Germline Mutation Landscape in Chinese Breast Cancer Patients

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INTRODUCTION

Genetic testing for patients with breast cancer (BCa) patients may change the routine patient care and shift toward more personalized managing and treatment strategies. Testing germline mutations in BRCA1/2 has become a part of the standard clinical practice for patients with BCa. However, our understanding of genetic epidemiology of BCa is mainly driven by data from Caucasian populations and it has been evident that gene alterations may be ethnic specific in breast cancer.

To elucidate the landscape of germline mutations in Chinese patients with breast cancer, we retrospectively analyzed the clinical data of 356 patients with BCa who were treated at the Department of Breast Oncology, Peking University Cancer Hospital from January 2013 to December 2019. Associations between deleterious genes mutations and age of onset, family history, phenotype and survival in terms of disease-free survival (DFS) and overall survival (OS) were explored.

METHODS

Patients & Sample collection:
356 breast cancer patients with metastases treated at the Department of Breast Oncology Peking University Cancer Hospital from January 2013 to December 2019 were selected. Peripheral blood mononuclear cells were isolated from blood samples and genomic DNA were extracted for capture-based NGS sequencing.

NGS assay:
A large comprehensive 600 gene panel (PredicineATLAS™, Huidu Shanghai Medical Sciences) was used to detect germline mutations in the covered genes with average 300x sequencing depth.

Germline DNA analysis:.
Candidate variants with low base quality, mapping scores, and other quality metrics were removed. Candidate variants with an allelic frequency <15%, or with less than eight distinct reads containing the mutation, were excluded. Unknown variants in repeat regions were also excluded. Pathogenic or likely pathogenic variants are classified based on ACMG Standards and Guidelines and are further included as deleterious mutations in this study.

Table 1. Specifications of PredicineATLAS DNA panel

Parameter	PredicineATLAS™ DNA Panel
Regions Analyzed	600 genes
Panel Size	2.4Mb
Assay Sensitivity	5%
Sequencing Depth	>300X
Turnaround Time	1-2 weeks
Input Sample Type	Whole-blood, PBMC

RESULTS

Deleterious variants identified by PredicineATLAS™ panel

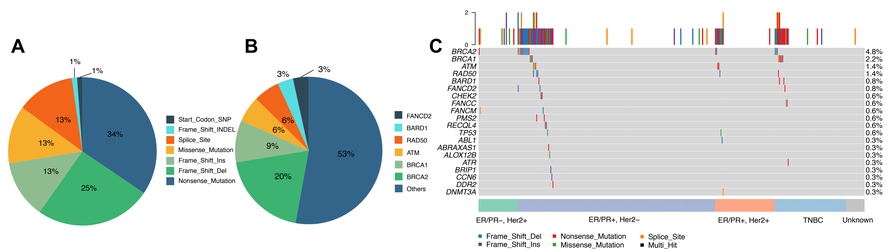

Figure 2. A: a Pie chart representing distribution of different types of mutations. B: A Pie chart representation of the overall distribution of the 46 mutated genes with total 87 detected deleterious variants. C: Heatmap representation of the top 20 detected deleterious genes across cancer subtype patients.

Association of deleterious variants and prognostic clinical variables

Table 2. Comparison of genomic alterations between BRCA1/2 mutation carriers and non-carriers among different prognostic variables.

Variables	BRCA1		P value	BRCA2		P value	Total Patients (N=356)
	Noncarrier (N=348)	Carrier (N=8)		Noncarrier (N=339	Carrier (N=17)		
Age at diagnosis (mean)	48.8	48.8	0.99	49.2	41.1	**0.003**	48.8
Family History							
Breast/ovarian	34	1	**0.04**	31	4	0.17	35
Other cancers	60	4		62	2		64
No	254	3		246	11		257
Tumor grade							
I-II	172	2	**0.03**	163	11	0.79	174
III	91	6		92	5		97
Lymph node (count)							
N0 (0)	101	1		93	9		102
N1 (1-3)	77	4	0.12	80	1	**0.008**	81
N2 (4-9)	54	0		53	1		54
N3 (>9)	46	0		40	6		46
Molecular subtype							
TN	61	5		63	3		66
ER/PR+, Her2-	179	3	**0.04**	171	11	0.88	182
ER/PR+, Her2+	55	0		53	2		55
ER/PR-, Her2+	36	0		35	1		36

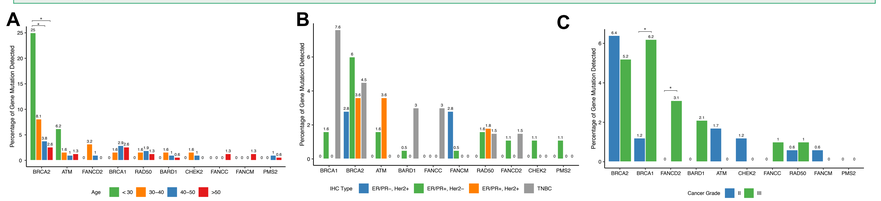

Figure 2. Comparison of percentage of individual gene mutation among different clinical subgroups.
Comparison of percentage of individual gene mutation among clinical subgroups for the top 10 mutated genes in age subgroup (a), IHC subtypes (b), and cancer grade (c).

Association between clinical parameters and survival outcome

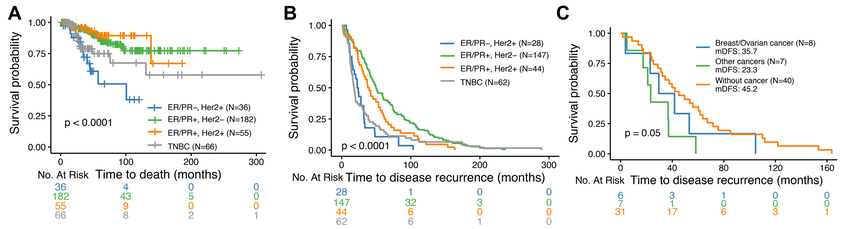

Figure 3. Comparison of overall survival and disease-free survival among clinical subgroups. A-B: Comparison of overall survival from diagnosis (a), disease-free survival (b) among breast cancer subtype groups for all patients. C: Disease-free survival by family history for ER/PR+, Her2+ subgroup patients.

Survival analysis of deleterious mutation variants

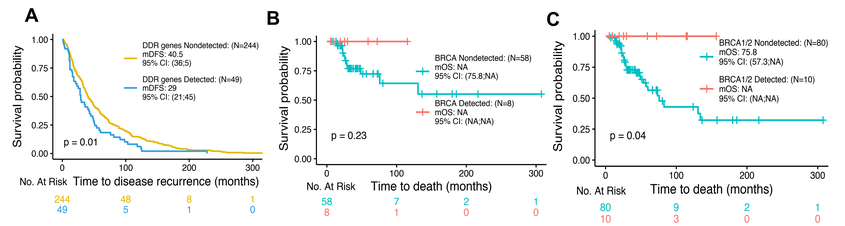

Figure 4. Overall survival comparison between mutation carriers and non-carriers.
A: Comparison of the DFS between DDR mutation carriers and non-carriers. B: BRCA1/2 carriers tend to have prolonged overall survival in triple-negative breast cancer. C: Stronger association with BRCA1/2 mutation carriers and overall survival was observed with additional 26 TNBC patients previously tested with a smaller NGS panel.

CONCLUSIONS

Our results revealed that the dominant deleterious variations identified by our 600 genes PredicineATLAS™ panel for the breast cancer patients were BRCA2, BRCA1, ATM, and RAD50. Consistent with previous studies, patients with family history of cancers and higher tumor grade were more likely to be BRCA1 carriers. BRCA1 mutations were strongly enriched in TNBC. Patients with high degree of axillary lymph node metastasis were more likely to harbor BRCA2 mutations. Survival probability varied in different subtype patients, and ER/PR-, Her2+ had the worst overall survival. Furthermore, patients with family history of cancers had worse survival outcomes for Her2+ patients. BRCA1/2 carriers had prolonged survival compared to non-carriers.

This is a comprehensive analysis of germline mutation spectrum in a large Chinese patient cohort with breast cancer. Mutations identified by our large comprehensive 600 gene panels will advance our understanding of the overall deleterious mutation landscape in Chinese populations with different clinical features as well as the mutation influence on survival outcomes.