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Mutation screening of the *RNF8, UBC13* and *MMS2* genes in Northern Finnish breast cancer families

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Abstract

Background: Currently known susceptibility genes such as *BRCA1* and *BRCA2* explain less than 25% of familial aggregation of breast cancer, which suggests the involvement of additional susceptibility genes. RNF8, UBC13 and MMS2 are involved in the DNA damage response pathway and play important roles in BRCA1-mediated DNA damage recognition. Based on the evidence that several players in the ubiquitin-mediated BRCA1-dependent DDR seem to contribute to breast cancer predisposition, *RNF8, UBC13* and *MMS2* were considered plausible candidate genes for susceptibility to breast cancer.

Methods: The entire coding region and splice junctions of *RNF8, UBC13* and *MMS2* genes were screened for mutations in affected index cases from 123 Northern Finnish breast cancer families by using conformation sensitive gel electrophoresis, high resolution melting (HRM) analysis and direct sequencing.

Results: Mutation analysis revealed several changes in *RNF8* and *UBC13*, whereas no aberrations were observed in *MMS2*. None of the found sequence changes appeared to associate with breast cancer susceptibility.

Conclusions: The present data suggest that mutations in *RNF8, UBC13* and *MMS2* genes unlikely make any sizeable contribution to breast cancer predisposition in Northern Finland.

Background

Breast cancer is the most frequent malignancy among women [1], and the presence of a family history is one of the most fundamental risk factors for the disease [2]. Currently known susceptibility genes including *BRCA1, BRCA2, ATM, CHEK2, PALB2, RAD51C* and *BRIP1* explain less than 25% of familial breast cancer. The rest of the cases could be explained by mutations in mainly moderate and low penetrance cancer susceptibility genes together with environmental factors. Many of the genes already associated with breast cancer susceptibility encode proteins that operate together with BRCA1 and BRCA2 in the DNA damage response pathway (DDR) [3-7]. Other genes with similar functions thus represent good candidates for being new susceptibility genes.

Recent evidence indicates ubiquitin chain formation, recognitionand breakdown at the site of DNA double-strand breaks (DSB) as an essential component of the DDR [8]. RNF8 is a RING-finger ubiquitin ligase (E3), which is recruited to the sites of DNA damage after ATM/ATR-dependent phoshorylation of the H2AX histone variant [9-11]. Together with its ubiquitin-conjugating enzyme (E2) partner UBC13 it mediates K63-linked polyubiquitin conjugation to histones H2A and H2AX. The RNF8/UBC13-dependent histone ubiquitylation is then amplified by the RNF168 E3-ligase acting in concert with UBC13 [12]. Ubiquitynated histones are recognized by RAP80 through its ubiquitin interaction motifs (UIMs), which provide an ubiquitin recognition element to target the BRCA1 E3 ligase, Abraxas, MERIT40, BRCC45 and a K63-ubiquitin specific deubiquitinating enzyme BRCC36 to DSBs. Each of these activities is required for appropriate checkpoint and repair responses to ionizing radiation [13-15]. Depletion of RNF8 or UBC13 *in vitro* leads to inhibition of the recruitment of 53BP1, BRCA1, RAP80 and Abraxas to DSB sites [9-11,16]. It has also been demonstrated that the depletion of RNF8 leads to increased ionizing radiation sensitivity and defective G2/M checkpoint [9-11]. In addition, *Rnf8*$^{-/-}$ mice display increased genomic instability and higher risk for tumorigenesis, proposing that RNF8 is a novel tumor suppressor [17].

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Besides RNF8, the ubiquitin E2 variant (UEV) MMS2 seems to be essential for certain functions of UBC13. MMS2 forms a complex with UBC13 [18], and this heterodimer formation has been demonstrated to be essential for the DNA damage repair function of UBC13 [19]. Suppression of UBC13 or MMS2 has been shown to increase the sensitivity to DNA damaging agents [19], although the exact role of MMS2 in DDR is still unclear [20].

We have previously reported a potentially deleterious germline variant of *RAP80* (del81E) that abrogated ubiquitin binding and DNA damage response in breast cancer cases [21]. Additionally, recent findings of an extensive genome-wide linkage consortium study suggested an association between the rare allele of single nucleotide polymorphism (SNP) rs8170 in *MERIT40* and an increased propensity for hormone receptor-negative breast cancer, both in the general population and in *BRCA1* mutation carriers [22]. Based on the evidence that several players in the ubiquitin-mediated BRCA1-dependent DDR seem to contribute to breast cancer predisposition (summarized in Table 1), we decided to examine the role of *RNF8, UBC13* and *MMS2* in familial breast cancer by performing a comprehensive mutation screening of these genes in 123 Northern Finnish breast cancer families.

Methods

Study population

Affected index cases of 123 breast cancer families from Northern Finland were screened for germline mutations in the *RNF8, UBC13* and *MMS2* genes. From the studied families, 77 were classified as high-risk ones, defined as follows: 1) three or more cases of breast and/or ovarian cancer in first or second-degree relatives (median age 49 years, variation 37-80 years), or 2) two cases of breast cancer in first- or second-degree relatives, of which at least one with early disease onset (age ≤ 35 years), bilateral disease or multiple primary tumors. Most of the high-risk families presented three or more cancer cases. The remaining 46 families with moderate disease susceptibility indicated two cases of breast cancer in first- or second-degree relatives. Fourteen of the studied index cases had previously been tested positive for known breast cancer-associated germline mutations in *BRCA1* or *BRCA2* (eleven) and *PALB2* (three). DNA samples from anonymous cancer-free female individuals obtained from Finnish Red-Cross blood donors (N = 104-299, depending on the tested mutation), originating from the same geographical region as the studied cancer cases, were used as controls. All patients had given their informed consent for acquisition of pedigree data and blood specimens for the study of cancer susceptibility gene mutations. Approval to perform the study was obtained from the Ethical Board of the Northern Ostrobothnia Health Care District and the Finnish Ministry of Social Affairs and Health.

Table 1 Key operators in the BRCA1-dependent ubiquitin -mediated DNA damage recognition pathway and their currently known role in breast cancer predisposition

Gene	Previous studies on the role in breast cancer predisposition	Disease related alterations
RNF8	Not done	-
RNF168	Not done [a]	-
UBC13	Not done	
RAP80	Mutation screening [21,27-29]	del81E [21]
Abraxas	Mutation screening [27,29]	N. I.
MERIT40	Mutation screening [30] GWAS [22]	N. I. rs8170 [22]
BRCC45	Not done	-
BRCC36	Not done	-

[a] Homozygous mutations in this gene have been demonstrate to result in RIDDLE syndrome [12].

GWAS, genome wide association study; N. I., not identified.

DNA extraction and mutation analysis

Genomic DNA was extracted from blood lymphocytes using either the standard phenol-chloroform method or the Puregene D-50K purification kit (Gentra, Minneapolis, MN, USA). Mutation screening of the coding regions and exon-intron boundaries of the *RNF8, UBC13* and *MMS2* genes was carried out by conformation sensitive gel electrophoresis (CSGE) [23], high resolution melting (HRM) analysis [24], or by direct sequencing. Samples with band shifts in CSGE or deviant melt curves in HRM were reamplified and sequenced with Li-Cor IR2 4200-S DNA Analysis system (Li-Cor, Inc., Lincoln, NE, USA) or with capillary sequencing using ABI3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). For Li-Cor the Sequi Therm EXEL II DNA Sequencing Kit-LC (Epicentre Technologies, Madison, WI, USA) and for ABI the Big dye terminator kit v1.1 (Applied Biosystems, Foster City, CA, USA) were used. Chromatograms were interpreted using CodonCode Aligner v. 3.5.4 (Codon Code Corporation, Dedham, MA, USA) and with MEGA4 [25]. Oligonucleotides for CSGE, HRM and sequencing (Table 2) were designed using Primer3 software [26], based on sequence information obtained from public databases (NC_000006.11, NC_000012.11 and NC_000008.10).

Statistical and bioinformatical analysis

Carrier frequencies between patients and healthy controls were compared by using Pearson Chi-Square or Fisher's exact test in PASW Statistics (version 18 for Windows, SPSS Inc., Chicago, IL, USA), which was also used for the generation of odds ratios and confidence

Table 2 Primers used for the screening of *RNF8, UBC13* and *MMS2*

Gene	Exon	Forward primer (5'-3')	Reverse primer (5'-3')	PCR fragment size (bp)
RNF8	1	GCGAGGAGACCTCTCGAATC	TCCTCTCTGCCATTCATTCA	498
	2	TGCTGCTGGTTGATGAGAT	AAATAAAAGTCATTAGGCTTCTG	250
	3a	AAGAAGACGAAAATCATGAAGC	TAATTCATCCAAACTGAATTTCC	294
	3b	CCTTGTCTTTCCCCAAAGAAT	TTACTTGGCTCAAGGGCAGT	242
	3c	AGTGGCCAGTACACCCTCTG	TTCACATTCATAACGGCTTCA	240
	3d	GGTGACCATGTCCAGGATTC	AAGACCACTCTTGCCCTTCC	260
	4	CAGGAGATTTTCCACCTGCT	GGTCATGTGATGCCTGTTTG	271
	5	CAGGCATGTTTGTGGCTAAA	CCTAGCAACCCTTGCACTGT	242
	6	CCTGTCCCATTTTGCATTTT	AAGGGGTGAGCAACTGTTC	197
	7	GCCCTTAAGATGGGATTGTTG	TCCCTTTACTCCTCCCCATT	483
	8	AGGGAAATACAGGCTCCTCA	CAAGTGACTGAGGGCTTCCT	220
UBC13	1	GACTTCCACTCGTGCGTGA	TCCTCAGCACCCGACTTC	264
	2	TTGGGAGATTGGAGCTGTTC	TGGAATGCTTAAGAGAAAAAGGA	430
	3	GTCTGTGGGAGGGAAGTGAA	CCCATAGCAAGCCATTTTGT	385
	4	ATCTTTCAGCCCTGATCCAA	GAGGGGCCACTGCTTTTA	448
MMS2	1	CCCGGCCCTCATGAACTT	GGTCCCAGGCTACGCTCT	411
	2	AGGGGATTTGGTCTTTTTGG	CACGTGGGAAGCATCAATAA	421
	3	GCACTTAGACATTAATATTTTAGGTA	TTTTGGCTTAACAAAGGTCCTC	331
	4	TGCTTAACAAATTGGTGCCATA	GCTGCATTTTTCCTCCTGTT	408

intervals. All alterations were checked with NNSplice software for potential splicing effects http://www.fruitfly.org/seq_tools/splice.html.

Results

The mutation analysis of *RNF8* revealed two exonic, two intronic and three 5'UTR variants. Only one of these variants was novel (not reported the NCBI SNP database, http://www.ncbi.nlm.nih.gov/SNP/). Both of the observed exonic variants of *RNF8* were synonymous. In the *UBC13* gene, one unreported and one known intronic variant were observed, whereas no sequence alterations were observed in *MMS2*. All observed alterations in *RNF8* and *UBC13* were assessed for possible effects on consensus splice sites, but none of them had a predicted effect on splicing. In order to evaluate possible pathogenicity of the observed changes, their frequencies were compared between cases and healthy control individuals. None of the found sequence changes, however, appeared to associate with breast cancer susceptibility (Table 3).

Discussion

RNF8, UBC13 and MMS2 have important roles in the maintenance of genomic integrity and cell-cycle checkpoint control [9-11,19]. Based on their involvement in DDR and importance in BRCA1-mediated DNA damage recognition it was considered possible that mutations in these genes might contribute to hereditary predisposition to breast cancer.

In the current study, the whole coding region of the *RNF8, UBC13* and *MMS2* genes was systematically screened for mutations in 123 breast cancer families. No deleterious sequence alterations were observed in any of the genes. Previous studies have suggested that the *RNF8* gene could be novel tumor suppressor [17], but it seems that germline mutations predisposing to breast cancer in this gene do not exist or, at least, are very rare. It is of interest that another E3 ligase, RNF168, which acts together with UBC13 to amplify the RNF8-dependent histone ubiquitylation has been shown to be defected in RIDDLE syndrome, which is an immunodeficiency and radiosensitivity disorder. However, it is still unclear whether RIDDLE syndrome is associated with genome instability or increased tumor incidence [12].

Conclusion

The present data suggest that mutations predisposing to breast cancer are either very rare or absent in the coding region of the *RNF8, UBC13* and *MMS2* genes, which could possibly point to the essentiality of their protein products in the DNA damage response and other functions maintaining genomic integrity. Although a small study like this cannot exclude the possibility of some other rare mutations in *RNF8, UBC13* and *MMS2* might predispose to breast cancer, based on our findings they unlikely make any sizeable contribution to cancer predisposition. To our knowledge, this is the first study reporting the mutation screening of the *RNF8, UBC13* and *MMS2* genes in familial breast cancer cases.

Table 3 Observed alterations in the *RNF8*,*UBC13* and *MMS2* genes in Finnish breast cancer families

Gene	Nucleotide change	rs number	Carrier frequency		P-value
			Familial cases	Controls	(OR; 95% CI)
RNF8	*RNF8*ex1-36 C > T (5'-UTR)	-	4.8% (6/123)	1.9% (2/104)	0.29 (2.6; 0.52-13.2)
	*RNF8*ex1-150 G > T (5'-UTR)	rs4714059	12.2% (15/123)	19.2% (20/104)	0.20 (0.58; 0.28-1.21)
	*RNF8*ex1-134 C > G (5'-UTR)	rs195420	22.8% (28/123)	18.3% (19/104)	0.42 (1.32; 0.69-2.53)
	*RNF8*ex4+17 A > G (intron)	rs77440008	1.6% (2/123)	5.9% (16/273)	0.07 (0.27; 0.06-1.17)
	*RNF8*ex7-6 C > T (intron)	rs2284923	41.5% (51/123)	46.7% (121/259)	0.38 (0.81; 0.52-1.25)
	*RNF8*ex7 G1344A (Thr448Thr)	rs2284922	36.6% (45/123)	41.1% (111/270)	0.44 (0.83; 0.53-1.28)
	*RNF8*ex7 G1377A (Lys459Lys)	rs34150698	17.9% (22/123)	19.3% (52/270)	0.78 (0.91; 0.53-1.59)
UBC13	*UBC13*ex3+17C > T (intron)	rs7969431	3.3% (4/123)	4.7% (14/299)	0.61 (0.68; 0.22-2.12)
	*UBC13*ex4-18 G > T (intron)	-	1.6% (2/123)	3.4% (10/297)	0.52 (0.47; 0.10-2.20)
MMS2	-	-	-	-	-

OR, Odds ratio; CI, confidence interval; UTR, untranslated region.

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Authors' contributions
MV carried out the mutation screening and data analysis, and drafted the manuscript. RW and KP designed the study and revised the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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