42P Impact of germline mutations on breast cancer prognosis in Kazakh population

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Breast cancer shows a high incidence both in Kazakhstan and worldwide. Presence of BRCA1 and BRCA2 genes defects, as well as non-BRCA genes can increase the risk of BC and they are still under the study. There is evidence of the effect of germline mutations on the survival outcomes of breast cancer patients, according to the molecular characteristics of the tumor in different subgroups. .

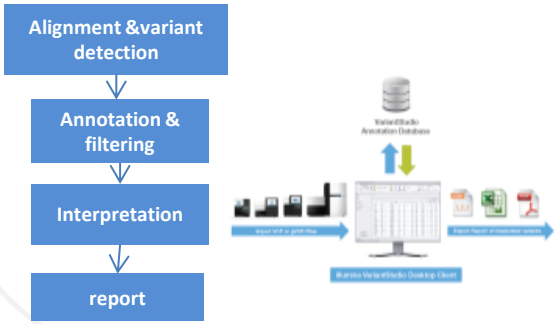
MATERIALS AND METHODS

The study enrolled 227 unrelated patients from Kazakh population (the average age 34.25 ± 4.56) with BC. Genomic DNA was obtained from peripheral blood and sequencing was performed using TruSight Cancer Kit on the MiSeq platform..

TruSight Cancer 94-Gene pre-disposition Panel for detecting Germline mutations

AIP	BUB1B	DDB2	EXT2	FANCL	MEN1	PALB2	RB1	SLX4	WRN
ALK	CDC73	DICER1	EZH2	FANCM	MET	PHOX2B	RECQL4	SMAD4	WT1
APC	CDH1	DIS3L2	FANCA	FH	MLH1	PMS1	RET	SMARCB1	XPA
ATM	CDK4	EGFR	FANCB	FLCN	MSH2	PMS2	RHBDF2	STK11	XPC
BAP1	CDKN1C	EPCAM	FANCC	GATA2	MSH6	PRF1	RUNX1	SUFU	
BLM	CDKN2A	ERCC2	FANCD2	GPC3	MUTYH	PRKAR1A	SBDS	TMEM127	
BMPR1A	CEBPA	ERCC3	FANCE	HNF1A	NBN	PTCH1	SDHAF2	TP53	
BRCA1	CEP57	ERCC4	FANCF	HRAS	NF1	PTEN	SDHB	TSC1	
BRCA2	CHEK2	ERCC5	FANCG	KIT	NF2	RAD51C	SDHC	TSC2	
BRIP1	CYLD	EXT1	FANCI	MAX	NSD1	RAD51D	SDHD	VHL	

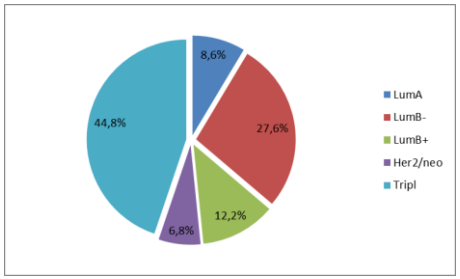
BIOINFORMATICS



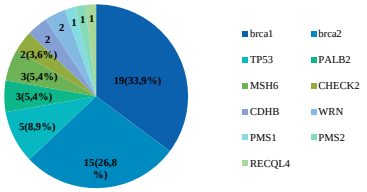
RESULTS

Bioinformatics analysis of NGS data identified 58 pathogenic variants, the heterozygous state were found in 50 (26.4%) patients, 8 (12.5%) variants were not previously described in databases.The most frequent pathogenic mutations were in the genes BRCA1 (24 variants (37.5%) and BRCA2 (18 (28.1%)). Additional pathogenic variants were identified in the non-BRCA genes (APC, ATM, BLM, CHEK2, PALB2, TP53, ERCC2, FANCA, FANCM, NBN, PMS1, PMS2, SDHB and XPA). 84 of patients (43,3%) had early stage BC,101(52,0%) local advanced, 9(4,6%) with advanced forms of BC. 45(23,2%) had disease progression after complex treatment: bone mts in 10 cases, 6 patient had liver mts, 11- lung and 6 patients had brain mts, 12 – combination of different metastasis- visceral crisis. 6 cases showed cancer related death, 5 of them had metastasis in CNS. Luminal A and B was in 27(13,9%) and 81(41,7%) cases, 20(10,3%) patients had Her2 enriched an 64(32,9%) had triple negative subtype of tumor according IHC. The triple negative molecular subtype of the tumor was found most in the BRCA1-associated group, almost two times higher than in the group of patients without pathogenic mutations (58.3% versus 29.5%, $\chi 2 = 9.45$, $p = 0.002$, the difference is statistically significant. Her2 enreached and triple negative subgroup had worse OS than Luminal subtypes (hazard ratio, HR 1.20 95% CI: 1.12-1.51) and worse OS showed 3 patients with combination of pathogenic BRCA1/2, CHEK2, PALB2, TP53 mutations.

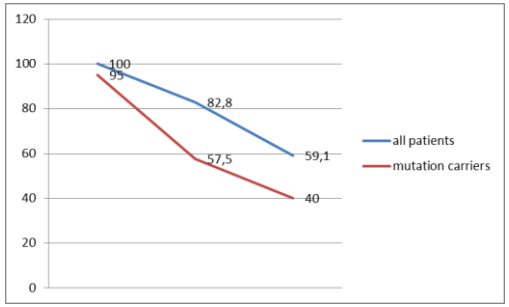
BC Tumor subtypes



NGS data analysis of mutations



Kaplan- Meier 5- year overall survival in both group



Analysis of the dependence of clinical characteristics with mutations

BREAST CANCER	All patients (n=227)	Patients with BRCA1/2 mutations (n=39)	mutations Patients with extra-BRCA mutations (n=19)	Patients with no pathogenic mutations (n =169)	P- value
Median Age [Min-Max]	34.25 ± 4.56]	33[21-44]	39 [27-51]	30 [19-42]	0.420
Subtype					
Luminal A	28 (12,3%)	3 (10.7%)	2 (7.1%)	23 (82.1%)	0.005
Luminal B	99 (43,6%)	15 (15.2%)	8 (8.1%)	76 (76.8%)	
Her2 positive	23 (10,3%)	1 (4.4%)	3 (13.0%)	19 (82.6%)	
Triple negative	75 (33.0%)	20 (26.7%)	6 (8%)	49 (65.3%)	
Disease progression					0.003
Yes	51 (22.5%)	9 (17.6%)	8 (15.7%)	34 (66.7%)	
No	176 (77.1%)	30 (17.1%)	11 (6.25%)	135 (76.7%)	

Conclusion

The presence of germline mutations in combination with aggressive subtypes significantly decrease overall survival in young women with breast cancer in Kazakh population

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