

IDENTIFICATION OF A RECURRENT PATHOGENIC VARIANT IN *BRIP1*

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HYPOTHESIS / PURPOSE

- Pathogenic variants in *BRIP1* are known to be associated with an increased risk of breast and ovarian cancer; however, little is known about the spectrum of pathogenic variants seen in this gene.
- The aim of this study was to analyze the spectrum of pathogenic variants detected in *BRIP1* and the types of cancer associated with these variants.

METHODS

- We identified male and female individuals positive for pathogenic variants in *BRIP1* through clinical testing with a 25-gene hereditary cancer panel.
- Pathogenic variants (PVs) were defined as all mutations that received a laboratory classification of Deleterious or Suspected Deleterious.
- Individuals were referred for panel testing due to a personal and/or family history of cancer.
- Personal and family cancer histories were obtained from provider report on the test request forms.

RESULTS

- Of the 112,449 individuals tested, 314 (0.3%) were found to have a PV in *BRIP1*, which composes 3.9% of the PVs identified in the testing population.
- 20/314 individuals with a *BRIP1* PV had a second PV in another gene.
- 7/314 *BRIP1* PVs were large rearrangements.
- PVs in *BRIP1* were identified in 310 females and 4 males. Due to the low number of males, they were excluded from further analysis.
- Figure 1 shows the personal cancer histories for women with a PV in *BRIP1*.
 - 55/310 (17.7%) women had a personal diagnosis of ovarian cancer, which is notably higher than the remaining testing population (6.4%).
 - The mean age of diagnosis for women with ovarian cancer who carry a PV in *BRIP1* was 62.7 years.

- A single variant, c.2392C>T (p.Arg798*), made up 90/310 (29.0%) of the *BRIP1* PVs detected in women (Table 1).
 - This variant has been previously identified in multiple individuals ascertained for suspicion of inherited cancer risk or Fanconi Anemia.
- There were no substantial differences in the personal cancer histories for individuals who carry the c.2392C>T variant relative to all other *BRIP1* PVs.
- The mean age of diagnosis for women with ovarian cancer who carry the c.2392C>T mutation is 67.6 years.

- Additional recurring PVs in *BRIP1* observed in this population are shown in Table 1.
- 56.7% of patients with the c.2392C>T variant reported to be of Western/Northern European ancestry, compared to 49.7% in all patients with *BRIP1* pathogenic variants (Table 2).
- Interestingly, the previously described recurrent *BRIP1* Spanish variant (c.1702_1703del) was not detected.

FIGURE 1. Personal Cancer History for All Women with a Pathogenic Variant in *BRIP1**

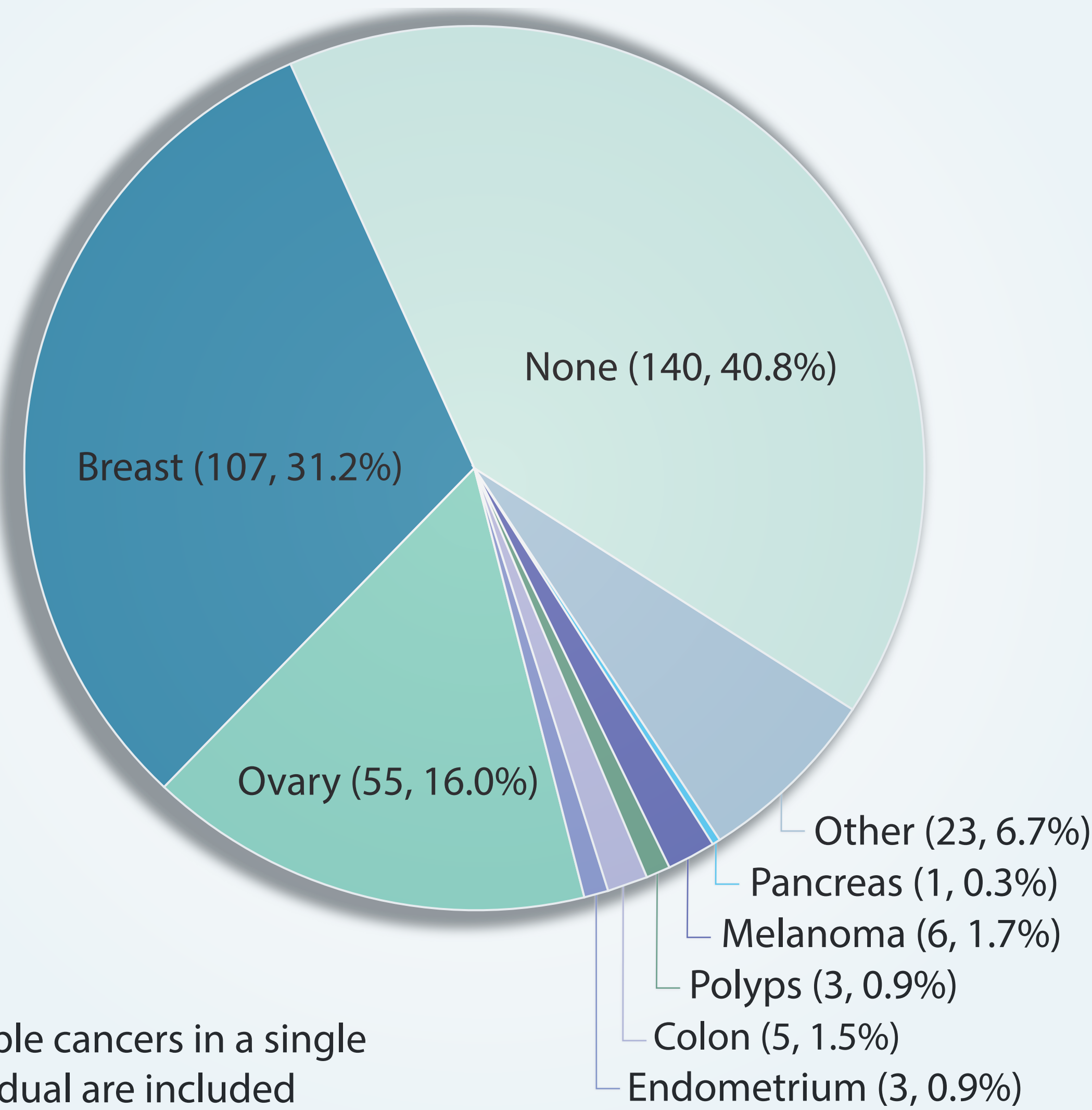


TABLE 1. Ten Most Common Recurrent PVs in *BRIP1*

Variant	N
c.2392C>T (p.Arg798*)	90
c.2010dupT (p.Glu671*)	13
c.1871C>A (p.Ser624*)	12
c.2255_2256del (p.Lys752Argfs*12)	11
c.2400C>G (p.Tyr800*)	11
c.1372G>T (p.Glu458*)	11
c.2038_2039dupTT (p.Leu680Phefs*9)	10
c.1045G>C (p.Ala349Pro)	9
c.2990_2993del (p.Thr997Argfs*61)	9
c.133G>T (p.Glu45*)	8

TABLE 2. Ancestry of *BRIP1* PV Carriers

Specified Ancestry	All <i>BRIP1</i> Mutation Carriers N (%)	<i>BRIP1</i> c.2392C>T Carriers N (%)
Western / Northern Europe	154 (49.7%)	51 (56.7%)
Central / Eastern Europe	21 (6.8%)	4 (4.4%)
Latin American / Caribbean	16 (5.2%)	8 (8.9%)
African	15 (4.8%)	2 (2.2%)
Ashkenazi	4 (1.3%)	0 (0%)
Asian	4 (1.3%)	0 (0%)
Native American	3 (1.0%)	0 (0%)
Neareast / Mideast	2 (0.6%)	0 (0%)
None Specified	63 (20.3%)	18 (20.0%)
Multiple Ancestries	28 (9.0%)	7 (7.8%)

CONCLUSIONS

- We identified 314 individuals with a PV in *BRIP1* through testing with a 25-gene hereditary cancer panel. PVs in *BRIP1* were observed in patients of all ancestries.
- Women with ovarian cancer were enriched in the population of *BRIP1* PV carriers (17.7%) compared to the overall testing population (6.5%), supporting the previously demonstrated association of *BRIP1* with ovarian cancer risk.
- A single truncating variant, c.2392C>T, was observed in 29.0% of women with a PV in *BRIP1*.