**Use of a Comprehensive 66-Gene Cholestasis Sequencing Panel in 2171 Cholestatic Infants, Children, and Young Adults**

**SUPPLEMENTARY DIGITAL CONTENT**

The majority of samples (83%) were submitted from HCPs in the United States (**Figure S1**). Samples were submitted by 641 HCPs. The majority of HCPs submitted 1 to 2 samples (**Table S1**). Gastroenterology and hepatology were the most common specialties (63%) among HCPs who provided specialty information.

**Figure S1. Total samples submitted by time and location.**

 

2433 samples as of December 31, 2017, data cut off.

**Table S1. Number of Samples Submitted Per Healthcare Provider**

|  |  |
| --- | --- |
| **Tests submitted** | **Healthcare provider, n (%)N=641** |
| 10+ | 45 (7) |
| 6-9 | 34 (5) |
| 3-5 | 106 (17) |
| 1-2 | 456 (71) |

**Table S2. Demographic Characteristics for Subjects Aged <3 Months, Aged 3 to <12 Months, Aged ≥12 Months, and Aged ≥18 Years**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **<3 months old****n=863** | **3 to <12 months old****n=367** | **≥12 months old****n=941** | **≥18 yrs oldn=163** |
| Sex, n (%) |  |  |  |  |
| Female | 298 (34.5) | 155 (42.2) | 390 (41.4) | 80 (49.1) |
| Male | 555 (64.3) | 200 (54.5) | 534 (56.7) | 82 (50.3) |
| Unknown, ambiguous, or missing | 10 (1.2%) | 12 (3.3%) | 17 (1.8%) | 1 (0.6) |
| Ethnicity, n (%) |  |  |  |  |
| Caucasian (Northwestern or Western European) | 217 (25.1) | 93 (25.3) | 315 (33.4) | 76 (46.6) |
| Hispanic | 142 (16.5) | 68 (18.5) | 220 (23.4) | 13 (8.0) |
| African American | 181 (21.0) | 54 (14.7) | 98 (10.4) | 22 (13.5) |
| Asian | 33 (3.8) | 19 (5.2) | 30 (3.2) | 5 (3.1) |
| Native American | 11 (1.3) | 12 (3.3) | 5 (0.5) | 0 |
| Other (includes Jewish-Ashkenazi, Jewish-Sephardic, Mediterranean, Native Hawaiian/Pacific Islander, and other) | 82 (9.5) | 42 (11.4) | 91 (9.7) | 17 (10.4) |
| Unknown | 197 (22.8) | 79 (21.5) | 182 (19.3) | 30 (18.4) |

Age for subjects 0 and 1 year of age are based on 'age in days' converted to a decimal value by dividing 'age in days' by 365.25. Age for subjects 2 years of age and older use whole number age in years for age calculations.

**Table S3.** **Diagnostic Yield (Number of Patients) of 66 Gene Cholestasis Panel Among Subjects
<3 Months Old**

|  |
| --- |
| **Patients with ≥1 pathogenic and/or likely pathogenic variant** |
| **Gene** | **Definite Diagnosisa** | **Potential Diagnosisb** | **Monoallelic**  | **Gene** | **Definite Diagnosisa** | **Potential Diagnosisb** | **Monoallelic**  |
| *ABCB11* | 4 | 1 | 4 | *NOTCH2* | 2 | n/a | n/a |
| *ABCB4* | 0 | 2 | 3 | *NPC1* | 3 | 4 | 0 |
| *ABCC2* | 3 | 7 | 9 | *PEX1* | 1 | 0 | 2 |
| *ABCG8* | 0 | 1 | 8 | *PEX12* | 1 | 0 | 0 |
| *AKR1D1* | 2 | 0 | 0 | *PEX6* | 1 | 0 | 2 |
| *ATP8B1* | 1 | 0 | 1 | *PKHD1* | 0 | 1 | 2 |
| *CFTR* | 0 | 10 | 34 | *POLG* | 2 | 0 | 5 |
| *CYP27A1* | 0 | 2 | 7 | *SERPINA1* | 11 | 1 | 32 |
| *DGUOK* | 1 | 0 | 0 | *SLC25A13* | 2 | 0 | 1 |
| *INVS* | 0 | 1 | 0 | *TJP2* | 2 | 0 | 1 |
| *JAG1* | 23 | n/a | n/a | *UGT1A1* | 0 | 1 | 4 |
| *MPV17* | 0 | 1 | 0 |  |  |  |  |
| **Genes with no pathogenic or likely pathogenic variants** |
| *ABCG5* | *DCDC2* | *LIPA* | *PEX11B* | *PEX5* | *TRMU* |
| *ALDOB* | *DHCR7* | *MKS1* | *PEX13* | *PEX7* | *VIPAS39* |
| *AMACR* | *EHHADH* | *NPC2* | *PEX14* | *SCP2* | *VPS33B* |
| *BAAT* | *FAH* | *NPHP1* | *PEX16* | *SLC10A1* |  |
| *CC2D2A* | *GPBAR1* | *NPHP3* | *PEX19* | *SLC10A2* |  |
| *CLDN1* | *HNF1B* | *NPHP4* | *PEX2* | *SLC27A5* |  |
| *CYP7A1* | *HSD17B4* | *NR1H4* | *PEX26* | *SMPD1* |  |
| *CYP7B1* | *HSD3B7* | *PEX10* | *PEX3* | *TMTM216* |  |

All genes are defined as contributing to disease in an autosomal recessive, biallelic fashion except *JAG1* and *NOTCH2* (which are considered autosomal dominant).

aDefinite diagnosis included genes with 2 alleles that were pathogenic or likely pathogenic (homozygous or heterozygous), or a single pathogenic or likely pathogenic allele for *JAG1* or *NOTCH2*.

bPotential diagnosis included genes with one pathogenic/likely pathogenic allele + one VOUS.

**Table S4.** **Diagnostic Yield (Number of Patients) of 66 Gene Cholestasis Panel Among Subjects
≥18 Years Old**

|  |
| --- |
| **Patients with ≥1 pathogenic and/or likely pathogenic variant** |
| **Gene** | **Definite Diagnosisa** | **Potential Diagnosisb** | **Monoallelic**  | **Gene** | **Definite Diagnosisa** | **Potential Diagnosisb** | **Monoallelic**  |
| *ABCB11* | 1 | 0 | 1 | *JAG1* | 1 | 0 | 1 |
| *ABCB4* | 0 | 2 | 4 | *LIPA* | 0 | 0 | 3 |
| *ABCC2* | 0 | 1 | 3 | *NOTCH2* | 1 | 0 | 1 |
| *AKR1D1* | 0 | 0 | 1 | *NPC1* | 0 | 0 | 1 |
| *ALDOB* | 0 | 0 | 4 | *PEX1* | 1 | 0 | 0 |
| *CC2D2A* | 0 | 0 | 1 | *PEX2* | 0 | 0 | 1 |
| *CFTR* | 0 | 1 | 9 | *POLG* | 1 | 0 | 2 |
| *CYP27A1* | 1 | 1 | 0 | *SERPINA1* | 0 | 0 | 5 |
| *DHCR7* | 0 | 0 | 1 | *SMPD1* | 0 | 0 | 1 |

|  |
| --- |
| **Genes with no pathogenic or likely pathogenic variants** |
| *ABCG5* | *DCDC2* | *INVS* | *PEX11B* | *PEX6* | *UGT1A1* |
| *ABCG8*  | *DGUOK* | *MKS1* | *PEX12* | *PKHD1* |  |
| *AMACR* | *EHHADH* | *NPHP1* | *PEX13* | *SLC10A1* |  |
| *ATP8B1* | *GPBAR1* | *NPHP3* | *PEX14* | *SLC10A2* |  |
| *BAAT* | *HNF1B* | *NPHP4* | *PEX16* | *SLC27A5* |  |
| *CYP7A1* | *HSD17B4* | *NR1H4* | *PEX19* | *TJP2* |  |
| *CYP7B1* | *HSD3B7* | *PEX10* | *PEX26* | *TRMU* |  |

All genes are defined as contributing to disease in an autosomal recessive, biallelic fashion except *JAG1* and *NOTCH2* (which are considered autosomal dominant).

aDefinite diagnosis included genes with 2 alleles that were pathogenic or likely pathogenic (homozygous or heterozygous), or a single pathogenic or likely pathogenic allele for *JAG1* or *NOTCH2*.

bPotential diagnosis included genes with one pathogenic/likely pathogenic allele + one VOUS.

**Supplemental Text**

Approximately one-half of the samples (n=1081 [49.8%]) included at least one 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code. A total of 184 different ICD-10 codes were reported. The most frequently reported (≥5%) were obstruction of bile duct (n=239 [11%]), other disorders of bilirubin metabolism (n=146 [7%]), abnormal levels of other serum enzymes (n=130 [6%]), and other specified perinatal digestive system disorders (n=128 [6%]). Since there is no uniform single ICD-10 code for neonatal and infantile cholestasis, these diagnoses were assumed to represent similar clinical presentations.