The Prevalence of Mosaicism in Common Cancer Susceptibility Genes from Individuals Undergoing Sequential Testing

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BACKGROUND

- Next generation sequencing (NGS) for germline mutations can identify likely somatic variants represented by low NGS read frequencies.
- These variants may represent true constitutional mosaicism, hematologic disorders, technical artifacts or circulating tumor burden; however, recent literature indicates that they most likely represent clonal hematopoiesis.
- Clonal hematopoiesis has been associated with risk for primary and secondary leukemias, cardiovascular disease, and decreased overall survival (Jaiswal et al. NEJM. 2014;371:2488).
- Previous studies have associated an increased risk of carrying a somatic variant with clinical factors, including personal cancer history and age.

OBJECTIVE

- From a large hereditary cancer clinical cohort, identify likely somatic NGS variants and explore factors contributing to this mosaicism.

METHODS

GENETIC TESTING

- We assessed individuals who had multi-gene pan-cancer panel testing through a large genetic laboratory (Myriad Genetic Laboratories; N=348,543).
- Likely somatic variants (NGS read frequency of 10-30%) classified as pathogenic, likely pathogenic, or uncertain were evaluated.

ANALYSIS

- Logistic regression analysis was used to determine the risk of carrying a likely somatic variant after adjusting for:
  - Personal cancer history (affected vs unaffected)
  - Age (<50 vs ≥50 years)
  - Germline mutation status
  - Clinical indication for testing.
- Odds ratios (OR) and 95% confidence intervals (CI) are reported.

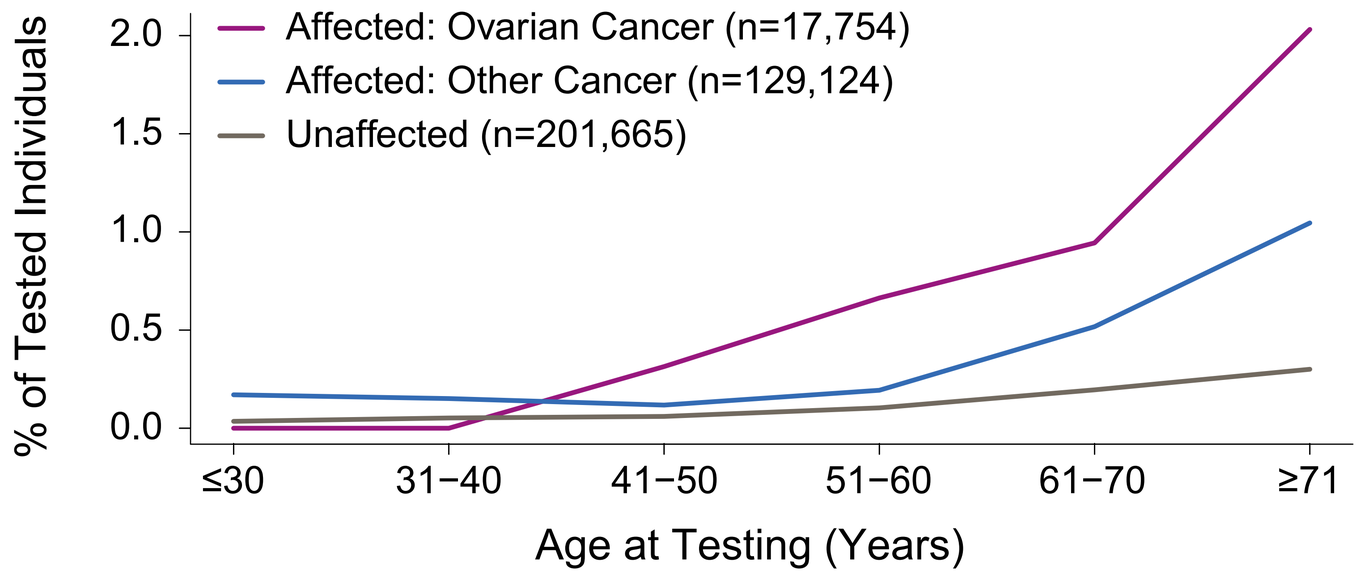
RESULTS

- 753 (0.22%) individuals were identified as carrying a likely somatic variant, most commonly in *TP53* (29%), *ATM* (20%), or *CHEK2* (29%).
- 609 (80.9%) individuals with a likely somatic variant had a personal history of cancer, compared to 42.1% in the overall testing population.
  - Individuals with a history of cancer showed an increased incidence of mosaic mutations at older ages (Table 1, Figure 1).
  - This trend was most prominent among individuals with ovarian cancer (Figure 1), who likely received chemotherapy prior to testing.
- Age at testing (≥50 years) and personal history of cancer were associated with a significantly increased likelihood of carrying a likely somatic variant (Table 1).

Table 1. Risk of Carrying a Likely Somatic Variant

Clinical Variable	OR	95% CI	p-value
Cancer History (Affected)	3.3	(2.7, 4.0)	<0.0001
Age at Testing (≥50 years)	3.1	(2.5, 3.7)	<0.0001
Germline Mutation Status (Carrier)	1.2	(0.9, 1.5)	0.2111

Figure 1. Prevalence of Likely Somatic Variants



- 68 (9.0%) individuals with a likely somatic variant also had a pathogenic germline variant.
  - Germline mutation carrier subset analyses showed no significant differences, except for an enrichment of likely somatic variants in *ATM* mutation carriers (p=0.0066).

CONCLUSIONS

- The presence of likely somatic variants was associated with advanced age and a history of cancer. The most prominent trend was seen in ovarian cancer, possibly due to differences in the amount or type of chemotherapy exposure.
- Likely somatic variants were identified mostly in genes known to be associated with clonal hematopoiesis. Collectively, this supports clonal hematopoiesis as the most likely cause of the majority of mosaic findings in this cohort.
- Germline *ATM* mutation carriers may be predisposed to developing clonal hematopoiesis.

Presented at ASHG on October 19, 2017