**SUPPLEMENTAL DIGITAL CONTENT (SDC)**

**SDC TABLES**

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**SDC TABLES**

**SDC Table 1. Demographics and Clinical Characteristics of Tested Participants vs. Those Eligible but Not Tested**

1. **ALGS**

|  | | *Tested (N=70)* | | *Eligible, Not Tested (N=137)* | |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Variable* |  | *n* | *freq (%) or stats* | *n* | *freq (%) or stats* | *p-value\** |
| Female |  | 70 | 25 (35.7%) | 134 | 56 (41.8%) | 0.400 |
| Race | White | 67 | 52 (77.6%) | 134 | 84 (62.7%) | 0.103 |
|  | Black |  | 6 (9.0%) |  | 20 (14.9%) |  |
|  | Other |  | 9 (13.4%) |  | 30 (22.4%) |  |
| Hispanic |  | 70 | 12 (17.1%) | 130 | 31 (23.8%) | 0.271 |
| Parental education | High school equivalent or less | 66 | 14 (21.2%) | 120 | 39 (32.5%) | 0.103 |
|  | Some college/trade school or more |  | 52 (78.8%) |  | 81 (67.5%) |  |
| Age at consent (years), mean (SD) |  | 70 | 6.7 (3.9) | 137 | 5.9 (4.4) | 0.145 |
| Follow-up time (years), median (IQR) |  | 70 | 6.0 (3.8, 8.0) | 133 | 2.0 (0.7, 4.8) | **<.001** |

1. **PFIC**

|  | | *Tested (N=43)* | | *Eligible, Not Tested (N=119)* | |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Variable* |  | *n* | *freq (%) or stats* | *n* | *freq (%) or stats* | *p-value\** |
| Female |  | 43 | 22 (51.2%) | 119 | 74 (62.2%) | 0.207 |
| Race | White | 43 | 32 (74.4%) | 118 | 79 (66.9%) | 0.522 |
|  | Black |  | 5 (11.6%) |  | 13 (11.0%) |  |
|  | Other |  | 6 (14.0%) |  | 26 (22.0%) |  |
| Hispanic |  | 42 | 5 (11.9%) | 118 | 30 (25.4%) | 0.069 |
| Parental education | High school equivalent or less | 39 | 12 (30.8%) | 111 | 46 (41.4%) | 0.239 |
|  | Some college/trade school or more |  | 27 (69.2%) |  | 65 (58.6%) |  |
| Age at consent (years), mean (SD) |  | 43 | 7.2 (4.7) | 119 | 5.7 (4.8) | **0.035** |
| Follow-up time (years), median (IQR) |  | 43 | 5.1 (2.3, 7.7) | 118 | 1.9 (0.1, 3.9) | **<.001** |

1. **A1AT**

|  | | *Tested (N=102)* | | *Eligible, Not Tested (N=176)* | |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Variable* |  | *n* | *freq (%) or stats* | *n* | *freq (%) or stats* | *p-value\** |
| Female |  | 102 | 29 (28.4%) | 175 | 80 (45.7%) | **0.005** |
| Race | White | 102 | 94 (92.2%) | 174 | 164 (94.3%) | 0.506 |
|  | Black |  | 0 (0.0%) |  | 1 (0.6%) |  |
|  | Other |  | 8 (7.8%) |  | 9 (5.2%) |  |
| Hispanic |  | 100 | 5 (5.0%) | 173 | 11 (6.4%) | 0.645 |
| Parental education | High school equivalent or less | 93 | 11 (11.8%) | 164 | 23 (14.0%) | 0.617 |
|  | Some college/trade school or more |  | 82 (88.2%) |  | 141 (86.0%) |  |
| Age at consent (years), mean (SD) |  | 102 | 6.5 (3.6) | 176 | 6.5 (5.3) | 0.210 |
| Follow-up time (years), median (IQR) |  | 102 | 4.4 (2.7, 7.2) | 175 | 2.1 (0.1, 4.1) | **<.001** |

Abbreviations: A1AT, alpha one antitrypsin deficiency; ALGS, Alagille Syndrome; IQR, interquartile range; PFIC, progressive familial intrahepatic cholestasis; SD, standard deviation.

**SDC Table 2. Categorical Distribution of IQ Scores by Disease Group**

|  | | *ALGS (N=70)* | | *PFIC (N=43)* | | *A1AT (N=102)* | |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Variable* |  | *n* | *freq (%)* | *n* | *freq(%)* | *n* | *freq (%)* | *Overall p-value* |
| Full Scale IQ (FSIQ) | ≥100 | 69 | 28 (40.6%) | 43 | 19 (44.2%) | 102 | 58 (56.9%) | 0.065 |
|  | 85-99 |  | 21 (30.4%) |  | 16 (37.2%) |  | 31 (30.4%) |  |
|  | 70-84 |  | 14 (20.3%) |  | 8 (18.6%) |  | 9 (8.8%) |  |
|  | <70 |  | 6 (8.7%) |  | 0 (0.0%) |  | 4 (3.9%) |  |
| p-value vs. norms | |  | 0.003 |  | 0.499 |  | 0.225 |  |
| Verbal IQ / Verbal Comprehension Index (VIQ/VCI) | ≥100 | 69 | 31 (44.9%)\* | 43 | 24 (55.8%) | 102 | 63 (61.8%)\* | **0.007** |
|  | 85-99 |  | 20 (29.0%) |  | 15 (34.9%) |  | 33 (32.4%) |  |
|  | 70-84 |  | 14 (20.3%) |  | 4 (9.3%) |  | 3 (2.9%) |  |
|  | <70 |  | 4 (5.8%) |  | 0 (0.0%) |  | 3 (2.9%) |  |
| p-value vs. norms | |  | 0.078 |  | 0.606 |  | 0.011 |  |
| Performance IQ / Perceptual Reasoning Index (PIQ/PRI) | ≥100 | 70 | 31 (44.3%)\* | 43 | 20 (46.5%) | 102 | 66 (64.7%)\* | 0.101 |
|  | 85-99 |  | 26 (37.1%) |  | 17 (39.5%) |  | 20 (19.6%) |  |
|  | 70-84 |  | 10 (14.3%) |  | 5 (11.6%) |  | 12 (11.8%) |  |
|  | <70 |  | 3 (4.3%) |  | 1 (2.3%) |  | 4 (3.9%) |  |
| p-value vs. norms | |  | 0.605 |  | 0.922 |  | 0.009 |  |
| Working Memory Index (WMI)\*\* | ≥100 | 51 | 14 (27.5%) | 26 | 10 (38.5%) | 60 | 22 (36.7%) | 0.520 |
|  | 85-99 |  | 24 (47.1%) |  | 13 (50.0%) |  | 26 (43.3%) |  |
|  | 70-84 |  | 5 (9.8%) |  | 2 (7.7%) |  | 8 (13.3%) |  |
|  | <70 |  | 8 (15.7%) |  | 1 (3.8%) |  | 4 (6.7%) |  |
| p-value vs. norms | |  | <.001 |  | 0.295 |  | 0.038 |  |
| Processing Speed Index (PSI)\*\* | ≥100 | 51 | 22 (43.1%) | 26 | 12 (46.2%) | 60 | 25 (41.7%) | 0.931 |
|  | 85-99 |  | 14 (27.5%) |  | 9 (34.6%) |  | 18 (30.0%) |  |
|  | 70-84 |  | 12 (23.5%) |  | 3 (11.5%) |  | 12 (20.0%) |  |
|  | <70 |  | 3 (5.9%) |  | 2 (7.7%) |  | 5 (8.3%) |  |
| p-value vs. norms | |  | 0.055 |  | 0.325 |  | 0.009 |  |

Abbreviations: A1AT, alpha one antitrypsin deficiency; ALGS, Alagille Syndrome; PFIC, progressive familial intrahepatic cholestasis; WISC-IV, Wechsler Intelligence Scale for Children-IV.

\*ALGS vs. A1AT, p<0.05

No significant differences found between ALGS vs. PFIC or PFIC vs. A1AT (p>0.05 for all).

\*\*WMI and PSI are only included in WISC-IV.

**SDC Table 3. Univariate Linear Regression for Continuous FSIQ, Adjusted for Parental Education**

|  | | *ALGS* | | | | *PFIC* | | | | *A1AT* | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Variable* |  | *Estimate (95% CI)* | *Adj*  *p-value* | *Unadj p-value* | *Partial R2* | *Estimate (95% CI)* | *Adj*  *p-value* | *Unadj p-value* | *Partial R2* | *Estimate (95% CI)* | *Adj*  *p-value* | *Unadj p-value* | *Partial R2* |
| Age at testing (years) |  | -1.0 (-2.0, 0.1) | 0.964 | 0.071 |  | 0.5 (-0.6, 1.5) | 0.962 | 0.367 |  | -0.5 (-1.4, 0.5) | 0.971 | 0.341 |  |
| Parental education | High school equivalent or less | Ref |  |  |  | Ref |  |  |  | Ref |  |  |  |
|  | Some college/trade school or more | 8.4 (-1.9, 18.7) | 0.964 | 0.108 |  | 11.9 (2.4, 21.3) | 0.375 | **0.016** | 15% | 16.6 (6.9, 26.3) | **0.023** | **0.001** | 11% |
| Sex | Female | Ref |  |  |  | Ref |  |  |  | Ref |  |  |  |
|  | Male | 1.1 (-7.6, 9.7) | 0.964 | 0.806 |  | 1.6 (-7.6, 10.7) | 0.962 | 0.730 |  | -0.6 (-7.6, 6.5) | 0.971 | 0.870 |  |
| Pruritus | None/mild | Ref |  |  |  | Ref |  |  |  | Ref |  |  |  |
|  | Active/bleeding | -6.1 (-14.8, 2.5) | 0.964 | 0.159 |  | -5.8 (-15.7, 4.1) | 0.962 | 0.240 |  | -17.2 (-47.4, 13.1) | 0.971 | 0.263 |  |
| History of xanthoma(s) | Absent | Ref |  |  |  | Ref |  |  |  | Ref |  |  |  |
|  | Present | -8.2 (-17.3, 0.9) | 0.964 | 0.076 |  | -9.8 (-38.6, 18.9) | 0.962 | 0.493 |  | Not estimable |  |  |  |
| CEPH | aCEPH | Ref |  |  |  | Ref |  |  |  | Ref |  |  |  |
|  | pCEPH | -0.9 (-11.3, 9.5) | 0.964 | 0.869 |  | 2.8 (-12.1, 17.7) | 0.962 | 0.708 |  | -4.4 (-16.5, 7.7) | 0.971 | 0.472 |  |
|  | dCEPH1 | 4.7 (-7.1, 16.6) | 0.964 | 0.426 |  | -1.8 (-18.7, 15.2) | 0.962 | 0.835 |  | -2.4 (-11.4, 6.5) | 0.971 | 0.590 |  |
| Cardiac disease severity | Mild/none | Ref |  |  |  |  |  |  |  |  |  |  |  |
|  | Severe | -7.6 (-17.2, 2.1) | 0.964 | 0.121 |  |  |  |  |  |  |  |  |  |
| Any renal abnormality | Absent | Ref |  |  |  |  |  |  |  |  |  |  |  |
|  | Present\* | -4.5 (-14.7, 5.7) | 0.964 | 0.380 |  |  |  |  |  |  |  |  |  |
| Height-for-age z-score | | 2.8 (-0.7, 6.3) | 0.964 | 0.116 |  | 2.5 (-1.3, 6.4) | 0.962 | 0.190 |  | 2.7 (-0.3, 5.8) | 0.971 | 0.081 |  |
| Weight-for-age z-score | | 2.3 (-1.0, 5.7) | 0.964 | 0.170 |  | 0.2 (-4.5, 4.9) | 0.962 | 0.932 |  | -1.2 (-4.2, 1.9) | 0.971 | 0.449 |  |
| BMI z-score |  | 1.7 (-1.6, 5.0) | 0.964 | 0.308 |  | -2.4 (-6.8, 2.0) | 0.962 | 0.282 |  | -3.1 (-6.1, -0.0) | 0.971 | **0.049** | 4% |
| Total bilirubin (mg/dL), log2 | | -0.4 (-3.2, 2.3) | 0.964 | 0.757 |  | -3.2 (-5.9, -0.5) | 0.472 | **0.021** | 14% | -0.1 (-3.1, 3.0) | 0.971 | 0.971 |  |
| GGTP (U/L), log2 | | -1.1 (-5.5, 3.2) | 0.964 | 0.606 |  | 0.3 (-2.6, 3.2) | 0.962 | 0.841 |  | 0.6 (-1.8, 3.0) | 0.971 | 0.634 |  |
| AST (U/L), log2 |  | 0.3 (-5.2, 5.7) | 0.964 | 0.924 |  | -3.0 (-7.9, 1.9) | 0.962 | 0.219 |  | 0.3 (-3.6, 4.1) | 0.971 | 0.888 |  |
| Alkaline phosphatase (U/L), log2 | | -6.8 (-13.4, -0.3) | 0.964 | **0.041** | 7% | -5.8 (-11.8, 0.2) | 0.962 | 0.057 |  | 2.5 (-3.2, 8.1) | 0.971 | 0.387 |  |
| INR, log2 |  | 4.8 (-13.0, 22.6) | 0.964 | 0.592 |  | 5.4 (-15.0, 25.7) | 0.962 | 0.593 |  | 13.0 (-13.1, 39.2) | 0.971 | 0.322 |  |
| BUN (mg/dl), log2 | | -0.8 (-11.7, 10.2) | 0.964 | 0.889 |  | -6.0 (-17.6, 5.7) | 0.962 | 0.304 |  | 5.1 (-3.1, 13.3) | 0.971 | 0.218 |  |
| Creatinine (mg/dl), log2 | | -8.5 (-19.0, 2.1) | 0.964 | 0.114 |  | 0.2 (-5.1, 5.5) | 0.962 | 0.941 |  | 4.7 (-0.9, 10.3) | 0.971 | 0.097 |  |
| ALT (U/L), log2 |  | -1.7 (-6.5, 3.0) | 0.964 | 0.466 |  | -0.5 (-4.4, 3.5) | 0.962 | 0.811 |  | 0.8 (-2.0, 3.5) | 0.971 | 0.587 |  |
| APRI, log2 |  | -0.5 (-4.7, 3.7) | 0.964 | 0.819 |  | -1.6 (-5.0, 1.7) | 0.962 | 0.322 |  | 0.2 (-2.4, 2.7) | 0.971 | 0.896 |  |
| APRI | <1 | Ref |  |  |  | Ref |  |  |  | Ref |  |  |  |
|  | 1-1.5 | 6.5 (-7.2, 20.1) | 0.964 | 0.346 |  | 0.7 (-29.2, 30.7) | 0.962 | 0.962 |  | -5.9 (-22.2, 10.5) | 0.971 | 0.476 |  |
|  | >1.5 | -1.0 (-13.6, 11.5) | 0.964 | 0.870 |  | -1.5 (-14.9, 11.9) | 0.962 | 0.820 |  | 3.5 (-5.0, 12.0) | 0.971 | 0.416 |  |
| FIB-4, log2 |  | -1.1 (-4.6, 2.5) | 0.964 | 0.547 |  | -0.9 (-4.3, 2.5) | 0.962 | 0.602 |  | -0.8 (-3.6, 2.0) | 0.971 | 0.588 |  |
| Albumin (g/dl) |  | 10.9 (1.8, 20.1) | 0.482 | **0.020** | 10% | 12.7 (4.5, 20.9) | 0.082 | **0.003** | 22% | 1.8 (-4.3, 7.8) | 0.971 | 0.562 |  |
| Hemoglobin (g/dl) | | -0.1 (-3.3, 3.1) | 0.964 | 0.964 |  | 3.7 (0.3, 7.2) | 0.784 | **0.036** | 13% | -1.8 (-4.9, 1.2) | 0.971 | 0.226 |  |
| Platelet count (per 50 x 103/mm3) | | 0.5 (-1.7, 2.7) | 0.964 | 0.677 |  | 0.2 (-1.6, 2.0) | 0.962 | 0.816 |  | -0.6 (-2.5, 1.2) | 0.971 | 0.507 |  |

Abbreviations: A1AT, alpha one antitrypsin deficiency; aCEPH, absent clinically-evident portal hypertension; ALGS, Alagille Syndrome; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CEPH, clinically-evident portal hypertension; CI, confidence interval; dCEPH, definite clinically-evident portal hypertension; FIB-4, Fibrosis-4; FSIQ, full scale intelligence quotient; GGTP, gamma glutamyl transpeptidase; INR, international normalized ratio; pCEPH, possible clinically-evident portal hypertension; PFIC, progressive familial intrahepatic cholestasis.

1Bass LM, Shneider BL, Henn L, et al. Clinically evident portal hypertension: An operational research definition for future investigations in the pediatric population. *J Pediatr Gastroenterol Nutr* 2019;68:763-767.

\*Renal involvement was defined as dysplastic kidney, single kidney, renal tubular acidosis, or other renal abnormality reported on initial history.

**SDC Table 4. Disease-Specific Clinical Characteristics and Genetic Testing of Children with Inherited Cholestatic Liver Disease**

|  | | *freq (%)* | | |
| --- | --- | --- | --- | --- |
| *Variable* |  | *ALGS (N=70)* | *PFIC (N=43)* | *A1AT (N=102)* |
| Cardiac disease severity | Mild/none | 53 (75.7%) |  |  |
|  | Severe\* | 17 (24.3%) |  |  |
| Any renal abnormality\*\* |  | 15 (21.4%) |  |  |
| JAG1 mutation | Testing not done | 4 (5.7%) |  |  |
|  | No known mutations | 6 (8.6%) |  |  |
|  | Total gene deletion | 4 (5.7%) |  |  |
|  | Protein truncating | 16 (22.9%) |  |  |
|  | Missense | 13 (18.6%) |  |  |
|  | Splicing | 27 (38.6%) |  |  |
| ATP8B1 mutation | Testing not done |  | 13 (30.2%) |  |
|  | No known mutations |  | 22 (51.2%) |  |
|  | Missense |  | 4 (9.3%) |  |
|  | Splicing |  | 2 (4.7%) |  |
|  | Synonymous |  | 2 (4.7%) |  |
| ABCB11 mutation | Testing not done |  | 13 (30.2%) |  |
|  | No known mutations |  | 16 (37.2%) |  |
|  | Missense |  | 11 (25.6%) |  |
|  | Splicing |  | 1 (2.3%) |  |
|  | Multiple mutation types |  | 2 (4.7%) |  |
| ABCB4 mutation | Testing not done |  | 25 (58.1%) |  |
|  | No known mutations |  | 10 (23.3%) |  |
|  | Protein truncating |  | 1 (2.3%) |  |
|  | Missense |  | 4 (9.3%) |  |
|  | Splicing |  | 1 (2.3%) |  |
|  | Multiple mutation types |  | 2 (4.7%) |  |
| A1AT Phenotype | ZZ |  |  | 92 (90.2%) |
|  | SZ |  |  | 8 (7.8%) |
|  | Unknown |  |  | 2 (2.0%) |
| Abbreviations: A1AT, alpha one antitrypsin deficiency; ALGS, Alagille Syndrome; PFIC, progressive familial intrahepatic cholestasis  \*Severe cardiac disease was defined as having at least one of the following: pulmonary valve stenosis, Tetralogy of Fallot, ventricular/atrial septal defect, pulmonary atresia, hypoplastic right ventricle, aortic coarctation, aortic root dilatation, and/or aortic stenosis. All other cardiac defects were considered mild.  \*\*Renal involvement was defined as dysplastic kidney, single kidney, renal tubular acidosis, or  other renal abnormality reported on initial history. | | | | | |

**SDC FIGURES**

**SDC Figure 1. ALGS FSIQ Scores by Cardiac Disease Severity**

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Severe cardiac disease was defined as having ≥1 of the following: pulmonary valve stenosis, Tetralogy of Fallot, ventricular/atrial septal defect, pulmonary atresia, hypoplastic right ventricle, aortic coarctation, aortic root dilatation, and/or aortic stenosis. Participants with only peripheral pulmonary artery stenosis, patent ductus arteriosus (PDA), patent foramen ovale (PFO), or no reported conditions were considered to have mild cardiac disease.

**SDC Figure 2. Flow Diagram**



**SDC Figure 3a. FSIQ by Gene Mutation Class, ALGS and PFIC**



**SDC Figure 3b. FSIQ by Gene Mutation Class, A1AT**

