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Response to Spagnoli et al.

To the Editor: With great interest we have read the correspondence from Spagnoli et al.[1] to our publication on CALFAN (low γ-glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration) syndrome due to mutations in *SCYL1*[2]. Spagnoli and colleagues describe a case of a 7-year-old girl affected by a cerebellar syndrome, cerebellar atrophy, ocular motility disorder, and intellectual disability, with prominent language involvement. By exome sequencing, a novel homozygous variant in *SCYL1* [c.1534dupT, p.(Cys512Leufs*8)] (NM_020680.3) was identified and classified as likely pathogenic. Apart from the neurological phenotype, the authors report recurrent episodes of acute respiratory insufficiency with pleural effusion, whereas the hepatic phenotype was not in the focus of the report.

The neurological phenotype of the presented individual, describing a cerebellar neurodegeneration, fits well with SCYL1 deficient patients as reported in 2015 by Schmidt and colleagues[3] and other single phenotypic descriptions,[4] which led to the OMIM entry 616719 (spinocerebellar ataxia, autosomal recessive 21; SCAR21). Furthermore, the neurological phenotype is in line with the presentation of the muscle deficient (*mdf*) mouse[5,6] due to variants in *SCYL1*. Conclusively and considering the type of the *SCYL1* variant found in the now-presented individual, it is convincing that the patient's neurological phenotype is due to the discovered novel homozygous *SCYL1* variant. In our cohort of SCYL1 deficient patients,[2] we have described a phenotypic spectrum of the neurological involvement ranging from an isolated microcephaly to impaired speech development with regression, mild mental retardation, and severe cerebellar motor dysfunction (broad gait, tremor in hands, stoppage gait), which become more severe while growing up. The variety of the penetrance of symptoms holds true also for the hepatic phenotype ranging from low γ-glutamyl-transferase cholestasis up to episodes of acute liver failure. Hence SCYL1 deficiency can lead to a clinical spectrum of symptoms involving brain and liver, which led us to choose the acronym CALFAN syndrome (low γ-glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration syndrome).

However, the liver phenotype is not the focus of the correspondence; nevertheless, the episodes of abdominal distension in early infancy as well as the resulting hepatosplenomegaly could be the result of a liver involvement. The patient was not followed by the authors during infancy and no more details on the hepatic involvement are provided. It would be interesting if a low γ-glutamyl-transferase cholestasis was present—even without major clinical complaints.

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Spagnoli and colleagues describe frequent airway infections in infancy and acute respiratory distress with pleural infusions. It stays unclear whether these infections were of invasive character (pneumoniae) or of atypical origin. Acute respiratory distress can be of various origin. The authors hypothesize that this recurrent clinical feature might be caused by variants in *SCYL1*, as the machinery of intracellular trafficking is ubiquitous in all cells and may therefore affect every organ. To our knowledge, there is neither a published case of SCYL1 deficiency with respiratory involvement nor is there one within our cohort of unpublished patients. Future work on SCYL1 deficiency will elucidate this question. For now, we do refrain from adding this feature to the overall phenotypic spectrum unless more cases with respiratory insufficiency will be published.

Interestingly, Spagnoli and colleagues report acute neurological regression during febrile episodes. This has not been reported before in patients with CALFAN syndrome/*SCYL1* mutations, but it could affirm our pathomechanistic observation that high temperatures have an impact on the intracellular transport machinery (unpublished data). This is of special interest as an influence of elevated temperature on the protein level was shown already in another congenital disorder of intracellular trafficking—NBAS deficiency.[7,8] The overlap of the phenotypic spectrum between SCYL1 deficiency and NBAS deficiency is striking, but important questions are still to be answered. To learn more about the natural history, organ specificity, and genotype–phenotype correlation, every single case with new phenotypic features and new genetic variants is of importance and will help to expand our understanding and knowledge about these rare diseases.

DISCLOSURE

The authors declare no conflicts of interest.

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REFERENCES

1. 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 2018 October; https://doi.org/10.1038/s41436-018-0389-6. [Epub ahead of print].
2. 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;20:1255–1265.
3. 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;97:855–861.

4. 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; 38:600–608.
5. Schmidt WM, Kraus C, Hoger H, et al. Mutation in the Scyl1 gene encoding amino-terminal kinase-like protein causes a recessive form of spinocerebellar neurodegeneration. EMBO Rep. 2007;8:691–697.
6. Womack JE, MacPike A, Meier H. Muscle deficient, a new mutation in the mouse. J Hered. 1980;71:68.
7. 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;97:163–169.
8. 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;39:3–16.

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