Do candidate genes increase clinical utility of hereditary cancer panels? When less is more

Jennifer Herrera-Mullar[1], Meghan C. Towne[1], Carolyn Horton[1], Amybeth Weaver[1], Jennifer M. Huang[1], Devon Lamb Thrush[1], Kelly Radtke[1], Bess Wayburn[1]

[1]Ambry Genetics, Aliso Viejo, CA

Jherreramullar@ambrygen.com

BACKGROUND

- Next generation sequencing (NGS) has spurred gene discovery and allowed for the creation of multigene panel tests (MGPT) for hereditary cancer predisposition (HCP).
- These discoveries have resulted in larger HCP-MGPT over the last decade.
- The goal of larger HCP-MGPT is to increase diagnostic yield.
- How does the inclusion of candidate HCP genes impact diagnostic yield?

WHAT IS A CANDIDATE GENE?

A gene that has been reported in the literature, but evidence is insufficient to characterize the gene-disease relationship. Also known as limited evidence genes or preliminary evidence genes.

METHODS

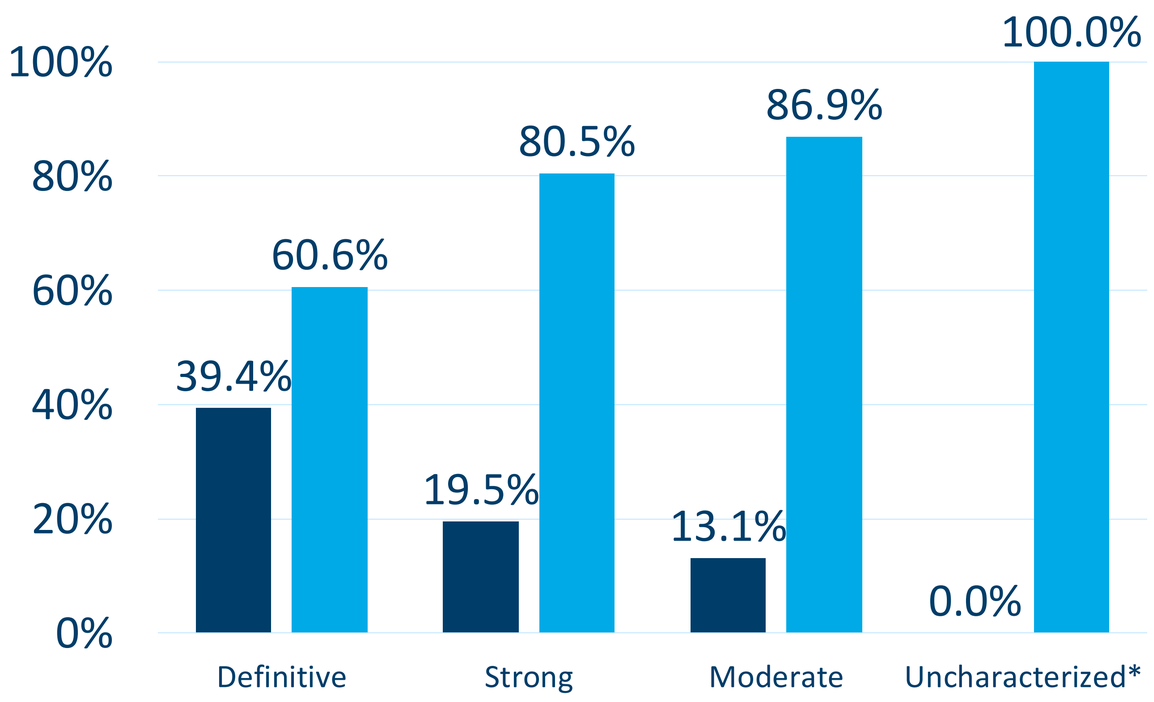
- Reported variants on HCP-MGPT offered (between 2014-2022) at a commercial laboratory were retrospectively reviewed.
- The frequency of pathogenic (P), likely pathogenic (LP) variants, and VUS were recorded and categorized according to four different GDV categories: uncharacterized (genes with limited/disputed GDV), moderate, strong, and definitive based on evaluation of published clinical and experimental evidence **[Figure 1]**.
- Select genes with moderate or limited GDV for HCP at the start of the time frame (n=20) were reviewed for changes to GDV category **[Table 2].**
- GDVs were assessed in accordance with the ClinGen GDV framework, and variants were classified in accordance with ACMG guidelines.

TABLE 1. Gene-Disease Validity (GDV) Scoring

Genetic Evidence			
Evidence type	**Information type**		**Points**
Case control Data	Size of study, appropriate matching/controlling of variables, clinically and statistically significant odds ratios and confidence intervals		+/- 0 – 6
Case Level Data	pLOF (consistent with genetic data)	*Not applicable for common disease/diseases with incomplete penetrance (start at default 0.1)	2 default*
	Other (default 0.1 points with no additional evidence)	Functional evidence, co-segregation, *de novo*, hotspot [allow additional weight 0.5 – 1]	0.1 - 2
Statistics	Excess of *de novo*, AR disease with extensive pedigree (LOD >3)		0 – 2
Experimental Evidence			
Evidence type	**Information type**		**Points**
Function	Biochemical function, protein interaction, expression		0 – 2
Gene Disruption	In vitro experiments, mechanism consistent with reported variants, rescue experiments, experiments showing dosage effect		0 – 2
Model Organism	Gene function similar to pathology of human disease, genotype and phenotype match human disease		0 – 2

GDV Category		Total Points
Definitive	Characterized	17+ known mechanism
Strong		13+
Moderate		8 - 12
Limited	Uncharacterized	>0 - 7
No Known Disease Relationship		0
Disputed		-6 - <0

FIGURE 1. Reported Variant Classification by GDV Score (91-gene Hereditary Cancer MGPT)



*Includes Limited and Disputed

TABLE 2. GDV Score Changes Over Time for Select Genes

Gene	HCP-related phenotype	GDV at addition	GDV Current
POT1	Melanoma and sarcoma	moderate	definitive
CTNNA1	Diffuse gastric cancer	moderate	moderate
EGFR	Lung cancer	moderate	moderate
LZTR1	Schwannomatosis	moderate	moderate
EGLN1	PGL/PCC	moderate	limited
KIF1B	PGL/PCC	moderate	limited
RECQL	Breast cancer	moderate	disputed
BLM (AD)	Breast cancer	moderate	disputed
FANCC (AD)	Breast cancer	moderate	disputed
NBN (AD)	Breast cancer	moderate	disputed

Gene	HCP-related phenotype	GDV at addition	GDV Current
XRCC2	Breast cancer	moderate	disputed
RAD50 (AD)	Breast cancer	moderate	disputed
MRE11A (AD)	Breast cancer	moderate	disputed
RPS20	Colorectal cancer	limited	limited
PALLD	Pancreatic cancer	limited	limited
MLH3	Colorectal cancer	limited	limited
GALNT12	Colorectal cancer	limited	limited
TERT	Melanoma	limited	limited
FAM175A	Breast cancer	limited	disputed
RINT1	Breast cancer	limited	disputed

AD – autosomal dominant; PGL/PCC –pheochromocytoma/ paraganglioma

TAKE HOME POINTS

1. The inclusion of candidate genes on HCP-MGPT did not affect the diagnostic yield, but substantially increased the VUS rate.
2. Higher GDV scores resulted in more clinically actionable (LP/P) variants. Lower GDV scores resulted in higher VUS rates.
3. Most candidate genes either remained limited evidence or were downgraded to disputed during the time period assessed.

SCAN ME