Potential of predispositional genetic screening for dominant actionable disorders: prevalence of genomic variants in 16,000 individuals

Edward D. Esplin¹, Shan Yang², Eden Haeverfield³, Swaroop Aradhya³, Robert Nussbaum¹

¹Invitae Corporation, San Francisco, CA, USA
Contact: Ed.Esplin@invitae.com

Background

The ACMG recommendations for the reporting of secondary findings in a set of 59 curated genes in patients undergoing whole-exome or whole-genome sequencing (WES/WGS) indicate a growing awareness that finding clearly pathogenic variants in certain genes is potentially medically actionable regardless of the original indication for testing. Few studies have estimated the number of actionable findings per unaffected individual on a large scale (Amendola, et al. PMID:25637381; Natarajan, et al. PMID:27831900), in part due to the cost limitations of WES/WGS. Even fewer studies have compared the rates of secondary findings among multiple ethnicities. We report an initial estimate of the prevalence of potential secondary findings in more than 16,000 unaffected individuals and the prevalence of those findings by ethnicity in a dataset generated with an expanded, multi-gene panel.

Methods

Per an IRB-approved protocol, we analyzed de-identified data for 124 genes associated with Mendelian conditions considered medically actionable by an expert panel (see ACMG abstract #5122). The list includes nearly all of the genes recommended by the ACMG in 2016 for reporting as secondary findings in WES/WGS. We reviewed de-identified sequence data for two groups of individuals: (1) 10,812 patients referred exclusively for cancer genetic testing, and (2) 5553 patients referred exclusively for non-cancer genetic testing. Using the 124-gene set, we analyzed variants in cardiovascular genes in the cancer genetic testing group, and in the non-cancer genetic testing group, we analyzed variants in cancer-related genes. We included variants as loss of function (LOF) if they were frameshift, nonsense, or splice-site disruption mutations and removed known non-pathogenic LOF variants, but we did no further manual curation. These calculated pathogenic variants (CPVs) were stratified according to reported ethnicity. Patients’ personal and family histories, stripped of all protected health information (PHI) were available from referring clinicians for this analysis.

Results

Among 5553 individuals without reported personal or family histories of a heritable cancer predisposition, we observed 162 CPVs in cancer predisposition-related genes, a prevalence rate of 2.9% (Figure 1B).

Compared with the ACMG 56, the 124-gene panel identified a greater number of CPVs (Figure 2), likely related to the screening of additional genes. One or more CPVs were identified in 76 different genes, with more than 20 CPVs each being identified in CHEK2, APOB, ATM, and BRCA2 (Figure 3).

The distribution of CPVs in cancer predisposition genes by ethnicity demonstrated the highest estimated prevalence in Asian participants, followed by White/Caucasian, Hispanic, Black/African American, and Ashkenazi Jewish participants (Figure 4A). The low prevalence of cardiovascular gene CPVs observed in Asian individuals may be related to the number of individuals assessed (Figure 4B). We observed overall differences, but none reached statistical significance.

Conclusions

The overall estimated prevalence of actionable secondary findings in this study is higher than that in recent reports but is likely underestimated due to the stringency of the automated CPV classification process, which is a limitation. This study provides an initial estimate of overall and ethnicity-specific prevalence rates and evidence to suggest the potential for genetic screening in ostensibly healthy individuals to have clinical impact. The ability to generate this information with an expanded multi-gene panel also highlights the need for research to improve the rapid identification and thoughtful return of medically actionable findings to healthy individuals.