Received: 1 December 2023 | Revised: 11 March 2024 | Accepted: 12 March 2024

DOI: 10.1002/jimd.12733

REVIEW

JIMD SSIEM WILEY

Genetic aetiologies of acute liver failure

Robert Hegarty[1,2] | **Richard J. Thompson**[1,2]

[1]Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London, UK

[2]Institute of Liver Studies, King's College London, London, UK

Correspondence
Robert Hegarty, Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London, UK.
Email: roberthegarty@nhs.net

Communicating Editor: Sander M Houten

Abstract

Acute liver failure (ALF) is a rare, rapidly evolving, clinical syndrome with devastating consequences where definitive treatment is by emergency liver transplantation. Establishing a diagnosis can be challenging and, historically, the cause of ALF was unidentified in up to half of children. However, recent technological and clinical advances in genomic medicine have led to an increasing proportion being diagnosed with monogenic aetiologies of ALF. The conditions encountered include a diverse group of inherited metabolic disorders each with prognostic and treatment implications. Often these disorders are clinically indistinguishable and may even mimic disorders of immune regulation or red cell disorders. Rapid genomic sequencing for children with ALF is, therefore, a key component in the diagnostic work up today. This review focuses on the monogenic aetiologies of ALF.

KEYWORDS

acute liver failure, hepatology, liver transplantation, mitochondria

1 | INTRODUCTION

Acute liver failure (ALF) is a sudden-onset, often life-threatening, condition defined by coagulopathy, conjugated hyperbilirubinaemia and variable presence of encephalopathy.[1] The clinical phenotype of ALF reflects the nature and extent of liver damage, its rate of evolution against the adequacy of hepatic regeneration.[2] It is defined by the Paediatric Acute Liver Failure Study Group as a hepatic-based coagulopathy of a prothrombin time (PT) ≥15 s or INR ≥1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy or a PT ≥20 s or INR ≥2.0 regardless of the presence or absence of clinical hepatic encephalopathy.[3] It is an umbrella term of a common pathway resulting from a variety of insults including infectious, metabolic, immunological, toxic and vascular aetiologies. Arriving at a diagnosis can be challenging due to the rapidly progressive nature of the condition with significant morbidity and mortality.[4] Historically, indeterminate cases represented the largest diagnostic category representing approximately half of cases.[3] However, over the past decade, the proportion of children remaining undiagnosed has decreased owing to the incorporation of next generation sequencing in clinical practice.[5,6] This review focuses on the monogenetic aetiologies of ALF.

2 | THE EVOLUTION OF THE DEFINITION OF ALF

The definition of ALF has been debated and its exact parameters subject to revision over the years. The term fulminant hepatic failure was originally defined by Trey et al. in 1970 as a potentially reversible, severe liver injury, with an onset of encephalopathy within 8 weeks of symptom appearance and in the absence of pre-existing liver disease.[7] Paediatricians adopted the definition with the caveat that encephalopathy may be difficult to recognise in young children.[8] The designation used by O'Grady et al. recognised hyperacute, acute and subacute patterns of ALF dependent on the time interval

between development of jaundice and onset of encephalopathy as a prognostic marker where hyperacute ALF, paradoxically, have the highest rates of survival.[9] Despite the different designations, the clinical syndrome of ALF regardless of aetiology is that of a severe liver injury that evolves over days or weeks: prolonged INR, decline in mental function, peripheral vasodilation, features of the systemic inflammatory response and ultimately multi-organ failure.[10] In children, ALF encompasses a broad group of conditions including monogenic diseases each with prognostic implications.

3 | DISORDERS OF AMINO ACID METABOLISM

Ornithine transcarbamylase deficiency is the most common urea cycle disorder caused by damaging variants in the *OTC* gene on chromosome Xp21.1. Affected males may become symptomatic within the first week of life with severe consequences including hyperammonaemia, ALF, coma and death. In a series of 37 affected patients, 29 (78%) experienced ALF including 6 females.[11] Female heterozygotes are however mostly asymptomatic (>80%)[12] or affected by recurrent episodes of ALF[13] which can occur during childhood or adulthood[14] including during pregnancy.[15] At present, liver transplantation (LT) continues to be the main treatment option for those with severe disease who survive the initial, metabolic decompensation.[16] The decision for this could be guided by individual phenotype and residual OTC activity: ≤4.3% is associated with higher mortality rates and ≤16.0% is associated with a higher number of hyperammonaemic events.[17] Using a yeast-based functional assay, missense OTC variants can be classified to neonatal and late-onset forms as a further tool to aid clinical decision-making.[18] The clinical efficacy of hepatocyte transplantation for urea cycle disorders as a bridge to LT is eagerly anticipated.[19,20]

Citrullinaemia type 1 is caused by deficiency of argininosuccinate synthetase encoded by *ASS1*. Affected patients suffer from hyperammonaemia, encephalopathy and seizures and rarely ALF.[21,22] Residual enzyme activity of ≤8.1% has been reported to correlate with worse disease severity as well as cognitive outcome and may be used to inform decisions such as LT.[23] Both liver replacement and auxiliary transplantation, can be performed to treat frequent decompensations and ALF with good effect.[24,25] In citrullinaemia type 2, pathogenic variants in *SLC25A13* result in deficiency of citrin—a mitochondrial aspartate glutamate carrier primarily expressed in the liver, heart and kidney.[26] Affected infants exhibit conjugated hyperbilirubinaemia which typically resolves by 1 year with treatment.[27] ALF is unusual but recognised and may necessitate LT.[28]

Hyperornithinaemia, hyperammonaemia and homocitrullinuria syndrome (*SLC25A15*) is another urea cycle disorder implicated in ALF.[29]

Tyrosinaemia type I is caused by variants in *FAH* encoding for the enzyme fumarylacetoacetate hydrolase responsible for the final step in the tyrosine catabolic pathway. Most patients with tyrosinaemia type I presenting with ALF are neonates or infants but can also be seen in adults who are non-adherent to treatment. Treatment with nitisinone blocks the catabolic pathway of tyrosine leading to the reduction in toxic intermediate metabolites and used alongside a low tyrosine and phenylalanine diet.[30] In patients affected by ALF, it is possible to rescue them, while nitisinone treatment takes effect, with critical care support. Then, 1 week has been suggested as a possible time-period given for this before LT should be offered if the patient is clinically stable.[31]

4 | DISORDERS OF CARBOHYDRATE METABOLISM

Galactose-1-phosphate uridylyltransferase deficiency caused by mutations in *GALT* is the cause of classic galactosaemia. Newborns present with jaundice, hepatomegaly, coagulopathy, poor feeding, hypoglycaemia and cataracts[32] and is one of the main differential diagnoses for ALF in this age group.[33,34] Urgent removal of galactose from the diet is necessary as soon as the diagnosis is suspected and, if positive, there is an initial slowing of liver dysfunction followed by a full recovery. Newborn screening provides an opportunity for diagnosis either before or just as the infant presents with ALF but should be performed in the first 1–3 days of life.[35,36] Occurrence of long-term complications such as reduced cognitive ability, language impairment, decreased bone mass and hypergonadotrophic hypogonadism in women occur irrespective to the clinical severity of presentation/continued galactose-restricted diet.[37] Rarely, hereditary fructose intolerance due to aldolase, fructose-bisphosphate B deficiency (*ALDOB*) may present as neonatal infantile ALF in association with lactic acidosis and renal tubular defect.[38] The presence of fructose-containing infant formulas and in over-the-counter medications may be the precipitant.[39] In both conditions, elimination of galactose and fructose, respectively, from the diet restores liver function swiftly. Cytosolic phosphoenol carboxykinase (*PCK1*) has also been reported to cause transient ALF coinciding with a diarrhoea illness in a 9-month-old boy.[40] Avoidance of gluconeogenesis by use of glucose polymer emergency regimen prevented further

decompensations. Another interesting condition is glycogen storage disorder 1b characterised by liver and kidney dysfunction with neutropenia caused by pathogenic variants in *SLC37A4*. *SLC37A4* encodes a glucose-6-phosphate (G6P) transporter at the endoplasmic reticulum (ER) disrupting liver Golgi homeostasis (pH and morphology), glycosylation and coagulation factors levels.[41] Carriers of variants in the gene experience liver dysfunction and coagulopathy.[42]

Transaldolase 1 deficiency is an inherited metabolic disorder of the pentose phosphate pathway in which G6P is converted to ribose-5-phosphate through a series of reactions. Patients can present prenatally with intrauterine growth restriction and/or oligohydramnios; in the neonatal period, with dysmorphism, cardiovascular defects and liver dysfunction; or later in life with a milder phenotype.[43] While liver involvement is common, ALF as a presentation is rare and reported in one case report in a newborn with low birthweight and multi-organ failure including respiratory failure, hypotonia, cardiomegaly, cutis laxa and dysmorphism.[44] Urine polyol analysis followed by transaldolase enzyme activity measurement from cultured fibroblasts and sequencing of *TALDO1* lead to the diagnosis. Other series collating the clinical features of this rare disorder describe chronic liver disease with variable degrees of fibrosis and even hepatocellular carcinoma.[43,45–47]

5 | DISORDERS OF FATTY ACID METABOLISM

Liver dysfunction in mitochondrial fatty acid oxidation defects (FAOD) is common often manifesting as hepatomegaly and steatosis with or without episodes of hypertransaminasaemia.[48] Diagnosis is suggested by lack of ketone production with hypoglycaemia, and hyperammonaemia during fasting, typically in late infancy. Recurrent ALF leading to LT has been reported in acyl-CoA dehydrogenase long chain deficiency[49,50] although there has not been any reports of patients confirmed to harbour biallelic mutations in *ACADL*. ALF has also been reported in carnitine transporter deficiency including those related to solute carrier family 22 member 5 (*SLC22A5*)[51] in newborns presenting with cardiorespiratory distress, hypoglycaemia, hyperammonaemia, elevated serum creatine kinase and liver dysfunction progressing to ALF.[52] The babies in general responded to carnitine supplementation along with low-fat/high-carbohydrate diet with frequent feedings and MCT supplementation. In the early onset electron transfer flavoprotein deficiency (*ETFDH*) or multiple acyl-CoA dehydrogenase deficiency disrupted electron transfer to the respiratory chain from fatty acid and amino acid oxidation can lead to liver dysfunction.[53] An infant presenting with respiratory distress in association with reduced conscious level, hypotonia, hypoglycaemia, lactic acidosis and hyperammonaemia succumbed to multi-organ failure. Individuals may be affected during pregnancy syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) due to FAOD in the foetus or in an undiagnosed, expectant mother.[54,55] When considering FAOD altogether, *liver failure* was reported in 11–27% children but is rarely severe and does not require LT.[56,57] Furthermore, acute presentations are considered historical today with effective newborn screening programs in place.

6 | DISORDERS OF ENERGY SUBSTRATE METABOLISM

The succinyl-coenzyme A ligase is a tricarboxylic acid cycle enzyme encoded by *SUCLG1* and *SUCLA2*. Its deficiency leads to encephalomyopathic mitochondrial depletion syndrome with methylmalonic aciduria. The most frequent clinical findings in those affected are hypotonia and psychomotor retardation with liver involvement only seen in patients with *SUCLG1* mutations.[58] Those affected by the severe infantile lactic acidosis phenotype may develop concurrent ALF with a poor outlook although LT has been carried out in one patient.[5,59]

The pyruvate metabolism enzyme dihydrolipoamide dehydrogenase (DLD; or pyruvate dehydrogenase E3 subunit) oxidises lipoic acid to serve as an electron sink for the four mitochondrial keto-acid dehydrogenases including pyruvate dehydrogenase.[60] Biallelic pathogenic variants in *DLD* result in DLD deficiency of which the hepatic manifestation results in recurrent ALF triggered by physiological stress, infection and fasting.[61] These patients generally spontaneously recover from episodes of hepatic cytolysis which can persist into adulthood. Some patients exhibit a milder disease course or combined hepatic and neurological symptoms with no clear genotype–phenotype correlations.[62,63]

7 | MITOCHONDRIAL DISORDERS

Liver dysfunction in mitochondrial disorders is frequently encountered, but the severity is highly variable. Mitochondrial hepatopathies are estimated to affect approximately 10–22% of children with respiratory chain abnormalities.[64,65] ALF affects a smaller proportion of these children or 1.5% when considering the full spectrum of children with ALF.[4] However, this proportion increases to 20% among the neonatal age group.[66,67] Organs vary by their

susceptibility to mitochondrial DNA (mtDNA) maintenance defects and the susceptibility of a given tissue for specific defects change with the age of the patient: the newborn liver with disruption to mtDNA maintenance and replication are most susceptible to ALF while isolated deficiencies in respiratory chain complex less so.[68]

7.1 | Disorders of mtDNA maintenance and replication

The mtDNA polymerase responsible for replication of the mitochondrial genome is encoded by *POLG*. There is a continuum of overlapping phenotypes with a variable age of disease onset, degree of organ involvement and severity in those affected.[69] ALF caused by mutations in *POLG* as part of the myocerebrohepatopathy spectrum present in neonates with devastating clinical consequences. In older children, the diagnosis may only become apparent with Alpers–Huttenlocher syndrome in whom sodium valproate is commenced and is the precipitant of ALF.[70] LT in these children are usually contraindicated due to the high risk of death after LT[71,72] although it may be considered in those with later onset and milder disease.[73] Rarely, variants in *POLG2* encoding the polymerase gamma accessory subunit can lead to ALF in those with the early onset phenotype as reported in two infants who died.[74,75] MtDNA replication is also maintained by *TWNK* encoding a helicase required for unwinding mtDNA. In its severe form, mtDNA depletion syndrome ensues with ALF and neurological abnormalities at birth.[76,77]

DGUOK encoding the mitochondrial deoxyguanosine kinase phosphorylates purine nucleotides necessary for mtDNA replication. The mitochondrial inner membrane protein encoded by *MPV17* is involved in maintaining membrane potential.[78] The hepatocerebral phenotypes are characterised by hypoglycaemia, lactic acidosis and failure to thrive associated with a rapidly progressive abnormal neurology (nystagmus, hypotonia and peripheral neuropathy).[79] The outcome for these patients are generally poor and the mortality rate for those presenting in the first 6 months of life can be as high as 70%.[80,81] Interestingly, a recurrent homozygous variant encoding a p.Asn46Ser missense mutation, in *DGUOK* has been implicated in idiopathic noncirrhotic portal hypertension, rapidly progressive cirrhosis and as well as reversible liver failure.[82,83] Select individuals with a missense genotype with a milder neurological phenotype may be considered for LT in DGUOK deficiency[84–86] and MPV17 deficiency with one survivor being 17 years post LT.[81]

ALF has been reported in two patients thought to be deficient with mitochondrial ribonucleotide reductase small subunit (*RRM2B*), an enzyme that catalyses the conversion of ribonucleoside diphosphates to deoxyribonucleoside diphosphates. Both patients were heterozygous for a frameshift mutation and reduction in respiratory chain complex activity and p53R2, gene product of *RRM2B*, were demonstrated in liver tissue.[87] One patient underwent LT following the third episode of ALF with normal neurocognitive development in the subsequent 4 years.

7.2 | Disorders of mitochondrial gene expression

tRNA 5-methylaminomethyl-2-thiouridylate-methyltransferase (TRMU) deficiency caused by biallelic pathogenic variants in *TRMU* result in the phenotypic spectrum of reversible ALF.[88] The enzyme carries out the post-translation modification (thiolation) of mitochondrial tRNAs and its deficiency causes impaired synthesis of mtDNA-encoded proteins with subsequent mitochondrial respiratory chain dysfunction.[89] Supportive therapy can help recover infants from ALF which can occur multiple times—hence, *transient*, *infantile liver failure*. Early supplementation with exogenous L-cysteine or *N*-acetylcysteine may help as cysteine is the substrate for TRMU thiolation.[90] LT is required in those who do not recover and reported in 11/62 cases.[89]

Reports of ALF secondary to deficiency in mitochondrial aminoacyl-tRNA synthetases (ARSs) are rarer, such as in the case of a newborn mitochondrial leucyl- or phenylalanyl-tRNA synthetase (*LARS2* and *FARS2*) deficiencies[91–93]; linked to sodium valproate administration in a 6-year-old with tryptophanyl-tRNA synthetase (*WARS2*) deficiency.[94] All patients died with multi-organ involvement.

Mitochondrial protein translation is maintained by the actions of several regulatory factors along each step of translation initiation, elongation, termination and recycling of the ribosome.[95] *GFM1* encodes mitochondrial GTPase that catalyses ribosomal translation elongation. Disease associated with *GFM1* is usually devastating and lead to combined oxidative phosphorylation deficiency, with or without ALF and death in infancy.[96–98] Similar phenotypes are reported in mitochondrial elongation factor Ts deficiency (*TSFM*) where affected individuals are born with intrauterine growth retardation and lactic acidosis progressing to ALF.[99,100]

7.3 | Nuclear encoded disorder of oxidative phosphorylation

ALF is also seen in deficiencies of the oxidative phosphorylation complex subunits and assembly factors

caused by mtDNA depletion or defects of mtDNA translation. In a series of 157 patients with respiratory chain complex deficiencies, *liver failure* was a clinical feature in 20%.[101] Complex I deficiency is the most frequent mitochondrial disorder accounting for up to 30% of cases.[102] Liver disease is usually not a feature in complex I deficiency that arise from mutations in mtDNA, nuclear-encoded structural subunits or assembly factors. It has been demonstrated in the mouse liver that hepatocyte specific loss of complex I function confers no overt liver phenotype because hepatocytes use alternative electron donors for the electron transport chain.[103] One exception is the mitochondrial acyl-CoA dehydrogenase family member 9, an assembly factor of complex I, with ACAD activity. Its deficiency predominantly affects the muscular system; however, it has been reported to cause ALF in infants[87,104,105] or 4% of those affected.[106] ALF has been reported in those with variants in *BCS1L*—a chaperone protein for complex III assembly—such as in a newborn with multisystemic disease who died[107] as well as in a 10 months old who underwent living related LT with normal neurology 2 years after transplantation.[108] Mutations in *UQCRC2*, another component of complex III, can also cause a similar hepatic picture.[109] Deficiency of cytochrome c oxidase, the terminal respiratory chain complex, manifests as a heterogeneous group of disorders[110] with a rare case of fatal, neonatal onset ALF reported in mutations in *SCO1*.[111]

7.4 | Mitochondrial membrane biogenesis and remodelling

3-Methylglutaconic aciduria, deafness, encephalopathy, Leigh-like (MEGDEL) syndrome caused by mutations in *SERAC1* manifests as neonatal collapse characterised by hypoglycaemia, lactic acidosis, truncal hypotonia and encephalopathy with[112,113] or without ALF.[114] Increasingly, the phenotypic spectrum is recognised to be broad with cerebral, otologic, ophthalmologic, cardiac, endocrine, muscular abnormalities being reported.[115] The liver dysfunction in those infants that survive may improve over the first year of life, but severe neurological disease with spasticity, refractory dystonia and psychomotor development arrest and/or regression subsequently ensues.[113,116] *SERAC1* encodes a protein located at the interface of mitochondria and ER involved in phosphatidylglycerol remodelling important for mitochondrial function and intracellular cholesterol trafficking—MEGDEL syndrome can be considered both a form of complex lipid and mitochondrial disorder.[117]

8 | DISORDERS OF VESICULAR TRAFFICKING

ALF secondary to NBAS deficiency is considered one of the archetypal, monogenic causes of ALF typically presenting as hyperacute ALF triggered by febrile illness. Association of *NBAS* with human disease was first reported in 2010 in a description of a group of patients from a remote region in northeastern Siberia known as the Yakut population. Affected patients with the c.5741G > A, p.Arg1914His substitution exhibited short stature, optic nerve atrophy and Pelger–Huët anomaly characterised by abnormal nuclear shape in neutrophils (SOPH syndrome).[118] Subsequently, a distinct group of patients presenting with recurrent episodes of ALF but without the above features were described.[119,120] We now understand that those harbouring variants in the coding region of the Sec39 domain (amino acids 722-1369) mainly experience ALF, while those with variants in the C-terminus including that seen in the Yakut population show a predominantly multisystemic phenotype without ALF.[121] The difference in these phenotypes may be explained by whether NBAS, being a component of syntaxin 18, disrupts Golgi-to-ER retrograde transport[120] or even nonsense mediated decay.[122] Variants in *NBAS* have also been encountered in relatively high frequency in patients with primary hemophagocytic lymphohistiocytosis (HLH) with a dysregulated lytic vesicle transport pathway being implicated in the pathophysiology.[123] The frequency of ALF may decrease with time[120] but LT can treat and prevent future episodes of ALF.[5] Hepatocyte transplantation may also be effective in bridging the child to recovery or LT.[124]

Rad50 interacting protein 1 (RINT1) is a protein associated with NBAS and Zeste White 10 (ZW10) forming the NBAS-RINT1-ZW10 (NRZ) complex, a multisubunit machinery in the ER involved in lipid droplet homeostasis and golgi-ER trafficking.[125] RINT1 deficiency also results in fever-triggered ALF starting in infancy/early childhood along with the skeletal features of vertebral and hip abnormalities.[126] Episodes of ALF associated with spastic paraparesis, ataxia and dysmorphism (anteverted nose, high-arched palate, wide forehead and low-set ears) was described more recently in three patients.[125]

Disruptive mutations in *SCYL1* have also been described in patients with early onset recurrent ALF, peripheral neuropathy and ataxia.[127] The protein is localised at the Golgi apparatus and involved in the retrograde trafficking of proteins by the membrane trafficking machinery mediated by coatomer (COPI)-coated vesicles.[128] Affected patients experience episodes of ALF triggered by febrile illness from infancy. Over time, the liver crises may subside but progress to liver fibrosis and

chronic liver disease warranting LT.[129] Neurological symptoms may develop in parallel with delayed motor milestones, cerebellar ataxia and sensory motor neuropathy along with subtle skeletal features of short stature, abnormal radiographic features of the hips and scoliosis.[129,130]

Wolcott–Rallison syndrome due to mutations in *EIF2AK3* is characterised by neonatal diabetes mellitus, recurrent ALF and skeletal dysplasia. The eukaryotic translation initiation factor 2 alpha kinase 3 protein is located in the ER and functionally involved at a convergence point of different stress pathways known as the *integrated stress response* reducing the overload of proteins entering the ER of a stressed cell.[131] Apoptosis ensues following a maladaptive protein-folding and secretory capacity at the ER. The increased physiological demands for this process during a febrile illness may be the trigger of ALF. Liver and pancreas transplantation may provide cure to the affected organs.[132,133]

9 | ARSs DEFICIENCIES

ARSs are highly conserved, ubiquitously expressed enzymes essential to covalently linking a tRNA molecule to its cognate amino acid. Different amino acids have ARS enzymes encoded by one of 17 cytoplasmic ARSs, 17 mitochondrial ARSs and 3 bifunctional enzymes that act in both compartments. This emerging group of disease show considerable clinical variability with the neurological system most frequently affected.[134] Liver disease in the form of ALF has been reported in association with *LARS1*[135,136] and *IARS1*[137,138] encoding the cytoplasmic leucyl and isoleucyl-tRNA synthetases, respectively. Patients experience abnormal liver function within the first year of life which may progress to ALF at times of physiologic stress. Patients are also affected by intrauterine growth retardation, anaemia, neurodevelopmental delay, seizures and hypotonia and if they survive episodes of hepatic dysfunction may become less severe with age.[139] By contrast, other ARSs are reported to cause cholestatic and steatotic liver disease *YARS1*,[140] *MARS1*,[141] *FARS1*[142] encoding tyrosyl, methionyl and phenylalanyl synthetases, respectively.

10 | WILSON DISEASE

Wilson disease is an inherited disorder of copper metabolism caused by mutations in *ATP7B* encoding a transmembrane copper-transporting ATPase.[143] Pathological copper accumulation particularly in the liver and brain lead to the clinical manifestations although children are more likely to present with hepatic disease including ALF in up to approximately, 20–33% of cases.[144] ALF carries a high mortality rate without LT.[145] The phenotype of Wilson disease is diverse and it is not clear why some patients present with ALF while others do not. It may be related to the fact that most patients with Wilson disease presenting with ALF, in fact, have underlying cirrhosis[146] and they are manifesting acute on chronic liver failure.[147] Comparable genotypes were found between ALF and chronic liver disease Wilson disease patients implicating environmental factors more so than genotype in the precipitation of ALF.[148]

11 | NIEMANN–PICK TYPE C

Niemann–Pick type C is a neurovisceral lysosomal lipid storage disorder caused by mutations in *NPC1* or *NPC2*. The mode of clinical presentation is highly variable from a neonatal rapidly fatal disorder to an adult onset chronic neurodegenerative disease.[149] ALF is seen in a small subset of patients with neonatal onset disease which is fatal.[150] LT is usually not an option in these infants given the poor neurological outlook.[151] However, a recent report of successful LT and normal neurology 5 years after LT incorporating the use of miglustat, a glucosylceramide synthase inhibitor, post LT highlights the evolving treatment options based on individual mutations and new therapeutic drugs.[152]

12 | ZELLWEGER SPECTRUM DISORDERS

Zellweger spectrum disorders are a heterogeneous group of disorders characterised by defective peroxisomes. Liver disease is an important feature in patients with Zellweger spectrum disorder and a frequent cause of death.[153] The disease is most severe in those presenting in neonates or infancy exhibiting dysmorphism, severe hypotonia, feeding difficulty, epileptic seizures and signs of liver dysfunction in the form of cholestasis and hepatomegaly which may rapidly progressive to ALF.[154] Neonatal ALF is fatal as demonstrated in mouse knock-out models of *Pex2*, *Pex5* and *Pex13* that die shortly after birth.[155–157]

13 | CONGENITAL DISORDERS OF GLYCOSYLATION

Congenital disorders of glycosylation (CDG) are an expanding group of disorders with genetic defects in N-glycosylation, *O*-glycosylation, lipid glycosylation and

those that impact multiple glycosylation pathways.[158] Liver involvement within CDGs is common and seen in about 22–30% of cases although the nature and extent of disease is highly variable.[159] The spectrum can range from trivial elevation in transaminases, steatosis and hepatomegaly to chronic, liver disease and cirrhosis.[160,161] However, cases presenting with true ALF are limited to a small number of isolated reports of mannose phosphate isomerase (MPI)-CDG (type 1b) or suspected CDG based on transferrin isoelectric focusing but without genetic confirmation.[33,162] Even among the MPI-CDG characterised by a triad of digestive, hepatic and endocrine symptoms, liver disease is most frequently in the form of fibrosis and portal hypertension.[163]

14 | DISORDERS OF IMMUNE REGULATION

ALF is a recognised complication of hyperinflammatory states caused by inborn errors of immunity. Persistent immune cell activation can be genetically determined such as in cases of familial HLH[164] which is accountable for 2–4% of all cases of ALF.[3,165,166] Familial HLH cases caused by genetic defects in *PRF1*, *UNC13D*, *STX11* or *STXBP2* result in profoundly impaired NK-cell and CD8+ T-cell cytotoxic function.[167] Presentation is usually within 2 years of birth, including the neonatal period where infants are born in poor condition with hydrops fetalis.[168] Genetically confirmed cases with fatal outcomes have been implicated in *PRF1* (familial HLH2)[169,170] and *STXBP2* (familial HLH5).[171] In a 5-year-old with X-linked lymphoproliferative disease (*XIAP*) with dysregulated inflammasome activity, ALF and bone marrow failure was successfully treated by liver and bone marrow transplantation.[172] In a study looking at 30 children <24 months of age with ALF of indeterminate aetiology, 9 (30%) were found to have biallelic and 10 (33.3%) monoallelic variants in familial HLH genes including *PFR1*, *UNC13D*, *RAB27A* and *LRBA* although the pathogenicity of some of the reported variants were uncertain.[1] Treatment of ALF in the context of secondary HLH by LT is usually contraindicated as the recurrence risk is high (56%).[173]

The liver injury pattern and inflammatory milieu that is observed in HLH shares similar characteristics to *indeterminate* ALF cases characterised with elevated ferritin, soluble interleukin 2 receptor (sIL2R) levels and low fibrinogen.[174] These patients are more likely to require LT (46%) compared to the group with known diagnoses (19%)[175] with high levels of sIL2R correlating with higher chance of death or LT.[176] Mechanistically, in mouse models of acute hepatitis with viral CD8 induction, perforin-mediated killing was demonstrated as a critical process.[177] These observations provide insight into the unique characterisation of children, previously healthy, affected with *indeterminate* ALF with high infiltrates of CD8+ T-cells in the liver compared to known causes[178] as well as in peripheral blood.[179] Immunosuppressive therapies are being investigated in the TRIUMPH trial of high dose methylprednisolone or equine anti-thymocyte globulin in the treatment of ALF (https://classic.clinicaltrials.gov/ct2/show/NCT04862221). The discovery of human leukocyte antigen alleles that are associated[180,181] as well as protective[182] are providing an insight to the genetic propensity to ALF in these children.

Monogenic autoinflammatory disorders have also been implicated in ALF marked by unprovoked episodic or chronic inflammatory symptoms driven by primary dysfunction of the innate immune system. Type 2 autoimmune hepatitis were found in haploinsufficiency of A20, caused by mutations in *TNFAIP3*[183] as well as *STAT1*,[184] *FOXP3*,[185] *AIRE*,[186] *ZNFX1*[187] and *ITCH*.[188]

15 | RED CELL DISORDERS

Liver dysfunction can be seen in newborns with extreme haemolytic anaemia and conjugated hyperbilirubinaemia.[189] Hereditary haemolytic anaemias, particularly defects involving the red blood cell (RBC) cytoskeleton and deficiencies of the RBC enzyme can cause significant liver dysfunction leading to ALF. Red cell membrane disorders disrupt cell membrane stability resulting in irregular shape, increased fragility and membrane loss.[190] Spectrin, a cytoskeletal protein constituted in part by the βI-spectrin subunit (*SPTB*), when deficient can cause hydrops, severe nonimmune haemolytic anaemia progressive conjugated hyperbilirubinaemia and coagulopathy.[191] Furthermore, pyruvate kinase deficiency caused by mutations in the *PKLR* gene resulting in similar neonatal phenotype of severe anaemia, conjugated hyperbilirubinaemia and coagulopathy.[192,193] ALF has also been seen in a newborn with severe congenital anaemia, hydrops, persistent pulmonary hypertension and cleft palate subsequently diagnosed with biallelic variants in *CDAN1*—a congenital dyserythropoietic anaemia and a rare inborn error of erythropoiesis.[194] The liver pathology as ellucidated from liver histopathological specimens from autopsy allude to (a) haemolysis and hepatic sequestration of red cells as well as (b) bile ductule obstruction due to bilirubin overload and (c) hepatocyte loss due to shocked liver. Diagnosis in these infants can be challenging: abnormalities of erythrocyte morphology on blood smear are common in neonates; the requirement for transfusions makes

TABLE 1 Monogenic aetiologies of acute liver failure, their reported presenting age groups and diagnostic investigations that may be considered prior to NGS.

Disorder	Age group	Investigations
Disorders of amino acid metabolism		
OTC	Male neonates (older in girls)	Blood ammonia, AA; urinary OA, purines/pyrimidines (orotic acid excretion)
ASS1	Neonates to young children	
SLC25A13		
SLC25A15		
FAH		Blood succinylacetone; urinary OA, succinylacetone
Disorders of carbohydrate metabolism		
GALT	Neonates	Blood galactose; galactose-1-phosphate in erythrocytes
ALDOB	Neonates to infants	Urinary AA, sugar chromatogram
PCK1		Blood ammonia, AA; urinary OA
SLC37A4	Infants to adults	Glycoprotein isoelectrophoresis
Disorders of fatty acid metabolism		
ACADVL	Infants to young children	Blood acylcarnitine analysis; urinary OA
SLC22A5	Neonates	Blood acylcarnitine analysis; urinary OA; enzyme activity in fibroblasts
ETFDH	Infant	
TALDO1	Neonates	Urinary/plasma polyols; enzyme activity in fibroblasts
Disorders of energy substrate metabolism		
SUCLG1	Neonates to infants	Blood lactate; plasma AA; urine OA; muscle respiratory chain enzyme activity
SUCLA2		
DLD		Blood lactate; plasma AA; urine OA; enzyme activity in fibroblasts
Mitochondrial disorders		
POLG	Neonates to infants or older[a]	Blood lactate, pyruvate, AA; urinary lactate; muscle respiratory chain enzyme activity
POLG2	Neonates	
TWNK		
DGUOK		
MPV17	Neonates to infants	
RRM2B	Infants to adolecents	
TRMU	Neonates and infants	
LARS2		
FARS2		
WARS2	Young child[a]	
GFM1	Neonates	
TSFM		
ACAD9	Neonates to infants	
BCS1L		
UQCRC2		
SCO1	Neonates	
SERAC1		
Disorders of vesicular trafficking		
NBAS	Infants to young adults	
RINT1	Infants to young children	
SCYL1		Blood γ-glutamyl-transferase

(Continues)

TABLE 1 (Continued)

Disorder	Age group	Investigations
EIF2AK3		Blood glucose
Aminoacyl-tRNA synthetase deficiencies		
LARS1	Neonates to young children	
IARS1		
Wilson disease		
ATP7B	Young children to young adults	Blood caeruloplasmin, copper; urine copper; Kayser–Fleischer rings
Niemann–Pick type C		
NPC1	Neonates	Blood chitotriosidase activity, white cell enzymology; filipin staining of skin fibroblasts
Disorders of immune regulation		
PRF1	Neonates to infants	Blood ferritin, triglycerides, fibrinogen, perforin, granule release assay, soluble CD25
UNC13D		
STX11		
STXBP2		
ZNFX1	Infants to young children	
XIAP	Young child	Blood lymphocyte subpopulations, immunoglobulin G, A and M, XIAP, SAP
TNFAIP3	Infants and young children	
STAT1		Blood autoantibody profile, signal transducer and activator of transcription 1 phosphorylation
FOXP3	Young child	Blood lymphocyte subpopulations, immunoglobulin G, A and M
AIRE	Infants and young children	Blood autoantibody profile
ITCH	Infant	
Red cell disorders		
SPTB	Neonates	Peripheral blood/bone marrow smear
PKLR		
CDAN1		

Note: The table lists previously reported monogenic aetiologies of ALF. The investigations column are conventional laboratory tests that may be considered prior to genetic testing which is increasingly performed at the outset in ALF to help make decisions regarding emergency liver transplantation.
Abbreviations: AA, amino acid; ALF, acute liver failure; OA, organic acid; SAP, signalling lymphocytic activation molecule associated protein; XIAP, X-linked inhibitor of apoptosis protein.
[a]Sodium valproate administration was the precipitant of ALF.

biochemical testing unreliable[189] and it is difficult to clinically distinguish these infants from alternative aetiologies of neonatal ALF.

16 | UTILITY OF RAPID SEQUENCING IN ALF

Genome testing forms a fundamental component of the diagnostic work up in paediatric ALF today. In a clinical syndrome where a genetic aetiology is suspected in 20–37% of cases,[5,6] molecular diagnostics by high throughput sequencing is increasingly relied upon to guide patient management. In paediatric ALF, this is around the identification of candidates who are suitable for emergency, life-saving, LT or, indeed, those that are not because: (a) an effective, alternative treatment is available (e.g., galactosaemia), (b) LT is deemed futile (e.g., multisystemic disorders with severe neurological outlook) or (c) they are expected to recover with supportive management (e.g., reversible ALF in TRUM deficiency). However, the application of genetic sequencing is dependent on the timeframe in which the results may become available: paediatric ALF pose unique challenges as patients can lose

hepatic function within days and the clinical course is dynamic, unpredictable and rapidly progressive.[3,33,175] Furthermore, often these patients are difficult to distinguish from one another in the critical care setting. Rapid exome or genome sequencing[195–202] carried out in parallel with conventional diagnostic tests (Table 1) shows promise to enable timely, individualised, treatment decisions. Genome sequencing has shown superior diagnostic rates and cost-effectiveness[196,203] which coupled with a virtual panel (i.e., a phenotype-driven panel) may provide the efficiency required for paediatric ALF.

17 | CONCLUSIONS

ALF is a rapidly evolving clinical syndrome with devastating consequences. Reaching a diagnosis is challenging but earlier, more precise diagnosis is now possible with the technological and clinical advances in genomics. Challenges still remain, for instance, with regards to the speed at which clinically relevant, variant information is made available. Nonetheless, clinicians are better placed than ever to make individualised treatment decisions in this clinical syndrome marred by diverse aetiologies.

AUTHOR CONTRIBUTIONS

RH and RT contributed to the conception and design of the article. RH drafted the initial version of the manuscript. RT critically reviewed the manuscript. Article guarantor: Robert Hegarty.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

ORCID

Robert Hegarty https://orcid.org/0000-0002-5893-6464

REFERENCES

1. Hadzic N, Molnar E, Height S, et al. High prevalence of hemophagocytic lymphohistiocytosis in acute liver failure of infancy. *J Pediatr*. 2022;250:67-74.e1.
2. Bernal W, McPhail MJ. Acute liver failure. *J Hepatol*. 2021; 74(6):1489-1490.
3. Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006;148(5):652-658.
4. Squires JE, Alonso EM, Ibrahim SH, et al. North American Society for Pediatric Gastroenterology, Hepatology, and nutrition position paper on the diagnosis and management of pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2022; 74(1):138-158.
5. Hegarty R, Gibson P, Sambrotta M, et al. Study of acute liver failure in children using next generation sequencing technology. *J Pediatr*. 2021;236:124-130.
6. Lenz D, Schlieben LD, Shimura M, et al. Genetic landscape of pediatric acute liver failure of indeterminate origin. *Hepatology*. 2023.
7. Trey C, Davidson CS. The management of fulminant hepatic failure. *Prog Liver Dis*. 1970;3:282-298.
8. Bhaduri BR, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. *Semin Liver Dis*. 1996;16(4):349-355.
9. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342(8866):273-275.
10. Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. Acute liver failure: a curable disease by 2024? *J Hepatol*. 2015;62(1 Suppl):S112-S120.
11. Laemmle A, Gallagher RC, Keogh A, et al. Frequency and pathophysiology of acute liver failure in ornithine Transcarbamylase deficiency (OTCD). *PloS One*. 2016;11(4):e0153358.
12. Ibrahim MS, Gold JI, Woodall A, Yilmaz BS, Gissen P, Stepien KM. Diagnostic and management issues in patients with late-onset ornithine transcarbamylase deficiency. *Children*. 2023;10(8):1368.
13. Selvanathan A, Hertzog A, Lemberg DA, Ellaway C. Ornithine transcarbamylase deficiency presenting as acute liver failure in girls: a paediatric case series. *J Pediatr Gastroenterol Nutr*. 2020;71(2):208-210.
14. Brassier A, Gobin S, Arnoux JB, et al. Long-term outcomes in ornithine transcarbamylase deficiency: a series of 90 patients. *Orphanet J Rare Dis*. 2015;10:58.
15. Weiss N, Mochel F, Rudler M, et al. Peak hyperammonemia and atypical acute liver failure: the eruption of an urea cycle disorder during hyperemesis gravidarum. *J Hepatol*. 2017;68:185-192.
16. Garcia Vega M, Andrade JD, Morais A, et al. Urea cycle disorders and indications for liver transplantation. *Front Pediatr*. 2023;11:1103757.
17. Scharre S, Posset R, Garbade SF, et al. Predicting the disease severity in male individuals with ornithine transcarbamylase deficiency. *Ann Clin Transl Neurol*. 2022;9(11):1715-1726.
18. Lo RS, Cromie GA, Tang M, et al. The functional impact of 1,570 individual amino acid substitutions in human OTC. *Am J Hum Genet*. 2023;110(5):863-879.
19. Meyburg J, Opladen T, Spiekerkotter U, et al. Human heterologous liver cells transiently improve hyperammonemia and ureagenesis in individuals with severe urea cycle disorders. *J Inherit Metab Dis*. 2018;41(1):81-90.
20. Smets F, Dobbelaere D, McKiernan P, et al. Phase I/II trial of liver-derived mesenchymal stem cells in pediatric liver-based metabolic disorders: a prospective, open label, multicenter, partially randomized, safety study of one cycle of heterologous human adult liver-derived progenitor cells (HepaStem) in urea cycle disorders and Crigler-Najjar syndrome patients. *Transplantation*. 2019;103(9):1903-1915.
21. de Groot MJ, Cuppen M, Eling M, et al. Metabolic investigations prevent liver transplantation in two young children with citrullinemia type I. *J Inherit Metab Dis*. 2010;33(Suppl 3): S413-S416.
22. Faghfoury H, Baruteau J, de Baulny HO, Haberle J, Schulze A. Transient fulminant liver failure as an initial presentation in citrullinemia type I. *Mol Genet Metab*. 2011; 102(4):413-417.
23. Zielonka M, Kolker S, Gleich F, et al. Early prediction of phenotypic severity in citrullinemia type 1. *Ann Clin Transl Neurol*. 2019;6(9):1858-1871.

24. Vara R, Dhawan A, Deheragoda M, et al. Liver transplantation for neonatal-onset citrullinemia. *Pediatr Transplant*. 2018;22(4):e13191.
25. Shanmugam NP, Valamparampil JJ, Reddy MS, et al. Auxiliary partial orthotopic liver transplantation for monogenic metabolic liver diseases: single-centre experience. *JIMD Rep*. 2019;45:29-36.
26. Saheki T, Kobayashi K, Iijima M, et al. Adult-onset type II citrullinemia and idiopathic neonatal hepatitis caused by citrin deficiency: involvement of the aspartate glutamate carrier for urea synthesis and maintenance of the urea cycle. *Mol Genet Metab*. 2004;81(Suppl 1):S20-S26.
27. Ohura T, Kobayashi K, Tazawa Y, et al. Clinical pictures of 75 patients with neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). *J Inherit Metab Dis*. 2007;30(2):139-144.
28. Zhang MH, Gong JY, Wang JS. Citrin deficiency presenting as acute liver failure in an eight-month-old infant. *World J Gastroenterol*. 2015;21(23):7331-7334.
29. Fecarotta S, Parenti G, Vajro P, et al. HHH syndrome (hyperornithinaemia, hyperammonaemia, homocitrullinuria), with fulminant hepatitis-like presentation. *J Inherit Metab Dis*. 2006;29(1):186-189.
30. Das AM. Clinical utility of nitisinone for the treatment of hereditary tyrosinemia type-1 (HT-1). *Appl Clin Genet*. 2017;10:43-48.
31. Chinsky JM, Singh R, Ficicioglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. *Genet Med*. 2017;19(12):1380-1395.
32. Celik M, Akdeniz O, Ozbek MN, Kirbiyik O. Neonatal classic galactosemia-diagnosis, clinical profile and molecular characteristics in unscreened Turkish population. *J Trop Pediatr*. 2022;68(6):1-8.
33. Hegarty R, Hadzic N, Gissen P, Dhawan A. Inherited metabolic disorders presenting as acute liver failure in newborns and young children: King's College Hospital experience. *Eur J Pediatr*. 2015;174(10):1387-1392.
34. Bitar R, Thwaites R, Davison S, Rajwal S, McClean P. Liver failure in early infancy: aetiology, presentation, and outcome. *J Pediatr Gastroenterol Nutr*. 2017;64(1):70-75.
35. Padilla CD, Lam ST. Issues on universal screening for galactosemia. *Ann Acad Med Singapore*. 2008;37(12 Suppl):39-43.
36. Bernhardt I, Glamuzina E, Ryder B, et al. The risk of classical galactosaemia in newborns with borderline galactose metabolites on newborn screening. *JIMD Rep*. 2023;64(2):180-186.
37. Bosch AM. Classic galactosemia: dietary dilemmas. *J Inherit Metab Dis*. 2011;34(2):257-260.
38. Bouteldja N, Timson DJ. The biochemical basis of hereditary fructose intolerance. *J Inherit Metab Dis*. 2010;33(2):105-112.
39. Li H, Byers HM, Diaz-Kuan A, et al. Acute liver failure in neonates with undiagnosed hereditary fructose intolerance due to exposure from widely available infant formulas. *Mol Genet Metab*. 2018;123(4):428-432.
40. Santra S, Cameron JM, Shyr C, et al. Cytosolic phosphoenolpyruvate carboxykinase deficiency presenting with acute liver failure following gastroenteritis. *Mol Genet Metab*. 2016;118(1):21-27.
41. Raynor A, Haouari W, Ng BG, et al. SLC37A4-CDG: new biochemical insights for an emerging congenital disorder of glycosylation with major coagulopathy. *Clin Chim Acta*. 2021;521:104-106.
42. Ng BG, Sosicka P, Fenaille F, et al. A mutation in SLC37A4 causes a dominantly inherited congenital disorder of glycosylation characterized by liver dysfunction. *Am J Hum Genet*. 2021;108(6):1040-1052.
43. Williams M, Valayannopoulos V, Altassan R, et al. Clinical, biochemical, and molecular overview of transaldolase deficiency and evaluation of the endocrine function: update of 34 patients. *J Inherit Metab Dis*. 2019;42(1):147-158.
44. Verhoeven NM, Wallot M, Huck JH, et al. A newborn with severe liver failure, cardiomyopathy and transaldolase deficiency. *J Inherit Metab Dis*. 2005;28(2):169-179.
45. Eyaid W, Al Harbi T, Anazi S, et al. Transaldolase deficiency: report of 12 new cases and further delineation of the phenotype. *J Inherit Metab Dis*. 2013;36(6):997-1004.
46. Grammatikopoulos T, Hadzic N, Foskett P, et al. Liver disease and risk of hepatocellular carcinoma in children with mutations in TALDO1. *Hepatol Commun*. 2022;6(3):473-479.
47. Balasubramaniam S, Wamelink MM, Ngu LH, et al. Novel heterozygous mutations in TALDO1 gene causing transaldolase deficiency and early infantile liver failure. *J Pediatr Gastroenterol Nutr*. 2011;52(1):113-116.
48. Olpin SE. Pathophysiology of fatty acid oxidation disorders and resultant phenotypic variability. *J Inherit Metab Dis*. 2013;36(4):645-658.
49. Odaib AA, Shneider BL, Bennett MJ, et al. A defect in the transport of long-chain fatty acids associated with acute liver failure. *N Engl J Med*. 1998;339(24):1752-1757.
50. Alonso EM. Acute liver failure in children: the role of defects in fatty acid oxidation. *Hepatology*. 2005;41(4):696-699.
51. Jain S, Kumar K, Malhotra S, Sibal A. Rare case of primary carnitine deficiency presenting as acute liver failure. *BMJ Case Rep*. 2022;15(7):1-3.
52. Iacobazzi V, Invernizzi F, Baratta S, et al. Molecular and functional analysis of SLC25A20 mutations causing carnitine-acylcarnitine translocase deficiency. *Hum Mutat*. 2004;24(4):312-320.
53. Keshri S, Goel AK, Johns J, Shah S. "liver failure in an infant of late-onset glutaric aciduria type II": case report. *Indian J Clin Biochem*. 2023;38(4):545-549.
54. Santos L, Patterson A, Moreea SM, Lippiatt CM, Walter J, Henderson M. Acute liver failure in pregnancy associated with maternal MCAD deficiency. *J Inherit Metab Dis*. 2007;30(1):103.
55. Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab*. 2000;71(1–2):182-189.
56. Baruteau J, Sachs P, Broue P, et al. Clinical and biological features at diagnosis in mitochondrial fatty acid beta-oxidation defects: a French pediatric study from 187 patients. *J Inherit Metab Dis*. 2014;37(1):137-139.
57. Saudubray JM, Martin D, de Lonlay P, et al. Recognition and management of fatty acid oxidation defects: a series of 107 patients. *J Inherit Metab Dis*. 1999;22(4):488-502.
58. Carrozzo R, Verrigni D, Rasmussen M, et al. Succinate-CoA ligase deficiency due to mutations in SUCLA2 and SUCLG1:

phenotype and genotype correlations in 71 patients. *J Inherit Metab Dis*. 2016;39(2):243-252.
59. Van Hove JL, Saenz MS, Thomas JA, et al. Succinyl-CoA ligase deficiency: a mitochondrial hepatoencephalomyopathy. *Pediatr Res*. 2010;68(2):159-164.
60. Wongkittichote P, Cuddapah SR, Master SR, et al. Biochemical characterization of patients with dihydrolipoamide dehydrogenase deficiency. *JIMD Rep*. 2023;64(5):367-374.
61. Brassier A, Ottolenghi C, Boutron A, et al. Dihydrolipoamide dehydrogenase deficiency: a still overlooked cause of recurrent acute liver failure and Reye-like syndrome. *Mol Genet Metab*. 2013;109(1):28-32.
62. Alfarsi A, Alfadhel M, Alameer S, et al. The phenotypic spectrum of dihydrolipoamide dehydrogenase deficiency in Saudi Arabia. *Mol Genet Metab Rep*. 2021;29:100817.
63. Cameron JM, Levandovskiy V, Mackay N, et al. Novel mutations in dihydrolipoamide dehydrogenase deficiency in two cousins with borderline-normal PDH complex activity. *Am J Med Genet A*. 2006;140(14):1542-1552.
64. Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. *Ann Neurol*. 2001;49(3):377-383.
65. Cormier-Daire V, Chretien D, Rustin P, et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. *J Pediatr*. 1997;130(5):817-822.
66. Garcia-Cazorla A, De Lonlay P, Nassogne MC, Rustin P, Touati G, Saudubray JM. Long-term follow-up of neonatal mitochondrial cytopathies: a study of 57 patients. *Pediatrics*. 2005;116(5):1170-1177.
67. Taylor SA, Whitington PF. Neonatal acute liver failure. *Liver Transpl*. 2016;22(5):677-685.
68. Gorman GS, Chinnery PF, DiMauro S, et al. Mitochondrial diseases. *Nat Rev Dis Primers*. 2016;2:16080.
69. Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. *Nat Rev Neurol*. 2019;15(1):40-52.
70. Hynynen J, Komulainen T, Tukiainen E, et al. Acute liver failure after valproate exposure in patients with POLG1 mutations and the prognosis after liver transplantation. *Liver Transpl*. 2014;20(11):1402-1412.
71. Mindikoglu AL, King D, Magder LS, Ozolek JA, Mazariegos GV, Shneider BL. Valproic acid-associated acute liver failure in children: case report and analysis of liver transplantation outcomes in the United States. *J Pediatr*. 2011;158(5):802-807.
72. Thomson MA, Lynch S, Strong R, Shepherd RW, Marsh W. Orthotopic liver transplantation with poor neurologic outcome in valproate-associated liver failure: a need for critical risk-benefit appraisal in the use of valproate. *Transplant Proc*. 2000;32(1):200-203.
73. McKiernan P. Acute liver failure after valproate exposure: liver transplantation may be indicated beyond childhood. *Liver Transpl*. 2014;20(11):1287-1289.
74. Borsche M, Dulovic-Mahlow M, Baumann H, et al. POLG2-linked mitochondrial disease: functional insights from new mutation carriers and review of the literature. *Cerebellum*. 2023.
75. Hoff KE, DeBalsi KL, Sanchez-Quintero MJ, et al. Characterization of the human homozygous R182W POLG2 mutation in mitochondrial DNA depletion syndrome. *PloS One*. 2018;13(8):e0203198.
76. Li X, Li L, Sun Y, et al. Whole exome sequencing reveals two novel compound heterozygous mutations in TWNK as a cause of the hepatocerebral form of mitochondrial DNA depletion syndrome: a case report. *BMC Med Genet*. 2019;20(1):146.
77. Prasad C, Melancon SB, Rupar CA, et al. Exome sequencing reveals a homozygous mutation in TWINKLE as the cause of multisystemic failure including renal tubulopathy in three siblings. *Mol Genet Metab*. 2013;108(3):190-194.
78. Jacinto S, Guerreiro P, de Oliveira RM, et al. MPV17 mutations are associated with a quiescent energetic metabolic profile. *Front Cell Neurosci*. 2021;15:641264.
79. Uusimaa J, Evans J, Smith C, et al. Clinical, biochemical, cellular and molecular characterization of mitochondrial DNA depletion syndrome due to novel mutations in the MPV17 gene. *Eur J Hum Genet*. 2014;22(2):184-191.
80. Shimura M, Kuranobu N, Ogawa-Tominaga M, et al. Clinical and molecular basis of hepatocerebral mitochondrial DNA depletion syndrome in Japan: evaluation of outcomes after liver transplantation. *Orphanet J Rare Dis*. 2020;15(1):169.
81. Vara R, Pinon M, Fratter C, Hegarty R, Hadzic N. Hepatic presentations of mitochondrial DNA depletion syndrome in children: a single tertiary liver centre experience. *J Inherit Metab Dis*. 2023;46(4):634-648.
82. Vilarinho S, Sari S, Yilmaz G, et al. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic noncirrhotic portal hypertension. *Hepatology*. 2016;63(6):1977-1986.
83. Sarzi E, Bourdon A, Chretien D, et al. Mitochondrial DNA depletion is a prevalent cause of multiple respiratory chain deficiency in childhood. *J Pediatr*. 2007;150(5):531-534.
84. Hassan S, Mahmoud A, Mohammed TO, Mohammad S. Pediatric liver transplantation from a living donor in mitochondrial disease: good outcomes in DGUOK deficiency? *Pediatr Transplant*. 2020;24(4):e13714.
85. Jankowska I, Czubkowski P, Rokicki D, et al. Acute liver failure due to DGUOK deficiency-is liver transplantation justified? *Clin Res Hepatol Gastroenterol*. 2021;45(1):101408.
86. Grabhorn E, Tsiakas K, Herden U, et al. Long-term outcomes after liver transplantation for deoxyguanosine kinase deficiency: a single-center experience and a review of the literature. *Liver Transpl*. 2014;20(4):464-472.
87. Valencia CA, Wang X, Wang J, et al. Deep sequencing reveals novel genetic variants in children with acute liver failure and tissue evidence of impaired energy metabolism. *PloS One*. 2016;11(8):e0156738.
88. Zeharia A, Shaag A, Pappo O, et al. Acute infantile liver failure due to mutations in the TRMU gene. *Am J Hum Genet*. 2009;85(3):401-407.
89. Vogel GF, Mozer-Glassberg Y, Landau YE, et al. Genotypic and phenotypic spectrum of infantile liver failure due to pathogenic TRMU variants. *Genet Med*. 2023;25:100314.
90. Murali CN, Soler-Alfonso C, Loomes KM, et al. TRMU deficiency: a broad clinical spectrum responsive to cysteine supplementation. *Mol Genet Metab*. 2021;132(2):146-153.
91. Riley LG, Rudinger-Thirion J, Schmitz-Abe K, et al. LARS2 variants associated with hydrops, lactic acidosis, sideroblastic anemia, and multisystem failure. *JIMD Rep*. 2016;28:49-57.
92. Chen W, Rehsi P, Thompson K, et al. Clinical and molecular characterization of novel FARS2 variants causing neonatal mitochondrial disease. *Mol Genet Metab*. 2023;140(3):107657.
93. Almannai M, Wang J, Dai H, et al. FARS2 deficiency; new cases, review of clinical, biochemical, and molecular spectra,

and variants interpretation based on structural, functional, and evolutionary significance. *Mol Genet Metab*. 2018;125(3): 281-291.
94. Vantroys E, Smet J, Vanlander AV, et al. Severe hepatopathy and neurological deterioration after start of valproate treatment in a 6-year-old child with mitochondrial tryptophanyl-tRNA synthetase deficiency. *Orphanet J Rare Dis*. 2018; 13(1):80.
95. Wang F, Zhang D, Zhang D, Li P, Gao Y. Mitochondrial protein translation: emerging roles and clinical significance in disease. *Front Cell Dev Biol*. 2021;9:675465.
96. Coenen MJ, Antonicka H, Ugalde C, et al. Mutant mitochondrial elongation factor G1 and combined oxidative phosphorylation deficiency. *N Engl J Med*. 2004;351(20):2080-2086.
97. Valente L, Tiranti V, Marsano RM, et al. Infantile encephalopathy and defective mitochondrial DNA translation in patients with mutations of mitochondrial elongation factors EFG1 and EFTu. *Am J Hum Genet*. 2007;80(1):44-58.
98. Ravn K, Schonewolf-Greulich B, Hansen RM, et al. Neonatal mitochondrial hepatoencephalopathy caused by novel GFM1 mutations. *Mol Genet Metab Rep*. 2015;3:5-10.
99. Smeitink JA, Elpeleg O, Antonicka H, et al. Distinct clinical phenotypes associated with a mutation in the mitochondrial translation elongation factor EFTs. *Am J Hum Genet*. 2006; 79(5):869-877.
100. Vedrenne V, Galmiche L, Chretien D, de Lonlay P, Munnich A, Rotig A. Mutation in the mitochondrial translation elongation factor EFTs results in severe infantile liver failure. *J Hepatol*. 2012;56(1):294-297.
101. von Kleist-Retzow JC, Cormier-Daire V, de Lonlay P, et al. A high rate (20%-30%) of parental consanguinity in cytochrome-oxidase deficiency. *Am J Hum Genet*. 1998;63(2):428-435.
102. Fassone E, Rahman S. Complex I deficiency: clinical features, biochemistry and molecular genetics. *J Med Genet*. 2012;49(9): 578-590.
103. Lesner NP, Wang X, Chen Z, et al. Differential requirements for mitochondrial electron transport chain components in the adult murine liver. *Elife*. 2022;11:1-29.
104. He M, Rutledge SL, Kelly DR, et al. A new genetic disorder in mitochondrial fatty acid beta-oxidation: ACAD9 deficiency. *Am J Hum Genet*. 2007;81(1):87-103.
105. Haack TB, Danhauser K, Haberberger B, et al. Exome sequencing identifies ACAD9 mutations as a cause of complex I deficiency. *Nat Genet*. 2010;42(12):1131-1134.
106. Repp BM, Mastantuono E, Alston CL, et al. Clinical, biochemical and genetic spectrum of 70 patients with ACAD9 deficiency: is riboflavin supplementation effective? *Orphanet J Rare Dis*. 2018;13(1):120.
107. de Lonlay P, Valnot I, Barrientos A, et al. A mutant mitochondrial respiratory chain assembly protein causes complex III deficiency in patients with tubulopathy, encephalopathy and liver failure. *Nat Genet*. 2001;29(1):57-60.
108. Iwama I, Baba Y, Kagimoto S, et al. Case report of a successful liver transplantation for acute liver failure due to mitochondrial respiratory chain complex III deficiency. *Transplant Proc*. 2011;43(10):4025-4028.
109. Gaignard P, Eyer D, Lebigot E, et al. UQCRC2 mutation in a patient with mitochondrial complex III deficiency causing recurrent liver failure, lactic acidosis and hypoglycemia. *J Hum Genet*. 2017;62(7):729-731.
110. Vesela K, Hansikova H, Tesarova M, et al. Clinical, biochemical and molecular analyses of six patients with isolated cytochrome c oxidase deficiency due to mutations in the SCO2 gene. *Acta Paediatr*. 2004;93(10):1312-1317.
111. Valnot I, Osmond S, Gigarel N, et al. Mutations of the SCO1 gene in mitochondrial cytochrome c oxidase deficiency with neonatal-onset hepatic failure and encephalopathy. *Am J Hum Genet*. 2000;67(5):1104-1109.
112. Vilarinho S, Choi M, Jain D, et al. Individual exome analysis in diagnosis and management of paediatric liver failure of indeterminate aetiology. *J Hepatol*. 2014;61(5):1056-1063.
113. Sarig O, Goldsher D, Nousbeck J, et al. Infantile mitochondrial hepatopathy is a cardinal feature of MEGDEL syndrome (3-methylglutaconic aciduria type IV with sensorineural deafness, encephalopathy and Leigh-like syndrome) caused by novel mutations in SERAC1. *Am J Med Genet A*. 2013;161A (9):2204-2215.
114. Sequeira S, Rodrigues M, Jacinto S, Wevers RA, Wortmann SB. MEGDEL syndrome: expanding the phenotype and new mutations. *Neuropediatrics*. 2017;48(5):382-384.
115. Finsterer J, Scorza FA, Fiorini AC, Scorza CA. MEGDEL syndrome. *Pediatr Neurol*. 2020;110:25-29.
116. Harbulot C, Paquay S, Dorboz I, et al. Transient neonatal renal failure and massive polyuria in MEGDEL syndrome. *Mol Genet Metab Rep*. 2016;7:8-10.
117. Wortmann SB, Vaz FM, Gardeitchik T, et al. Mutations in the phospholipid remodeling gene SERAC1 impair mitochondrial function and intracellular cholesterol trafficking and cause dystonia and deafness. *Nat Genet*. 2012;44(7):797-802.
118. Maksimova N, Hara K, Nikolaeva I, et al. Neuroblastoma amplified sequence gene is associated with a novel short stature syndrome characterised by optic nerve atrophy and Pelger-Huet anomaly. *J Med Genet*. 2010;47(8):538-548.
119. Haack TB, Staufner C, Kopke MG, et al. Biallelic mutations in NBAS cause recurrent acute liver failure with onset in infancy. *Am J Hum Genet*. 2015;97(1):163-169.
120. Staufner C, Haack TB, Kopke MG, et al. Recurrent acute liver failure due to NBAS deficiency: phenotypic spectrum, disease mechanisms, and therapeutic concepts. *J Inherit Metab Dis*. 2016;39(1):3-16.
121. Staufner C, Peters B, Wagner M, et al. Defining clinical subgroups and genotype-phenotype correlations in NBAS-associated disease across 110 patients. *Genet Med*. 2020;22(3): 610-621.
122. Hegarty RI V, Huang Z, Tengfei S, Grammatikopoulos T, Thompson R. Acute liver failure in NBAS deficiency: characterisation of pathobiology using fibroblasts from affected patients. *J Pediatr Gastroenterol Nutr*. 2022;74:705.
123. Bi X, Zhang Q, Chen L, et al. NBAS, a gene involved in cytotoxic degranulation, is recurrently mutated in pediatric hemophagocytic lymphohistiocytosis. *J Hematol Oncol*. 2022; 15(1):101.
124. Dhawan A, Chaijitraruch N, Fitzpatrick E, et al. Alginate microencapsulated human hepatocytes for the treatment of acute liver failure in children. *J Hepatol*. 2020;72(5): 877-884.

125. Launay N, Ruiz M, Planas-Serra L, et al. RINT1 deficiency disrupts lipid metabolism and underlies a complex hereditary spastic paraplegia. *J Clin Invest*. 2023;133(14):1-17.
126. Cousin MA, Conboy E, Wang JS, et al. RINT1 Bi-allelic variations cause infantile-onset recurrent acute liver failure and skeletal abnormalities. *Am J Hum Genet*. 2019;105(1):108-121.
127. Schmidt WM, Rutledge SL, Schule R, et al. Disruptive SCYL1 mutations underlie a syndrome characterized by recurrent episodes of liver failure, peripheral neuropathy, cerebellar atrophy, and ataxia. *Am J Hum Genet*. 2015;97(6):855-861.
128. Hamlin JN, Schroeder LK, Fotouhi M, et al. Scyl1 scaffolds class II Arfs to specific subcomplexes of coatomer through the gamma-COP appendage domain. *J Cell Sci*. 2014;127(Pt 7):1454-1463.
129. Lenz D, McClean P, Kansu A, et al. SCYL1 variants cause a syndrome with low gamma-glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration (CALFAN). *Genet Med*. 2018;20(10):1255-1265.
130. Shohet A, Cohen L, Haguel D, et al. Variant in SCYL1 gene causes aberrant splicing in a family with cerebellar ataxia, recurrent episodes of liver failure, and growth retardation. *Eur J Hum Genet*. 2019;27(2):263-268.
131. Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. *Nat Rev Neurol*. 2017;13(8):477-491.
132. Habeb AM, Deeb A, Johnson M, et al. Liver disease and other comorbidities in Wolcott-Rallison syndrome: different phenotype and variable associations in a large cohort. *Horm Res Paediatr*. 2015;83(3):190-197.
133. Tzakis AG, Nunnelley MJ, Tekin A, et al. Liver, pancreas and kidney transplantation for the treatment of Wolcott-Rallison syndrome. *Am J Transplant*. 2015;15(2):565-567.
134. Fuchs SA, Schene IF, Kok G, et al. Aminoacyl-tRNA synthetase deficiencies in search of common themes. *Genet Med*. 2019;21(2):319-330.
135. Casey JP, McGettigan P, Lynam-Lennon N, et al. Identification of a mutation in LARS as a novel cause of infantile hepatopathy. *Mol Genet Metab*. 2012;106(3):351-358.
136. Lenz D, Smith DEC, Crushell E, et al. Genotypic diversity and phenotypic spectrum of infantile liver failure syndrome type 1 due to variants in LARS1. *Genet Med*. 2020;22(11):1863-1873.
137. Kopajtich R, Murayama K, Janecke AR, et al. Biallelic IARS mutations cause growth retardation with prenatal onset, intellectual disability, muscular hypotonia, and infantile hepatopathy. *Am J Hum Genet*. 2016;99(2):414-422.
138. Smigiel R, Biela M, Biernacka A, et al. New evidence for association of recessive IARS gene mutations with hepatopathy, hypotonia, intellectual disability and growth retardation. *Clin Genet*. 2017;92(6):671-673.
139. Casey JP, Slattery S, Cotter M, et al. Clinical and genetic characterisation of infantile liver failure syndrome type 1, due to recessive mutations in LARS. *J Inherit Metab Dis*. 2015;38(6):1085-1092.
140. Esteve C, Roman C, DeLeusse C, et al. Novel partial loss-of-function variants in the tyrosyl-tRNA synthetase 1 (YARS1) gene involved in multisystem disease. *Eur J Med Genet*. 2021;64(10):104294.
141. La Fay C, Hoebeke C, Juzaud M, et al. Deep phenotyping of MARS1 (interstitial lung and liver disease) and LARS1 (infantile liver failure syndrome 1) recessive multisystemic disease using human phenotype ontology annotation: overlap and differences. Case report and review of literature. *Eur J Med Genet*. 2021;64(11):104334.
142. Schuch LA, Forstner M, Rapp CK, et al. FARS1-related disorders caused by bi-allelic mutations in cytosolic phenylalanyl-tRNA synthetase genes: look beyond the lungs! *Clin Genet*. 2021;99(6):789-801.
143. Czlonkowska A, Litwin T, Dusek P, et al. Wilson disease. *Nat Rev Dis Primers*. 2018;4(1):21.
144. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. *Liver Transpl*. 2005;11(4):441-448.
145. European Association for Study of Liver. EASL clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-685.
146. Davies SE, Williams R, Portmann B. Hepatic morphology and histochemistry of Wilson's disease presenting as fulminant hepatic failure: a study of 11 cases. *Histopathology*. 1989;15(4):385-394.
147. Devarbhavi H, Reddy VV, Singh R. Wilson disease presenting with acute on chronic liver failure: a single-center experience of outcome and predictors of mortality in 68 patients. *J Clin Exp Hepatol*. 2019;9(5):569-573.
148. Nayagam JS, Jeyaraj R, Foskett P, et al. ATP7B genotype and chronic liver disease treatment outcomes in Wilson disease: worse survival with loss-of-function variants. *Clin Gastroenterol Hepatol*. 2023;21(5):1323-1329 e1324.
149. Vanier MT. Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2010;5:16.
150. Vanier MT, Wenger DA, Comly ME, Rousson R, Brady RO, Pentchev PG. Niemann-Pick disease group C: clinical variability and diagnosis based on defective cholesterol esterification. A collaborative study on 70 patients. *Clin Genet*. 1988;33(5):331-348.
151. Yamada N, Inui A, Sanada Y, et al. Pediatric liver transplantation for neonatal-onset Niemann-Pick disease type C: Japanese multicenter experience. *Pediatr Transplant*. 2019;23(5):e13462.
152. Lemoine CP, Superina R, Mohammad S. Normal long-term neurologic and graft outcome after liver transplantation in an infant with Neimann-Pick type C disease. *Am J Transplant*. 2022;22(2):646-648.
153. Berendse K, Koot BGP, Klouwer FCC, et al. Hepatic symptoms and histology in 13 patients with a Zellweger spectrum disorder. *J Inherit Metab Dis*. 2019;42(5):955-965.
154. Klouwer FC, Berendse K, Ferdinandusse S, Wanders RJ, Engelen M, Poll-The BT. Zellweger spectrum disorders: clinical overview and management approach. *Orphanet J Rare Dis*. 2015;10:151.
155. Baes M, Veldhoven V. Hepatic dysfunction in peroxisomal disorders. *Biochim Biophys Acta*. 2016;1863(5):956-970.
156. Maxwell M, Bjorkman J, Nguyen T, et al. Pex13 inactivation in the mouse disrupts peroxisome biogenesis and leads to a Zellweger syndrome phenotype. *Mol Cell Biol*. 2003;23(16):5947-5957.
157. Keane MH, Overmars H, Wikander TM, et al. Bile acid treatment alters hepatic disease and bile acid transport in

peroxisome-deficient PEX2 Zellweger mice. *Hepatology*. 2007; 45(4):982-997.
158. Lefeber DJ, Freeze HH, Steet R, Kinoshita T. Congenital disorders of glycosylation. In: Varki A, Cummings RD, Esko JD, et al., eds. *Essentials of Glycobiology*. 4th ed. Cold Spring; 2022:599-614.
159. Marques-da-Silva D, Dos Reis FV, Monticelli M, et al. Liver involvement in congenital disorders of glycosylation (CDG). A systematic review of the literature. *J Inherit Metab Dis*. 2017; 40(2):195-207.
160. Colantuono R, D'Acunto E, Melis D, Vajro P, Freeze HH, Mandato C. Liver involvement in congenital disorders of glycosylation: a systematic review. *J Pediatr Gastroenterol Nutr*. 2021;73(4):444-454.
161. Witters P, Honzik T, Bauchart E, et al. Long-term follow-up in PMM2-CDG: are we ready to start treatment trials? *Genet Med*. 2019;21(5):1181-1188.
162. Brett A, Pinto C, Carvalho L, Garcia P, Diogo L, Goncalves I. Acute liver failure in under two year-olds—are there markers of metabolic disease on admission? *Ann Hepatol*. 2013;12(5): 791-796.
163. Cechova A, Altassan R, Borgel D, et al. Consensus guideline for the diagnosis and management of mannose phosphate isomerase-congenital disorder of glycosylation. *J Inherit Metab Dis*. 2020;43(4):671-693.
164. Lee PY, Cron RQ. The multifaceted immunology of cytokine storm syndrome. *J Immunol*. 2023;210(8):1015-1024.
165. Durand P, Debray D, Mandel R, et al. Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. *J Pediatr*. 2001;139(6):871-876.
166. Lenz D, Horby Jorgensen M, Kelly D, et al. Etiology and outcome of adult and pediatric acute liver failure in Europe. *J Pediatr Gastroenterol Nutr*. 2023;77(1):115-120.
167. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332-1343.
168. Stapp J, Wilkerson S, Stewart D, Coventry S, Mo JQ, Bove KE. Fulminant neonatal liver failure in siblings: probable congenital hemophagocytic lymphohistiocytosis. *Pediatr Dev Pathol*. 2006;9(3):239-244.
169. Vermeulen MJ, de Haas V, Mulder MF, Flohil C, Fetter WP, van de Kamp JM. Hydrops fetalis and early neonatal multiple organ failure in familial hemophagocytic lymphohistiocytosis. *Eur J Med Genet*. 2009;52(6):417-420.
170. Danhaive O, Caniglia M, Devito R, Piersigilli F, Corchia C, Auriti C. Neonatal liver failure and haemophagocytic lymphohistiocytosis caused by a new perforin mutation. *Acta Paediatr*. 2010;99(5):778-780.
171. Thadchanamoorthy V, Jayatunga MTR, Dayasiri K, et al. Exome sequencing detected an extremely rare case of foetal onset familial haemophagocytic lymphohistiocytosis type 5 presenting with hydrops foetalis. *BMC Med Genomics*. 2021; 14(1):50.
172. Chartier ME, Deheragoda M, Gattens M, et al. Successful auxiliary liver transplant followed by hematopoietic stem cell transplantation in X-linked lymphoproliferative disease type 1. *Liver Transpl*. 2021;27(3):450-455.
173. Amir AZ, Ling SC, Naqvi A, et al. Liver transplantation for children with acute liver failure associated with secondary hemophagocytic lymphohistiocytosis. *Liver Transpl*. 2016; 22(9):1245-1253.
174. Alonso EM, Horslen SP, Behrens EM, Doo E. Pediatric acute liver failure of undetermined cause: a research workshop. *Hepatology*. 2017;65(3):1026-1037.
175. Narkewicz MR, Horslen S, Hardison RM, et al. A learning collaborative approach increases specificity of diagnosis of acute liver failure in pediatric patients. *Clin Gastroenterol Hepatol*. 2018;16(11):1801-1810 e1803.
176. Bucuvalas J, Filipovich L, Yazigi N, et al. Immunophenotype predicts outcome in pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2013;56(3):311-315.
177. Welz M, Eickhoff S, Abdullah Z, et al. Perforin inhibition protects from lethal endothelial damage during fulminant viral hepatitis. *Nat Commun*. 2018;9(1):4805.
178. Chapin CA, Burn T, Meijome T, et al. Indeterminate pediatric acute liver failure is uniquely characterized by a CD103(+) CD8(+) T-cell infiltrate. *Hepatology*. 2018;68(3):1087-1100.
179. Chapin CA, Burn TM, Diamond T, Loomes KM, Alonso EM, Behrens EM. Effector memory CD8 T-cells as a novel peripheral blood biomarker for activated T-cell pediatric acute liver failure. *PloS One*. 2023;18(6):e0286394.
180. Ho A, Orton R, Tayler R, et al. Adeno-associated virus 2 infection in children with non-A-E hepatitis. *Nature*. 2023; 617(7961):555-563.
181. Morfopoulou S, Buddle S, Torres Montaguth OE, et al. Genomic investigations of unexplained acute hepatitis in children. *Nature*. 2023;617(7961):564-573.
182. Okamoto T, Okajima H, Ogawa E, Yurugi K, Hatano E. The protective association of HLA-B*52:01, HLA-C*12:02, and DQB1*06:01 alleles with severe acute hepatitis of unknown origin in Japanese children. *J Hepatol*. 2023;80:e119-e121.
183. Pandurangi S, Malik A, Owens J, Valencia CA, Miethke AG, Center for Autoimmune Liver Disease Research Group. Deleterious variants in TNFAIP3 are associated with type II and seronegative pediatric autoimmune hepatitis. *J Hepatol*. 2023; 80:e26-e28.
184. Boehmer DFR, Koehler LM, Magg T, et al. A novel complete autosomal-recessive STAT1 LOF variant causes immunodeficiency with hemophagocytic lymphohistiocytosis-like hyperinflammation. *J Allergy Clin Immunol Pract*. 2020; 8(9):3102-3111.
185. Lopez SI, Ciocca M, Oleastro M, et al. Autoimmune hepatitis type 2 in a child with IPEX syndrome. *J Pediatr Gastroenterol Nutr*. 2011;53(6):690-693.
186. Sakaguchi H, Mizuochi T, Haruta M, et al. AIRE gene mutation presenting at age 2 years with autoimmune retinopathy and steroid-responsive acute liver failure: a case report and literature review. *Front Immunol*. 2021;12:687280.
187. Vavassori S, Chou J, Faletti LE, et al. Multisystem inflammation and susceptibility to viral infections in human ZNFX1 deficiency. *J Allergy Clin Immunol*. 2021;148(2):381-393.
188. Kleine-Eggebrecht N, Staufner C, Kathemann S, et al. Mutation in ITCH gene can cause syndromic multisystem autoimmune disease with acute liver failure. *Pediatrics*. 2019;143(2): e20181554.
189. Christensen RD, Nussenzveig RH, Yaish HM, Henry E, Eggert LD, Agarwal AM. Causes of hemolysis in neonates

with extreme hyperbilirubinemia. *J Perinatol*. 2014;34(8):616-619.
190. Agarwal AM, Nussenzveig RH, Reading NS, et al. Clinical utility of next-generation sequencing in the diagnosis of hereditary haemolytic anaemias. *Br J Haematol*. 2016;174(5):806-814.
191. Richmond CM, Campbell S, Foo HW, et al. Rapid identification of biallelic SPTB mutation in a neonate with severe congenital hemolytic anemia and liver failure. *Mol Syndromol*. 2020;11(1):50-55.
192. Raphael MF, Van Wijk R, Schweizer JJ, et al. Pyruvate kinase deficiency associated with severe liver dysfunction in the newborn. *Am J Hematol*. 2007;82(11):1025-1028.
193. Roy NB, Wilson EA, Henderson S, et al. A novel 33-gene targeted resequencing panel provides accurate, clinical-grade diagnosis and improves patient management for rare inherited anaemias. *Br J Haematol*. 2016;175(2):318-330.
194. Hegarty R. Pathogenic variants in *CDAN1* as a cause of severe congenital anaemia, acute liver failure and dysmorphism. 2023.
195. Miller NA, Farrow EG, Gibson M, et al. A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases. *Genome Med*. 2015;7:100.
196. French CE, Dolling H, Megy K, et al. Refinements and considerations for trio whole-genome sequence analysis when investigating Mendelian diseases presenting in early childhood. *HGG Adv*. 2022;3(3):100113.
197. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid targeted genomics in critically ill newborns. *Pediatrics*. 2017;140(4):e20162854.
198. Wells CF, Boursier G, Yauy K, et al. Rapid exome sequencing in critically ill infants: implementation in routine care from French regional hospital's perspective. *Eur J Hum Genet*. 2022;30(9):1076-1082.
199. Australian Genomics Health Alliance Acute Care Flagship, Lunke S, Eggers S, et al. Feasibility of ultra-rapid exome sequencing in critically ill infants and children with suspected monogenic conditions in the Australian public health care system. *JAMA*. 2020;323(24):2503-2511.
200. Freed AS, Clowes Candadai SV, Sikes MC, et al. The impact of rapid exome sequencing on medical management of critically ill children. *J Pediatr*. 2020;226:202-212.e1.
201. Owen MJ, Batalov S, Ellsworth KA, et al. Rapid whole genome sequencing for diagnosis of single locus genetic diseases in critically ill children. *Methods Mol Biol*. 2023;2621:217-239.
202. Dimmock DP, Clark MM, Gaughran M, et al. An RCT of rapid genomic sequencing among seriously ill infants results in high clinical utility, changes in management, and low perceived harm. *Am J Hum Genet*. 2020;107(5):942-952.
203. Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. *J Med Genet*. 2018;55(11):721-728.

How to cite this article: Hegarty R, Thompson RJ. Genetic aetiologies of acute liver failure. *J Inherit Metab Dis*. 2024;47(4):582-597. doi:10.1002/jimd.12733