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Case Report

Thyroid and Breast Cancer in 2 Sisters With Monoallelic Mutations in the Ataxia Telangiectasia Mutated (*ATM*) Gene

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Abstract

The presence of a bidirectional risk for metachronous carcinomas among women with thyroid and breast cancer is well established. However, the underlying risk factors remain poorly understood.

Two sisters developed papillary thyroid cancer (PTC) at age 32 and 34 years, followed by ductal carcinoma of the breast at 44 and 42 years. The 2 children of the younger sister developed ataxia-telangiectasia; the son also developed lymphoblastic lymphoma and his sister died secondary to acute lymphoblastic leukemia (ALL). They were found to be compound heterozygous for ataxia telangiectasia mutated (*ATM*) gene mutations (c.3848T>C, p.L1283P; and c.802C>T, p.Q268X). Exome sequencing of the 2 sisters (mother and aunt of the children with ataxia-telangiectasia) led to the detection of the pathogenic monoallelic *ATM* mutation in both of them (c.3848T>C; minor allele frequency [MAF] < 0.01) but detected no other variants known to confer a risk for PTC or breast cancer.

The findings suggest that monoallelic *ATM* mutations, presumably in conjunction with additional genetic and/or nongenetic factors, can confer a risk for developing PTC and breast cancer.

Key Words: thyroid cancer, breast neoplasms, ataxia telangiectasia, ATM protein, neoplastic syndromes, genetic predisposition to disease

Abbreviations: ALL, acute lymphoblastic leukemia; ATM, ataxia telangiectasia mutated; CLS, Cowden-like syndrome; CS, Cowden syndrome; ER, estrogen receptor; FNMTC, familial non-medullary thyroid cancer; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; PTC, papillary thyroid cancer.

Familial nonmedullary thyroid cancer (FNMTC) can present as nonsyndromic or syndromic malignancy [1]. FNMTC, in particular papillary thyroid cancer (PTC), appears to have a strong genetic component. However, with the exception of syndromic forms such as Gardner (*APC* gene mutations) or Cowden syndrome (*PTEN* gene mutations), the search for highly penetrant causal genes has only provided limited positive results, suggesting that FNMTC is predominantly a polygenic/multifactorial disorder with variable penetrance involving a number of low-penetrance alleles [2].

Carcinomas of the thyroid and breast are among the most frequent malignancies among females [3]. Importantly, women with a history of breast cancer have an increased risk for developing metachronous thyroid carcinomas, and vice versa [4]. The mechanisms underlying this bidirectional relationship remain largely elusive but suggest an influence of common contributing factors such as genetic predisposition; hormonal factors including estrogen, obesity and lifestyle, endocrine disruptors; and in some instances secondary effects related to the therapy of the initial malignancy. Surveillance, Epidemiology, and End Results (SEER) data suggest that women with thyroid cancer who develop breast cancer tend to be younger relative to the average breast cancer patient [5], they are more likely to develop follicular thyroid cancers compared with female patients with thyroid cancer who do not develop breast cancer, and metachronous carcinomas of the breast are more likely hormone receptor–positive and of mixed ductal and lobular invasive type [5, 6].

Methods

Case Description

Patient (II.1) and her sister (II.2) are 2 Brazilian siblings of Spanish and Portuguese ancestry (Fig. 1).

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Patient II.1 was diagnosed with papillary thyroid cancer (PTC) at the age of 32 years. She underwent total thyroidectomy and treatment with 100 mCi iodine 131 (^{131}I). Detailed TNM staging has not been documented in the available records. At the age of 44 years, she was diagnosed with bilateral breast cancer that was positive for estrogen and progesterone receptors (ER, PR) (Cell Marque Cat# 249R-17, RRID: AB_1158014, https://antibodyregistry.org/search?q=AB_1158014, and Agilent Cat# M3569, RRID: AB_2532076, https://antibodyregistry.org/search.php?q=AB_2532076), as well as for human epidermal growth factor receptor 2 (HER2) (Agilent Cat# M7269, RRID: AB_2246560, https://antibodyregistry.org/search?q=AB_2246560) by immunohistochemistry. The treatment consisted of neoadjuvant chemotherapy (paclitaxel; fluorouracil, doxorubicin, and cyclophosphamide; and trastuzumab), followed by bilateral mastectomy and radiation. She was subsequently treated with tamoxifen for 2 years, which was then replaced by anastrozole. She is deemed to be in remission.

Her sister (II.2; Fig. 1) was diagnosed with PTC at the age of 34 years. She underwent total thyroidectomy with central neck dissection. The histology showed a multifocal classic papillary thyroid cancer with a dominant lesion of 1.7 cm in the right lobe with minimal extrathyroidal extension, as well as angiolymphatic invasion. She had 4 of 10 positive lymph nodes in the lateral cervical compartments on the right, and 1 of 6 positive nodes in the central right compartment. The final staging was T1bN1bM0 (TNM/AJCC eighth edition). She was then treated with 100 mCi ^{131}I. Surveillance exams did not show any evidence of residual or recurrent thyroid cancer. At the age of 42 years, she was diagnosed with intraductal carcinoma of the right breast (TisN0M0), that was positive for ER, PR, and HER2. She opted to undergo bilateral mastectomy since she was aware she was a carrier of a mutation in the *ATM* gene (see below). She did not receive any other forms of therapy.

Because the association between thyroid and breast cancer occurs in Cowden syndrome (CS) and Cowden-like syndrome (CLS), the patients were thoroughly evaluated for the presence of associated diseases, and the only findings were head circumferences (58.5 and 59 cm) that were clearly above the 97th percentile for females after correction for height (168 and 171 cm) [7].

The 2 children of patient II.2 (III.1 and III.2, Fig. 1) were diagnosed with ataxia-telangiectasia at the age of 7 years. The boy (III.1) had more severe neurologic manifestations than his sister, in whom the diagnosis was established after completing molecular analyses in her sibling. III.2 developed acute lymphocytic leukemia (ALL) at the age of 7 years, and she died at 9 years despite therapy. Her brother (III.1) developed lymphoblastic lymphoma at the age of 22 years and he currently (2021) is undergoing conventional chemotherapy.

Informed Consent

Informed consent was obtained to perform Sanger sequencing of the *ATM* gene and subsequently for performing whole exome sequencing.

Molecular Analyses

Direct sequencing of the *ATM* gene

Because of the clinical presentation with a suspicion of ataxia-telangiectasia in III.1, the *ATM* gene was submitted to Sanger sequencing using germline DNA extracted from peripheral white blood cells (primers and methodological details available upon request). After the identification of compound heterozygous *ATM* mutations, his sister (III.2), mother (II.2), and aunt (II.1) also underwent molecular testing; the father was not available for testing.

Whole exome sequencing, variant calling, and annotation

With the knowledge that the mother (II.2) and the aunt (II.1) of the patient with ataxia-telangiectasia both harbor the same monoallelic *ATM* mutation, and because of their

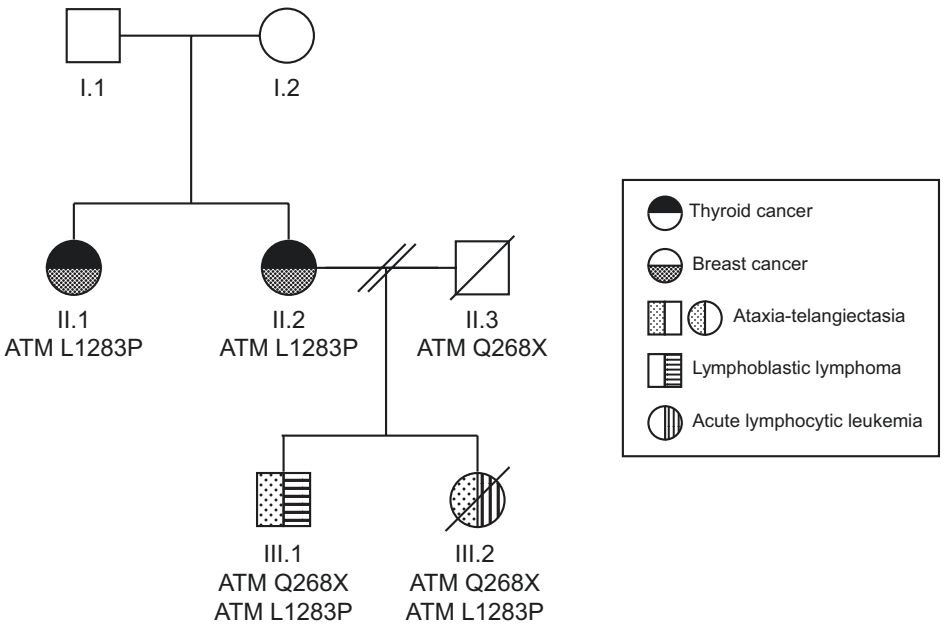

Figure 1. Pedigree of the family with 2 sisters (II.1 and II.2) with breast cancer and papillary thyroid cancer and a monoallelic mutation in the *ATM* gene.

breast and thyroid cancer phenotype, we performed whole exome sequencing (WES) in these patients using an Illumina HiSeq2500 platform with a read length of approximately 100 × 100 base pairs. The on-target coverage was, on average, 100×. Sequence reads were mapped to the human reference genome GRCh37/hg19 using Burrows-Wheeler Aligner (BWA-mem). Further details on variant calling, filtering, estimation of minor allele frequencies, and software used for the prediction of pathogenicity of variants is included in Supplemental materials [8].

Results

Direct Mutational Analysis of the *ATM* Gene

Analysis of the *ATM* gene in the siblings (III.1 and III.2) with ataxia-telangiectasia revealed the presence of compound heterozygous mutations (*ATM* c.3848T>C, p.L1283P and *ATM* c.802C>T, p.Q268X; minor allele frequency for both variants < 0.01). The mother (II.2) and aunt (II.1) were both found to be monoallelic carriers of the *ATM* c.3848T>C (rs730881389; p.L1283P) variant. This variant is classified as being likely pathogenic by ClinVar, SIFT (score 0) and Polyphen (score 1). The substitution of leucine at position 1283 by proline results in an alteration of the protein structure and mobility, thereby affecting its function. No prevalence data about rs730881389 is available in the Genome Aggregation Database (gnomAD) [9] or ABraOM (Brazilian genomic variants, Arquivo Brasileiro Online de Mutações) [10].

Whole Exome Sequencing

Whole exome sequencing did not reveal variants in genes known to be associated with a risk for familial nonmedullary thyroid cancer (FNMTC), breast cancer, or Cowden-like syndrome/Cowden syndrome in the 2 affected sisters (Table 1 in Supplemental materials) [8]. However, they were found to have a second single nucleotide variant in the *ATM* gene (c.5557G>A, p.D1853N; rs1801516) which is predicted to be benign. The search for shared variants in other genes did not reveal any pathologic variant according ClinVar [11], but there were a few variants of uncertain significance associated with cancer according Varsome [12] (Table 2 in Supplemental materials) [8].

Discussion

The bidirectional risk for developing metachronous breast and thyroid cancer in women is well established, but the underlying genetic and nongenetic mechanisms remain incompletely understood. In the family presented here, the 2 sisters (II.1 and II.2) with PTC and breast cancer were found to carry a monoallelic mutation in the *ATM* gene (c.3848T>C; p.L1283P). This sequence variant is extremely uncommon and has been previously reported in patients with ataxia-telangiectasia [13]. The 2 children of II.2 were found to be compound heterozygous for *ATM* gene mutations (III.1 and III.2 in Fig. 1) and developed a classic ataxia-telangiectasia phenotype, as well as ALL (III.2) and lymphoblastic lymphoma (III.1).

The ATM protein is primarily located in the nucleus where it plays a central role as a guardian of cell division and DNA repair through activation of several enzymes. Biallelic mutations in the *ATM* gene lead to ataxia-telangiectasia (Online Mendelian Inheritance in Man [OMIM] #208900), an autosomal recessive disorder characterized by cerebellar degeneration, telangiectasias, cancer and radiation susceptibility, as well as immunodeficiency. Monoallelic mutations in the *ATM* gene have been associated with an increased risk for developing a wide spectrum of malignancies, including cancers of the breast, stomach, bladder, pancreas, lung, ovaries, and melanoma. ATM protein-truncating variants were strongly associated with ER-positive breast cancers in a very recent study including 60 466 women with breast cancer [14]. In contrast, a possible correlation between the presence of *ATM* variants and thyroid cancer is more controversial. Certain *ATM* genotypes and haplotypes were reported to be associated with an increased thyroid cancer risk [15-20], although some of the proposed variants (rs373759 G>A; rs4988099 A>G; rs1801516 G>A; rs664677 T>C; rs609429 G>C) or haplotypes could not be confirmed as susceptibility factors in the meta-analysis by Kang et al [21]. Of note, some studies have suggested that *ATM* mutations might be associated with a risk for developing thyroid carcinomas, in particular FNMTC. For example, Wang et al have reported *ATM* variants (rs1800057 and rs149711770) in 2 families with FNMTC, but without breast cancer [2]. The cBioPortal, which compiles datasets from different cancer studies, lists somatic *ATM* mutations in 2.4% of thyroid cancers and in 2.7% of breast cancers [22].

A role for ATM in thyroid carcinogenesis is indirectly supported by experimental studies [23]. In thyroid cancer, expression of HMGN4, a member of the high mobility group N (HMGN) family, is elevated in several types of thyroid carcinomas. In vitro, HMGN4 overexpression downregulates the expression of the tumor suppressors ATM, ATRX (Alpha Thalassemia/Mental Retardation Syndrome X-Linked), and BRCA2 (Breast Cancer Related 2), and it leads to an increase of the DNA damage marker γH2AX. Similarly, overexpression of HMGN4 in vivo in transgenic mice results in the formation of preneoplastic lesions in the thyroid of transgenic mice [23].

Cowden syndrome (CS; OMIM #158350), also known as *PTEN* (phosphatase and tensin homolog) hamartoma tumor syndrome (PHTS) is associated with different types of cancer, including carcinomas of the thyroid and the breast [24]. Establishing the clinical diagnosis can be challenging and guidelines by the National Comprehensive Cancer Network (NCCN) provide a framework [25]. Clinical constellations that resemble Cowden syndrome, but do not fulfill all the criteria, are referred to as Cowden-like syndrome (CLS) [24]. Genetically, CS and CLS are heterogeneous. In addition to the initially identified mutations in the *PTEN* gene, variants in a spectrum of other genes (*SDHB-D*, *SEC23B*, *KLLN*, *PARP4*, *AKT1*, *PIK3CA*, *USF3*, and *TTN)* have been implicated in their pathogenesis [24]. Among the pleiotropic manifestations of CS and CLS, the concomitant occurrence of carcinomas of the breast and the thyroid have been reported repeatedly [3]. Although mutations in the ataxia telangiectasia mutated (*ATM*) gene have not been reported as cause of CLS, the 2 sisters presented here have a phenotype that is reminiscent of this entity.

According to ClinVar there were no shared pathologic variants in the exomes of the 2 sisters [11]. Using Varsome [12], we identified a few variants of uncertain significance. Among them, it is interesting to note that mutations of *CDC27* have rarely been identified in thyroid cancer [26], and CDC27

alterations have also been associated with breast cancer susceptibility [27]. Moreover, CTBP2 protein overexpression has been observed in follicular thyroid cancer [28], as well as breast cancer [29].

The clinical and genomic findings in this family suggest that ATM mutations may predispose to the development of PTC and breast cancer, and that ATM mutations can play a role in FNMTC, findings that need to be corroborated. Moreover, it remains to be elucidated whether the monoallelic ATM mutation identified in the 2 sisters with thyroid and breast cancer may confer an increased risk through haploinsufficiency or in conjunction with other genetic or nongenetic modifiers.

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Disclosures

The authors have no conflicts of interest to report and declare that there are no competing financial interests.

Data Availability

The data sets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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