Gene 573 (2015) 333–337

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short communication

Does familial breast cancer and thymoma suggest a cancer syndrome? A family perspective

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ARTICLE INFO

Article history:
Received 22 May 2015
Received in revised form 25 August 2015
Accepted 31 August 2015
Available online 4 September 2015

Keywords:
Hereditary cancer syndrome
Breast/ovarian cancer
Thymoma
BRCA1 gene
Mutation

ABSTRACT

Concurrence of breast cancer or thymoma with other malignancies in individual families is often observed, but the familial concurrence of breast cancer and thymoma has not yet been reported. Herein we reported a family encompassing five breast/ovarian cancer patients and two thymoma patients. Whole genome linkage analysis detected no haplotype co-segregating with both types of the tumors. In all patients with breast/ovarian cancer, genetic analysis revealed a clinically untested variant c.5141T>G in exon 18 of the *BRCA1* gene, which could be a cancer-causing variant based on the functional study of Lee et al. (2010) and our current pedigree analysis. In the two thymoma patients in our family, targeted sequencing of *RAD51L1* and *BMP2* genes in and near the translocation site of chromosome 14 and 20 previously reported in two thymoma families, did not find any pathogenic mutation. In the present study, we identified a clinically unconfirmed *BRCA1* variant segregating with breast/ovarian cancer patients in an individual family, suggesting it to be clinically functional. Our evidence, however, did not support the notion that the concurrent appearance of breast cancer and thymoma in our family represents a familial cancer syndrome caused by the same genetic disorder.

1. Introduction

Concurrence of breast cancer or thymoma with other malignancies in individual families has been described (Purtilo et al., 1981; Offit et al., 2003; Tehrani et al., 2010). Breast cancer, the most common malignancy in women, often co-occurs with other malignancies such as ovarian, pancreatic, brain cancer or sarcoma in familial cancer syndromes. Some of the syndromes have been defined as autosomal dominant disorders, such as hereditary breast and ovarian cancer, Li-Fraumeni, Lynch, Cowden, Peutz-Jeghers, and Ataxia-Telangiectasia syndrome caused by mutations in the *BRCA1*/*BRCA2*, *TP53*/*CHEK2*, *MSH2*/*MLH1*/*MSH6*, *PTEN*, *STK11* and *ATM* genes, respectively (Malkin et al., 1990; de Jong et al., 2002; Waite and Eng, 2002; Lynch and de la Chapelle, 2003; Garber and Offit, 2005).

Thymoma is the most common neoplasm in the anterosuperior mediastinum. Familial occurrence of thymoma is rare with a prevalence of 1 to 4 per million (Nicodeme et al., 2005). The cause of familial thymoma is largely unknown. Deminatti et al. (1994) and Nicodeme et al. (2005) reported a familial thymoma with a translocation between chromosome 14q and chromosome 20p (Deminatti et al., 1994; Nicodeme et al., 2005). Multiple studies of thymoma patients have shown an increased risk of different malignancies such as colorectal adenocarcinoma, lung cancer, hematologic malignancies and autoimmune diseases in family members (Levy et al., 1998; Yen et al., 2011). Some researchers suggest that thymoma associated with other malignancies in the family herald a hereditary cancer syndrome (Tehrani et al., 2010). Thus far, familial occurrence of breast cancer and thymoma has not yet been reported.

Here we report a family with both breast/ovarian cancer and thymoma patients. The malignancies are inherited in an autosomal dominant pattern (Fig. 1). The types of malignancies did not match the known familial cancer syndromes. We assume a new cancer syndrome caused by a common genetic defect and perform a whole genome linkage analysis, expecting to identify the potential genetic disorder that causes a cancer syndrome of breast/ovarian cancer and thymoma.

Abbreviations: BC, breast cancer; BIC, Breast Cancer Information Core; ESP, NHLBI Exome Sequencing Project; LOD, log of the odds; NCBI dbSNP, National Center for Biotechnology Information Human SNP Database; OC, ovarian carcinoma; UCC, uterine cervix carcinoma; UTR, untranslated region(s).

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http://dx.doi.org/10.1016/j.gene.2015.08.069
0378-1119/

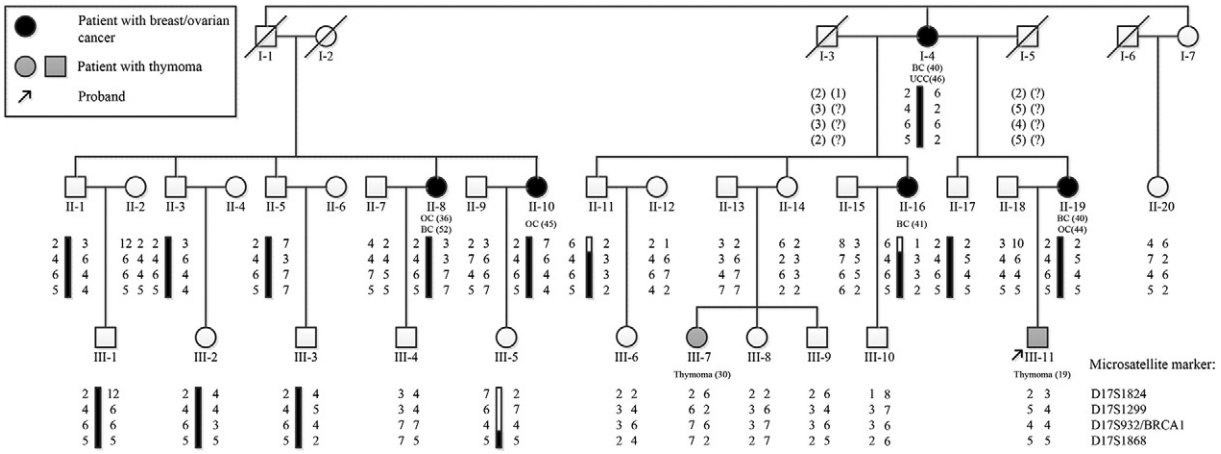

Fig. 1. Pedigree of the three-generation family. Patients with breast/ovarian cancer are shown by black symbols. Patients with thymoma are shown by grey symbols. Numbers shown below each individual indicate the genotypes of the microsatellite markers in chromosomal order. The black bars represent the mutation associated haplotype. Arrow indicates the proband. BC breast cancer, UCC uterine cervix carcinoma, OC ovarian carcinoma.

2. Materials and methods

2.1. Pedigree and subjects

We studied a large three-generation Chinese family with breast/ovarian cancer and thymoma recruited from the Department of Cardiothoracic Surgery, Medical School Affiliated Drum Tower Hospital, Nanjing University, consisting of 38 family members, 33 of whom are living, including five subjects diagnosed with breast/ovarian cancer and two subjects with thymoma (Fig. 1). The proband was referred to the department for the diagnosis of thymoma. The pedigree showed that the malignancies were inherited in an autosomal dominant pattern with incomplete penetrance. Blood samples were obtained from affected and unaffected family members for genetic analysis. Additional information including the type of cancer, current age, age of diagnosis and treatment of the patient was also obtained (Table 1). A questionnaire on the environmental exposure was completed in the studied family, including living environment, chemical carcinogens (insecticides, herbicides and painting dyes), infectious agent (Epstein Barr virus, cytomegalovirus) and radiation exposure. As a control group, 100 unrelated healthy individuals without known malignancies were also recruited.

2.2. Ethics statement

The study was approved by the Ethical Committee of Medical School Affiliated Drum Tower Hospital, Nanjing University. Informed consent was obtained from all individual participants included in the study.

2.3. DNA isolation

Genomic DNA was extracted from peripheral blood samples of collected family members and controls using a Qiagen DNA Mini blood Kit (Qiagen, Hilden, Germany) according to manufacturer instruction. DNA purity and concentration were assessed by the NanoDrop2000 spectrophotometer (Thermo Fisher Scientific, Florida, USA) and DNA quality was assessed by agarose gel electrophoresis.

2.4. Linkage and haplotype analysis

Whole genome linkage analysis was performed with 400 microsatellite markers from a commercially available set ABI PRISM Linkage Mapping Set V2.5 MD10 (Applied Biosystems, Foster City, CA). The markers were amplified by polymerase chain reaction (PCR). Markers were genotyped in all family members obtained, and linkage analysis was performed with ABI Prism 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and the length of each allele was determined by the GeneMapper software (Applied Biosystems, Foster City, CA). Two-point log of the odds (LOD) scores were calculated by computer program MLINK (Cottingham et al., 1993). To minimize the number of crossovers in the family, haplotypes were constructed and assigned.

2.5. BRCA1 mutation screening by Sanger sequencing

Mutation analysis was performed by direct DNA sequencing of all coding exons and all intron-exon boundaries including at least 50

Table 1
Clinical data of the affected family members.

Patient ID	Gender	Tumor type	Age, years	Age at diagnosis, years	Treatments received
I-4	Female	Breast cancer Carcinoma in situ of the uterine cervix	84	40 46	Right breast resected at diagnosis; underwent radiotherapy and chemotherapy; uterine resected
II-8	Female	Ovarian carcinoma Left breast cancer in situ	55	36 52	Ovarian resected at diagnosis; left breast resected
II-10	Female	Ovarian carcinoma in situ	52	45	Ovarian resected at diagnosis
II-16	Female	Breast cancer	61	41	Right breast resected at diagnosis; underwent radiotherapy and chemotherapy; left breast were resected at age 43
II-19	Female	Breast cancer Ovarian carcinoma in situ	51	40 44	Right breast resected at diagnosis; underwent radiotherapy and chemotherapy; underwent ovarian resection
III-7	Female	Thymoma	44	30	Underwent radiotherapy and chemotherapy
III-11	Male	Thymoma	25	19	Underwent radiotherapy and chemotherapy