Testing reportedly healthy individuals for a panel of 59 medically actionably genes: are 59 genes enough?

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BACKGROUND

The timely diagnosis of disease is essential for increasing positive health outcomes for patients and their families. Advances in next-generation sequencing have made genomic testing more affordable and has facilitated increased discussion around improving population health through genomic approaches. The identification of individuals who unknowingly carry pathogenic variants in disease associated genes may result in increased preventative care and/or management. The American College of Medical Genetics has generated recommendations for reporting of secondary findings in 59 genes defined as medically actionable in 2016 (PMID: 27854360). Studies suggest that 1 – 4% of individuals tested have clinically actionable results (PMID: 27831900, 28008009), with one report as high as 16% of individuals tested (PMID: 31239557). Here we present data from 193 reportedly healthy adults referred for a gene panel that consists of the 59 medically actionable genes.

METHODS

Comprehensive clinical grade sequencing (single gene analysis, gene panels, whole exome sequencing, whole genome sequencing) has been validated in our laboratory for detection of single nucleotide and copy number variation. Primary data processing was performed using the Edico DRAGEN system and bioinformatic analysis using our in-house proprietary program ODIN (Ordered Data Interpretation Network). Variants are then classified using the ACMG standards and guidelines for the interpretation of sequence variants (PMID: 25741868). Given the lack of clinical utility in returning variants of uncertain significance in healthy individuals, as well as literature which suggests that variants of uncertain significance should not be returned in individuals with no evidence of a phenotype (PMID: 30453057, 25232850), our laboratory has implemented a policy of returning only pathogenic and likely pathogenic variants for panel testing of healthy individuals; variants of uncertain significance are not returned.

RESULTS

- Reportable variants in the healthy adult cohort presented here were detected in 14 individuals (7.25%).
- Reportable findings include pathogenic and likely pathogenic variants detected in the following genes: *APOB*, *ATP7B, LDLR*, *MUTYH,* and *MYBPC3,* as well as a risk factor variant in the *APC* gene. Single pathogenic variants in autosomal recessive genes were returned.

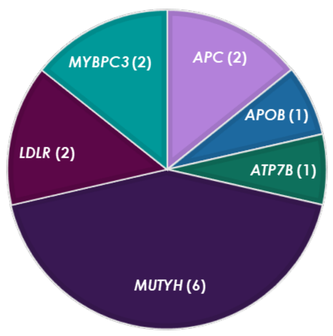

Figure 1: Genes in which pathogenic and likely pathogenic variants were detected in our healthy adult cohort

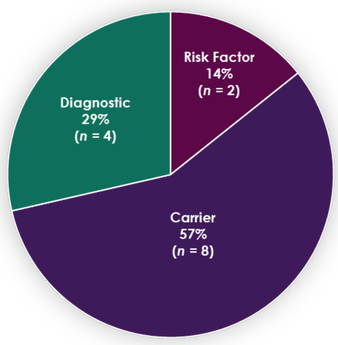

Figure 2: Reportable results result returned in 14 individuals (7.25%) referred for testing. The type of result returned includes diagnostic, carrier status, and variants associated with increased risk

VARIANTS DETECTED

- In a healthy adult population of 193 patients, we found reportable variants in 14 cases (7.25%). Variants were detected in the *APOB*, *ATP7B, LDLR*, *MUTYH, MYBPC3* and *APC* genes.

Gene	OMIM	Disease	Inheritance	Exon/Intron	DNA Change	Protein Change	Classification
APOB	107730	Hypercholesterolemia, due to ligand-defective apo B; Hypobetalipoproteinemia	Autosomal Dominant; Autosomal Recessive	29	c.13028_13029delAT	-	Likely Pathogenic (Carrier)
ATP7B	606882	Wilson disease	Autosomal Recessive	18	c.3809A>G	p.Asn1270Ser	Pathogenic (Carrier)
LDLR	606945	Hypercholesterolemia, familial; LDL cholesterol level QTL2	Autosomal Dominant	3	c.259T>G	p.Trp87Gly	Pathogenic (Diagnostic)
LDLR	606945	Hypercholesterolemia, familial; LDL cholesterol level QTL2	Autosomal Dominant	9	c.1322T>C	p.Ile441Thr	Pathogenic (Diagnostic)
MUTYH	604933	MUTYH-Associated polyposis	Autosomal Recessive	13	c.1187G>A	p.Gly396Asp	Pathogenic (Carrier)
MUTYH	604933	MUTYH-Associated polyposis	Autosomal Recessive	7	c.536A>G	p.Tyr179Cys	Pathogenic (Carrier)
MUTYH	604933	MUTYH-Associated polyposis	Autosomal Recessive	7	c.536A>G	p.Tyr179Cys	Pathogenic (Carrier)
MUTYH	604933	MUTYH-Associated polyposis	Autosomal Recessive	13	c.1187G>A	p.Gly396Asp	Pathogenic (Carrier)
MUTYH	604933	MUTYH-Associated polyposis	Autosomal Recessive	7	c.536A>G	p.Tyr179Cys	Pathogenic (Carrier)
MUTYH	604933	MUTYH-Associated polyposis	Autosomal Recessive	13	c.1187G>A	p.Gly396Asp	Pathogenic (Carrier)
MYBPC3	600958	Cardiomyopathy, dilated, 1MM; Cardiomyopathy, hypertrophic, 4; Left ventricular noncompaction 10	Autosomal Dominant	11	c.927-2A>G	-	Pathogenic (Diagnostic)
MYBPC3	600958	Cardiomyopathy, dilated, 1MM; Cardiomyopathy, hypertrophic, 4; Left ventricular noncompaction 10	Autosomal Dominant	13	c.1224-2A>G	-	Pathogenic (Diagnostic)
APC	611731	Familial adenomatous polyposis (FAP)	Autosomal Dominant	16	c.3920T>A	p.Ile1307Lys	Risk Factor
APC	611731	Familial adenomatous polyposis (FAP)	Autosomal Dominant	16	c.3920T>A	p.Ile1307Lys	Risk Factor

GENE PANEL: 59 MEDICALLY ACTIONABLE GENES

- Gene panel utilized consists of the 59 medically actionable genes recommended by the ACMG for return in clinical genomic sequencing. Table from PMID: 27854360.

Phenotype	MIM disorder	Typical age of onset	Gene	MIM Gene	Inheritance
Hereditary breast and ovarian cancer	604370	Adult	*BRCA1*	113705	AD
	612555		*BRCA2*	600185	
Li-Fraumeni syndrome	151623	Child/adult	*TP53*	191170	AD
Peutz-Jeghers syndrome	175200	Child/adult	*STK11*	602216	AD
Lynch syndrome	120435	Adult	*MLH1*	120436	AD
			MSH2	609309	
			MSH6	600678	
			PMS2	600259	
Familial adenomatous polyposis	175100	Child/adult	*APC*	611731	AD
MYH-associated polyposis; adenomas, multiple colorectal, FAP type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456	Adult	*MUTYH*	604933	AR
	132600				
Juvenile polyposis	174900	Child/adult	*BMPR1A*	601299	AD
			SMAD4	600993	
Von Hippel–Lindau syndrome	193300	Child/adult	*VHL*	608537	AD
Multiple endocrine neoplasia type 1	131100	Child/adult	*MEN1*	613733	AD
Multiple endocrine neoplasia type 2	171400	Child/adult	*RET*	164761	AD
	162300				
Familial medullary thyroid cancer	155240	Child/adult	*RET*	164761	AD
PTEN hamartoma tumor syndrome	158350	Child/adult	*PTEN*	601728	AD
Retinoblastoma	180200	Child	*RB1*	614041	AD
Hereditary paragangliomapheochromocytoma syndrome	168000 (PGL1)	Child/adult	*SDHD*	602690	AD
	601650 (PGL2)		*SDHAF2*	613019	
	605373 (PGL3)		*SDHC*	602413	
	115310 (PGL4)		*SDHB*	185470	
Tuberous sclerosis complex	191100	Child	*TSC1*	605284	AD
	613254		*TSC2*	191092	
WT1-related Wilms tumor	194070	Child	*WT1*	607102	AD
Neurofibromatosis type 2	101000	Child/adult	*NF2*	607379	AD

Phenotype	MIM disorder	Typical age of onset	Gene	MIM Gene	Inheritance
Ehlers-Danlos syndrome, vascular type	130050	Child/adult	*COL3A1*	120180	AD
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700	Child/adult	*FBN1*	134797	AD
	609192		*TGFBR1*	190181	
	610168		*TGFBR2*	190182	
	613795		*SMAD3*	603109	
	611788		*ACTA2*	102620	
	132900		*MYH11*	160745	
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197	Child/adult	*MYBPC3*	600958	AD
	192600		*MYH7*	160760	
	601494		*TNNT2*	191045	
	613690		*TNNI3*	191044	
	115196		*TPM1*	191010	
	608751		*MYL3*	160790	
	612098		*ACTC1*	102540	
	600858		*PRKAG2*	602743	
	301500		*GLA*	300644	XL
	608758		*MYL2*	160781	AD
	115200		*LMNA*	150330	
Catecholaminergic polymorphic ventricular tachycardia	604772	Child/adult	*RYR2*	180902	AD
Arrhythmogenic right ventricular cardiomyopathy	609040	Child/adult	*PKP2*	602861	AD
	607450		*DSP*	125647	
	610476		*DSC2*	125645	
	604400		*TMEM43*	612048	
	610193		*DSG2*	125671	
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	192500	Child/adult	*KCNQ1*	607542	AD
	613688		*KCNH2*	152427	
	603830		*SCN5A*	600163	
	601144				
Familial hypercholesterolemia	143890	Child/adult	*LDLR*	606945	AD
	144010		*APOB*	107730	
	603776		*PCSK9*	607786	
Wilson disease	277900	Child	*ATP7B*	606882	AR
Ornithine transcarbamylase deficiency	311250	Newborn (male), child (female)	*OTC*	300461	XL
Malignant hyperthermia susceptibility	145600	Child/adult	*RYR1*	180901	AD
	601887		*CACNA1S*	114208	

DISCUSSION

- Despite the debate over the utility of this list of medically actionable genes in asymptomatic individuals, a significant number of individuals with reportable findings have been identified (7.25%).
- Should we be limiting ourselves to only 59 genes? Is a different list of medically actionable genes needed for the healthy population? Some institutions have already attempted to address this, such as the Geisinger-76 gene list.
- The basic paradigm of AD/AR disease is changing. Genes which have been traditionally classified as causing AR disease are now reported to also cause AD disease (such as *CAPN3*) and timely intervention may improve quality of life.
- Given the rate of new gene discovery and the improved understanding of disease inheritance, is it now time to more seriously consider guidelines around exome/genome sequencing in the healthy population?
- The concerns of the ACMG around frequent detection of low penetrance alleles and the added follow-up costs these results may yield need further discussion and guidance (PMID: 31239558).