Original Article

Genetic background and clinical characteristics of infantile hyperammonemia

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Background: This study was conducted to analyze the genetic spectrum and clinical characteristics of infantile hyperammonemia.

Methods: Between January 2016 and June 2020, we retrospectively enrolled infantile hyperammonemia patients with definitive genetic diagnosis at the Children's Hospital of Fudan University. Based on the age of hyperammonemia onset, patients were grouped into neonatal and post-neonatal subgroups to compare their genetic and clinical features.

Results: Collectively, 136 pathogenic or likely pathogenic variants of the 33 genes were identified. Fourteen genes were reported with hyperammonemia (42%, 14/33), with *SLC25A13* and *MUT* being the top two detected genes. In contrast, 19 genes, which have not been previously reported with hyperammonemia, were detected (58%, 19/33), in which *JAG1* and *ABCC8* were the most frequently mutated genes. Compared with post-neonatal hyperammonemia, neonatal patients with hyperammonemia presented with higher rates of organic acidemia (P=0.001) and fatty acid oxidation disorder (P=0.006), but a lower rate of cholestasis (P<0.001). Patients with neonatal hyperammonemia had a higher ratio of peak plasma ammonia level ≥500 μmol/L (P=0.003) and were more likely to receive precision medicine (P=0.027); however, they had a refractory clinical course (P=0.001) and poorer prognosis than the infantile group.

Conclusions: There were significant differences in the genetic spectrum, clinical features, clinical course, and outcomes between infants with different hyperammonemia onset ages.

Keywords: Genetics; hyperammonemia; infants; neonates

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Introduction

Hyperammonemia (HA) refers to an increased blood ammonia level, which can cause irreversible damage to the central nervous system, especially in pediatric patients (1). Normal plasma ammonia levels in premature newborns, full-term newborns, infants, and children decrease with time, but their reference values have not been well defined thus far (2-4). In this study, we used plasma ammonia ≥100 μmol/L

as the diagnostic threshold for infantile HA.

HA is primarily caused by severe liver diseases, infections, and certain drugs. However, in children, especially infants, inborn errors of metabolism (IEM) play an important role in the development of HA (5-8). IEM is a heterogeneous group of disorders with complex clinical manifestations. Most patients with inherited HA exhibit non-specific symptoms, such as poor feeding, lethargy, dyspnea, or hypothermia, which rapidly progress to convulsions or coma; these general symptoms make it difficult to differentiate HA from conditions such as sepsis (9,10). The time window for clinical diagnosis is very short, and timely etiology-based therapy is critical. The diagnostic rate of IEM has improved with the use of mass spectrometry. However, the spectrum of diseases that can be detected by mass spectrometry is limited, and the detection results are affected by several factors such as patient condition and the treatment given, which may cause misdiagnosis and underdiagnosis (11).

Next-generation sequencing (NGS) is applicable to a wide spectrum of diseases, and the outcomes are generally not affected by atypical clinical manifestations and laboratory tests, which can be used for the early diagnosis of disease and indicate possible underlying genetic causes (12). NGS has been applied to the early diagnosis and precision therapy of many disorders, such as infantile epilepsy, neonatal metabolic acidosis, and neonatal hypernatremia (13-15). For infantile HA, precision treatment based on orphan drugs, liver stem cell transplantation, gene therapy, and prenatal treatment have been increasingly reported (16-21). All of those previous studies were based on the application of genetic analysis to diagnosis, and NGS was the key diagnostic method used (21).

The known genetic causes of infantile HA mainly include urea cycle disorder (UCD), organic acidemia (OA), and fatty acid oxidation disorder (FAOD) (6-8,22,23). A wide range of genes have been identified and reported in the human phenotype ontology associated with infantile HA (24-26). However, in clinical practice, the status of several other genes, such as *ABCC8* (27) and *GALT* (28,29), in HA remains unknown. In the present study, we conducted a retrospective analysis of a cohort with genetically confirmed diagnosis of infantile HA to expand its genetic background. To the best of our knowledge, this is the most comprehensive study to determine the genetic background of infantile HA. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-359/rc).

Highlight box

Key findings

- There were significant differences in the genetic spectrum, clinical features, clinical course, and outcomes between infants with different hyperammonemia onset ages.

What is known and what is new?

- Urea cycle defects, organic acidemia, and fatty acid oxidation disorders are the most common inborn errors of metabolism associated with hyperammonemia.
- Genetic spectrum, clinical features, clinical course, and outcomes vary with age of infantile hyperammonemia onset.
- Genetic features underlying cholestasis may be associated with hyperammonemia.

What is the implication, and what should change now?

- Further studies regarding the genetic profile and related metabolic pathways of HA should be carried out.
- Early NGS analysis is needed if HA is suspected.

Methods

Study population

We enrolled infants diagnosed with HA at the Children's Hospital of Fudan University from January 2016 to June 2020. The inclusion criteria were as follows: (I) HA onset before 1 year of age, (II) plasma ammonia level ≥100 μmol/L as indicated by more than two tests during the same hospital stay, and (III) genetic diagnosis using NGS. The exclusion criteria were as follows: (I) liver failure secondary to severe infection, respiratory failure or graft-versus-host disease, severe gastrointestinal bleeding, long-term total parenteral nutrition, and history of valproate use; (II) maternal autoimmune conditions; and (III) failure to obtain informed consent from the parents. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University (No. 2015-130). Written informed consent was obtained from patients' parents or legal guardians.

Clinical subgroup classification

Clinical information was obtained from the medical record system. The clinical course of each case was classified

as follows: (I) refractory, the last blood ammonia level during one hospital stay ≥100 μmol/L after treatment; (II) controllable, the last blood ammonia level during one hospital stay <100 μmol/L after treatment; and (III) self-limiting, the last blood ammonia level during one hospital stay <100 μmol/L without treatment. Follow-up information was extracted from the outpatient medical record system, and cases with missing follow-up information were followed up via telephone.

NGS

Genomic DNA was extracted from the blood samples of patients using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and enriched using the Agilent (Santa Clara, CA, USA) ClearSeq Inherited Disease panel kit for 2,742 gene sequencing or the Agilent SureSelect XT Human All Exon V5 for clinical exome sequencing. NGS was performed using the Illumina HiSeq2000/2500 platform. The identified variants were classified based on the American College of Medical Genetics (ACMG) guidelines (30). The detected causal variants were confirmed by performing Sanger sequencing on a Biosystems 3500 DNA Analyzer and analyzed using Mutation Surveyor V4.0.9. More details are available in our previous studies (15,31).

Statistical analysis

The data were analyzed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables with non-normal variables are reported as median [interquartile range (IQR)]. Categorical variables are presented as frequencies and percentages. The chi-square test or Fisher's exact test was used for comparison. Significance was set at $P<0.05$.

Results

Study population

We enrolled 85 infants with hyperammonemia who had a definite genetic diagnosis. The median age of onset was 54 days (IQR, 10–114 days). The study included 54 male (64%, 54/85) and 31 female (36%, 31/85) patients who were divided into two subgroups according to age of onset: neonate group (32 cases, 38%) and infant group (53 cases, 62%). The dominant phenotypes (a patient may have had more than one clinical phenotype) were neurological abnormality (31%), glucose metabolism disturbance (26%), metabolic acidosis (24%), respiratory failure (15%), and electrolyte disturbance (14%) (*Table 1*).

Genetic spectrum of infantile HA

Collectively, 136 pathogenic or likely pathogenic (P/LP) variants were identified in 33 genes, with 110 reported variants and 26 novel variants (Table S1). Of the genes identified, fourteen have been associated to HA (42%, 14/33), with *SLC25A13* and *MUT* being the top two detected genes (22%, 18/85). Nineteen genes, which have not been previously reported with HA, were detected in this study (58%, 19/33), of which *JAG1* and *ABCC8* were the most frequently mutated genes (16%, 14/85).

Recurrent conditions included cholestasis (55%, 47/85), OA (14%, 12/85), UCD (7%, 6/85), and FAOD (6%, 5/85), with *SLC25A13*, *MUT*, *CPS1*, and *SLC25A20* being the most frequently detected genes in each classification, respectively.

Genetic features of infantile HA depending on onset age

Subgroups with different ages of onset showed different conditions. The proportions of OA ($P=0.001$), FAOD ($P=0.006$), and cholestasis ($P<0.001$) showed significant differences between the two subgroups (*Table 1*). *MUT* (19%, 6/32) was the most frequently detected gene in the neonatal group, whereas in the post-neonatal group, the most frequently mutated gene was *SLC25A13* (21%, 11/53).

In cases of refractory HA (21%, 18/85), all mutated genes in the neonatal group were reported with HA, with *MUT* being the most frequently identified gene (*Figure 1*). In the post-neonatal group, mutated *ABCB11*, *CYP7B1*, and *MPV17*, which have not been previously reported with the HA phenotype, were associated with refractory HA; and all these cases presented with primary liver failure.

In controllable or self-limiting HA cases (79%, 67/85), mutations in *SLC25A13*, *JAG1*, and *ABCC8* were detected in more than five cases, accounting for 37% (25/67) of all cases. Mutated *SLC25A13* and most mutated *JAG1* (7/8) were detected in the infantile group, and all cases presented a cholestatic phenotype. In the neonatal group, *ABCC8* was the most frequently mutated gene, and all cases presented with hypoglycemia and mild to moderate elevation of liver enzymes. Notably, mutated *JAG1* and *ABCC8* with the hypoglycemic phenotype have not been previously reported with HA.

Table 1 Comparison of metabolic condition spectrum and clinical features of infantile hyperammonemia with different ages of onset

Clinical features	Total, N=85, n [%]	Neonatal, N=32, n [%]	<1 year, N=53, n [%]	P value
Metabolic condition spectrum				
OA	12 [14]	10 [31]	2 [4]	0.001
FAOD	5 [6]	5 [16]	0 [0]	0.006
UCD	6 [7]	4 [13]	2 [4]	0.416
Cholestasis	47 [55]	6 [19]	41 [77]	<0.001
Clinical features				
Peak NH_3 ≥500 μmol/L	9 [11]	8 [25]	1 [2]	0.003
Neurologic abnormality	26 [31]	21 [66]	5 [9]	<0.001
Respiratory failure	13 [15]	11 [34]	2 [4]	<0.001
Circulatory failure	6 [7]	4 [13]	2 [4]	0.192
Hepatic failure	7 [8]	0 [0]	7 [13]	0.042
Severe infection	8 [9]	5 [16]	3 [6]	0.146
Malformation	9 [11]	4 [13]	5 [9]	0.935
Metabolic acidosis	20 [24]	14 [44]	6 [11]	0.001
Hyperlactacidemia	6 [7]	3 [9]	3 [6]	0.668
Glucose metabolic disturbance	22 [26]	13 [41]	9 [17]	0.016
Electrolyte disturbance	12 [14]	9 [28]	3 [6]	0.010
Treatment				
Arginine	31 [36]	16 [50]	15 [28]	0.051
CRRT	2 [2]	2 [6]	0 [0]	0.133
Precision medicine	30 [35]	16 [50]	14 [26]	0.027
Clinical course of HA				
Self-limited	23 [27]	5 [16]	18 [34]	0.065
Controllable	44 [52]	14 [44]	30 [57]	0.251
Refractory	18 [21]	13 [41]	5 [9]	0.001
Clinical outcomes				
Improved	56 [66]	12 [38]	44 [83]	<0.001
Withdrew treatment	22 [26]	15 [47]	7 [13]	0.001
Died	7 [8]	5 [16]	2 [4]	0.098

OA, organic acidemia; FAOD, fatty acid oxidation disorder; UCD, urea cycle disorder; CRRT, continuous renal replacement therapy; Precision medicine refers to special formula or diet, drugs and liver transplantation; HA, hyperammonemia.

Clinical characteristics of inherited HA according to the age of onset

To investigate the characteristics of inherited HA according to the age of onset, we compared the clinical phenotypes of the neonatal and infantile groups. We found significant differences in the clinical features, clinical course, and outcomes between the two subgroups.

In the neonatal subgroup, 25% cases (8/32) presented with a peak plasma ammonia level ≥500 μmol/L, compared to 2% cases in the infantile group (1/53, P=0.003). Neonatal

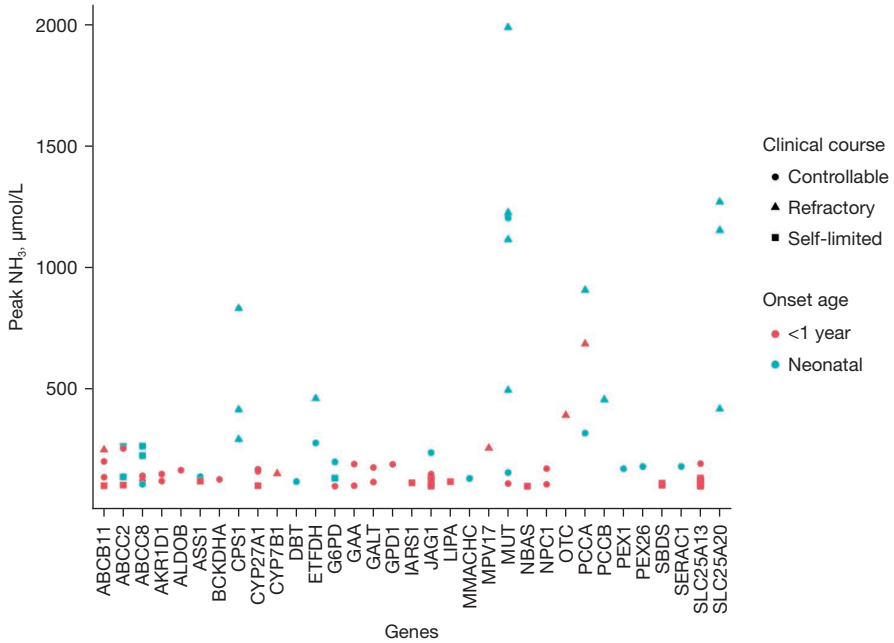

Figure 1 Genetic background and distribution of peak plasma ammonia level in subgroups with different onset age; neonatal hyperammonemia (denoted by blue) and patients with hyperammonemia onset before one year old (denoted by red). Circles, triangles, and squares represent controllable, refractory, and self-limiting clinical courses, respectively (R software 4.0.1 was used to create the artwork).

patients with HA showed higher rates of neurological abnormalities (P<0.001), respiratory failure (P<0.001), metabolic acidosis (P=0.001), glucose metabolism disturbance (P=0.016), and electrolyte disturbances (P=0.010) than infantile patients (*Table 1*). Infants with HA were more likely to present with hepatic failure than neonates (P=0.042).

In our study, 35% (30/85) patients received precision medicine, including special formula or diet, drugs and liver transplantation (details in Table S1). There is no significant statistical difference between neonatal group (16/32, 50%) and infant group (14/53, 26%, P=0.027).

Among the neonatal subgroup, 41% patients (13/32) presented with a refractory clinical course, compared to just 9% patients in the infant group (5/53, P=0.001). Clinical outcomes in the infant group were generally better than those in the neonatal group, with 83% patients showing improvement (44/53) and only 13% patients (7/53) withdrawing the treatment in consideration of the poor prognosis. In contrast, in the neonatal group, only 38% (12/32) patients had good prognoses (P<0.001), and 47% (15/32) patients withdrew from the treatment (P=0.001) given the poor prognosis.

Discussion

We observed a significantly different genetic spectrum between patients with neonatal and post-neonatal HA. In our cohort, the genetic spectrum of neonatal HA mainly included OA, FAOD, and UCD, while the proportion of these disorders was lower in the post-neonatal subgroup, which is consistent with the etiological profile reported previously (6-8,22,23). Defects in the function of any enzyme or carrier involved in the urea cycle can cause primary HA. HA caused by OA and FAOD is secondary to the functional inhibition of enzymes involved in the urea cycle by their metabolites and the reduction in substrates required for urea synthesis (5). We speculate that this difference in the genetic spectrum between subgroups based on the age of onset is because the severity of most cases of UCD, OA, and FAOD is related to the degree of enzyme-related defects in the corresponding metabolic pathways (32). Patients with reduced enzyme activity may have an earlier onset of the disease, exhibit more severe clinical presentations (higher plasma ammonia level), and may not survive the neonatal period. In other words, patients with UCD, OA, or FAOD onset after 1 month of

age may exhibit lower ammonia levels, and therefore, were not included in our cohort. This also explains why patients in the neonatal subgroup showed higher rates of a refractory clinical course and poor prognosis. Furthermore, there are relatively few UCD patients in our study, the reason may be that UCD patients died too quickly to be included in this study.

In this study, hereditary liver disease was the main genetic cause of HA onset before one year of age. Neonatal-onset type II citrullinemia (MIM 605814, *SLC25A13*) (neonatal intrahepatic cholestasis caused by citrin deficiency, NICCD) is the most common hereditary liver disease in this study. NICCD is known to cause mild, self-limiting HA. NICCD pathogenesis involves citrin deficiency caused by the pathogenic variants of *SLC25A13*, which leads to the insufficient transfer of aspartic acid into the cytoplasm and affects its utilization for urea cycle substrate synthesis (10). Other cholestasis-related genes, such as *JAG1*, *ABCC2*, and *ABCB11*, have not been reported to cause HA phenotype. In our study, most patients with cholestasis did not show significantly elevated transaminase levels, suggesting that in patients presenting with HA along with cholestasis, the phenotype may be related to cholestasis itself.

Pathogenic variants of *ABCC8* were frequently observed in our cohort (7%, 6/85). Neonatal diabetes caused by *ABCC8* defects may be associated with HA phenotype (27). The authors speculated that elevated serum leucine and glutamic acid levels during ketoacidosis promote the oxidative deamination of glutamic acid to increase blood ammonia levels. However, in our study, the six patients with *ABCC8* defects presented with hyperinsulinemia rather than diabetes. Therefore, *ABCC8*-specific pathogenesis must be clarified further. HA can present with hyperinsulinism/hyperammonemia syndrome (MIM 606762, *GLUD1*), wherein an excessive increase in the activity of *GLUD1*-encoded glutamate dehydrogenase (GDH) increases glutamate oxidative deamination and glutamate consumption, which leads to a reduction in N-acetylglutamate (NAG), the activator of the urea cycle rate-limiting enzyme, thus indirectly affecting urea synthesis (33). GDH overactivity can increase the ATP/ADP ratio in islet cells, thereby closing the K^+-ATP channel, depolarizing the cell membrane, and opening the calcium channel, leading to insulin release. Variants of *ABCC8* cause abnormalities in the K^+-ATP channel in islet cells (34), which may be associated with GDH activity to some extent.

Two patients in our cohort had galactosemia (MIM 230400, *GALT*). Although one patient had liver failure, the HA was controllable. In a previous case report of galactosemia, a neonatal patient with mildly elevated transaminase levels developed transient HA. The authors speculated that this may be due to the toxic effects of galactose on hepatocytes (28). In a phenotype-genotype analysis of five patients with galactosemia, one patient with HA carried the c. 687 G >A variant as one of the patients in the cohort of our present study (29). This perhaps suggests a correlation between this *GALT* variant and HA; however, further studies are needed.

We also observed HA in three children with hemolytic anemia and G6PD deficiency (favism) (MIM 300908, *G6PD*), including one with cholestasis, one with severe infection, and another with bilirubin encephalopathy. Since patients exhibiting severe hemolysis (such as severe fracture and trauma) may present with HA (10), HA in patients with G6PD deficiency may be related to severe hemolysis.

This study expanded the spectrum of pathogenic variants associated with infantile HA and enriched its possible genetic background. However, this study has certain limitations. First, we must admit that our definitions of clinical subgroup classification may have some potential conflicts. Second, NGS cannot detect all pathogenic variants, and thus, its use in a clinical setting may lead to underdiagnosis. Third, we did not elucidate the mechanism underlying the correlation between the variants detected in this study and HA; hence, further research is needed to fully understand this relationship. Finally, this was a retrospective single-center study with few participants and limited phenotypic data, which may result in bias. Therefore, a prospective multi-center study including more participants should be carried out in the future.

Conclusions

In this study, we performed NGS to reveal the genetic background and clinical characteristics of infantile HA. In clinical practice, when IEM is considered, blood ammonia should be routinely tested. We recommend early NGS analysis if HA is suspected. Based on the toxic effects of various metabolic products on hepatocytes and the extensive linkages between various metabolic pathways, the genetic profile and related metabolic pathways of HA deserve further study.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-359/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-359/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-359/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study involving human participants was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University (No. 2015-130). Written informed consent was obtained from patients' parents or legal guardians.

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Table S1 Genetic spectrum of the 85 enrolled infantile hyperammonemia patients

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_type	Clinvar_type	Classification of variant	Precision treatment
1	post-neonatal	M	SLC25A13	193	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Maternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
1	post-neonatal	M	SLC25A13	193	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon5:c.457_459delinsG(p.Q153Vfs*21)	Paternal	.	.	.	P	
2	post-neonatal	F	SLC25A13	134	Hom	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon6:c.615+5G>A	Paternal	PMID 14680984. SEE HGMD DISEASE: Hepatitis, idiopathic neonatal. SEE HGMD COMMENT: aka Mutation [X]/p.A206fs212X.;	DM	Pathogenic/Likely_pathogenic	LP	
2	post-neonatal	F	SLC25A13	134	Hom	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon6:c.615+5G>A	Maternal	PMID 14680984. SEE HGMD DISEASE: Hepatitis, idiopathic neonatal. SEE HGMD COMMENT: aka Mutation [X]/p.A206fs212X.;	DM	Pathogenic/Likely_pathogenic	LP	
3	post-neonatal	M	SLC25A13	130	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon16:c.1661insGAGATTACAGGTGGCTGCCCGGGC (p.A554Gfs*17)	-	.	.	Pathogenic	P	
3	post-neonatal	M	SLC25A13	130	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	-	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
4	post-neonatal	M	SLC25A13	128	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Paternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: aka c.851del4 p.R284fs286X/Mutation [I].;	DM	Pathogenic	P	
4	post-neonatal	M	SLC25A13	128	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	IVS16ins3kb	Maternal	PMID 15542392	DM	Pathogenic	LP	
5	post-neonatal	F	SLC25A13	124	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Paternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
5	post-neonatal	F	SLC25A13	124	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon6:c.615+5G>A	Maternal	PMID 14680984. SEE HGMD DISEASE: Hepatitis, idiopathic neonatal. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	LP	
6	post-neonatal	F	SLC25A13	120	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Maternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
6	post-neonatal	F	SLC25A13	120	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon11:c.1064G>A(p.R355Q)	Paternal	PMID 24586645. SEE HGMD DISEASE: Intrahepatic cholestasis, neonatal. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	
7	post-neonatal	F	SLC25A13	110	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Maternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
7	post-neonatal	F	SLC25A13	110	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	IVS16ins3kb	Paternal	PMID 15542392	DM	Pathogenic	LP	
8	post-neonatal	M	SLC25A13	107	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_855delTATG(p.M285PfsTer2)	Paternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
8	post-neonatal	M	SLC25A13	107	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon6:c.615+5G>A	Maternal	PMID 14680984. SEE HGMD DISEASE: Hepatitis, idiopathic neonatal. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	LP	
9	post-neonatal	M	SLC25A13	107	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_855delTATG(p.M285PfsTer2)	-	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
9	post-neonatal	M	SLC25A13	107	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon1:c.15G>A(p.K5K)	-	PMID 18392553. SEE HGMD DISEASE: Citrin deficiency. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	
10	post-neonatal	F	SLC25A13	104	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon14:c.1399C>T(p.R467X)	Paternal	PMID 20376801. SEE HGMD DISEASE: Intrahepatic cholestasis, neonatal. SEE HGMD COMMENT: ;	DM	.	P	
10	post-neonatal	F	SLC25A13	104	Het	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Maternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: ;	DM	Pathogenic	P	

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_ type	Clinvar_type	Classification of variant	Precision treatment
11	post-neonatal	F	SLC25A13	100	Hom	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Maternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: aka c.851del4 p.R284fs286X/Mutation [I].;	DM	Pathogenic	P	
11	post-neonatal	F	SLC25A13	100	Hom	AR	Citrullinemia, adult-onset type II, [MIM:603471]; Citrullinemia, type II, neonatal-onset, [MIM:605814]	7	NM_014251:exon9:c.852_856delinsA(p.M285Pfs*2)	Paternal	PMID 10369257. SEE HGMD DISEASE: Citrullinaemia, adult onset, type II. SEE HGMD COMMENT: aka c.851del4 p.R284fs286X/Mutation [I].;	DM	Pathogenic	P	
12	neonatal	M	MUT	1988	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon4:c.787G>A(p.G263R)	Maternal	.	.	.	VUS	L-carnitine
12	neonatal	M	MUT	1988	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon3:c.627insCT(p.K210*)	Paternal	PMID 26454439. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	.	P	L-carnitine
13	neonatal	F	MUT	1226	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon2:c.289insAC(p.P97Tfs*7)	Paternal	.	.	.	P	
13	neonatal	F	MUT	1226	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255: exon6:c.1159A>C (p.T387P)	Maternal	.	.	.	LP	
14	neonatal	M	MUT	1204	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon9:c.1675A>G(p.R559G)	Paternal	.	.	.	VUS	L-carnitine, special formula
14	neonatal	M	MUT	1204	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon10:c.1677-1G>A	Maternal	PMID 16281286. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Pathogenic	P	L-carnitine, special formula
15	neonatal	F	MUT	1115	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon3:c.730insTTG(p.D244Lfs*39)	Paternal	PMID 16281286. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Pathogenic	P	L-carnitine
15	neonatal	F	MUT	1115	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon10:c.1679G>A(p.C560Y)	Maternal	PMID 16435223. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	L-carnitine
16	neonatal	M	MUT	495	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon6:c.1106G>A(p.R369H)	-	PMID 9285782. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	L-carnitine, special formula, liver transplantation
16	neonatal	M	MUT	495	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon5:c.914T>C(p.L305S)	-	PMID 16281286. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Likely_pathogenic	LP	L-carnitine, special formula, liver transplantation
17	neonatal	M	MUT	156	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon6:c.1243G>A(p.E415K)	-	.	.	.	VUS	L-carnitine, special formula
17	neonatal	M	MUT	156	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon4:c.756insAC(p.H252Qfs*6)	-	PMID 23430940. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	.	P	L-carnitine, special formula
18	post-neonatal	M	MUT	111	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:c.1677-1G>A	-	PMID 16281286. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Pathogenic	P	special formula
18	post-neonatal	M	MUT	111	Het	AR	Methylmalonic aciduria, mut(0) type, [MIM:251000]	6	NM_000255:exon3:c.730insTTG(p.D244Lfs*39)	-	PMID 16281286. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Pathogenic	P	special formula
19	neonatal	M	CPS1	832	Het	AR	Carbamoylphosphate synthetase I deficiency, [MIM:237300]	2	NM_001875:exon20:c.2440C>T(p.R814W)	De novo	PMID 21120950. SEE HGMD DISEASE: Carbamoyl phosphate synthetase I deficiency. SEE HGMD COMMENT: ;	DM	Uncertain_significance	P	
19	neonatal	M	CPS1	832	Het	AR	Carbamoylphosphate synthetase I deficiency, [MIM:237300]	2	NM_001875:exon37:c.4316insCCAA(p.N1442_ T1443insN)	Maternal	NoDM CM114390 related	DM	.	VUS	
20	neonatal	M	CPS1	415	Het	AR	Carbamoylphosphate synthetase I deficiency, [MIM:237300]	2	NM_001875:exon14:c.1412C>A(p.T471N)	-	PMID 20578160. SEE HGMD DISEASE: Carbamoyl phosphate synthetase I deficiency. SEE HGMD COMMENT: ;	DM	.	LP	citrulline, L-carnitine
20	neonatal	M	CPS1	415	Het	AR	Carbamoylphosphate synthetase I deficiency, [MIM:237300]	2	NM_001875:exon11:c.1145C>T(p.P382L)	-	PMID 21120950. SEE HGMD DISEASE: Carbamoyl phosphate synthetase I deficiency. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	citrulline, L-carnitine
21	neonatal	F	CPS1	293	Het	AR	Carbamoylphosphate synthetase I deficiency, [MIM:237300]	2	NM_001875:exon17:c.1981G>A(p.G661S)	-	NoDM CM120167 related	DM	.	LP	citrulline, L-carnitine
21	neonatal	F	CPS1	293	Het	AR	Carbamoylphosphate synthetase I deficiency, [MIM:237300]	2	NM_001875:exon11:c.1145C>T(p.P382L)	-	PMID 21120950. SEE HGMD DISEASE: Carbamoyl phosphate synthetase I deficiency. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	citrulline, L-carnitine

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_ type	Clinvar_type	Classification of variant	Precision treatment
22	neonatal	F	PCCA	907	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:exon13:c.1146insCA(p.R383Kfs*6)	-	.	.	.	P	liver transplantation
22	neonatal	F	PCCA	907	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:exon2:c.127C>T(p.Q43X)	-	NoDM CD190468 related	DM	.	P	liver transplantation
22	neonatal	F	PCCA	907	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:exon19:c.1676G>T(p.W559L)	-	PMID 10518292. SEE HGMD DISEASE: Propionic acidaemia. SEE HGMD COMMENT: ;	DM	Conflicting:Benign(2)%3BLikely_benign(1)%3BPathogenic(1)%3BUncertain_ significance(1)	LP	liver transplantation
23	post-neonatal	F	PCCA	686	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:c.1845+1G>A	Paternal	.	.	Pathogenic	P	
23	post-neonatal	F	PCCA	686	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:exon6:c.442_443delinsG(p.N149Tfs*35)	Maternal	PMID 30274917. SEE HGMD DISEASE: Propionic acidaemia. SEE HGMD COMMENT: ;	DM	.	P	
24	neonatal	M	PCCA	318	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:exon3:c.231+1G>A	-	NoDM CS066305 related	DM	Pathogenic	P	special formula
24	neonatal	M	PCCA	318	Het	AR	Propionicacidemia, [MIM:606054]	13	NM_000282:exon7:c.596T>A(p.V199D)	-	.	.	.	VUS	special formula
25	neonatal	M	SLC25A20	1270	Het	AR	Carnitine-acylcarnitine translocase deficiency, [MIM:212138]	3	NM_000387:exon3:c.270delC	Maternal	PMID 11592821. SEE HGMD DISEASE: Carnitine-acylcarnitine carrier deficiency. SEE HGMD COMMENT: ;	DM	.	P	L-carnitine
25	neonatal	M	SLC25A20	1270	Het	AR	Carnitine-acylcarnitine translocase deficiency, [MIM:212138]	3	NM_000387:intron2:c.199-10T>C	Paternal	PMID 10697964. SEE HGMD DISEASE: Carnitine-acylcarnitine carrier deficiency. SEE HGMD COMMENT: DM 1. NULL;	DM	Pathogenic	LP	L-carnitine
26	neonatal	M	SLC25A20	1153	Het	AR	Carnitine-acylcarnitine translocase deficiency, [MIM:212138]	3	NM_000387:exon3:c.270delC	Maternal	PMID 11592821. SEE HGMD DISEASE: Carnitine-acylcarnitine carrier deficiency. SEE HGMD COMMENT: ;	DM	.	P	L-carnitine
26	neonatal	M	SLC25A20	1153	Het	AR	Carnitine-acylcarnitine translocase deficiency, [MIM:212138]	3	NM_000387:intron2:c.199-10T>C	Paternal	PMID 10697964. SEE HGMD DISEASE: Carnitine-acylcarnitine carrier deficiency. SEE HGMD COMMENT: DM 1. NULL;	DM	Pathogenic	LP	L-carnitine
27	neonatal	M	SLC25A20	418	Het	AR	Carnitine-acylcarnitine translocase deficiency, [MIM:212138]	3	NM_000387:exon6:c.550G>T(p.G184X)	Maternal	PMID 31965297. SEE HGMD DISEASE: Carnitine-acylcarnitine translocase deficiency. SEE HGMD COMMENT: Suppl. *Table 3*.;	DM	.	P	
27	neonatal	M	SLC25A20	418	Het	AR	Carnitine-acylcarnitine translocase deficiency, [MIM:212138]	3	NM_000387:exon3:c.199-10T>G	Paternal	PMID 10697964. SEE HGMD DISEASE: Carnitine-acylcarnitine carrier deficiency. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	
28	neonatal	F	ASS1	139	Het	AR	Citrullinemia, [MIM:215700]	9	NM_000050:exon6:c.379C>T(p.R127W)	-	PMID 19006241. SEE HGMD DISEASE: Citrullinaemia. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	
28	neonatal	F	ASS1	139	Het	AR	Citrullinemia, [MIM:215700]	9	NM_000050:exon15:c.1168G>A(p.G390R)	-	PMID 2358466. SEE HGMD DISEASE: Citrullinaemia. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	LP	
29	post-neonatal	F	ASS1	121	Het	AR	Citrullinemia, [MIM:215700]	9	NM_000050:exon6:c.379C>T(p.R127W)	-	PMID 19006241. SEE HGMD DISEASE: Citrullinaemia. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	
29	post-neonatal	F	ASS1	121	Het	AR	Citrullinemia, [MIM:215700]	9	NM_000050:exon15:c.1168G>A(p.G390R)	-	PMID 2358466. SEE HGMD DISEASE: Citrullinaemia. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	LP	
30	neonatal	F	ETFDH	461	Het	AR	Glutaric acidemia IIC, [MIM:231680]	4	NM_004453:exon9:c.1109G>T(p.G370V)	Maternal	.	.	.	VUS	
30	neonatal	F	ETFDH	461	Het	AR	Glutaric acidemia IIC, [MIM:231680]	4	NM_004453:exon2:c.99G>A(p.W33X)	Paternal	.	.	.	P	
31	neonatal	F	ETFDH	278	Hom	AR	Glutaric acidemia IIC, [MIM:231680]	4	NM_004453.3(ETFDH):c.1586A>G(p.H529R)	-	PMID 24522293. SEE HGMD DISEASE: Acyl-CoA dehydrogenation deficiency, riboflavin-responsive. SEE HGMD COMMENT: ;	DM	.	LP	L-carnitine, vitamin B2, high-glycemic and low-fat diet
31	neonatal	F	ETFDH	278	Hom	AR	Glutaric acidemia IIC, [MIM:231680]	4	NM_004453.3(ETFDH):c.1586A>G(p.H529R)	-	PMID 24522293. SEE HGMD DISEASE: Acyl-CoA dehydrogenation deficiency, riboflavin-responsive. SEE HGMD COMMENT: ;	DM		LP	L-carnitine, vitamin B3, high-glycemic and low-fat diet

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_ type	Clinvar_type	Classification of variant	Precision treatment
32	post-neonatal	F	NBAS	100	Het	AR	Infantile liver failure syndrome 2, [MIM:616483]; Short stature, optic nerve atrophy, and Pelger-Huet anomaly, [MIM:614800]	2	NM_015909:exon30:c.3436insCAGTG(p.A1146Qfs*14)	Paternal	.	.	.	P	
32	post-neonatal	F	NBAS	100	Het	AR	Infantile liver failure syndrome 2, [MIM:616483]; Short stature, optic nerve atrophy, and Pelger-Huet anomaly, [MIM:614800]	2	NM_015909:exon52:c.6859G>T(p.D2287Y)	Maternal	.	.	.	VUS	
33	post-neonatal	F	NBAS	100	Het	AR	Infantile liver failure syndrome 2, [MIM:616483]; Short stature, optic nerve atrophy, and Pelger-Huet anomaly, [MIM:614800]	2	NM_015909:exon7:c.426C>G(p.Y142X)	Maternal	PMID 31965297. SEE HGMD DISEASE: Infantile liver failure syndrome 2. SEE HGMD COMMENT: Suppl. *Table 3*.;	DM	.	P	
33	post-neonatal	F	NBAS	100	Het	AR	Infantile liver failure syndrome 2, [MIM:616483]; Short stature, optic nerve atrophy, and Pelger-Huet anomaly, [MIM:614800]	2	NM_015909:exon31:c.3596G>A(p.C1199Y)	Paternal	PMID 28629372. SEE HGMD DISEASE: Recurrent acute liver failure, fever related. SEE HGMD COMMENT: Biallelic with c.6611_6612insCA;	DM	.	LP	
34	post-neonatal	F	OTC	392	Het	X-linked recessive	Ornithine transcarbamylase deficiency, [MIM:311250]	X	NM_000531:exon9:c.944T>G(p.V315G)	De novo	PMID 10946359. SEE HGMD DISEASE: Ornithine transcarbamylase deficiency. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	
35	neonatal	M	PCCB	456	Het	AR	Propionicacidemia, [MIM:606054]	3	NM_000532:exon13:c.1339C>T(p.L447F)	-	.	.	Likely_pathogenic	VUS	L-carnitine, special formula
35	neonatal	M	PCCB	456	Het	AR	Propionicacidemia, [MIM:606054]	3	NM_000532:exon12:c.1215_1216delinsC(p.G407Afs*36)	-	NoDM CD1618263 related	DM	Pathogenic	P	L-carnitine, special formula
36	post-neonatal	M	BCKDHA	128	Het	AR	Maple syrup urine disease, type Ia, [MIM:248600]	19	NM_000709:exon2:c.110insAC(p.R40Qfs*11)	Paternal	PMID 8037208. SEE HGMD DISEASE: Maple syrup urine disease. SEE HGMD COMMENT: ;	DM	Pathogenic	P	special formula, vitamin B1
36	post-neonatal	M	BCKDHA	128	Het	AR	Maple syrup urine disease, type Ia, [MIM:248600]	19	NM_000709:exon5:c.565C>T(p.R189C)	Maternal	.	.	Uncertain_significance	VUS	special formula, vitamin B1
37	neonatal	M	DBT	119	Het	AR	Maple syrup urine disease, type II, [MIM:248600]	1	NM_001918:exon2:c.75_77delinsG(p.C26Wfs*2)	-	PMID 8430702. SEE HGMD DISEASE: Maple syrup urine disease. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	P	special formula
37	neonatal	M	DBT	119	Het	AR	Maple syrup urine disease, type II, [MIM:248600]	1	NM_001918:exon11:c.1291C>T(p.R431X)	-	PMID 31119508. SEE HGMD DISEASE: Maple syrup urine disease. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	P	special formula
38	neonatal	M	MMACHC	132	Het	AR	Methylmalonic aciduria and homocystinuria, cblC type, [MIM:277400]	1	NM_015506: exon4:c.567dupT (p.I190YfsTer13)	Parental	PMID 19370762. SEE HGMD DISEASE: Methylmalonic aciduria & homocystinuria, cblC type. SEE HGMD COMMENT: ;	DM	Pathogenic	P	L-carnitine, vitamin B12
38	neonatal	M	MMACHC	132	Het	AR	Methylmalonic aciduria and homocystinuria, cblC type, [MIM:277400]	1	NM_015506: exon1:c.80A>G (p.Q27R)	Maternal	PMID 16311595. SEE HGMD DISEASE: Methylmalonic aciduria. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	L-carnitine, vitamin B12
39	neonatal	M	SERAC1	181	Hom	AR	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome, [MIM:614739]	6	NM_032861:exon6:c.442C>T(p.R148X)	Maternal	PMID 22683713. SEE HGMD DISEASE: 3-methylglutaconic aciduria, impaired OXPHOS, deafness, encephalopathy, dystonia & Leigh-like syndrome. SEE HGMD COMMENT: ;	DM	Pathogenic	P	L-carnitine, coenzyme Q10, vitamin B2
39	neonatal	M	SERAC1	181	Hom	AR	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome, [MIM:614739]	6	NM_032861:exon6:c.442C>T(p.R148X)	Paternal	PMID 22683713. SEE HGMD DISEASE: 3-methylglutaconic aciduria, impaired OXPHOS, deafness, encephalopathy, dystonia & Leigh-like syndrome. SEE HGMD COMMENT: ;	DM	Pathogenic	P	L-carnitine, coenzyme Q10, vitamin B2
40	neonatal	F	JAG1	238	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon15:c.1932C>A(p.C644X)	-	NoDM CD157130 related	DM	.	P	
41	post-neonatal	M	JAG1	150	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon4:c.551G>A(p.R184H)	-	PMID 9585603. SEE HGMD DISEASE: Alagille syndrome. SEE HGMD COMMENT: ;	DM	Pathogenic	P	liver transplantation
42	post-neonatal	M	JAG1	134	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon25:c.3104_3105delinsA(p.I1035Kfs*14)	-	NoDM CI062276 related	DM	.	P	
43	post-neonatal	M	JAG1	133	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon4:c.686G>A(p.C229Y)	-	PMID 11058898. SEE HGMD DISEASE: Alagille syndrome. SEE HGMD COMMENT: ;	DM	.	LP	
44	post-neonatal	M	JAG1	131	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon6:c.783C>G(p.Y261X)	De novo	.	.	.	P	
45	post-neonatal	M	JAG1	108	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon4:c.550C>T(p.R184C)	De novo	PMID 9585603. SEE HGMD DISEASE: Alagille syndrome. SEE HGMD COMMENT: ;	DM	Pathogenic	P	

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_type	Clinvar_type	Classification of variant	Precision treatment
46	post-neonatal	F	JAG1	106	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon1:c.62T>C(p.L21P)	-	.	.	Likely_pathogenic	VUS	
46	post-neonatal	F	JAG1	106	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214:exon1:c.67_68delinsC(p.A23Pfs*23)	-	NoDM CD062191 related	DM	.	P	
47	post-neonatal	M	JAG1	100	Het	AD	Alagille syndrome 1, [MIM:118450]; Tetralogy of Fallot, [MIM:187500]	20	NM_000214: exon18:c.2230C>T (p.R744X)	-	PMID 9585603. SEE HGMD DISEASE: Alagille syndrome. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
48	neonatal	M	ABCC8	265	Het	AD/AR	Diabetes mellitus, noninsulin-dependent, [MIM:125853]; Diabetes mellitus, permanent neonatal 3, with or without neurologic features, [MIM:618857]; Diabetes mellitus, transient neonatal 2, [MIM:610374]; Hyperinsulinemic hypoglycemia, familial, 1, [MIM:256450]; Hypoglycemia of infancy, leucine-sensitive, [MIM:240800]	11	NM_000352:exon34:c.4181T>G (p.M1394R)	-	PMID 23266803. SEE HGMD DISEASE: Hyperinsulinism. SEE HGMD COMMENT: ;	DM	.	LP	
49	neonatal	M	ABCC8	226	Het	AD/AR	Diabetes mellitus, noninsulin-dependent, [MIM:125853]; Diabetes mellitus, permanent neonatal 3, with or without neurologic features, [MIM:618857]; Diabetes mellitus, transient neonatal 2, [MIM:610374]; Hyperinsulinemic hypoglycemia, familial, 1, [MIM:256450]; Hypoglycemia of infancy, leucine-sensitive, [MIM:240800]	11	NM_000352: exon20:c.2475+1G>A	-	PMID 28757749. SEE HGMD DISEASE: Hyperlysinaemia, congenital. SEE HGMD COMMENT: Succesful treatment - Subtotal pancreatectomy;	DM	.	P	
50	neonatal	F	ABCC8	144	Het	AD/AR	Diabetes mellitus, noninsulin-dependent, [MIM:125853]; Diabetes mellitus, permanent neonatal 3, with or without neurologic features, [MIM:618857]; Diabetes mellitus, transient neonatal 2, [MIM:610374]; Hyperinsulinemic hypoglycemia, familial, 1, [MIM:256450]; Hypoglycemia of infancy, leucine-sensitive, [MIM:240800]	11	NM_000352.3:c.1108A>G(p.R370G)	Maternal	PMID 18596924. SEE HGMD DISEASE: Hyperinsulinism. SEE HGMD COMMENT: Descr. as D370G in Fig. 2, R370G in Fig. 1. Mut. ;	DM	.	LP	
51	post-neonatal	M	ABCC8	141	Het	AD/AR	Diabetes mellitus, noninsulin-dependent, [MIM:125853]; Diabetes mellitus, permanent neonatal 3, with or without neurologic features, [MIM:618857]; Diabetes mellitus, transient neonatal 2, [MIM:610374]; Hyperinsulinemic hypoglycemia, familial, 1, [MIM:256450]; Hypoglycemia of infancy, leucine-sensitive, [MIM:240800]	11	NM_000352:exon15:c.2051_2054dupGCTA	-	.	.	.	P	
52	post-neonatal	M	ABCC8	123	Het	AD/AR	Diabetes mellitus, permanent neonatal, [MIM:606176]; Diabetes mellitus, noninsulin-dependent, [MIM:125853]; Diabetes mellitus, transient neonatal 2, [MIM:610374]; Hyperinsulinemic hypoglycemia, familial, 1, [MIM:256450]; Hypoglycemia of infancy, leucine-sensitive, [MIM:240800]	11	NM_000352:exon35:c.4307G>A(p.R1436Q)	-	PMID 10615958. SEE HGMD DISEASE: Hypoglycaemia, persistent hyperinsulinaemic. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	
53	neonatal	M	ABCC8	108	Het	AD/AR	Diabetes mellitus, noninsulin-dependent, [MIM:125853]; Diabetes mellitus, permanent neonatal 3, with or without neurologic features, [MIM:618857]; Diabetes mellitus, transient neonatal 2, [MIM:610374]; Hyperinsulinemic hypoglycemia, familial, 1, [MIM:256450]; Hypoglycemia of infancy, leucine-sensitive, [MIM:240800]	11	NM_000352: exon2:c.221G>A (p.R74Q)	-	PMID 9618169. SEE HGMD DISEASE: Hyperinsulinism. SEE HGMD COMMENT: ;	DM	Pathogenic	LP	
54	neonatal	F	ABCC2	264	Het	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon27:c.3825C>G(p.Y1275X)	-	PMID 16549534. SEE HGMD DISEASE: Dubin-Johnson syndrome. SEE HGMD COMMENT: ;	DM	.	P	
54	neonatal	F	ABCC2	264	Het	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon12:c.1535T>C(p.L512P)	-	.	.	.	VUS	
55	post-neonatal	F	ABCC2	255	Het	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon16:c.2078G>A(p.G693E)	Maternal	.	.	.	VUS	
55	post-neonatal	F	ABCC2	255	Het	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon9:c.1177C>T(p.R393W)	Paternal	PMID 15870973. SEE HGMD DISEASE: Dubin-Johnson syndrome. SEE HGMD COMMENT: ;	DM	Likely_pathogenic	LP	
56	post-neonatal	M	ABCC2	105	Hom	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon9:c.1177C>T(p.R393W)	-	PMID 15870973. SEE HGMD DISEASE: Dubin-Johnson syndrome. SEE HGMD COMMENT: ;	DM	Likely_pathogenic	LP	
56	post-neonatal	M	ABCC2	105	Hom	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon9:c.1177C>T(p.R393W)	-	PMID 15870973. SEE HGMD DISEASE: Dubin-Johnson syndrome. SEE HGMD COMMENT: ;	DM	Likely_pathogenic	LP	
57	neonatal	M	ABCC2	138	Het	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon31:c.4343G>A(p.G1448D)	-	.	.	.	VUS	
57	neonatal	M	ABCC2	138	Het	AR	Dubin-Johnson syndrome, [MIM:237500]	10	NM_000392:exon30:c.4237insGCT(p.H1414Lfs*18)	-	.	.	.	P	

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_ type	Clinvar_type	Classification of variant	Precision treatment
58	post-neonatal	M	ABCB11	250	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon21:c.2594C>T(p.A865V)	Maternal	PMID 28733223. SEE HGMD DISEASE: Intrahepatic cholestasis, benign recurrent. SEE HGMD COMMENT: Along with p.R1231Q;	DM	Benign/Likely_benign	LP	
58	post-neonatal	M	ABCB11	250	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon7:c.499G>A(p.A167T)	Paternal	PMID 19845854. SEE HGMD DISEASE: Intrahepatic cholestasis, familial progressive. SEE HGMD COMMENT: ;	DM	.	LP	
59	post-neonatal	M	ABCB11	202	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon18:c.2086C>T(p.R696W)	Paternal	PMID 24969679. SEE HGMD DISEASE: Intrahepatic cholestasis, familial progressive 2. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	liver transplantation
59	post-neonatal	M	ABCB11	202	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon6:c.477+6T>A	Maternal	.	.	.	VUS	liver transplantation
60	post-neonatal	M	ABCB11	137	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon8:c.677C>T(p.S226L)	Maternal	PMID 20232290. SEE HGMD DISEASE: Intrahepatic cholestasis, familial progressive 2. SEE HGMD COMMENT: ;	DM	.	LP	
60	post-neonatal	M	ABCB11	137	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon4:c.141insGCTTC(p.F47Lfs*13)	Paternal	.	.	.	P	
61	post-neonatal	F	ABCB11	102	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon24:c.3169C>T(p.R1057X)	Maternal	PMID 9806540. SEE HGMD DISEASE: Intrahepatic cholestasis, familial progressive 2. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
61	post-neonatal	F	ABCB11	102	Het	AR	Cholestasis, progressive familial intrahepatic 2, [MIM:601847]; Cholestasis, benign recurrent intrahepatic, 2, [MIM:605479]	2	NM_003742:exon8:c.667C>T(p.R223C)	Paternal	PMID 21404481. SEE HGMD DISEASE: Intrahepatic cholestasis, familial benign. SEE HGMD COMMENT: ;	DM?	Uncertain_significance	VUS	
62	post-neonatal	M	CYP27A1	170	Hom	AR	Cerebrotendinous xanthomatosis, [MIM:213700]	2	NM_000784:exon7:c.1263+1G>A	-	PMID 8827518. SEE HGMD DISEASE: Cerebrotendinous xanthomatosis. SEE HGMD COMMENT: ;	DM	Pathogenic	P	chenodeoxycholic acid
62	post-neonatal	M	CYP27A1	170	Hom	AR	Cerebrotendinous xanthomatosis, [MIM:213700]	2	NM_000784:exon7:c.1263+1G>A	-	PMID 8827518. SEE HGMD DISEASE: Cerebrotendinous xanthomatosis. SEE HGMD COMMENT: ;	DM	Pathogenic	P	chenodeoxycholic acid
63	post-neonatal	M	CYP27A1	161	Het	AR	Cerebrotendinous xanthomatosis, [MIM:213700]	2	NM_000784:exon9:c.1477-2A>C	-	PMID 28623566. SEE HGMD DISEASE: Cerebrotendinous xanthomatosis. SEE HGMD COMMENT: ;	DM	Pathogenic	P	chenodeoxycholic acid, liver transplantation
63	post-neonatal	M	CYP27A1	161	Het	AR	Cerebrotendinous xanthomatosis, [MIM:213700]	2	NM_000784:exon2:c.379C>T(p.R127W)	-	PMID 10430841. SEE HGMD DISEASE: Cerebrotendinous xanthomatosis. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	LP	chenodeoxycholic acid, liver transplantation
64	post-neonatal	M	CYP27A1	102	Het	AR	Cerebrotendinous xanthomatosis, [MIM:213700]	2	NM_000784:exon7:c.1214G>A(p.R405Q)	-	PMID 9186905. SEE HGMD DISEASE: Cerebrotendinous xanthomatosis. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	LP	chenodeoxycholic acid
64	post-neonatal	M	CYP27A1	102	Het	AR	Cerebrotendinous xanthomatosis, [MIM:213700]	2	NM_000784:exon9:c.1477-2A>C	-	PMID 28623566. SEE HGMD DISEASE: Cerebrotendinous xanthomatosis. SEE HGMD COMMENT: ;	DM	Pathogenic	P	chenodeoxycholic acid
65	neonatal	F	G6PD	200	Het	XLR/XLD	Hemolytic anemia, G6PD deficient (favism), [MIM:300908]	X	NM_001042351:exon12:c.1388G>A(p.R463H)	-	PMID 1953767. SEE HGMD DISEASE: Glucose-6-phosphate dehydrogenase deficiency. SEE HGMD COMMENT: G6PD Kaiping/Anant/Dhon/Petrich-like/Sapporo-like/Wosera.;	DM	Pathogenic	LP	
65	neonatal	F	G6PD	200	Het	XLR/XLD	Hemolytic anemia, G6PD deficient (favism), [MIM:300908]	X	NM_001042351.2:c.1024C>T(p.L342F)	-	PMID 8364584. SEE HGMD DISEASE: Glucose-6-phosphate dehydrogenase deficiency. SEE HGMD COMMENT: G6PD Chinese-5. aka C13184T.;	DM	Conflicting:Likely_ pathogenic(1)%3BUncertain_significance(2)	LP	
66	post-neonatal	M	G6PD	100	Hemi	X-linked dominant	Hemolytic anemia, G6PD deficient (favism), [MIM:300908]	X	NM_001042351:exon5:c.404A>C(p.N135T)	-	PMID 12064901. SEE HGMD DISEASE: Glucose-6-phosphate dehydrogenase deficiency. SEE HGMD COMMENT: ;	DM	.	LP	
67	neonatal	M	G6PD	133	Hemi	XLR/XLD	Hemolytic anemia, G6PD deficient (favism), [MIM:300908]	X	NM_001042351.2:c.1388G>A(p.R463H)	-	PMID 1953767. SEE HGMD DISEASE: Glucose-6-phosphate dehydrogenase deficiency. SEE HGMD COMMENT: G6PD Kaiping/Anant/Dhon/Petrich-like/Sapporo-like/Wosera.;	DM	Pathogenic	LP	

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_ type	Clinvar_type	Classification of variant	Precision treatment
68	post-neonatal	F	NPC1	172	Het	AR	Niemann-Pick disease, type D, [MIM:257220]; Niemann-Pick disease, type C1, [MIM:257220]	18	NM_000271:exon4:c.352_353delAG(p.Gln119fs)	-	.	.	Pathogenic	P	
68	post-neonatal	F	NPC1	172	Het	AR	Niemann-Pick disease, type D, [MIM:257220]; Niemann-Pick disease, type C1, [MIM:257220]	18	NM_000271:exon13:c.2000C>T(p.S667L)	-	PMID 16143556. SEE HGMD DISEASE: Niemann-Pick disease, type C. SEE HGMD COMMENT: ;	DM	.	LP	
69	post-neonatal	M	NPC1	108	Het	AR	Niemann-Pick disease, type D, [MIM:257220]; Niemann-Pick disease, type C1, [MIM:257220]	18	NM_000271:exon11:c.1757+3_1757+6del	Maternal	PMID . SEE HGMD DISEASE: Niemann-Pick disease, type C. SEE HGMD COMMENT: ;	DM	.	VUS	
69	post-neonatal	M	NPC1	108	Het	AR	Niemann-Pick disease, type D, [MIM:257220]; Niemann-Pick disease, type C1, [MIM:257220]	18	NM_000271:exon22:c.3254_3256delinsG(p.Y1085Cfs*11)	Paternal	.	.	.	P	
70	post-neonatal	F	AKR1D1	150	Het	AR	Bile acid synthesis defect, congenital, 2, [MIM:235555]	7	NM_005989:exon6:c.613_614delinsC(p.L205Pfs*2)	Maternal	.	.	.	P	chenodeoxycholic acid
70	post-neonatal	F	AKR1D1	150	Het	AR	Bile acid synthesis defect, congenital, 2, [MIM:235555]	7	NM_005989:exon7:c.716T>C(p.L239S)	Paternal	PMID 30809085. SEE HGMD DISEASE: 3-oxo-Delta(4)-steroid 5beta-reductase deficiency. SEE HGMD COMMENT: Protein change descr. in Suppl. *Table 1*.;	DM		LP	chenodeoxycholic acid
71	post-neonatal	M	AKR1D1	121	Het	AR	Bile acid synthesis defect, congenital, 2, [MIM:235555]	7	NM_005989:exon7:c.773T>C(p.I258T)	Maternal	.	.	Uncertain significance	VUS	chenodeoxycholic acid
71	post-neonatal	M	AKR1D1	121	Het	AR	Bile acid synthesis defect, congenital, 2, [MIM:235555]	7	NM_005989:exon6:c.580-13T>A	Paternal	PMID 31337596. SEE HGMD DISEASE: 3-oxo-Delta(4)-steroid 5beta-reductase deficiency. SEE HGMD COMMENT: ;	DM	.	LP	chenodeoxycholic acid
72	post-neonatal	M	GAA	191	Het	AR	Glycogen storage disease II, [MIM:232300]	17	NM_000152:exon2:c.503G>C(p.R168P)	Maternal	PMID 25526786. SEE HGMD DISEASE: Glycogen storage disease 2, late-onset. SEE HGMD COMMENT: ;	DM	Uncertain_significance	LP	
72	post-neonatal	M	GAA	191	Het	AR	Glycogen storage disease II, [MIM:232300]	17	NM_000152:exon14:c.1958C>A(p.T653N)	Paternal	PMID 21488274. SEE HGMD DISEASE: Glycogen storage disease 2. SEE HGMD COMMENT: ;	DM	.	LP	
73	post-neonatal	M	GAA	102	Het	AR	Glycogen storage disease II, [MIM:232300]	17	NM_000152:exon13:c.1771delinsCG(p.T593Dfs*43)	-	NoDM CM165553 related	DM	Uncertain_significance	P	
73	post-neonatal	M	GAA	102	Het	AR	Glycogen storage disease II, [MIM:232300]	17	NM_000152:exon11:c.1561G>C(p.E521Q)	-	PMID 18425781. SEE HGMD DISEASE: Glycogen storage disease 2. SEE HGMD COMMENT: ;	DM	Likely_pathogenic	LP	
74	post-neonatal	M	GALT	177	Het	AR	Galactosemia, [MIM:230400]	9	NM_000155:exon7:c.687G>A(p.K229K)	Paternal	PMID 28173647. SEE HGMD DISEASE: Galactosaemia. SEE HGMD COMMENT: ;	DM?	Uncertain_significance	LP	soy- based formula
74	post-neonatal	M	GALT	177	Het	AR	Galactosemia, [MIM:230400]	9	NM_000155:exon10:c.1052C>A(p.P351H)	Maternal	.	.	Pathogenic	VUS	soy- based formula
75	post-neonatal	F	GALT	117	Het	AR	Galactosemia, [MIM:230400]	9	NM_000155:exon10:c.958G>A(p.A320T)	-	PMID 7887416. SEE HGMD DISEASE: Galactosaemia. SEE HGMD COMMENT: ;	DM	Conflicting:Likely_ pathogenic(1)%3BUncertain_significance(1)	LP	soy- based formula
75	post-neonatal	F	GALT	117	Het	AR	Galactosemia, [MIM:230400]	9	NM_000155:exon6:c.558C>G(p.H186Q)	-	NoDM CM170257 related	DM	Likely_pathogenic	VUS	soy- based formula
76	post-neonatal	F	SBDS	113	Hom	AR/Complex	Shwachman-Diamond syndrome, [MIM:260400]	7	NM_016038:exon2:c.258+2T>C	Paternal	PMID 12496757. SEE HGMD DISEASE: Shwachman-Diamond syndrome. SEE HGMD COMMENT: aka C84fsX3.;	DM	Pathogenic	P	
76	post-neonatal	F	SBDS	113	Hom	AR/Complex	Shwachman-Diamond syndrome, [MIM:260400]	7	NM_016038:exon2:c.258+2T>C	De novo	PMID 12496757. SEE HGMD DISEASE: Shwachman-Diamond syndrome. SEE HGMD COMMENT: aka C84fsX3.;	DM	Pathogenic	P	
77	post-neonatal	M	SBDS	104	Het	AR/Complex	Shwachman-Diamond syndrome, [MIM:260400]	7	NM_016038:exon2:c.258+2T>C	Paternal	PMID 12496757. SEE HGMD DISEASE: Shwachman-Diamond syndrome. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
77	post-neonatal	M	SBDS	104	Het	AR/Complex	Shwachman-Diamond syndrome, [MIM:260400]	7	NM_016038:exon2:c.184A>T(p.K62X)	Maternal	PMID 27290639. SEE HGMD DISEASE: Multiorgan involvement (liver, kidney, hemopoethic system), skeletal dysplasia, growth failure, and complex I deficiency. SEE HGMD COMMENT: ;	DM	Pathogenic/Likely_pathogenic	P	
77	post-neonatal	M	SBDS	104	Het	AR/Complex	Shwachman-Diamond syndrome, [MIM:260400]	7	NM_016038:exon2:c.183T>C(p.S61S)	Maternal	NoDM CP035464 related	DM	Pathogenic	VUS	

Table S1 (*continued*)

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Table S1 (*continued*)

Sample	Subgroup	Gender	Gene	Peak NH_3	Zygo	Inherit	OMIM	Chr	Variant	Source	HGMD	HGMD_ type	Clinvar_type	Classification of variant	Precision treatment
78	post-neonatal	F	ALDOB	166	Het	AR	Fructose intolerance, hereditary, [MIM:229600]	9	NM_000035:exon7:c.673_674delinsA(p.E225Rfs*5)	-	.	.	.	P	fructose-free diet
78	post-neonatal	F	ALDOB	166	Het	AR	Fructose intolerance, hereditary, [MIM:229600]	9	NM_000035: exon4:c.325-1G>A	-	NoDM CS043627 related	DM	Likely_pathogenic	P	fructose-free diet
79	post-neonatal	M	CYP7B1	152	Het	AR	Spastic paraplegia 5A, autosomal recessive, [MIM:270800]; Bile acid synthesis defect, congenital, 3, [MIM:613812]	8	NM_004820:exon3:c.334C>T(p.R112X)	Paternal	PMID 18367963. SEE HGMD DISEASE: Cholestasis, severe. SEE HGMD COMMENT: ;	DM	Pathogenic	P	chenodeoxycholic acid
79	post-neonatal	M	CYP7B1	152	Het	AR	Spastic paraplegia 5A, autosomal recessive, [MIM:270800]; Bile acid synthesis defect, congenital, 3, [MIM:613812]	8	NM_004820:exon1:c.102C>A(p.C34X)	Maternal	.	.	.	P	chenodeoxycholic acid
80	post-neonatal	M	GPD1	190	Het	AR	Hypertriglyceridemia, transient infantile, [MIM:614480]	12	NM_005276:exon7:c.901G>T(p.E301X)	Maternal	.	.	.	P	
80	post-neonatal	M	GPD1	190	Het	AR	Hypertriglyceridemia, transient infantile, [MIM:614480]	12	NM_005276:exon3:c.220-2A>G	Paternal	PMID 28944580. SEE HGMD DISEASE: Obesity, insulin resistance, fatty liver & short stature. SEE HGMD COMMENT: ;	DM	.	P	
81	post-neonatal	M	IARS1	114	Het	AR	Growth retardation, impaired intellectual development, hypotonia, and hepatopathy, [MIM:617093]	9	NM_002161:exon15:c.1497_1498del	Maternal	.	.	.	P	
81	post-neonatal	M	IARS1	114	Het	AR	Growth retardation, impaired intellectual development, hypotonia, and hepatopathy, [MIM:617093]	9	NM_002161:exon14:c.1310C>T	Paternal	PMID 27426735. SEE HGMD DISEASE: Growth retardation, prenatal onset with intellectual disability, muscular hypotonia & hepatopathy. SEE HGMD COMMENT: Intermediate but significant growth impairment in yeast. functional study.;	DM	Pathogenic	LP	
82	post-neonatal	M	LIPA	119	Het	AR	Wolman disease, [MIM:278000]; Cholesteryl ester storage disease, [MIM:278000]	10	NM_000235:exon7:c.796G>T(p.G266X)	Maternal	PMID 8617513. SEE HGMD DISEASE: Cholesterol ester storage disease. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
82	post-neonatal	M	LIPA	119	Het	AR	Wolman disease, [MIM:278000]; Cholesteryl ester storage disease, [MIM:278000]	10	NM_000235:exon3:c.193C>T(p.R65X)	Paternal	PMID 9554751. SEE HGMD DISEASE: Cholesterol ester storage disease. SEE HGMD COMMENT: ;	DM	Pathogenic	P	
83	post-neonatal	M	MPV17	257	Het	AR	Charcot-Marie-Tooth disease, axonal, type 2EE, [MIM:618400]; Mitochondrial DNA depletion syndrome 6 (hepatocerebral type), [MIM:256810]	2	NM_002437:exon4:c.263_266delinsT(p.K88del)	Paternal	PMID 17694548. SEE HGMD DISEASE: Liver failure in infancy. SEE HGMD COMMENT: ;	DM	Likely_pathogenic	LP	L-carnitine, coenzyme Q10, vitamin B2
83	post-neonatal	M	MPV17	257	Het	AR	Charcot-Marie-Tooth disease, axonal, type 2EE, [MIM:618400]; Mitochondrial DNA depletion syndrome 6 (hepatocerebral type), [MIM:256810]	2	NM_002437:exon6:c.405C>G(p.Y135X)	Maternal	.	.	.	P	L-carnitine, coenzyme Q10, vitamin B2
84	neonatal	F	PEX1	172	Het	AR	Heimler syndrome 1, [MIM:234580]; Peroxisome biogenesis disorder 1B (NALD/IRD), [MIM:601539]; Peroxisome biogenesis disorder 1A (Zellweger), [MIM:214100]	7	NM_000466:exon12:c.2050C>T(p.Q684X)	Paternal	.	.	Uncertain_significance	P	
84	neonatal	F	PEX1	172	Het	AR	Heimler syndrome 1, [MIM:234580]; Peroxisome biogenesis disorder 1B (NALD/IRD), [MIM:601539]; Peroxisome biogenesis disorder 1A (Zellweger), [MIM:214100]	7	NM_000466:exon20:c.3043G>T(p.E1015X)	Maternal	.	.	.	P	
85	neonatal	F	PEX26	181	Hom	AR	Peroxisome biogenesis disorder 7A (Zellweger), [MIM:614872]; Peroxisome biogenesis disorder 7B, [MIM:614873]	22	NM_017929:exon2:c.28_29delinsG(p.L12Sfs*70)	Maternal	PMID 30968598. SEE HGMD DISEASE: Peroxisome biogenesis disorder. SEE HGMD COMMENT: ;	DM	Uncertain_significance	P	
85	neonatal	F	PEX26	181	Hom	AR	Peroxisome biogenesis disorder 7A (Zellweger), [MIM:614872]; Peroxisome biogenesis disorder 7B, [MIM:614873]	22	NM_017929:exon2:c.28_29delinsG(p.L12Sfs*70)	Paternal	PMID 30968598. SEE HGMD DISEASE: Peroxisome biogenesis disorder. SEE HGMD COMMENT: ;	DM	Uncertain_significance	P	

F: female; M: male; AD: autosomal dominant; Zygo: zygote; Inherit: inheritance; AR: autosomal recessive; Chr: chromosome; P: pathogenic; LP: likely pathogenic; VUS: variant of uncertain significance.

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