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ATM c.7570G>C is a high-risk allele for breast cancer

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Abstract

ATM is generally described as a moderate-risk breast cancer susceptibility gene. However, some of *ATM* variants might encounter higher risk. *ATM* c.7570G>C, p.Ala2524Pro, (rs769142993) is a pathogenic Finnish founder variant causative for recessively inherited ataxia-telangiectasia. At cellular level, it has been reported to have a dominant-negative effect. *ATM* c.7570G>C has recurrently been described in Finnish breast cancer families and unselected case cohorts collected from different parts of the country, but the rarity of the allele (MAF 0.0002772 in Finns) and lack of confirming segregation analyses have prevented any conclusive risk estimates. Here, we describe seven families from genetic counseling units with *ATM* c.7570G>C variant showing co-segregation with breast cancer. Further analysis of the unselected breast cancer cohort from Northern Finland (n = 1822), a geographical region previously indicated to have enrichment of the variant, demonstrated that c.7570G>C significantly associates with breast cancer, and the risk is estimated as high (odds ratio [OR] = 8.5, 95% confidence interval [CI] = 1.04-62.46, $P = .018$). Altogether, these results place *ATM* c.7570G>C variant among the high-risk alleles for breast cancer, which should be taken into consideration in genetic counseling.

KEYWORDS
ATM, breast cancer, founder variant, high-risk

What's new?

Ataxia-telangiectasia mutated (*ATM*) is a known breast cancer susceptibility gene. Estimates of breast cancer risk associated with *ATM*, however, are complicated by the rarity of pathogenic *ATM* alleles. Here, using selected breast cancer families and an unselected breast cancer cohort from Northern Finland, the authors calculated risk estimates for *ATM* c.7570G>C, a variant recurrently encountered in Finnish patients with increased breast cancer risk. Analyses show that c.7570G>C is associated with breast cancer and carries a high-risk for disease among patients from Northern Finland. The findings indicate that *ATM* c.7570G>C is a high-risk variant, with possible implications for genetic counseling.

Abbreviations: ACMG, American College of Medical Genetics; A-T, ataxia telangiectasia; ATM, ataxia-telangiectasia mutated; CI, confidence interval; ER, estrogen receptor; FAT domain, FRAP-ATM-TRRAP (FAT) domain; FATC, FAT carboxy-terminal; HER2, human epidermal growth factor receptor 2; MAF, minor allele frequency; MV, missense variant; OR, odds ratio; PR, progesterone receptor; PVs, pathogenic variants; SiSU, sequencing initiative Suomi; VUS, variant of uncertain significance.

Katri Pylkäs and Outi Kuismin have been considered as Shared senior authorship.

1 | INTRODUCTION

Strong inherited predisposition to breast cancer has been estimated to account for approximately 10% of all breast cancer cases. Investigations based on tumor-only sequencing have indicated that the proportion of breast cancer with germline origin might be even higher.[1] Ataxia-telangiectasia mutated gene *(ATM)* is among the commonly acknowledged breast and ovarian cancer susceptibility genes conferring moderate-to-high risk susceptibility when mutated.[2] *ATM* is known for the larger number of variants of uncertain significance (VUS) and likely pathogenic variants (PVs) compared with other genes.[3-5]

ATM encodes a protein kinase with crucial role in the initiation of the signaling cascades leading to the repair of DNA double-strand breaks.[6] Homozygous or compound heterozygous pathogenic germline *ATM* variants cause recessively inherited ataxia telangiectasia (A-T), which is a rare childhood-onset disorder typically characterized by cerebellar neurodegeneration, telangiectasia, immunodeficiency, radiation sensitivity and cancer susceptibility. The A-T related cancers include lymphoma, leukemia and brain cancer.[7-9] *ATM* has long been considered as a breast cancer susceptibility gene based on its biological function and increased breast cancer risk among obligate carriers in the A-T families.[5,10-13]

The rarity of individual pathogenic *ATM* alleles has complicated the population-based estimates of the breast cancer risk and different variants have usually been combined for the analysis. This strategy has placed *ATM* in the moderate-risk category with an estimation of 2-fold risk for the predisposing alleles, and this risk appears to be restricted particularly to estrogen receptor (ER) positive breast cancer.[14-16] However, there is evidence that some *ATM* variants can be associated with higher risk. It has been suggested that particularly rare, pathogenic missense variants in the evolutionarily conserved sites in the last third of the ATM protein, containing FAT (FRAP-ATM-TRRAP), kinase and FATC (FAT carboxy-terminal) domains, can confer on average even higher cancer risk than truncating variants.[17] The evidence is the most robust for the recurrent *ATM* c.7271C>T, p.Val2424Gly, located in the FAT domain. Studies have shown that it associates with very high risk for breast cancer with an odds ratio estimate of 11.0 (95% CI 1.42-85.7%) based on unselected cases. [18]

ATM (NM_000051.4) c.7570G>C, (rs769142993, GRCh37 chr11:108302225G>C, hg38 chr11:108331498G>C) variant leads to p.Ala2524Pro change in the evolutionarily conserved site in the FAT domain and shows dominant-negative effect on the kinase activity. *ATM* c.7570G>C is a pathogenic Finnish founder variant initially reported in two A-T patients.[4,19,20] Its association with breast cancer predisposition has been studied along other *ATM* PVs in breast cancer families and unselected case cohorts collected from different parts of the country. The observed frequencies of variants have, however, remained low preventing the risk estimates for individual *ATM* alleles. Nevertheless, there is increasing evidence of *ATM* c.7570G>C clustering particularly to Northern Finland.[4,5,21]

As *ATM* c.7570G>C is recurrently encountered in the genetic counseling units in patients with increased risk for breast cancer, there is a need for clearer risk estimates. Here, using both selected breast cancer families from the clinics and so far the largest Northern Finnish unselected breast cancer case cohort (n = 1822), we show that c.7570G>C significantly associates with breast cancer and the risk is estimated as high. This is the first allele-specific breast cancer risk estimation for *ATM* c.7570G>C variant in Finnish population, and the result should be taken into consideration in genetic counseling.

2 | MATERIALS AND METHODS

The data for pedigree analysis consisted of seven families with carriers of *ATM* c.7570G>C variant and indication of inherited susceptibility to breast cancer. Two families were provided by clinical genetic counseling unit at Turku University Hospital and five at Oulu University Hospital.

The unselected breast cancer cohort consisted of 1822 consecutive breast cancer cases diagnosed at the Oulu University Hospital during the years 2000-2019 and were unselected for the family history of cancer and age at disease onset.

2.1 | Variant detection in families

Diagnostic gene panel test composing of approximately 20 genes was performed for DNA samples extracted from peripheral blood samples from index patients. Sanger sequencing of *ATM* was performed for the A-T patients and for the segregation analysis in the families.

2.2 | Variant detection in unselected cohort

Genotyping was performed for DNA samples extracted from peripheral blood by using high-resolution melt analysis (CFX96, Bio-Rad, Hercules, CA, USA) with Type-It HRM reagents (Qiagen, Hilden, Germany). Verification of all detected *ATM* c.7570G>C variants were confirmed with Sanger sequencing in Biocenter Oulu Sequencing Center (ABI3130xl, Applied Biosystem, Foster City, CA, USA).

3 | RESULTS

3.1 | Clinical and genetic characteristics of families with *ATM* c.7570G>C variant

Pedigrees of seven families (A-G) with genotyped individuals and diagnosed cancers are shown in Figure 1, and all families were negative for other known breast cancer predisposing variants tested in the clinical panel setting. Table 1 shows the characteristics of breast tumors of *ATM* c.7570G>C carriers in these families, most of these being ductal, and ER and PR positive. In family A, the analysis confirmed the co-

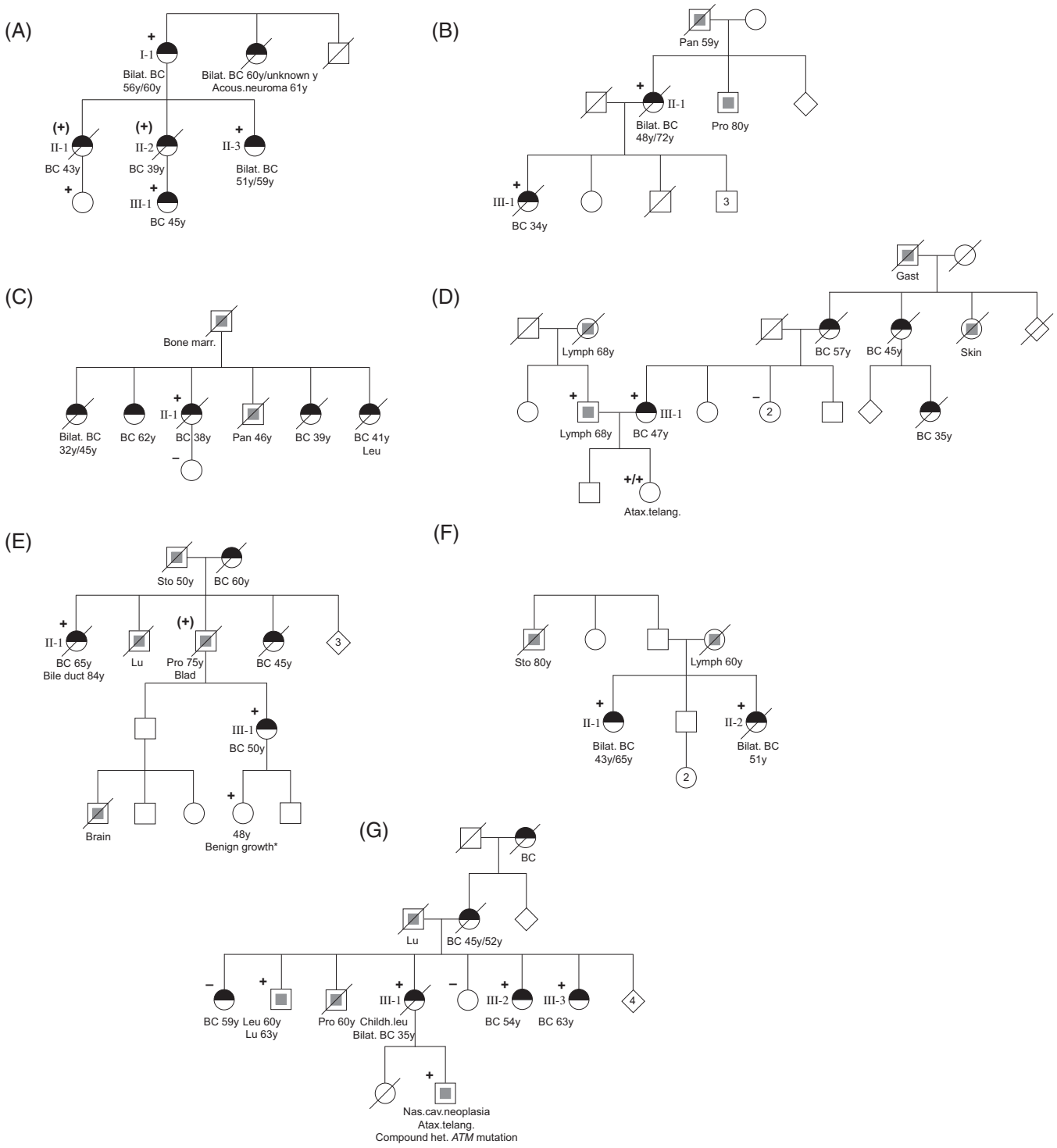

FIGURE 1 Pedigrees of seven families (A-G) showing genotyped individuals and diagnosed cancers. Acous.neuroma, acoustic neuroma; Atax. telang., ataxia-telangiectasia; BC, breast cancer; Bilat, bilateral; Blad, bladder cancer; Bone marr, bone marrow; Gast/Sto, gastric/stomach cancer; Het, heterozygous; Leu, leukemia; Lu, lung cancer; Lymph, lymphoma; Nas.cav, nasal cavity; Pan, pancreatic cancer; Pro, prostate cancer.
*Sclerosing adenosis fibrocystic mastpathy and fibroadenosis, no atypia and no malignant

segregation of the family's breast cancer cases with *ATM* c.7570G>C, indicating a very high risk for the disease. In this family, the five confirmed or obligatory *ATM* c.7570G>C carriers had a total of seven breast cancers, two of *ATM* c.7570G>C carriers having a bilateral disease. Family B showed two *ATM* c.7570G>C carriers, one with bilateral breast cancer and the other diagnosed at early age, 34 years, and in family C, *ATM* c.7570G>C was also observed in early-onset case, 38 years. Family D shows both parents as carriers of *ATM* c.7570G>C and their child homozygous for *ATM* c.7570G>C and with A-T. This female with a clinical diagnosis of A-T is at present in her

TABLE 1 Breast tumor characteristics of *ATM* c.7570G>C, p.Ala2524Pro carriers in families A-G

Family	Person	Cancer (age at dg)	Histology grade	Receptor status
A	I-1	Bilat. BC (56,60)	Ductal G3; NA G3	NA; NA
A	II-1	BC (43)	Lobular G2	NA; NA
A	II-2	BC (39)	NA	
A	II-3	Bilat. BC (51,59)	Ductal G3; ductal G3	ER+, PR+, HER2−; ER+, PR−, HER2+
A	III-1	BC (45)	Multifocal ductal G2	ER+, PR+, HER2+
B	II-1	Bilat. BC (48, 72)	Ductal; Ductal, 2	ER+, PR+; ER+, PR+, HER−
B	III-1	BC (34)	Ductal, 2	NA
C	II-1	BC (38)	Ductal; NA	ER+, PR+
D	III-1	BC (47)	Ductal	ER+, PR+, HER2−
E	II-1	BC (65)	Ductal G2	ER+, PR+, HER2−
E	III-1	BC (50)	Multifocal ductal G2	ER+, PR+, HER2−
F	II-1	Bilat. BC (43, 65)	Ductal; ductal G2	NA; ER+, PR+, HER2−
F	II-2	Bilat. BC (51)	Ductal G3; ductal G2	ER+, PR+, HER2−
G	III-1	Bilat. BC (35)	NA	NA
G	III-2	BC (54)	Multifocal ductal	ER−, PR−, HER+
G	III-3	BC (63)	Ductal, 3	ER+, PR+, HER2−

Abbreviation: NA, Unknown.

TABLE 2 Frequency of the *ATM* c.7570G>C, p.Ala2524Pro variant in Northern Finnish unselected breast cancer cases and controls

Cohort	N	WT	%	Mut	%	OR	95% CI	*P* value[a]
Unselected Br	1822	1811	99.40	11	0.60	8.05	1.04–62.46	.018
Controls[b]	1327	1326	99.90	1	0.075			

[a]Fisher's exact test (2-sided).
[b]SISu North Ostrobothnia.

40's and she has never had any cancer. Her mother had breast cancer at the age of 47 years and father was diagnosed with lymphoma at 68 years. In families C ja D, there were multiple family members with breast cancer but unfortunately segregation analysis could not be performed. In family E, the *ATM* c.7570G>C carrier had breast cancer at the age of 65 and had breast cancer recurrency after 17 years of initial breast cancer with same histology as primary cancer (II-1). Another carrier in the family had multifocal breast cancer at the age of 50 (III-1). The *ATM* c.7570G>C variant segregated with bilateral breast cancer in two sisters in family F. In family G, four siblings had breast cancer and three of them were carries of *ATM* c.7570G>C. One sibling (III-1) had bilateral breast cancer at 35 years after childhood leukemia. In this family, there was a male A-T-case, compound heterozygote for *ATM* c.7570G>C, and he had nasal cavity neoplasia in his 30's. The two A-T-cases shown here (Figure 1) have initially been reported by Laake et al.[14]

In total, of the confirmed 16 *ATM* c.7570G>C carriers in these families, 6 (37.5%) had bilateral breast cancer. Most breast cancers in these families were diagnosed after 40 years but there were also breast cancer cases diagnosed from 34 years onwards, indicating an early disease onset (mean 49, median 47.5 and range 34-65 years). These families (A-G) were also reported to have other types of cancer, including lymphoma, leukemia and prostate cancer in confirmed *ATM* c.7570G>C carries. No ovarian cancer was reported in currently identified *ATM* c.7570G>C carriers or their family members.

3.2 | Genotyping in unselected breast cancer cohort

Genotyping of *ATM* c.7570G>C variant in Northern Finnish unselected breast cancer cohort revealed 11 cases as heterozygous *ATM* c.7570G>C carriers (11/1822, 0.6%). This was significantly higher compared with healthy controls from this geographical region (1/1327, 0.075%, SiSu), $P = .018$, odds ratio [OR] = 8.5, 95% confidence interval [CI] = 1.04-62.46 (Table 2). The mean age at disease onset for the unselected carriers was 61.25 years (minimum 43, maximum 78 and median 57 years), which is similar to that in the unselected cohort in general (mean 58.3 and median 58 years). *ATM* c.7570G>C carriers from the unselected cohort were also reported to have family history of breast cancer and several other cancers, including stomach and lung cancer (Table 3), but no additional samples were available for the mutation testing. Of the *ATM* c.7570G>C carriers breast tumors most were ductal (8/11) and all were ER-and PR-positive (Table 4), similarly to the tumors reported in families A-G.

3.3 | ACMG classification of *ATM* c.7570G>C

Based on these results, *ATM* c.7570G>C variant should be classified as pathogenic, according to the ACMG (American College of Medical Genetics) guidelines[22] (PS3, PM1, PP1, PP3, PP5 and PS4).

TABLE 3 Family history of cancer for *ATM* c.7570G>C, p.Ala2524Pro carriers from Northern Finnish unselected breast cancer cohort

Index ID-Cancers/ tumors (age at diagnosis)	Breast cancer(s) in first and/or second degree relatives (age)	Other cancers in first and/or second degree relatives (age)
Uns1 Br (63) + papillary thy (28)	–	Spine (NA), Skin (NA), Csu (NA)
Uns2 Br (58)	Br (42)	–
Uns3 Br (66)	–	Thy
Uns4 Br (43 and 65)	Bil Br (51) + Lung (65), Br (48), Br (NA)	Lymphoma (64)
Uns5 Br (68)	Br (NA)	Sto (NA), Sto (NA), Sto (NA)
Uns6 Br (54)	–	–
Uns7 Br (78) + skin (NA)	–	Csu (NA)
Uns8 Br (46)	–	Sto (45)
Uns9 Br (57)	–	Lung (50)
Uns10 Br (56)	–	Lung (66)
Uns11 Br (55)	–	–

Abbreviations: Br, breast cancer; Csu, cancer site unknown; NA, unknown; Sto, stomach cancer; Thy, thyroid cancer; Uns, unselected cohort.

TABLE 4 Breast tumor characteristics of *ATM* c.7570G>C, p.Ala2524Pro carriers in unselected breast cancer cohort

Index ID	Morphology	Receptor status (ER, PR, HER2)
Uns1	Ductal	ER+, PR+, HER−, G2
Uns2	Lobular	ER+, PR+, HER−, G2
Uns3	Lobular	ER+, PR+, HER−, G2
Uns4	Ductal	ER+, PR+, HER+, G2
Uns5	Lobular	ER+, PR+, HER−, G3
Uns6	Ductal	ER+, PR+, HER+, G1
Uns7	Ductal	ER+, PR+, HER−, G2
Uns8	Ductal	ER+, PR+, HER−, G3
Uns9	Ductal	ER+, PR+, HER−, G2
Uns10	Ductal	ER+, PR+, HER−, G2
Uns11	Ductal	ER+, PR+, HER−, G3

Abbreviations: ER, Estrogen receptor; G, gradus; PR, progesterone receptor; Uns, unselected cohort.

4 | DISCUSSION

ATM gene is an established breast cancer susceptibility gene, generally placed in the moderate-risk category with a combined estimation of 2-fold risk for the predisposing alleles. The estimated lifetime breast cancer risk varies in different studies from 13% to 33% by the age of 80 years.[15,23-25] According to the ClinVar database, up to 1500 PVs have been reported in the *ATM* gene in the context of A-T syndrome and/or hereditary cancer-predisposing syndrome. Previous studies have suggested that the breast cancer risk is higher for carriers of an *ATM* loss-of-function variants than it is for carriers of an *ATM* deleterious missense variants (MVs). For the MVs, the increased risk is particularly associated with the variants that locate in the FAT and kinase domain of the protein.[15,17,23] Although collectively considered as moderate breast cancer risk alleles, some of the *ATM* variants potentially cause higher breast cancer risk. This has previously been demonstrated for *ATM* c.7271T>G, (p.Val2424Gly), having up to 60% lifetime breast cancer by the age of 70 years.[18,24,26] Currently studied *ATM* missense variant, c.7570G>C, p.Ala2524Pro has previously been reported in the context of both A-T and breast cancer, and functional studies using the mutation carrier lymphoblast cell lines have demonstrated that p.Ala2524Pro leads to defective ATM kinase activity. Although clearly pathogenic for A-T, the risk estimations for breast cancer have been missing.[4,13]

This study was initiated from the observations in genetic counseling provided for breast cancer families, where *ATM* c.7570G>C showed co-segregation with the disease. In these families, the mean age of first breast cancer varied between 34 and 65 years and there was also excess of bilateral disease. This indicated a high or very high risk for breast cancer, thus contradicting the general classification of the *ATM* variants as moderate risk alleles. As the variant had been indicated to be enriched in in North Ostrobothnia region in Northern Finland,[4,21] the use of unselected case cohort from this geographical region provided an opportunity to test the association of *ATM* c.7570G>C with breast cancer susceptibility at the population level and establish risk estimates. Based on these results, *ATM* c.7570G>C is significantly enriched in the breast cancer cohort and the 8.05-fold occurrence in cases compared with controls is in the range of high-risk allele. This supports the observations from the clinics, although the carriers identified in the unselected cohort had their breast cancer diagnosis later age.

In this study, most of the currently reported breast cancers with *ATM* c.7570G>C were ductal, and all except one, were ER- and PR-positive and no cases were triple-negative. This supports data from previous studies that report *ATM* PVs increasing the risk for ER positive breast cancer in particular, and being negatively associated with triple-negative breast cancer and ER-negative tumor phenotypes.[14-16,27] *ATM* gene mutations have also previously been suggested to increase the risk for bilateral breast cancer.,[28,29] which was strongly supported by the studied families from the clinics. Recommendation for female *ATM* c.7570G>C carriers has been that the surveillance starts from 40 years onwards.[30] As the currently reported families presented breast cancer cases also from 34 years onwards, it suggests that in those families with younger breast cancer patients' the follow-up regimen should start earlier, for example from 30 years onwards. The current recommendation for female *ATM* c.7570G>C carriers is follow-up by annual magnetic resonance imaging, especially if pedigree suggests high risk for breast cancer.[30-32] Although evidence is insufficient for risk-reducing mastectomy for carriers of *ATM* PV, the segregation analysis of one of the families (A) indicated very high breast cancer risk for *ATM* c.7570G>C carriers and therefore, prophylactic mastectomy was a choice in this family.

To conclude, this study provides further evidence that missense mutations in functionally conserved domains of ATM can cause high risk

for breast cancer, suggesting that these protein domains could also harbor other high-risk MVs. For the currently studied Finnish founder mutation c.7570G>C, p.Ala2524Pro, the breast cancer risk is estimated high based on the variant's segregation with the disease in the families and supported by population-based risk estimates. To our knowledge this is the first time that high-risk status has been established for c.7570G>C allele and the result should be taken into consideration in genetic counseling.

AUTHOR CONTRIBUTIONS

Minna Kankuri-Tammilehto, Anna Tervasmäki, Minna Kraatari-Tiri, Elisa Rahikkala, Katri Pylkäs and Outi Kuismin designed the study and drafted the manuscript. Anna Tervasmäki and Katri Pylkäs carried out the unselected cohort analysis, Minna Kankuri-Tammilehto, Minna Kraatari-Tiri, Elisa Rahikkala and Outi Kuismin collected the families from the clinic. Katri Pylkäs and Anna Tervasmäki performed the statistical analyses. Minna Kankuri-Tammilehto, Katri Pylkäs, Minna Kraatari-Tiri, Elisa Rahikkala and Outi Kuismin contributed samples and patient information. All authors contributed to and approved the final manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author.

ETHICS STATEMENT

The studies on the families and unselected cohort were approved by the Ethics Committee of the Northern Ostrobothnia Hospital District (EETTMK: 186/2020, 100/2016, amendments 2021, 2022) with written informed consent was obtained from the participants. The study was conducted in compliance with the Declaration of Helsinki.

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