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Original Research

Exome sequencing identifies a recurrent variant in *SERPINA3* associating with hereditary susceptibility to breast cancer

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Abstract ***Background:*** Breast cancer is strongly influenced by hereditary risk factors. Yet, the known susceptibility genes and genomic loci explain only about half of the familial component of the disease. To identify novel breast cancer predisposing gene defects, here we have performed massive parallel sequencing for Northern Finnish breast cancer cases.
Methods: Ninety-eight breast cancer cases with indication of hereditary disease susceptibility were exome sequenced. Data filtering strategy focused on predictably deleterious rare variants that were still enriched in the sequenced cohort. Findings were confirmed with additional, geographically matched breast cancer cohorts.
Results: A recurrent heterozygous splice acceptor variant, c.918-1G>C, in *SERPINA3*, was identified, and it was significantly enriched both in the hereditary (6/201, 3.0%, p = 0.006, OR 5.1, 95% CI 1.7–14.8) and unselected breast cancer cohort (26/1569, 1.7%, p = 0.009, OR 2.8, 95% CI 1.3–6.2). *SERPINA3* c.918-1G>C carriers were also significantly more likely to have a rare tumor subtype, medullary breast cancer, than the non-carriers (4/26, 15.4%, p = 0.000014, OR 42.9, 95% CI 11.7–157.1).

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Conclusion: These findings demonstrate that c.918-1G>C germline variant in *SERPINA3* gene, encoding a member of the serine protease inhibitor class, is a novel breast cancer predisposing allele.

1. Introduction

Since the identification of the major breast cancer susceptibility genes, *BRCA1* and *BRCA2*, extensive efforts have been taken to find additional inherited risk factors [1]. This has led into discovery of several breast cancer–associated genes and genomic loci with variable levels of disease risk [2]. The majority of the moderate-to-high-risk breast cancer susceptibility genes, including *BRCA1* and *BRCA2*, but also others such as *PALB2*, *CHEK2* and *ATM*, encode essential DNA damage response (DDR) proteins. Even in the era of massive parallel sequencing, the analysis has often been limited to DDR pathway and has resulted in the identification of rare breast cancer predisposing alleles e.g. in *RECQL*, *FANCM* and *ERCC3* genes [3–6]. The moderate-to-high-risk susceptibility genes are all characterized by rare, mostly loss-of-function pathogenic variants conferring breast cancer predisposition. Despite these findings, so far identified genetic susceptibility factors explain only about half of the familial component of breast cancer [7], making the identification of additional inherited risk factors and understanding their contribution to disease onset imperative. For this purpose, here we have performed exome sequencing for 98 Northern Finnish breast cancer patients with indication of hereditary disease susceptibility. The founder populations provide advantage for the rare variant approach, as they harbor founder variants of higher prevalence than outbred populations. The contribution of a gene to the disease is easier to prove, if several families with the same predisposing variant can be identified. This has been shown to be the case for instance for *PALB2* [8] and *MCPH1* [9] founder variants identified in Finnish population.

Using a filtering strategy not limited to any predefined functional pathway, we identified a recurrent splice acceptor variant in *SERPINA3* gene, encoding a member of the serine protease inhibitor class, significantly enriched in the analyzed patient cohorts. Based on the results, we propose a novel link between *SERPINA3* and inherited breast cancer predisposition.

2. Materials and methods

2.1. Discovery cohort in exome sequencing

Patient cohort selected for exome sequencing consisted of 98 index cases affected with breast cancer from Northern Finnish families negative for *BRCA1*, *BRCA2* and *PALB2* gene pathogenic founder variants [10,11]. The following selection criteria, indicating an inherited predisposition to the disease, were used: 1) index cases from families with three or more breast and/or ovarian cancer cases in first- or second-degree relatives (n = 83), 2) index cases from families with two cases of breast, or breast and ovarian cancer in first- or second-degree relatives, of which at least one with early disease onset (<35 years), bilateral disease or multiple primary tumors (n = 7) and 3) breast cancer cases diagnosed at or below the age of 40 (n = 8). TruSeq Rapid Exome Library Prep Kit, covering 45 Mb of the genome and 99.4% of the RefSeq genes, was used for library preparation. Sequencing was done using Illumina's NextSeq550 platform in high-output, pair-ended 2 × 76 cycles mode, followed by FASTQ generation within BaseSpace (Illumina). This resulted in mean read depth of 66.3x for the samples for the captured region. In total, mean of 90.2% of the captured region was covered at least by 10 reads for the analyzed samples. Data analysis was done within BaseSpace Biocomputing environment using BWA enrichment (BWA Genome Alignment Software, GATK Variant Caller) v.2.1.2.0 and VariantStudio v.3.0 for sequence alignment to reference genome (human genome 19), variant calling, annotation, filtering and classification of the variants. The manual examination and visualization of the sequence data were done using the Integrative Genomics Viewer v.2.4.19. Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org/) and Sequencing Initiative Suomi (SISu, http://www.sisuproject.fi/) databases were used for filtering out common variants.

Variants identified in exome sequencing of 98 index cases were filtered using the following criteria: 1) inclusion of variants with predicted harmful effect on protein: protein truncations (non-sense, frameshift and splice site variants), in-frame insertions/deletions and amino acid changes predicted to be deleterious using two different algorithms (PolyPhen and SIFT), 2) inclusion of variants absent from or with minor allele frequency <0.01 in dbSNP, Ensembl, ExAC and SISu databases, 3) exclusion of known non-pathogenic/pathogenic variants and 4) inclusion of variants that were observed at least in three individuals in the discovery cohort.

2.2. Variant genotyping

Variants passing the filtering criteria were genotyped using Agena Bioscience MassARRAY System

(Sequenom Inc., FIMM) and High-Resolution Melt (HRM) analysis (CFX96, Bio-Rad) with Type-It HRM reagents (Qiagen). Sanger sequencing (ABI3500xL Genetic Analyzer, Applied Biosystems) was used for confirmation of the variants.

2.3. Case–control cohorts

The frequency of variants passing the filtering was evaluated in geographically matched Northern Finnish unselected breast cancer case cohort. This consisted of 1569 consecutive breast cancer cases unselected for the family history of cancer and age at disease onset, diagnosed at the Oulu University Hospital during the years 2000–2016. Clinical parameters for unselected breast cancer cases were obtained from pathology reports and included KI-67 status, tumor grade, TNM (tumor, nodes, metastasis) classification, tumor morphology, estrogen (ER), progesterone (PR) and HER2 receptor status, and tumor subtype.

An additional cohort of 103 breast cancer cases with indication of inherited predisposition was used for genotyping of *SERPINA3* c.918-1G>C. This consisted of index cases from *BRCA1*, *BRCA2, PALB2* and *MCPH1* pathogenic founder variant negative [9–11] breast cancer families with 1) with three or more breast and/or ovarian cancer cases in first- or second-degree relatives (n = 42), 2) two cases of breast, or breast and ovarian cancer in first- or second-degree relatives, of which at least one with early disease onset (<35 years), bilateral disease or multiple tumors (n = 22) and 3) two cases of breast cancer in first- or second-degree relatives (n = 39).

Finrisk data from Northern Ostrobothnia (Sequencing Initiative Suomi (SISu), http://www.sisuproject.fi/) and/or geographically matched anonymous Northern Finnish Red Cross blood donors were used as controls (n = 985–1327) for comparison.

This study included written informed consent from all the participating individuals. The research is covered by appropriate ethical and research permits (Northern Ostrobothnia Health Care District Research permit [285/2016] and Ethical Committee statement [100/2016], and National institute for health and welfare permit [THL/1670/5.05.00/2016]).

2.4. Statistical analyses

χ^2 test or Fisher's exact test was used to compare the allele frequencies between cases and controls, and also for the comparison of the tumor characteristics between the *SERPINA3* c.918-1G>C carrier and non-carrier patients. All p-values were two-sided. Benjamini–Hochberg method was used to control the false discovery rate (FDR) for multiple comparisons for the tested germline variants [12]. After Benjamini–Hochberg procedure (FDR = 0.05), p-values below 0.01 were considered statistically significant. The 5-year breast cancer–specific survival (BCSS) between the *SERPINA3* c.918-1G>C carriers (n = 26) and non-carriers (n = 1417) from the unselected breast cancer cohort was compared by univariate Kaplan–Meier analysis and Cox regression. The time from date of diagnosis to the last follow-up or death was calculated as survival time. All statistical analyses were performed using IBM SPSS Statistics 26.0 for Windows (IBM Corp.).

2.5. In silico analysis for effects on splicing

In silico tools (BDGP Splice Site Prediction [13] (https://www.fruitfly.org/seq_tools/splice.html) and NetGene2 [14] (http://www.cbs.dtu.dk/services/NetGene2/) were used to predict the consequences of the splice acceptor variant *SERPINA3* c.918-1G>C.

2.6. Loss of heterozygosity analysis

Genomic DNA was extracted from 14 FFPE tumors of *SERPINA3* c.918-1G>C carriers using GeneRead DNA FFPE Kit (Qiagen). Loss of heterozygosity (LOH) was evaluated by sequencing of a 147 bp amplicon flanking the variant site. Peak height values from sequence chromatograms were compared between tumor and corresponding normal DNA samples to assess the allelic ratios. Allelic imbalance values >1.67 or <0.60 were considered as indicators of LOH.

3. Results

In total, 36 variants passed the filters (2 non-sense, 1 frameshift, 5 splice site, 1 in-frame insertion, 1 in-frame deletion and 26 predicted deleterious missense variants) and were analyzed further in additional geographically matched cohorts (Table S1). Of these, splice acceptor variant in *SERPINA3* (serpin peptidase inhibitor, clade A member 3, NM_001085.4:c.918-1G>C, rs199710314) was found significantly enriched in the unselected breast cancer cohort used for validation and thus selected for more detailed investigation.

SERPINA3 c.918-1G>C was present in 4/98 of the exome-sequenced index cases (4.1%). All four heterozygous carriers were negative for any other previously reported breast cancer–associated variants. *SERPINA3* encodes for a 423 amino acid protein SERPINA3, also known as α1-antichymotrypsin (α1-ACT), that acts as a plasma protease inhibitor [15]. Unlike other serpins, SERPINA3 has the ability to bind to DNA (Fig. 1a), although the functional significance of DNA binding is unclear [15]. By binding targeted proteases to the reactive center loop (RCL) (Fig. 1a), SERPINA3 proteolytically inhibits the activity of several serine proteases including chymotrypsin, cathepsin G and mast cell chymases. *In silico* tools predicted that the *SERPINA3* c.918-1G>C variant abolishes the canonical splice

acceptor and activates a new acceptor site right next to the original splice site. This results in deletion of two nucleotides and frameshift, thereby creating a premature stop at the codon position 309 (Fig. 1b) and eliminating the RCL domain of the protein.

In total, the frequency of *SERPINA3* c.918-1G>C was evaluated in 1770 breast cancer cases: 201 cases with suspected inherited susceptibility for the disease (hereafter referred as hereditary cohort) and 1569 cases unselected for family history of cancer (Table 1). The highest prevalence for *SERPINA3* c.918-1G>C was observed among cases from the hereditary cohort (6/201, 3.0%), whereas only 8 of the 1327 healthy controls (0.6%) carried the variant (p = 0.006, OR 5.1, 95% CI 1.7–14.8). The association with breast cancer was replicated with the unselected breast cancer cohort, where 26 additional *SERPINA3* c.918-1G>C carriers were identified (26/1569, 1.7%, p = 0.009, OR 2.8, 95% CI 1.3–6.2).

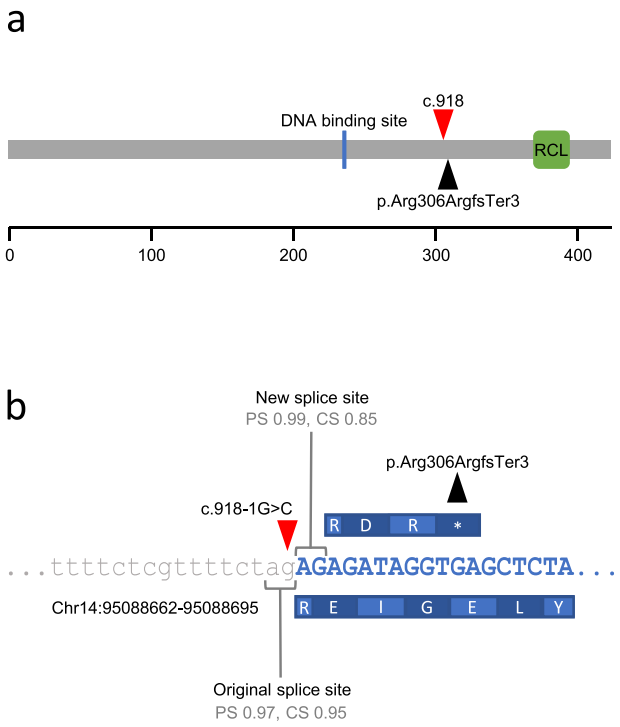

Fig. 1. SERPINA3 and the effect of c.918-1G>C splice acceptor variant. (a) Schematic presentation of the SERPINA3 protein. DNA binding site comprises the amino acids 235–237, and RCL domain amino acids 369–394. RCL = reactive center loop [32]. (b) Predicted effect of *SERPINA3* c.918-1G>C variant on splicing. The *in silico* tools give a score between 0 and 1 to demonstrate a splice site prediction; scores closest to 1 indicate strongest predictions. PS = BDGP Splice Site Prediction score; CS = NetGene2 confidence score. Red arrows point to the position at DNA level and black arrows at the level of translation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

All available information and additional DNA samples from the identified *SERPINA3* c.918-1G>C carrier families were used to study the potential segregation of the variant with cancer phenotype (Table S2). One-third (9/26) of the unselected cases had at least one breast cancer case among their first- or second-degree relatives, providing further support for breast cancer association. Besides initially studied index cases, four samples from relatives affected with breast cancer were available for variant testing. Of these, three were positive for *SERPINA3* c.918-1G. The relatives of *SERPINA3* c.918-1G>C carriers were also reported to have several other types of malignancies, the most common being stomach cancer occurring in 22% of the families (7/32), and head and neck cancers (5/32, 16%).

The comparison of the tumor characteristics (Table S3) between *SERPINA3* c.918-1G>C carriers and non-carriers from the unselected cohort showed a significant enrichment of medullary breast cancer, a rare tumor subtype, among the carriers (4/26, 15.4%, p = 0.000014, OR 42.9, 95% CI 11.7–157.1). Although based on small sample sizes, this rare subtype enrichment supports the contribution of this germline variant to the tumorigenesis in the carriers. No other associations with the tumor characteristics or 5-year BCSS were detected (Fig. S1). There was no difference in the average age at disease onset between the carriers (mean = 58 years, variation 36–87 years) and non-carriers (mean = 58 years, variation 28–93 years) in the unselected cohort. The LOH analysis of the *SERPINA3* locus demonstrated that the wild-type allele was retained in the breast tumors (Fig. S2), a feature that is typical for moderate risk breast cancer alleles [2].

Table 1
Frequency of the *SERPINA3* c.918-1G>C variant in breast cancer cases and controls.

Cohort	N	WT	%	Mut[c]	%	OR	95% CI	p[d]
Hereditary BC[a]	201	195	97.0	6	3.0	5.1	1.7–14.8	0.006
Unselected BC	1569	1543	98.3	26	1.7	2.8	1.3–6.2	0.009
All BC	1770	1738	98.2	32	1.8	3.0	1.4–6.6	0.003
Controls[b]	1327	1319	99.4	8	0.6			

BC, breast cancer; *CI*, confidence interval; *Mut*, variant carrier; *OR*, odds ratio; *WT*, wild-type.
[a] Includes the 98 exome-sequenced cases.
[b] SISu North Ostrobothnia.
[c] All heterozygous.
[d] $\chi 2$ test or Fisher's exact test.

4. Discussion

Current study provides strong genetic evidence for the association of *SERPINA3* c.918-1G>C with inherited breast cancer predisposition in the Finnish population. In the currently analyzed cohorts *SERPINA3* c.918-1G>C was identified in 3.0% cases with indication of hereditary predisposition to the disease and in 1.7% of the breast cancer cases unselected for family history of the disease or age at diagnosis. Based on the case–control comparisons, the risk conferred by *SERPINA3* c.918-1G>C allele falls in the range typical for moderate risk alleles [16] (2.8-fold based on unselected cases and fivefold based on hereditary cases). The variant showed significant association with medullary carcinoma, a rare subtype with relatively favorable prognosis, and curiously also enriched in *BRCA1* germline mutation carriers [17]. The *SERPINA3* c.918-1G>C carrier families had also history of several other cancer types, including stomach cancer and cancers of the head and neck, indicating that the cancer spectrum associated with *SERPINA3* variants might extend beyond breast cancer.

The encoded SERPINA3 is an inhibitor of several serine proteases and acts as an acute phase reactive protein. It has been reported to have roles in a variety of physiological activities such as inflammatory response [18], complement activation [19], regulation of lipid metabolic processes [20], wound healing, extracellular matrix remodeling [21] and apoptosis [15]. Variants of this gene can influence protease targeting and thereby also be tissue specific. Overexpression of SERPINA3 has been observed in several cancer types, including endometrial cancer, melanoma, glioma and breast cancer [22–25]. Its high expression has been demonstrated to positively correlate with poor prognosis in patients with colon [26], breast [27], lung [28,29] and gastric cancers [30]. Recently, a new role for SERPINA3 was discovered as a transcriptional regulator of genes related to hepatocellular carcinoma progression by inducing telomere elongation, cell proliferation, migration and invasion [31]. *SERPINA3* has been reported to be estrogen-inducible, and its mRNA level has been suggested to be significant predictor of good prognosis in hormone receptor (ER and/or PR)-positive breast cancer patients [25]. Taken together, various lines of evidence suggest that alterations in multifunctional SERPINA3 have a role in malignancy development.

In conclusion, the current genetic data demonstrates that germline variant in *SERPINA3* gene, c.918-1G>C, associates with breast cancer. Based on the case–control comparison, the risk associated with it is about threefold compared with non-carriers. Although rare, this Finnish founder allele is enriched in Northern Finland with statistically significant association with breast cancer. According to GnomAD database (https://gnomad.broadinstitute.org/), this gene harbors other deleterious alleles that could be relevant in other populations. Addition of *SERPINA3* to the growing list of genes with functions beyond DDR pathway to harbor predisposing alleles underscores that diverse mechanisms are likely to be relevant to breast cancer pathogenesis. Which of the numerous functions of *SERPINA3* is relevant for breast cancer predisposition in particular, warrants further investigation.

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Author contributions

Katri Pylkäs, Susanna Koivuluoma, Anna Tervasmäki, Jukka Moilanen and Outi Kuismin conceived and designed the study. Outi Kuismin, Saila Kauppila, Robert Winqvist and Katri Pylkäs provided the study material. Katri Pylkäs, Susanna Koivuluoma, Anna Tervasmäki and Timo Kumpula performed the experiments and data analysis. Susanna Koivuluoma and Katri Pylkäs wrote the manuscript, and all the authors read and approved the final manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.10.033.

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