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ORIGINAL ARTICLE

Mutations of BRCA1/2 Genes in the West of Turkey and Genotype-Phenotype Correlations

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SUMMARY

Background: **Mutations of the BRCA1/2 genes are associated with increased breast and ovarian cancer. The aim of this study was to investigate the founder mutations of the BRCA1 and BRCA2 genes in the Turkish population in the Aegean region as well as their genotype-phenotype correlations.**
Methods: **All the patients were provided with BRCA1/2 testing criteria according to the National Comprehensive Cancer Network. QIAseq Targeted DNA Panels were used for the BRCA1/2 coding regions.**
Results: **Of the 181 studied patients, 38 (21%) were found to carry pathogenic or likely pathogenic mutations, while 20 (11%) patients were found to carry variants of unknown significance. The most common pathogenic mutations were NM_000059.4:c.2765dup in the BRCA2 gene and NM_007300.4:c.981_982del and NM_007294.3:c.5266dup in the BRCA1 gene. p.Lys3326* was the most frequently detected variant of unknown significance (6/181). Regarding genotype-phenotype correlations, the NM_007300.4:c.981_982del mutation in BRCA1 gene was found to be milder in terms of breast cancer. The most frequent cancers other than those related to BRCA genes, observed in the relatives of the patients who had pathogenic variants and variants of unknown significance, were endometrium cancer and leukemia, respectively.**
Conclusions: **NM_007294.3:c.5266dup was found to be a candidate founder mutation in the Turkish population. NM_007300.4:c.981_982del mutation seems to have a milder course in terms of breast cancer. A significantly increased frequency of p.Lys3326* variant in breast cancer and ovarian cancer patients compared with that in the 1,000 Genomes Project suggesting that this variant has a slight effect on BRCA2 function.**
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Supplementary Tables and Figures

Supplemental Table 1. Patients who carry a pathogenic/likely pathogenic mutation and clinicopathologic properties in the study.

Patients who carry a pathogenic/likely pathogenic mutation and clinicopathologic properties in the study																				
CN	Age	Age at diag-nosis	Type of the tumor	Family history with BRCA- related cancers and other cancers					Tumor characteristics							Pathogenic and likely pathogenic mutations		
				1st degree	2nd relatives	3rd relatives	other		ER	PR	CerbB2	Ki-67	G			BRCA1	BRCA2	
							CA											
1	67	66	BC	BC (50, 50)	OC (NA NA) BC (34)	BC (NA NA)	-		-	-	-	H	p			-	c.2765dupT p.K923fs*13	
2	35	31	BC	BC (57)	BC (52)	-	-		+	-	-	H	p				c.2765dupT p.K923fs*13	
3	38	38	BC	BC (50)	BC (40 NA NA)	-	-		NA	NA	NA	NA	NA				c.2765dupT p.K923fs*13	
4	35	32	BC	-	-	-	-		+	-	-	H	m				c.2765dupT p.K923fs*13	
5	47	BC	BC (NA NA)	-	-	-	-		NA	NA	NA	NA	NA				c.2765dupT p.K923fs*13	
6 Sister of 2	46	-	-	BC (57, 31)	BC (52)	-	-		-	-	-	-	-				c.2765dupT p.K923fs*13	
7	42	42	BC	BC (60)	-	-	-		-	-	+	H	p				c.2765dupT p.K923fs*13	
8[m]	61	-	-	BC (NA)	-	-	-		-	-	-	-	-				c.2765dupT p.K923fs*13	
9	46	42	BC	BC (48) BC&OC (50, 70)	-	-	-		+	+	+	H	m				c.2765dupT p.K923fs*13	
10	59	59	OC	-	-	-	-		NA	NA	NA	NA	p			c.981_982 delAT p.C328*		

Supplemental Table 1. Patients who carry a pathogenic/likely pathogenic mutation and clinicopathologic properties in the study (continued).

Patients who carry a pathogenic/likely pathogenic mutation and clinicopathologic properties in the study																			
CN	Age	Age at diag-nosis	Type of the tumor	Family history with BRCA- related cancers and other cancers				Tumor characteristics						Pathogenic and likely pathogenic mutations	
				1st degree relatives	2nd degree relatives	3rd degree relatives	other CA	ER	PR	CerbB2	Ki-67		G	BRCA1	BRCA2
11 *	52	37 50	OC (bl) BC	-	-	-	-	+	-	-	L	m		c.981_982 delAT p.C328*	
12	61	61	BC	-	-	-	EC (sister, mother-grandma)	+	-	-	H	m		c.981_982 delAT p.C328*	
13	71	67	BC	NA	NA	NA	NA	+	-	-	H	w		c.981_982 delAT p.C328*	
14	67	67	BC&EC (serous)	-	-	-	Larynx ca (mother)	+	+	-	H	w		c.981_982 delAT p.C328*	c.658_659 delGTp. V220fs*4
15	73	70	OC	-	-	-	-	NA	NA	NA	NA	NA		c.981_982 delAT p.C328*	
16	58	58	BC	-	-	-	EC (sister) lung ca (brother)	-	-	-	H	p		c.5266 dupC p.Q1756fs*74	
17	59	59	BC	BC (40, 36)	BC (70)	-	-	+	-	+	L	m		c.5266 dupC p.Q1756fs*74	
18	44	38	BC (bl)	PC	-	-	-							c.5266dupC p.Q1756fs*74	
19	36	36	BC	-	-	-	EC (grand-mother)	-	-	-	H	p		c.5266dupC p.Q1756fs*74	
20	44	38	BC (bl)	PC, BC (70)	PrC	PrC	Larynx ca (grnad-mother)	NA	NA	NA	NA	NA		c.5266dupC p.Q1756fs*74	

Supplemental Table 1. Patients who carry a pathogenic/likely pathogenic mutation and clinicopathologic properties in the study (continued).

Patients who carry a pathogenic/likely pathogenic mutation and clinicopathologic properties in the study														
CN	Age	Age at diagnosis	Type of the tumor	Family history with BRCA- related cancers and other cancers				Tumor characteristics					Pathogenic and likely pathogenic mutations	
				1st degree	2nd relatives	3rd relatives	other CA	ER	PR	Cerb B2	Ki-67	G	BRCA1	BRCA2
21	40	36	BC	-	-	-	-	-	+	+	H	p	c.5266dupC p.Q1756fs*74	
22	30	27	BC	-	BC (50)	-		+	-	+	L	m		c.67+1G>A splice site
23	57	53	OC (bl)	-	-	-	-							c.5351dupA p.N1784fs*3
24	40	36	BC	-	PrC	-	-	-	-	+	H	p		c.10095delCins GAATTAT p.S3366fs*4
25	21	-	-	BC (40, 32)	-	BC (40)	-							c.2975delC p.T992fs*8
26[m]	66	64	BC	-	-	-	-	+	+	+	H	m		3847_3848 delGT p.V1283fs*2
27	50	46	OC	-	-	BC (28)	-						c.3825dupA p.L1276fs*11	
28**	54	27	BC	PC (65)	BC (30, 30)	-	-	NA	NA	NA	NA	NA	c.4695delA p.E1565fs*36	

CN - case number, CA - cancer, BC - breast cancer, OC - ovarian cancer, BC&OC - both breast and ovarian cancer in the same patient, EC - endometrium cancer, PC - pancreatic cancer, PrC - prostate cancer, CC - colon cancer, ER - estrogen receptor, PR - progesterone receptor, G - grade, w - well differentiated, m - moderately differentiated, p - poorly differentiated, NA - not available, (-) - negative, * - both ductal and lobular carcinoma, ** - medullary cancer, bl - bilateral, ca - cancer, m - male).

Supplemental Table 2. Patients who carry a variant of unknown significance and clinicopathologic properties in the study.

Patients who carry a variant of unknown significance and clinicopathologic properties in the study																		
CN	Age	Age at diag-nosis	Type of the tumor	Family history with BRCA- related and other cancers				Tumor characteristics						Variants of Unknown Significance	
				1st degree	relatives		other	ER	PR	Cerb B2	Ki-67	G	BRCA1	BRCA2
					2nd	3rd	CA							
1	37	36	BC(bl)	-	-	-	-	+	+	+	L	w		c.9976A>T p.K3326*
2	61	61	BC	-	-	-	Larynx ca (sister) Leukemia (aunt)	-	-	-	H	p		c.9976A>T p.K3326*
3	46	45	BC	BC (55)	BC (40)	-	Leukemia (mother)	+	-	+	H	m		c.9976A>T p.K3326*
4	44	44	BC	BC (48)	-	-	-	-	-	+	H	p		c.9976A>T p.K3326* c.4928T>C p.V1643A
5	NA	NA	NA	NA										c.9976A>T p.K3326*
6[m]	56	-	-	-	-	-	-							c.9976A>T p.K3326*
7	62	59	OC	-	-	-	Gastric ca (mother)	-	-	-	H	p		c.2731G>C p.E911Q
8	49	47	BC	-	-	-	-	-	-	-	H	p		c.385G>T p.D129Y

Supplemental Table 2. Patients who carry a variant of unknown significance and clinicopathologic properties in the study (continued).

Patients who carry a variant of unknown significance and clinicopathologic properties in the study																							
CN	Age	Age at diag-nosis	Type of the tumor	Family history with BRCA- related and other cancers						Tumor characteristics						Variants of Unknown Significance	
				1st degree	2nd relatives	3rd relatives	other	CA		ER	PR	Cerb B2	Ki-67	G		BRCA1	BRCA2
9	57	57	BC	-	-	-	-			-	-	-	H	p			c.3318C>G p.S1106R
10	46	45	BC	BC (55)	BC (40)	-	Leukemia (mother)			+	-	+	H	p			c.9976A>T p.K3326
11	43	-	-	BC	OC	-	-										c.3318C>G p.S1106R
13	51	50	BC	-	-	-	-			-	-	-	H	p		c.4843G>A p.A1615T	
14	47	46	BC	-	-	-	-			+	+	+	L	w			c.799G>A p.G267R
15	40	40	BC	-	-	-	-										c.4898T>C p.I1633T
16	59	-	-	BC (61)	BC (69)	BC (NA)	Gastric ca, EC										c.10253_10256delTCTA p.I3418fs*?
17	61	61	BC	-	BC (69)	BC (NA)	Gastric ca, EC			NA	NA	NA	NA	NA			c.10253_10256delTCTA p.I3418fs*?

Supplemental Table 2. Patients who carry a variant of unknown significance and clinicopathologic properties in the study (continued).

Patients who carry a variant of unknown significance and clinicopathologic properties in the study													Variants of Unknown Significance	
CN	Age	Age at diag-nosis	Type of the tumor	Family history with BRCA- related and other cancers				Tumor characteristics					BRCA1	BRCA2
				1st degree	2nd relatives	3rd relatives	other CA	ER	PR	Cerb B2	Ki-67	G		
18	42	42	BC	-	-	-	Leukemia (brother)	+	-	-				c.1550A>G p.N517S
19	40	38	BC	-	-	BC	-	NA	NA	NA	NA	NA		c.4779A>C p.E1593D
20	46	42	BC	-	-			+	-	-				c.1550A>G p.N517S

CN - case number, BC - breast cancer, OC - ovarian cancer, EC - endometrium cancer, ER - estrogen receptor, PR - progesterone receptor, G - grade, w - well differentiated, m - moderately differentiated, p - poorly differentiated, NA - not available, (–) - negative, m - male).