |
|---|---|---|---|
| ΔF508 | IVS8/5T | 16 | |
| W1282X | IVS8/5T | 9 | |
| ΔF508 | R117H(7T) | 4 | |
| N1303K | IVS8/5T | 2 | |
| IVS8/5T | IVS8/5T | 2 | |
| ΔF508 | R117C | 1 | |
| ΔF508 | D1152H | 1 | 58.6 |
| ΔF508 | S50Y | 1 | |
| R553X | R117H(7T) | 1 | |
| R117H(7T) | R117H(7T) | 1 | |
| G542X | IVS8/5T | 1 | |
| 1717−1G→A | IVS8/5T | 1 | |
| 1525−1G→A | IVS8/5T | 1 | |
| IVS8/5T | Unknown | 4 | |
| ΔF508 | Unknown | 4 | |
| W1282X | Unknown | 2 | |
| R553X | Unknown | 1 | 20.0 |
| 4173delC | Unknown | 1 | |
| D614G | Unknown | 1 | |
| 1716+12T→C | Unknown | 1 | |
| Unknown | Unknown | 15 | 21.4 |

NOTE.—The known CFTR mutations screened included ΔF508, G542X, G551D, N1303K, R553X, W1282X, ΔI507, 1717−1G→A, R560T, S549N, 621+1G→T, and R117H.

carrying the 5T variant alone (without any known CF mutations) have been found in proportions higher than expected among CBAVD patients (Osborne et al. 1994; Chillon et al. 1995).

We analyzed the CFTR genotypes for 70 unrelated CBAVD patients (with unknown etiology) recruited from the Microsurgical Epididymal Sperm Aspiration and In Vitro Fertilization program at the University of California, Irvine (Patrizio et al. 1993). The genomic DNA samples were obtained from peripheral lymphocytes and were analyzed in three stages. The samples were first screened by allele-specific oligonucleotide hybridization (Kristidis et al. 1993) for a list of common CFTR mutations (table 1), known to account for ~80% CF chromosomes in North America (The Cystic Fibrosis Genetic Analysis Consortium 1994). Seven mutant alleles were identified (table 1). Heteroduplex analysis was then performed on the remaining unknown samples by using Hydrolink gels (Keen et al. 1991) for all 27 exons of the CFTR gene, followed by direct DNA sequencing (Zielenski et al. 1991). Seven additional mutations were identified (table 1); two of them, 4173delC (exon 22) and S50Y (281C→A; exon 2), were not described elsewhere (Zielenski et al., in press). Together, 9 patients (13%) were found to have two CFTR mutations and 40 patients (57%) had a single known CFTR mutation.

We next examined whether the length of the T tract in intron 8 (Chu et al. 1993) could account for some of the unknown CFTR alleles in the above patient population. Our result showed that 38 CBAVD chromosomes carried the 5T variant, corresponding to a frequency (27%) five times greater than that observed for a random population (Chu et al. 1993) ($P < .001$). Although phase was not determined for the majority of patients, it was possible to deduce their CFTR genotypes according to previous haplotype analysis of known CF mutations (Kiesewetter et al. 1993). Accordingly, 30 patients could be assigned as heterozygotes for a known CFTR mutation and the 5T variant (table 1). Two patients with no known CFTR mutations appeared to be homozygous for this variant. Together, these data were consistent with the suggestion that the 5T variant was a "very mild" CFTR mutation specific for CBAVD.

Previous studies indicated that the frequency for the 5T variant could be as high as 5% in the population (Chu et al. 1993; Kiesewetter et al. 1993). If this variant could indeed cause CBAVD, then its frequency combined with that of cystic fibrosis mutations (.02) would predict that ~1 in 222 (0.45%) Caucasian men could suffer from CBAVD. Since the incidence of CBAVD is expected to be ~1 in 1,000, on the basis of the data reported elsewhere (Lipschultz 1980; Jequier et al. 1985), it was apparent that the 5T variant could not be fully penetrant. In fact, it was reported that 2.1% of the fathers of CF patients were heterozygous for the 5T variant and another CFTR mutation (Chillon et al. 1995).

To obtain a better estimate of the degree of penetrance for the 5T variant, we performed a genotype analysis using the parents of previously characterized CF families. The result showed that 2 of 104 paternal and 5 of 106 maternal "non-CF" alleles could be discerned to harbor the 5T variant (1.9% and 4.7%, respectively). Although the difference was not statistically significant, the values were similar to those recently reported by others (Chillon et al. 1995). If absence of phenotype in females is assumed, the degree of penetrance for the 5T variant with respect to CBAVD could be deduced as .60. While this number seems to be reasonable, a more accurate estimate awaits a larger sample size and additional methods of analyses. Nevertheless, it is clear that the 5T variant in intron 8 of the CFTR gene is a specific allele for CBAVD with reduced penetrance.

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## The Ataxia-Telangiectasia–Variant Genes 1 and 2 Are Distinct from the Ataxia-Telangiectasia Gene on Chromosome 11q23.1

*To the Editor:*

The autosomal recessive disorder ataxia-telangiectasia (AT) was linked to chromosome 11q22-23 in 1988 (Gatti et al. 1988). A recent publication reports now on a gene, ATM, located in this region and found to be mutated in patients from the four complementation groups—A, C, D, and E (Savitsky et al. 1995)—that have been established so far (Jaspers et al. 1988). These findings indicate that ATM is probably the sole gene causing the disease. In the course of identification of the gene by positional cloning, the AT region was physically mapped by cosmid and YAC contigs (Ambrose et al. 1994; Rotman et al. 1994*a;* Uhrhammer et al. 1994), and various highly polymorphic microsatellite markers that can be tested by PCR-based protocols were isolated (Rotman et al. 1994*b;* Vanagaite et al. 1994, 1995; Uhrhammer et al. 1995).

AT variant 1 (AT-V1, Nijmegen breakage syndrome; Jaspers et al. 1988) and AT variant 2 (AT-V2, Berlin breakage syndrome; Wegner et al. 1988) patients share cytogenetic features with AT, such as spontaneous