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► To cite this version:

Rebecca Schüle, Dagmar Timmann, Corrie Erasmus, Jennifer Reichbauer, Melanie Wayand, et al.. Solving unsolved rare neurological diseases-a Solve-RD viewpoint. European Journal of Human Genetics, 2021, 29 (9), pp.1332-1336. 10.1038/s41431-021-00901-1 . hal-03983726

HAL Id: hal-03983726

<https://hal.science/hal-03983726>

Submitted on 11 Feb 2023

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Solving unsolved rare neurological diseases—a Solve-RD viewpoint

Rebecca Schüle^{1,2,3} · Dagmar Timmann⁴ · Corrie E. Erasmus⁵ · Jennifer Reichbauer^{1,2} · Melanie Wayand^{1,2} · Solve-RD-DITF-RND · Bart van de Warrenburg^{3,6} · Ludger Schöls^{1,2,3} · Carlo Wilke^{1,2} · Andrea Bevo⁷ · Stephan Zuchner⁸ · Sergi Beltran^{9,10,11} · Steven Laurie⁹ · Leslie Matalonga⁹ · Holm Graessner^{3,12} · Matthis Synofzik^{1,2,3} · The Solve-RD Consortium

Received: 13 October 2020 / Revised: 9 April 2021 / Accepted: 16 April 2021 / Published online: 10 May 2021
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Introduction

Rare genetic neurological disorders (RND; ORPHA:71859) are a heterogeneous group of disorders comprising >1700 distinct genetic disease entities. However, genetic discoveries have not yet translated into dramatic increases of diagnostic yield and indeed rates of molecular genetic diagnoses have been stuck at about 30–50% across NGS modalities and RND phenotypes [1, 2]. Existence of yet unknown disease genes as well as shortcomings of commonly employed NGS technologies and analysis pipelines in detecting certain variant types are typically cited to explain the low diagnosis rates.

To increase the diagnostic yield in RNDs - one of the four focus disease groups in Solve-RD - we follow two major approaches, that we will here present and exemplify: (i) systematic state-of the art re-analysis of large cohorts of unsolved whole-exome/genome sequencing (WES/WGS) RND datasets; and (ii) novel-omics approaches. Based on the way Solve-RD systematically organizes researchers' expertise to channel this approach [3], the European Reference Network for Rare Neurological Diseases (ERN-RND) has established its own Data Interpretation Task Force (DITF) within SOLVE-RD, which is currently composed of clinical and genetic experts from 29 sites in 15 European countries.

Members of the Solve-RD-DITF-RND and The Solve-RD Consortium are listed in below Acknowledgements.

These authors contributed equally: Holm Graessner, Matthis Synofzik

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41431-021-00901-1>.

✉ Rebecca Schüle
rebecca.schuele-freyer@uni-tuebingen.de

- ¹ Hertie Institute for Clinical Brain Research (HIH), Center of Neurology, University of Tübingen, Tübingen, Germany
- ² German Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Tübingen, Germany
- ³ European Reference Network for Rare Neurological Diseases, Tübingen, Germany
- ⁴ Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, Essen, Germany
- ⁵ Department of Pediatric Neurology, Radboud University Medical Center, Amalia Children's Hospital, Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands
- ⁶ Department of Neurology, Donders Centre for Brain, Cognition

Systematic re-analysis of coding variation

Unsolved WES datasets (fastq) from 2048 families with RNDs were submitted by clinical sites of ERN-RND [4] to the RD-Connect Genome-Phenome Analysis Platform. Genomic data were processed and filtered as detailed [5]. The Solve-RD SNV/Indel working group reported back 74,456 variants in

and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands

- ⁷ Department of Pediatric Neurology and Developmental Medicine, University Children's Hospital, Tübingen, Germany
- ⁸ Dr. John T. Macdonald Foundation Department of Human Genetics, John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA
- ⁹ CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST), Barcelona, Spain
- ¹⁰ Universitat Pompeu Fabra (UPF), Barcelona, Spain
- ¹¹ Facultat de Biologia, Departament de Genètica, Microbiologia i Estadística, Universitat de Barcelona (UB), Barcelona, Spain
- ¹² Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany

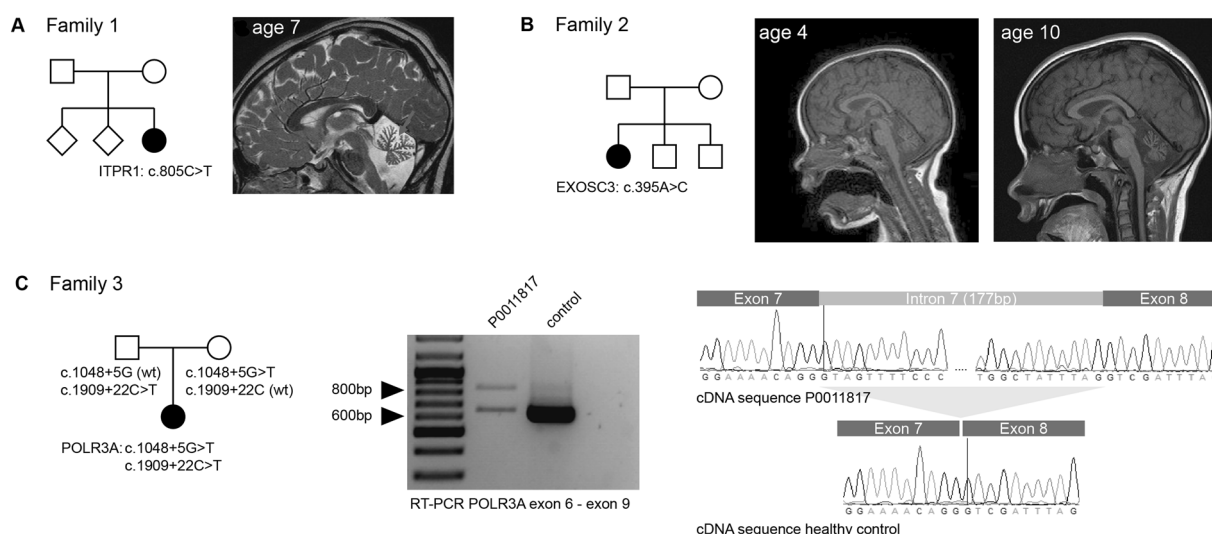


Fig. 1 Clinical information and functional variant validation for families 1–3. A Pedigrees and cranial MRI of patient 1 (*NM_001168272.1(ITPR1):c.805C>T*, *p.(Arg269Trp)*). Mid-sagittal MRI (T2) shows marked cerebellar atrophy at age 7. **B** Pedigree and longitudinal MRIs taken from patient 2 (pontocerebellar atrophy—*NM_016042.3(EXOSC3):c.395A>C*, *p.(Asp132Ala)*). MRIs demonstrate marked cerebellar atrophy while brainstem volume is not affected. **C** Pedigree, segregation analysis and functional analysis in family 3. The index cases carries two intronic *POLR3A* variants. Variant c.1048+5G>T is located in intron 7; RT-PCR with primers

binding to sequences in exon (forward) and exon 9 (reverse) demonstrate presence of an aberrant transcript that is absent in controls. Specific amplification of this additional band and sequencing revealed that all 177 bp of intron 7 are included in the transcript. A nonsense codon in intron 7 presumably leads to termination of translation (*p.Phe352_Arg353ins(23)Ter*). The variant c.1909+22C>T has previously been demonstrated to lead to inclusion of the first 19 nucleotides from intron 14 into the final transcript and consequently to shift of the reading frame [8].

2246 individuals, which were ranked according to their likelihood of being causative. One thousand nine hundred and forty-three variants in 1155 individuals (average 1.68 variants/individual) were classified as rank 1 (genotype matches OMIM and variant (likely) pathogenic according to ACMG).

Based on these results and the work of the RND DITF 44 cases could be solved by this systematic re-analysis approach, which equals 29% of the re-analysed cases for which feedback was available. Reasons for solving cases were firstly updates of the respective ClinVar entry of identified variants between the time of the initial genetic workup and the Solve-RD re-analysis due to now additional available evidence. One example is the re-classification of variants in highly variably genes like *ITPR1* between 2016 and 2020 [6] (Fig. 1A).

Second, use of human phenotype ontology-based phenotypes [7] rather than diagnostic categories as well as consideration of variant-specific rather than gene-specific phenotypes enabled detection of functionally relevant variants because initial analysis focused on disease-specific panels. Mis-classification of phenotypes in RNDs is a common problem due to the considerable overlap between diagnostic categories especially in phenotypes affecting more than one neurological system. This approach i.e. allowed identification of a causative variant in *EXOSC3* (c.395A>C) that is typically associated with a ‘milder’ clinical disease course and lacking the hallmark pontine atrophy characteristic for *EXOSC3*-associated disease (Fig. 1B).

Analysis of non-coding variation

The relative contribution of non-coding variation to RNDs has not been established yet and will be systematically explored by Solve-RD by combining WGS and RNA Seq. We will evaluate the added value of RNA Seq in early onset sporadic cases (Trio-WGS), multiplex recessive and dominant families.

In the meantime, the exon–intron boundaries commonly covered by WES already allow at least a glimpse into the realm of non-coding variants. Indeed, the systematic Solve-RD re-analysis top-listed a single heterozygous intronic variant in the *POLR3A* gene (*NM_007055.3(POLR3A):c.1909T>A: c.1909+22G>A*, *p.Tyr637Cysfs*14*) that had recently been shown to be a frequent cause of spastic ataxia [8] in trans with a second loss-of-function *POLR3A* variant in an unsolved adult patient with a spastic ataxia phenotype. No second coding *POLR3A* variant was identified. However, a variant in intron 7 of the *POLR3A* gene was discovered in the WES data (*NM_007055.3(POLR3A): c.1048+5G>T*). RT-PCR from whole blood revealed an aberrant transcript that was absent in controls. Specific amplification and sequencing demonstrated the inclusion of all 177 bp of intron 7 into the final mRNA transcript. On protein level, this change is predicted to insert 23 amino acids coded by intron 7, followed by a stop codon (*p.Phe352_Arg353ins(23)Ter*) (Fig. 1C).

Finding novel variations through novel omics

Scientific rationale drives application of novel-omics technologies in Solve-RD. From the large variety of different omics technologies that will be used by SOLVE-RD, we here present the example of long-range WGS for ataxias, which has just been initiated. For ataxias >25% of all autosomal-dominant and >50% of all autosomal-recessive ataxia patients remain unsolved despite advanced WES analysis [9]. Ataxias are unique in so far as repeat expansions represent the most frequent disease cause. Seventy-five percent of all known autosomal-dominant ataxia cases and 50% of all known autosomal-recessive ataxia cases are caused by repeat expansions [10]. We thus hypothesize that a substantial share of repeat-expansion disorders is still to be found in the large share of still unsolved WES-negative ataxia cases. Therefore, in Solve-RD we will be using long-range WGS in family ‘triplets’ from autosomal-dominant ataxia families, which will be stringently enriched for novel repeat-expansion disorders: namely only families negative not only on WES and frequent SCA repeats, but also on short-read WGS and for which DNA from >2 affected and >2 non-affected family members are available. In a first round of submission, 20 families with 44 ‘slots’ have been submitted and we are awaiting data in 2021.

Conclusion

This viewpoint presents and exemplifies the approach being taken by Solve-RD to diagnostically solve unsolved RND. While re-analysis so far succeeded in 29% of cases, scientifically rational ‘beyond the exome’ approaches are being implemented to further unravel new RND causing genes.

Acknowledgements We thank the patients and their families for supporting this study.

Solve-RD-DITF-RND Jonathan Baets^{13,14,15}, Peter Balicza¹⁶, Patrick Chinnery¹⁷, Alexandra Dürr^{18,19,20}, Tobias Haack¹², Holger Hengel^{2,21}, Rita Horvath²², Henry Houlden²³, Erik-Jan Kamsteeg²⁴, Christoph Kamsteeg²⁴, Katja Lohmann²⁵, Alfons Macaya²⁶, Anna Marcé-Grau²⁶, Ales Maver²⁷, Judit Molnar¹⁶, Alexander Münchau²⁵, Borut Peterlin²⁷, Olaf Riess^{12,28}, Ludger Schöls^{2,21}, Rebecca Schüle^{2,21}, Giovanni Stevanin^{18,19,20,29,30}, Matthias Synofzik^{2,21}, Vincent Timmerman^{31,32}, Bart van de Warrenburg³³, Nienke van Os^{33,34}, Jana Vandrovcova²³, Melanie Wayand^{2,21}, Carlo Wilke^{2,21}

¹³Peripheral Neuropathy Research Group, University of Antwerp, Antwerp, Belgium; ¹⁴Neuromuscular Reference Centre, Department of Neurology, Antwerp University Hospital, Antwerpen, Belgium; ¹⁵Laboratory of Neuromuscular Pathology, Institute Born-Bunge, University of Antwerp, Antwerpen, Belgium; ¹⁶Semelweis University Budapest, Budapest, Hungary; ¹⁷Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany; ¹⁸Institut National

de la Santé et de la Recherche Médicale (INSERM) U1127, Paris, France; ¹⁹Centre National de la Recherche Scientifique, Unité Mixte de Recherche (UMR), Paris, France; ²⁰Unité Mixte de Recherche en Santé 1127, Université Pierre et Marie Curie (Paris 06), Sorbonne Universités, Paris, France; ²¹Department of Neurodegeneration, Hertie Institute for Clinical Brain Research (HIH), University of Tübingen, Tübingen, Germany; ²²University of Cambridge, England, UK; ²³Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK; ²⁴Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands; ²⁵University of Lübeck, Lübeck, Germany; ²⁶Hospital Vall d'Hebron, Barcelona, Spain; ²⁷University of Ljubljana, Ljubljana, Slovenia; ²⁸Centre for Rare Diseases, University of Tübingen, Tübingen, Germany; ²⁹Institut du Cerveau-ICM, Paris, France; ³⁰Ecole Pratique des Hautes Etudes, Paris Sciences et Lettres Research University, Paris, France; ³¹Peripheral Neuropathy Research Group, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; ³²Institute Born Bunge, Antwerp, Belgium; ³³Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands; ³⁴Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands

The Solve-RD Consortium Olaf Riess^{12,28}, Tobias B. Haack¹², Holm Graessner^{12,28}, Birte Zurek^{12,28}, Kornelia Ellwanger^{12,28}, Stephan Ossowski¹², German Demidov¹², Marc Sturm¹², Julia M. Schulze-Hentrich¹², Rebecca Schüle^{2,21}, Christoph Kessler^{2,21}, Melanie Wayand^{2,21}, Matthias Synofzik^{2,21}, Carlo Wilke^{2,21}, Andreas Trasschütz^{2,21}, Ludger Schöls^{2,21}, Holger Hengel^{2,21}, Peter Heutink^{2,21}, Han Brunner^{24,33,35}, Hans Scheffer^{24,35}, Nicoline Hoogerbrugge^{24,36}, Alexander Hoischen^{24,36,37}, Peter A. C. 't Hoen^{36,38}, Lisenka E. L. M. Vissers^{24,33}, Christian Gilissen^{24,36}, Wouter Steyaert^{24,36}, Karolis Sablauskas²⁴, Richarda M. de Voer^{24,36}, Erik-Jan Kamsteeg²⁴, Bart van de Warrenburg^{33,34}, Nienke van Os^{33,34}, Iris te Paske^{24,36}, Erik Janssen^{24,36}, Elke de Boer^{24,33}, Marloes Steehouwer²⁴, Burcu Yaldiz²⁴, Tjitske Kleefstra^{24,33}, Anthony J. Brookes³⁹, Colin Veal³⁹, Spencer Gibson³⁹, Marc Wadley³⁹, Mehdi Mehtarizadeh³⁹, Umar Riaz³⁹, Greg Warren³⁹, Farid Yavari Dizjikan³⁹, Thomas Shorter³⁹, Ana Töpf⁴⁰, Volker Straub⁴⁰, Chiara Marini Bettolo⁴⁰, Sabine Specht⁴⁰, Jill Clayton-Smith⁴¹, Siddharth Banka^{41,42}, Elizabeth Alexander⁴¹, Adam Jackson⁴¹, Laurence Faivre^{43,44,45,46,47}, Christel Thauvin^{44,45,46,47}, Antonio Vitobello⁴⁵, Anne-Sophie Denommé-Pichon⁴⁵, Yannis Dufourd^{45,46}, Emilie Tisserant⁴⁵, Ange-Line Bruel⁴⁵, Christine Peyron^{48,49}, Aurore Pélissier⁴⁹, Sergi Beltran^{9,10}, Ivo Glynne Gut¹⁰, Steven Laurie¹⁰, Davide Piscia¹⁰, Leslie Matalonga¹⁰, Anastasios Papakostantinou¹⁰, Gemma Bullich¹⁰, Alberto Corvo¹⁰, Carles Garcia¹⁰, Marcos Fernandez-Callejo¹⁰, Carles Hernández¹⁰, Daniel Picó¹⁰, Ida Paramonov¹⁰, Hanns Lochmüller¹⁰, Gulcin Gumus⁵⁰, Virginie Bros-Facer⁵¹, Ana Rath⁵², Marc Hanauer⁵², Annie Olry⁵², David Lagorce⁵², Svitlana Havrylenko⁵², Katia Izem⁵², Fanny Rigour⁵², Giovanni Stevanin^{18,19,20,29,30}, Alexandra Dürr^{19,20,29,53}, Claire-Sophie Davoine^{19,20,29,30}, Léna Guillot-Noel^{19,20,29,30}, Anna Heinzmann^{19,20,29,54}, Giulia Coarelli^{19,20,29,54}, Gisèle Bonne⁵⁵, Teresinha Evangelista⁵⁵, Valérie Allamand⁵⁵, Isabelle Nelson⁵⁵, Rabah Ben Yaou^{55,56,57}, Corinne Metay^{55,58}, Bruno Eymard^{55,56}, Enzo Cohen⁵⁵, Antonio Atalaia⁵⁵, Tanya Stojkovic^{55,56}, Milan Macek Jr.⁵⁹, Marek Turnovec⁵⁹, Dana Thomasová⁵⁹, Radka Pourová Kremlíková⁵⁹, Vera Franková⁵⁹, Markéta Havlovicová⁵⁹, Vlastimil Kremlík⁵⁹, Helen Parkinson⁶⁰, Thomas Keane⁶⁰, Dylan Spalding⁶⁰, Alexander Senf⁶⁰, Peter Robinson⁶¹, Daniel Danis⁶¹, Glenn Robert⁶², Alessia Costa⁶², Christine Patch^{62,63}, Mike Hanna⁶⁴, Henry Houlden⁶⁵, Mary Reilly⁶⁴, Jana Vandrovcova⁶⁵, Francesco Muntoni^{66,67}, Irina Zaharieva⁶⁶, Anna Sarkozy⁶⁶, Vincent Timmerman^{31,32}, Jonathan Baets^{13,14,15}, Liedewei Van de Vondel^{13,32}, Danique Beijer^{13,32}, Peter de Jonghe^{14,32}, Vincenzo

Nigro^{68,69}, Sandro Banfi^{68,69}, Annalaura Torella⁶⁸, Francesco Musacchia^{68,69}, Giulio Piluso⁶⁸, Alessandra Ferlini⁷⁰, Rita Selvatici⁷⁰, Rachele Rossi⁷⁰, Marcella Neri⁷⁰, Stefan Aretz^{17,71}, Isabel Spier^{17,71}, Anna Katharina Sommer⁷¹, Sophia Peters⁷¹, Carla Oliveira^{72,73,74}, Jose Garcia Pelaez^{72,73}, Ana Rita Matos^{72,73}, Celina São José^{72,73}, Marta Ferreira^{72,73}, Irene Gullo^{72,73,74}, Susana Fernandes^{72,75}, Luzia Garrido⁷⁶, Pedro Ferreira^{72,73,77}, Fátima Carneiro^{72,73,74}, Morris A. Swertz⁷⁸, Lennart Johansson⁷⁸, Joeri K. van der Velde⁷⁸, Gerben van der Vries⁷⁸, Pieter B. Neerinx⁷⁸, Dieuwke Roelofs-Prins⁷⁸, Sebastian Köhler⁷⁹, Alison Metcalfe^{82,80}, Alain Verloes^{81,82}, Séverine Drunat^{81,82}, Caroline Rooryck⁸³, Aurelien Trimouille⁸⁴, Raffaele Castello⁶⁹, Manuela Morleo⁶⁹, Michele Pinelli⁶⁹, Alessandra Varavallo⁶⁹, Manuel Posada De la Paz⁸⁵, Eva Bermejo Sánchez⁸⁵, Estrella López Martín⁸⁵, Beatriz Martínez Delgado⁸⁵, F. Javier Alonso García de la Rosa⁸⁵, Andrea Ciolfi⁸⁶, Bruno Dallapiccola⁸⁶, Simone Pizzi⁸⁶, Francesca Clementina Radio⁸⁶, Marco Tartaglia⁸⁶, Alessandra Renieri^{87,88,89}, Elisa Benetti⁸⁷, Peter Balicza⁹⁰, Maria Judit Molnar⁹⁰, Ales Maver⁹¹, Borut Peterlin⁹¹, Alexander Münchau⁹², Katja Lohmann⁹², Rebecca Herzog⁹², Martje Pauly⁹², Alfons Macaya⁹³, Anna Marcé-Grau⁹³, Andres Nascimiento Osorio⁹⁴, Daniel Natera de Benito⁹⁴, Hanns Lochmüller^{95,96,97}, Rachel Thompson^{95,97}, Kiran Polavarapu⁹⁵, David Beeson⁹⁸, Judith Cossins⁹⁸, Pedro M. Rodriguez Cruz⁹⁸, Peter Hackman⁹⁹, Mridul Johari⁹⁹, Marco Savarese⁹⁹, Bjarne Udd^{99,100,101}, Rita Horvath¹⁰², Gabriel Capella¹⁰³, Laura Valle¹⁰³, Elke Holinski-Feder¹⁰⁴, Andreas Laner¹⁰⁴, Verena Steinke-Lange¹⁰⁴, Evelin Schröck¹⁰⁵, Andreas Rump^{105,106}

³⁵Department of Clinical Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands; ³⁶Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands; ³⁷Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Medical Center, Nijmegen, The Netherlands; ³⁸Center for Molecular and Biomolecular Informatics, Radboud University Medical Center, Nijmegen, The Netherlands; ³⁹Department of Genetics and Genome Biology, University of Leicester, Leicester, UK; ⁴⁰John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; ⁴¹Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; ⁴²Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Health Innovation Manchester, Manchester, UK; ⁴³Dijon University Hospital, Genetics Department, Dijon, France; ⁴⁴Dijon University Hospital, Centre of Reference for Rare Diseases: Development disorders and malformation syndromes, Dijon, France; ⁴⁵Inserm - University of Burgundy-Franche Comté UMR1231 GAD, Dijon, France; ⁴⁶Dijon University Hospital, FHU-TRANSLAD, Dijon, France; ⁴⁷Dijon University Hospital, GIMI Institute, Dijon, France; ⁴⁸University of Burgundy-Franche Comté, Dijon Economics Laboratory, Dijon, France; ⁴⁹University of Burgundy-Franche Comté, FHU-TRANSLAD, Dijon, France; ⁵⁰EURORDIS-Rare Diseases Europe, Sant Antoni Maria Claret 167, Barcelona, Spain; ⁵¹EURORDIS-Rare Diseases Europe, Plateforme Maladies Rares, Paris, France; ⁵²INSERM, US14 - Orphanet, Plateforme Maladies Rares, Paris, France; ⁵³Centre de Référence de Neurogénétique, Hôpital de la Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; ⁵⁴Hôpital de la Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; ⁵⁵Sorbonne Université, INSERM UMRS_974, Center of Research in Myology, Paris, France; ⁵⁶AP-HP, Centre de Référence de Pathologie Neuromusculaire Nord, Est, Ile-de-France, Institut de Myologie, G.H. Pitié-Salpêtrière, Paris, France; ⁵⁷Institut de Myologie, Equipe Bases de données, G.H. Pitié-Salpêtrière, Paris, France; ⁵⁸AP-HP, Unité Fonctionnelle de Cardiogénétique et Myogénétique Moléculaire et

Cellulaire, G.H. Pitié-Salpêtrière, Paris, France; ⁵⁹Department of Biology and Medical Genetics, Charles University Prague-2nd Faculty of Medicine and University Hospital Motol, Prague, Czech Republic; ⁶⁰European Bioinformatics Institute, European Molecular Biology Laboratory, Wellcome Genome Campus, Hinxton, Cambridge, UK; ⁶¹Jackson Laboratory for Genomic Medicine, Farmington, CT, USA; ⁶²Florence Nightingale Faculty of Nursing and Midwifery, King's College, London, UK; ⁶³Genetic Counselling, Genomics England, Queen Mary University of London, Dawson Hall, London, UK; ⁶⁴MRC Centre for Neuromuscular Diseases and National Hospital for Neurology and Neurosurgery, UCL Queen Square Institute of Neurology, London, UK; ⁶⁵Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK; ⁶⁶Dubowitz Neuromuscular Centre, UCL Great Ormond Street Hospital, London, UK; ⁶⁷NIHR Great Ormond Street Hospital Biomedical Research Centre, London, UK; ⁶⁸Dipartimento di Medicina di Precisione, Università degli Studi della Campania "Luigi Vanvitelli", Napoli, Italy; ⁶⁹Telethon Institute of Genetics and Medicine, Pozzuoli, Italy; ⁷⁰Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; ⁷¹Institute of Human Genetics, University of Bonn, Bonn, Germany; ⁷²i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal; ⁷³IPATIMUP - Institute of Molecular Pathology and Immunology of the University of Porto, Porto, Portugal; ⁷⁴Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal; ⁷⁵Department of Genetics, Faculty of Medicine, University of Porto, Porto, Portugal; ⁷⁶CHUSJ, Centro Hospitalar e Universitário de São João, Porto, Portugal; ⁷⁷Faculty of Sciences, University of Porto, Porto, Portugal; ⁷⁸Department of Genetics, Genomics Coordination Center, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ⁷⁹NeuroCure Cluster of Excellence, Charité Universitätsklinikum, Charitéplatz 1, Berlin, Germany; ⁸⁰College of Health, Well-being and Life-Sciences, Sheffield Hallam University, Sheffield, UK; ⁸¹Department of Genetics, Assistance Publique-Hôpitaux de Paris - Université de Paris, Robert DEBRE University Hospital, 48 bd SERURIER, Paris, France; ⁸²INSERM UMR 1141 "NeuroDiderot", Hôpital R DEBRE, Paris, France; ⁸³University of Bordeaux, MRGM INSERM U1211, CHU de Bordeaux, Service de Génétique Médicale, Bordeaux, France; ⁸⁴Laboratoire de Génétique Moléculaire, Service de Génétique Médicale, CHU Bordeaux - Hôpital Pellegrin, Place Amélie Raba Léon, Bordeaux Cedex, France; ⁸⁵Institute of Rare Diseases Research, Spanish Undiagnosed Rare Diseases Cases Program (SpainUDP) & Undiagnosed Diseases Network International (UDNI), Instituto de Salud Carlos III, Madrid, Spain; ⁸⁶Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy; ⁸⁷Med Biotech Hub and Competence Center, Department of Medical Biotechnologies, University of Siena, Siena, Italy; ⁸⁸Medical Genetics, University of Siena, Siena, Italy; ⁸⁹Genetica Medica, Azienda Ospedaliero-Universitaria Senese, Siena, Italy; ⁹⁰Institute of Genomic Medicine and Rare Diseases, Semmelweis University, Budapest, Hungary; ⁹¹Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; ⁹²Institute of Neurogenetics, University of Lübeck, Lübeck, Germany; ⁹³Neurology Research Group, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁹⁴Neuromuscular Disorders Unit, Department of Pediatric Neurology, Hospital Sant Joan de Déu, Barcelona, Spain; ⁹⁵Department of Neuropediatrics and Muscle Disorders, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; ⁹⁶Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain; ⁹⁷Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, ON, Canada; ⁹⁸Nuffield Department of Clinical Neurosciences, University

of Oxford, Oxford, UK; ⁹⁹Folkhälsan Research Centre and Medicum, University of Helsinki, Helsinki, Finland; ¹⁰⁰Tampere Neuromuscular Center, Tampere, Finland; ¹⁰¹Vasa Central Hospital, Vaasa, Finland; ¹⁰²Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; ¹⁰³Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain; ¹⁰⁴Medical Genetics Center (MGZ), Munich, Germany; ¹⁰⁵Institute for Clinical Genetics, Faculty of Medicine Carl Gustav Carus, Technical University Dresden, Dresden, Germany; ¹⁰⁶Center for Personalized Oncology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

Funding The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 779257. Data were analysed using the RD-Connect Genome-Phenome Analysis Platform, which received funding from EU projects RD-Connect, Solve-RD and EJP-RD (Grant Numbers FP7 305444, H2020 779257, H2020 825575), Instituto de Salud Carlos III (Grant Numbers PT13/0001/0044, PT17/0009/0019; Instituto Nacional de Bioinformática, INB) and ELIXIR Implementation Studies. The study was further funded by the Federal Ministry of Education and Research, Germany, through the TreatHSP network (01GM1905 to RS and LS), the National Institute of Neurological Diseases and Stroke (R01NS072248 to SZ and RS), the European Joint Program on Rare Diseases-EJP-RD COFUND-EJP N° 825575 through funding for the PROSPAX consortium (441409627 to MS, RS and BvW). CW was supported by the PATE program of the Medical Faculty, University of Tübingen. CEE received support from the Dutch Princess Beatrix Muscle Fund and the Dutch Spieren voor Spieren Muscle fund. Authors on this paper are members of the European Reference Network for Rare Neurological Diseases (ERN-RND, Project ID 739510). Open Access funding enabled and organized by Projekt DEAL.

Compliance with ethical standards

Conflict of interest HG receives/has received research support from the Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF), the Bundesministerium für Gesundheit (BMG) and the European Union (EU). He has received consulting fees from Roche. He has received a speaker honorarium from Takeda. The authors declare no competing interests.

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