

Are Cancer Risks for the *CHEK2* Founder Mutation c.1100del Applicable to Other Pathogenic Variants in *CHEK2*?

Amanda Gammon, MS, LCGC¹; John Abernethy, MS²; Eric Rosenthal, PhD²;
Heidi Goringe, MS, LCGC²; Krystal Brown, PhD²; John Kidd, MS²; Susan Manley, MS, CGC, MBA²

1. Huntsman Cancer Institute, Salt Lake City, UT 2. Myriad Genetic Laboratories, Inc., Salt Lake City, UT

OBJECTIVES

- Current cancer risk estimates for pathogenic variants (PVs) in *CHEK2* are based largely on studies of the c.1100del founder mutation common in individuals of European ancestry.
- We compared the clinical histories of individuals with c.1100del to those with other PVs in *CHEK2* to determine if these risk estimates are applicable to other *CHEK2* PVs.
- This is an important issue in the era of panel testing, as risk estimates are often based on founder mutations studied in limited populations.

METHODS

GENETIC TESTING

- Individuals ascertained for suspected hereditary cancer risk were tested with a clinical 25-gene hereditary cancer panel between September 20, 2013 and August 14, 2015.
- Sequencing and large rearrangement analysis was performed for all the genes in the panel, except *EPCAM* (large rearrangement only).
- Variants with a laboratory classification of Deleterious or Suspected Deleterious were regarded as pathogenic.

ANALYSIS OF CLINICAL HISTORY

- Clinical information was obtained via healthcare provider report on the test request forms.
- 50 individuals with PVs in *CHEK2* and in another gene were excluded from the cohort.
- Age at diagnosis was evaluated based on the first age of cancer diagnosis for individuals with more than one instance of cancer.
- Individuals with the *CHEK2* c.1100del mutation were analyzed separately.

RESULTS

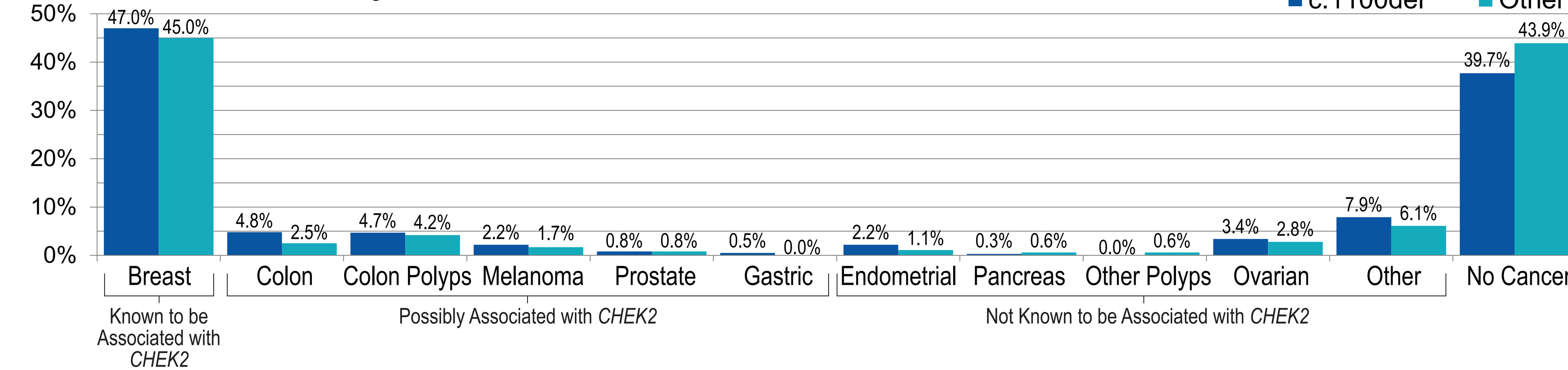
- Of 1002 individuals identified with a PV in *CHEK2*, 642 (64.1%) had c.1100del (Figure 1).
- 360 (35.9%) individuals had one of 95 unique other PVs in *CHEK2*.
- PVs other than c.1100del were found in individuals of all ancestries (Table 1).
 - Individuals of European, Ashkenazi Jewish, or Native American ancestry had more c.1100del mutations than other *CHEK2* PVs.
 - Individuals of African or Latin American ancestry had an equal or smaller number of c.1100del mutations than other *CHEK2* PVs.
 - Individuals of Asian or Near/Middle Eastern ancestry exclusively had *CHEK2* PVs other than c.1100del.

Table 1. Ancestry of Individuals with PVs in *CHEK2*

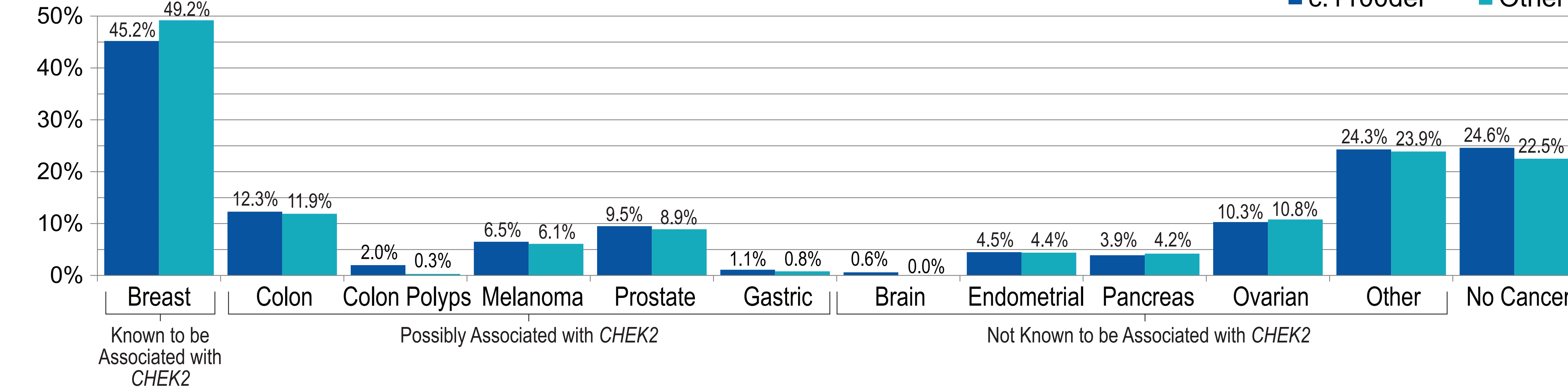
Ancestry	c.1100del	Other	Total
Western/Northern European	361 (69.3%)	160 (30.7%)	521
Central/Eastern European	53 (68.8%)	24 (31.2%)	77
Ashkenazi Jewish	17 (77.3%)	5 (22.7%)	22
Native American	8 (80.0%)	2 (20.0%)	10
African	4 (50.0%)	4 (50.0%)	8
Latin American/Caribbean	4 (13.3%)	26 (86.7%)	30
Asian	0 (0%)	9 (100%)	9
Near/Middle Eastern	0 (0%)	6 (100%)	6
Multiple Ancestries Indicated	74 (61.2%)	47 (38.8%)	121
None Specified	121 (61.1%)	77 (38.9%)	198
Total	642 (64.1%)	360 (35.9%)	1002

Figure 1. (A) Personal and (B) Family Cancer History of Individuals with PVs in *CHEK2*

A. Personal Cancer History



B. Family Cancer History



- We found no evidence of significant differences in the cancer rates associated with c.1100del versus other PVs in *CHEK2* based on personal or family cancer histories (Figure 1).
- There was also no evidence of significant differences in cancer rates based on:
 - Early onset breast cancer (< 50 years)
 - Triple-negative breast cancer
 - Median age at first breast cancer diagnosis (47 vs 48)

CONCLUSIONS

- Risk estimates for *CHEK2* carriers based on c.1100del appear to be applicable to individuals with any PV in *CHEK2* based on this analysis.
- Additional research is needed to completely characterize the cancer spectrum and degree of cancer risk associated with PVs in *CHEK2*. Multi-center collaborations collecting pathology reports from PV carriers with cancer will be particularly valuable.