Heterozygous Pathogenic Nonsense ATM Variant Resulting in Unusually High Gastric Cancer Susceptibility

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Abstract

We describe the unusual presentation of familial early-onset gastric cancer due to a heterozygous pathogenic variant in the *ATM* gene. The proband had gastric cancer (age 45), and reported a sister deceased for diffuse gastric cancer (age 30) and another sister who developed diffuse gastric cancer (age 52) and ovarian serous cancer. Next Generation Sequencing for cancer susceptibility genes (*APC*, *ATM*, *BRD1*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *RECQL1*, *SMAD4*, *STK11*, *TP53*) identified the truncating c.5944C>T, p.(Gln1982*) variant in *ATM* (NM_000051.3; NP_000042.3) in the proband. The variant segregated in the living affected sister and in the unaffected daughter of the deceased sister. Heterozygous *ATM* variants appear to significantly increase the risk for pancreatic, breast, gastric and prostatic cancer and, to a reduced extent, ovarian and colon cancer and melanoma, with moderate penetrance and variable expressivity. Familial gastric cancer is an unusual presentation for *ATM*. The occurrence of gastric cancer in this family suggests that individual variants may result in different, specific risks. Genotype-phenotype correlations are challenging, given the low penetrance and variable expressivity for *ATM* variants. Careful family history assessment is pivotal for prevention planning, strengthened by the availability of molecular diagnoses.

Introduction

The molecular landscape of monogenic cancer susceptibility is varied and complex. The reduced penetrance for these phenotypes and the frequency of sporadic cases can hamper the research on this field, and specific risks for individual variants or genes are often not available. Gastric cancer is a common and severe neoplasm with poor prognosis, being the fourth cause of cancer mortality worldwide. Ten percent of gastric cancer cases are familial (Hansford 2015). The *CDH1* (E-cadherin; MIM*192090) gene is an ascertained cause of Hereditary Diffuse Gastric Cancer (MIM#137215), a highly penetrant autosomal dominant condition (Hansford 2015). Pathogenic variants in other genes, including *ATM* (Ataxia-Telangiectasia Mutated; MIM*607585), can cause gastric cancer susceptibility, usually alongside with risks for other neoplasms (McKinley 2021).

We report on a family ascertained for hereditary gastric cancer, with a heterozygous pathogenic truncating variant in *ATM*. The frequency of gastric cancer appears to be unusually high for variants in this gene.

Case Report

The proband (II:3, Fig.1), was a 65-year-old man referred for personal and familial history of early-onset gastric cancer. He was diagnosed with intestinal type gastric cancer at age 45. He reported a sister (II:2) deceased for diffuse gastric cancer at age 30, with an unaffected 44-year-old daughter (III:1). He also reported a 70-year-old sister (II:6) who had diffuse gastric cancer at age 52 and serous ovarian cancer at age 54. The proband's parents died of chronic obstructive pulmonary disease. The Next Generation

Sequencing (NGS) analysis of a panel of cancer susceptibility genes (*APC, ATM, BRD1, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, RECQL1, SMAD4, STK11, TP53*) was performed on genomic DNA from the proband, using the Ion Personal Genome Machine platform and the Torrent suite 5.10 tools (Thermo Fisher Scientific, Carlsbad, CA, USA).

Molecular testing identified the heterozygous c.5944C>T, p.(Gln1982*) variant in *ATM* (Ataxia-Telangiectasia Mutated. MIM*607585;NM_000051.3;NP_000042.3). Sanger sequencing confirmed its occurrence in heterozygosity in the proband (II:3), his sister (II:6) and his niece (III:1), indirectly demonstrating the carrier status of II:2 (Fig.1). The variant is very rare (allele count=0, GnomAD v2.1.1 and v.3.1.1). It is reported as associated with Ataxia-Telangiectasia in homozygosity (Alonazi 2018) and is classified as Pathogenic according to the American College of Medical Genetics and Genomics guidelines. Involved individuals were offered genetic counseling. Written informed consent was gathered before any test.

Discussion

ATM encodes for a multifunctional serine/threonine kinase acting as a DNA double-strand break sensor. The Double-Strand Break response pathway regulates DNA damage repair and cell replication control, involving proteins such as BRCA1, PLAB2, BRCA2 and RAD51, whose genes are implied in cancer susceptibility conditions (Zaki-Dizaji 2017).

Biallelic pathogenic variants in *ATM* cause Ataxia-Telangiectasia (MIM#208900), an autosomal recessive condition characterized by ataxia, immunodeficiency, telangiectasias, radiosensitivity and leukemia/lymphoma susceptibility (Jerzak 2018).

Heterozygous *ATM* pathogenic variants are known to result in significant breast cancer susceptibility (MIM#114480), but also confer increased risk for gastric, pancreatic, colorectal, ovarian and prostate cancers (Jerzak 2018).

The study of these variants is hindered by their frequency in the general population, from 0.3% to 1% (Choi 2016; Hall 2021) the reduced penetrance for cancer susceptibility and the overall frequency of the implied malignancies. The National Comprehensive Cancer Network guidelines quantify risks and suggest surveillance only for breast cancer (Daly 2021). Other prevention options are left to the clinician's choice. A recent study demonstrated a moderate-to-high risk for pancreatic, prostatic, gastric and female breast malignancies, and a low-to-moderate risk for breast ductal carcinoma *in situ*, ovarian, colorectal, male breast cancers and melanoma (Hall 2021). These data support considering surveillance also for other tumors. The authors also suggest that genotype-phenotype assumption can be made for some mutations (Hall 2021).

The role of *ATM* in gastric cancer was first suggested by Genome-Wide Association Studies (Helgason 2015) and reports of individual families with high gastric cancer rates (Huang 2015). The frequency of

deleterious *ATM* variants in gastric cancer cases was thereby demonstrated to be significantly higher than in controls (Huang 2015). Apparently, there is no correlation with specific gastric cancer histotypes (Helgason 2015).

Odds ratios for specific malignancies in *ATM* variant carriers are emerging, but there are only few detailed clinical reports of families displaying a higher-than-expected gastric cancer occurrence (Huang 2015). Such reports are important, as they might suggest whether individual mutations result in specific risks. Even if genotype-phenotype assumptions cannot be made, the high occurrence of specific malignancies should prompt to always take into account personal and familial history when defining oncology surveillance for individuals harboring such mutations, with a personalized and tailored approach.

Familial early-onset gastric cancer with high penetrance is an unusual presentation for *ATM* variants. In the family we report, three siblings were affected by early-onset gastric cancer and one of them also presented ovarian cancer. No history of other *ATM*-related disorders was reported. The c.5944C>T variant detected in this family has been only described in homozygosity in a single patient with Ataxia-Telangiectasia, with no information about family history (Alonazi 2018). Usually, homozygous and compound heterozygous nonsense and frameshift deletions in *ATM* result in severe Ataxia-Telangiectasia phenotype, while less deleterious missense variants appear to be less common among pathogenic alleles and result in milder clinical pictures (Alonazi 2018). Genotype-phenotype correlations for the cancer susceptibility phenotypes are more elusive. For most cancers and variants, no assumption can be made. Some missense variants appear to determine a higher risk for breast cancer compared to truncating mutations (Hall 2021)

We believe the nonsense variant identified in the family might correlate with a specifically higher gastric cancer risk, but further research is needed to provide an assertion.

The family discussed here shows how a defined clinical presentation can lead to unexpected molecular findings, with multiple significant counseling challenges. Genetic counseling should take into account both the malignancy risk and the chances of Ataxia-Telangiectasia in the offspring. Given the conservative guidelines and the lack of data on specific malignancy risks and on genotype-phenotype correlation, clinical geneticists and oncogeneticists should opt for a tailored comprehensive approach integrating guidelines, individual and family history and molecular data.

Declarations

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Competing interests

The authors declare no conflict of interest.

Data availability

All data will be available upon reasonable request by contacting the corresponding author

Code availability

Not applicable

Authors' contribution

Study design: DG, GM. Draft: DG, GM. Data collection: DG, GM, EM. Data curation: SP, MP. Methodology: FL, CS, AG, SS. Formal Analysis: FL, CS, AG, SS. Visualization: DG, GM, AG, MP. Review and editing: SP, MP, AP. Supervision: SP, MP, AP.

COMPLIANCE WITH ETHICAL STANDARDS

Ethics approval

The study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The research complies with the ethic requirements of the authors' institutions.

Consent to participate

All involved individuals provided informed consent to participate

Consent for publication

All involved individuals provided informed consent for publication

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Figures

Figure 1

Pedigree of the family and ATM variant A) Pedigree of the family The proband (II:3) presented gastric cancer at age 45 His sister II:2 died at age 30 due to gastric cancer while II:6 presented gastric cancer at age 52 and ovarian cancer at age 54 The genotype for ATM position c5944 is also presented B)Figure legend C) Visualization of the c5944C>T ATM variant on Integrative Genome Viewer (IGV) The BAM file is from the Next Generation Sequencing experiment performed on II:3 The image also displays the homozygous ATM (NM_0000514) c5948A>G variant (rs659243) The variant is classified as “Benign” according to the ACMG guidelines) and has an allele frequency of 100% in GnomAD v211 and v311 It is thus to be considered the wild type allele for that position D) Sanger validation of the variant, forward strand E) Sanger validation of the variant, reverse strand