Cancer Phenotype of Biallelic *CHEK2* Mutation Carriers

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BACKGROUND

- Carriers of biallelic pathogenic variants (PVs) in the breast cancer risk genes *BRCA2*, *ATM,* and *PALB2* have a more severe phenotype than monoallelic PV carriers.[1]
- There is currently no defined phenotype associated with biallelic PVs in *CHEK2*.
- Current NCCN guidelines recommend annual mammography and consideration of breast MRI for women with monoallelic *CHEK2* PVs beginning at age 40.
- It is important to understand if biallelic carriers have a more penetrant phenotype for which more intensive intervention might be required.
- This study compared the cancer phenotypes of women with biallelic and monoallelic *CHEK2* PVs to determine if biallelic carriers displayed a more severe clinical phenotype.

METHODS

- Female monoallelic (N=5,387) and biallelic (N=37) carriers of *CHEK2* PVs were identified through clinical pan-cancer panel testing at a commercial testing laboratory (Myriad Genetic Laboratories, Inc.) between September 2013 and November 2018.
  - Only biallelic carriers of PVs confirmed to be *in trans* were included; 11 unconfirmed were excluded.
  - *CHEK2* I157T (c.470T>C) and c.1283C>T (p.Ser428Phe) and carriers of PVs in genes other than *CHEK2* were excluded.
  - Both monoallelic and biallelic carriers were primarily White/Non-Hispanic in this cohort, with possible enrichment for Hispanic/Latino in the biallelic carriers (Table 1).

Table 1. Ancestry Distribution by Mutation Type

Ancestry	Monoallelic	Biallelic
Total	5,387	26
White/Non-Hispanic	3,665 (68.0%)	18 (69.2%)
Hispanic/Latino	302 (5.6%)	4 (15.4%)
Other*	255 (4.7%)	0
Multiple	294 (5.5%)	2 (7.7%)
Not Provided	871 (16.2%)	2 (7.7%)

*Other includes Ashkenazi Jewish, Black/African, Native American, Middle Eastern, Asian, Pacific Islander, and other.

- An analysis was also performed comparing monoallelic (N=2,828) and homozygous (N=13) carriers of the *CHEK2* founder mutation c.1100del.
- Fisher's Exact tests were used to determine the significance of differences between monoallelic and biallelic *CHEK2* carriers. P-values <0.05 were considered significant.

RESULTS

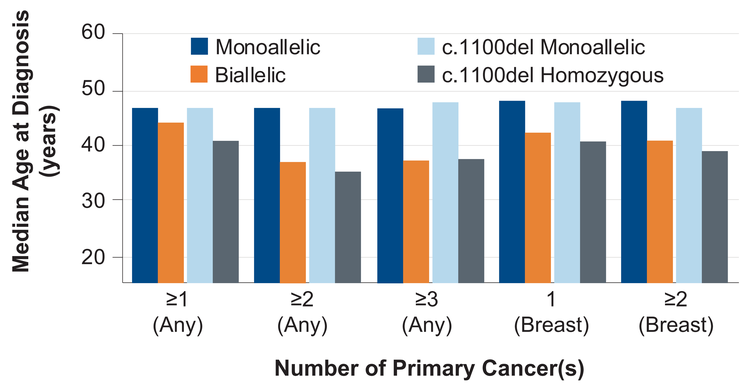
- Breast cancer frequency was significantly higher in biallelic carriers of PVs in *CHEK2* than in monoallelic carriers (p=0.0005; Table 2).
- Biallelic carriers were diagnosed with breast cancer at or before age 50 more often than monoallelic carriers (p=0.0004; Table 2).

Table 2. Primary Breast Cancer Distribution Among Monoallelic and Biallelic CHEK2 PV Carriers

Variable	Monoallelic	Biallelic	p-value
Breast Cancer (any age)	2,283 (42.4%)	20 (76.9%)	0.0005
Breast Cancer (≤50 years)	1,344 (24.9%)	15 (57.7%)	0.0004
Breast Cancer (any age) + 2nd Primary Breast Cancer	447 (8.3%)	6 (23.1%)	0.0180
Breast Cancer (any age) + Any Non-Breast Cancer	266 (4.9%)	3 (11.5%)	0.1364

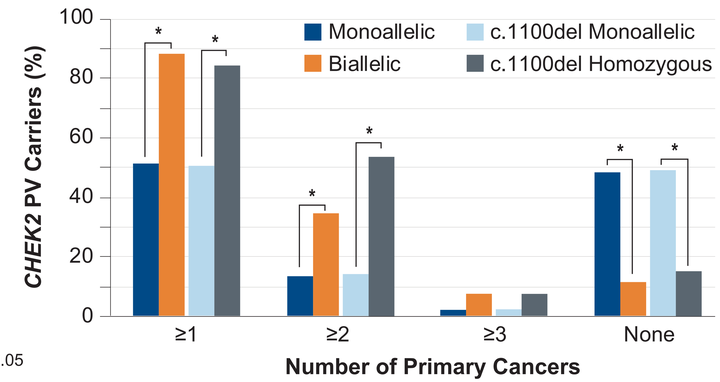
- Biallelic carriers were not significantly more likely to be diagnosed with any cancer at a younger age (Fig. 1).

Figure 1. Age at Primary Cancer Diagnosis



- Biallelic carriers were more likely to have a second breast cancer compared to monoallelic carriers (p=0.0180; Table 2).
- The percentage of women with any cancer diagnosis and with more than one primary diagnosis was significantly higher in biallelic carriers (p=0.0001 and p=0.0061, respectively; Fig. 2).
- Similar trends were observed when our analysis was limited to women monoallelic or homozygous for *CHEK2* c.1100del (Table 3, Fig. 1, and Fig. 2).

Figure 2. Number of Cancer Diagnoses for all CHEK2 PV Carriers



*p<0.05

Table 3. Primary Breast Cancer Distribution Among c.1100del Monoallelic and Homozygous CHEK2 PV Carriers

Variable	c.1100del Monoallelic	c.1100del Homozygous	p-value
Breast Cancer (any age)	1192 (42.1%)	10 (76.9%)	0.0204
Breast Cancer (≤50 years)	693 (24.5%)	7 (53.8%)	0.0222
Breast Cancer (any age) + 2nd Primary Breast Cancer	245 (8.7%)	4 (30.8%)	0.0218
Breast Cancer (any age) + Any Non-Breast Cancer	153 (5.4%)	3 (23.1%)	0.0309

CONCLUSIONS

- In this cohort, biallelic *CHEK2* PV carriers were at a higher risk for developing breast cancer than monoallelic carriers, were more likely to be diagnosed at age ≤50, and to have multiple primary breast cancers.
- Biallelic *CHEK2* PV carriers in this cohort also appeared to have a higher risk of cancer overall, although no individual non-breast cancer was significantly enriched.
- More intensive management may be appropriate for women with biallelic *CHEK2* PVs compared with current recommendations for monoallelic carriers.

Reference:1. Rahman, N. and Scott R.H. *Hum Mol Genet.* 2007; 16 Spec No 1:R60-6.

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