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Genetic Heterogeneity of Breast-Ovarian Cancer Revisited

To the Editor:

We have recently reported the results of a linkage analysis of 145 breast-ovarian cancer families (Narod et al. 1995). Each family has three or more cases of early-onset breast cancer (age <60) or of ovarian cancer, and all families have at least one case of ovarian cancer (there were nine site-specific ovarian cancer families). Overall, we estimated that 76% of the families were linked to the BRCA1 locus.

Among the 145 families studied, there were only 10 families that gave multipoint lod scores <-0.80, with markers flanking BRCA1, and that therefore were considered unlikely to be linked to this locus. Since the submission of our report, the BRCA1 gene has been identified (Miki et al. 1994), and the BRCA2 locus has been mapped to chromosome 13q (Wooster et al. 1994). Additional studies have now revealed the genetic basis of each of these 10 families—3 families were found to carry BRCA1 mutations, and 7 families show positive linkage to the BRCA2 locus.

IARC 2850 carries a BRCA1 mutation leading to the loss of exon 5. This family originally gave a multipoint lod score of -1.71 at BRCA1, but it can now be seen that the family contains two sporadic cases of cancer and that two recombination events have occurred between the flanking markers D17S250 and D17S579. The second family with a BRCA1 mutation is CRC 128. This mutation in this family leads to premature chain termination at codon 285. Because of the presence of a sporadic case of breast cancer in this family, at age 35 years, the lod score to BRCA1 is -0.91. Family RUL49 is a Dutch family with four early-onset breast cancers, one male breast cancer, and three ovarian cancers. Recently the family has been found to carry a BRCA1 frameshift mutation leading to termination at codon 780 (Hogervorst et al. 1995). Because of a sporadic early-onset breast cancer, the BRCA1 lod score is negative (-1.11). This is a rare example of a family with male breast cancer and a BRCA1 mutation. A second example has been reported by Struewing et al. (1995).

The other seven families appear to be linked to BRCA2, with multipoint lod scores ranging from 0.93 to 3.70 (table 1). Five of these families contain cases of male breast cancer, and five contain only a single case of ovarian cancer. For six families the evidence of linkage to BRCA2 is very strong (lod scores >1.6); for the other family (ICELAND 2204) the linkage evidence is more modest.

In summary, none of the 145 families in this large data set now provides clear evidence against both linkage to BRCA1 and linkage to BRCA2. These results indicate that BRCA1 and BRCA2 account for the majority of breast-ovarian cancer families. Studies are now underway that will estimate the proportions of breast cancer families attributable to each of these loci. It remains possible that a third breast cancer locus will be found, but it is unlikely that this locus will account for a significant proportion of families with breast and ovarian cancer.

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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