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Research Letter

Analysis of *BRCA1* and *BRCA2* Mutations in an Iranian Family With Hereditary Breast and Ovarian Cancer Syndrome

To the Editor:

To date, *BRCA1* and *BRCA2* mutations have been reported in breast and ovarian cancer families from a wide range of ethnic groups. Founder mutations have been described for several ethnic or geographically-isolated groups, in both *BRCA1* and *BRCA2* [Szabo and King, 1997; Moslehi et al., 2000; Neuhausen, 2000]. Identifying founder mutations in a population can lead to more efficient genetic screening and accurate genetic counseling of individuals at risk [Neuhausen, 2000].

The hereditary proportions of breast and ovarian cancer in Iran are not known, and there are no reports of *BRCA1* or *BRCA2* mutations for breast and ovarian cancer families. Iran occupies a position at one of the main crossroads of historical Asian and European migration, and its population is ethnically diverse. Iran has a rich history, starting from 2000 BC with the Arianne (an offshoot of Indo-European tribes) migration to the Near East. During its 4,000-year history, Iran has been conquered by many empires—the 67 million Iranians currently living in Iran are composed of a majority of Ariannes, as well as Asians, Semites, and other ethnic groups. Therefore, it is possible that there may be founder mutations responsible for the disease among one or more minority ethnic groups.

We report a novel *BRCA1* mutation in a family with four cases of ovarian cancer and one case of breast cancer in close relatives (Fig. 1). This family belongs to the subgroup of Azari Iranians. The proband in this family presented for genetic testing at the age of 49 after having been diagnosed with serous cystadenocarcinoma of the ovary at the age of 42. Her mother died of epithelial ovarian cancer at the age of 68. One of her sisters was diagnosed with epithelial ovarian cancer at the age of 52. The proband's maternal aunt was diagnosed with epithelial ovarian cancer at the age of 67 and her maternal first cousin was diagnosed with breast cancer at the age of 40. This family history is strongly suggestive of the presence of a dominant cancer susceptibility gene. Because of the strong predisposition to ovarian cancer in the family, two of the proband's sisters had total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) at the ages of 42 and 56. There were no reports of consanguineous marriages in this family. The proband and her two sisters were tested for common mutations in the *BRCA1* and *BRCA2* genes using the heteroduplex analysis and single strand conformation polymorphism (SSCP) of exons 2 and 20 of the *BRCA1* gene and performing the protein truncation test (PTT) on exon 11 of the *BRCA1* gene and exons 10 and 11 of the *BRCA2* gene. PTT demonstrated an abnormal result in exon 11 of the *BRCA1* gene in the three sisters. Upon sequencing, the abnormality was found to be a novel mutation, G2031T, at codon 638 (BIC accession no. 6432). This nonsense mutation replaces glutamic acid with a stop codon that leads to a truncated protein. This mutation has never been previously reported.

It is not yet known if this unique mutation represents an isolated case, or is a founder mutation in Iran. Other Iranian families with hereditary breast and ovarian cancer should be tested for mutations in the *BRCA1* and *BRCA2* genes in order to define the proportion of such families whose predisposition is attributable to mutations in these two genes. If the *BRCA1* exon 11 G2031T is found in additional families, then it may be prudent to screen a larger sample of Iranian breast and

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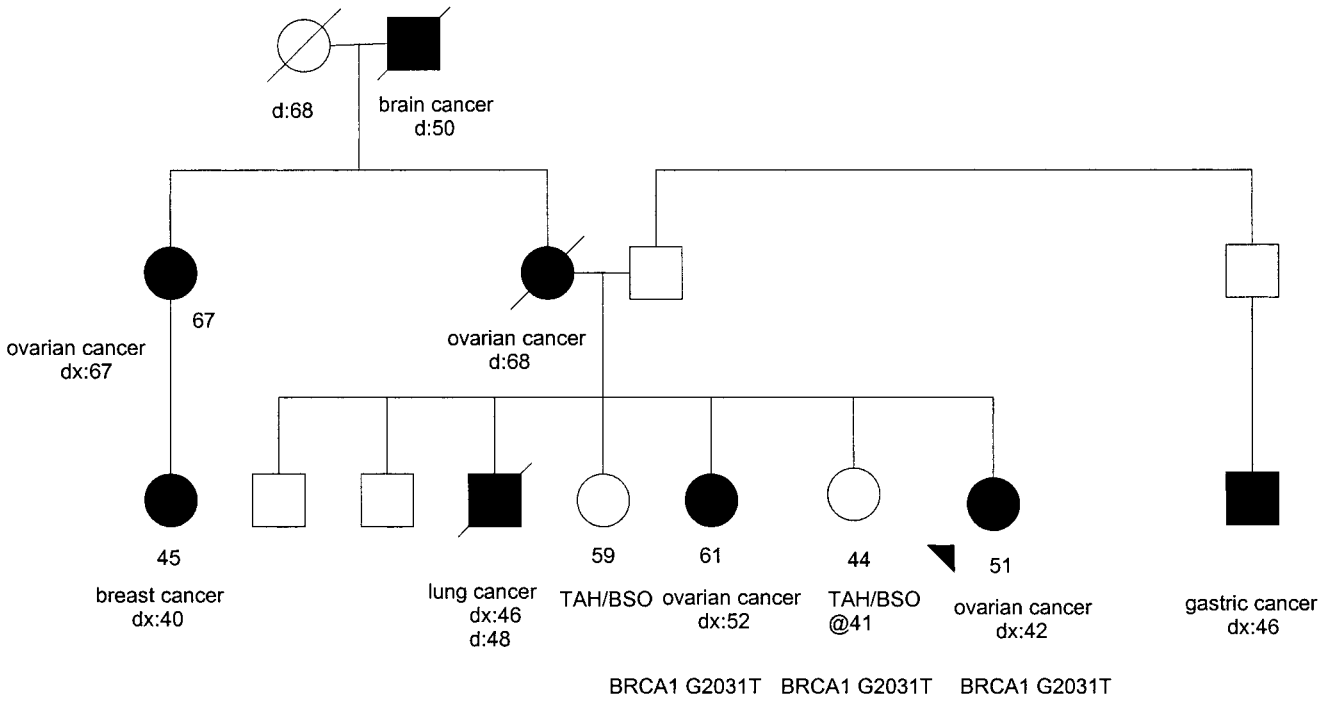

Fig. 1. Pedigree of the Iranian Family A.

ovarian cancer patients to assess the prevalence of this mutation.

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