Comprehensive Analysis of Cholestasis Genetic Panel Results From 2016 to 2022 in Children and Young Adults: Insights Into Diagnostic Yield

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Faculty Disclosure

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Mirum Pharmaceuticals, Inc.		X						
3-D Matrix, Inc.		X						

Genetic Causes of Cholestasis Are Diverse

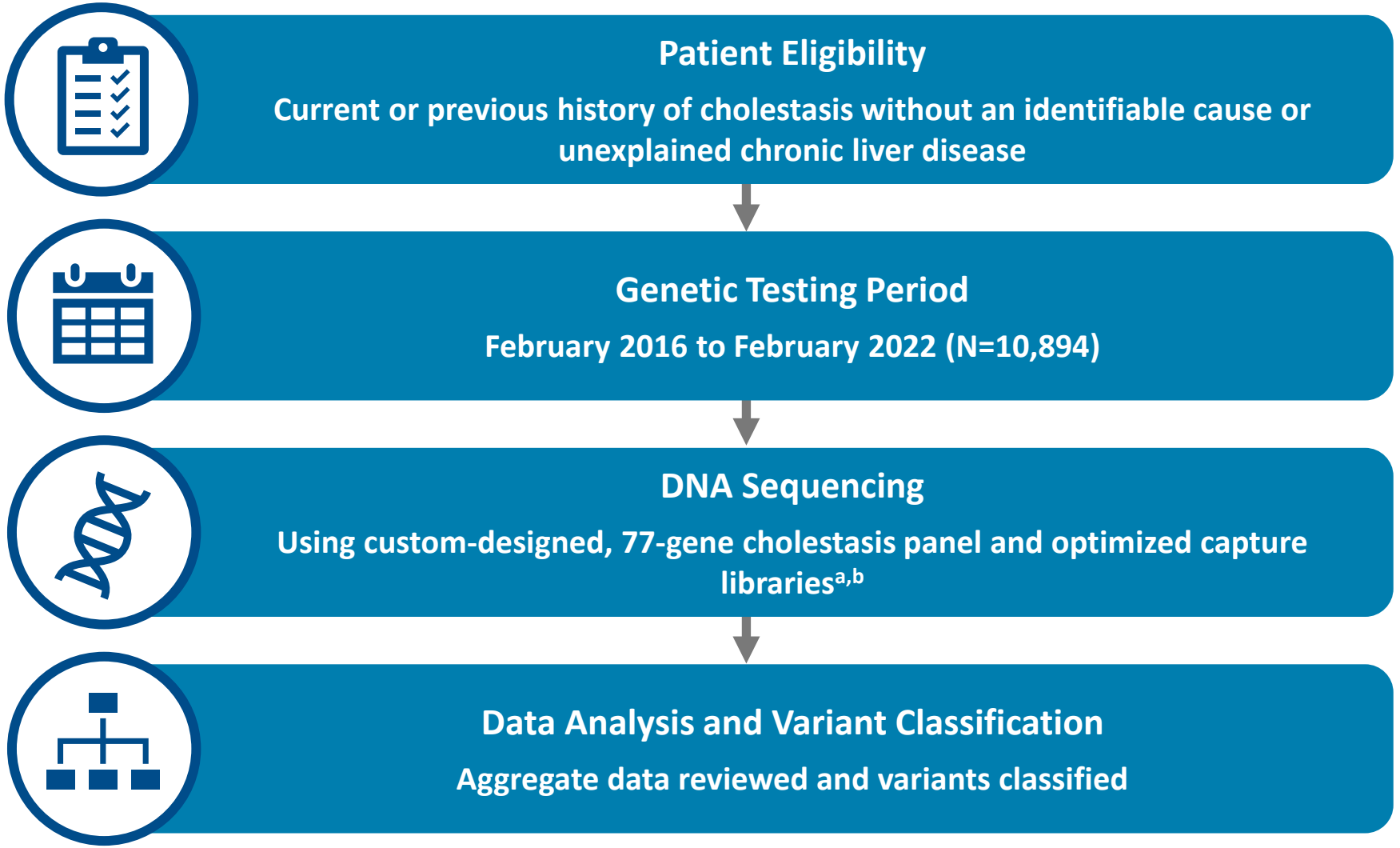
- Impairment of bile flow can result from a diverse range of hepatobiliary disorders, including[1-4]:
  - Progressive familial intrahepatic cholestasis
  - Alagille syndrome
  - Cerebrotendinous xanthomatosis
  - Other bile acid synthesis disorders
  - Alpha-1-antitrypsin deficiency
  - Cystic fibrosis
  - Polycystic kidney disease
- Genetic etiology accounts for approximately 25% of cases of neonatal cholestasis.[5-8]
- Diagnosis can be challenging due to variable clinical presentation and overlap between genetic conditions.[2,3]
- Next-generation sequencing using a cholestasis gene panel is an efficient method for identification of genetic causes and may facilitate accurate diagnoses and targeted interventions.[2,9-13]

OBJECTIVE:

To present a summary of the results of >10,000 cholestasis panel tests and provide insights into diagnostic yield.

1. Sticova E, et al. *Can J Gastroenterol Hepatol*. 2018;2018:2313675. **2.** Karpen SJ, et al. *J Pediatr Gastroenterol Nutr*. 2021;72(5):654-660. **3.** Fawaz R, et al. *J Pediatr Gastroenterol Nutr*. 2017;64(1):154-168. **4.** Kısa PT, et al. *Metab Brain Dis*. 2021;36(6):1201-1211. **5.** NORD. Accessed March 20, 2025. https://rarediseases.org/rare-diseases/idiopathic-neonatal-hepatitis. **6.** Feldman AG, et al. *Nat Rev Gastroenterol Hepatol*. 2019;16(6):346-360. **7.** Feldman AG, et al. *Neoreviews*. 2021;22(12):e819-e836. **8.** Balistreri WF, et al. *Clin Liver Dis*. 2006;10(1):27-v. **9.** Mirum Pharmaceuticals Cholestasis Sponsored Testing. PreventionGenetics. Accessed March 17, 2025. https://www.preventiongenetics.com/sponsoredTesting/Mirum_Cholestasis. **10.** Chen H-L, et al. *J Pediatr*. 2019;205:153-159.e6. **11.** Lipiński P, et al. *Front Pediatr*. 2020;8:414. **12.** Almes M, et al. *Diagnostics (Basel)*. 2022;12:1169. **13.** Chen C-B, et al. *J Pediatr*. 2023;258:113408.

Methods



[a]DNA sequencing was performed using custom-designed and optimized capture libraries (SureSelect by Eurofins/Emory Genetics Laboratory [2016-2021] and PGxome® by PreventionGenetics [2021-2024]). [b]Cholestasis panel was initially composed of 57 genes, with 9 and 11 genes added in 2017 and 2022, respectively.

Methods

Variant Classification According to Diagnostic Laboratory Guidelines and ACMG/AMP Criteria

- Benign
- Likely benign
- Pathogenic
- Likely pathogenic
- Variant of uncertain significance

Definitive diagnoses

- Pathogenic or likely pathogenic variants consistent with the mode of inheritance of the disorder

Potential diagnoses

- Recessive disorders: genes with 1 pathogenic or likely pathogenic allele and 1 variant of uncertain significance
- Autosomal dominant disorders: 1 variant of uncertain significance, eg, in *JAG1* or *NOTCH2*

ACMG, American College of Genetics and Genomics; AMP, Association for Molecular Pathology.
Richards S, et al. *Genet Med*. 2015;17(5):405-424.

Genes Included in the Cholestasis Sequencing Panel

Bile acid synthesis disorders due to single enzyme defects	*AKR1D1, AMACR, BAAT, CYP27A1, CYP7A1, CYP7B1, DHCR7, HSD3B7, SLC27A5*
Peroxisomal disorders, including Zellweger spectrum disorders	*PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7*
Progressive familial intrahepatic cholestasis	*ABCB11, ABCB4, ATP8B1, MYO5B, NR1H4, TJP2*
Alagille syndrome	*JAG1, NOTCH2*
Alpha-1-antitrypsin deficiency	*SERPINA1*
Cystic fibrosis	*CFTR*
Polycystic kidney disease	*PKHD1*
Other genetic causes of cholestasis	*ABCC2, ABCG5, ABCG8, ALDOB, CC2D2A, CLDN1, DCDC2, DGUOK, FAH, GPBAR1, HNF1B, HSD17B4, INVS, LIPA, MKS1, MPV17, NPC1, NPC2, NPHP1, NPHP3, NPHP4, POLG, SCP2, SLC10A1, SLC10A2, SLC25A13, SMPD1, TMEM216, TRMU, UGT1A1, VIPAS39, VPS33B, ABCG5, ABCG8, ACADM, ACOX2, AKR1C4, DNAH11, DNAH6, EHHADH, FOXJ1, GNAS, KMT2D, MMP21, PKD1L1, SLC51A, SLC51B, SLCO1B1, SLCO1B3, SLCO1B3, TALDO1, UTP4*

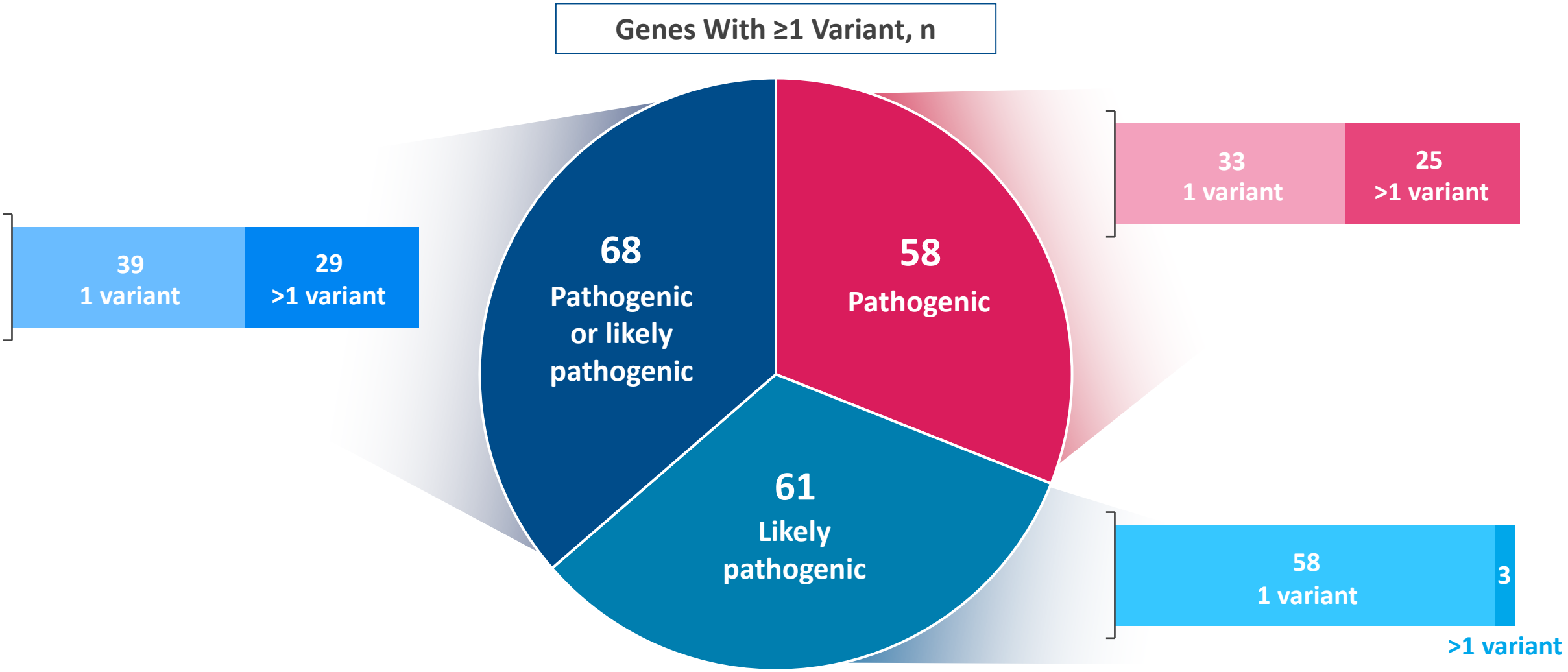
Key Demographics and Baseline Characteristics

Parameter[a]	Total (N=10,894)
Age, range, y	0-88
Age category	
<1 y	5570 (51.1)
1-10 y	2850 (26.2)
11-17 y	1477 (13.6)
>18 y	997 (9.2)
Sex[b]	
Female	1281/3275 (39.1)
Male	1994/3275 (60.9)
Ethnicity	
Caucasian/Northwestern European	3681 (33.8)
Hispanic	2010 (18.5)
African American	1621 (14.9)
Asian	658 (6.0)
Native American	104 (1.0)
Other	122 (1.1)
Unknown	2080 (19.1)
Mixed/multiple	618 (5.7)

Most patients (51.1%) were less than 1 year of age at the time of genetic testing

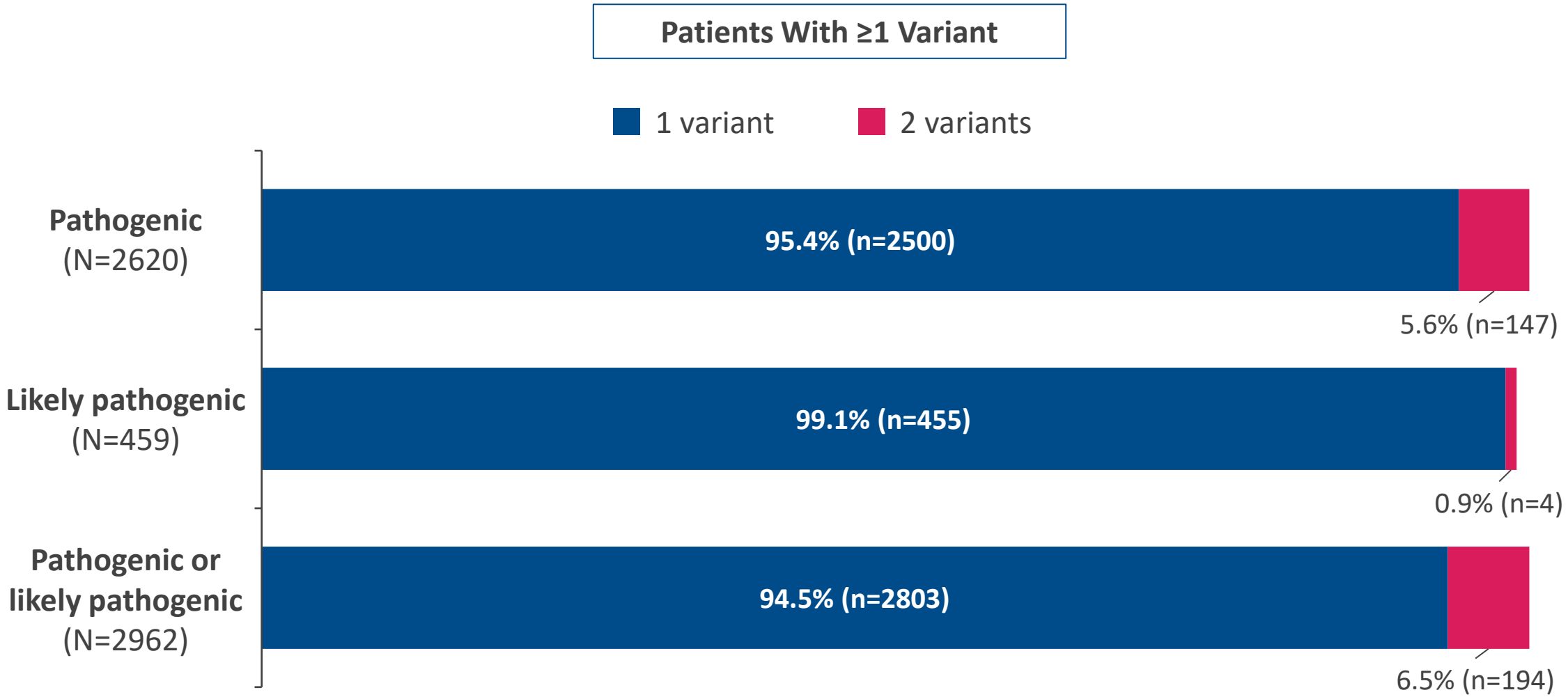
[a]Values are n (%) except where otherwise indicated.
[b]Sex data were only available from PreventionGenetics.

Frequency of Genes With Pathogenic and Likely Pathogenic Variants



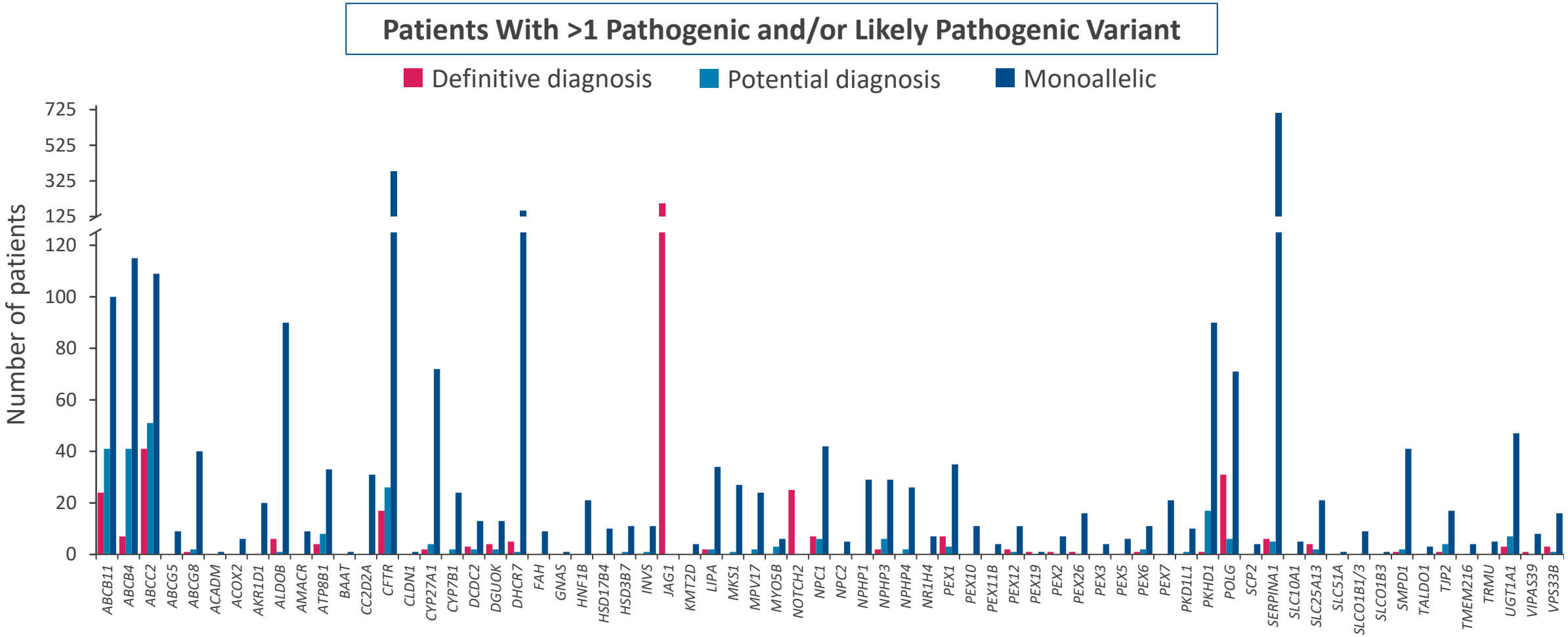
88% of genes in the panel had ≥1 pathogenic or likely pathogenic variant

Frequency of Pathogenic and Likely Pathogenic Variants



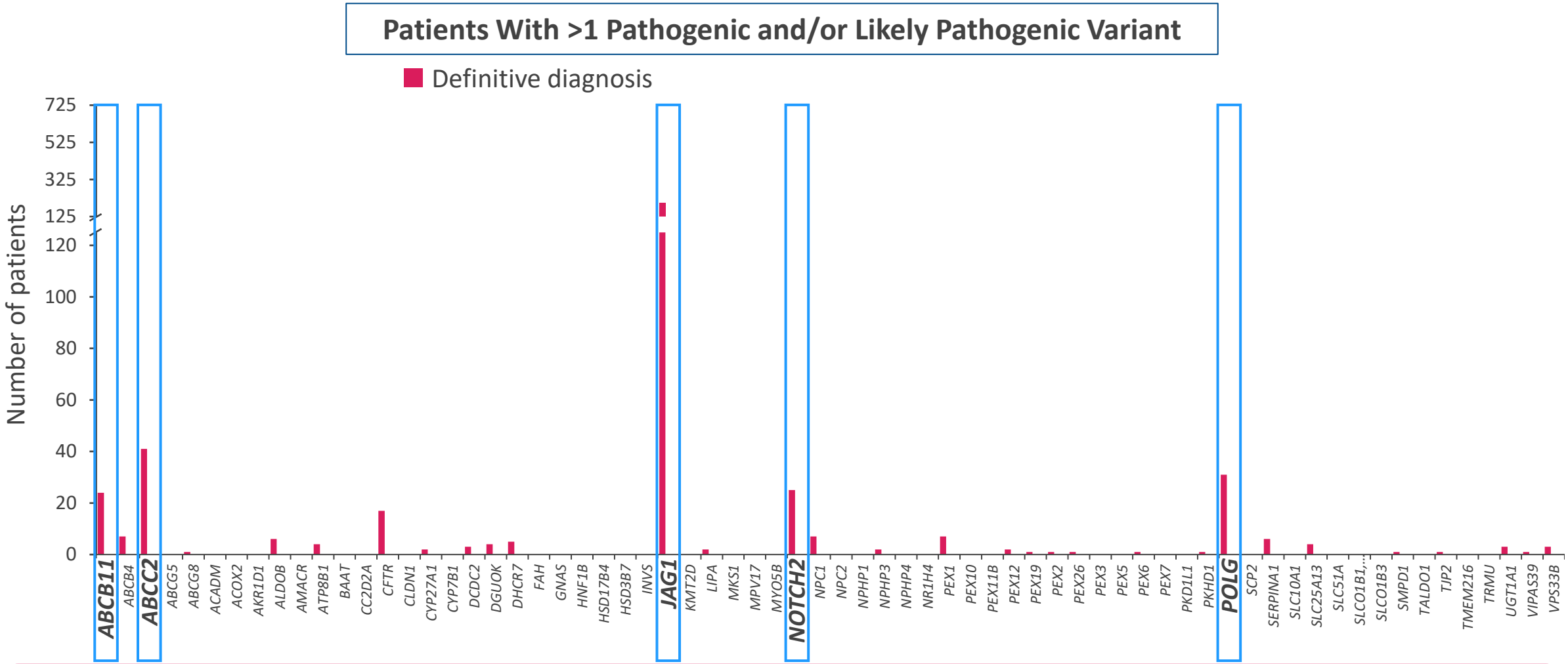
Most patients with disease-causing variants carried only a single pathogenic or likely pathogenic variant

Frequency of Patients With Definitive and Potential Diagnoses



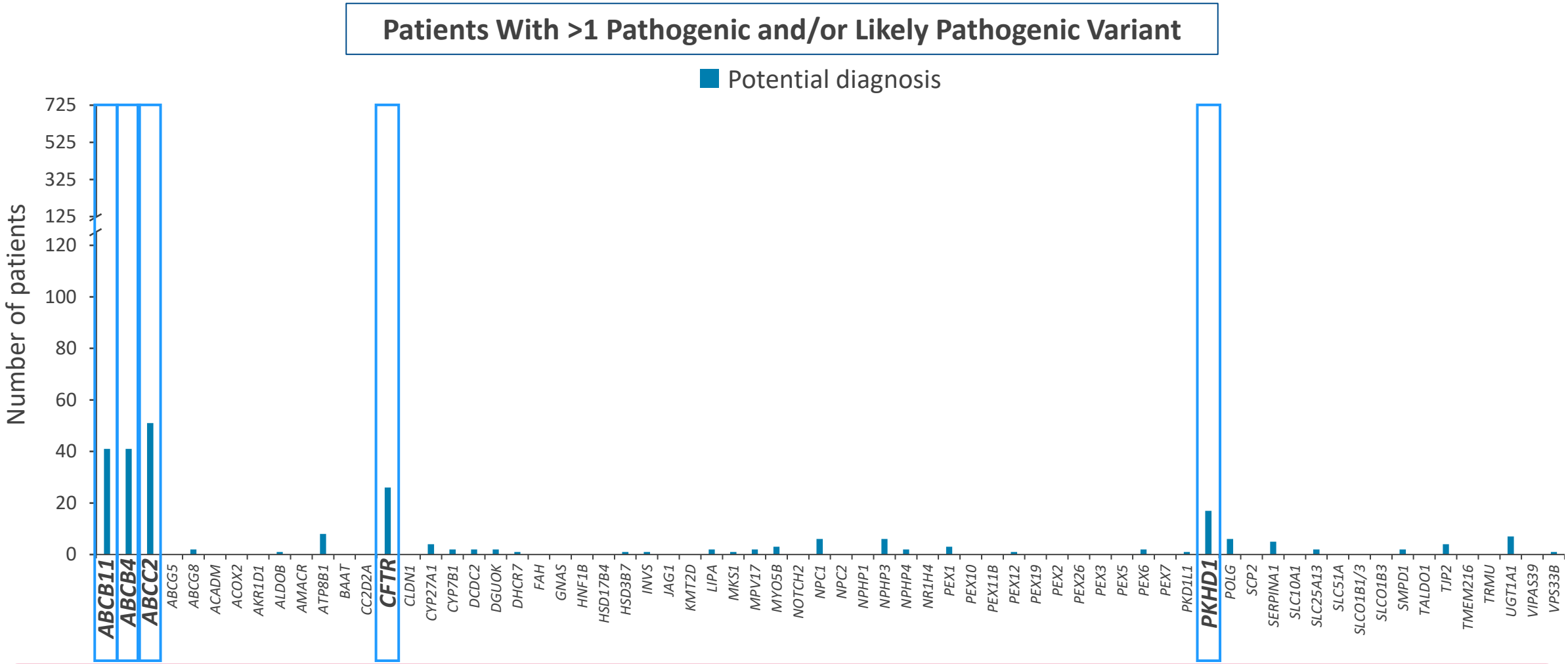
Overall, diagnostic yield was 3.8% among patients with a definitive diagnosis (n/N=411/10,894) and 2.3% among patients with a potential diagnosis (n/N=256/10,894)

Frequency of Patients With Definitive Diagnoses



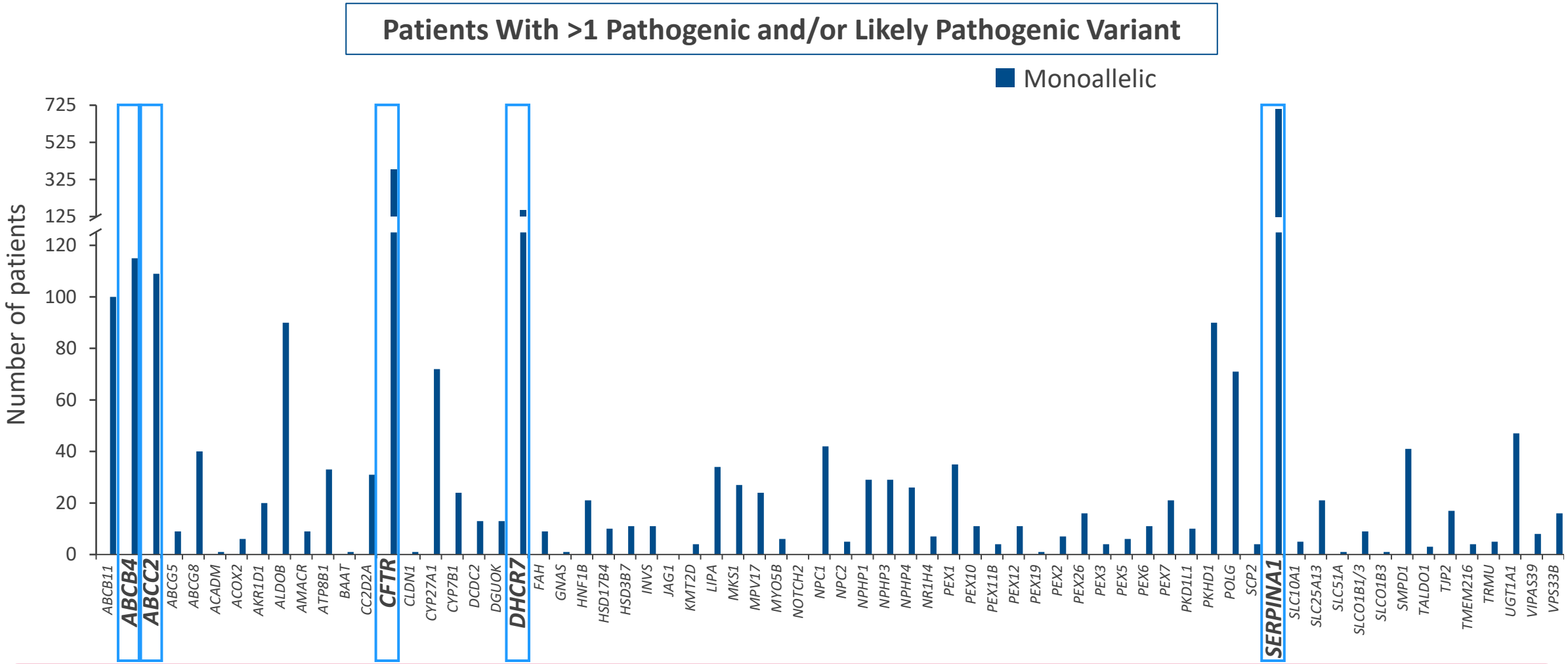
Definitive diagnoses were most common in genes *JAG1* (n=197), *ABCC2* (n=41), *POLG* (n=31), *NOTCH2* (n=25), and *ABCB11* (n=24)

Frequency of Patients With Potential Diagnoses



Potential diagnoses were most common in genes *ABCC2* (n=51), *ABCB4* (n=41), *ABCB11* (n=41), *CFTR* (n=26), and *PKHD1* (n=17)

Frequency of Patients With Monoallelic Variants



Monoallelic variants were most common genes in *SERPINA1* (n=705), *CFTR* (n=379), *DHCR7* (n=158), *ABCB4* (n=115), and *ABCC2* (n=109)

Conclusions

- Data from 6 years of cholestasis next-generation sequencing panels highlight its critical role in diagnosing and identifying complex genetic variants associated with cholestasis.
- Sequencing was especially beneficial for infants under 1 year of age, facilitating early detection.
- This panel provides insights into the genetic basis of cholestasis, facilitating more accurate diagnoses, and potential therapeutic strategies.

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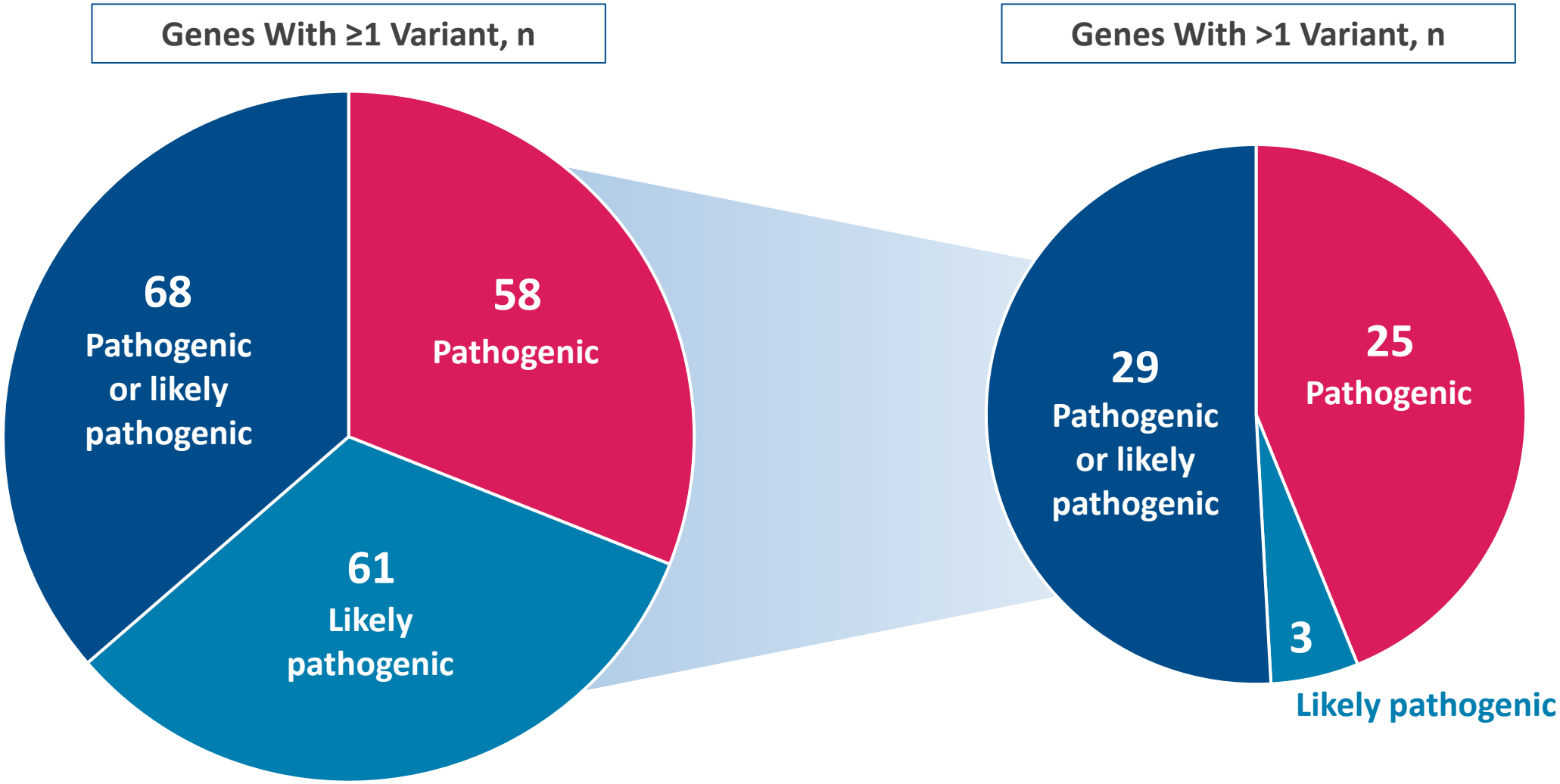
Disclosures

- BJH is a consultant for Mirum Pharmaceuticals, Inc., and 3-D Matrix, Inc.
- EG has nothing to disclose
- AP is an employee of Sanofi and previous employee of Travere Therapeutics
- TP and RD are employees of Mirum Pharmaceuticals, Inc., and previous employees of Travere Therapeutics
- WK is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharmaceuticals, Travere Therapeutics, and Gilead Sciences

Thank You!

Back-up Slides

Frequency of Genes With Pathogenic and Likely Pathogenic Variants



88% of genes in the panel had ≥1 pathogenic or likely pathogenic variant

Combinations of Variants by Disorder

Bile Acid Synthesis Disorders Due to Single Enzyme Defects and Cerebrotendinous Xanthomatosis

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
AKR1D1				20		74
AMACR				9		100
BAAT				1		99
CYP27A1	2		4	72		261
CYP7A1						167
CYP7B1			2	24		134
DHCR7	3	2	1	158		173
HSD3B7			1	11		135
SLC27A5[a]						244

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Peroxisomal Disorders, Including Zellweger Spectrum Disorders

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
PEX1[a]	5	2	3	35		269
PEX10				11		158
PEX11B				4		65
PEX12	2		1	11		92
PEX13						92
PEX14						138
PEX16						87
PEX19	1			1		109
PEX2	1			7		88
PEX26	1			16		131
PEX3				4		48
PEX5				6		181
PEX6[a]	1		2	11		252
PEX7				21		63

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Progressive Familial Intrahepatic Cholestasis

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
ABCB11[a]	17	7	41	100	3	466
ABCB4[a]	5	2	41	115	1	506
ATP8B1	3	1	8	33		331
MYO5B			3	6		143
NR1H4				7		108
TJP2	1		4	17		395

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Alagille Syndrome

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
JAG1				197		253
NOTCH2[a]				25		366

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Alpha-1-antitrypsin Deficiency

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
SERPINA1	4	2	5	705		205

Combinations of Variants by Disorder

Cystic Fibrosis

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
CFTR[a]	14	3	26	379	1	973

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Polycystic Kidney Disease

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
PKHD1[a]	1		17	90	2	1139

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Other Genetics Causes of Cholestasis

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
ABCC2[a]	26	15	51	109		597
ABCG5				9		297
ABCG5, ABCG8						6
ABCG8[a]	1		2	40		383
ACADM				1		
ACOX2				6		76
AKR1C4						54
ALDOB[a]	5	1	1	90		201
CC2D2A[a]				31		414
CLDN1				1		42
DCDC2	2	1	2	13		115
DGUOK	3	1	2	13		142
DNAH11						1
DNAH6						1
EHHADH						252
FAH				9		92
FOXJ1						1
GNAS				1		84
GPBAR1						158
HNF1B				21		119
HSD17B4				10		181
INVS[a]			1	11		266
KMT2D				4		256

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Other Genetics Causes of Cholestasis

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
LIPA	2		2	34		98
MKS1			1	27		276
MMP21						1
MPV17			2	24		34
NPC1[a]	6	1	6	42	1	314
NPC2				5		105
NPHP1				29		172
NPHP3[a]		2	6	29		291
NPHP4[a]			2	26		789
PKD1L1[a]			1	10		182
POLG[a]	30	1	6	71		388
SCP2				4		79
SLC10A1[a]				5		238
SLC10A2[a]						312
SLC25A13	4		2	21		187

[a]More than 2 variants of uncertain significance.

Combinations of Variants by Disorder

Other Genetics Causes of Cholestasis

Gene	Homozygous pathogenic/likely pathogenic, n	2 pathogenic/ likely pathogenic alleles, n	2 alleles: 1 variant of uncertain significance + 1 pathogenic/likely pathogenic, n	1 pathogenic/ likely pathogenic allele, n	Homozygous variant of uncertain significance, n	1 or 2 heterozygous alleles variant of uncertain significance, n
SLC51A				1		25
SLC51B						6
SLCO1B1, SLCO1B3				9		
SLCO1B3				1		106
SMPD1		1	2	41		258
TALDO1				3		31
TMEM216				4		51
TRMU				5		140
UGT1A1[a]	1	2	7	47		259
UTP4						43
VIPAS39		1		8		129
VPS33B[a]	2	1	1	16		164

[a]More than 2 variants of uncertain significance.