

## REVIEW

# Disorders of vesicular trafficking presenting with recurrent acute liver failure: NBAS, RINT1, and SCYL1 deficiency

Bianca Peters<sup>1</sup> | Tal Dattner<sup>1</sup> | Lea D. Schlieben<sup>2,3</sup> | Tian Sun<sup>1</sup> |  
Christian Staufner<sup>1</sup>  | Dominic Lenz<sup>1</sup> 

<sup>1</sup>Medical Faculty Heidelberg, Center for Paediatric and Adolescent Medicine, Department I, Division of Paediatric Neurology and Metabolic Medicine, Heidelberg University, Heidelberg, Germany

<sup>2</sup>School of Medicine, Institute of Human Genetics, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

<sup>3</sup>Institute of Neurogenomics, Computational Health Centre, Helmholtz Zentrum München, Neuherberg, Germany

## Correspondence

Dominic Lenz, Center for Paediatric and Adolescent Medicine, University Hospital Heidelberg, Im Neuenheimer Feld 430, Heidelberg 69120, Germany.  
Email: [dominic.lenz@med.uni-heidelberg.de](mailto:dominic.lenz@med.uni-heidelberg.de)

## Funding information

Bundesministerium für Bildung und Forschung, Grant/Award Number: 01GM1906B

**Communicating Editor:** Carlos R. Ferreira

## Abstract

Among genetic disorders of vesicular trafficking, there are three causing recurrent acute liver failure (RALF): NBAS, RINT1, and SCYL1-associated disease. These three disorders are characterized by liver crises triggered by febrile infections and account for a relevant proportion of RALF causes. While the frequency and severity of liver crises in NBAS and RINT1-associated disease decrease with age, patients with *SCYL1* variants present with a progressive, cholestatic course. In all three diseases, there is a multisystemic, partially overlapping phenotype with variable expression, including liver, skeletal, and nervous systems, all organ systems with high secretory activity. There are no specific biomarkers for these diseases, and whole exome sequencing should be performed in patients with RALF of unknown etiology. NBAS, SCYL1, and RINT1 are involved in antegrade and retrograde vesicular trafficking. Pathomechanisms remain unclarified, but there is evidence of a decrease in concentration and stability of the protein primarily affected by the respective gene defect and its interaction partners, potentially causing impairment of vesicular transport. The impairment of protein secretion by compromised antegrade transport provides a possible explanation for different organ manifestations such as bone alteration due to lack of collagens or diabetes mellitus when insulin secretion is affected. Dysfunction of retrograde transport impairs membrane recycling and autophagy. The impairment of vesicular trafficking results in increased endoplasmic reticulum stress, which, in hepatocytes, can progress to hepatocytolysis. While there is no curative therapy, an early and consequent implementation of an emergency protocol seems crucial for optimal therapeutic management.

## KEYWORDS

CALFAN, disorders of vesicular trafficking, ILFS2, ILFS3, NBAS, pediatric acute liver failure, recurrent acute liver failure, RINT1, SCYL1

## 1 | INTRODUCTION

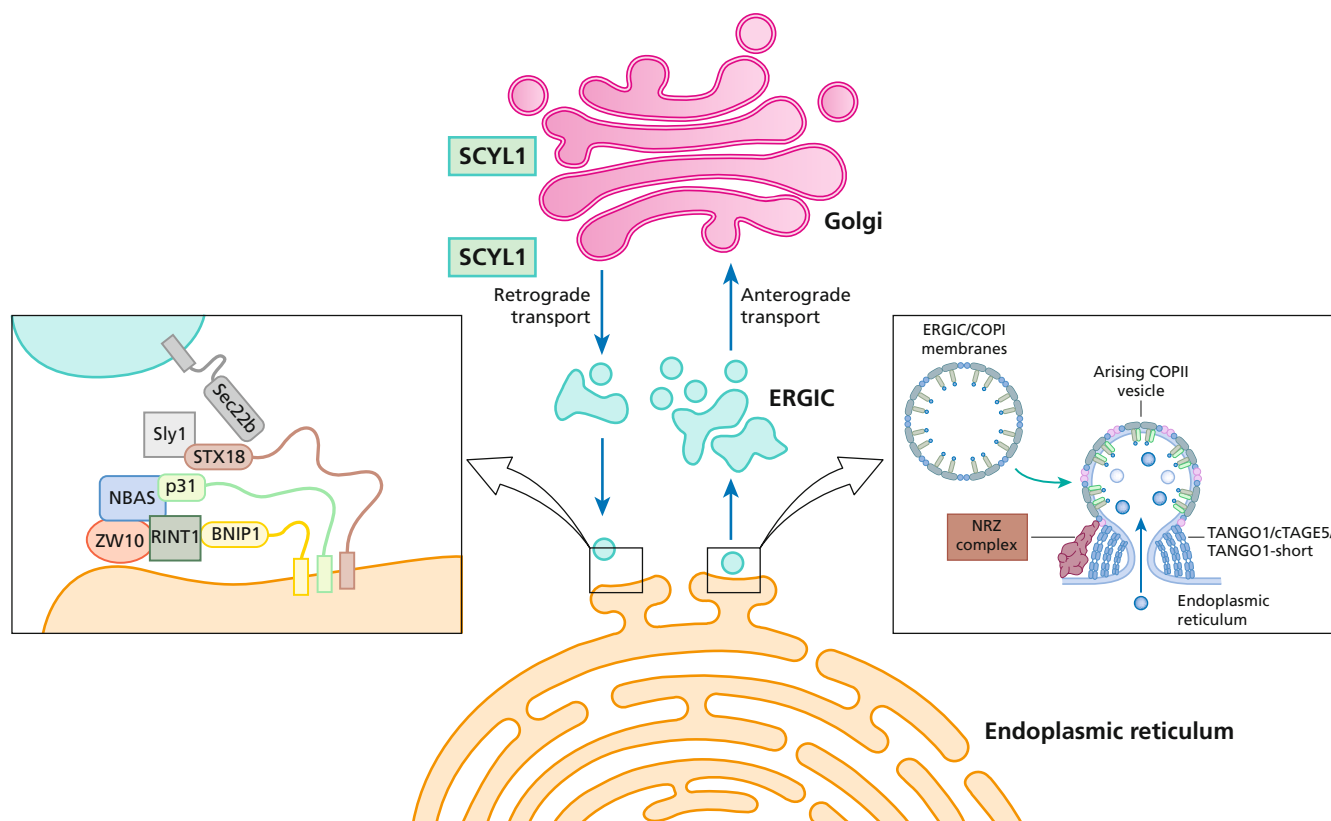
Pediatric acute liver failure (PALF) is a rare but life-threatening event. Epidemiological data on PALF is sparse,<sup>1</sup> but it accounts for approximately 8% of pediatric liver transplants performed in the United States (US) annually.<sup>2</sup> Clinical signs of PALF include abdominal pain, vomiting, jaundice, hepatosplenomegaly, ascites, and hepatic encephalopathy. Although an internationally standardized definition is lacking, PALF is most commonly defined according to the inclusion criteria of the PALF study group in the US: biochemical evidence of acute liver injury (elevated hepatic transaminase activity) or hepatocyte dysfunction characterized by elevated bilirubin as well as hepatic coagulopathy (elevated international normalized ratio (INR)  $\geq 1.5$  with evidence of hepatic encephalopathy, or INR  $\geq 2.0$  with or without encephalopathy) not corrected by vitamin K occurring in children without a known chronic liver disease.<sup>3</sup> In cases of recurrent episodes of acute liver failure, this definition is challenged, as there typically is an underlying, predisposing, mostly genetic—and therefore known—chronic condition affecting the liver. In most cases, liver function recovers in the interval, but in some cases, hepatic transaminases may remain above the upper limit of normal also in between the episodes of acute decompensation. The etiologies of PALF can be categorized as infectious, metabolic, and other genetic, autoimmune, vascular, toxin- or drug-related. In Europe, infectious and metabolic diseases are the most common causes.<sup>4</sup> The etiology of PALF remained unclear in up to 50% of cases,<sup>3–6</sup> which has improved by standardized diagnostic approaches<sup>7</sup> and in particular by the introduction of Next Generation Sequencing techniques in the field of hepatology.<sup>8</sup>

In this context, an increasing number of novel disease genes have been identified as “new” causes of PALF in recent years, which has significantly reduced the proportion of indeterminate PALF.<sup>9–12</sup> This gain in knowledge has been driven in particular by better availability of exome and genome sequencing in routine diagnostics. Among those are genetic disorders that predispose to episodes of severe liver dysfunction, which can be triggered by fever, infection, fasting, or stress. As these triggers can occur repeatedly, affected patients suffer from recurrent acute liver failure (RALF). These disorders can be categorized into four groups: urea cycle disorders (UCD), disorders of energy metabolism, disorders of protein translation, and disorders of vesicular trafficking.

Urea cycle disorders (UCDs) are caused by inherited deficiencies of the enzymes or transporters of the urea cycle pathway, leading to hyperammonemia. All UCDs

can be complicated by acute or chronic hepatic dysfunction, yet there are two predominant ones presenting with RALF: ornithine transcarbamylase (OTC) deficiency (OMIM #311250)<sup>13,14</sup> and hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome (OMIM#238970).<sup>15,16</sup> Beside febrile infections, high protein intake or catabolic phases can trigger liver crisis in these conditions. Disorders of energy metabolism presenting with RALF involve two specific mitochondrial diseases: tRNA mitochondrial 2-thiouridylase deficiency (*TRMU*; OMIM #613070)<sup>17</sup> and Dihydrolipoamide dehydrogenase deficiency (*DLD*; OMIM # 246900).<sup>18</sup> Disorders of protein translation include a growing group of recently identified cytosolic aminoacyl-tRNA synthetase (ARS) deficiencies, associated with different tissue-specific phenotypes. These include biallelic pathogenic variants in cytosolic leucyl-tRNA synthetase gene (*LARS1*) causing infantile liver failure syndrome 1 (ILFS1; OMIM # 615438),<sup>9,19,20</sup> biallelic pathogenic variants in cytosolic isoleucyl-tRNA synthetase gene (*IARS1*) leading to growth retardation, impaired intellectual development, hypotonia, and hepatopathy (GRIDHH; OMIM # 617093)<sup>21,22</sup> and biallelic pathogenic variants in the cytosolic methionyl-tRNA synthetase gene (*MARS1*) causing interstitial lung and liver disease (ILLD; OMIM #615486).<sup>23–25</sup> Also associated with the control of protein translation, Wolcott-Rallison syndrome (WRS), caused by mutations in *EIF2AK3*, presents with neonatal or early childhood-onset diabetes, growth retardation, bone alterations with epiphyseal dysplasia and RALF (OMIM #226980).<sup>26,27</sup>

However, the most prominent and emerging group is disorders of vesicular trafficking with NBAS (neuroblastoma amplified sequence) deficiency as the most prevalent disease entity in this category.<sup>8</sup> Disorders of cellular trafficking are inherited in an autosomal-recessive fashion, and to date, 346 genes have been shown to be involved in intracellular trafficking and linked to human disease.<sup>28</sup> Although cellular trafficking is an essential process in all cell types, defects in specific components of the trafficking system often manifest as tissue-specific phenotypes.<sup>29</sup> While a relevant fraction of these diseases affect the liver, only three are causing RALF (Figure 1)<sup>28</sup>: infantile liver failure syndrome type 2 (ILFS2) and type 3 (ILFS3) caused by pathogenic variants in *NBAS* and *RINT1*, respectively, as well as CALFAN (low gamma-glutamyltransferase ( $\gamma$ GT)-cholestasis, acute liver failure triggered by febrile infections, and neurodegeneration) syndrome associated with mutations in *SCYL1* (SCY1 like pseudokinase 1). This is the first systematic overview of the clinical presentation and pathomechanisms of these three vesicular trafficking disorders presenting with RALF.



**FIGURE 1** Role of NBAS, RINT1, and SCYL1 in vesicular trafficking. NBAS together with RINT1 and ZW10 form the NRZ complex which is part of the Syntaxin18 complex, a target soluble N-ethylmaleimide-sensitive factor attachment protein receptor (t-SNARE) at the endoplasmic reticulum, responsible for the docking and fusion of COPI vesicles in the retrograde transport between the GOLGI apparatus and the endoplasmic reticulum (ER). This same NRZ complex is equally involved in anterograde transport at the ER exit site, interacting with the TANGO1/cTAGE5/TANGO1-short ring for arising COPII vesicles to recruit ERGIC/COPI membranes.<sup>48</sup> SCYL1 scaffolds COPI vesicles in retrograde transport at the cis Golgi stack. Furthermore, it plays a role in GOLGI morphology. BNIP1, BCL2 interacting protein 1; ERGIC, ER-Golgi intermediate compartment; NBAS, neuroblastoma amplified sequence; NRZ complex, NBAS, RINT1, ZW10 complex; p31, Vesicle transport protein USE1; RINT-1, RAD50 interactor 1; SCYL1, SCYL1 like pseudokinase 1; Sec22b, SEC22 homolog B; Sly1: SH3-domain protein expressed in Lymphocytes 1; STX18, Syntaxin-18; ZW10, zw10 kinetochore protein.

## 2 | MAIN

### 2.1 | Infantile liver failure syndrome type 2—NBAS

Biallelic pathogenic variants in the neuroblastoma-amplified sequence (NBAS) gene are associated with a heterogeneous spectrum of clinical symptoms affecting multiple organ systems. By 2023, more than 160 cases have been published.<sup>30–44</sup> Patients in the literature originate from all continents and there is a wide genetic diversity with more than 70 distinct pathogenic variants identified.

NBAS-associated disease was first described in 2010 in the Yakut population, an isolated population living in the east of Russia. A homozygous missense variant (c. [5741G>A]; p.[Arg1914His]) was identified causing a clinical syndrome with short stature, optic atrophy, and

Pelger–Huët anomaly (SOPH syndrome; MIM: 614800).<sup>45</sup> Next, in 2015 biallelic variants in NBAS were associated with RALF referred to as infantile liver failure syndrome type 2 (ILFS2; MIM: 616483).<sup>11</sup> In 2020, a genotype–phenotype-association was described, dividing the phenotypic spectrum into three clinical subgroups based on the affected region of the NBAS protein ( $\beta$  propeller domain, Sec39 domain, C-terminus).<sup>43</sup> Still, this subgroup classification has its limitations, as it cannot be applied to all genotypes, and phenotypes may differ within one subgroup. Nevertheless, the classification applies to the majority of patients and simplifies the presentation of the heterogeneous phenotype.

Patients with missense variants affecting the Sec39 domain of NBAS present a predominantly hepatic phenotype, characterized by RALF. The only commonly reported trigger of liver crises is febrile infections. Typically, the first liver crisis occurs in infancy (median age of

onset 12 months), with a decreasing frequency and severity with increasing age. However, there are also cases of acute liver failure in early adulthood in this subgroup. Most patients suffer at least one severe crisis that meets the PALF study group inclusion criteria. Besides the fever-associated liver crises, Sec39 patients show normal liver function in the interval and only a few other disease manifestations, including short stature in about one-third of cases, mild facial anomalies, and NK (natural killer) cell deficiency to some extent (Table 1; Figure 2, Table S1).<sup>43</sup>

Patients with missense variants affecting the C-terminal part of the NBAS protein present with a multisystemic phenotype including short stature, delayed bone age, reduced bone mineral density (up to an osteogenesis imperfecta phenotype), marked facial dysmorphism, cutis laxa, reduced levels of immunoglobulins, optic atrophy, motor development delay, muscular hypotonia, and insulin-dependent diabetes (Table 1; Figure 2, Table S2).<sup>30–44</sup> Unlike in the Sec39 subgroup, these symptoms are independent of the patient's body temperature and do not improve with age. Most patients present with

**TABLE 1** Clinical phenotypes of NBAS, RINT1, and SCYL1 deficiency.

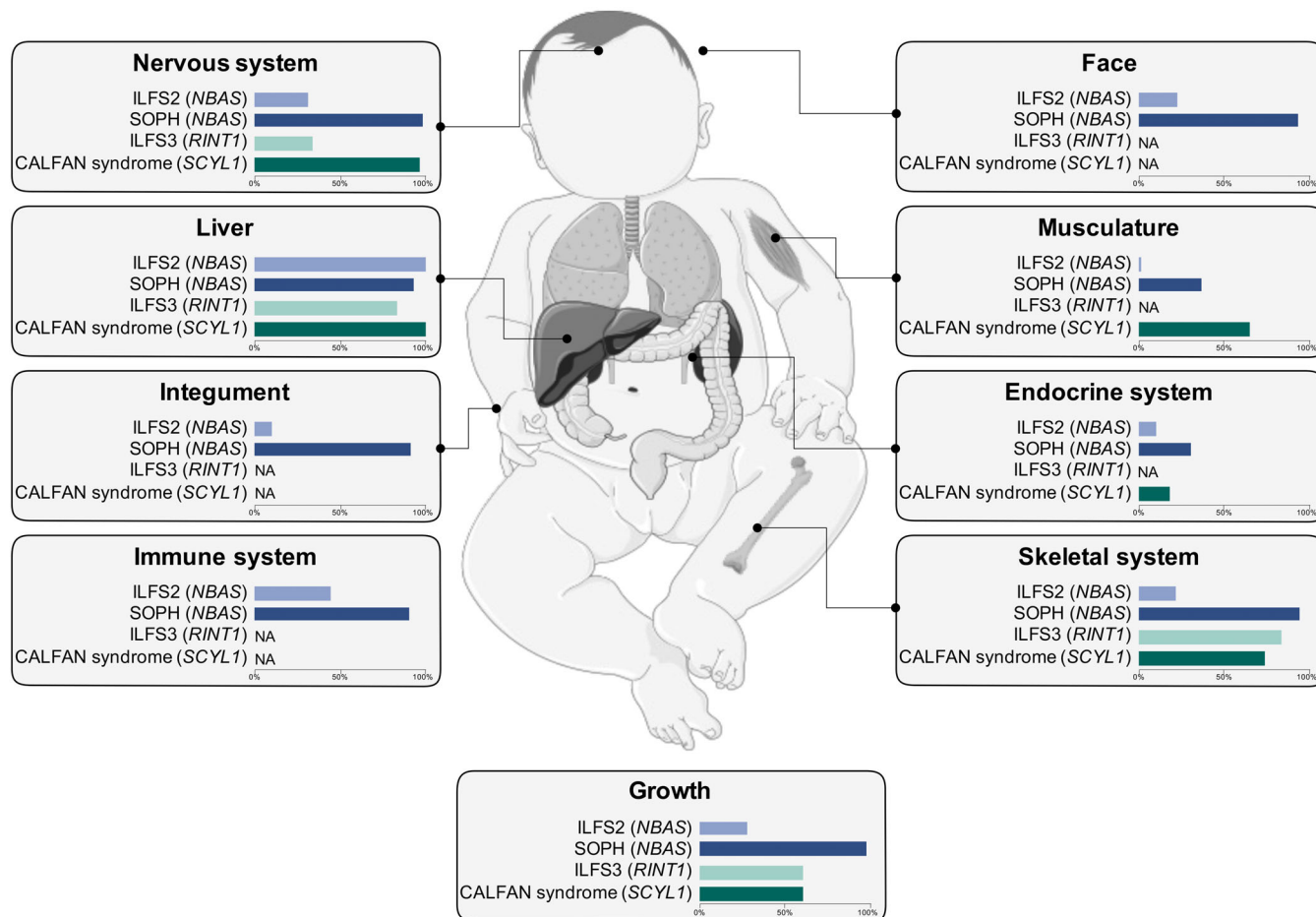
| Affected gene<br>Subgroup             | NBAS-associated diseases                               |                                                                                             | ILFS3                                                                                                            | CALFAN syndrome                                                                         |
|---------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
|                                       | NBAS                                                   |                                                                                             | RINT1                                                                                                            | SCYL1                                                                                   |
|                                       | ILFS2 <sup>a</sup>                                     | SOPH <sup>a</sup>                                                                           |                                                                                                                  |                                                                                         |
| Liver                                 | PALF/RALF; typically, massively elevated transaminases | Continuously elevated hepatic transaminases, increase during crisis                         | PALF                                                                                                             | Recurrent low- $\gamma$ GT cholestatic liver dysfunction, developing fibrosis, PALF     |
| Triggers of liver crisis              | Fever/infection                                        |                                                                                             | Fever/infection                                                                                                  | Fever/infection                                                                         |
| Age at onset of liver crises (median) | 12 months ( $n = 26$ ; range: 0–39 months)             | 7 months ( $n = 12$ ; range: 0–132 months)                                                  | 12 months ( $n = 5$ , range: 8–120 months)                                                                       | 12 months ( $n = 20$ ; range: 4–48 months)                                              |
| Mortality                             | 7 ( $n = 36$ )                                         | 4 ( $n = 28$ )                                                                              | 3 ( $n = 6$ )                                                                                                    | 0 ( $n = 23$ )                                                                          |
| Skeletal system                       | Short stature                                          | Short stature, vertebral body abnormalities, delayed bone age, reduced bone mineral density | Short stature, vertebral body abnormalities, kyphosis, wormian bones                                             | Short stature, hip/femur dysplasia, scoliosis, lumbar lordosis, vertebral abnormalities |
| Nervous system                        | Mild brain atrophy                                     | Motor development delay, muscular hypotonia, optic atrophy                                  | Motor development delay, spastic paraparesis, ataxia, nystagmus, optic nerve hypoplasia, intellectual disability | Peripheral neuropathy, ataxia, tremor, global developmental delay, optic atrophy        |
| Immune system                         | Reduced NK cell number and function                    | Reduced levels of immunoglobulins reduced NK cell number and function                       |                                                                                                                  |                                                                                         |
| Facial appearance                     | Mild/some patients: flat cheekbones, hypotelorism      | Marked: triangular face, broad forehead, progeroid appearance                               | Wide forehead, low-set ears, anteverted nose                                                                     |                                                                                         |
| Others                                |                                                        | Endocrine system: insulin-dependent diabetes                                                |                                                                                                                  | Lung: recurrent episodes of acute respiratory insufficiency ( $n = 1$ )                 |

*Note:* Description of the main clinical findings in patients with ILFS2, SOPH, ILFS3, and CALFAN syndrome.

Abbreviations: CALFAN, low  $\gamma$ GT-cholestasis, acute liver failure triggered by febrile infections, and a variable neurodegeneration; ILFS2, infantile liver failure syndrome type 2; ILFS3, infantile liver failure syndrome type 3; NK cell, natural killer cell; PALF, pediatric acute liver failure; RALF, recurrent acute liver failure; SOPH, short stature, optical atrophy, and Pelger-Huët anomaly.

<sup>a</sup>Furthermore, there are patients with overlapping symptoms (combined phenotype), especially when variants affect the  $\beta$  propeller domain of the NBAS protein.<sup>43</sup>

## Frequency of phenotypic abnormalities



**FIGURE 2** Frequency of phenotypic abnormalities in ILFS2, SOPH, ILFS3, and CALFAN syndrome. Human phenotype ontology terms with a frequency of 2 and higher are displayed to show phenotypic differences in ILFS2, SOPH, ILFS3, and CALFAN syndrome. Underlying individual data can be found in the supplemental Tables S1–S4. CALFAN, low  $\gamma$ -glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration; ILFS2, infantile liver failure syndrome type 2; ILFS3, infantile liver failure syndrome type 3; NA, not available; NBAS, neuroblastoma amplified sequence; RINT1, RAD50 interactor 1; SCYL1, SCY1 like pseudokinase 1; SOPH, short stature, optical atrophy, and Pelger-Huët anomaly.

increased hepatic transaminases during febrile infections. However, only a minority of patients fulfill the PALF criteria and, in most patients, there is no normalization when without fever, but continuously elevated transaminases and continuous hepatomegaly. A severe combined phenotype with multisystemic involvement and RALF is observed in most patients with missense variants affecting the  $\beta$ -propeller domain of NBAS protein. Notably, the lethality of fever-associated PALF is high in this group (22%). For further details see Figures S1, S2 and Table S3.<sup>43</sup>

Till today, two distinct cellular functions of the NBAS protein have been reported: firstly, NBAS is involved in retrograde and anterograde vesicular trafficking between endoplasmic reticulum (ER) and Golgi. NBAS is a peripheral membrane component of an ER tethering complex

that interacts with the target soluble N-ethylmaleimide-sensitive factor attachment protein receptors (t-SNAREs) p31 (Vesicle transport protein USE1), BNIP1 (BCL2 interacting protein 1), and STX18 (syntaxin18) at the ER and the vesicle soluble N-ethylmaleimide-sensitive factor attachment protein receptors (v-SNARE) Sec22b (SEC22 homolog B) on transport vesicles,<sup>46</sup> mediating the fusion of Golgi-derived coat protein complex I (COPI)-coated vesicles with the ER.<sup>47</sup> NBAS serves as a link between p31 and ZW10 (Zeste White 10)-RINT-1 (RAD50-interacting protein 1) (Figure 1). In addition, the complex of NBAS, RINT1, and ZW10 (NRZ complex) is necessary for the protein TANGO1 (Transport and Golgi organization protein 1 homolog) to recruit membranes of the ER-Golgi intermediate compartment (ERGIC).<sup>48</sup> As a transmembrane protein at the ER, TANGO1 is required for the

assembly of coat protein complex II (COPII) vesicles for the anterograde transport and export of proteins (Figure 1).<sup>49</sup> This process links retrograde membrane flux to anterograde cargo transport. In line with this function, increased ER stress markers have been observed in NBAS deficient patient cells,<sup>11,50</sup> which may lead to hepatocytolysis or cell death, although the precise mechanisms remain to be elucidated.

The secondary role of the NBAS protein is localized nonsense-mediated mRNA decay (NMD).<sup>51</sup> NBAS recruits the NMD factor UPF1 (Regulator of nonsense transcripts 1) to the membrane of the ER, thereby enabling the degradation of NMD substrates translated in the ER.<sup>52</sup> It is hypothesized that this mechanism could contribute to the chronic, multisystem phenotype in NBAS-related disease.

## 2.2 | Infantile liver failure syndrome type 3—*RINT1*

Biallelic variants in the RAD50-interacting protein (*RINT1*) gene, which like *NBAS* encodes a subunit of the NRZ complex, are associated with a multisystemic disease affecting the liver, bone, and nervous system (Table 1; Figure 2, Table S4).<sup>10,53</sup> *RINT1*-associated disease (MIM: #618641) or *RINT1* deficiency was first described in 2019 in three unrelated individuals,<sup>10</sup> originating from Europe and East Asia. All three individuals presented with the same splice variant (resulting in exon skipping and a frameshift with premature termination) combined with a missense variant or an in-frame deletion. Patient fibroblasts showed decreased levels of *RINT1* protein compared to controls.<sup>10</sup> In 2023, the genetic and phenotypic spectrum was extended by three further patients originating from Europe, sharing the same in-frame deletion in the homozygous state or combination with a loss-of-function variant.<sup>53</sup> Five of the six reported patients experienced at least one episode of acute liver failure precipitated by fever; hence, this disorder was named infantile liver failure syndrome 3 (ILFS3; OMIM # 618641). The onset of liver crises was very broad and ranged from 8 months to 10 years of age. A total of two patients died of PALF at the ages of 14 months and 3 years, respectively. Liver function fully or partially recovered to normal function between acute episodes. Whether the frequency and severity of liver crises decrease with age, as is the case in patients with NBAS deficiency, cannot be answered based on the existing data. One patient showed normalized transaminases for the first time at the age of 8 years, indicating an improvement with age. However, another patient experienced his first documented liver crisis as late as 10 years of age.

As in NBAS-associated disease, there are persistent extrahepatic symptoms in *RINT1*-associated disease. Notably, skeletal and nervous system involvement differs significantly between the three patients reported by Cousin et al.<sup>10</sup> and the three recently described by Lounay et al.,<sup>53</sup> while there is phenotypic consistency within each group. Considering that within each of the two groups, all three patients share at least one variant, a genotype–phenotype association in *RINT1*-associated disease seems likely. Additional data will help to further investigate this association.

Skeletal symptoms include vertebral body abnormalities with anterior beaking, and hypoplasia (resembling individuals with lysosomal storage disease, such as mucopolysaccharidoses), kyphosis, wormian bones, and short stature (three out of six patients). Normal psychomotor development is described for all three patients reported by Cousin et al.<sup>10</sup> The three recently described patients expanded the phenotypic spectrum with profound alterations of the nervous system including delayed motor development, spastic paraplegia (onset between 18 months and 3 years of life), ataxia, nystagmus, and optic nerve hypoplasia (Table 1, Table S4).<sup>53</sup>

As described above, *RINT1* protein, together with NBAS and ZW10 forms the NRZ complex, involved in anterograde and retrograde transport between ER and Golgi (Figure 1). Furthermore, *RINT1* binds UV radiation resistance-associated gene protein (UVRAG) to the ER, linking Golgi-to-ER retrograde transport and autophagy. When autophagy is initiated, UVRAG dissociates from *RINT1* decreasing Golgi-to-ER retrograde transport.<sup>10,54</sup> Moreover, abnormal Golgi morphology and impaired autophagy were observed in *RINT1* deficient fibroblasts.<sup>10</sup>

No effect on NBAS levels was observed in fibroblasts of *RINT1* patients in the Cousin et al.<sup>10</sup> cohort, and all three patients showed no neurological symptoms. However, in patients with neurological symptoms, a concomitant reduction in NBAS and ZW10 levels was observed, indicating a potential causal relationship between loss of NRZ complex integrity and function and the neurological phenotype.<sup>53</sup>

## 2.3 | CALFAN syndrome—*SCYL1*

CALFAN syndrome (OMIM #616719) is a rare condition in children characterized by low  $\gamma$ GT-cholestasis, acute liver failure triggered by febrile infections, and a variable neurodegeneration. The underlying cause is biallelic mutations in *SCYL1*, resulting in impaired protein function. Known variants are found throughout the entire gene and affect all domains.

The condition was initially described in 2015 as SCAR21 (spinocerebellar ataxia, autosomal recessive 21; OMIM #616719) in three patients from two families who were found to have a predominant neurological phenotype with neurodegeneration and ataxia.<sup>55</sup> An additional study published in 2018 added seven more patients from five families who presented with a predominant hepatic phenotype with RALF and low- $\gamma$ GT-cholestasis.<sup>12</sup> The subsequently described patients exhibited a more variable phenotype compared to the initial study. In addition to the predominant hepatic phenotype with RALF triggered by febrile infections, a spectrum of neurological symptoms was observed (speech delay, mental retardation, secondary microcephaly, and variable motor dysfunction), while ataxia, polyneuropathy, cerebellar vermis atrophy, and optic atrophy were the main symptoms reported in the initial publication. Moreover, abnormalities in other organ systems such as short stature and skeletal anomalies have been reported since then. The later reported patients showed an early onset of liver disease in the first year of life, with neurological symptoms appearing progressively at a later stage, suggesting an age-dependent progression of the neurological phenotype (see also Table 1, Figure 2, and Table S5).<sup>12,31,55–65</sup>

SCYL1 is the approximately 120 kDa heavy product of the *SCYL1* gene located on the long arm of chromosome XI (11q13.1). The protein, composed of 808 amino acids, contains an N-terminal protein kinase domain, which is assumed to be catalytically inactive.<sup>66</sup> At the C-terminus is an interaction domain with COPB1 (Coatomer subunit beta). SCYL1 is expressed in all human tissues, is localized in the cytosol, and has various functions in cell metabolism. First, it directly interacts with tRNA, facilitating their transport out of the nucleus.<sup>67</sup> Second, SCYL1 is also involved in maintaining Golgi homeostasis, and cells depleted of SCYL1 exhibit an enlarged and disorganized Golgi apparatus.<sup>68</sup> Last, SCYL1 plays a crucial role in intracellular transport by interacting with COPI via the C-terminus. Knockdown of SCYL1 in cells results in impaired retrograde trafficking of proteins from the Golgi apparatus to the ER,<sup>66</sup> which was also confirmed in patient cells.<sup>12</sup>

### 3 | DISCUSSION

Disorders of vesicular trafficking causing RALF include three recently identified, yet relatively frequent, genetic causes. The collective review of these three autosomal recessive entities (NBAS, RINT1, and SCYL1 associated disease) shows a remarkable overlap of clinical symptoms and protein functions, allowing knowledge transfer, e.g., for pathomechanisms and therapies, and providing ideas for further research.

### 3.1 | Clinical presentation

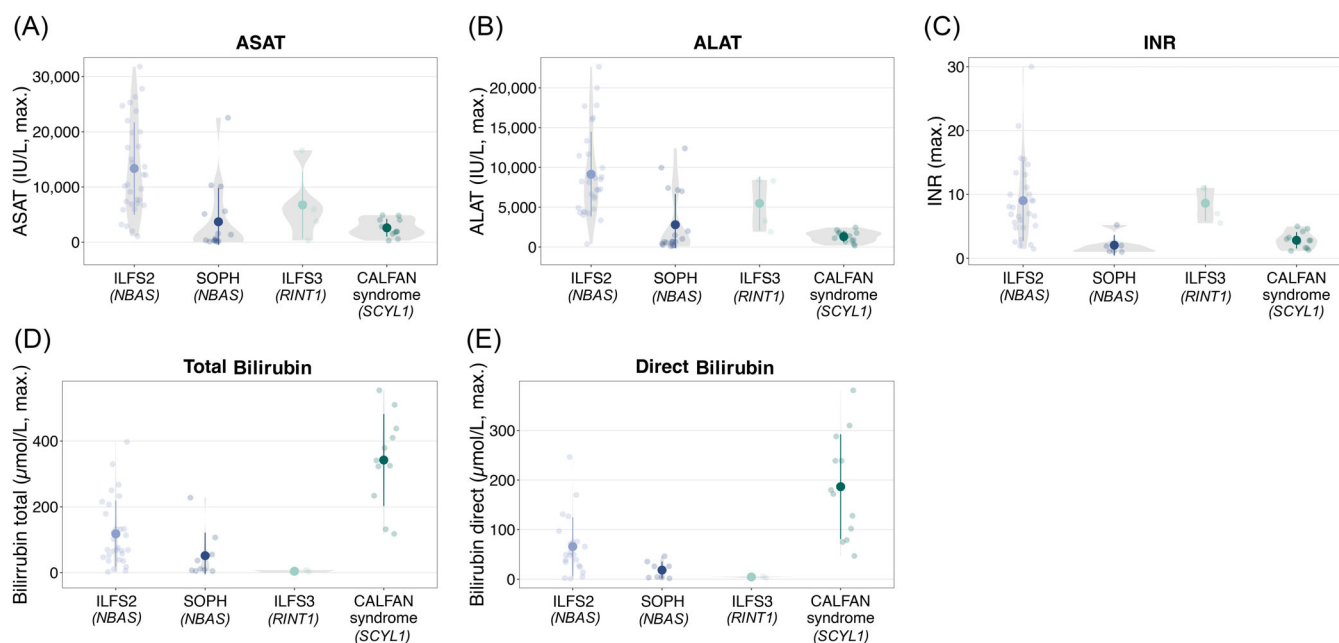
In all three diseases, fever-dependent acute episodes with increased transaminases up to fulminant PALF can occur. Comparing phenotypes of NBAS and RINT1 patients is limited by the small number of patients with RINT1. Based on the patients known so far, there is relevant clinical overlap, which is in line with both proteins being subunits of the NRZ complex. The first liver crises occur in infancy or childhood, which interestingly was the age with the highest proportion of indeterminate PALF in previous studies.<sup>3</sup> In NBAS-associated ILFS2, high transaminases indicate severe hepatic cytolysis (max. ASAT mean: 13359 U/L ( $n = 32$ ); max. ALAT mean: 9146 U/L ( $n = 32$ ); Figure 3, Tables S1 and S2). In patients with RINT1-associated disease, the increase in transaminases tends to be lower (max. ASAT mean 6753 U/L; max. ALAT mean 5481 U/L ( $n = 5$ ); Figure 3, Table S4). In both diseases, there are patients presenting with complete normalization of transaminases between intervals and patients with continuously elevated transaminases. In all patients increase in transaminases is fever-dependent. The frequency and severity of liver crises seem to decrease with increasing age in both diseases.

In line with different localization of SCYL1 within the cell, the hepatic phenotype of patients with SCYL1 differs. The majority of cases have a progressive, cholestatic course, and hepatocytolysis is less fulminant (Figure 3). In SCYL1 deficient patients, PALF is a rarer event, also mainly occurring in the first years of life.<sup>12,31,55–65</sup>

The broad involvement of organ systems beyond the liver reflects a relevant function of NBAS, RINT1, and SCYL1 in several other cell types. Extrahepatic functions are affected independently of the patient's body temperature, with a continuous, or even progressive course. Although with different characteristics, all three diseases involve the skeletal and nervous systems. NBAS deficiency displays the widest spectrum of organ involvement, with alterations of the immune system, endocrine system, or integument. Yet, with more than 160 patients known, NBAS deficiency presents by far the largest cohort. Likely, the identification of additional patients with pathogenic *RINT1* and *SYCL1* variants will broaden the phenotypic spectrum of these diseases (Tables S1–S5).

### 3.2 | Diagnosis

A recent study showed that in 37% of PALF cases of unknown etiology, a genetic diagnosis could be established by whole exome sequencing (WES),<sup>8</sup> highlighting the importance of genetic causes of PALF. In RALF, even approximately 60% of cases can be solved with WES.



**FIGURE 3** Laboratory phenotype of most severe hepatic decompensations in ILFS2 (NBAS), SOPH (NBAS), ILFS3 (RINT1), and CALFAN syndrome (SCYL1). Laboratory characterization of hepatic decompensations ASAT, ALAT, liver function (INR), total bilirubin as well as direct bilirubin using violin plots. Bold dots indicate the median, bars indicate the 25th to 75th percentile. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CALFAN, low  $\gamma$ -glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration; ILFS2, infantile liver failure syndrome type 2; ILFS3, infantile liver failure syndrome type 3; INR, international normalized ratio; IU/L, international units per liter; max., maximal; NBAS, neuroblastoma amplified sequence; RINT1, RAD50 interactor 1; SCYL1, SCY1 like pseudokinase 1; SOPH, short stature, optical atrophy, and Pelger-Huët anomaly.

Given the clinical overlap of NBAS, RINT1, and SCYL1-associated diseases and the lack of biomarkers, only genetic testing allows for rapid and reliable diagnosis, while searching for other differential diagnoses at the same time. Early diagnosis is particularly important for the implementation of prevention and treatment strategies discussed below. Genetic testing of close relatives of affected patients should be considered, especially in siblings to allow pre-symptomatic diagnosis and awareness of a potential risk of PALF. There are reports that in patients with NBAS deficiency diagnosed due to family history before the onset of symptoms, liver crises are milder or even prevented by early treatment.<sup>69</sup>

### 3.3 | Pathomechanisms

While no patients with biallelic loss-of-function variants in NBAS or RINT1 are known, biallelic loss-of-function variants in SCYL1 have been observed indicating a pivotal role of NBAS and RINT1 proteins, whereas a loss of SCYL1 seems to be compatible with life.

Reduced protein levels in affected patients indicate a substantial impairment of protein translation and/or stability. Remarkably, patients with RINT1 variants also

have reduced protein levels of NBAS and ZW10, with RINT1 abundance correlating with NBAS levels.<sup>53</sup> A similar effect is observed in knockdown studies of NBAS, with reduced levels of p31, also a subunit of the syntaxin18 complex.<sup>11</sup> Taken together, this suggests instability of the syntaxin18 complex or altered expression of other components resulting from variants in RINT1 and NBAS.

There is evidence for impairment of vesicular trafficking in NBAS, RINT1, and SCYL1 deficiency. Membrane trafficking is a crucial process in all tissues but is particularly important in hepatocytes, which secrete a large number of proteins into the bloodstream. NBAS, RINT1, and SCYL1 are localized between the ER and Golgi and are required for antegrade and retrograde transport.

Retrograde transport is important for membrane recycling for organelle homeostasis and for returning proteins to the ER that may have been inappropriately delivered. The syntaxin18 complex (including NBAS, RINT1, ZW10, and p31) is a t-SNARE (target soluble N-ethylmaleimide-sensitive factor attachment protein receptor) at the ER, necessary for the fusion of Golgi-derived vesicles with the ER membrane.<sup>46</sup> Fibroblasts from patients with NBAS deficiency show impaired vesicle tethering to the ER.<sup>11,70</sup> There is evidence of thermal susceptibility of the

syntaxin18 complex as a possible explanation for fever-induced hepatic crisis: In fibroblasts from patients with NBAS deficiency, a temperature shift from 37 to 40°C leads to a further decrease in the levels of NBAS and p31,<sup>70</sup> indicating elevated temperature itself contributes to the development of liver crises, at least in NBAS associated disease. In RINT1 deficient cells there is a trend toward less protein with an increase in temperature, although this is not statistically significant.<sup>10</sup> Fibroblasts from patients with RINT1 and SCYL1 mutations show enlarged or fragmented Golgi, particularly after culturing the cells at 40°C.<sup>10,53,68</sup>

The NRZ complex is also involved in antegrade transport, which directs proteins synthesized in the ER to the Golgi for post-translational modification and export. The NRZ complex is required for the protein TANGO1 to recruit membranes of the ER-Golgi intermediate compartment (ERGIC) for the formation of (large) COPII vesicles.<sup>48</sup> Loss of TANGO1, RINT1, or NBAS in fibroblasts impairs the anterograde transport of collagen VII, leading to accumulation of collagen VII in the ER.<sup>48</sup> Biallelic truncating variants affecting *TANGO1* gene cause a syndrome with short stature, skeletal abnormalities with osteopenia, clinodactyly and brachydactyly, insulin-dependent diabetes mellitus, mild mental disability and sensorineural hearing loss (Ondotochondrodysplasia 2 with hearing loss and diabetes, ODCD2, OMIM # 619269).<sup>71</sup> In affected cells, it has been demonstrated that the secretion of different collagens is impaired. Aberrant export and secretion of proteins in NBAS and RINT1 deficiency may explain the cargo-selective and thus tissue-specific phenotypes. Likewise, the export of proinsulin from the ER is COPII-dependent. Blocking COPII-dependent export leads to ER stress and apoptosis of pancreatic beta cells,<sup>72</sup> a possible cause of insulin-dependent diabetes in patients with NBAS deficiency. Disruption of vesicular trafficking is supported by the fact that, affected organ systems such as skin, bone, liver, and connective tissues are very sensitive to impaired secretory traffic, reflecting the high secretory load in these tissues.<sup>29</sup>

Linked to intracellular trafficking, there is evidence for impaired autophagy. Inefficient or aberrant intracellular vesicle trafficking can result in an impaired endocytic pathway, thereby affecting lysosome homeostasis and autophagy, which, when impaired, results in cytotoxic stress. The biogenesis of autophagic vacuoles is a trafficking pathway that delivers cargo to the lysosomes and involves COPI-coated vesicles, in the formation of which the NRZ complex is involved.<sup>73</sup> Autophagy is a process necessary for bone growth.<sup>74</sup> Interestingly, homozygous intronic variants affecting BNIP1 (BCL2 interacting protein 1), also a component of the syntaxin18 complex, are associated with disproportionate short stature and

skeletal dysplasia.<sup>75</sup> In fibroblasts from affected patients increase in autophagosomes and decreased autophagic flux were observed.<sup>75</sup> Impaired autophagic flux and resulting ER stress were also found to play a pathogenic role in liver diseases, mainly chronic liver affections such as alcoholic and non-alcoholic fatty liver disease.<sup>76,77</sup>

Impaired vesicular trafficking and autophagy lead to ER stress with activation of the integrated stress response (ISR) and generation of reactive oxygen species (ROS) with the aim of restoring cellular homeostasis. However, if the intensity or duration of stress is high, the cascade may lead to hepatocytolysis, which is reflected by high levels of transaminases in acute liver failure. The role of ER stress is supported by the increased expression of RNA associated with ER stress in NBAS-deficient fibroblasts.<sup>11</sup> RINT1 loss in the brain is associated with increased expression of C/EBP homologous (CHOP), a marker of the ISR.<sup>78</sup> Interestingly, ER stress and apoptosis also play a role in the pathogenesis of Wolcott-Rallison syndrome, which shows remarkable clinical overlap, presenting with recurrent hepatic dysfunction up to liver failure, skeletal dysplasia, immunological abnormalities, and diabetes mellitus.<sup>79</sup> The affected *EIF2AK3* gene encodes an ER transmembrane protein, which detects the accumulation of misfolded proteins in the ER and subsequently activates the expression of stress-related proteins.<sup>80</sup> Further research is needed to understand whether Wolcott-Rallison syndrome and the here described disorders of vesicular trafficking share a common pathomechanistic pathway causing the clinically similar presentation.

Taken together, in the three disorders NBAS, RINT1, and SCYL1 deficiency, there is evidence for disrupted vesicle trafficking and ER membrane fusion, resulting in impaired protein secretion and autophagy and subsequently increased ER stress, which induces hepatocyte cell death. Detailed understanding of these processes and possible therapeutic interventions requires further research.

### 3.4 | Therapy

As with most diseases caused by defective vesicular trafficking, there are currently no specific, curative therapies, however, early emergency management during febrile infections can prevent further deterioration. Hence, medical education of close relatives and the primary care team together with an emergency treatment card with clear instructions, is key to optimal management in these life-threatening situations.

Early antipyretic therapy has been reported to reduce the frequency and severity of acute hepatic crises in

patients with NBAS deficiency.<sup>69,70,81</sup> A similar effect might be expected in patients with RINT1 and SCYL1. For the treatment of fever, in addition to physical measures, we recommend metamizole (8–16 mg/kg body weight as a single dose orally or parenterally at minimal intervals of 6 h, maximum single dose: 1000 mg). Considering the risk of bleeding, ibuprofen should be avoided in patients with a risk of PALF. The fact that paracetamol toxicity induces the ISR and hence, the production of reactive oxidative species,<sup>82</sup> a process suspected to play a role in the pathogenesis of NBAS-, RINT1-, and SCYL1-associated liver diseases, argues against the use of paracetamol in these patients. By the same logic, N-acetylcysteine (NAC), which has been shown to be an effective antioxidant in the treatment of paracetamol-induced PALF,<sup>83</sup> may be a therapeutic option for liver crises. In many centers, intravenous NAC is part of the general management of acute liver failure in adults, as it was found to have some benefit also in non-paracetamol induced liver failure with an adequate safety profile.<sup>84,85</sup> Yet, in pediatric patients, NAC is not a standard treatment for PALF. In a double-masked, placebo-controlled trial NAC did not improve 1-year survival in non-acetaminophen PALF.<sup>86</sup> Given the suspected pathomechanism, a positive experience in individual patients (unpublished data), and the low side effect profile, the use of NAC in liver crisis in NBAS, RINT1, and SCYL1 deficient patients can be considered and is conducted in the authors' institution. Systematic evaluation is needed to determine the potential benefit of NAC.

Further therapeutic strategies include the administration of anabolic infusions with glucose and lipids. Based on individual cases, a beneficial effect on the course of liver crises in patients with NBAS deficiency has been reported,<sup>70</sup> however, a systematic analysis is lacking; the same holds for SCYL1 and RINT1 deficient patients.

There are reports of six patients with NBAS deficiency, two patients with RINT1 deficiency, and four patients with CALFAN syndrome who underwent liver transplantation. None of them experienced further liver crises. Given the natural course in NBAS and RINT1 deficiency and the risks associated with liver transplantation, we consider the liver transplantation in these diseases to be a treatment of last resort. However, a liver transplant might be discussed in cases with, for example, deceased siblings where a severe phenotype can be assumed. In patients with SCYL1, the progressive neurologic phenotype is a potential contraindication for liver transplantation. In principle, diseases caused by genetic variants could be subject to gene therapy.<sup>87</sup> However, the authors are not aware of any current approach in this direction, plus the large size of the NBAS gene and respective protein (271 kDa) poses a major challenge in the case of NBAS deficiency.

## 4 | CONCLUSION

NBAS, RINT1, and SCYL1-associated diseases account for a significant proportion of RALF triggered by febrile infections. The extrahepatic phenotype of all three disorders mainly affects the nervous and skeletal systems—both organ systems with high secretory activity like the liver. Disruption of vesicular trafficking causes ER stress leading to cell death is reflected by hepatocytolysis during PALF episodes. No curative treatments exist so far, but early emergency management is crucial in the life-threatening episodes of PALF.

## AUTHOR CONTRIBUTIONS

All authors contributed actively to this manuscript. The concept for this review was made by BP and DL. The first draft of the manuscript was written by BP and TD. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## ACKNOWLEDGEMENTS

Figure 1 has been partly created using [BioRender.com](https://www.biorender.com). Open Access funding enabled and organized by Projekt DEAL.

## FUNDING INFORMATION

LDS was supported by the BMBF (German Federal Ministry of Education and Research) through the mitoNET German Network for Mitochondrial Diseases (grant number 01GM1906B). The authors declare that no funds, grants, or other support were received related to the study.

## CONFLICT OF INTEREST STATEMENT

Bianca Peters, Tal Dattner, Lea D. Schlieben, Tian Sun, Christian Stauffer, and Dominic Lenz declare that they have no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to most parts of this article as no new data were created or analyzed in this study. The few new data in this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

## PATIENT CONSENT STATEMENT

The authors confirm that written informed consent has been obtained from patients where data were not retrieved from publications.

## ORCID

Christian Staufner  <https://orcid.org/0000-0002-1403-9075>

Dominic Lenz  <https://orcid.org/0000-0002-9561-8190>

## REFERENCES

1. Lenz D, Hørby Jørgensen 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.
2. Kwong AJ, Ebel NH, Kim WR, et al. OPTN/SRTR 2020 annual data report: liver. *Am J Transplant.* 2022;22(Suppl 2):204-309.
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. Kathemann S, Bechmann LP, Sowa JP, et al. Etiology, outcome and prognostic factors of childhood acute liver failure in a German Single Center. *Ann Hepatol.* 2015;14(5):722-728.
5. Narkewicz MR, Dell Olio D, Karpen SJ, et al. Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement. *J Pediatr.* 2009;155(6):801-806.e1.
6. Kulkarni S, Perez C, Pichardo C, et al. Use of Pediatric Health Information System database to study the trends in the incidence, management, etiology, and outcomes due to pediatric acute liver failure in the United States from 2008 to 2013. *Pediatr Transplant.* 2015;19(8):888-895.
7. 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.e3.
8. Lenz D, Schlieben LD, Shimura M, et al. Genetic landscape of pediatric acute liver failure of indeterminate origin. *Hepatology.* 2023. doi:10.1097/HEP.0000000000000684. Epub ahead of print.
9. 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.
10. 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.
11. Haack TB, Staufner C, Köpke 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.
12. 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.
13. Gallagher RC, Lam C, Wong D, Cederbaum S, Sokol RJ. Significant hepatic involvement in patients with ornithine transcarbamylase deficiency. *J Pediatr.* 2014;164(4):720-725.e6.
14. 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.
15. Martinelli D, Diodato D, Ponzi E, et al. The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. *Orphanet J Rare Dis.* 2015;10:29.
16. Mhanni AA, Chan A, Collison M, et al. Hyperornithinemia-hyperammonemia-homocitrullinuriasyndrome (HHH) presenting with acute fulminant hepatic failure. *J Pediatr Gastroenterol Nutr.* 2008;46(3):312-315.
17. 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.
18. 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.
19. Casey JP, Slaterry 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.
20. 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.
21. 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.
22. Orenstein N, Weiss K, Opreescu SN, et al. Bi-allelic IARS mutations in a child with intra-uterine growth retardation, neonatal cholestasis, and mild developmental delay. *Clin Genet.* 2017;91(6):913-917.
23. 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.
24. Lenz D, Stahl M, Seidl E, et al. Rescue of respiratory failure in pulmonary alveolar proteinosis due to pathogenic MARS1 variants. *Pediatr Pulmonol.* 2020;55(11):3057-3066.
25. van Meel E, Wegner DJ, Cliften P, et al. Rare recessive loss-of-function methionyl-tRNA synthetase mutations presenting as a multi-organ phenotype. *BMC Med Genet.* 2013;14:106.
26. Durocher F, Faure R, Labrie Y, Pelletier L, Bouchard I, Laframboise R. A novel mutation in the EIF2AK3 gene with variable expressivity in two patients with Wolcott-Rallison syndrome. *Clin Genet.* 2006;70(1):34-38.
27. Wolcott CD, Rallison ML. Infancy-onset diabetes mellitus and multiple epiphyseal dysplasia. *J Pediatr.* 1972;80(2):292-297.
28. García-Cazorla A, Oyarzábal A, Saudubray JM, Martinelli D, Dionisi-Vici C. Genetic disorders of cellular trafficking. *Trends Genet.* 2022;38(7):724-751.
29. Yarwood R, Hellicar J, Woodman PG, Lowe M. Membrane trafficking in health and disease. *Dis Model Mech.* 2020;13(4):dmm043448.
30. Akesson LS, Rius R, Brown NJ, et al. Distinct diagnostic trajectories in NBAS-associated acute liver failure highlights the need for timely functional studies. *JIMD Rep.* 2022;63(3):240-249.
31. Chavany J, Cano A, Roquelaure B, et al. Mutations in NBAS and SCYL1, genetic causes of recurrent liver failure in children: three case reports and a literature review. *Arch Pediatr.* 2020;27(3):155-159.
32. Cheng Y, Xia Z, Huang C, Xu H. Case report: a novel cause of acute liver failure in children: a combination of human herpesvirus-6 infection and homozygous mutation in NBAS gene. *J Clin Lab Anal.* 2022;36(5):e24343.
33. Gu JL, Wang WJ, Li L, Zheng YJ, Mao XN. A novel compound heterozygous mutation in NBAS gene causes SOPH syndrome and liver function damage. *Zhonghua Er Ke Za Zhi.* 2019;57(6):487-489.

34. Jiang B, Xiao F, Li X, Xiao Y, Wang Y, Zhang T. Case report: pediatric recurrent acute liver failure caused by neuroblastoma amplified sequence (NBAS) gene mutations. *Front Pediatr*. 2020;8:607005.
35. Jiang T, Ouyang W, Tan Y, Tang L, Zhang H, Li S. Clinical features and genetic testing of a child with hepatic failure syndrome type 2. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2022;39(2):181-184.
36. Khoreva A, Pomerantseva E, Belova N, et al. Complex multi-system phenotype with immunodeficiency associated with NBAS mutations: reports of three patients and review of the literature. *Front Pediatr*. 2020;8:577.
37. Lacassie Y, Johnson B, Lay-Son G, et al. Severe SOPH syndrome due to a novel NBAS mutation in a 27-year-old woman-review of this pleiotropic, autosomal recessive disorder: mystery solved after two decades. *Am J Med Genet A*. 2020;182(7):1767-1775.
38. Lenz D, Pahl J, Hauck F, et al. NBAS variants are associated with quantitative and qualitative NK and B cell deficiency. *J Clin Immunol*. 2021;41(8):1781-1793.
39. Li ZD, Abuduxikuer K, Zhang J, et al. NBAS disease: 14 new patients, a recurrent mutation, and genotype-phenotype correlation among 24 Chinese patients. *Hepatol Res*. 2020;50(11):1306-1315.
40. Lipiński P, Greczan M, Piekutowska-Abramczuk D, et al. NBAS deficiency due to biallelic c.2809C>G variant presenting with recurrent acute liver failure with severe hyperammonemia, acquired microcephaly and progressive brain atrophy. *Metab Brain Dis*. 2021;36(7):2169-2172.
41. Nazmi F, Ozdogan E, Mungan NO, Arikan C. Liver involvement in neuroblastoma amplified sequence gene deficiency is not limited to acute injury: fibrosis silently continues. *Liver Int*. 2021;41(10):2433-2439.
42. Seo Y, Kim TY, Won D, et al. Genetic spectrum and characteristics of autosomal optic neuropathy in Korean: use of next-generation sequencing in suspected hereditary optic atrophy. *Front Neurol*. 2022;13:978532.
43. 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.
44. Suzuki S, Kokumai T, Furuya A, et al. A 34-year-old Japanese patient exhibiting NBAS deficiency with a novel mutation and extended phenotypic variation. *Eur J Med Genet*. 2020;63(11):104039.
45. 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-Huët anomaly. *J Med Genet*. 2010;47(8):538-548.
46. Aoki T, Ichimura S, Itoh A, et al. Identification of the neuroblastoma-amplified gene product as a component of the syntaxin 18 complex implicated in Golgi-to-endoplasmic reticulum retrograde transport. *Mol Biol Cell*. 2009;20(11):2639-2649.
47. Hatsuzawa K, Hirose H, Tani K, Yamamoto A, Scheller RH, Tagaya M. Syntaxin 18, a SNAP receptor that functions in the endoplasmic reticulum, intermediate compartment, and cis-Golgi vesicle trafficking. *J Biol Chem*. 2000;275(18):13713-13720.
48. Raote I, Ortega-Bellido M, Santos AJ, et al. TANGO1 builds a machine for collagen export by recruiting and spatially organizing COPII, tethers and membranes. *Elife*. 2018;7:7.
49. Saito K, Chen M, Bard F, et al. TANGO1 facilitates cargo loading at endoplasmic reticulum exit sites. *Cell*. 2009;136(5):891-902.
50. Ji J, Yang M, Jia J, et al. A novel variant in NBAS identified from an infant with fever-triggered recurrent acute liver failure disrupts the function of the gene. *Hum Genome Var*. 2023;10(1):13.
51. Anastasaki C, Longman D, Capper A, Patton EE, Cáceres JF. Dhx34 and Nbas function in the NMD pathway and are required for embryonic development in zebrafish. *Nucleic Acids Res*. 2011;39(9):3686-3694.
52. Longman D, Jackson-Jones KA, Maslon MM, et al. Identification of a localized nonsense-mediated decay pathway at the endoplasmic reticulum. *Genes Dev*. 2020;34(15-16):1075-1088.
53. 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):e162836.
54. He S, Ni D, Ma B, et al. PtdIns(3)P-bound UVRAG coordinates Golgi-ER retrograde and Atg9 transport by differential interactions with the ER tether and the beclin 1 complex. *Nat Cell Biol*. 2013;15(10):1206-1219.
55. Schmidt WM, Rutledge SL, Schüle 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.
56. Campos T, Leão Teles E, Rodrigues E, Nogueira C, Vilarinho L, Leão M. Two genetic disorders (TRMU and SCYL1) explaining transient infantile liver failure in one patient. *Integ Mol Med*. 2020;7(2):1-3.
57. Incecik F, Herguner OM, Willems P, Mungan NO. Spinocerebellar ataxia-21 in a Turkish child. *Ann Indian Acad Neurol*. 2018;21(1):68-70.
58. Isa HM, Alkaabi JF, Alhammadi WH, Marjan KA. Recurrent acute liver failure in a Bahraini child with a novel mutation of spinocerebellar ataxia-21. *Cureus*. 2023;15(3):e36249.
59. Li JQ, Gong JY, Knisely AS, Zhang MH, Wang JS. Recurrent acute liver failure associated with novel SCYL1 mutation: a case report. *World J Clin Cases*. 2019;7(4):494-499.
60. McNiven V, Gattini D, Siddiqui I, et al. SCYL1 disease and liver transplantation diagnosed by reanalysis of exome sequencing and deletion/duplication analysis of SCYL1. *Am J Med Genet A*. 2021;185(4):1091-1097.
61. 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.
62. Smith ED, Radtke K, Rossi M, et al. Classification of genes: standardized clinical validity assessment of gene-disease associations aids diagnostic exome analysis and reclassifications. *Hum Mutat*. 2017;38(5):600-608.
63. Spagnoli C, Frattini D, Salerno GG, Fusco C. On CALFAN syndrome: report of a patient with a novel variant in SCYL1 gene and recurrent respiratory failure. *Genet Med*. 2019;21(7):1663-1664.
64. Yigit S, Albayrak HM, Perk Yücel P, Usgu S, Yakut Y. The outcomes of an individualized physical therapy program in

- CALFAN syndrome: a case report. *Pediatr Phys Ther.* 2022; 34(3):432-437.
65. Youssef M, Mascia KL, McGuire B, et al. CALFAN (low  $\gamma$ -glutamyl transpeptidase (GGT) cholestasis, acute liver failure, and neurodegeneration) syndrome: a case report with 3-year follow-up after liver transplantation in early adulthood. *Case Reports Hepatol.* 2023;2023:3010131.
  66. Burman JL, Bourbonniere L, Philie J, et al. Scyl1, mutated in a recessive form of spinocerebellar neurodegeneration, regulates COPI-mediated retrograde traffic. *J Biol Chem.* 2008;283(33):22774-22786.
  67. Chafe SC, Mangroo D. Scyl1 facilitates nuclear tRNA export in mammalian cells by acting at the nuclear pore complex. *Mol Biol Cell.* 2010;21(14):2483-2499.
  68. Burman JL, Hamlin JN, McPherson PS. Scyl1 regulates Golgi morphology. *PLoS One.* 2010;5(3):e9537.
  69. Ono S, Matsuda J, Watanabe E, et al. Novel neuroblastoma amplified sequence (NBAS) mutations in a Japanese boy with fever-triggered recurrent acute liver failure. *Hum Genome Var.* 2019;6:2.
  70. Staufner C, Haack TB, Köpke 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.
  71. Lekszas C, Foresti O, Raote I, et al. Biallelic TANGO1 mutations cause a novel syndromal disease due to hampered cellular collagen secretion. *Elife.* 2020;9:9.
  72. Fan J, Wang Y, Liu L, et al. cTAGE5 deletion in pancreatic  $\beta$  cells impairs proinsulin trafficking and insulin biogenesis in mice. *J Cell Biol.* 2017;216(12):4153-4164.
  73. van der Vaart A, Griffith J, Reggiori F. Exit from the Golgi is required for the expansion of the autophagosomal phagophore in yeast *Saccharomyces cerevisiae*. *Mol Biol Cell.* 2010;21(13):2270-2284.
  74. Cinque L, Forrester A, Bartolomeo R, et al. FGF signalling regulates bone growth through autophagy. *Nature.* 2015; 528(7581):272-275.
  75. Holling T, Bhavani GS, von Elsner L, et al. A homozygous hypomorphic BNIP1 variant causes an increase in autophagosomes and reduced autophagic flux and results in a spondylo-epiphyseal dysplasia. *Hum Mutat.* 2022;43(5):625-642.
  76. González-Rodríguez A, Mayoral R, Agra N, et al. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. *Cell Death Dis.* 2014;5(4):e1179.
  77. Lin CW, Zhang H, Li M, et al. Pharmacological promotion of autophagy alleviates steatosis and injury in alcoholic and non-alcoholic fatty liver conditions in mice. *J Hepatol.* 2013;58(5):993-999.
  78. Grigaravicius P, Kaminska E, Hübner CA, McKinnon PJ, von Deimling A, Frappart PO. Rint1 inactivation triggers genomic instability, ER stress and autophagy inhibition in the brain. *Cell Death Differ.* 2016;23(3):454-468.
  79. Senée V, Vattem KM, Delépine M, et al. Wolcott-Rallison syndrome: clinical, genetic, and functional study of EIF2AK3 mutations and suggestion of genetic heterogeneity. *Diabetes.* 2004;53(7):1876-1883.
  80. Julier C, Nicolino M. Wolcott-Rallison syndrome. *Orphanet J Rare Dis.* 2010;5:29.
  81. Balasubramanian M, Hurst J, Brown S, et al. Compound heterozygous variants in NBAS as a cause of atypical osteogenesis imperfecta. *Bone.* 2017;94:65-74.
  82. Ferret PJ, Hammoud R, Tulliez M, et al. Detoxification of reactive oxygen species by a nonpeptidyl mimic of superoxide dismutase cures acetaminophen-induced acute liver failure in the mouse. *Hepatology.* 2001;33(5):1173-1180.
  83. Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev.* 2018;2(2):Cd003328.
  84. Sanabria-Cabrera J, Tabbai S, Niu H, et al. N-acetylcysteine for the management of non-acetaminophen drug-induced liver Injury in adults: a systematic review. *Front Pharmacol.* 2022; 13:876868.
  85. 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(6):100828.
  86. Squires RH, Dhawan A, Alonso E, et al. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. *Hepatology.* 2013;57(4):1542-1549.
  87. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. *Science.* 2018;359:6372.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Peters B, Dattner T, Schlieben LD, Sun T, Staufner C, Lenz D. Disorders of vesicular trafficking presenting with recurrent acute liver failure: NBAS, RINT1, and SCYL1 deficiency. *J Inherit Metab Dis.* 2025;48(1): e12707. doi:10.1002/jimd.12707