A Common Mutation in BRCA2 That Predisposes to a Variety of Cancers Is Found in Both Jewish Ashkenazi and Non-Jewish Individuals

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Abstract

Recent studies have identified mutations in the breast and ovarian cancer susceptibility gene 2 (BRCA2), one which has been found in the germline of several males and one female affected with breast cancer. To establish the carrier frequency of this mutation in a large population of individuals affected with cancer, we evaluated constitutional DNA isolated from 83 individuals diagnosed with breast cancer and 93 diagnosed with ovarian cancer at any age, 42 of whom reported a family history of cancer. Using a simple allele-specific PCR-based nonradioactive method, we detected a total of eight individuals (4.5%) carrying a 1-bp deletion at nucleotide 6174 of the BRCA2 gene (6174delT). The age of disease onset in the mutant allele carriers was highly variable and typically late onset (41–72 years for breast cancer and 48–73 years for ovarian cancer). Evaluation of family histories for the eight mutant allele carriers revealed that several individuals had significant cancer histories that included, in addition to breast and/or ovarian cancer, an increased incidence of colon, esophageal, pancreatic, stomach, and hematopoietic cancers. Interestingly, seven of the eight individuals were of Ashkenazi Jewish descent. Haplotype data for the mutant allele carriers using markers spanning the region of the BRCA2 gene on chromosome 13q12–q13 suggest that only two of the confirmed Jewish Ashkenazi individuals share a single common ancestry, indicating several independent origins for this mutation. These data provide evidence for the presence of a specific BRCA2 mutation which has its origins in both Jewish Ashkenazi and non-Jewish populations. The observed representation of specific mutations within a subgroup of the general population may potentially help contribute to the development of inexpensive and routine tests such as the one described in our study.

Introduction

Some families suffer from an extraordinarily high incidence of breast and ovarian cancers. It has been estimated that 5–10% of all cases may be due to an inherited predisposition, but the exact number and distribution of predisposing genes is unknown. The existence of cancer-prone families has prompted an intense search for the genes which may predispose individuals to breast and ovarian cancers and may contribute to the far more common sporadic forms of these diseases. Building on the results of linkage studies, two groups have recently identified a second breast and ovarian cancer susceptibility gene, referred to as BRCA2 (1–4). Germline mutations in BRCA2 are thought to account for as much as 70% of inherited breast cancers not linked to BRCA1 (2). In addition, Couch et al. (5) recently identified several mutations in the BRCA2 gene in males affected with breast cancer and in individuals from site-specific female breast and breast-ovarian cancer families. One of these mutations, referred to as 6174delT, was observed in 3 of the 11 mutant allele carriers in that series. One individual, a male diagnosed with breast, rectal, and esophageal cancers was determined by us to be of Jewish ancestry (5).

In the present study, we used a simple AS-PCR-based nonradioactive method to screen for the 6174delT BRCA2 mutation in Jewish and non-Jewish women and men who were affected with cancer and who had a strong family history of breast and/or ovarian cancer. In addition, we evaluated a large panel of women diagnosed with breast and ovarian cancer who were unselected for family history or ethnicity. Our studies suggest that the 6174delT mutation in BRCA2 is present within both the Jewish Ashkenazi and non-Jewish populations. Furthermore, haplotype analysis of the mutant allele carriers suggests several independent origins for this recurrent mutation. Our results indicate that it may be possible to develop rapid and effective screening methods for determining BRCA2 mutation carrier status in cancer patients.

Materials and Methods

Blood and Tissue Samples. As part of a Fox Chase Cancer Center Internal Review Board approval protocol, primary ductal carcinomas of the breast and epithelial tumors of the ovary were obtained from consenting patients undergoing surgery at the American Oncological Hospital and at Lankenau Hospital in Philadelphia from 1990 to 1996. Additional samples were obtained from the Cooper Hospital (Camden, NJ) and the Gynecological Oncology Group/Cooperative Human Tissue Network Ovarian Tissue Bank (Columbus, OH). Accompanying adjacent nonneoplastic breast and ovarian tissues and peripheral blood samples were also obtained. Tumor histopathological classifications were determined according to the typing scheme of the WHO. Tumor materials utilized in determination of hereditary genetic transmission of disease from deceased individuals were obtained as paraffin-embedded samples from outside facilities. Peripheral blood samples were also obtained from consenting affected and unaffected high-risk family members through the Family Risk Assessment Program with the approval of Fox Chase Cancer Center's Internal Review Board. In addition, consent forms signed by all of the Family Risk Assessment Program patients participating in our study allowed for such samples to be used for a wide range of research purposes, including screening for mutations in candidate predisposing genes.

Determination of Family History. Forty-two cancer-prone families (24 breast cancer only, 2 ovarian cancer only, and 16 breast-ovarian cancer kindreds) were evaluated in this study. For each family, a pedigree was prepared on the basis of a detailed family history of an informed family member. Cancers in individuals reporting a personal history of disease were confirmed by either a pathology report, hospital records, or death certificate when such records were available. A disease was considered potentially familial in its inheritance pattern if the family contained at least three first- or second-degree relatives who had been diagnosed with cancer. The pedigree, whenever possible, included historical information spanning several generations as well as data regarding cancer profiles of all affected individuals and

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ethnicity information. In particular, individuals were asked about "childhood religious upbringing" with "Jewish" being one of the choices. Because more than 80% of world Jewry is comprised of individuals of Ashkenazi descent and since all Jewish individuals in our study reported that their ancestors came from Eastern Europe, no inquiries were made to distinguish between Sephardic and Ashkenazi subgrouping. Information on specific European cities and/or regions of origin of ancestors was also included in the pedigree.

Screening Criteria. Candidates for genetic evaluation fell within one of the three following categories: (a) affected with breast cancer (any age) and unselected for ethnicity and family history; (b) affected with ovarian cancer (any age) and unselected for ethnicity and family history; and (c) affected with breast and/or ovarian cancer and reporting a family history of at least one first-degree relative with breast and/or ovarian cancer (any age). If a BRCA2 mutation was found in a research participant in categories a or b, a retrospective history of cancer in their families was obtained through medical records. Otherwise, these individuals were treated as sporadic cases of either breast or ovarian cancer, and no family history or ethnic information was obtained.

DNA Isolation. Genomic DNA was prepared from fresh blood and tumor samples as described previously (6). Isolation of DNA from paraffin-embedded samples was performed as described previously (7).

AS-PCR Analysis of the BRCA2 6174delT Mutation. The PCR was performed in a reaction volume of 10 μl containing 100 ng genomic DNA as template, 10 μM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, 0.001% gelatin, 1 μM of both the forward and reverse primer, 60 μM of each deoxynucleotidetriphosphate, 5% DMSO, and 0.5 units AmpliTaq DNA polymerase (Perkin Elmer/Cetus). Following an initial denaturation step at 94°C for 4 min, DNA was amplified through 20 cycles consisting of 5-s denaturing at 94°C, 1-min annealing at 70°C-0.5°C/cycle, and 1-min extension at 72°C. The samples were then subjected to an additional 35 cycles, consisting of 5-s denaturation at 94°C, 1-min annealing at 60°C, 1-min extension at 72°C, and a final extension at 72°C for 5 min. The primer sequences used to detect the mutant allele were 5′-TTGTGGGATTTTTAGCACACGAAG-3′ (mut sense) and 5′-GCTTTCCTCACTTGCTGCTACTAATCCC-3′ (wt antisense). The integrity of the DNA was evaluated using 5′-TTGTGGGATTTTTAGCACACGAAG-3′ (mut sense) and 5′-GCTTTCCTCACTTGCTGCTACTAATCCC-3′ (wt sense) and the wt antisense primer. Ten μl of the PCR reaction products were separated on a 2% agarose gel and stained with ethidium bromide. The detection of a 271-bp fragment using the mut sense/wt antisense primer set indicates that the individual carries a mutant allele. Positive control DNAs are included in each evaluation. Mutations detected using AS-PCR analysis were verified by amplifying the DNA using the BRCA2 primer set (exon 11.11) described by Couch et al. (5) and by directly sequencing the DNA.

Confirmation of the 6174delT Mutation by DNA Sequencing. The DNA isolated from mutant allele carriers was amplified by PCR, and the product was separated from primers using Wizard resin (Promega) according to the manufacturer’s specifications. The purified DNA was subjected to cycle sequencing using an automated fluorescence-based cycle sequencer (Model 377A Automated Sequencer; Applied Biosystems) and taq dye terminator chemistry. Sequencing primers were the same as those used to amplify the template. To test the sensitivity of our assay, we sequenced 30 DNAs which failed to produce a 271-bp fragment when amplified using the 6174delT-specific mutant primer set as described above. As expected, all 30 samples yielded wild type sequences.

Haplotyp Analysis. Haplotypes were constructed for 6174delT BRCA2 mut allele carriers using the following six microsatellites: D13S290, D13S260, D13S171, D13S267, D13S218, and D13S263, which span the region of 13q containing the BRCA2 gene (8, 9). Simple tandem repeat polymorphisms were typed using methods we have described previously (6, 10).

Results

Screening for the 6174delT BRCA2 Mutation in Breast and Ovarian Cancer Patients Unselected for Ethnicity and Family History. Fifty-one women diagnosed with either infiltrating ductal carcinoma or ductal carcinoma in situ (unselected for ethnicity and family histories of cancer) were screened using AS-PCR analysis and direct DNA sequencing for the 6174delT BRCA2 mutation in exon 11 (Fig. 1). We found that this method was rapid, reliable, and highly sensitive for detecting this recurrent mutation. No false positives were detected in any of the samples evaluated (see “Materials and Methods”). The 6174delT mutation in BRCA2 presumably results in a frameshift and premature termination of translation and, thus, is unlikely to be a benign polymorphism. One individual (AKG-261) was found to carry the BRCA2 mutation (Table 1). This woman was diagnosed with infiltrating ductal carcinoma (grade III) at age 44 years. Medical records indicated that AKG-261 was of Jewish ancestry and had a family history consisting of a maternal grandmother diagnosed with breast cancer at age 50 years, a paternal grandmother diagnosed with gastric cancer, and a paternal aunt with lymphoma in her 50s. We next evaluated DNA isolated from 83 individuals with epithelial ovarian cancer. Two malignant tumors, AKG-67 and AKG-296, were found to be homozygous for this mutation. Evaluation of the two individuals’ constitutional DNA indicated that the mutation was present in their germline. AKG-67, a Caucasian Protestant female, was diagnosed with stage IV ovarian cancer at age 60 years. Four years later, the woman relapsed and was found to have developed a metastatic poorly differentiated adenocarcinoma with serous features and rare psammoma bodies found on the omentum, appendix, bladder, and ovarian surfaces. The woman reported no family history of breast and/or ovarian cancer; however, her son was diagnosed with lymphocytic lymphoma and her sister with leukemia (ages unknown; Table 1). AKG-296 was diagnosed with stage IIIIC ovarian cancer at age 73 years. She reported being of Jewish ancestry and had a personal history of breast cancer and a family history consisting of a mother with breast cancer (age 47 years; Table 1). Fifty additional women diagnosed with either benign ovarian tumors ($n = 40$) or ovarian tumors of low malignant potential ($n = 10$) were also tested, and no mutations were detected.

Screening for BRCA2 Mutations in High-Risk Families. We next sought to establish the frequency of the 6174delT mutation in individuals affected with breast and/or ovarian cancer who reported a family history of cancer. Affected individuals reporting one or more first-degree relatives with breast and/or ovarian cancer (at any age) were screened as described above. Of the 42 high-risk families tested (24 breast cancer only, 2 ovarian cancer only, and 16 breast-ovarian cancer kindreds), 5 were found to contain this frameshift mutation. Interestingly, all five reported they were of Jewish ancestry. Review of the types of cancer observed in some of these BRCA2 mutant allele families was striking. For example, in kindred AKG-8775 the mutation was detected in a woman diagnosed with ovarian cancer at age 58 years (Figs. 1 and 2). Her sister, who was diagnosed with late-onset breast cancer (68 years), was positive for the mutation; however, her mother (breast cancer at age 78 years) was found to be negative. Using archival material from the proband’s father, who was diagnosed with colon cancer in his 60s, we were able to determine that the 6174delT mutation was inherited paternally (Fig. 2). In this aspect, the proband reports an extraordinary paternal family history of cancer, including four cancers of the colon, three cancers of the breast, two cancers of the stomach, two cancers of the uterus, two cancers of the lymphatic system, and one cancer each of the pancreas, brain, lung, and oral cavity. No obvious environmental factors such as smoking were reported by the proband, which may have contributed to the development of some of these varied cancers. Family AKG-204 reports a similar diversity of cancers (i.e., six colon, four breast, and one each of the pancreas, esophagus, skin, and lung) (Table 1 and Fig. 2). Family AKG-16652 is less spectacular; however, the mutation was detected in a Jewish male diagnosed with breast cancer at age 52 years and his asymptomatic brother. The proband’s mother was diagnosed with breast cancer at age 43 years. In another family (AKG-13), the only evidence of cancer was two sisters with late-onset breast cancer (67 and 72 years old; Table 1). These results suggest that mutations in
BRCA2 IN CANCERS OF DIVERSE ORIGINS

Fig. 1. Detection of the 6174delT mutation using an AS-PCR-based method. Constitutional DNA was amplified using primer pairs specific for the 6174delT mutation or the wild-type sequence. A, ethidium bromide-stained agarose gels of PCR amplified the mut (top) or wt (bottom) BRCA2 sequence in exon 11. Upper panel, PCR products generated using the 6174delT-specific mut primer set. A 271-bp product is observed in Lanes 2, 4, and 7, representing mutant allele carriers in family AKG8775. Absence of the 271-bp fragment in the remaining lanes indicates that the individual is homozygous for the wild-type BRCA2 sequence. A constant band less than 100 bp in length is observed for all lanes and represents background primer by-products. Lower panel, PCR products (271 bp) generated using the wt primer set. A 100-bp DNA ladder is included in the first nonsample lane for both agarose gels. B, sequence analysis of the mut (upper panel) and wt (lower panel) PCR products. Constitutional DNA isolated from a mutant allele carrier (heterozygote) and a normal control (homozygous 96) was amplified and sequenced as described in "Materials and Methods." Top arrow, position of the deleted T nucleotide at position 6174 of the BCRA2 cDNA sequence. The frameshift mutation results in overlapping sequences in the heterozygote's constitutional DNA beginning at the position of the deletion. Lower panel, wild-type sequence profile.

BRCA2 may predispose to a variety of cancers and that the penetrance is highly variable.

Haplotype Analysis of Unrelated 6174delT Mutant Allele Carriers. To study haplotype association, individuals carrying the 6174delT mutation were typed using six microsatellite polymorphisms spanning the BRCA2 gene; these were from centromere to telomere: D13S290, D13S260, D13S171, D13S267, D13S218, and D13S263 (8, 9). In cases where only a single affected individual was available, DNA isolated from normal/tumor tissue pairs was used for loss of heterozygosity analysis to determine the tumor haplotype. Two of the eight 6174delT mutant allele carriers who were Jewish shared a common haplotype for all of the six markers tested (Table 2). The
Table 1: Families showing germline BRCA2 mutation 6174delT in breast only and breast-ovarian cancer-prone families and affected individuals unselected for family history

<table>
<thead>
<tr>
<th>Designation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Codon</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>6174delT</td>
<td>11</td>
<td>AGT GGA AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual</th>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Codon</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKG-261&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
<tr>
<td>AKG-296&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
<tr>
<td>AKG-204&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
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<tr>
<td>AKG-778&lt;sup&gt;f&lt;/sup&gt;</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
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<tr>
<td>AKG-877&lt;sup&gt;f&lt;/sup&gt;</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
<tr>
<td>AKG-16652&lt;sup&gt;f&lt;/sup&gt;</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual</th>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Codon</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer patient</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
<tr>
<td>Ovarian cancer patients</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
<tr>
<td>High-risk kindreds</td>
<td>17</td>
<td>GGC GAG AAT C-AGG GAA ATC</td>
<td>1982</td>
<td>Stop 2003</td>
</tr>
</tbody>
</table>

<sup>a</sup> Designation of mutations conserving as much normal sequence as possible when exact starting nucleotide is ambiguous. Underlined base, deleted nucleotide in mutant allele carrier.

<sup>b</sup> Number of verified cases of breast and ovarian cancer in the family. A research participant with both breast and ovarian cancer was counted in each total. Bilateral breast cancers were counted as two separate cancers.

<sup>c</sup> Confirmed Jewish ancestry.

<sup>d</sup> Germline mutation was identified in an individual affected with breast cancer without prior knowledge of a family history of breast and/or ovarian cancer.

<sup>e</sup> Confirmed non-Jewish ancestry.

<sup>f</sup> Germline mutation was identified in an individual affected with ovarian cancer without prior knowledge of a family history of breast and/or ovarian cancer.

<sup>g</sup> Male was diagnosed with breast cancer at age 52 years.

In this study, we evaluated the frequency of a single bp deletion at nucleotide 6174 of BRCA2 in three populations of individuals affected with either breast or ovarian cancer. We used a simple and highly effective method (e.g., AS-PCR) to detect the presence of the 6174delT mutation in a group of women diagnosed with breast cancer (any age), but who were unselected for a family history of cancer and contribution to the frequency that was observed in the population of women and men affected with cancer.

Discussion

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Table 2. Haplotype analysis of BRCA2 6174delT mutant allele carriers for chromosome 13q markers

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>D13S290</th>
<th>D13S260</th>
<th>D13S171</th>
<th>D13S267</th>
<th>D13S218</th>
<th>D13S263</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKG-7880</td>
<td>F</td>
<td>F</td>
<td>E</td>
<td>C</td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td>AKG-8775</td>
<td>F</td>
<td>E</td>
<td>E</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>AKG-16652</td>
<td>F/F</td>
<td>C/F</td>
<td>F/F</td>
<td>C/F</td>
<td>D/D</td>
<td>D/G</td>
</tr>
<tr>
<td>AKG-204</td>
<td>F/F</td>
<td>F/F</td>
<td>A/F</td>
<td>F/F</td>
<td>D/D</td>
<td>G/H</td>
</tr>
<tr>
<td>AKG-226</td>
<td>F/F</td>
<td>D/F</td>
<td>A/A</td>
<td>C/F</td>
<td>D/D</td>
<td>B/H</td>
</tr>
<tr>
<td>AKG-67</td>
<td>F</td>
<td>E</td>
<td>F</td>
<td>E</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>AKG-261</td>
<td>F</td>
<td>C/F</td>
<td>E</td>
<td>E</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>AKG-296</td>
<td>B/F</td>
<td>B/E</td>
<td>E</td>
<td>C/D</td>
<td>D</td>
<td>E/F</td>
</tr>
<tr>
<td>AKG-13</td>
<td>C/F</td>
<td>F/F</td>
<td>B/B</td>
<td>F/F</td>
<td>A/D</td>
<td>D/G</td>
</tr>
</tbody>
</table>

* Indicates the most frequently occurring allele for that polymorphism.

Mutation in this individual was previously reported by Couch et al. (5).
diversity of cancers observed in some of our BRCA2-mutant families has been observed by others (14, 21) and is reminiscent of the cancers reported in hereditary nonpolyposis colorectal cancer (Lynch II) families and Li-Fraumeni kindreds (22–25). Of significance, we have observed increased chromosomal abnormalities in lymphocytes of individuals carrying a mutant BRCA2, suggesting that increased genomic instability due to inactivation of BRCA2 may account for the wide range of tumors observed.4 Overall, our results suggest that mutations in BRCA2 predispose to breast (male and female) cancer, ovarian cancer, and most likely cancers of the colon, esophageal, pancreas, stomach, and lymphatic system. We also observed a number of lung, brain, and endometrial tumors. However, additional studies are in progress to assess the function of BRCA2 and to clearly demonstrate a role for the inactivation of BRCA2 in the etiology of these various cancers.

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