Molecular diagnosis as an incidental finding from preconception carrier screening

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1. Introduction

Carrier screening to identify individuals or couples at-risk for having children with severe autosomal recessive and X-linked conditions is recommended by both the American College of Medical Genetics and Genomics (ACMGG) and the American College of Obstetricians and Gynecologists (ACOG)[1-2]. Although screening was initially limited to a few conditions in high-risk populations[3-4], the application of next-generation sequencing (NGS) methods to carrier screening allows clinical laboratories to perform simultaneous testing of hundreds of genes in a single assay. While these expanded carrier screens offer greater sensitivity and increased yield[5-6], they also present new opportunities to detect clinically-significant findings unrelated to the intended scope of testing. In the context of preconception carrier screening, the detection of pathogenic variants in either a homozygous or compound heterozygous state may represent an incidental disclosure of a disease status unknown to the patient or referring physician, particularly for conditions associated with reduced penetrance or variable presentation. Herein, we report the prevalence of such findings identified through targeted carrier screening.

2. Methods

- A retrospective analysis of 73,753 carrier screening records was performed for cases tested from October 2017 to June 2020.
- All results were reviewed for the presence of homozygous or compound heterozygous variants of known phase in an autosomal recessive gene.
- Results for male specimens were reviewed for the presence of hemizygous variants in an X-linked gene.

3. Results

- A total of 474 cases were identified involving 14 genes predicted to result in at least 17 distinct Mendelian disorders of varying severity.
- 401/474 cases (85%) had variants associated with asymptomatic or mild presentations
  - Includes 308 homozygous alpha-thalassemia 3.7 deletion carriers and 93 homozygous Duarte (D2) galactosemia carriers
- 68/73 cases (93%) were enriched for deleterious variants associated with moderate to profound recessive conditions (Tables 1-2).
- 2 male specimens were identified with pathogenic hemizygous deletions of the DMD gene (exon 45-47 deletion, exon 43-47 deletion).

4. Summary

- These data indicate that a small percentage of individuals undergoing carrier screening will have an incidental finding that may require clinical evaluation.
- It is often impossible to determine whether individuals with a molecular diagnosis are affected or symptomatic due to limited access to clinical information.
- The frequency of cases is likely underestimated in this study due to masking of non-targeted variants in panel genes. Comprehensive review of all coding regions as well as increasing the number of genes included on carrier screening panels is predicted to increase the percentage of cases identified.

Tables

Disease	Gene Symbol	Variant	Variant Classification	No. of Cases	% of Cases
Hereditary Fructose Intolerance	*ALDOB*	c.1005C>G	P	1	0.0033
Wilson Disease	*ATP7B*	c.2804C>T	P	1	0.0029
Wilson Disease	*ATP7B*	c.2383C>T	P	1	0.0029
Wilson Disease	*ATP7B*	c.3207C>A	P	1	0.0029
Cystic Fibrosis	*CFTR*	c.1521_1523delCTT	P	2	0.0027
Cystic Fibrosis	*CFTR*	c.3209G>A	LP	1	0.0014
Dihydropyrimidine dehydrogenase deficiency	*DPYD*	c.1905+1G>A	P	1	0.0033
Pompe disease	*GAA*	c.-32-13T>G	P	2	0.0065
Hemoglobin C disease	*HBB*	c.19G>A	P	5	0.0068
Sickle cell disease	*HBB*	c.20A>T	P	18	0.0244
Hemoglobin E disease	*HBB*	c.79G>A	P	5	0.0068
Familial Mediterranean fever	*MEFV*	c.2177T>C	P	5	0.0146
Abetalipoproteinemia	*MTTP*	c.1783C>T	P	1	0.0029
Phenylalanine hydroxylase deficiency	*PAH*	c.1139C>T	P	1	0.0029
Phenylalanine hydroxylase deficiency	*PAH*	c.442-1G>A	P	1	0.0029
Phenylalanine hydroxylase deficiency	*PAH*	c.1208C>T	P	1	0.0029
Spinal Muscular Atrophy	*SMN1*	exon 7 deletion	P	2	0.0027

Table 1. Cases with homozygous variants in autosomal recessive genes. P=Pathogenic, LP=Likely Pathogenic

Disease	Gene Symbol	Genotype(s)	No. of Cases	% of Cases
Hemoglobin H disease	*HBA1/HBA2*	--SEA/ααCS	1	0.0021
Hemoglobin SC disease	*HBB*	c.[19>A];[20A>T]	19	0.0026
Familial Mediterranean Fever	*MEFV*	c.[2080A>G];[2177T>C], c.2040G>C];[c.2080A>G]	3	0.0088
Phenylalanine hydroxylase deficiency	*PAH*	c.[143T>C];[165delT]	1	0.0029

Table 2. Cases with compound heterozygous variants in autosomal recessive genes

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