Received: 21 December 2020 | Revised: 26 February 2021 | Accepted: 27 February 2021

DOI: 10.1111/cge.13952

CLINICAL GENETICS WILEY

LETTER TO THE EDITOR

Clinical and molecular delineation of spondylocostal dysostosis type 3

To the Editor,

Spondylocostal dysostosis (SCDO) is a heterogeneous group of rare spine disorders defined by multiple vertebral segmentation defects (M-SDV) and rib anomalies. Patients with SCDO present with short trunk short stature and mild to significant scoliosis. Severely reduced thorax size and a loss of natural thoracic kyphosis might lead to respiratory insufficiency in some affected individuals. Seven subtypes are differentiated based on the affected gene, including SCDO3

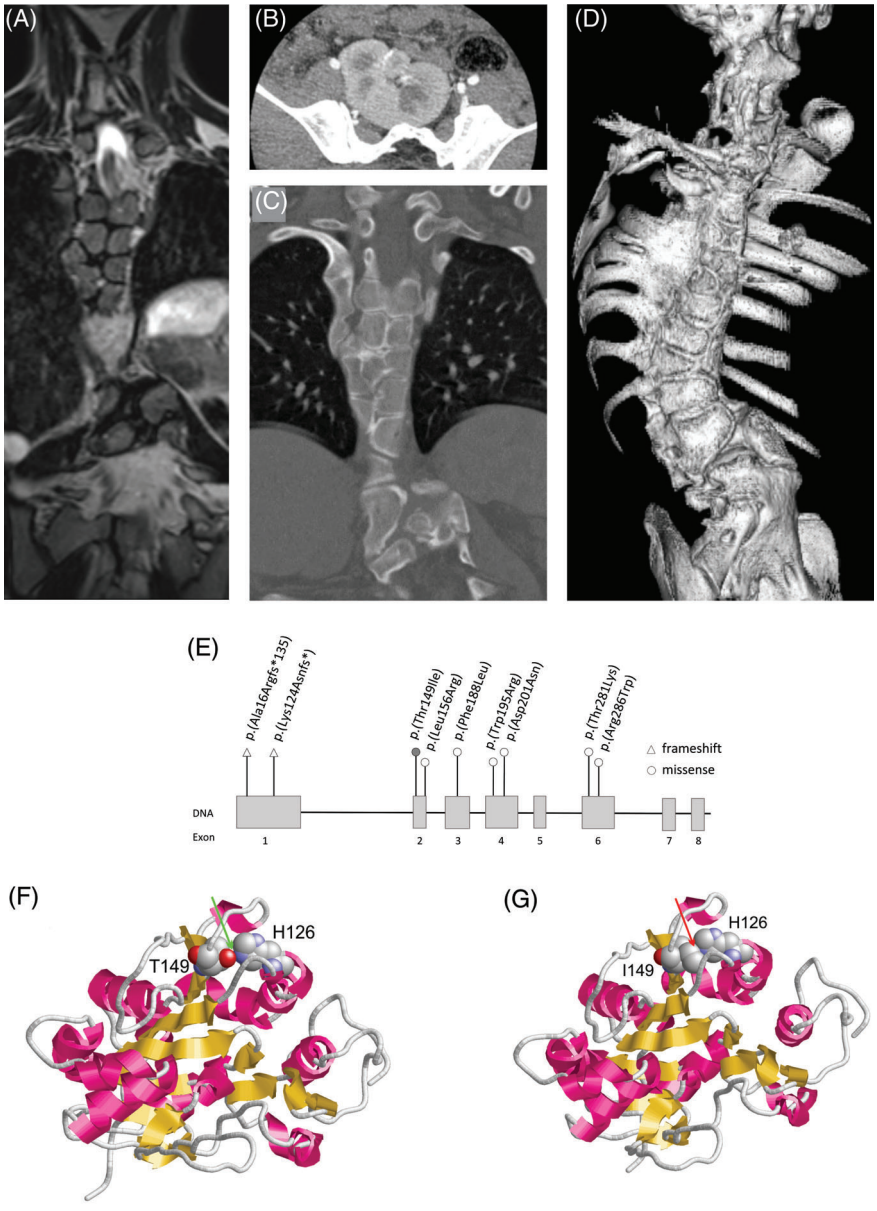

FIGURE 1 T2-weighted (A), T1-weighted (B,C) MRI images and 3D-CT-reconstruction (D) images of the affected individual. Severe segmentation defects of vertebrae of thoracic and lumbar spine with hemivertebrae, butterfly vertebrae and solitary pelvic kidney. Whole spine reconstruction showing severe kyphoscoliosis with dysplastic spine and rib anomalies (rib fusion, dysplasia, aplasia of 9th or 10th rib). (E) Schematic representation of *LFNG* gene and localization of published mutations in patients with SCDO3.[1-4] The variant described in this study is located in exon 2 of *LFNG* (NM_001040167.1) and highlighted in gray. (F,G) Effect of the p.(Thr149Ile) variant on the LFNG structure. (F) Structure of wild type LFNG in ribbon presentation. Thr149 (T149) and the adjacent His126 (H126) are shown in space-filled presentation. A green arrow marks a stabilizing side chain hydrogen bond between both residues. (G) Structure of the p.(Thr149Ile) (T149I) variant, which lacks the side chain hydrogen bond. Instead, an unfavorable steric overlap is observed (indicated by a red arrow). CT, computed tomography; MRI, magnetic resonance imaging [Colour figure can be viewed at wileyonlinelibrary.com]

associated with autosomal recessive pathogenic variants in *LFNG*. *LFNG* belongs to the Fringe genes encoding a family of glycosyltransferases in the Notch signaling pathway and is localized to the Golgi. The Notch pathway is essential throughout embryonic development and regulates somite formation.[1] To date five patients with frameshift or missense variants in *LFNG* gene presenting with M-SDV were published.[1-4] Two individuals showed further minor nonspine-related anomalies (hernia, camptodactyly), but no major organ involvement has been described in SCDO3 patients so far.

We report a 17-year-old individual from healthy consanguineous parents with generalized vertebral segmentation defects, rib anomalies and further nonskeletal findings (Figure 1(A)–(D)). In WES, we identified a homozygous missense variant c.446C>T, p.(Thr149Ile) in *LFNG*, not previously described in SCDO3 patients or genetic databases (Figure 1(E)). The variant was predicted to impair protein function in Notch signaling, a mechanism previously described (Figure 1 (F),(G)).

Although the five previously reported cases had isolated skeletal anomalies or minor nonspine-related features, here the reported individual presented with various additional anomalies including solitary pelvic kidney, uterine dysgenesis mayer-rokitansky-küster-hauser syndrome, absence epilepsy, and inner ear deafness. A part of these anomalies could also be attributed to the MURCS association (MUllerian duct aplasia, unilateral Renal agenesis, Cervicothoracic Somite anomalies).[5]

As no other genetic variants were identified, neither in the exome nor in chromosomal microarray analysis, we propose that the phenotypic spectrum of this syndrome can be much broader, perhaps depending on the localization and nature of the affected variant, although we cannot exclude a blended phenotype due to an undetected additional variant. Identification of additional individuals with mutations in *LFNG* will help to clarify the phenotypic spectrum of SCDO3.

ACKNOWLEDGMENTS

We thank all participants and their families for taking part in this study. We also thank the Exome Aggregation Consortium and the groups that provided exome variant data for comparison. A full list of contributing groups can be found at http://exac.broadinstitute.org/about. This study was supported by grants from the German Research Foundation (DFG; grants TH 896/3-4 and TH 896/7-1) to Christian T. Thiel. The study was approved by the ethics committee of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). Informed consent was obtained from the patient and her parents.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.13952.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Sarah Schuhmann,[1] Heiko Koller,[2] Heinrich Sticht,[3] Cornelia Kraus,[1] Mandy Krumbiegel,[1] Steffen Uebe,[1] Arif B. Ekici,[1] André Reis,[1] and Christian T. Thiel,[1]

[1]*Institute of Human Genetics, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany*
[2]*Universitätsklinik für Neurochirurgie, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany*
[3]*Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg FAU, Erlangen, Germany*

Correspondence
Christian T. Thiel, Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg FAU, Schabachanlage 10, 91054 Erlangen, Germany.
Email: christian.thiel@uk-erlangen.de

ORCID

Christian T. Thiel https://orcid.org/0000-0003-3817-7277

REFERENCES

1. Sparrow DB, Chapman G, Wouters MA, et al. Mutation of the LUNATIC FRINGE gene in humans causes spondylocostal dysostosis with a severe vertebral phenotype. *Am J Hum Genet*. 2006;78:28-37.
2. Lefebvre M, Dieux-Coeslier A, Baujat G, et al. Diagnostic strategy in segmentation defect of the vertebrae: a retrospective study of 73 patients. *J Med Genet*. 2018;55:422-429.
3. Takeda K, Kou I, Mizumoto S, et al. Screening of known disease genes in congenital scoliosis. *Mol Genet Genomic Med*. 2018;6:966-974.
4. Otomo N, Mizumoto S, Lu HF, et al. Identification of novel *LFNG* mutations in spondylocostal dysostosis. *J Hum Genet*. 2019;64:261-264.
5. Guerrier D, Mouchel T, Pasquier L, Pellerin I. The Mayer-Rokitansky-Kuster-Hauser syndrome (congenital absence of uterus and vagina)—phenotypic manifestations and genetic approaches. *J Negat Results Biomed*. 2006;5:1.