Phenotype Comparison Between Founder and Non-Founder *CHEK2* Mutation Carriers

Tracey Leedom,[1] Holly LaDuca,[1] Rachel McFarland,[1] Shuwei Li,[1] Elizabeth Chao[1,2]
[1]Ambry Genetics, Aliso Viejo, CA, 92656
[2]Department of Pediatrics, University of California, Irvine, CA, 92697

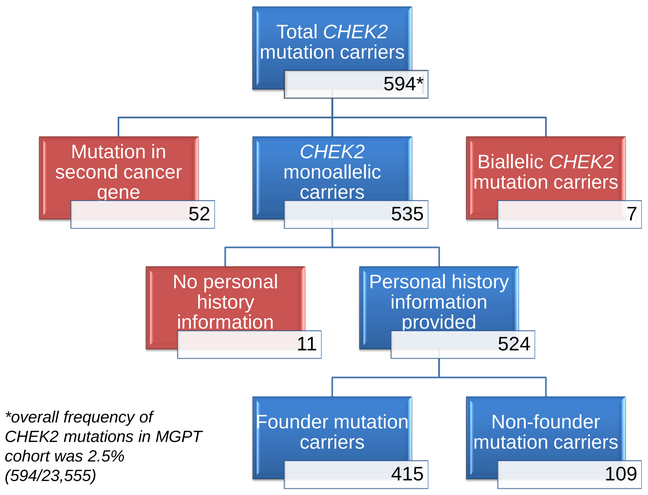
BACKGROUND

- Mutations in the *CHEK2* gene confer an increased risk of developing multiple types of cancers, including, breast, colon, prostate, thyroid, ovarian, and kidney.[1-3] Increased risks of male breast cancer have also been reported.[4]
- Several founder mutations in *CHEK2* have been identified in individuals of Eastern European and Ashkenazi Jewish ancestries. [1,5-7]
- The purpose of this study was to assess the phenotypes and molecular characteristics of *CHEK2* mutation carriers in a multi-gene cancer panel cohort, with a focus on comparing phenotypes of founder and non-founder mutation carriers.

METHODS

- Reviewed personal and family cancer history of individuals with *CHEK2* pathogenic mutations or likely pathogenic variants ('mutations') reported on multi-gene panel testing (MGPT) from March 2012-December 2014
  - Excluded individuals with additional mutations in non-*CHEK2* genes, biallelic *CHEK2* mutations, or no personal or family history information provided
  - Excluded family members negative for the familial *CHEK2* mutation
- Compared clinical histories of *CHEK2* founder mutation carriers (c.1100delC, p.I157T, p.S428F, EX8_9del, and c.444+1G>A) to non-founder mutation carriers
- Compared clinical histories of *CHEK2* mutation carriers to MGPT-negative controls (n=8,315) reported on multi-gene panel testing from March 2012-June 2014
- Statistical analyses performed using Fisher's exact test and multivariate testing, controlling for age at testing, type of multi-gene panel ordered, ethnicity, and gender

CHEK2 POSITIVE COHORT



**overall frequency of CHEK2 mutations in MGPT cohort was 2.5% (594/23,555)*

DEMOGRAPHICS

Demographic	n	%
Ethnicity		
African American	3	0.6%
Asian	4	0.8%
Ashkenazi Jewish	54	10.3%
Caucasian	414	79.0%
Hispanic	5	1.0%
Mixed Ethnicity	13	2.5%
Middle Eastern	1	0.2%
Native American	1	0.2%
Unknown	29	5.5%
Gender		
Female	479	91.4%
Male	45	8.6%
Panel Ordered		
BreastNext	255	48.7%
OvaNext	86	16.4%
ColoNext	59	11.3%
CancerNext	117	22.3%
CancerNext- Expanded	7	1.3%

RESULTS

Non-founders vs. Founders

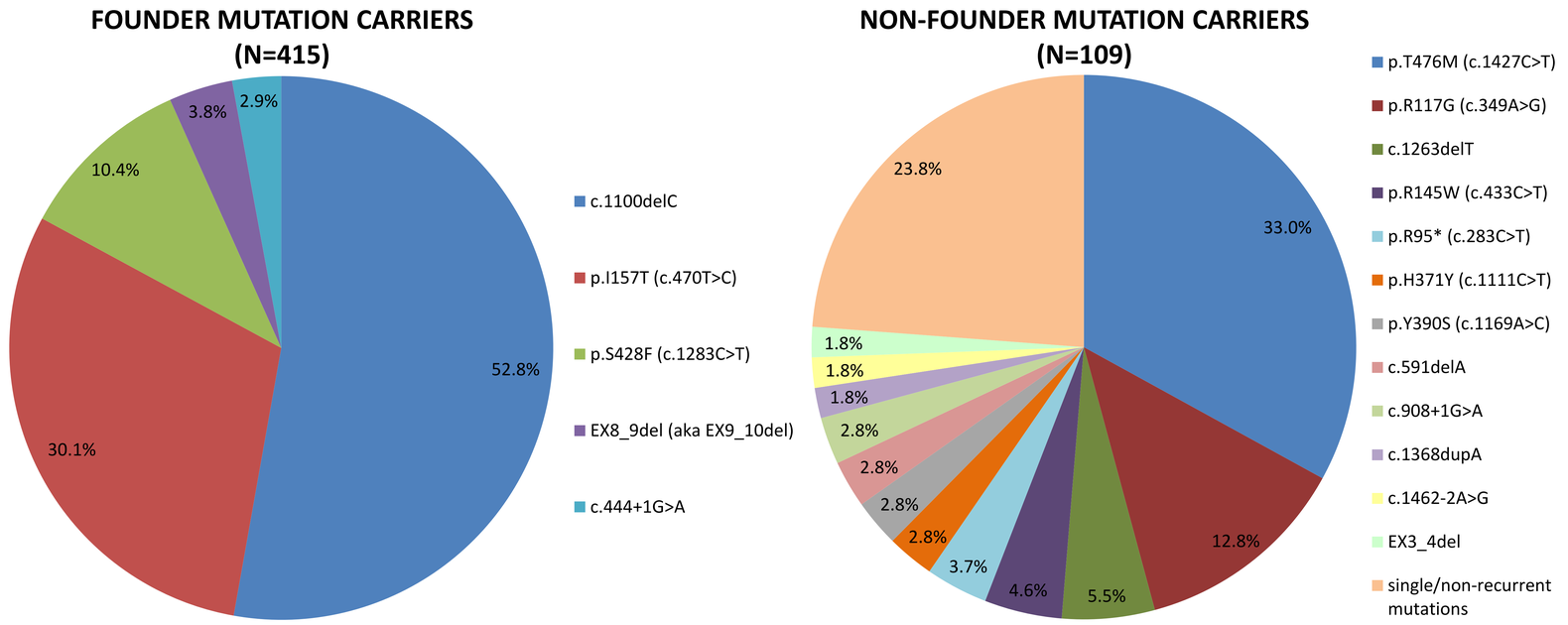
- No significant differences were observed between clinical histories of founder and non-founder *CHEK2* mutation carriers.

All *CHEK2* positives vs. MGPT negatives

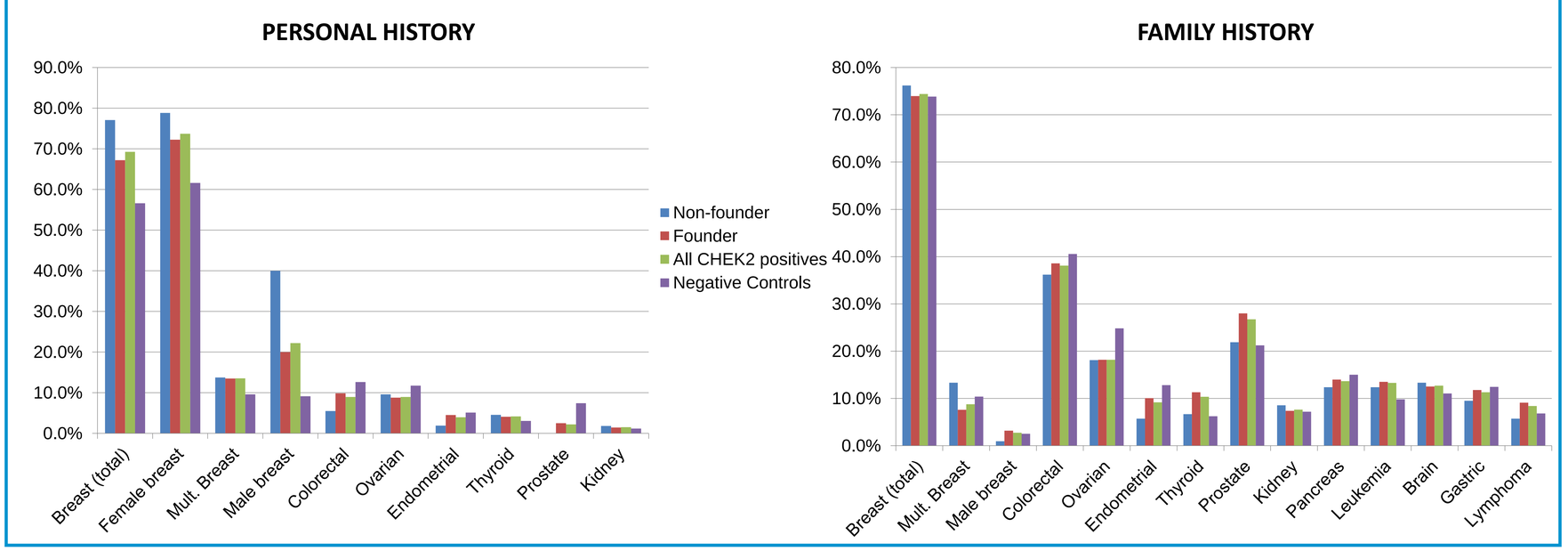
	Fisher's exact			Multivariate
	OR	P-value	95% CI	P-value
Phx breast (total)	1.728	1.0e-8	[1.423,2.104]	1.4e-6
Phx female breast	1.744	7.5e-8	[1.411,2.167]	1.1e-5
Phx male breast	1.472	5.0e-3	[1.118,1.917]	4.4e-3
Phx mult. breast	2.840	9.0e-3	[1.202,6.176]	1.2e-2
Fhx prostate	1.355	4.0e-3	[1.098,1.665]	6.3e-3
Fhx ovarian	0.671	5.4e-4	[0.527,0.848]	6.2e-3
Fhx leukemia	1.412	1.5e-2	[1.066,1.848]	3.0e-2
Fhx thyroid	1.739	5.6e-4	[1.264,2.353]	3.2e-4

- *CHEK2* mutation carriers were significantly more likely to have a personal history of breast cancer (both male and female) and a history of multiple primary breast cancers (phx mult. breast) than MGPT negative controls.
- *CHEK2* mutation carriers were significantly more likely to have a family history of prostate cancer, leukemia, and thyroid cancer than MGPT-negative controls, and were less likely to have a family history of ovarian cancer.

CHEK2 MUTATION SPECTRUM



CLINICAL HISTORIES OF *CHEK2* MUTATION CARRIERS AND MGPT-NEGATIVE CONTROLS



TAKE-HOME POINTS

- No significant differences were observed between clinical histories of *CHEK2* founder and non-founder carriers, suggesting that cancer risks reported in *CHEK2* founder populations may be generalizable to all *CHEK2* mutation carriers
- All *CHEK2* carriers were more likely to have a personal history of breast cancer (female, male, and multiple primary breast) than non-carriers, consistent with previous reports.
- The fact that no significant differences were observed between *CHEK2* carriers and non-carriers for other *CHEK2*-associated cancers (i.e. colorectal, prostate, thyroid, and kidney) is likely due to a selection bias of the MGPT cohort toward breast indications, as there were relatively lower numbers of these cancers reported compared with breast cancer.

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