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# **Incorporating Genomic Analysis in the Clinical Practice of Hepatology**

A Thesis Submitted to the Yale University School of Medicine  
in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

David Hun Chung  
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## **ABSTRACT**

### **INCORPORATING GENOMIC ANALYSIS IN THE CLINICAL PRACTICE OF HEPATOLOGY**

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In the past two decades, whole-exome sequencing has been successfully demonstrated as an indispensable instrument in uncovering the genetic etiology underlying numerous types of unexplained liver disease. Characterization of these illnesses into distinct molecular disease entities has revolutionized understanding of pathophysiology and has translated into improved guidance on management, treatment and prognosis for patients. However, hepatologists have been slow to welcome the technology into their mainstream clinical practice, largely due to inadequate training in genomic medicine. There thus remains a pressing need to create various forums through which clinicians can gain better appreciation for the value of genetic analysis in the field of hepatology and amass the knowledge and confidence to incorporate genetic analysis into their own clinical practice.

To address this need, we aimed to facilitate the dissemination of new information on liver disease with an underlying genetic etiology through a two-pronged approach: (1) the generation of an online database housing genotype-phenotype correlation information for diseases affecting the liver, and (2) the promotion of a multidisciplinary Hepatology Genome Rounds series.

In this Thesis, we detail the creation of a comprehensive database focused on genetic liver diseases, reflecting the genotypic and phenotypic profiles of more than 7,500 individuals with genetic variants across 269 genes. This newly developed database will provide clinicians and researchers a centralized source for information on genotype-phenotype correlation to aid in diagnosis and education. In addition, we demonstrate that the Hepatology Genome Rounds series, which is an interdisciplinary forum highlighting hepatology cases of clinical interest and educational value, is an important venue for the distribution of genomic knowledge within the field of hepatology and for providing ongoing education to providers and trainees in genomic medicine. We describe our single-center experience, which has led to the reconsideration of diagnoses in two patients and an improved understanding of genotype-phenotype correlations across all cases. As the value of genetic analysis continues to emerge in understanding human disease and pathophysiology, we foresee similar approaches being adopted at other institutions and in additional specialties in coming years for further propagation of genomics in clinical medicine.

## **ACKNOWLEDGEMENTS**

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## INTRODUCTION

### *The Rise of Genomics in Clinical Medicine*

Towards the end of the 20th century, significant technological advances ushered in a new era of diagnostic capabilities in which the underlying genetic basis and pathophysiology of both common and rare diseases could be better understood.

Fine-mapping and linkage analysis, combined with confirmatory Sanger sequencing, allowed investigators to map alleles linked to disease for the first time,<sup>1</sup> and in 1983, the first marker responsible for a human genetic disease was identified, when a polymorphic DNA marker on chromosome 4 linked to Huntington's disease was discovered in a study of two families.<sup>2</sup> The field of hepatology reaped the benefit of these developments, as detailed pedigree analyses of families with alpha-1-antitrypsin deficiency, Wilson disease and hereditary hemochromatosis resulted in the determination of implicated genes, namely *SERPINA1*, *ATP7B* and *HFE*, respectively.<sup>3-7</sup> The discovery of the etiology of such monogenic disorders in the 1980s and 1990s paved the way for enhanced diagnostic tests amid an improved understanding of disease mechanisms and yielded concrete changes to management and treatment in the subsequent three decades.<sup>8</sup>

Nevertheless, the early genomic discovery process was inefficient as it often required confirmatory studies for pathogenicity using cell-based and/or animal models. It was not until the completion of the Human Genome Project (HGP) in 2003 and the introduction of microarray testing, next-generation sequencing

(NGS) technologies and in silico models for pathogenicity prediction that genomics-based discovery and diagnosis gained speed in the laboratory and the clinical setting.<sup>1,7</sup> Whole-exome sequencing (WES) was successfully used in 2009 for clinical diagnosis,<sup>9</sup> and its utility was further demonstrated the following year through the discovery of a new gene underlying an inherited disease of unknown etiology.<sup>10</sup> The adoption of these technologies has been facilitated in recent years by the rapid decrease in sequencing costs to less than USD 1,000 per genome.<sup>8</sup>

Within the field of medicine today, WES is a fundamental tool for clinical investigation, with a successful diagnostic rate estimated at 50-80% in newborns and 25-50% in adults with late-onset phenotypes across a range of genetic disease entities.<sup>11-14</sup> Furthermore, its incorporation into the clinical realm has accelerated not only diagnostic capabilities but also our understanding of disease pathophysiology, conception of genotype-phenotype relationships and research into groundbreaking therapeutics.

### *Whole-Exome Sequencing in Hepatology*

The application of WES within the field of hepatology has been fruitful, with its effective use to diagnose both adult and pediatric populations living with unexplained liver disease and to discover novel genes underlying unexplained liver-associated phenotypes that are now beginning to be understood.<sup>15,16</sup>

Through the incorporation of WES into the diagnostic framework for patients, our research group has uncovered and described five novel liver diseases

caused by recessive mutations in *DGUOK*, *GIMAP5*, *KIF12*, *SLC51A* and *ACOX2*. Biallelic loss-of-function mutations in *DGUOK* and *GIMAP5* were discovered in patients with non-cirrhotic portal hypertension,<sup>17,18</sup> *KIF12* and *SLC51A* deficiency underlie pediatric cholestatic liver diseases,<sup>19,20</sup> and recessive mutations in *ACOX2* cause a bile acid synthesis disorder.<sup>21</sup>

Beyond its critical role in the identification of the genetic underpinnings of previously unexplained phenotypes, genomic analysis has brought tangible benefits to patients in the form of appropriate modifications of management and treatment based on additional insights into disease mechanisms.<sup>15,16,18-22</sup>

Despite the evidence of its revolutionary utility across the clinician-patient spectrum from diagnosis to treatment and the dwindling financial barriers that limited its use just a few decades ago, the field of hepatology has adopted WES into the clinical sphere at only a gradual pace. The slow uptake is however not unique to this sub-specialty and is likely in part a reflection of widespread inadequate training and/or experience in genomic medicine, which can manifest in a myriad of ways, including but not limited to difficulty in determining when genetic analysis may be suitable, inability to proficiently comprehend genetic reports and unfounded yet common biases that WES is of use only in children and/or result in a large list of variants of uncertain significance (VUS) to produce any incremental benefits to patient care.<sup>7,23</sup>

Therefore, the field of hepatology, and in turn our patients, stands to benefit from greater availability of educational opportunities and the dissemination of

relevant genomic information. This Thesis explores two avenues: (1) the publicization of a liver disease-focused online database on genotype-phenotype correlations and (2) the promotion of an interdisciplinary series of Hepatology Genome Rounds, through which these objectives could be achieved. These have sprouted from preexisting models of clinical collaboration, education and information dissemination within clinical medicine.

### *Databases as Information Exchange*

Databases are a common form of information sharing utilized across numerous industries for a myriad of purposes. Databases have long been used within medicine as well, as a critical tool in administrative oversight, public health, quality control, among others.<sup>24</sup> As early as 1979, the field of genomics benefited from the organization of information in this format, with the founding of the Los Alamos Sequence Database, now known as GenBank, as a home for nucleotide sequences.<sup>25</sup> With the advent of NGS technologies in recent decades, the amount of data to be stored, organized and presented has skyrocketed in a near-exponential fashion, and the wide availability of genomics resources and tools today, often at a multinational or national level, reflects this trend.

Genotype-phenotype databases, which document genetic variants and/or the phenotypes of affected patients, have been critical in furthering our understanding of human disease by offering greater public access to such data. Clinicians and researchers today have a swath of resources to choose from to suit their needs from large-scale databases which are comprehensive in their

coverage of Mendelian diseases, such as ClinVar, Online Mendelian Inheritance in Man (OMIM) and Orphanet, to smaller-scale databases that focus on specific specialties, diseases and/or genes.<sup>26</sup> Examples of the latter include the National Cancer Institute's Genomic Data Commons (GDC), the Amyotrophic Lateral Sclerosis online Database (ALSoD), the Registry of Hereditary Auto-Inflammatory Disorders Mutations (INFEVERS) and the Clinical and Functional Translation of *CFTR* (CFTR2).<sup>27-30</sup>

However, currently available genotype-phenotype repositories suffer from several limitations. Firstly, information across the array of resources lacks standardization, as there is no automatic mechanism by which large-scale databases are updated to reflect either new publications or additions to smaller-scale databases.<sup>26</sup> Much of the information must either be manually curated, which is time consuming and does not occur on a regular basis, or is reliant on user submissions.<sup>7</sup> Secondly, the content of genotype-phenotype datasets remains heavily weighted toward genotype information, with phenotypic characterization often reduced to just the name of the disease. This has made it difficult for clinicians to accurately interpret WES data and assess any existing pathogenicity claims with certainty, hampering advancements in patient care.<sup>26</sup>

Within the field of hepatology, numerous genomic databases have also arisen in recent years as our molecular understanding of liver disease has grown. Bioinformatics support for hepatocellular carcinoma (HCC) is the most robust, with a number of databases offering integrated datasets on chromosomal aberration studies and gene expression profiles in patients with HCC.<sup>31</sup>

Nevertheless, these databases are similarly disjointed with limited standardization and are rich in genotypic data and lacking in phenotypic content.<sup>31</sup> Specifically, there is no single centralized genotype-phenotype database or resource currently dedicated to the field of hepatology that serves as a repository of genetic variant information and corresponding phenotypic features. As such, clinicians must often rely on generalized databases such as OMIM for genotype-phenotype correlation in liver disease.<sup>7,31</sup>

A database exclusive to genes associated with liver disease, extensively cataloguing genotypes and phenotypes and updated at a predetermined frequency both through manual curation and user input, will fill a need in the field of hepatology for a unified resource for genotype-phenotype correlation. This Thesis will detail the creation and implementation of the Liver Gene Database, which aims to make genotype-phenotype information widely accessible for clinicians, with the hope that this will assist in diagnosis, impact clinical care and allow for a comprehensive yet nuanced view of genetic liver diseases.

### *The Practice of Interdisciplinary Medicine*

Modern clinical medicine is often described as a team sport, and the interdisciplinary collaboration that has entered the mainstream across several fields typifies this ethos.

Tumor boards, which have become standard-of-care in oncology, are among the most representative of this model of collaborative medicine. The

discussions that ensue amid the assembly of multiple disciplines within a singular dedicated space enable disease stratification in commonly encountered cancers, clinical correlation with radiological and pathological findings in more complex oncologic cases and the formulation of recommendations reflecting the many years of combined experience among experts. These tumor boards are indeed not an isolated intellectual exercise, and in a large proportion of cases, result in novel insights that accelerate and optimize patient care through changes in diagnosis and/or medical and surgical management. A review of available data reveals that clinical care, whether diagnostic stage or treatment recommendations, was modified in 18-52% of patients following tumor board discussions.<sup>32-39</sup>

Whether statistically significant improvements in clinical outcomes are achieved as a result of these conferences remains to be seen. A matched-pair analysis of 454 patients with 66 different tumors at the University of Bonn revealed that patients who were discussed at three or more tumor board sessions experienced significantly longer survival than those who were not discussed at all. However, overall survival did not differ significantly in patients discussed at either one or two sessions, and response to treatment, relapse-free survival and time to progression were not significantly different across all cohorts.<sup>40</sup> Similarly, a smaller study of patients with high-grade glioma in Singapore demonstrated no significant differences in median survival in patients reviewed at tumor boards.<sup>41</sup> Nonetheless, institutions have reported statistically significant improvements in measures of quality of care, such as use of adjuvant chemotherapy and time from surgery to initiation of radiation therapy,<sup>41,42</sup> as a

result of tumor rounds, indicating that they are not without important contributions to clinical care.

In addition to their immediate impact on patient care, tumor boards offer academic medical centers the complementary benefit of representing an educational experience for individuals across the training continuum.<sup>32</sup> Therefore, this model of interdisciplinary collaboration, which can easily be adopted across different sub-specialties due to its flexibility, carries immense potential as a vehicle for both continuing education and optimization of care delivery. Comparable conference formats are being increasingly incorporated into the care continuum in non-oncologic sub-specialties within internal medicine,<sup>43,44</sup> and as awareness increases around the diagnostic and therapeutic potential of genomic analysis, multidisciplinary genomic partnerships have been launched and/or proposed in disciplines such as cardiology and hematopathology.<sup>45,46</sup> It appears likely that as our knowledge base of the genetic origins of human disease continues to grow, numerous specialties will stand to benefit from and value cross-collaboration in the form of conferences to review complex cases and, in turn, advance the care we provide for our patients.

The concept of an interdisciplinary forum featuring liver diseases with underlying genetic etiologies may be novel, but within the field of hepatology, clinicians have already become acquainted with this multidisciplinary format of care provision through tumor boards for HCC. This Thesis will discuss the implementation of a single-center series of Hepatology Genome Rounds,

featuring clinically complex and educational patient cases of liver disease with an underlying genetic etiology.

## **STATEMENT OF PURPOSE**

As clinical care in the field of hepatology stands to benefit from greater accessibility to and incorporation of genetic information, the specific aims of this

Thesis are twofold:

- (1) To develop a liver-focused gene database that provides clinicians and researchers a centralized resource for information on genotype-phenotype correlations to advance our understanding of genetic liver diseases and to aid in clinical diagnosis, and
- (2) To establish and promote the Hepatology Genome Rounds series as a multidisciplinary forum through which genomic information and education are incorporated and disseminated while caring for patients with liver disease.

## METHODS

### Liver Gene Database

#### *Compilation of Genes*

A list of genes associated with liver disease was generated from OMIM using “hepatic,” “cirrhosis” and “liver” as phenotypic query terms (last accessed November 24, 2021). Initial results were fine-tuned to exclude alternative gene names, genes attributed to liver disease in the setting of somatic mutations, genes associated with increased risk or susceptibility rather than causation, genes with only an isolated, single case of liver involvement in the literature and genes associated with anatomical yet no functional abnormalities. This initial search yielded a list of 261 genes.<sup>7</sup> Eight additional genes (i.e., *GIMAP5*, *KIF12*, *LSR*, *MYO5B*, *PPM1F*, *USP53*, *WDR83OS*, *ZFYVE19*), mutations of which have recently been demonstrated to cause liver disease,<sup>18,22,47-49</sup> were also included for a final compilation of 269 genes (Figure 1, Supplemental Table 1).

#### *Literature Search*

A literature search was carried out in PubMed for each of the 269 genes. The search queried for the gene symbol and the terms “liver,” “hepatic” and “hepato” in the title and/or abstract, yielding an initial collection of 20,838 publications. The query dates for the individual genes ranged from April 25, 2022, to October 31, 2022. The literature collection was then manually filtered and curated to focus on English-language original articles and case reports detailing patient-specific genetic variants and associated presenting phenotypes. Foreign-language manuscripts with accompanying English-language abstracts from which sufficient genotypic and phenotypic information could be extracted were

included. Following the manual curation process, 1,748 publications remained for review.

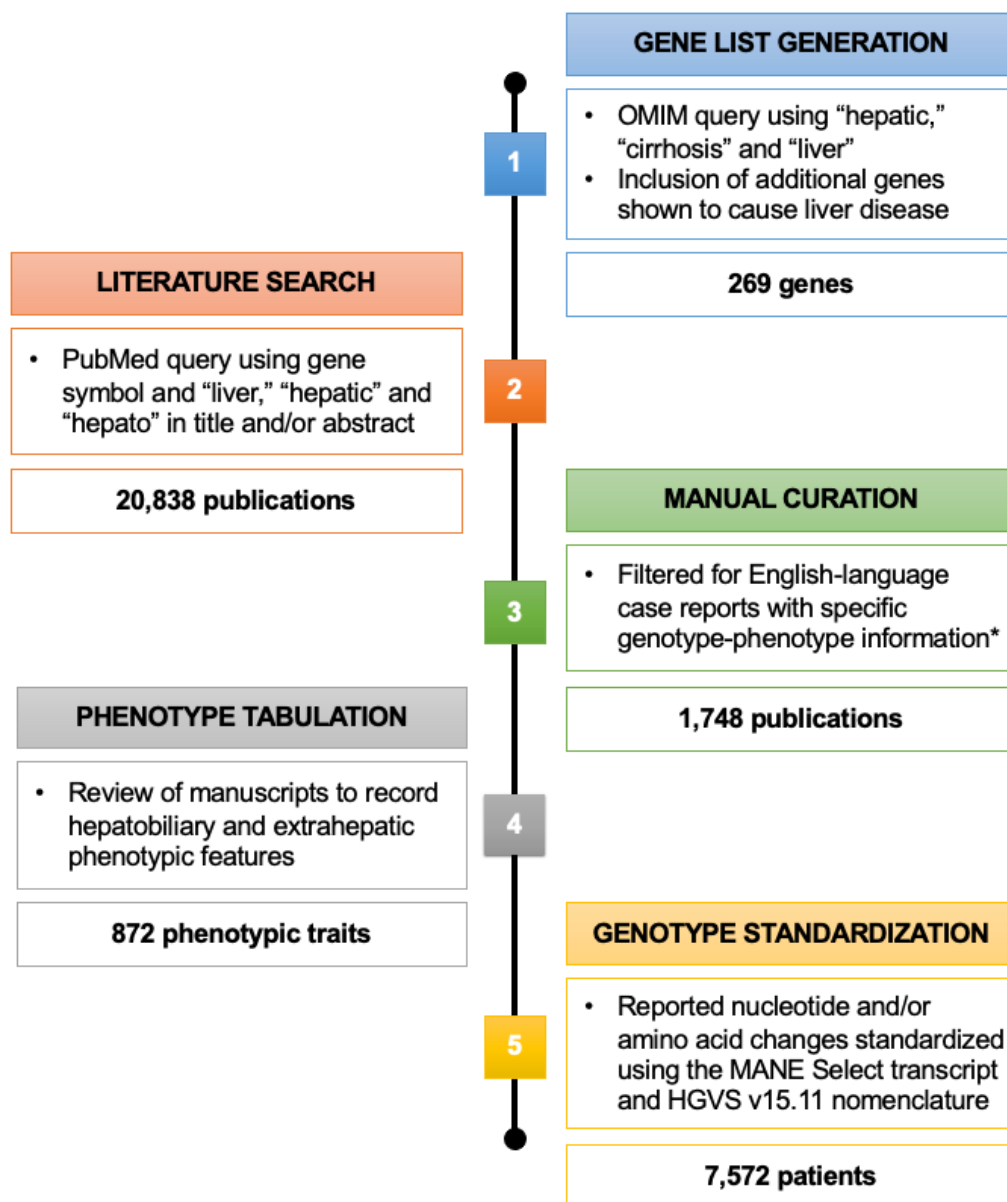


Figure 1. Summary of methods utilized during the data collection process for the Liver Gene Database. \*The filtering process entailed exclusion of review articles and manuscripts that did not specify genetic variants and/or phenotypic features. Foreign-language articles with English-language abstracts with sufficient genotype and phenotype information were included.

### *Data Collection*

A spreadsheet was designed for reproducible genotype-phenotype data collection. Based on an initial review of at least 1 or 2 manuscripts pertaining to

each gene, a comprehensive list of hepatic and extrahepatic phenotypic features was generated, including both those appearing with greater frequency and those that were less common and in certain instances unique to specific diseases, to reflect the wide scope of liver disease. This preliminary phenotype list was utilized to carry out further data collection, and as additional manuscripts were reviewed, phenotypic traits were added as necessary. Treatments utilized were also noted, albeit without analysis on the efficacy thereof. In all, 7,572 patients were reviewed, and their clinical presentations were tabulated across 872 phenotypic traits (Supplemental Tables 2, 3).

#### *Genotype Standardization*

For each patient, the reported genotype, including nucleotide and/or amino acid change, was recorded. All reported mutations were subsequently standardized to facilitate genotype comparison. The standardization process involved conversion of a reported cDNA mutation to its equivalent using the MANE Select transcript of each gene as the reference sequence,<sup>50</sup> and/or confirmation of the variant and the consequence to the resulting protein using ClinVar and Ensembl Variant Effect Predictor. Variants such as large-scale deletions encompassing multiple genes or those extending beyond the 5' or 3' untranslated regions were reported as genomic variants referenced to Genome Reference Consortium Human Build 38 (GRCh38/hg38). Genotypes reported solely as amino acid changes, without the underlying nucleotide variant, were standardized as such, as identical amino acid changes can in many instances be produced by multiple nucleotide sequence variants. The formatting of all

variants was further standardized to reflect the latest nomenclature proposed by the Human Genome Variation Society (HGVS) in version 15.11.<sup>51</sup>

### *Website Development*

The database is currently in development and will operate using PostgreSQL, an advanced open-source relational database that can store and execute on thousands of records. The front-end of the website will be built with Django, a Python language-based open-source web development framework. Basic data visualization within the site will be displayed using R Shiny, which is a package that allows interactive web applications to be built from R code. The website itself will be hosted on Yale Spinup, which supports PostgreSQL, and is expected to be launched for public use by clinicians and researchers in spring 2023.

### *Database Update*

Alerts were created in PubMed corresponding to the initial query, consisting of the gene symbol and the terms “liver,” “hepatic” and “hepato” in the title and/or abstract. The new manuscripts underlying the alerts will be reviewed on a quarterly basis, and the processes of manual literature curation, data collection and genotype standardization as described above will be performed. The website will also house a form that allows for clinician and researcher input of genotype-phenotype information, which will also be reviewed quarterly and uploaded to the database upon verification.

## Hepatology Genome Rounds

Clinical cases of educational value from Yale New Haven Hospital were selected to be highlighted during Hepatology Genome Rounds. These one-hour sessions were planned in coordination with colleagues from the Departments of Genetics and Pathology, as well as with colleagues from other departments involved in the cases as appropriate. Each meeting consisted of the clinical presentation of a patient, genetic analysis results, liver biopsy findings and a holistic discussion of the patient's illness in the context of available information in the literature on the disease, gene and/or variant(s) of interest (Figure 2).

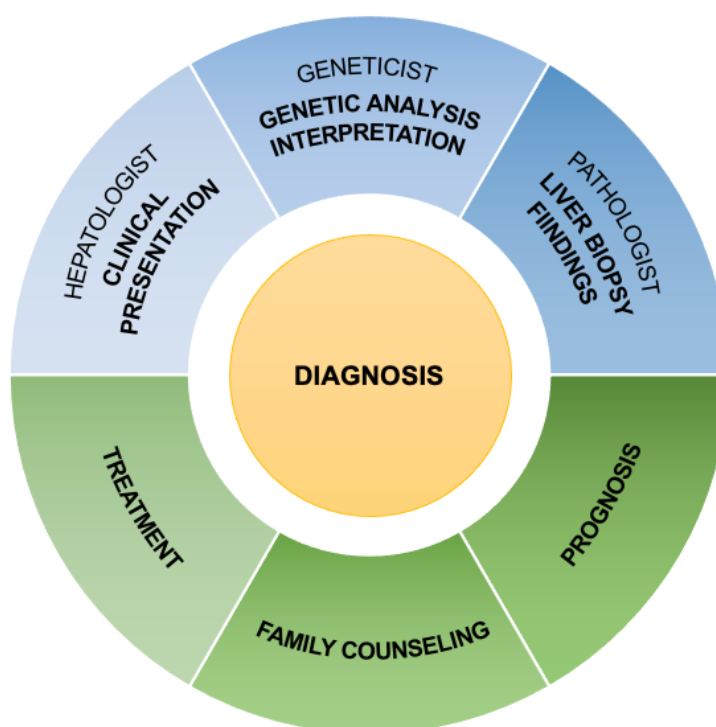


Figure 2. Hepatology Genome Rounds: Interdisciplinary collaboration in complex and/or atypical cases allows for direct impact on multiple aspects of clinical care.

Each discussion was further designed to convey a specific learning objective within the field of genomic medicine. Existing listservs were leveraged to generate interest and attendance across all levels of training.

To obtain feedback for this inaugural multidisciplinary series, multiple-choice pre-session and post-session surveys were made available via Zoom to all attendees. Prior to the start of the case presentation an inquiry about attendee characteristics, e.g., level of training, attendance at prior sessions, was launched. At the conclusion of the session, a multiple-choice survey was launched to assess satisfaction, perceived educational benefit, applicability to attendees' clinical practice and achievement of specific session objectives. To allow for further reflection, a few days following the conference, a Qualtrics survey was distributed to attendees to elicit open-ended feedback about their experience.

## **STATEMENT OF WORK**

Sílvia Vilarinho, MD, conceptualized both the Liver Gene Database and the Hepatology Genome Rounds. Melanie Zheng, MD, carried out the generation of the initial list of genes from OMIM in anticipation of data collection for the Liver Gene Database. Upon her graduation and departure from Yale School of Medicine, I conducted the literature review of these liver disease-associated genes, designed the spreadsheet for data collection and generated genotype-phenotype datasets for the construction and publication of the Liver Gene Database. In addition, the Hepatology Genome Rounds series was initially launched in 2021 by Dr. Vilarinho and Dr. Zheng. Upon Dr. Zheng's graduation, I served as the primary organizer, presenter and moderator of the Hepatology Genome Rounds, and its frequency was increased to bimonthly.

## RESULTS

### Liver Gene Database

The database houses genotype-phenotype correlation information for 7,572 patients diagnosed with 331 diseases involving the liver across 269 causative genes (Table 1).

Table 1. Liver Gene Database, version 1, content summary.

	No. Reviewed
Genes	269
Diseases	331
Patients	7,572

The website allows users to search for the frequency of various hepatobiliary and extrahepatic phenotypic features in patients with mutations in each gene (Figure 3).

For example, among 17 total patients reviewed in the literature with mutations in *AKR1D1*, a search reveals that 16 of them were found to have elevated transaminases, 10 had giant cell transformation and/or hepatitis on liver biopsy and 2 had rickets (Figure 4A, 4B). The reported and standardized genotype information for each patient reviewed is also made available (Table 2), with the ability to further filter for phenotypic features by a specific variant. For instance, filtering for the NM\_005989.4:c.587del;p.Cys196Serfs\*11 variant in *AKR1D1* yields a total of 3 patients, with a set of phenotypic features distinctive from that of the larger pool of all patients (Figure 4C).

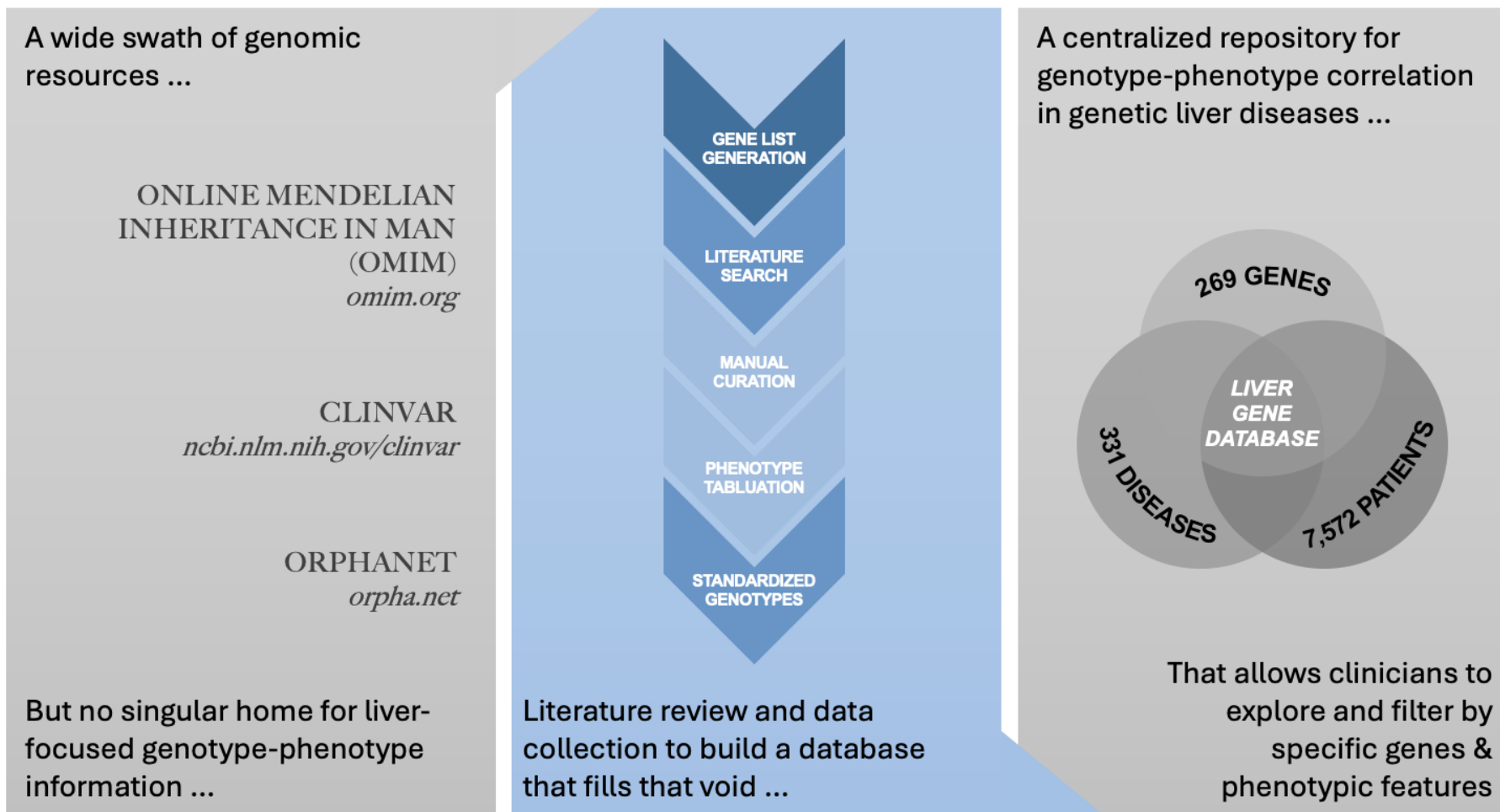


Figure 3. The Liver Gene Database fills a void in the bioinformatics space for clinicians and researchers interested in genotype-phenotype correlation in genetic liver diseases.

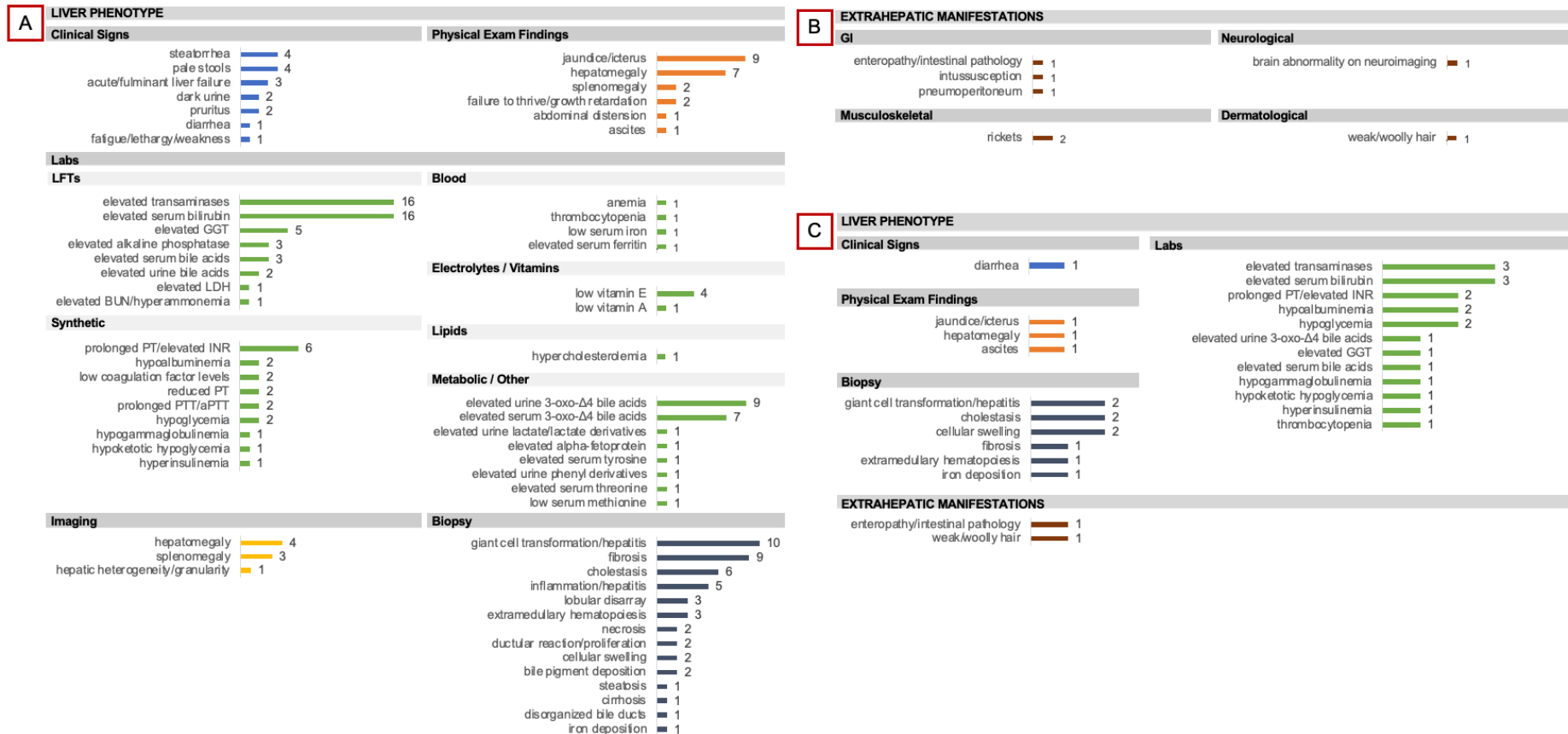


Figure 4. Schematic representation of (A) hepatobiliary and (B) extrahepatic phenotype of patients found to have biallelic mutations in *AKR1D1* causing bile acid synthesis defect, type 2. (C) Clinical phenotype of the three patients found to harbor homozygous NM\_005989.4:c.587del variants in *AKR1D1*. Bar graphs denote the number of patients with the associated feature and a verified mutation in *AKR1D1*. Total number of patients reviewed with *AKR1D1* mutations was 17, which have been reported in 10 articles.<sup>52-61</sup> Last updated July 6, 2022.

Table 2. Genotype details of patients with recessive mutations in *AKR1D1*.

Patient No.	PMID	Reported <sup>52-61</sup>		Standardized/HGVS			Zygosity
		Nucleotide change	Amino acid consequence	Reference sequence	Nucleotide change	Amino acid consequence	
1	28697823	c.579+2delT		NM_005989.4	c.579+2del		compound het
		c.853C>T	p.Gln285*	NM_005989.4	c.853C>T	p.Gln285*	compound het
2	23679950	c.587delG	p.Cys196Serfs*11	NM_005989.4	c.587del	p.Cys196Serfs*11	homozygous
3	23679950	c.587delG	p.Cys196Serfs*11	NM_005989.4	c.587del	p.Cys196Serfs*11	homozygous
4	23679950	c.587delG	p.Cys196Serfs*11	NM_005989.4	c.587del	p.Cys196Serfs*11	homozygous
5	23160874	c.866G>A	p.Arg266Gln	NM_005989.4	c.797G>A	p.Arg266Gln	single het
6	23160874	c.737G>A	p.Gly223Glu	NM_005989.4	c.668G>A	p.Gly223Glu	compound het
		c.850C>T	p.Arg261Cys	NM_005989.4	c.781C>T	p.Arg261Cys	compound het
7	23323017	c.797G>A	p.Arg266Gln	NM_005989.4	c.797G>A	p.Arg266Gln	single het
8	23323017	c.396C>A		NM_005989.4	c.396C>A	p.Tyr132*	compound het
		c.722A>T	p.Asp241Val	NM_005989.4	c.722A>T	p.Asp241Val	compound het
9	8707100; 12970144	c.662C>T	p.Pro198Leu	NM_005989.4	c.593C>T	p.Pro198Leu	homozygous
10	12970144	c.511delT		NM_005989.4	c.442del	p.Cys148Valfs*16	homozygous
11	12970144	c.385C>T	p.Leu106Phe	NM_005989.4	c.316C>T	p.Leu106Phe	homozygous
12	18243262	c.662C>T	p.Pro198Leu	NM_005989.4	c.593C>T	p.Pro198Leu	homozygous
13	31337596	c.74C>T	p.Thr25Ile	NM_005989.4	c.74C>T	p.Thr25Ile	compound het
		c.580-13T>A		NM_005989.4	c.580-13T>A		compound het
14	31337596	c.853C>T	p.Gln285*	NM_005989.4	c.853C>T	p.Gln285*	homozygous
15	31337596	c.148C>T	p.Arg50*	NM_005989.4	c.148C>T	p.Arg50*	compound het
		c.797G>A	p.Arg266Gln	NM_005989.4	c.797G>A	p.Arg266Gln	compound het
16	15030995	c.467C>G	p.Pro133Arg	NM_005989.4	c.398C>G	p.Pro133Arg	compound het
		c.850C>T	p.Arg261Cys	NM_005989.4	c.781C>T	p.Arg261Cys	compound het
17	15030995	c.467C>G	p.Pro133Arg	NM_005989.4	c.398C>G	p.Pro133Arg	compound het
		c.850C>T	p.Arg261Cys	NM_005989.4	c.781C>T	p.Arg261Cys	compound het

Standardization per HGVS version 15.11. PMID: PubMed reference number; HGVS: Human Genome Variation Society.

<b>A</b>	SEARCH RESULTS				elevated urine 3-oxo-Δ4 bile acids
	Gene Symbol	Associated Disease	No. of Patients Analyzed	% of Patients with Phenotypic Trait	
	<i>AKR1D1</i>	Congenital bile acid synthesis defect 2 (CBAS2)	17	<div><div></div></div>	53%

<b>B</b>	SEARCH RESULTS				elevated serum methionine
	Gene Symbol	Associated Disease	No. of Patients Analyzed	% of Patients with Phenotypic Trait	
	<i>ADK</i>	Hypermethioninemia due to adenosine kinase deficiency (HMAKD)	13	<div><div></div></div>	100%
	<i>CBS</i>	Cystathione beta-synthase deficiency (CBS)	3	<div><div></div></div>	100%
	<i>TFAM</i>	Mitochondrial DNA depletion syndrome 15, hepatocerebral type (MTDPS15)	2	<div><div></div></div>	100%
	<i>POLG2</i>	Mitochondrial DNA depletion syndrome 16, hepatic type (MTDPS16)	1	<div><div></div></div>	100%
	<i>TRMU</i>	Liver failure, infantile, transient (LFIT)	27	<div><div></div></div>	63%
	<i>SLC25A13</i>	Cholestasis, neonatal intrahepatic, caused by citrin deficiency (NICCD)	157	<div><div></div></div>	48%
	<i>RINT1</i>	Infantile liver failure syndrome 3 (ILFS3)	3	<div><div></div></div>	33%
	<i>C1QBP</i>	Combined oxidative phosphorylation deficiency 33 (COXPD33)	4	<div><div></div></div>	25%
	<i>FAH</i>	Tyrosinemia 1 (TYRSN1)	69	<div><div></div></div>	17%
	<i>DGUOK</i>	Mitochondrial DNA depletion syndrome 3 (MTDPS3)	81	<div><div></div></div>	16%
	<i>SLC25A13</i>	Citrullinemia 2 (CTLN2)	22	<div><div></div></div>	14%
	<i>TALDO1</i>	Transaldolase deficiency (TALDOD)	18	<div><div></div></div>	11%
	<i>SERAC1</i>	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL)	25	<div><div></div></div>	8%
	<i>GFM1</i>	Combined oxidative phosphorylation deficiency (COXPD1)	22	<div><div></div></div>	5%
	<i>GALT</i>	Galactosemia1 (GALAC1)	31	<div><div></div></div>	3%
	<i>MPV17</i>	Mitochondrial DNA depletion syndrome 6 (MTDPS6)	67	<div><div></div></div>	3%
	<i>POLG</i>	Mitochondrial DNA depletion syndrome 4A (MTDPS4A)	128	<div><div></div></div>	2%
	<i>NBAS</i>	NBAS deficiency	134	<div><div></div></div>	1%

Figure 5. (A) Database-wide search for patients with elevated urine 3-oxo-Δ4 bile acids yields only congenital bile acid synthesis defect due to *AKR1D1* mutations, while (B) a database-wide search for patients with elevated serum methionine yields patients with variants across numerous genes.

Furthermore, the database allows users to search generally across all genes and diseases for specific phenotypic traits. As an example, searching for patients with elevated urine 3-oxo-Δ4 bile acids reveals that this finding is likely

quite specific to congenital bile acid synthesis defect 2 associated with *AKR1D1*, as no patients with any other diseases documented in the database were discovered to exhibit this phenotype (Figure 5A).

In contrast, a database-wide search for a more common laboratory abnormality such as elevated serum methionine results in a longer list of genes, demonstrative of the lack of specificity of this finding and the many patients in which this phenotype was observed across various disease entities (Figure 5B).

### Hepatology Genome Rounds

The Hepatology Genome Rounds series was inaugurated in 2021 as a bimonthly, virtual, single-center conference at Yale School of Medicine. Ten sessions have been held thus far as a collaborative effort among the Departments of Internal Medicine, Genetics and Pathology. Patients with mutations in various genes such as *ABCB4* and *ABCB11* have been featured, with session objectives ranging from a general introduction to the field of genomic medicine at the initiation of the series to more specialized topics within the field and/or reiteration of important principles in later sessions (Table 3).

Table 3. Overview of the Hepatology Genome Rounds and session objectives.

Session	Session Objective
1	To introduce the application of genomic analysis in clinical medicine
2	To illustrate the available modalities of genetic testing and the analytic processes for SNV and CNV
3	To emphasize the role of clinical acumen in genetic analysis and interpretation
4	To consider re-analysis when genotype-phenotype correlation remains unclear
5	To describe lean NAFLD as an entity distinct from metabolic syndrome-related NAFLD

6	To elucidate the utility of re-analysis when additional phenotypic characteristics emerge
7	To demonstrate the contribution of both rare and common variants to liver disease
8	To illustrate the role of WES in uncovering the etiology behind chronic, unexplained liver disease
9	To convey the value of interpreting genetic reports within the entire clinical context, especially in rare adulthood diseases
10	To consider genetic analysis in lean patients with no visceral adiposity and unexplained fatty liver disease

NAFLD, nonalcoholic fatty liver disease; WES, whole-exome sequencing; SNV, single nucleotide variant; CNV copy number variant.

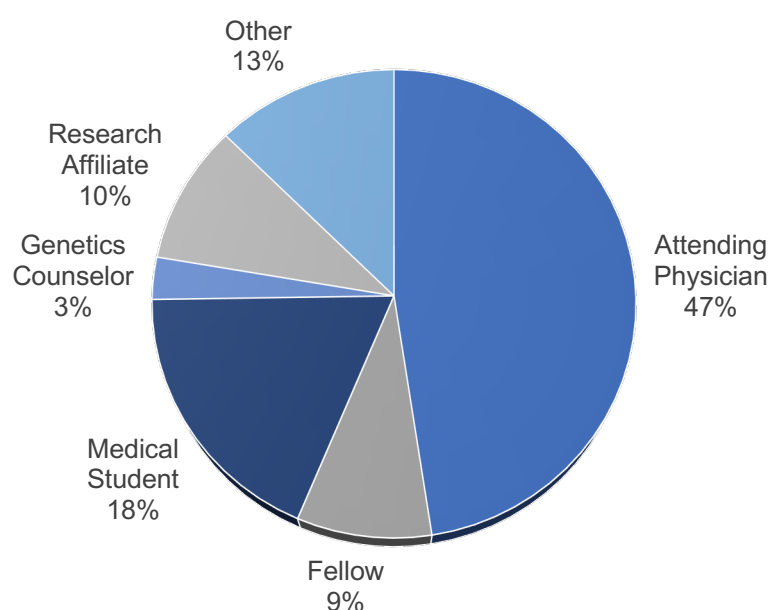


Figure 6. Mean attendee makeup across ten Hepatology Genome Rounds sessions.<sup>62</sup>

The conferences were attended by individuals across different levels of training, including attending physicians, fellows, medical students, genetic counselors and research affiliates (Figure 6). Prior exposure to genomic medicine varied as well, with a proportion of attendees having received formal training, others having incorporated genetic testing within their clinical practice, some having attended earlier sessions of our series and others having had no previous education within the field (Figure 7).

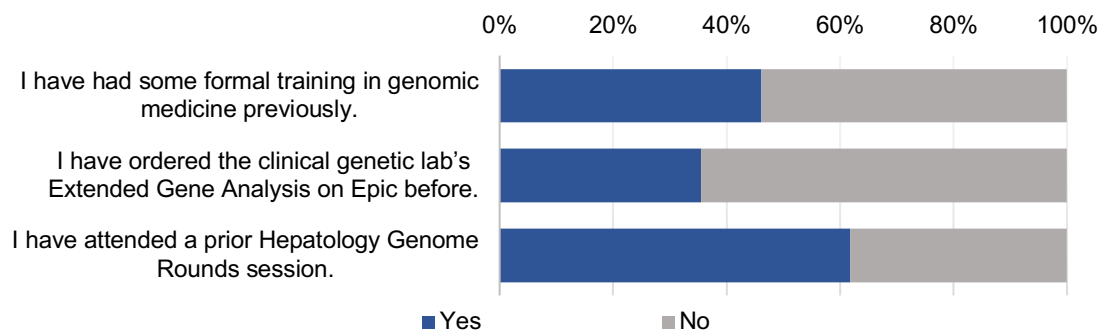


Figure 7. Limited prior exposure to genomic medicine among attendees of Hepatology Genome Rounds series.<sup>62</sup>

According to post-session surveys, most respondents across all sessions agreed or strongly agreed with statements aligned with the achievement of our session objectives (Figure 8A). All respondents in 7 out of the 10 sessions indicated either agreement or strong agreement. Only one single participant indicated either disagreement or strong disagreement in any of the conferences. 96% of survey respondents also expressed that the sessions were useful (Figure 8B), with 100% further indicating after our sessions that they recognized the value of genetic analysis for clinical reasoning and diagnosis within clinical hepatology. Just over half of our participants anticipated utilizing genetic testing within their clinical practice in the near future, with over 80% of attendees reporting that the availability of guidelines from a professional society of hepatologists would further encourage their use of genomic technologies.

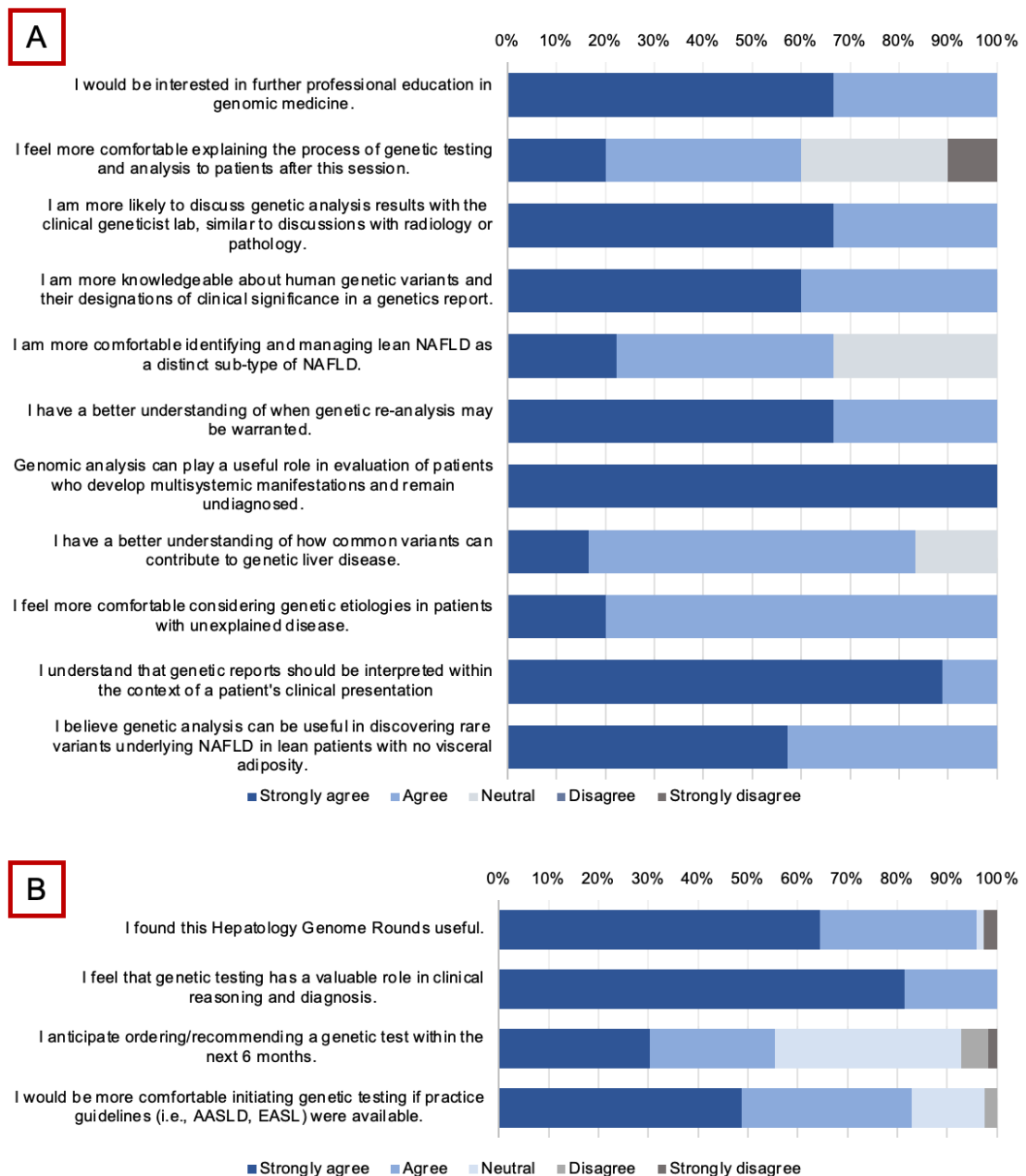


Figure 8. (A) Attendee assessment of the achievement of session objectives, (B) Applicability and utility of Hepatology Genome Rounds to attendees' clinical practice.<sup>62</sup> NAFLD, nonalcoholic fatty liver disease; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver.

Open-ended feedback via the Qualtrics survey was largely positive:

*"very well organized and moderated"*

*"seems to be working well..."*

*"enjoyed it"*

*"The Genome Rounds' case analysis helps a lot"*

One respondent recommended greater incorporation of open discussion time among participants into the format of the sessions.

Though the series has been largely educational, serving as a forum for highlighting recent cases of clinical interest at our institution, the discussions have also resulted in the reconsideration of initial diagnoses in two patients.

## **DISCUSSION**

### **Liver Gene Database**

#### *An Informational Hub*

The Liver Gene Database represents the culmination of efforts to bring into existence a centralized hub for gene disease relationship and genotype-phenotype information across all known diseases with liver involvement. It has been our experience in our research group that one of the main bottlenecks in WES analysis and interpretation is the inadequacy of existing tools for phenotype exploration and correlation for a given genotype. Though many resources exist, information is often neither consistent nor complete, limiting the ability of clinicians and researchers to rely on a single repository of data to adequately assess variant pathogenicity or relevance to the phenotype of the patient in question. It is our hope that the database's first iteration which reflects illness manifestations across 269 genes, 872 phenotypic traits and 7,572 patients provides a comprehensive view of the spectrum of genetic liver disease. We envision that, through its continuous updates, it will adapt to reflect novel emergent diseases and/or syndromes which become better understood and are re-formulated. Hence, it will continue to serve as a useful resource for clinicians and researchers within the field of hepatology worldwide.

#### *A Timely Resource*

One of the primary benefits of the Liver Gene Database will be its quarterly update, which will consist of a review of all new manuscripts detailing genotypic and corresponding phenotypic information in patients with variants across the 269 genes, as well as the inclusion of new and/or previously overlooked genes

and variants brought to our attention via user submissions. Because most of the generalized databases that hepatologists currently depend on are user-driven, without manual curation at a regular frequency, information displayed in these resources is typically not up to date.<sup>7</sup>

Our need to add genes such as *GIMAP5*, *KIF12*, *LSR*, *MYO5B*, *PPM1F*, *USP53*, *WDR83OS* and *ZFYVE19* to the initial list of liver disease-associated genes generated from OMIM to serve as a comprehensive resource of liver-associated genes is reflective of this fact. Furthermore, the emergence of novel phenotypes that have yet to be captured in existing databases illustrates the limitations of the currently available resources. For example, a search for *ABHD5* in databases such as OMIM and UniProt yields Chanarin-Dorfman syndrome as the sole associated disease, with the OMIM entry for the gene *ABHD5* not having been updated for over two and a half years on the last accessed date.<sup>63</sup> It is only through a literature search that the documentation of a nonalcoholic fatty liver disease (NAFLD) phenotype, without the multisystemic features of Chanarin-Dorfman syndrome, due to either monoallelic or biallelic mutations in *ABHD5* was revealed.<sup>64,65</sup> It would be easy to disregard a mutation in *ABHD5* as irrelevant in a patient presenting with hepatic steatosis, if we were to depend on a cursory review of existing genotype-phenotype databases.

#### *A Source for Digestible Information*

In addition to its goal of reflecting the latest literature on genetic liver disease, the database is designed to offer clinicians, who are increasingly busy with both

clinical care and administrative work, an accessible tool that provides information in an easily digestible format. Particularly for those with limited training in genetics or who are not consistently involved in the care of patients with genetic liver diseases, the database can serve as a resource for rapid genotype-phenotype correlation information. The ability to search for a gene or disease and immediately view a list of observed phenotypic features and their frequency in affected patients, and vice versa, is powerful in today's care setting characterized by quick turnaround times from patient to patient.

For clinicians and researchers investigating gene-disease relationships and genotype-phenotype correlations, the database houses not only breadth but also depth of information for further analysis. The aggregation of heretofore scattered data will facilitate studies on specific variants, their associations with unique or distinguishing phenotypic features and/or their propensity to manifest as more or less severe phenotypic profiles.

The database was not initially conceived as a diagnostic tool, and we would rather characterize the database as an information repository for the dissemination of genomic knowledge in liver disease. This is important to emphasize especially given the fact that there exist many rare monogenic liver diseases in which only a handful of patients have been described. Nevertheless, it is possible in the future that, as our knowledge of the basis of genetic liver diseases grows and there is a corresponding increase in available genotype and phenotype data, the database will come to serve a more prominent role in the diagnostic pathway for patients with unexplained liver disease.

### *Challenges & Limitations*

A potential limitation in the implementation of the Liver Gene Database is in the ability to comprehensively and accurately document all genes reported in the literature to house pathogenic variants causing liver disease. A systematic approach to evaluate existing databases and the literature was utilized, as described herein, but with any given set of query terms, however well designed and conceived, it is likely that certain pertinent genes and/or manuscripts will have been excluded. We believe that the transparency of our methods and consistency of our application thereof throughout the construction of this novel database outweighs this foreseeable shortcoming. It is our belief that our regularly timed update protocols to include novel and previously overlooked genes associated with liver disease will also contribute to the robustness and quality of the database. We will further allow clinicians and researchers to submit their own findings through the website, as we recognize that a global effort will be required to maintain an up-to-date and clinically relevant gene database.

### **Hepatology Genome Rounds**

#### *A Clinical and Educational Mouthpiece*

The Hepatology Genome Rounds series was developed to reflect our vision that genomic analysis, when applied appropriately to an individual with an undiagnosed illness, combined with its interpretation, discussion and correlation within an interdisciplinary context, would not only assist in patient

diagnosis and optimal management but also propel forward our understanding of the natural history of chronic liver disease.

Buttressed by data on the success of WES as a diagnostic tool in unexplained liver disease, criteria have been proposed outlining which patients with liver disease are appropriate candidates for additional workup with WES.<sup>15,66</sup> Specifically, individuals who remain undiagnosed following extensive clinical investigation, present with a phenotype that is deemed atypical, have multisystemic, congenital and/or syndromic manifestations, are offspring from a family with a history of consanguinity and/or have a family history of hepatobiliary disease,<sup>67</sup> likely benefit from genetic analysis.

Nevertheless, WES not uncommonly yields several rare variants, for which insufficient data exists in the literature and for which our knowledge remains in its nascent stages to be readily designated as either pathogenic or benign. These variants which are labeled VUS, therefore, cannot be interpreted in a vacuum and merit placement within the patient's complete clinical picture.<sup>15,68,69</sup>

By providing a space in which analysis of genetic data and clinical information can occur in a comprehensive manner from multiple lenses simultaneously, the series allows healthcare professionals at all levels of training to collaborate to determine and/or refine a patient's diagnosis, which in turn serves as the basis from which changes to management, family counseling and guidance on prognosis can sprout (Figure 2). Furthermore, the sessions advance our understanding of the disease entities discussed, whether they be a novel

syndrome or expansion of a phenotype. The practice of genotype analysis with clinical correlation can lead to the appreciation of previously overlooked phenotypic features, especially in the presence of experts from multiple disciplines.

Over and above their direct contribution to the care of the patients discussed, the conferences have the potential to impart longitudinal changes to the ways in which clinicians practice. Whereas cross-disciplinary feedback may be limited in the traditional hospital setting, the series serves as a forum in which providers can hone their clinical acumen and translate their newfound insight into more effective practices such that patient care is optimized. For instance, vis-à-vis the discussions that ensue, clinical geneticists receive feedback on and determine points of primary importance to providers who receive genetic reports. They are henceforth able to tailor their reports for relevance and to facilitate comprehension, which is essential due to inconsistent genetic training and experience among clinicians. These modifications can set the stage for improved interdisciplinary communication in the clinical setting and for acceleration and/or standardization of patient care.

Pathologists also accrue benefits from participation, as their experience of discussing liver biopsy findings in a multidisciplinary setting differs from that of initial review in isolation. By featuring histopathology within broader discussions of patients' illnesses across multiple sessions, pathologists can gradually amass the insight and confidence to determine the appropriateness of

recommending genetic analysis to providers in select cases of undiagnosed liver disease.<sup>70</sup>

Alongside these clinical benefits, the Hepatology Genome Rounds series incorporates thematic elements from genomic medicine to provide a longitudinal and sequential learning experience. Increased incorporation of genetics education into the medical training curriculum has been seen as essential for decades.<sup>71</sup> However, programs continue to vary in the level of commitment to this field, and many trainees to this day feel underexposed and underprepared to critical components of genetic care such as instigating analysis and interpreting genetic reports.<sup>72</sup> Sustained educational efforts, which can occur within the format of such interdisciplinary rounds, will thus be vital to augmenting the series' eventual impact on the course of clinical care.

The series moreover possesses the potential to become a home for patient advocacy, as information and education are powerful in tackling longstanding stigma. As an example, not all individuals with a history of alcohol use will develop chronic liver disease. Rather, the small proportion of affected patients who progress to develop irreversible liver damage are likely enriched in genetic variants that increase their risk.<sup>73</sup> In a similar fashion, individuals who are found to have hepatic steatosis or a body mass index (BMI) which falls in the overweight or obese range may have mutations in *MC4R*, which encodes melanocortin-4 receptor, for which novel therapies are emerging.<sup>74</sup> For these patients, a diagnosis of alcoholic liver disease or obesity which is reached without adequate clinical investigation perpetuates entrenched stigma and is

essentially poor clinical care. Continued education among clinicians about such genetic risks and susceptibilities will lay the foundation for a greater awareness of cognitive biases and heuristics in medicine and will prompt providers to assess each patient holistically.

As a whole, the conferences are designed to advance our fundamental, tripartite mission of improving the quality of patient care, contributing to the body of scientific knowledge and supporting the continued education of medical professionals in the field of genomic medicine. In time, we hope that this sustained and continued work will generate best-practice clinical guidance for the diagnosis and management of patients with idiopathic liver disease. We envision that the generation of clinical guidance for the use of genomic analysis for the evaluation and management of liver disease will not only introduce standardization and precision but also expand access to and boost the provision of care for these patients.

Though limited in their scope and sample size, the multiple-choice and open-ended survey results (Figure 8) indicate the effectiveness of the current format of Hepatology Genome Rounds in increasing accessibility to genetic information within the field of hepatology, serving as a vehicle for continued education and provoking discussions that emphasize critical thinking and are applicable to patient care.

Our series has thus far largely been driven with a focus on education, highlighting recent cases of clinical interest at our institution, but we anticipate

that the format will continue to grow and adapt to feature contemporaneous cases, analogous to the clinical focus of tumor boards. This will allow real-time collaboration among specialists to produce changes in diagnosis, management and, it is our hope, even clinical outcomes.

Hepatology as a field is well primed to reap the benefits of the complete incorporation of genomic analysis into its scope of care. As genetic analysis becomes ever more affordable and available, the need for clinically relevant interpretation of genomic data will only grow. To meet this growing demand, we envision the expansion of our series into a multi-institutional format to increase accessibility to the full spectrum of genetic care for patients in need. We further anticipate that comparable interdisciplinary genomic discussion forums will be established across other specialties, as genomics becomes fully integrated into medical care as a core diagnostic modality.

### *Challenges & Limitations*

A logistical consideration in the conduct of Hepatology Genome Rounds has been the ability to maintain or grow our audience, given that genetic liver disease is a niche interest, not necessarily applicable to all clinicians and researchers at our institution. By sending reminder communications about the sessions with a preview of the case to be discussed, we aimed to draw providers and trainees with particular interest in the topic(s) to be discussed. We have also actively sought feedback in both a standardized and open-ended manner as described above to gain additional insight into how the series can be improved and evolve over time. The future we envision for Hepatology

Genome Rounds consists of multi-institutional and/or real-time case discussions, and while such expansion will certainly bring its own set of challenges, it is likely through facing them head-on that these sessions will achieve their full potential.

## **CONCLUSION**

Genomic analysis is an essential tool in understanding the etiology of chronic and unexplained liver disease. However, its adoption within clinical hepatology has been hampered in part by structural factors in medical education and training, including inadequate and inconsistent opportunities for genetic education. In this Thesis, we have proposed, developed and demonstrated two tools, namely the Liver Gene Database and the Hepatology Genome Rounds. These not only serve as potent vehicles for education and dissemination of genomic information in the field but also have the potential to contribute to advancements in patient care and our overall understanding of liver disease. In addition, these two entities do not exist in isolation, and we foresee their use and development as occurring in tandem, with genetic insights gained in the Hepatology Genome Rounds being reflected in the Liver Gene Database, and new updates to the repository contributing to the interpretation of complex cases in future Genome Rounds sessions. It is our hope that clinicians and researchers find these tools equally useful and that they view them as models for the continued propagation of genomic knowledge in both hepatology and other fields of medicine.

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## SUPPLEMENTARY MATERIALS

Supplemental Table 1. Summary of genes, diseases and patients reviewed for the Liver Gene Database.

Gene	Disease	Patients
<i>ABCB11</i>	Progressive familial intrahepatic cholestasis type 2	121
	Benign recurrent intrahepatic cholestasis type 2	33
	Intrahepatic cholestasis of pregnancy	5
<i>ABCB4</i>	Progressive familial intrahepatic cholestasis type 3	151
	Gallbladder disease 1	65
	Intrahepatic cholestasis of pregnancy	32
<i>ABCC2</i>	Dubin-Johnson syndrome	53
<i>ABCD3</i>	ABCD3 deficiency	1
<i>ABHD5</i>	Chanarin-Dorfman syndrome	51
	Non-alcoholic fatty liver disease	39
<i>ACAD9</i>	Mitochondrial complex I deficiency, nuclear type 20	12
<i>ACADM</i>	Acyl-CoA dehydrogenase medium-chain deficiency	1
<i>ACADVL</i>	Acyl-CoA dehydrogenase very long-chain deficiency	50
<i>ACOX1</i>	Peroxisomal acyl-CoA oxidase deficiency	8
<i>ACOX2</i>	ACOX2 deficiency	10
<i>ACVRL1</i>	Hereditary hemorrhagic telangiectasia type 2	41
<i>ADA2</i>	ADA2 deficiency	20
<i>ADK</i>	Adenosine kinase deficiency	13
<i>AGL</i>	Glycogen storage disease III	155
<i>AGPAT2</i>	Congenital generalized lipodystrophy 1	44
<i>AKR1D1</i>	AKR1D1 deficiency	17
<i>ALAS2</i>	X-linked protoporphyria	56
	X-linked sideroblastic anemia	5
<i>ALDOB</i>	Hereditary fructose intolerance	51
<i>ALG8</i>	ALG8 deficiency	11
	Autosomal dominant polycystic liver disease	5
<i>ALMS1</i>	Alström syndrome	123
<i>AMACR</i>	Alpha-methylacyl-CoA racemase deficiency	4
	Congenital bile acid synthesis defect 4	1
<i>ANKS6</i>	Nephronophthisis-related ciliopathy	9
<i>AP1S1</i>	MEDNIK syndrome	7
<i>APOA1</i>	Hypoalphalipoproteinemia, primary, 2	226
	Apolipoprotein AI-derived amyloidosis	1
<i>APOE</i>	Apolipoprotein E deficiency	14
<i>ASL</i>	Argininosuccinic aciduria	30
<i>ATP6AP1</i>	ATP6AP1 deficiency	21
<i>ATP6AP2</i>	ATP6AP2 deficiency	3
<i>ATP7B</i>	Wilson's disease	431
<i>ATP8B1</i>	Progressive familial intrahepatic cholestasis type 1	73
	Intrahepatic cholestasis of pregnancy	16
	Benign recurrent intrahepatic cholestasis type 1	10
<i>BBS1</i>	Bardet-Biedl syndrome	9
<i>BCS1L</i>	Complex III deficiency	23

	GRACILE syndrome	8
	Björnstad syndrome	1
<i>BLVRA</i>	Hyperbiliverdinemia	3
<i>BSC12</i>	Congenital generalized lipodystrophy type 2	66
<i>C10orf2</i>	Mitochondrial DNA depletion syndrome type 7	11
<i>C1QBP</i>	C1QBP deficiency	4
<i>CARS1</i>	Microcephaly, developmental delay and brittle hair syndrome	4
<i>CAV1</i>	Congenital generalized lipodystrophy type 3	1
<i>CAVIN1</i>	Congenital generalized lipodystrophy 4	16
<i>CBS</i>	Cystathione beta-synthase deficiency	3
<i>CC2D2A</i>	Joubert syndrome	21
	COACH syndrome	3
	Meckel syndrome type 6	1
<i>CCDC115</i>	Congenital disorder of glycosylation type Ilo	11
<i>CCDC47</i>	Trichohepatoneurodevelopmental syndrome	4
<i>CD55</i>	Complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy	11
<i>CEP164</i>	Nephronophthisis 15	7
<i>CEP19</i>	Morbid obesity and spermatogenic failure	11
	Bardet-Biedl syndrome	7
<i>CEP83</i>	Nephronophthisis 18	8
<i>CFTR</i>	Cystic fibrosis	89
<i>COG2</i>	Congenital disorder of glycosylation 2Q	1
<i>COG4</i>	Saul-Wilson syndrome	14
	Congenital disorder of glycosylation 2J	1
<i>COG5</i>	Congenital disorder of glycosylation 2I	8
<i>COG6</i>	Congenital disorder of glycosylation 2L	14
<i>COG7</i>	Congenital disorder of glycosylation 2E	5
<i>COQ2</i>	Coenzyme Q10 deficiency, primary, 1	3
<i>CP</i>	Aceruloplasminemia	47
<i>CPT1A</i>	Carnitine palmitoyltransferase 1A deficiency	24
<i>CPT2</i>	Carnitine palmitoyltransferase 2 deficiency, myopathic, stress-induced	4
	Carnitine palmitoyltransferase 2 deficiency, lethal neonatal	3
	Encephalopathy, acute, infection-induced, 4	1
<i>CSPP1</i>	Joubert syndrome 21	19
<i>CYBA</i>	Granulomatous disease, chronic, autosomal recessive, 4	2
<i>CYBB</i>	Granulomatous disease, chronic, X-linked	32
<i>CYC1</i>	Mitochondrial complex III deficiency, nuclear 6	2
<i>CYP7B1</i>	Congenital bile acid synthesis defect 3	13
<i>DCDC2</i>	Nephronophthisis 19	19
<i>DDOST</i>	Congenital disorder of glycosylation 1R	1
<i>DGUOK</i>	Mitochondrial DNA depletion syndrome 3	81
	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive 4	7
	Portal hypertension, non-cirrhotic	3
<i>DKC1</i>	Dyskeratosis congenita, X-linked	2
<i>DLD</i>	Dihydrolipoamide dehydrogenase deficiency	31
<i>DLL4</i>	Adams-Oliver syndrome 6	18

<i>DNAJB11</i>	Polycystic kidney disease 6 with or without polycystic liver disease	23
	Ivemark II syndrome	1
<i>DNAJC19</i>	3-methylglutaconic aciduria 5	41
<i>DPM1</i>	Congenital disorder of glycosylation 1E	5
<i>DYNC2H1</i>	Short-rib thoracic dysplasia 3 with or without polydactyly	74
<i>ENG</i>	Telangiectasia, hereditary hemorrhagic, 1	196
<i>EPM2A</i>	Epilepsy, progressive myoclonic 2	3
<i>ERCC4</i>	Xeroderma pigmentosum complementation group F	1
<i>ETF A</i>	Glutaric aciduria 2A	1
<i>ETF B</i>	Glutaric aciduria 2B	3
<i>ETFDH</i>	Glutaric aciduria 2C	37
<i>EXTL3</i>	Immunoskeletal dysplasia with neurodevelopmental abnormalities	6
<i>F5</i>	Budd-Chiari syndrome	3
	Factor V deficiency	1
<i>FADD</i>	Infections, recurrent, associated with encephalopathy, hepatic dysfunction and cardiovascular malformations	3
<i>FAH</i>	Tyrosinemia 1	69
<i>FAN1</i>	Interstitial nephritis, karyomegalic	12
<i>FARSA</i>	Rajab interstitial lung disease with brain calcifications 2	4
<i>FARSB</i>	Rajab interstitial lung disease with brain calcifications 1	7
<i>FBXL4</i>	Mitochondrial DNA depletion syndrome 13	10
<i>FECH</i>	Protoporphyrin, erythropoietic, 1	71
<i>FH</i>	Fumarate deficiency	1
<i>G6PC1</i>	Glycogen storage disease 1A	125
<i>GALM</i>	Galactosemia 4	8
<i>GALT</i>	Galactosemia 1	31
<i>GANAB</i>	Polycystic kidney disease 3 with or without polycystic liver disease	36
<i>GATA6</i>	Pancreatic agenesis and congenital heart defects	2
<i>GBA</i>	Gaucher disease	19
<i>GBE1</i>	Glycogen storage disease 4	27
<i>GDF2</i>	Telangiectasia, hereditary hemorrhagic, 5	4
<i>GFM1</i>	Combined oxidative phosphorylation deficiency 1	22
<i>GIMAP5</i>	Portal hypertension, non-cirrhotic, 2	8
<i>GLIS3</i>	Diabetes mellitus, neonatal, with congenital hypothyroidism	22
<i>GLRX5</i>	Anemia, sideroblastic, 3, pyridoxine-refractory	1
<i>GPD1</i>	Hypertriglyceridemia, transient infantile	21
<i>GYS2</i>	Glycogen storage disease 0	25
<i>HADH</i>	3- $\alpha$ -hydroxyacyl-CoA dehydrogenase deficiency	1
<i>HADHA</i>	Mitochondrial trifunctional protein deficiency	9
<i>HADHB</i>	Mitochondrial trifunctional protein deficiency	33
<i>HAMP</i>	Hemochromatosis 2B	3
<i>HFE</i>	Hemochromatosis 1	193
<i>HJV</i>	Hemochromatosis 2A	51
<i>HMGCS2</i>	3-hydroxy-3-methylglutaryl-CoA synthase-2 deficiency	14
<i>HNF1A</i>	Maturity-onset diabetes of the young 3	62
	Hepatic adenomas familial	1
<i>HSD17B4</i>	D-bifunctional protein deficiency	3
<i>HSD3B7</i>	Congenital bile acid synthesis defect 1	65

<i>IARS1</i>	Growth retardation, impaired intellectual development, hypotonia, and hepatopathy	4
<i>IFNG</i>	Immunodeficiency 69	2
<i>IFT122</i>	Cranioectodermal dysplasia 1	5
<i>IFT140</i>	Short-rib thoracic dysplasia 9 with or without polydactyly	76
<i>IFT172</i>	Short-rib thoracic dysplasia 10 with or without polydactyly	14
	Bardet-Biedl syndrome 20	4
<i>IFT43</i>	Cranioectodermal dysplasia 3	2
<i>IL21R</i>	Immunodeficiency 56	5
<i>INPP5E</i>	Joubert syndrome 1	35
<i>INSR</i>	Leprechaunism	7
<i>ITK</i>	Lymphoproliferative syndrome 1	2
<i>JAG1</i>	Alagille syndrome 1	211
<i>JAK2</i>	Budd-Chiari syndrome	25
	Polycythemia vera	18
	Thrombocythemia 3	16
	Myelofibrosis	6
	Leukemia, acute myelogenous	1
<i>KARS1</i>	Leukoencephalopathy, progressive, infantile-onset, with or without deafness	3
<i>KIF12</i>	Cholestasis, progressive familial intrahepatic, 8	13
<i>KRIT1</i>	Cerebral cavernous malformations 1	24
<i>KRT8</i>	Cirrhosis	5
<i>LARS1</i>	Infantile liver failure syndrome 1	23
<i>LARS2</i>	Hydrops, lactic acidosis, and sideroblastic anemia	1
<i>LBR</i>	Reynolds syndrome	1
<i>LIPA</i>	Cholesteryl ester storage disease	53
	Wolman disease	3
<i>LIPE</i>	Lipodystrophy, familial partial, 6	8
<i>LIPT1</i>	Lipoyltransferase 1 deficiency	1
<i>LMNA</i>	Lipodystrophy, familial partial, 2	129
	Hutchinson-Gilford progeria syndrome	14
<i>LOX</i>	Aortic aneurysm, familial thoracic 10	15
<i>LRP5</i>	Polycystic liver disease 4 with or without kidney cysts	11
<i>LRPPRC</i>	Mitochondrial complex IV deficiency, nuclear type 5	10
<i>LSR</i>	LSR deficiency	2
<i>LYRM4</i>	Combined oxidative phosphorylation deficiency 19	2
<i>MAN1B1</i>	Rafiq syndrome	15
<i>MARS1</i>	Interstitial lung and liver disease	5
<i>MICOS13</i>	Combined oxidative phosphorylation deficiency 37	3
<i>MICU1</i>	Myopathy with extrapyramidal signs	29
<i>MPI</i>	Congenital disorder of glycosylation 1B	16
<i>MPV17</i>	Mitochondrial DNA depletion syndrome 6	67
<i>MRM2</i>	Mitochondrial DNA depletion syndrome 17	1
<i>MRPL12</i>	Combined oxidative phosphorylation deficiency 45	3
<i>MRPL3</i>	Combined oxidative phosphorylation deficiency 9	4
<i>MRPL44</i>	Combined oxidative phosphorylation deficiency 16	2
<i>MRPS16</i>	Combined oxidative phosphorylation deficiency 2	1

<i>MRPS23</i>	Combined oxidative phosphorylation deficiency 46	1
<i>MRPS28</i>	Combined oxidative phosphorylation deficiency 47	1
<i>MTHFD1</i>	Combined immunodeficiency and megaloblastic anemia with or without hyperhomocysteinemia	5
<i>MTM1</i>	Myopathy, centronuclear, X-linked	16
<i>MYO5B</i>	Diarrhea 2, with microvillus atrophy, with or without cholestasis	42
	Isolated low-GGT cholestasis	39
<i>NBAS</i>	NBAS deficiency	134
<i>NCF1</i>	Granulomatous disease, chronic, autosomal recessive, 1	10
<i>NCF2</i>	Granulomatous disease, chronic, autosomal recessive, 2	3
<i>NEK1</i>	Short-rib thoracic dysplasia 6 with or without polydactyly	3
<i>NEK8</i>	Nephronophthisis 9	5
<i>NGLY1</i>	Congenital disorder of deglycosylation 1	52
<i>NHLRC1</i>	Epilepsy, progressive myoclonic 2	1
<i>NHLRC2</i>	Fibrosis, neurodegeneration, and cerebral angiomas	3
<i>NHP2</i>	Dyskeratosis congenita, autosomal recessive, 2	4
<i>NOP10</i>	Dyskeratosis congenita, autosomal recessive, 1	3
<i>NOTCH2</i>	Alagille syndrome 2	20
	Hajdu-Cheney syndrome	1
<i>NPC1</i>	Niemann-Pick disease C1	32
<i>NPHP3</i>	Nephronophthisis 3	62
	Renal-hepatic-pancreatic dysplasia 1	10
	Meckel syndrome 7	4
<i>NR1H4</i>	Cholestasis, progressive familial intrahepatic, 5	7
<i>NSMCE2</i>	Seckel syndrome 10	2
<i>OCLN</i>	Pseudo-TORCH syndrome 1	6
<i>OFD1</i>	Orofaciodigital syndrome 1	7
<i>OSTM1</i>	Osteopetrosis, autosomal recessive 5	3
<i>PARS2</i>	Developmental and epileptic encephalopathy 75	3
<i>PCK1</i>	Phosphoenolpyruvate carboxykinase deficiency, cytosolic	6
<i>PEX1</i>	Heimler syndrome 1	6
	Peroxisome biogenesis disorder 1A	5
<i>PEX10</i>	Peroxisome biogenesis disorder 6A	1
	Peroxisome biogenesis disorder 6B	2
<i>PEX13</i>	Peroxisome biogenesis disorder 11A	3
	Peroxisome biogenesis disorder 11B	2
<i>PEX19</i>	Peroxisome biogenesis disorder 12A	1
<i>PEX6</i>	Peroxisome biogenesis disorder 4A	4
	Peroxisome biogenesis disorder 4B	4
	Heimler syndrome 2	4
<i>PGM1</i>	Congenital disorder of glycosylation 1T	17
<i>PHKA2</i>	Glycogen storage disease 9A	122
<i>PHKB</i>	Glycogen storage disease 9B	18
<i>PHKG2</i>	Glycogen storage disease 9C	44
<i>PIGM</i>	Glycosylphosphatidylinositol biosynthesis defect 1	2
<i>PKD1</i>	Polycystic kidney disease 1 with or without polycystic liver disease	109
<i>PKD2</i>	Polycystic kidney disease 2 with or without polycystic liver disease	14
<i>PKHD1</i>	Polycystic kidney disease 4, with or without polycystic liver disease	127

<i>PMM2</i>	Congenital disorder of glycosylation 1A	92
<i>PNPLA2</i>	Neutral lipid storage disease with myopathy	13
<i>POLD1</i>	Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome	7
<i>POLG</i>	Mitochondrial DNA depletion syndrome 4A	128
	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, 1	3
	Sensory ataxic neuropathy dysarthria and ophthalmoparesis	2
	Mitochondrial DNA depletion syndrome 4B	1
	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive, 1	1
<i>POLG2</i>	Mitochondrial DNA depletion syndrome 16, hepatic type	1
<i>POMC</i>	Obesity, early-onset, with adrenal insufficiency and red hair	2
<i>PPA2</i>	Sudden cardiac failure, infantile	6
	Sudden cardiac failure, alcohol-induced	4
<i>PPARG</i>	Lipodystrophy, familial partial, 3	15
<i>PPM1F</i>	Syndrome of sclerosing cholangitis, short stature, hypothyroidism, and abnormal tongue pigmentation	2
<i>PRKCSH</i>	Polycystic liver disease 1 with or without kidney cysts	41
<i>PSMB4</i>	Proteasome-associated autoinflammatory syndrome 3	5
<i>PSMB8</i>	Proteasome-associated autoinflammatory syndrome 1	7
<i>PTF1A</i>	Pancreatic agenesis 2	44
<i>PTRH2</i>	Neurologic, endocrine, and pancreatic disease, multisystem, infantile-onset 1	7
<i>PYGL</i>	Glycogen storage disease 6	58
<i>QRSL1</i>	Combined oxidative phosphorylation deficiency 40	2
<i>RBCK1</i>	Polyglucosan body myopathy 1 with or without immunodeficiency	4
<i>RINT1</i>	Infantile liver failure syndrome 3	3
<i>RMND1</i>	Combined oxidative phosphorylation deficiency 11	5
<i>RNASEH2A</i>	Aicardi-Goutieres syndrome 4	3
<i>RPL11</i>	Diamond-Blackfan anemia 7	18
<i>RPS7</i>	Diamond-Blackfan anemia 8	1
<i>SBDS</i>	Shwachman-Diamond syndrome 1	5
<i>SCO1</i>	Mitochondrial complex IV deficiency, nuclear type 4	2
<i>SCYL1</i>	Spinocerebellar ataxia, autosomal recessive, 21	16
<i>SEC63</i>	Polycystic liver disease 2 with or without kidney cysts	23
<i>SERAC1</i>	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	25
<i>SERPINA1</i>	Alpha-1-antitrypsin deficiency	57
<i>SFTPA2</i>	Interstitial lung disease 2	15
<i>SH2D1A</i>	Lymphoproliferative syndrome, X-linked, 1	5
<i>SKIV2L</i>	Trichohepatoenteric syndrome 2	36
<i>SLC22A5</i>	Systemic primary carnitine deficiency	37
<i>SLC25A13</i>	Cholestasis, neonatal intrahepatic, caused by citrin deficiency	157
	Citrullinemia 2	22
<i>SLC25A15</i>	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	42
<i>SLC25A20</i>	Carnitine-acylcarnitine translocase deficiency	13
<i>SLC30A10</i>	Hypermanganesemia with dystonia 1	44
<i>SLC37A4</i>	Glycogen storage disease 1B	43
	Congenital disorder of glycosylation 2W	8

<i>SLC44A1</i>	Neurodegeneration, childhood-onset, with ataxia, tremor, optic atrophy, and cognitive decline	5
<i>SLC51A</i>	Cholestasis, progressive familial intrahepatic, 6	4
<i>SLCO1B1</i>	Hyperbilirubinemia, Rotor type	11
<i>SLCO1B3</i>	Hyperbilirubinemia, Rotor type	11
<i>SMPD1</i>	Niemann-Pick disease A	5
	Niemann-Pick disease B	4
<i>SP110</i>	Hepatic venoocclusive disease with immunodeficiency	18
<i>STAT2</i>	Pseudo-TORCH syndrome 3	2
<i>STN1</i>	Cerebroretinal microangiopathy with calcifications and cysts 2	2
<i>STT3B</i>	Congenital disorder of glycosylation 1X	1
<i>TALDO1</i>	Transaldolase deficiency	18
<i>TARS2</i>	Combined oxidative phosphorylation deficiency 21	2
<i>TERC</i>	Aplastic anemia	8
	Dyskeratosis congenita, autosomal dominant, 1	6
<i>TERT</i>	Dyskeratosis congenita, autosomal dominant, 2	6
<i>TFAM</i>	Mitochondrial DNA depletion syndrome 15, hepatocerebral type	2
<i>TFR2</i>	Hemochromatosis 3	28
<i>TJP2</i>	Cholestasis, progressive familial intrahepatic, 4	31
	Hypercholanemia, familial, 1	11
<i>TKFC</i>	Triokinase and FMN cyclase deficiency syndrome	4
<i>TMEM165</i>	Congenital disorder of glycosylation 2K	5
<i>TMEM199</i>	Congenital disorder of glycosylation 2P	8
<i>TMEM67</i>	Joubert syndrome 6	39
	Meckel syndrome 3	19
	COACH syndrome 1	14
	Nephronophthisis 11	11
	Isolated congenital hepatic fibrosis	6
	RHYNS syndrome	1
<i>TNFRSF1A</i>	Periodic fever, familial, autosomal dominant	28
<i>TRAF3IP1</i>	Senior-Loken syndrome 9	8
<i>TRAPPC11</i>	Muscular dystrophy, limb-girdle, autosomal recessive 18	17
<i>TREX1</i>	Aicardi-Goutieres syndrome 1	14
	Vasculopathy, retinal, with cerebral leukoencephalopathy and systemic manifestations	2
<i>TRIM37</i>	Mulibrey nanism	21
<i>TRMT10C</i>	Combined oxidative phosphorylation deficiency 30	2
<i>TRMU</i>	Liver failure, infantile, transient	27
<i>TTC37</i>	Trichohepatoenteric syndrome 1	32
<i>UGT1A1</i>	Gilbert syndrome	15
	Crigler-Najjar syndrome 1	13
	Crigler-Najjar syndrome 2	13
	Transient familial neonatal hyperbilirubinemia	1
<i>UNC13D</i>	Hemophagocytic lymphohistiocytosis, familial, 3	15
<i>UQCRC2</i>	Mitochondrial complex III deficiency, nuclear 5	4
<i>UROD</i>	Familial porphyria cutanea tarda	9
	Hepatoerythropoietic porphyria	1
<i>USP18</i>	Pseudo-TORCH syndrome 2	5

<i>USP53</i>	Cholestasis, progressive familial intrahepatic, 7, with or without hearing loss	28
<i>VHL</i>	von Hippel-Lindau disease	12
<i>VIPAS39</i>	Arthrogryposis, renal dysfunction and cholestasis syndrome 2	1
<i>VPS33B</i>	Arthrogryposis, renal dysfunction and cholestasis syndrome 1	26
<i>WDR19</i>	Nephronophthisis 13	13
	Cranioectodermal dysplasia 4	2
	Short-rib thoracic dysplasia 5 with or without polydactyly	1
<i>WDR35</i>	Cranioectodermal dysplasia 2	14
<i>WDR83OS</i>	Syndrome of intractable itching, hypercholanemia, dysmorphism, and intellectual disability	3
<i>YARS2</i>	Myopathy with lactic acidosis and sideroblastic anemia 2	3
<i>YY1AP1</i>	Grange syndrome	3
<i>ZFYVE19</i>	Congenital hepatic fibrosis	11
<b>Total</b>		<b>7,572</b>

Supplemental Table 2. Hepatobiliary phenotypic features tabulated in the Liver Gene Database.

Category	Phenotypic Features
<b>Clinical Signs</b>	abdominal pain
	fevers
	nausea/vomiting
	hematemesis
	diarrhea
	steatorrhea
	melena/hematochezia
	constipation
	pale stools
	dark urine
	pruritus
	coagulopathy
	polydipsia
	polyuria
	fatigue/lethargy/weakness
	exercise intolerance
	anorexia/poor oral intake
	feeding intolerance
	encephalopathy/altered mental status
	acute/fulminant liver failure
	unspecified liver dysfunction
<b>Physical Exam</b>	hepatomegaly
	splenomegaly
	jaundice/icterus
	green jaundice
	green plasma
	excoriations
	abdominal distension
	ascites
	varices/variceal bleeding
	gastrointestinal hemorrhage
	edema
	pallor
	failure to thrive/growth retardation
	overgrowth
	caput medusae
	spider nevi
	palmar erythema
	telangiectasia
	gynecomastia
	petechiae/purpura/ecchymoses
	acanthosis nigricans
	xanthoma
	striae
	overweight/obesity

Labs	LFTs	weight loss
		tachypnea/dyspnea
		elevated transaminases
		low transaminases
		elevated alkaline phosphatase
		elevated GGT
		elevated serum bilirubin
		elevated serum bile acids
		elevated urine bile acids
		elevated LDH
		elevated BUN/hyperammonemia
	Synthetic	low total protein
		hypoalbuminemia
		hypogammaglobulinemia
		hypergammaglobulinemia
		elevated IgG
		elevated IgE
		elevated IgM
		elevated IgA
		low coagulation factor levels
		elevated coagulation factor levels
		low antithrombin III
		low protein C
		low protein S
		prolonged PT/elevated INR
		reduced PT
		prolonged PTT/aPTT
		low fibrinogen
		elevated fibrinogen
		hypoglycemia
		hypoketotic hypoglycemia
		low CSF glucose
		hyperglycemia/impaired glucose tolerance
		positive epinephrine tolerance test
		hyperinsulinemia
		elevated HbA1c
	Lipids	hypertriglyceridemia
		hypotriglyceridemia
		hypercholesterolemia
		hypocholesterolemia
		elevated free fatty acids
		elevated unsaturated fatty acids
		elevated branched-chain fatty acids
		elevated medium chain fatty acids
		elevated very long chain fatty acids
		low plasmalogen levels in fibroblasts
		VLCFA accumulation in fibroblasts
		lipid accumulation in fibroblasts

		abnormal phospholipid profile in fibroblasts
		low apoA-II
		low apoC-II
		low apoE
		low hepatic lipase activity
		elevated steatocrit
	<b>Blood</b>	anemia
		microcytosis
		macrocytosis
		hemolysis
		polycythemia/erythrocytosis
		leukopenia
		lymphopenia
		neutropenia
		neutrophilia
		low NK cells
		thrombocytopenia
		leukocytosis
		granulocytosis
		monocytosis
		lymphocytosis
		abnormal proportion of lymphocyte subtypes
		eosinophilia
		thrombocytosis
		enlarged platelets
		poikilocytosis
		elevated RDW/anisocytosis
		elevated erythropoietin
		low serum iron
		elevated serum iron
		elevated mobilizable iron
		low serum ferritin
		elevated serum ferritin
		low transferrin saturation
		elevated transferrin saturation/low transferrin
		low transferrin/TIBC
		elevated transferrin/TIBC
		low hepcidin
		polychromasia
		spherocytes
		schistocytes
		target cells
		Pelger-Huët anomaly
		basophilic stippling
		elevated erythrocyte porphyrin
		Howell-Jolly bodies
		shortened telomere length
		hypocalcemia

	<b>Electrolytes / Vitamins</b>	hypercalcemia
		hypomagnesemia
		hypophosphatemia
		hyperphosphaturia
		low vitamin A
		low folate
		elevated folate
		low CSF 5-methyl-THF
		low vitamin B12
		low vitamin D
		elevated vitamin D
		low vitamin E
		low vitamin K
		low zinc
		hypermanganesemia
		elevated urine manganese
	<b>Metabolic / Other</b>	ketosis
		ketonuria
		acidosis
		alkalosis
		elevated serum lactate
		elevated urine lactate/creatinine ratio
		low lactate/pyruvate ratio
		elevated lactate/pyruvate ratio
		elevated urine lactate/lactate derivatives
		elevated CSF lactate
		low serum leptin
		low serum adiponectin
		low serum amylase
		elevated serum amylase
		low serum lipase
		hypocortisolemia
		hypercortisolemia
		low serum cortisol
		low ACTH
		elevated ACTH
		elevated serum uric acid
		decreased serum uric acid
		elevated CK
		myoglobinuria
		low IGF-1
		elevated IGF-1
		elevated alpha-fetoprotein
		elevated unconjugated biliverdin
		elevated serum 3-oxo- $\Delta$ 4 bile acids
		elevated urine 3-oxo- $\Delta$ 4 bile acids
		elevated serum 3-beta-hydroxy- $\Delta$ 5 bile acids
		elevated urine 3-beta-hydroxy- $\Delta$ 5 bile acids

	elevated serum C27 bile acids
	elevated urine C27 bile acids
	low serum C24 bile acids
	elevated bile acid intermediates in fibroblasts
	elevated serum oxysterol
	elevated serum 7-ketocholesterol
	low CSF orexin
	elevated serum pipecolic acid
	elevated pancreatic secretory trypsin inhibitor
	low serum trypsin
	low fecal trypsin
	low fecal elastase
	elevated fecal fat content
	elevated fecal reducing substances
	elevated urine iron
	low total serum copper
	elevated free serum copper
	elevated relative exchangeable copper
	elevated total serum copper
	low serum ceruloplasmin
	elevated urine copper
	low urine copper
	elevated urine glucose/glucosuria
	elevated serum galactose
	elevated urine galactose/galactosuria
	elevated urine galactitol
	low serum galactose-1-phosphate
	elevated serum galactose-1-phosphate
	elevated serum arabitol
	elevated urine arabitol
	elevated CSF arabitol
	elevated serum ribitol
	elevated urine ribitol
	elevated CSF ribitol
	elevated serum erythritol
	elevated urine erythritol
	elevated CSF erythritol
	elevated urine 7-carbon sugars
	elevated urine oligosaccharides
	elevated serum aldolase
	elevated serum alanine
	elevated urine alanine
	elevated CSF alanine
	low serum phenylalanine
	elevated serum phenylalanine
	elevated serum pyruvic acid
	elevated urine pyruvic acid
	elevated CSF pyruvic acid

	elevated serum pristanic acid
	elevated serum phytanic acid
	low serum sialic acid
	low serum glycine
	elevated serum glycine
	elevated urine glycine
	elevated urine delta-aminolevulinic acid
	elevated urine porphyrin
	elevated urine coproporphyrin isomer I
	elevated serum argininosuccinate
	low serum citrulline
	elevated serum citrulline
	elevated urine homocitrulline
	low serum arginine
	elevated serum arginine
	elevated serum tyrosine
	elevated serum tyrosine metabolites
	low serum tyrosine
	elevated urine tyrosine
	elevated urine tyrosine derivatives
	elevated urine phenyl derivatives
	elevated serum citric acid cycle intermediates
	elevated urine citric acid cycle intermediates
	elevated serum branched chain alpha-ketoacids
	elevated urine branched chain alpha-ketoacids
	elevated urine ethylmalonic acid
	elevated urine methylcitric acid
	low serum succinylacetone
	elevated serum succinylacetone
	elevated urine succinylacetone
	elevated urine argininosuccinate
	elevated serum glutamine
	elevated urine glutamine
	low serum ornithine
	elevated serum ornithine
	elevated urine ornithine
	elevated urine orotic acid
	low serum aspartate
	low serum glutamate
	elevated serum glutamate
	elevated serum proline
	low serum threonine
	elevated serum threonine
	low serum leucine
	elevated serum leucine
	low serum isoleucine
	elevated serum isoleucine
	elevated serum alloisoleucine

	low serum lysine
	elevated serum lysine
	low serum valine
	elevated serum valine
	low serum methionine
	elevated serum methionine
	elevated serum S-adenosylmethionine
	elevated serum S-adenosylhomocysteine
	elevated serum homocysteine
	elevated urine homocysteine
	elevated serum methylmalonic acid
	elevated urine methylmalonic acid
	elevated free serum cystine
	elevated serum serine
	elevated urine adenosine
	low free carnitine
	low total carnitine
	elevated free carnitine
	elevated total carnitine
	elevated serum C2 carnitine
	elevated serum C3 carnitine
	elevated serum C6 carnitine
	elevated serum C8 carnitine
	elevated serum C14:1-carnitine
	low serum acylcarnitines
	elevated serum acylcarnitines
	elevated urine acylcarnitines
	elevated serum long-chain acylcarnitines
	elevated stool alpha-1-antitrypsin
	abnormal N-linked glycosylation
	abnormal O-linked glycosylation
	elevated plasma lysosomal enzyme activity
	decreased fibroblast lysosomal enzyme activity
	decreased leukocyte lysosomal enzyme activity
	elevated serum dicarboxylic acids
	elevated urine dicarboxylic acids
	elevated urine 3-epoxy-acids
	low alpha-oxidation activity
	low beta-oxidation activity
	elevated serum 3-methylglutaconic acid
	elevated urine 3-methylglutaconic acid
	elevated serum 3-methylglutaric acid
	elevated urine 3-methylglutaric acid
	elevated urine dicarbonic acids
	elevated urine glutaric acid
	elevated urine 2-hydroxybutyric acid
	elevated urine 2-hydroxyisobutyric acid
	elevated urine 3-hydroxybutyric acid

		elevated urine 2-hydroxyglutaric acid
		elevated urine 3-hydroxyglutaric acid
		elevated urine 2-oxoglutaric acid
		elevated urine isovaleric acid
		elevated urine 2-hydroxyisovaleric acid
		elevated urine 3-hydroxyvaleric acid
		elevated urine N-acyl glycines
		elevated urine isovalerylglutamic acid
		elevated urine adipic acid
		elevated urine 4-hydroxy-6-methyl-2-pyrone
		elevated urine sarcosine
		elevated unspecified urine organic acids
		elevated carbohydrate-deficient transferrin test
		low coenzyme Q10 levels
		elevated fibroblast growth factor 21
		decreased pyruvate dehydrogenase activity in fibroblasts
		decreased dihydroxyacetonephosphate acyltransferase activity in fibroblasts
		absent peroxisomes in fibroblasts
		temperature-sensitive fibroblasts
		abnormally processed peroxisomal thiolase
		abnormally processed acyl-CoA oxidase
		decreased citric acid cycle enzyme activity in fibroblasts
		respiratory complex deficiencies
		decreased phosphorylase kinase activity in erythrocytes
		elevated chitotriosidase levels
<b>Imaging / Diagnostics</b>		hepatomegaly
		small liver
		irregular liver outline
		splenomegaly
		cholelithiasis
		enlarged gallbladder
		small gallbladder
		gallbladder agenesis/hypoplasia
		diminished gallbladder contraction
		thickened gallbladder wall
		thin gallbladder wall
		cholestasis
		portal hypertension
		enlarged hepatic veins
		congenital portosystemic shunt
		common hepatic artery stenosis
		portal/hepatic vein thrombosis
		portal vein stenosis
		hepatic veno-occlusion
		Budd-Chiari syndrome
		bile duct dilatation
		intrahepatic bile duct irregularities

	extrahepatic bile duct irregularities
	biliary atresia
	ascites
	hepatic hyperechogenicity
	hepatic hypoechogenicity
	hepatic hypodensity
	high hepatic intensity
	low hepatic intensity
	hepatic heterogeneity/granularity
	hepatic steatosis
	hepatic calcifications
	dilated common hepatic artery
	intrahepatic hypervascularization
	hepatic AV malformation
	hepatic hematoma
	hepatic abscess
	chronic hepatitis
	cholangitis
	peritonitis
	hepatic cysts
	hepatic nodules
	hepatic hemangiomas
	solid liver masses
	elevated liver stiffness
	lack of hepatic visualization on cholescintigraphy
	prolonged liver visualization
	increased iron content
	increased plasma anionic compound retention
	delayed gallbladder filling
	cirrhosis/nodular regenerative hyperplasia
<b>Biopsy</b>	inflammation/hepatitis
	anisonucleosis
	double nuclei/multinuclei
	giant cell transformation/hepatitis
	cholestasis
	cholangitis
	steatosis
	fibrosis
	necrosis
	cirrhosis
	regenerative changes
	dysplastic/irregular nodules
	nodular regenerative hyperplasia
	portal tract expansion
	small portal vein radicles
	ductopenia/bile duct loss
	bile duct dilatation
	ductular reaction/proliferation

	disorganized bile ducts
	lobular disarray
	cellular swelling
	apoptosis/nuclear dissolution
	sinusoidal dilation/congestion
	hepatic veno-occlusion
	edema
	peliosis hepatis
	vacuolar lesions
	eosinophilic inclusions
	Mallory bodies
	Lafora bodies
	cholesterol clefts
	bile pigment deposition
	granular bile
	other pigment deposition
	glycogen deposition
	increased glycogen content
	decreased glycogen content
	lipofuscin deposition
	iron deposition
	increased iron content
	amyloid deposition
	copper deposition
	copper-binding protein deposition
	increased copper content
	deposition of unidentified material
	ductal plate malformation/DPM-like features
	dilation/proliferation of ER
	pleomorphic mitochondria
	increased amount of mitochondria
	increased mitochondrial matrix density
	lack of dense matrix granules in mitochondria
	reduced number of mitochondrial cristae
	swollen mitochondria
	abnormal mitochondrial cristae morphology
	low levels of mitochondrial DNA
	low levels of cytochrome-c-oxidase
	low fructose 1-phosphate aldolase activity
	low pyruvate dehydrogenase complex activity
	low alpha-ketoglutarate dehydrogenase activity
	low branched-chain alpha-ketoacid dehydrogenase activity
	low phosphorylase kinase activity
	low argininosuccinate synthetase activity
	absence of peroxisomes
	peroxisomal size heterogeneity
	foamy histiocytes
	granuloma formation

	PAS positivity
	aberrant CD34 sinusoidal stain
	Gaucher cells
	autofluorescence
	macroscopically dark liver
	extramedullary hematopoiesis
	cysts
	adenoma
	hyperplastic liver tumor
	hepatocellular carcinoma
	cholangiocarcinoma

Supplemental Table 3. Extrahepatic phenotypic features tabulated in the Liver Gene Database.

Category	Phenotypic Features
GI	enteropathy/intestinal pathology
	esophagitis
	megaesophagus
	gastritis
	intussusception
	aphthous ulcers
	hyperphagia
	gastroesophageal reflux
	pyloric stenosis
	celiac artery stenosis
	superior mesenteric artery stenosis
	splenic artery stenosis
	splenic artery aneurysm
	pneumoperitoneum
	diverticulosis/diverticulitis
	gastrointestinal obstruction
	bowel edema
	bowel perforation
	malrotation
	dysmotility
	meconium ileus
	necrotizing enterocolitis
	anal fissure/fistula
	fecal incontinence
	pancreatitis
	periduodenal pancreas
	pancreatic steatosis
	pancreatic insufficiency
	pancreatic cysts
	pancreatic dysplasia
	pancreatic fibrosis
	pancreatic atrophy/small pancreas
	pancreatic agenesis/hypoplasia
	pancreatic iron overload
	splenic cyst
	splenic rupture
	splenorenal shunt
	angiodysplasia
	cecal volvulus
	aganglionic colon
	GI neoplasm
	GI amyloidosis
Endocrine	diabetes
	hyperthyroidism
	hypothyroidism

	thyroid neoplasm
	parathyroid neoplasm
	menstrual/reproductive irregularities
	breast neoplasm
	precocious puberty
	delayed puberty
	hypogonadism
	hyperandrogenism/hirsutism
	adrenal hypoplasia
	adrenal insufficiency
	adrenal calcifications
	pheochromocytoma
	hypopituitarism
	hyperparathyroidism
	hypoparathyroidism
	gout
<b>Neuro / Ophtho / HEENT</b>	developmental delay/cognitive impairment
	memory impairment
	neurocognitive disorder
	brain abnormality on neuroimaging
	brain atrophy on pathology
	degeneration/neuronal loss on brain pathology
	spinal cord abnormality on neuroimaging
	cerebrospinal leukodystrophy
	CSF pleocytosis
	elevated CSF amino acids/protein
	elevated CSF immunoglobulins
	elevated CSF interferon-alpha
	ataxia
	dysmetria
	hydrocephalus
	seizure
	stroke/intracranial hemorrhage
	intracranial neoplasm
	syncope
	coma/impaired consciousness
	vertigo
	tremor/twitching
	chorea
	athetosis
	extrapyramidal symptoms
	unspecified movement disorder/involuntary movements
	areflexia/hyporeflexia
	hyperreflexia/clonus
	hypotonia
	hypertonia/dystonia
	sensory deficit/neglect
	minor motor deficit

	hemiplegia/paraplegia/quadruplegia
	hearing impairment/loss
	preauricular fistula
	nystagmus
	vision loss/blindness
	abnormal visual phenomena
	abnormal pupillary light response
	papilledema/pseudopapilledema
	cataracts
	retinal artery occlusion
	retinopathy/retinal dystrophy
	glaucoma
	optic nerve atrophy
	optic cup enlargement/optic nerve cupping
	keratopathy
	posterior embryotoxon
	myopia
	hyperopia
	ocular motility abnormality
	periorbital edema
	ptosis
	setting sun sign
	strabismus
	amblyopia
	astigmatism
	ectopia lentis
	ectropion
	coloboma/aniridia
	iridonesis
	Kayser-Fleischer rings
	chalazion
	alacrima/hypolacrima
	epistaxis
	peripheral neuropathy
	neuromyotonia
	oral leukoplakia
	oral hamartoma
	dental/gingival abnormalities
	bruxism
	speech abnormalities
	swallowing dysfunction
	laryngeal amyloid
Psych	psychomotor retardation
	mood symptoms
	anxiety disorder
	behavioral abnormalities
	psychosis
	schizophrenia

<b>Cardiac / Pulm</b>	cardiomegaly/hypertrophy/cardiomyopathy
	cardiorespiratory dysfunction
	cardiac murmur
	chest pain
	pericardial effusion
	pleural effusion
	pulmonary edema
	pulmonary hypertension
	pulmonary embolism
	pulmonary infiltrates
	pulmonary fibrosis
	interstitial lung disease
	restrictive lung disease
	obstructive lung disease
	pulmonary neoplasm
	upper airway dysfunction
	diaphragmatic eventration
	hypertension
	metabolic syndrome
	coronary artery disease
	cardiac valve abnormality/disease
	aortic root dilation/aneurysm
	aortic dissection
	abdominal aortic aneurysm
	extra-aortic aneurysm
	sleep apnea
	sleep disturbance
	asthma
	bronchiectasis
	extrahepatic AV/capillary malformation
	cardiac arrhythmia/dysrhythmia
	prolonged QT interval
	cardiac iron deposition
	cardiac amyloidosis
	increased angiotensin converting enzyme levels
<b>MSK</b>	macrocephaly
	microcephaly
	dysmorphism
	skull defect/abnormalities
	pectus excavatum
	pectus carinatum
	spine deformity
	hip deformity/abnormalities
	osteoporosis/osteopenia/fracture
	osteopetrosis
	bone tumor
	joint disease/pain/abnormalities/contractures
	calcific stippling

	rickets
	advanced bone age
	delayed bone age
	limb-length inequality
	skeletal bowing
	genu valgum
	genu varum
	small hands/feet
	enlarged hands/feet
	carpal tunnel
	digital clubbing
	pressure ulcers
	pes cavus
	pes planus
	delayed motor development/functional motor decline
	spasticity
	myopathy/myalgia
	myositis
	abnormal glycogen accumulation in muscle
	lipid accumulation in muscle
	hemihypertrophy
	muscle atrophy
	muscle hypertrophy
	prominent musculature
	recurrent hernias
	rhabdomyolysis
<b>Rheum</b>	positive antiphospholipid antibodies
	positive lupus anticoagulant
	positive anticardiolipin antibodies
	positive B2 glycoprotein antibodies
	positive ANA
	positive anti-dsDNA
	positive anti-Sm
	positive anti-RNP
	positive anti-SSA
	positive anti-centromere antibodies
	positive anti-mitochondrial antibodies
	positive ANCA
	positive anti-scl-70 antibodies
	positive antierythrocyte antibodies
	positive anti-smooth muscle antibodies
	positive anti-striated muscle antibodies
	positive anti-thyroperoxidase antibodies
	positive anti-gastrin antibodies
	systemic lupus erythematosus
<b>Immune / Blood</b>	precipitating/recurrent infections
	precipitating vaccination
	septic shock/sepsis

	lymphadenopathy
	myeloproliferation
	lymphoproliferation
	acid-fast bacilli on biopsy
	arterial/venous thrombosis
	hemangioma
	Jordans anomaly
	abnormal respiratory burst
	thymic hypoplasia/atrophy
	enlarged thymus
	abnormal B cell subset populations
	impairment in cellular immunity
	low complement
	elevated Fas ligand
	elevated IL-1beta
	elevated IL-2 receptor
	elevated IL-4
	elevated IL-5
	elevated IL-6
	elevated IL-8
	elevated IL-10
	elevated IL-12
	elevated IL-19
	elevated IFN-gamma
	elevated interferon-stimulated gene transcripts
	low soluble p55
	granuloma formation
	lipid accumulation in leukocytes
	hypocellular marrow
	hyperplastic marrow
	porphyria
	dyserythropoiesis in bone marrow
	disturbed myelopoiesis in bone marrow
	lymphopenia in bone marrow
	absent iron stores in bone marrow
	ringed sideroblasts in bone marrow
	erythroid hyperplasia in bone marrow
	low megakaryocytic content in bone marrow
	megakaryocyte clustering/hyperplasia in bone marrow
	lymphoid follicles in bone marrow
	sea-blue histiocytes in bone marrow/spleen
	lymphohistiocytosis/hemophagocytic syndrome
	granulomatosis in bone marrow
	dysplastic bone marrow
	myelofibrosis/bone marrow failure
	Evans syndrome
	macrophage activation syndrome
<b>GU</b>	renal calculi

	renal cysts
	renal neoplasm
	anuria
	aminoaciduria
	proteinuria
	hematuria
	nephropathy
	renal artery stenosis
	renal amyloidosis
	nephromegaly
	renal atrophy/small kidneys
	genitourinary anatomical abnormalities
	urologic dysfunction
	inguinal hernia
	enlarged ovaries
	ovarian cysts
	cryptorchidism
	enlarged external genitalia
	hypospadia
	erectile dysfunction
	testicular pain
	pelvic/gonadal amyloidosis
<b>Derm</b>	ichthyosis
	hyperkeratosis
	hypohidrosis
	erythrodermia
	xerosis
	erythema nodosum
	cutis laxa
	decreased skin elasticity
	thickened skin
	fragile skin
	cutis marmorata
	livedo reticularis
	livedo racemosa
	photosensitivity
	hypopigmentation/depigmentation
	hyperpigmentation
	skin neoplasm
	reticulate pigmentation
	nevus flammeus
	café-au-lait spots
	adermatoglyphia
	non-specific induration
	rash/skin lesion
	mottling
	milium
	eczema/dermatitis

	psoriasis
	cutaneous ulcers
	cutaneous vasculitis
	Raynaud phenomenon
	histiocytosis/histiocytoma
	Lafora bodies
	cyanosis
	chilblains/pernio
	vitiligo
	alopecia
	weak/woolly hair
	nail irregularities/dystrophy
	abnormal hair growth pattern
	albinism
	premature greying of hair
	red hair pigmentation
	prominent vasculature
	abnormal subcutaneous fat distribution
	abnormal fat distribution
	lack of subcutaneous fat
	lack of visceral fat
<b>Perinatal / Congenital</b>	intrauterine growth restriction/low birth weight
	hydrops fetalis
	polyhydramnios
	oligohydramnios/anhydramnios
	congenital heart disease
	pulmonary hypoplasia/congenital pulmonary abnormalities
	infantile respiratory distress
	esophageal atresia
	abdominal wall defect
	meconium plug
	anal atresia/stenosis
	neural tube defect
	congenital chylothorax
	congenital nephrotic syndrome
	clubfoot
	persistent primary vitreous artery
	delayed fontanelle closure
	aplasia cutis
	chromosomal abnormality
	asplenia
	accessory spleen
	situs inversus/heterotaxy
	sudden infant death syndrome
<b>Genetic</b>	somatic/second-hit mutation
<b>Extrinsic</b>	alcohol-induced symptoms
	antibiotic-induced symptoms
	acetaminophen-induced symptoms

	aspirin-induced symptoms/Reye or Reye-like syndrome
	fructose-induced symptoms
	valproic acid exposure
	other drug-induced symptoms