Comprehensive analysis of the ACMG59 genes in parental samples submitted for exome evaluation yields a high positive rate

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INTRODUCTION

Background
The American College of Medical Genetics and Genomics recommends reporting secondary findings in 59 genes (ACMG59) associated with medically actionable monogenic disorders. This applies to all individuals undergoing whole exome (WES) or whole genome (WGS) sequencing, regardless of indication. Healthy parents who are tested alongside the proband for a trio analysis can also choose to receive secondary findings. Our study evaluates the frequency of medically actionable findings in the ACMG59 genes in probands and unaffected parents.

Methods
We analyzed de-identified data from 4,325 individuals who consented to receive secondary findings in the ACMG59 genes as part of exome sequencing. These analyses represent evaluations of probands and parental samples. We analyzed every individual separately and provided personalized reports if positive variants were identified.

Results
Pathogenic/likely pathogenic (P/LP) variants were identified in 256 of 4,325 (5.9%) individuals, including probands and parents. If heterozygous P/LP variants for ATP7B (Wilson disease) and MUTYH (Familial Adenomatous Polyposis 2) were excluded, the detection rate was 155 of 4,325 (3.6%). Of 2,195 unique cases (representing 1,020 proband, 220 duo, or 955 trio cases), 57 had findings in a proband only (37.0%), 38 had findings in a proband and one parent (24.7%), and 50 had findings in a parent only (32.5%). Parent-only findings were present in genes including those related to HBOC, Lynch syndrome, familial hypercholesterolemia, and cardiomyopathy.

Conclusions
Medically significant secondary findings are identified in 3.6% of individuals undergoing exome sequencing, and 5.9% if heterozygous variants in ATP7B and MUTYH are included. Notably, investigating secondary findings in the ACMG59 genes identified previously unknown personal and familial risk for certain types of actionable disorders in a parent only in one-third of positive findings. These findings may justify the use of a targeted gene panel including the ACMG59 genes to screen for hereditary disease risk in the general population.

BACKGROUND

- In 2013, the American College of Medical Genetics and Genomics (ACMG) issued a guidance related to the return of medically important genetic information to individuals undergoing diagnostic WES or WGS. The recommendation was to return medically important genetic variants identified during analysis, regardless of indication, in the 59 genes recognized by the ACMG as being medically actionable genes. These findings have revealed that at least 2-5% of tested individuals, including healthy parents tested in the context of a trio analysis, carry a P/LP variant in one of the 59 genes.[1-4]
- The return of secondary findings related to medically significant genetic changes detected in the ACMG59 genes is optional. Each family member undergoing WES, whether as the proband or as a supportive family member (such as a parent), has the choice to opt in to secondary findings.
- The ACMG59 secondary findings list is focused on genes associated with health conditions related to hereditary cancer, cardiovascular disorders, and other medically actionable conditions.[1,2]

METHODS

- We analyzed de-identified data from 4,325 individuals who consented to receive secondary findings in the ACMG59 genes as part of exome sequencing.
- These analyses represent evaluations of probands and parental samples.
- Data from each individual was analyzed separately for the ACMG59 genes and a personalized secondary findings report was generated for each family member.

THE ACMG59 GENES

Table 1. The 59 genes recommended be returned by the ACMG during genomic evaluation (WES/WGS)

ACMG59 Genes						
Cancer	APC	MLH1	PMS2	SDHB	TP53	
	BMPR1A	MSH2	PTEN	SDHC	TSC1	
	BRCA1	MSH6	RB1	SDHD	TSC2	
	BRCA2	MUTYH	RET	SMAD4	VHL	
	MEN1	NF2	SDHAF2	STK11	WT1	
Cardio	ACTA2	DSG2	KCNQ1	MYH7	PRKAG2	TGFBR2
	ACTC1	DSP	LDLR	MYL2	RYR2	TMEM43
	APOB	FBN1	LMNA	MYL3	SCN5A	TNNI3
	COL3A1	GLA	MYBPC3	PCSK9	SMAD3	TNNT2
	DSC2	KCNH2	MYH11	PKP2	TGFBR1	TPM1
Other	ATP7B	CACNA1S	OTC	RYR1		

Table 1. The 59 genes present on the ACMG59 gene list. There are 25 cancer-related genes, 30 cardiovascular-related genes, and 4 additional medically important genes. The ACMG list published in 2013 originally had 56 genes included, but it was updated to include 59 genes in 2016.[1,2]

RESULTS

Table 2 and Figure 1. Overall ACMG59 testing in 4,325 individuals undergoing exome sequencing

Family structure	Number of families	Percent of cohort
Proband-only	1,020	46.5%
Duos (Proband and 1 parent)	220	10.0%
Trios (Proband and 2 parents)	955	43.5%
Total cohort	2,195	100%

Table 2. The breakdown of family structures in individuals who opted in to the ACMG59 secondary findings evaluation as part of exome sequencing.
Figure 1. A breakdown of the relative proportions of proband only, duo and trio cases that opted in to secondary findings.

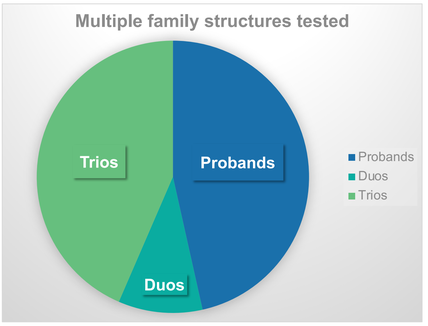


Table 3. All findings in the ACMG59 genes in 4,325 tested individuals

Description of findings	Excluded genes / variants	Number of findings	Positive rate
All P/LP findings	-	256	5.9%
P/LP findings excluding carrier results	ATP7B heterozygotes, AR variants in other genes (such as RYR1)	200	4.6%
P/LP findings excluding carrier results and MUTYH heterozygotes	Above, plus MUTYH heterozygotes	155	3.6%
P/LP findings excluding carrier results, MUTYH heterozygotes and increased risk alleles	Above, plus the APC I1307K increased risk allele	142	3.3%

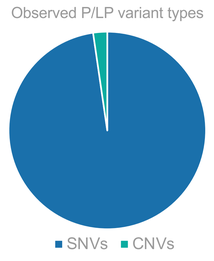
Table 3. All P/LP findings detected in 4,325 individuals, representing 2,195 unique family cases. All P/LP variants detected in the ACMG59 genes are reported; Invitae does not adhere to the strict reporting guidelines outlined in the Green *et al.* 2013 publication.

Table 4. Breakdown of 154 positive exome cases

Individual with finding	Positive findings	Percentage
Proband-only	57	37.0%
Proband + 1 parent	38	24.7%
Parent only	50	32.5%
More than 1 finding in parent(s) and/or proband	9	5.8%

Table 4. Positive findings in the ACMG59 genes by individual. Positive cases include MUTYH heterozygotes and APC increased risk alleles; carrier status has been excluded. Proband-only cases are higher due to the family structure breakdown of this cohort. In trio only cases with findings (n=101), these numbers are 2%, 29.7%, 42.6% and 5.9%, respectively.

Figure 2. P/LP variant types in the ACMG59 genes



Variant type	Percentage
Sequence-based variants (SNVs)	97.7%
Copy number variants (CNVs)	2.3%

Table 5. Positive results by gene

Genes with positive findings	
Cancer-related genes	APC, BRCA1, BRCA2, MEN1, MLH1, MSH2, MSH6, MUTYH (hom), MUTYH (het), PMS2, PTEN, RET, SDHB, SDHD, SMAD3, SMAD4, TSC1, VHL
Cardiovascular-related genes	ACTC1, APOB, COL3A1, DSC2, DSP, KCNH2, KCNQ1, LDLR, LMNA, MYBPC3, MYH7, PKP2, SCN5A, TNNI3, TNNT2
Genes for other medically important conditions	ATP7B (hom), CACNA1S, RYR1

DISCUSSION

- We observed a high positive findings rate in parental samples submitted for exome evaluation. One third of cases represented parent-only positive findings. If evaluating trio cases only, findings in a parent only represented 42.6% of results.
- The overall positive rate, including findings related to carrier status, MUTYH heterozygotes and the I1307K APC increased risk allele was 5.9%. If adhering to variant type reporting guidelines per the ACMG publication, the positive rate is 3.3%.
- There is the potential for a missed opportunity to provide clinically important information to ostensibly healthy parents if a full evaluation of the ACMG59 genes is not performed for each individual undergoing exome sequencing.
- These findings support providing access to medically relevant hereditary risk information for healthy individuals, and consideration for efforts to screen healthy individuals for hereditary conditions at the population level.

REFERENCES

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