Whole-exome sequencing reveals germline pathogenic variant landscape in multi-center Taiwanese breast cancer patient cohort at moderate to high hereditary genetic risks

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Background

The incidence of breast cancer in East Asia has been steadily increasing, with cases presenting approximately a decade earlier than those observed in Western populations. This study utilizes whole-exome sequencing (WES) to investigate the prevalence of hereditary germline pathogenic or likely pathogenic variants (PV) in Taiwanese breast cancer patients identified as having moderate to high hereditary genetic risk beyond NCCN criteria.

Method

Breast cancer patients with age at diagnosis less than 40 years, positive familial cancer history, bilateral cancer or multiple cancers, and triple negative breast cancer (TNBC) were enrolled from Linkou, Taipei and Kaohsiung hospital campuses of Chang Gung Medical Foundation. BRCA1/2 likelihood were evaluated with pathology-adjusted Manchester Scoring System (MSS3). (1) Whole-exome sequencing (WES) was conducted using the IDT Lotus DNA Library Prep Kit and xGen Exome Research Panel v2, with sequencing on the NovaSeq 6000 platform. Reads were aligned to the GRCh38 genome reference using DRAGEN v.3.9.3 with stringent quality metrics. Variants were filtered against databases such as dbSNP version 150 and Taiwan Biobank, annotated via wANNOVAR, and BRCA1/2 PVs were confirmed using Sanger sequencing.

Results

A cohort of 525 breast cancer patients were enrolled, revealing 36 individuals (6.9%) carrying confirmed germline BRCA1/2 PVs and another 28 patients (5.3%) carrying PVs in other non-BRCA hereditary breast and ovarian cancer (HBOC)-related genes (ATM, BARD1, BRIP1, CHEK2, MUTYH, PALB2, PMS2, RAD50, RAD51D, and TP53) (Figure1). Among the risk groups classified by the Manchester Scoring System, 72.8% were categorized as low (<10% risk), 15.2% were moderate (10-20%), and 12% were high risk (>20%) groups. The detection rate of BRCA PVs was 1.6% (6/382), 11.3% (9/80), and 33.3% (21/63) respectively in low to highs risk Manchester categories (Table4). For patients diagnosed with breast cancer under age 40 (n= 291,55%), the prevalence of BRCA1/2 PV was observed at 7.2% (21/291). Among patients with TNBC (n=78), the proportion of patients with BRCA1/2 PVs was notably higher, at 16.5% (n=13). In cases of bilateral breast cancers (n=43) (synchronous or metachronous), 12.8% (n=6) had BRCA1/2 PVs. Among the 16 male breast cancer patients, no BRCA 1/2 PV were detected. For individuals with a high Manchester Score but no detected BRCA1/2 PVs through sequencing, further analysis using the MLPA assay remains ongoing.

Table1. Demographic graphic data of participations (n=525) with whole exome sequencing.

Variables	No.	Median (range) or %
Age (years)		40 (19–89)
Family history	284	54.1
Bilateral breast cancer	43	8.2
Multiple cancer	42	8.0
Breast cancer stage		
0	82	15.6
I~III	398	75.8
IV/Recurrence	45	8.6
Breast cancer IHC		
HR+/HER2+	48	9.1
HR+/HER2-	359	68.4
HR-/HER2+	30	5.7
HR-/HER2-	78	14.9
Unknown	10	11.9

Table2. Age distribution of all breast cancer patients and the percentage of PV detection

Age at breast cancer diagnosis	Number of patients, N (%)	*BRCA1/2* PV N (%)	HBOC-related gene with PV N (%)	Cancer-related gene with PV N (%)
≤20	2 (0.4)	1 (2.8)	1 (1.6)	1 (1.3)
21~30	56 (10.7)	7 (19.4)	12 (18.8)	12 (16.0)
31~40	233 (44.4)	13 (36.1)	21 (32.8)	25 (33.3)
41~50	127 (24.2)	11 (30.6)	22 (34.4)	27 (36.0)
51~60	63 (12.0)	3 (8.3)	7 (10.9)	9 (12.0)
61~70	35 (6.7)	0	0	0
71~80	7 (1.3)	1 (2.8)	1 (1.6)	1 (1.3)
≥81	2 (0.4)	0	0	0
Total	525 (100)	36 (100)	64 (100)	75 (100)

Table3. Age distribution and percentage of BRCA PVs in TNBC patients

Age at breast cancer diagnosis	TNBC, N=78	TNBC with *BRCA1/2* PV, N=12 (15.4 %)	TNBC with *BRCA1* PV, N=9 (11.5%)
≤20	1 (1.3)	0	0
21~30	9 (11.5%)	3 (30.8)	3 (33.3)
31~40	26 (34.2)	5 (38.5)	2 (22.2)
41~50	21 (27.8)	2 (15.4)	2 (22.2)
51~60	15 (17.7)	2 (15.4)	2 (22.2)
61~70	6 (6.3)	0	0
71~80	0	0	0
≥81	0	0	0
Total	78 (100)	12 (100)	9 (100)

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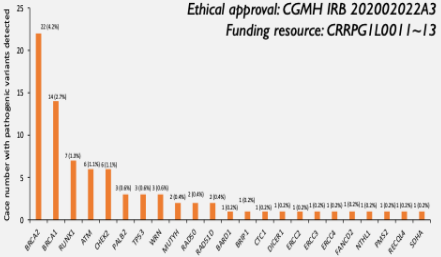


Figure1. Frequency of germline pathogenic variants cancer-related genes detection in our cohort

Table4. *BRCA1/2* PV detection in different Manchester score risk groups

Evaluated risk group	Total participants	Participants with detected *BRCA1/2* PV	Percentage of confirmed *BRCA1/2* PVs in respective risk group
low risk group	382 (72.8%)	6	1.6%
10-20% risk group	80 (15.2%)	9	11.3%
20% risk group	63 (12.0%)	21	33.3%
Total	525	36	6.9%

Conclusion

Whole-exome sequencing has provided valuable insights into the prevalence and distribution of germline pathogenic variants in HBOC-related genes among Taiwanese breast cancer patients with moderate to high hereditary risk. (2) The occurrence rates of BRCA1/2 pathogenic variants in the overall cohort and within triple-negative breast cancer patients align with trends observed in other breast cancer populations. (3)

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