disease: its significance and implications. Ann Intern Med 51:933–971

Vianna NJ, Davies JN, Polan AK, Wolfgang P (1974) Familial Hodgkin's disease: an environmental and genetic disorder. Lancet 2:854–857

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The 8765delAG Mutation in BRCA2 Is Common among Jews of Yemenite Extraction

To the Editor:

The proportion of high-risk families with BRCA2 mutations varies widely among populations. In Iceland, 8% of unselected breast cancer (BC) patients and 64% of patients with a definite family history of BC carry a founder mutation in BRCA2—995del5 (Thorlacius et al. 1997). In the Ashkenazi Jews, the 6174delT mutation is found in 24% of high-risk families and in 6% of unselected BC patients (Abeliovich et al. 1997; Levy-Lahad et al. 1997). Other ancient BRCA2 mutations have been summarized by Szabo and King (1997). Whereas some of the BRCA2 mutations were found in BC-only families, including the majority of families with male and female BC (Ford et al. 1998), other BRCA2 mutations, such as 6174delT, were found in BC/OC patients (i.e., those with BC and/or ovarian cancer [OC]).

In this letter, we describe the 8765delAG mutation in BRCA2, a founder mutation in Jews of Yemenite origin.

During the screening of BC/OC patients for mutations in the BRCA2 gene, PCR products of two patients (III-9 in family BC10 and III-6 in family BC149) of Yemenite extraction had mobility shifts, as determined by single-strand conformation polymorphism (SSCA) (fig. 1*a*). Sequencing of these fragments revealed a deletion of 2 bp (AG), one of three AGs starting at position 8761 (fig. 1*b*). The mutation was analyzed in genomic DNA of the patients and of their family members, by a *Bsm*AI restriction assay using a primer into which a mismatch was introduced (fig. 1*c*). Patient II-4 in family BC703 and patient III-2 in family BC703, who were referred to us because of their ethnic affiliation and positive family history, were analyzed directly for the mutation. The pedigrees of the three families are presented in figure 2. We could not find any relationship among the three families. In families BC10 and BC149, only BC was reported. In family BC703, one of the sisters had BC and

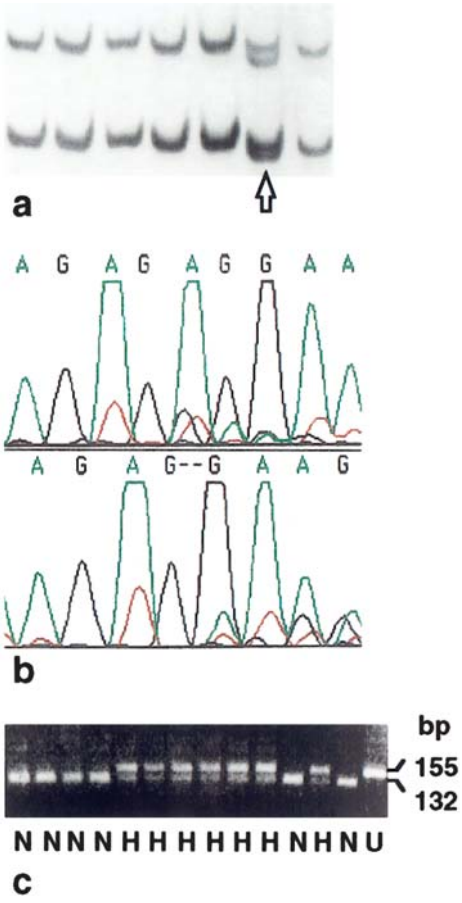

Figure 1 *a,* SSCA. The arrow indicates the fragment with mobility shift in patient III-1 of family BC10; and the other lanes contain DNA samples of unrelated BC/OC patients. PCR primers for amplification of exon 20 were retrieved from the Breast Cancer Information Core (1997); they are 20F, 5′-cactgtgcctggcctgatac-3′; and 20R, 5′-atgttaaattcaaagtctcta-3′. Amplification conditions were 35 cycles of 94°C for 30 s, 55°C for 1 min, and 72°C for 30 s; the size of the PCR product was 296 bp. SSCA was performed as described elsewhere (Zlotogora et al. 1995). *b,* Sequence of the 8765delAG mutation in exon 20 of BRCA2 The PCR fragments with mobility shift in SSCA were separated on 8% polyacrylamide gel, were excised from the gel, and were run on 1% low-melt-temperature agarose in tris-acetate/EDTA buffer. The DNA was cleaned with β-Agarase (NEB) and was precipitated with isopropanol. The purified PCR fragments were sequenced by the dideoxy terminator cycle–sequencing method with AmpliTaq DNA polymerase, FS (ABI Prism Ready Reaction Kit), and then were analyzed by use of an automatic DNA sequencer (ABI PRISM 310). The primers for sequencing were the same as those for SSCA. *c,* Restriction analysis (with *Bsm*AI) of the 8765delAG mutation in family members of the identified carriers. U = uncut; N = normal; and H = heterozygote. A mismatch was introduced into one of the primers, and, as a result, the normal allele acquired a *Bsm*AI restriction site. The PCR primers were 20F and misR (5′-gctgcttccttttcttcg*t-3′), and the size of the PCR product was 155 bp for the normal allele and 153 bp for the mutant allele. The PCR products were cut by *Bsm*AI (NEB) and were separated on NuSieve:agarose 3:1, were stained by ethidium bromide, and were visualized under a UV lamp. In the heterozygote, two bands—153 bp and 132 bp—were seen.

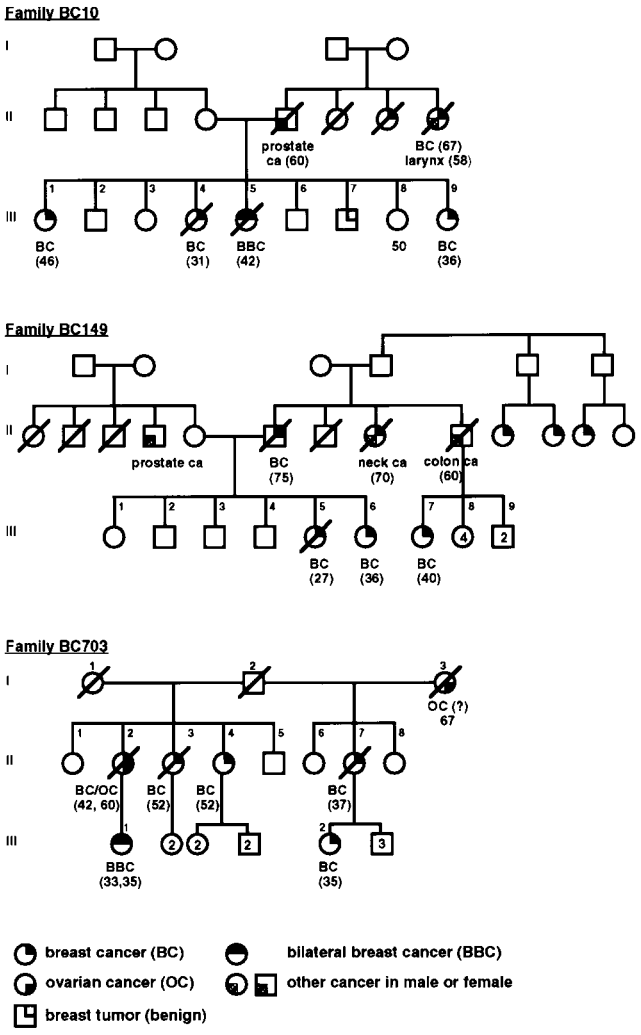

Figure 2 Pedigrees of three families with the 8765delAG mutation. Numbers in parentheses are the ages (in years) at diagnosis.

OC. In the three sibships there were 27 sisters (including the index cases); 13 of them had BC, 2 had bilateral BC, and 1 had BC and OC. The ages at diagnosis were 27–52 years, with a mean of 38.4 years. In all three families, the fathers were apparent carriers. In family BC10, the father had prostate cancer at the age of 60 years; in family BC149, the father had BC at the age of 75 years. The father (I-2) in family BC703 died at the age of 80 years of a cerebrovascular accident (stroke). Other cancers in the families were colon, neck, and laryngeal cancer.

Nine BC patients of Yemenite origin (two of whom were of mixed origin) and without family history of BC/OC were analyzed for the 8765delAG mutation, and none was found to be a carrier (table 1). In a sample of 140 healthy individuals of Yemenite origin, 1 carrier was identified. The control DNA samples were collected from unrelated and unselected individuals and were identified interms of a code number. The frequency (0.7%) of the 8675delAG mutation that was observed in this sample should be validated in a larger sample.

In addition, we tested the 8765delAG mutation in 41 Jewish BC patients—28 Ashkenazi Jews and 13 Sephardic and Oriental Jews (table 1)—who did not carry any of the Ashkenazi founder mutations (185delAG and 5382insC, in BRCA1 ; and 6174delT, in BRCA2). This group of patients met some of the criteria of hereditary BC, such as positive family history of BC and/or OC in three first-degree relatives, bilateral BC, both BC and OC, BC and other primary cancer, or early age at diagnosis (<30 years); some of these patients have been described elsewhere (Abeliovich et al. 1997). None of these patients was a carrier of the 8765delAG mutation, in support of the conclusion that the 8765delAG mutation is confined to the Yemenite Jews.

The haplotypes (D13S171 and D13S260) of the chromosomes bearing the 8765delAG mutation were analyzed in the three families (Lerer et al. 1994). The families all share the same haplotype: allele 7 with $(CA)_{n=5}$, of D13S171, and allele 7, with $(CA)_{n=21}$, of D13S260. In the anonymous carrier in the control group, we could not determine the haplotype, but, in both loci, one of the alleles was the same as that of the mutation's haplotype in the carrier patients. It thus has been concluded that this is a founder mutation in the Yemenite Jews. Among the Jewish people, the Yemenite Jews are a relatively small group that, until their immigration to Israel (during the last century), lived for many years in isolation. The same mutation previously has been described in two French Canadian patients (Phelan et al. 1996). Family members of the two French Canadian patients included 22 females with BC only, with mean age at diagnosis 49.2 years. It thus seems that the risk that the 8765delAG mutation confers on carriers is mainly (but not exclusively) with regard to BC. On the basis of the limited number of patients studied, it seems that the penetrance of the 8765delAG mutation is relatively high, since the carriers had a strong family history of BC; 13 of 27 first-degree relatives had BC, and the age at diagnosis was very early.

It would be of interest to compare the haplotype of the 8765delAG mutation in the Yemenite Jews with that in the French Canadians, although it is highly unlikely that the two groups share a mutation of common ancestral origin. Since the mutation is a deletion of AG in a stretch of AGAGAG, the chance of recurrent mutation resulting in AG deletion in this site might be higher than that in a site having a single AG.

Nine BC patients of Yemenite origin—eight of whom were diagnosed at age <50 years, including one patient with bilateral BC and one patient with two other primary tumors—were not carriers of this mutation, which

Table 1

Jewish BC Patients Who Were Analyzed for the 8765delAG Mutation, According to Clinical Diagnosis and Ethnic Affiliation

	No. (Age [Years] at Diagnosis)				
	Ashkenazim	Sephardim	Orientals	Yemenites	Total
Positive family history	16 (40–64)	4 (40–64)	2 (40–64)		22
BC:					
Unilateral	2 (25–29)	2[a] (25–29)	3 (25–29)	7 (20, 32, 35, 44, 46, 49, 55)[b]	14
Bilateral	9[c]	1	1 (29–65 [BC 40–43, OC 50–58])[d]	1 (BC 34, 38; OC 38)	11
BC and OC	1[e]				2
BC and other primary tumors				1[f]	1
Total	28	7	6	9	50

[a] One patient had a positive family history (i.e., at least three first-degree relatives with BC and/or OC).
[b] Two patients were of mixed origin (i.e., Yemenite/Ashkenazi and Yemenite/non-Ashkenazi).
[c] Four patients had a positive family history (i.e., at least three first-degree relatives with BC and/or OC).
[d] One patient had a positive family history (i.e., at least three first-degree relatives with BC and/or OC).
[e] One patient had a positive family history (i.e., at least three first-degree relatives with BC and/or OC).
[f] The other primary tumors were colon cancer and leukemia.

might indicate that the 8675delAG mutation is not the only BRCA mutation in the Yemenite Jews. Indeed, one BC patient of Yemenite origin (who was not included in this study) was identified as a carrier of the 5382insC mutation in BRCA1.

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Electronic-Database Information

Breast Cancer Information Core, http://www.nhgri.nih.gov/intramural_ research/lab_transfer/Bic

References

Abeliovich D, Kaduri L, Lerer I, Weinberg N, Amir G, Sagi M, Zlotogora J, et al (1997) The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet 60:505–514

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 62:676–689

Lerer I, Meiner V, Pashut-Lavon I, Abeliovich D (1994) Molecular diagnosis of Prader-Willi syndrome: parent-of-origin dependent methylation site and non-isotopic detection of $(CA)_n$ dinucleotide repeat polymorphism. Am J Med Genet 52:79–84

Levy-Lahad E, Catane R, Eisenberg S, Kauffman B, Hornreich G, Lishinsky E, Shohat M, et al (1997) Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. Am J Hum Genet 60: 1059–1067

Phelan CM, Lancaster JM, Tonin P, Gumbs C, Cochran C, Carter R, Ghadirian P, et al (1996) mutation analysis of the BRCA2 gene in 49 site specific breast cancer families. Nat Genet 13:120–122

Szabo CI, King M-C (1997) Population genetics of BRCA1 and BRCA2. Am J Hum Genet 60:1013–1020

Thorlacius S, Sigurdsson S, Bjarnadottir H, Olafsdottir G, Jonasson JG, Tryggvadottir L, Tulinius H, et al (1997) Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet 60:1079–1084

Zlotogora J, Lerer I, Bar-David S, Ergaz Z, Abeliovich D (1995) Homozygosity for Waardenburg syndrome. Am J Hum Genet 56:1173–1178

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Localization of a Gene (*CORD7*) for a Dominant Cone-Rod Dystrophy to Chromosome 6q

To the Editor:

The cone-rod dystrophies are a heterogeneous group of retinal disorders, often leading to registrable blindness, that are characterized by an initial loss of cone photo-