Analysis of unique mutation distribution, ethnicity and test indication trends in over 1,200 positive cases identified by inherited cancer screening

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Introduction

- Inherited cancer screening (ICS) seeks to identify at risk individuals for hereditary cancer syndromes (HCS).
- Individuals may elect to have a variety of genes tested to identify HCS and clarify future cancer risks.
- There has been little study of mutation distribution, ethnicity and test indication trends, such as personal and/or family history or cancer, across a large cohort.
- We analyzed the first 1,218 positive cases at Counsyl to analyze such trends. Uncertain and benign findings were excluded.

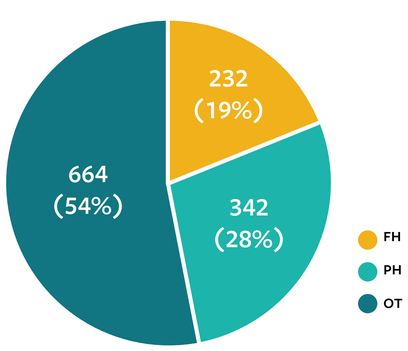
Methods

- Individuals were tested for mutation status in up to 36 genes by next-generation sequencing.
  - Positive Cases (PCS), defined as individuals with deleterious and/or likely deleterious mutations in >1 of the 36 genes tested, were queried.
  - Data was reviewed in a per-gene fashion as the total number of genes tested may vary by case.
- PCS were separated into cohorts by test indication as recorded from the test requisition form: Personal History with/without family history (PH) , Family History Only (FH) Other (OT): mixed PH/FH, unclear or unknown.
- Comparisons of total and unique mutation findings were recorded across cohorts.
  - PH and FH cohorts were further analyzed for gene-specific and ethnic trends.
  - Fisher's exact test was used to determine statistical significance.

Test Indication cohorts

Positive cases were identified in 27 genes with over half observed in individuals without reported personal history of cancer.

Figure 1: Cohort Distributions across Positive Cases



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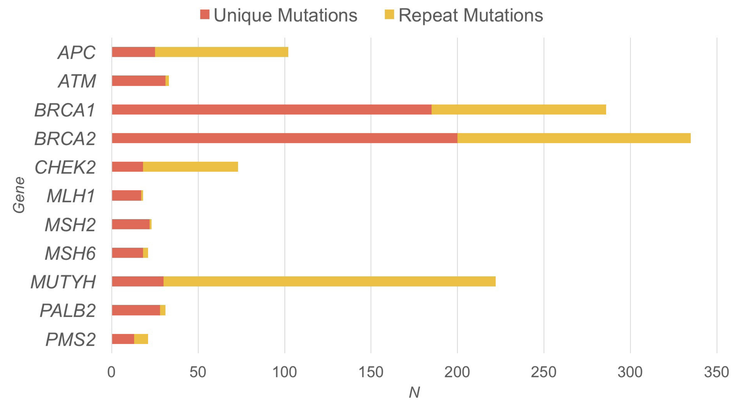
Study results

Unique Mutation Distribution

Unique mutations varied across cohorts and gene with the greatest number of unique mutations observed in the PH cohort and the *BRCA1* and *BRCA2* genes. Mutations were more often observed in high- or moderate- risk genes across cohorts (Figure 2).

Figure 2: Unique Mutation Count by Genes with >10 PCS Across Cohorts*



*16 genes including *BARD1, BRIP1, CDH1, CDKN2A, MEN1, MRE11A, NBN, RAD50, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, STK11, TP53, VHL* had <10 PCS each; unique mutations in 89% of these PCS (47/53).

Gene-Specific Trends Among PH/FH Cohorts

The PH cohort harbored mutations in some genes more frequently than the FH cohort and vice versa (Table 1). This finding was statistically significant (*) for *PALB2*: more PH cases had *PALB2* mutations than FH cases (p=0.000498).

Table 1. Comparison of Affected Gene by Cohort

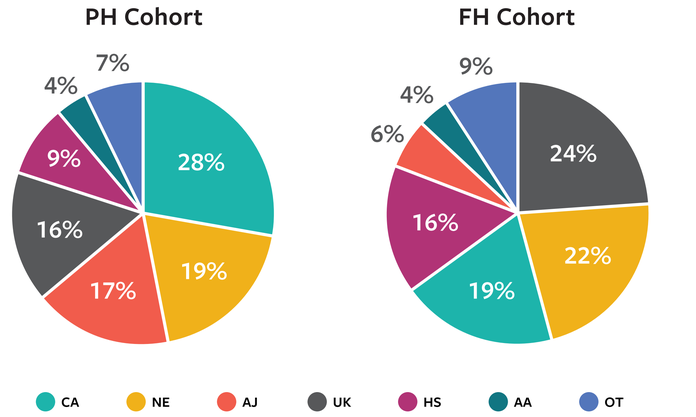
	Mutations more often observed in...	
Type of syndrome	**PH Cohort**	**FH Cohort**
Breast	*ATM, BRCA1, BRCA2, PALB2*, TP53*	*CDH1, CHEK2, STK11*
Ovarian	*BRIP, RAD51D*	*RAD51C*
Colorectal	*MLH1, MSH2*	*MSH5, PMS2, APC*
Other	*CDKN2A, VHL*	*SDHA, SDHB, SDHC, RET*

BMPR1A, CDK4, EPCAM, GREM1, MEN1, POLD1, POLE, PTEN, SMAD4 could not be compared between cohorts due to insufficient numbers.

Ethnicity trends among PH/FH cohorts

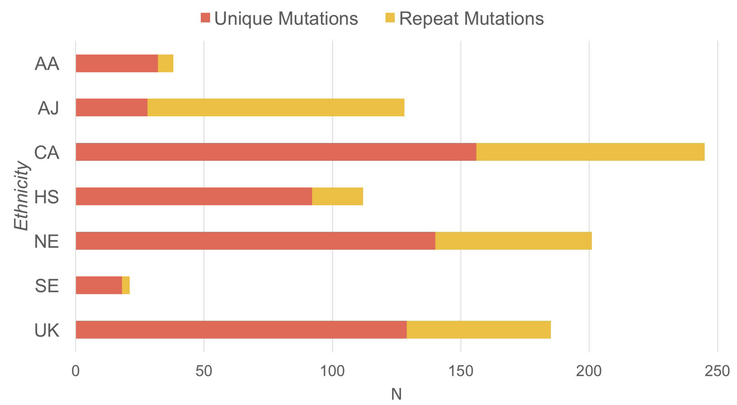
Self-reported ethnicities* were compared for ethnicities that contributed >3% to each cohort (Figure 3); no significant findings were observed. Total unique mutations across total positive cases were also analyzed for self-reported ethnicities with >20 PCS (Figure 4) to observe mutation count by ethnicity.

Figure 3: Reported Ethnicity in PH and FH Cohorts



(*) Individuals self-reported ethnicity in 1 of 15 categories including African/African American (AA); Ashkenazi Jewish (AJ); Mixed or Other Caucasian (CA); Hispanic (HS); Northern European (NE); Unknown (UK) (Figure 3). Other (OT) included East Asian, Finnish, French Canadian, Middle Eastern, Native American, Pacific Islander, South Asian, Southeast Asian, Southern European and contributed less than 3% to each cohort individually.

Figure 4: Unique Mutation Count in Common Ethnicities (n>20)



Conclusions

- Over half of the positive cases identified by ICS were associated with Family History Only indications which more often had mutations in non-BRCA genes.
- A variety of unique mutations were identified, however unique mutations occurred with the lowest frequently in previously reported genes with common mutations including *APC, CHEK2* and *MUTYH* and the AJ population, which is to be expected in the ICS setting.
- Non-European/Caucasian ethnicities had higher observed rates of unique mutations. Broader screening of a variety of ethnicities is needed to further extrapolate ethnic-specific mutation trends.