port in cells from patients with fatal peroxisomal disorders. J Cell Biol 130:51–65

Wiemer EA, Out M, Schelen A, Wanders RJ, Schutgens RB, van den Bosch H, Tager JM (1991) Phenotypic heterogeneity in cultured skin fibroblasts from patients with disorders of peroxisome biogenesis belonging to the same complementation group. Biochim Biophys Acta 1097:232–237

Yahraus T, Braverman N, Dodt G, Kalish JE, Morrell JC, Moser HW, Valle D, et al (1996) The peroxisome biogenesis disorder group 4 gene, PXAAA1, encodes a cytoplasmic ATPase required for stability of the PTS1 receptor. EMBO J 15:2914–2923

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A Breast Cancer Patient of Scottish Descent with Germ-Line Mutations in *BRCA1* and *BRCA2*

To the Editor:

Ramus et al. (1997) previously described an Ashkenazi Jewish patient found to have germ-line mutations in both breast and ovarian cancer–susceptibility genes, *BRCA1* and *BRCA2*. We report the first such example for the non-Jewish Caucasian population. The patient, who is indicated by an arrow in pedigree 232 (fig. 1), was of Scottish origin. She was diagnosed with breast cancer (grade 2 adenocarcinoma) at age 35 years. Simultaneous screening by protein truncation test of both *BRCA1* (exon 11) and *BRCA2* (exon 11) detected truncating

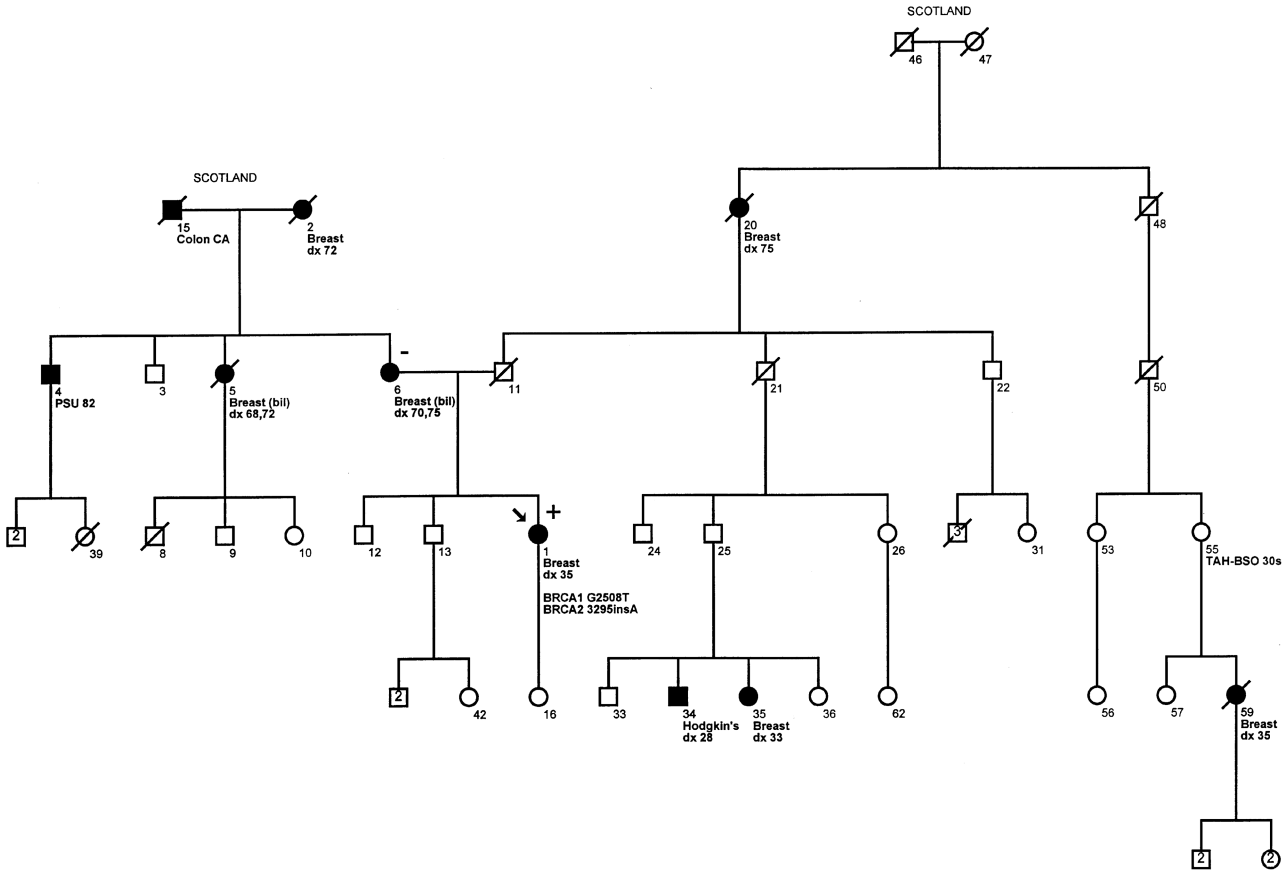

Figure 1 Pedigree of family 232. Blackened circles indicate affected women; blackened squares indicate affected men; and a diagonal slash indicates that the patient is deceased. Individual identification numbers appear directly below the symbols. Breast cancer is indicated with age at diagnosis ("dx"); bilateral breast cancer is indicated ("bil") with ages at diagnoses; "PSU" indicates primary site not known; and "TAH-BSO" indicates a complete abdominal hysterectomy, including bilateral oophorectomy. The plus sign (+) indicates the presence of the *BRCA1* G2508T mutation and the *BRCA2* 3295insA mutation, in the proband tested. The minus sign (−) indicates the absence of these two mutations in *BRCA1* and *BRCA2*.

mutations. Direct sequencing revealed *BRCA1* G2508T as a nonsense mutation resulting in Glu→stop codon and *BRCA2* 3295insA as an in-frame stop codon at position 1025. Mutation results were confirmed at a separate *BRCA1* and *BRCA2* testing facility in Toronto. These are novel mutations not previously reported in the Breast Cancer Information Core database.

This patient had a maternal and paternal history of breast cancer. The maternal side contained cases of postmenopausal breast cancer: her mother (patient 6) was diagnosed with bilateral breast cancer at ages 70 and 75 years, and her aunt (patient 5) was diagnosed at ages 68 and 72 years; her grandmother (patient 2) was diagnosed with breast cancer at age 72 years. The paternal side contained cases of premenopausal breast cancer: a cousin once removed (patient 35) was diagnosed with breast cancer at age 33 years, her grandmother (patient 20) was diagnosed at age 75 years, and a distant cousin (patient 59) was diagnosed at age 35 years. Interestingly, her mother did not have either mutation, suggesting that both *BRCA1* and *BRCA2* germ-line mutations originated from the father of the proband. This is consistent with the ages at onset of the women on the paternal side, indicating the presence of at least one of these mutations in the women diagnosed with premenopausal breast cancer. To date, no other family members are available for testing. For counseling of individuals identified as double heterozygotes for mutations in *BRCA1* and *BRCA2,* the risk of transmitting a breast cancer–susceptibility gene(s) to any offspring is 3/4.

The frequency of *BRCA1* and *BRCA2* mutations in the United Kingdom and Canada has been estimated at 1/850–1/500 individuals (Easton 1993; Ford et al. 1995); therefore, the likelihood of finding a double heterozygote in this population is between 1/700,000 and 1/250,000. It is estimated that, for individuals of Ashkenazi Jewish descent, the likelihood of being a carrier for one of three common *BRCA1* or *BRCA2* mutations is $\geqslant$1/50 (Roa 1996; Tonin et al. 1996); therefore, the likelihood of finding a double or compound heterozygote is ~1/2,500 for Ashkenazi Jewish families unselected for cancer.

This individual is the first example to date of a double heterozygote for the high-penetrance breast cancer–susceptibility genes, *BRCA1* and *BRCA2,* outside of the Ashkenazi Jewish population (Ramus et al. 1997). This finding is predictably rare, with a maximum frequency of 1/250,000. Our patient was diagnosed with early-onset breast cancer at age 35 years, an age typical of other *BRCA1/BRCA2*–associated breast cancers. Her case does not suggest a more severe presentation or younger age at diagnosis for women found to harbor germ-line mutations in both genes. We cannot generalize that complete screening of *BRCA1* and *BRCA2* in families with a previously identified mutation in either gene is necessary until other double heterozygotes are identified. However, if the family mutation is not found in women diagnosed with early-onset breast cancer or ovarian cancer, there is a basis for comprehensive screening of both genes.

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Electronic-Database Information

URLs for data in this article are as follows:

Breast cancer information core database, http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/

References

Ford D, Easton DF, Peto J (1995) Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 57:1457–1462

Easton DF, Ford D, Peto J (1993) Inherited susceptibility to breast cancer. Cancer Surv 18:1–17

Ramus SJ, Friedman LS, Gayther SA, Ponder BAJ (1997) A breast/ovarian cancer patient with germline mutations in both *BRCA1* and *BRCA2*. Nat Genet 15:14–15

Roa BB, Boyd AA, Vocik K, Richards CS (1996) Ashkenazi Jewish population frequencies for common mutations in *BRCA1* and *BRCA2*. Nat Genet 14:185–187

Tonin P, Weber B, Offit K, Couch F, Rebbeck TR, Neuhausen S, Godwin AK, et al (1996) Frequency of recurrent *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish breast cancer families. Nat Med 2:1179–1183

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Evidence of Founder Mutations in Finnish BRCA1 and BRCA2 Families

To the Editor:

Approximately 4%–10% of breast and ovarian cancer is thought to be inherited (Newman et al. 1988). Most hereditary ovarian cancer cases and a significant portion