Potential of predisposition genetic screening for dominant actionable cardiovascular conditions: Prevalence of genomic variants in 10,812 individuals

Shan Yang, Edward D. Esplin, Eden Haverfield, Swaroop Aradhya, Matteo Vatta, Robert L. Nussbaum
Invitae Corporation, San Francisco, CA

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Background

The ACMG published recommendations for reporting medically actionable pathogenic variants in a set of 59 curated genes as secondary findings in patients undergoing whole exome or genome sequencing.
In this analysis, we report an initial estimate of the prevalence of secondary findings in genes implicated in dominant cardiovascular disorders in 10,812 individuals referred for hereditary cancer gene testing for a personal or family history of cancer. We also looked at how often patients with a pathogenic or likely pathogenic variant (P/LP) in a gene associated with hereditary cancer also had a P/LP variant in a gene associated with a cardiovascular condition. These findings have potential to change clinical management for these patients.

Methods

1. Patient population: Per an IRB approved protocol, 10,812 de-identified patients originally referred for cancer genetic testing were analyzed. Patients' personal and family histories, stripped of all protected health information (PHI) were available from referring clinicians for this analysis.
2. Genes analyzed:
   a) 69 genes associated with Mendelian cardiovascular conditions in the Invitae Genetic Health Screen Panel (*).
   b) 31 genes associated with Mendelian cardiovascular conditions in the ACMG panel (**).
3. We identified known pathogenic or likely pathogenic variants and predicted LOF variants in genes for which LOF variants have established pathogenicity.
4. We stratified the patients according to self-reported ethnicity.
5. Patients with positive findings in both hereditary cancer associated genes and cardiovascular condition associated genes (double hits) were identified.

Results: Estimated prevalence

- In 10,812 de-identified individuals, we found 188 patients (1.74%) with pathogenic or likely pathogenic variants in 69 cardiovascular disorder-related genes in the Invitae Genetic Health Screen.
- Restricting our analysis to the 31 cardiovascular genes that the ACMG recommends be examined for secondary findings lowered the prevalence to 1.32%.
- Prevalence differences were observed across ethnic groups, but none reached statistical significance.

	All (10,812)	Caucasian (7,320)	Hispanic (706)	Black (667)	Ashkenazi Jewish (497)	Asian (241)
Positive findings Invitae Genetic Health Screen	188 (1.74%)	123 (1.68%)	8 (1.13%)	7 (1.05%)	10 (2.01%)	2 (0.83%)
Positive findings ACMG Recommendations	143 (1.32%)	95 (1.30%)	7 (0.99%)	6 (0.90%)	6 (1.21%)	2 (0.83%)

* Gene list for in-house Mendelian cardiovascular conditions associated genes:
ACTA2, ACTC1, APOB, COL3A1, DSC2, DSG2, DSP, FBN1, GLA, KCNH2, KCNQ1, LDLR, LMNA, MYBPC3, MYH11, MYL2, MYL3, MYH7, MYLK, PCSK9, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TPM1, F9, JUP, ACVRL1, CACNA1C, CACNB2, CASQ2, DMD, EMD, ENG, F5, GPD1L, HCN4, KCNE1, KCNE2, KCNJ2, LDLRAP1, PLN, PROC, PROS1, RBM20, SERPINC1, SGCD, TGFB3, CAV3, DES, BMPR2, CAV1, F2, FHL1, PRKG1, TGFB2, BAG3, ACTN2, CRYAB, CSRP3, TCAP, TNNC1, VCL

** Gene list for ACMG recommended Mendelian cardiovascular condition associated genes:
ACTA2, ACTC1, APOB, COL3A1, DSC2, DSG2, DSP, FBN1, GLA, KCNH2, KCNQ1, LDLR, LMNA, MYBPC3, MYH11, MYL2, MYL3, MYH7, MYLK, PCSK9, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TPM1

Results: Genes with positive findings

There were 33 unique cardiovascular genes on the Invitae Genetic Health Screen that were found to have pathogenic/likely pathogenic variants in patients tested for a hereditary cancer syndrome (Fig 1). Eighteen of these genes are on the ACMG list recommended for secondary finding reporting.

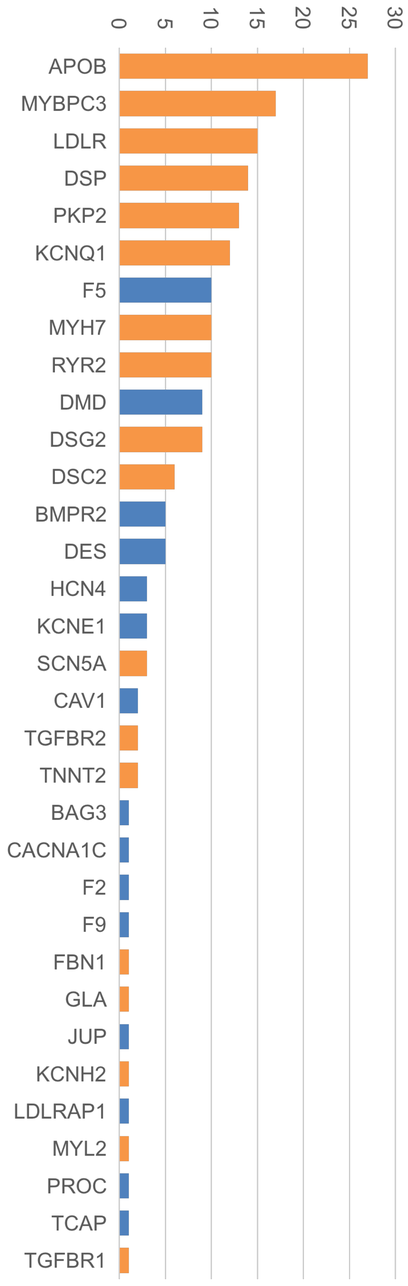

Fig 1. Counts of variants by genes that host pathogenic / likely pathogenic variants in all cancer patients.

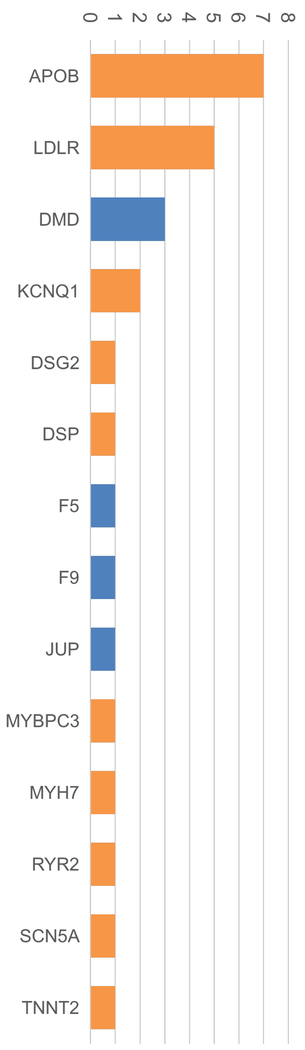

Fig 2. Counts of variants by genes that host pathogenic / likely pathogenic variants (P/LP) in patients who also have P/LP variants in cancer genes.

In both figures, orange bars represent ACMG genes. Blue bars are Invitae panel genes that are not in the ACMG list.

Results: Double hits

- We found 26 patients (0.24%) undergoing hereditary cancer syndrome testing who also had positive findings in cardiovascular genes on the Invitae panel.
- If only ACMG-recommended cardiovascular genes were considered, 20 (0.18%) patients had positive findings in both cancer and cardiovascular genes (Fig 2).

Conclusions

- Overall, 1 in 57 individuals (1.74%) without known hereditary cardiovascular disorders had positive findings in 69 genes on the Invitae Genetic Health Screen associated with Mendelian cardiovascular disorders; the prevalence was lower (1 in 76 or 1.32%) for 31 cardiovascular genes that the ACMG recommends to be examined for secondary findings.
- People with Caucasian and Ashkenazi Jewish ethnicity had a higher prevalence of positive cardiovascular findings than Hispanic, Black, and Asian individuals. However, the difference was not statistically significant.
- We also observed that 1 in 417 patients (0.24%) referred for heritable cancer syndrome testing carried P/LP variants in both cancer and cardiovascular genes. This information could be potentially important for guiding choice of chemotherapy with cardiotoxic effects.
- The overall prevalence was likely underestimated as we did not assess novel missense or copy number variants. Nonetheless, the findings observed in this study contribute to our knowledge concerning genetic screening for heritable cardiovascular disorders in individuals with a personal or family history of cancer.