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Clinical spectrum of POLR3-related leukodystrophy caused by biallelic *POLR1C* pathogenic variants

Laurence Gauquelin, MD, FRCPC,* Ferdy K. Cayami, MD,* László Sztriha, MD, PhD, Grace Yoon, MD, FRCPC, Luan T. Tran, MSc, Kether Guerrero, MSc, François Hocke, MD, Rosalina M.L. van Spaendonk, PhD, Eva L. Fung, MB, ChB, Stefano D'Arrigo, MD, Gessica Vasco, MD, PhD, Isabelle Thiffault, PhD, FACMG, Dmitriy M. Niyazov, MD, Richard Person, PhD, FACMG, Kara Stuart Lewis, MD, Evangeline Wassmer, MD, MSc, Trine Prescott, MD, Penny Fallon, MBBS, MRCPCH, Meriel McEntagart, MD, Julia Rankin, MD, PhD, Richard Webster, MBBS, MSc, FRACP, Heike Philippi, MD, Bart van de Warrenburg, MD, PhD, Dagmar Timmann, MD, Abhijit Dixit, MD, and Claire Searle, MB ChB, MRCP, DDD Study, Nivedita Thakur, MD, Michael C. Kruer, MD, Suvasini Sharma, MD, DM, Adeline Vanderver, MD, Davide Tonduti, MD, PhD, Marjo S. van der Knaap, MD, PhD, Enrico Bertini, MD, Cyril Goizet, MD, PhD, Sébastien Fribourg, PhD, Nicole I. Wolf, MD, PhD,‡ and Geneviève Bernard, MD, MSc, FRCPC‡

Correspondence
Dr. Bernard
genevieve.bernard@mcgill.ca

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Abstract

Objective

To determine the clinical, radiologic, and molecular characteristics of RNA polymerase III-related leukodystrophy (POLR3-HLD) caused by biallelic *POLR1C* pathogenic variants.

Methods

A cross-sectional observational study involving 25 centers worldwide was conducted. Clinical and molecular information was collected on 23 unreported and previously reported patients with POLR3-HLD and biallelic pathogenic variants in *POLR1C*. Brain MRI studies were reviewed.

*These authors contributed equally to the manuscript.

‡Dual senior authors.

From the Department of Neurology and Neurosurgery (L.G., L.T.T., K.G., G.B.), McGill University, Montreal, Canada; Department of Pediatrics (L.G., L.T.T., K.G., G.B.), McGill University, Montreal, Canada; Division of Clinical and Metabolic Genetics and Division of Neurology (L.G., G.Y.), The Hospital for Sick Children, University of Toronto, Toronto, Canada; Department of Child Neurology (F.K.C., M.S.V.D.K., N.I.W.), Emma Children's Hospital, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, and Amsterdam Neuroscience, Amsterdam, The Netherlands; Department of Clinical Genetics (F.K.C., R.M.V.S.), VU University Medical Center, Amsterdam, The Netherlands; Department of Human Genetics (F.K.C.), Center for Biomedical Research, Diponegoro University, Semarang, Indonesia; Department of Pediatrics (L.S.), Faculty of Medicine, University of Szeged, Szeged, Hungary; Child Health and Human Development Program (L.T.T., K.G., G.B.), Research Institute of the McGill University Health Center, Montreal, Canada; Division of Medical Genetics, Department of Specialized Medicine (L.T.T., K.G., G.B.), McGill University Health Center, Montreal, Canada; Centre de Référence Neurogénétique (F.H., C.G.), Service de Génétique, CHU Bordeaux, Bordeaux, France; Department of Pediatrics (E.L.F.), Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China; Developmental Neurology Department (S.D.A.), Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy; Neuroscience and Neurorehabilitation Department (G.V.), Bambino Gesu Children's Hospital, Rome, Italy; Center for Pediatric Genomic Medicine (I.T.), Children's Mercy Hospitals and Clinics, Kansas City, MO; University of Missouri–Kansas City School of Medicine (I.T.), Kansas City, MO; Department of Pathology and Laboratory Medicine (I.T.), Children's Mercy Hospitals, Kansas City, MO; Department of Pediatrics (D.M.N.), Section of Medical Genetics, Ochsner for Children, New Orleans, LA; GeneDx (R.P.), Gaithersburg, MD; Division of Neurology (K.S.L.), Barrow Neurological Institute, Phoenix Children's Hospital, Phoenix, AZ; Department of Pediatric Neurology (E.W.), Birmingham Children's Hospital, Birmingham, United Kingdom; Department of Medical Genetics (T.P.), Telemark Hospital, Skien, Norway; Department of Paediatric Neurology (P.F.), St Georges University Hospital NHS Foundation Trust, London, United Kingdom; Clinical Genetics Service (M.M.), St George's University Hospitals NHS Foundation Trust, London, United Kingdom; Clinical Genetics Department (J.R.), Royal Devon and Exeter Hospital NHS Trust, Exeter, United Kingdom; Department of Neurology and Neurosurgery (R.W.), The Children's Hospital at Westmead, Westmead, New South Wales, Australia; Center of Developmental Neurology (H.P.), Frankfurt, Germany; Department of Neurology (B.V.D.W.), Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands; Department of Neurology (D.T.), Essen University Hospital, University of Duisburg-Essen, Essen, Germany; Department of Clinical Genetics (A.D., C.S.), Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; Wellcome Sanger Institute (DDD Study), Wellcome Genome Campus, Cambridge, United Kingdom; Department of Pediatrics (N.T.), Division of Child Neurology, University of Texas Health Science Center, Houston, TX, United States of America; Movement Disorders Center and Neurogenetics Research Program (M.C.K.), Barrow Neurological Institute, Phoenix Children's Hospital, Phoenix, AZ; Program in Neuroscience (M.C.K.), Arizona State University, Tempe, AZ, United States of America; Division of Neurology (S.S.), Department of Pediatrics, Lady Hardinge Medical College and Associated Kalawati Saran Children's Hospital, New Delhi, India; Division of Neurology (A.V.), Children's Hospital of Philadelphia, Philadelphia, PA; Department of Neurology (A.V.), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States of America; Department of Child Neurology (D.T.), Neurological Institute C. Besta Foundation IRCCS, Milan, Italy; Department of Functional Genomics (M.S.V.D.K.), VU University, Amsterdam, The Netherlands; Unit of Neuromuscular and Neurodegenerative Disorders (E.B.), Laboratory of Molecular Medicine, Bambino Gesu Children's Hospital, Rome, Italy; Laboratoire MRGM, INSERM U1211, University Bordeaux, Bordeaux, France; Université de Bordeaux (S.F.), INSERM U1212, CNRS 5320, Bordeaux, France; and Department of Human Genetics (G.B.), McGill University, Montreal, Canada.

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Glossary

POLR3-HLD = RNA polymerase III-related leukodystrophy; **TCS** = Treacher Collins syndrome.

Results

Fourteen female and 9 male patients aged 7 days to 23 years were included in the study. Most participants presented early in life (birth to 6 years), and motor deterioration was seen during childhood. A notable proportion of patients required a wheelchair before adolescence, suggesting a more severe phenotype than previously described in POLR3-HLD. Dental, ocular, and endocrine features were not invariably present (70%, 50%, and 50%, respectively). Five patients (22%) had a combination of hypomyelinating leukodystrophy and abnormal craniofacial development, including 1 individual with clear Treacher Collins syndrome (TCS) features. Brain MRI revealed hypomyelination in all cases, often with areas of pronounced T2 hyperintensity corresponding to T1 hypointensity of the white matter. Twenty-nine different pathogenic variants (including 12 new disease-causing variants) in *POLR1C* were identified.

Conclusions

This study provides a comprehensive description of POLR3-HLD caused by biallelic *POLR1C* pathogenic variants based on the largest cohort of patients to date. These results suggest distinct characteristics of POLR1C-related disorder, with a spectrum of clinical involvement characterized by hypomyelinating leukodystrophy with or without abnormal craniofacial development reminiscent of TCS.

Leukodystrophies are a heterogeneous group of genetically determined disorders affecting the cerebral white matter, with or without involvement of the peripheral nervous system.[1,2] Hypomyelinating leukodystrophies, characterized by a severe and permanent myelin deficit, form a large subgroup within the leukodystrophies.[3–5]

RNA polymerase III–related leukodystrophy (POLR3-HLD) is typically characterized by a combination of neurologic and non-neurologic manifestations.[6,7] Cerebellar features are usually prominent, with pyramidal signs involving the lower more than the upper extremities. The non-neurologic manifestations include dental abnormalities, endocrine features, and myopia.[6] Brain MRI generally shows diffuse hypomyelination (mild T2 hyperintensity and variable T1 signal intensity of the white matter) with relative myelin preservation (T2 hypointensity) of specific structures.[4–6,8] Cerebellar atrophy and thinning of the corpus callosum are common associated findings.[6,8]

POLR3-HLD is an autosomal recessive disorder. It was first associated with pathogenic variants in *POLR3A* or *POLR3B*, encoding the largest subunits of RNA polymerase III.[6,9–13] It was also recently associated with a homozygous pathogenic variant in *POLR3K*.[14] In 2015, variants in *POLR1C*, encoding a common POLR1 and POLR3 subunit, were identified in 8 patients with POLR3-HLD.[15] Pathogenic variants in *POLR1C* were previously associated with autosomal recessive Treacher Collins syndrome (TCS), a congenital disorder of craniofacial development, in 3 unrelated patients.[16]

To date, the clinical spectrum of POLR3-HLD caused by biallelic *POLR1C* pathogenic variants has not been described in detail. We present a thorough phenotypic description of this condition by reporting the clinical, imaging, and molecular features of 23 genetically proven cases.

Methods

Twenty-three individuals were included in this multicenter cross-sectional study. The participants were recruited between 2016 and 2018 based on their clinical and radiologic features consistent with POLR3-HLD, combined with proven pathogenic variants in *POLR1C*. They were recruited from 25 different centers worldwide. Eight of the 23 patients have previously been published in the original article identifying *POLR1C* as a causative gene for POLR3-HLD, in 2015.[15]

A retrospective chart review was conducted for each participant. Participants of all ages were included in the study. Clinical and demographic information was collected through a questionnaire distributed to the referring physicians. Sex was documented as observed by the physicians. Consanguinity as well as ethnicity and/or country of origin were also assessed, as reported by the participants and their families.

Brain MRI studies of 22 participants were reviewed by G.B. and L.G. (11), N.I.W. (10), or D.T. (1). MRI was not available for 1 individual who died in the neonatal period. The available studies were analyzed based on established criteria for hypomyelination and previously published imaging characteristics of POLR3-HLD.[4–6,8] Biallelic pathogenic variants in *POLR1C* were identified or confirmed in clinically certified laboratories. The human genome version used for annotation was GRCh37/hg19.

Figure 3B was generated using the Lollipops software.[17] To generate figure 3C, the sequences of human POLR1C and yeast RPAC40 were aligned using Seaview.[18] The yeast equivalent residues found mutated in patients were identified using the sequence alignment and were positioned on the yeast RPAC40 taken from the POLR1 structure (PDB 5M5W).[19] Figure 3C was created using Pymol.[20]

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all participants or their legal representatives. Consent was obtained from 1 participant (patient 19) for disclosure of a photograph. The study was approved by the ethics committees of the McGill University Health Center (11-105-PED) and VU University Medical Center (2018.300). The patients and their families did not receive financial compensation for their participation in the study.

Data availability

The data sets were deposited in a publicly available database (ClinVar number SUB5043960). Anonymized data will be shared by request from any qualified investigator.

Results

Demographic data

Twenty-three individuals (14 female and 9 male patients) from 21 families were included in the study. There were 2 consanguineous families (patients 1 and 13). The patients' age at their last clinical assessment ranged from 7 days to 23 years (median 10 years). The demographic characteristics of the 23 participants are reported in table 1.

Neurologic manifestations

The clinical characteristics of the participants are summarized in table 1. The onset of symptoms was in infancy or childhood, ranging from birth to 6 years. Most patients (17/23, 74%) presented in the first 2 years of life, including 4 in the neonatal period. For the majority of participants, the initial symptoms consisted of motor difficulties (delayed motor development, tremor, or gait impairment). Limited information was available on patient 20.2, who died early in the neonatal period (at age 7 days). Of the other 22 individuals, 9 (41%) did not achieve independent walking, and ambulation was delayed in most of the remaining patients. Nine of 22 participants (41%) had dysphagia, and 5 of them required a gastrostomy tube (between ages 9 months and 10 years).

On examination, all 22 participants who were evaluated beyond the neonatal period had cerebellar signs (ataxia, dysarthria, dysmetria, intention tremor, and nystagmus), and many had prominent tremor. Pyramidal signs were often more pronounced in the lower extremities (14/22 participants, 64%). Dystonia was noted in 7/22 patients (32%). Cognitive impairment (intellectual disability and/or cognitive regression) was variable, seen in 15/21 individuals (71%) who were old enough to be evaluated. Global deterioration with infections was noted in almost half (10/22, 45%). In addition, seizures were reported in 5/22 patients (23%), 1 of whom had events during febrile episodes only and was not treated with antiepileptic medication.

Motor regression occurred in most of the patients (16/22, 73%) and was seen during childhood, between ages 2 and 8 years, except for 2 individuals who experienced regression later (at 12 and 16 years). The use of a wheelchair was often required before adolescence (13/22, 59%). Two of 23 patients died. One of them died in the neonatal period (patient 20.2), and the other at age 10 years (patient 19), both from cardiorespiratory failure. Both had presented in the neonatal period and exhibited abnormal craniofacial development. Patient 20.2 also had cardiac arrhythmias, respiratory distress syndrome, and suspected adrenal insufficiency.

Non-neurologic manifestations

Patient 19 was the only one described by the referring clinician as having facial features compatible with TCS, including downslanted palpebral fissures, strabismus, bitemporal narrowing, external ear abnormalities, cleft palate, and prominent micrognathia (figure 1). Four other individuals (patients 2, 3, 17, and 20.2) showed subtle evidence of abnormal craniofacial development, with mild mandibular hypoplasia. Of note, patient 9 did not exhibit craniofacial abnormalities but had laryngomalacia.

The entire dental, ocular, and endocrine features often seen in POLR3-HLD were not always present, but all patients were found to have at least 1 non-neurologic manifestation. Dental abnormalities were seen in 16/23 individuals (70%): delayed eruption, oligodontia or hypodontia, abnormal tooth shape, malocclusion, neonatal teeth, or frequent cavities. Half of the patients who were evaluated beyond the neonatal period had myopia (11/22, 50%). Short stature was present in 11/22 (50%).

Radiologic characteristics

Radiologic characteristics are presented in table 2 and figure 2. Brain MRI studies were available for 22/23 participants (96%). All showed diffuse hypomyelination, with relative preservation (T2 hypointensity) of specific structures. Preserved myelination of the anterolateral thalamus was seen in 21/22 individuals (95%), and optic radiation in 18/22 (82%). However, several patients did not exhibit all the radiologic characteristics previously described in POLR3-HLD. Relative myelin preservation was less consistently seen in the posterior limb of the internal capsule (12/22, 55%), dentate nucleus (12/22, 55%), and pallidum (11/22, 50%). In addition, 12/22 cases (55%) showed hypointense medial lemniscus. The presence of myelin islets (better myelinated areas within the white matter, T1 hyperintense and T2 hypointense[21]) was also noted in a few patients (3/22, 14%).

Table 1 Demographic, clinical, and molecular characteristics of 23 patients with POLR3-HLD caused by biallelic *POLR1C* pathogenic variants

Patient	cDNA	Protein	DNA	Protein	Sex/ethnicity and/or country of origin	Age at onset (y)	Use of a wheelchair (y)	Dysphagia/ G-tube (y)	Microcephaly	Cerebellar signs	Pyramidal signs	Dystonia	TCS phenotype	AbN craniofacial development	Myopia	Dental AbN	Short stature	Hypogonadotropic hypogonadism	Death (age)
1[a]	c.95A>T	p.Asn32Ile	c.95A>T	p.Asn32Ile	M/Libyan	1	–	–/–	–	+	+	–	–	–	–	+	+	–	–
2	c.221A>G	p.Asn74Ser	c.221A>G	p.Asn74Ser	M/Hungarian	1	6	+/10	–	+	+	–	–	+	–	+	–	NA	–
3	c.436T>C	p.Cys146Arg	c.883_ 885delAAG	p.Lys295del	M/Asian (Chinese)	1	–	+/–	+	+	+	+	–	+	–	+	+	pP	–
4	c.77C>T	p.Thr26Ile	c.326G>A	p.Arg109His	F/Caucasian (Armenian)	2	–	–/–	–	+	+	–	–	–	–	+	–	pP	–
5	c.193A>G	p.Met65Val	c.572G>A	p.Arg191Gln	F/Caucasian (Australian)	1.5	8	+/–	–	+	+	–	–	–	–	–	+	–	–
6	c.326G>A	p.Arg109His	c.970G>A	p.Glu324Lys	F/Caucasian (Turkish)	4	11	+/–	–	+	+	+	–	–	+	–	+	–	–
7	c.395G>A	p.Gly132Asp	c.461_ 462delAA	p.Lys154fs*4	F/Caucasian (German)	1.2	0	–/–	–	+	–	–	–	–	+	+	+	pP	–
8	c.281T>C	p.Val94Ala	c.785T>C	p.Ile262Thr	M/Caucasian (Dutch)	1.2	0	NA	–	+	–	–M	–	–	+	–	–	–	–
9[b] **(303565)**	**c.69+1G>A**	p.Asn24Asnfs55* (prediction)	c.836G>A	p.Arg279Gln	M/Caucasian (British)	0	NA	+/0.75	+	+	+	–	–	–L	–	+	–	pP	–
10.1	c.916_ 920delTATAT	p.Tyr306Leufs*4	**c.938C>T**	p.Thr313Met	M/Caucasian	4	–	–/–	–	+	–	–	–	–	–	+	–	–	–
10.2	c.916_ 920delTATAT	p.Tyr306Leufs*4	**c.938C>T**	p.Thr313Met	M/Caucasian	4	–	–/–	–	+	–	–	–	–	+	+	–	–	–
11	c.193A>G	p.Met65Val	**c.733G>A**	p.Val245Met	M/Caucasian (Dutch)	2	–	–/–	–	+	–	–	–	–	+	–	–	–	–
12	**c.313A>T**	p.Ile105Phe	c.916_ 920delTATAT	p.Tyr306Leufs*4	F/Caucasian (English)	3	12	–/–	+	+	–	–	–	–	+	+	–	pP	–

Continued

Table 1 Demographic, clinical, and molecular characteristics of 23 patients with POLR3-HLD caused by biallelic *POLR1C* pathogenic variants *(continued)*

Patient	cDNA	Protein	DNA	Protein	Sex/ethnicity and/or country of origin	Age at onset (y)	Use of a wheelchair (y)	Dysphagia/ G-tube (y)	Microcephaly	Cerebellar signs	Pyramidal signs	Dystonia	TCS phenotype	AbN craniofacial development	Myopia	Dental AbN	Short stature	Hypogonadotropic hypogonadism	Death (age)
13[a,b] (279603)	c.836G>A	p.Arg279Gln	c.836G>A	p.Arg279Gln	F/Caucasian (English)	2	7	−/−	+	+	+	+	−	−	−	−	+	pP	−
14	c.88C>T	p.Pro30Ser	c.916_920delTATAT	p.Tyr306Leufs*4	F/Norwegian	0.3	0	−/−	−	+	−	+	−	−	+	+	−	pP	−
15	c.221A>G	p.Asn74Ser	**c.502G>A**	p.Val168Met + splicing error	F/Caucasian (English)	0	0	+/1	+	+	+	+	−	−	+	+	+	pP	−
16	**c.79A>G**	p.Thr27Ala	**c.349G>C**	p.Ala117Pro	F/Caucasian	6	−	−/−	−	+	+	−	−	−	−	+	−	−	−
17	**c.322C>T**	p.His108Tyr	**c.325C>T**	p.Arg109Cys	F/Caucasian	0.4	0	+/−	+	+	+	−	−	+	−	+	−	−	−
18	**c.70-1G>A**	p.Asn24Profs27* (prediction)	c.835C>T	p.Arg279Trp	F/African American	2	11	−/−	+	+	+	−	−	−	−	−	+	pP	−
19	**c.699C>G**	p.Tyr233*	c.883_885delAAG	p.Lys295del	F/Caucasian	0	3	+/2	+	+	+	+	+	+	+	+	+	pP	10 y
20.1	c.88C>T	p.Pro30Ser	**c.615delC**	p.Gln206Lysfs*48	M/Caucasian	1	4	+/7	+	+	+	+	−	−	+C	+	+	pP	−
20.2	c.88C>T	p.Pro30Ser	**c.615delC**	p.Gln206Lysfs*48	F/Caucasian	0	NA	NA	+	NA	NA	NA	−	+	NA	−	NA	pP	7 d
21	c.77C>T	p.Thr26Ile	c.77C>T	p.Thr26Ile	F/Asian	3.5	−	-/-	−	+	−	−	−	−	+	+	+	pP	−

Abbreviations: AbN = abnormal; C = cataracts; G-tube = gastrostomy tube; L = laryngomalacia; M = myoclonus, NA = not available; P = puberty; pP = prepubertal; POLR3-HLD = RNA polymerase III-related leukodystrophy.
Patients 1–8 have previously been published.[15] Patients 9 and 13 have been reported in DECIPHER (identifier between brackets). Novel disease-causing variants are in bold.
[a] Consanguinity.
[b] Contribution of the DDD study.

Figure 1 Photograph of patient 19 showing facial features compatible with Treacher Collins syndrome (TCS)

Photograph of patient 19 at age 10 years. She had facial features in keeping with TCS, including downslanted palpebral fissures, strabismus, bitemporal narrowing, external ear abnormalities, cleft palate, and prominent micrognathia.

The vast majority exhibited thinning of the corpus callosum (21/22, 95%) and cerebellar atrophy (19/22, 86%), often mild. Posterior white matter atrophy was present in 7/22 cases (32%). Diffuse supratentorial atrophy was also seen in 6/22 participants (27%), without clear correlation with age or clinical severity.

In 16/22 individuals (73%), MRI revealed areas of prominent T1 hypointensity of the white matter, which is not typically seen in POLR3-HLD. One patient (patient 20.1) exhibited very atypical MRI features, with pronounced T2 hyperintensity and corresponding T1 hypointensity of the deep white matter and polymicrogyria.

Molecular findings

A total of 29 different variants in *POLR1C* were identified, including missense variants, frameshift variants, and splice site variants (table 1 and figure 3). Twelve novel disease-causing variants in *POLR1C* were identified. Four participants were homozygous, and 19 were compound heterozygous. The most common variants were c.916_920del (p.Tyr306-Leufs*4), identified in 4 individuals from 3 unrelated families (patients 10.1, 10.2, 12, and 14), c.88C>T (p.Pro30Ser), in 3 participants from 2 unrelated families (patients 14, 20.1, and 20.2), and c.221A>G (p.Asn74Ser), in 2 patients from 2 unrelated families (patients 2 and 15). Segregation was confirmed in family members for whom DNA was available for sequencing.

Discussion

Our findings suggest that POLR3-HLD caused by biallelic *POLR1C* variants is characterized by a spectrum of clinical features, with hypomyelinating leukodystrophy at times accompanied by craniofacial abnormalities reminiscent of TCS, with varying severity. In addition to the 5 patients who had a combination of neurologic and craniofacial manifestations, 1 patient had laryngomalacia without any other signs of abnormal craniofacial development. Narrowing of the airway is another common manifestation of TCS that is not typically seen in POLR3-HLD.[22]

TCS is a ribosomopathy, and all 3 genes implicated to date (*TCOF1*, *POLR1D*, and *POLR1C*) are involved in pre-rRNA transcription.[23] Most cases of TCS are caused by heterozygous pathogenic variants in *TCOF1*.[22,24,25] Autosomal recessive TCS attributed to pathogenic variants in *POLR1C* is rare, with only 5 affected individuals reported since 2011.[16,26] Of these 5 patients, 4 had normal motor development, and there was no information available for the fifth. Brain imaging findings were not reported.[16,26] POLR3-HLD is known to be associated with variable clinical severity, with later onset and very mild course in some patients.[6] There is 1 reported patient in the literature with no neurologic signs at age 21 years.[6] It is also well established that hypomyelination on brain MRI is not obligate in POLR3-related disorder.[27–30] Therefore, we cannot exclude that the 5 patients with TCS attributed to variants in *POLR1C* could have a mild form of POLR3-HLD, with only subtle neurologic manifestations, if any. We suspect that there is a spectrum of disease severity for both the hypomyelination and the non-neurologic manifestations in POLR3-HLD caused by biallelic *POLR1C* variants, as it is the case in patients carrying pathogenic variants in *POLR3A* or *POLR3B*.[6] It is likely that POLR1C-related disorder is underrecognized.

Our patients appeared overall to have a more severe neurologic phenotype than the previously reported patients with POLR3-HLD.[6] Individuals with biallelic *POLR1C* variants seem to have the most severe neurologic symptoms, followed by patients with biallelic *POLR3A* variants. At the other end of the spectrum, *POLR3B* is known to be associated with milder clinical features.[6] In our cohort, patients with an earlier onset of symptoms had a more severe clinical course, did not achieve ambulation, and were microcephalic, features that are very rarely associated with TCS.[22,24,25] There was no clear genotype-phenotype correlation. Two of the 4 patients with onset of symptoms in the neonatal period were also part of the group that had abnormal craniofacial development. Otherwise, the pattern of cerebellar and pyramidal signs seen in most of our 23 patients was consistent with the established phenotype of POLR3-HLD.

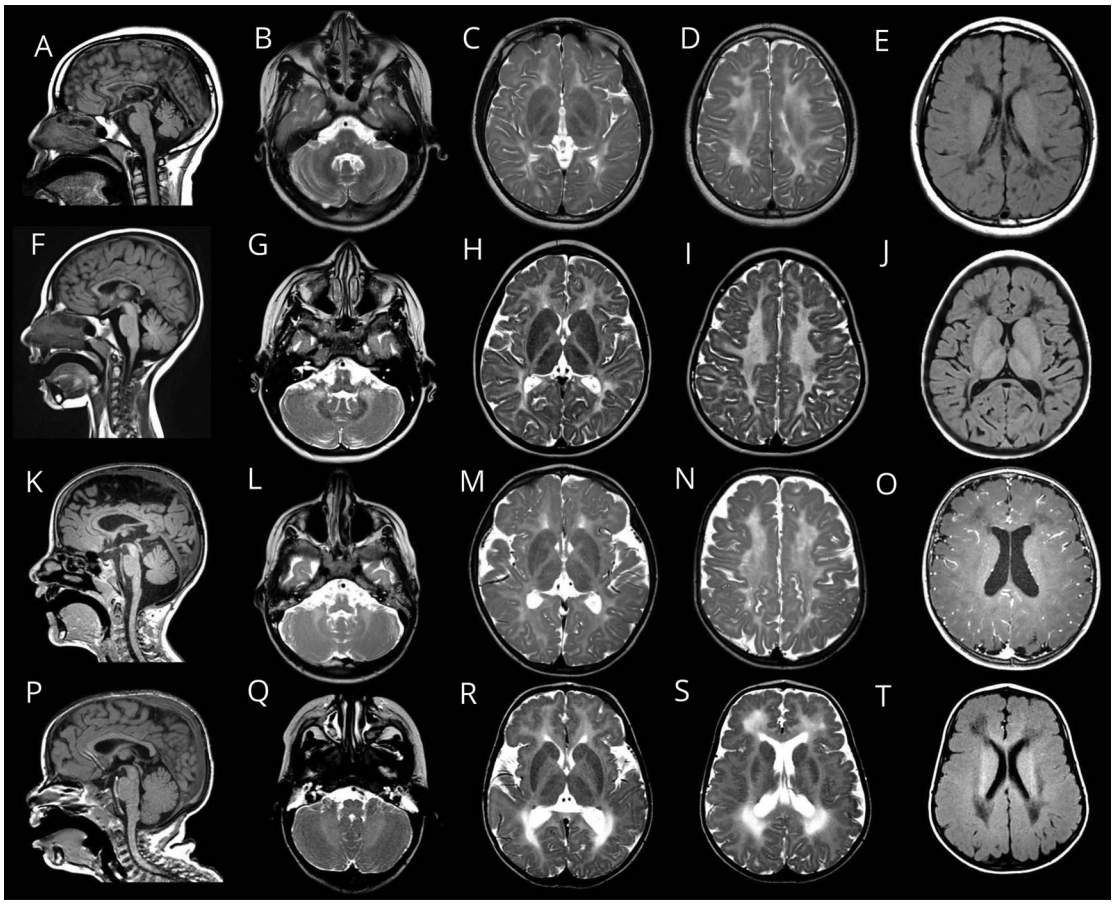
Neurologic manifestations are rarely seen in cases of typical TCS caused by heterozygous pathogenic variants in *TCOF1*.[22,24,25] Delayed speech development is thought to be secondary to

Table 2 Brain MRI characteristics of 22 patients with POLR3-HLD caused by biallelic *POLR1C* pathogenic variants

Patient	Hypomyelination	T2 Hypointense dentatus	T2 Hypointense pallidum	T2 Hypointense CST in PLIC	T2 Hypointense lateral thalamus	T2 Hypointense optic radiation	Thin corpus callosum	Posterior white matter atrophy	Supratentorial atrophy	Cerebellar atrophy	WM areas of marked T1 hypointensity	T2 Hypointense medial lemniscus	Other findings
1	+	+	+	−	+	+	+	−	+	+	+	+	
2	+	−	−	−	+	+	+	−	−	+	+	+	
3	+	−	+	−	−	+	+	−	−	+	+	−	
4	+	+	+	−	+	+	+	−	−	+	+	+	
5	+	−	−	+	+	+	+	−	−	+	+	−	
6	+	+	−	+	+	+	+	+	−	+	+	+	
7	+	−	−	+	+	+	+	−	−	+	+	−	
8	+	−	−	+	+	+	+	−	+	+	+	+	
9	+	+	−	+	+	+	+	−	+	−	+	+	
10.1	+	+	+	+	+	+	+	−	−	+	+	+	MI
10.2	+	+	+	+	+	+	+	−	−	+	+	+	MI
11	+	+	+	+	+	+	+	+	−	+	+	−	
12	+	+	+	−	+	+	+	+	−	+	−	−	
13	+	+	+	+	+	+	+	−	−	+	+	−	
14	+	−	−	−	+	−	−	−	−	−	−	−	
15	+	−	−	−	+	−	+	−	+	+	−	−	
16	+	+	+	−	+	+	+	+	+	+	+	+	
17	+	−	−	−	+	−	+	+	−	+	−	+	
18	+	+	+	+	+	+	+	−	−	+	+	+	
19	+	−	+	−	+	−	+	+	+	−	−	+	
20.1	+	−	−	+	+	+	+	−	−	+	+	−	PMG
20.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
21	+	+	−	+	+	+	+	+	−	+	−	−	MI

Abbreviations: CST = corticospinal tracts; MI = myelin islets; PLIC = posterior limb of the internal capsule; PMG = polymicrogyria; POLR3-HLD = RNA polymerase III-related leukodystrophy; NA = not available; WM = white matter.
Myelin islets and hypointense medial lemniscus are best assessed on 3T imaging.[21]

Figure 2 Brain MRI characteristics of 4 patients with POLR3-HLD caused by biallelic *POLR1C* pathogenic variants



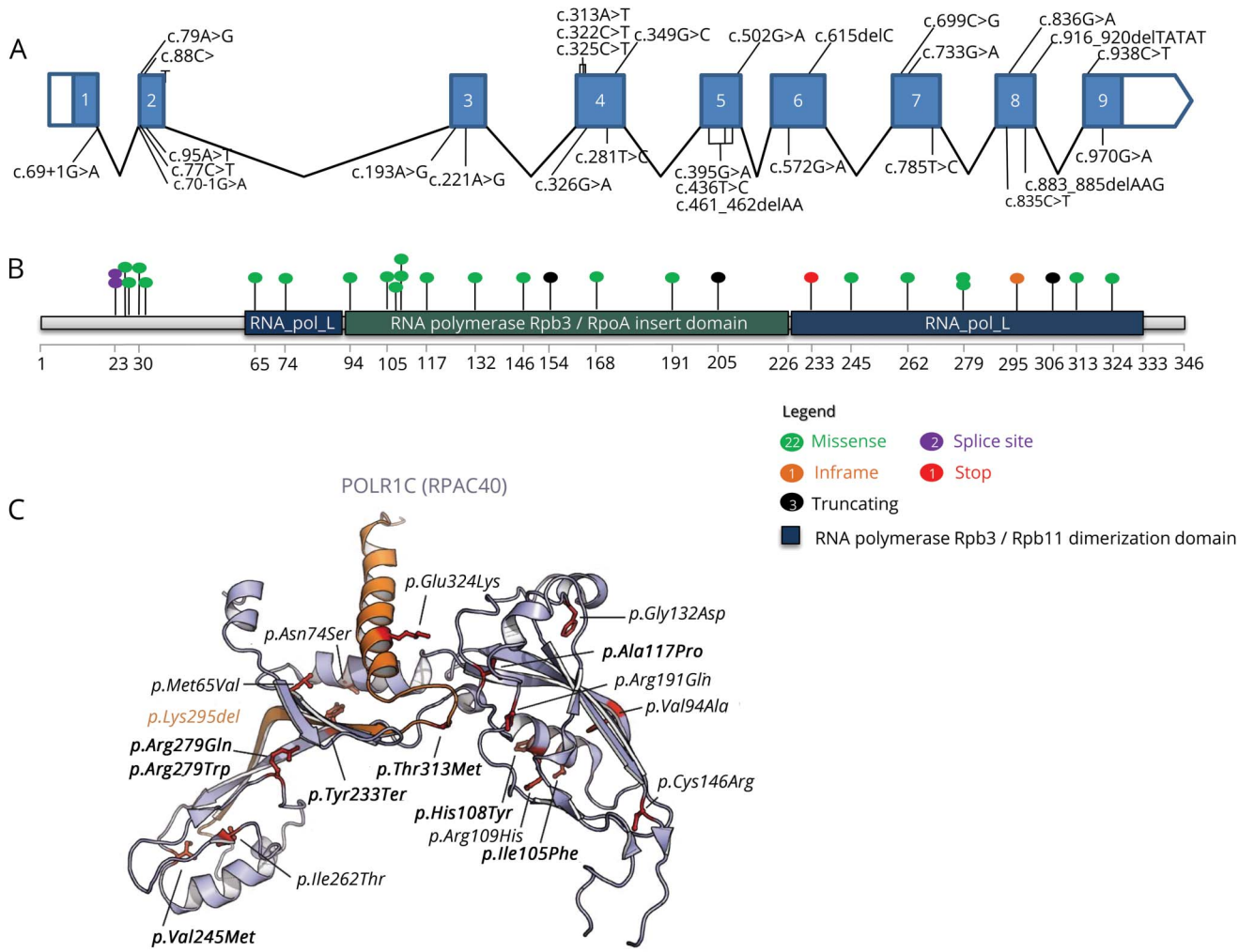
Sagittal T1 (A, F, K, and P), axial T2 (B–D, G–I, L–N, and Q–S) and axial T1 (E, J, O, and T) images. (A–E) MRI of patient 18 obtained at age 11 years showing diffuse hypomyelination with superimposed areas of pronounced T2 hyperintensity (C and D) and corresponding T1 hypointensity (E). Thinning of the corpus callosum and mild superior vermis atrophy are also seen (A), as well as preserved myelination of the dentate nucleus (B), globus pallidus, anterolateral nucleus of the thalamus, and optic radiation (C). (F–J) MRI of patient 4 obtained at age 5 years showing diffuse hypomyelination with preservation of the dentate nucleus (G), anterolateral nucleus of the thalamus, and optic radiation (H). There is also thinning of the corpus callosum and mild vermis atrophy (F). Areas of marked T2 hyperintensity of the white matter are seen (H and I), with corresponding pronounced T1 hypointensity (J). (K–O), MRI of patient 1 obtained at age 5 years showing a thin corpus callosum (K), relative preservation of myelination of the dentate nucleus (L), and absent T2 hypointensity of the corticospinal tracts in the posterior limb of the internal capsule (M). (P–T), MRI of patient 20.1 obtained at age 3 years showing areas of prominent T2 hyperintensity of the white matter (R and S) with corresponding T1 hypointensity (T), especially in the deep white matter. There is also bilateral frontal polymicrogyria (R, S, and T). POLR3-HLD = RNA polymerase III-related leukodystrophy.

conductive hearing loss, and delayed motor development is hypothesized to be associated with atypical and severe TCS presentation.[24] Intellectual disability is also very uncommon; there are 2 reported cases of TCS with intellectual disability caused by deletions of *TCOF1*, with the cognitive impairment being attributed to the deletion of contiguous genes.[25] In addition, there are a few reports of exceptionally severe cases of TCS with craniosynostosis and CNS anomalies (encephalocele and holoprosencephaly).[31] None of these patients had hypomyelination. Thus, the overlap between POLR3-HLD and TCS appears to be unique to POLR1C-related disorder, although variants in *POLR1A*, first associated with acrofacial dysostosis (another category of craniofacial malformations), have also recently been identified as causing leukoencephalopathy.[32]

A similar clinical overlap with another category of craniofacial defects was identified in POLR3A-related disorder. Biallelic *POLR3A* variants were found to cause Wiedemann-Rautenstrauch syndrome, a neonatal form of segmental progeria associated with growth retardation and abnormal facial features, with some patients also exhibiting progressive neurologic symptoms.[33] It was suggested that the specific combination of a variant with a strong functional effect on the protein with a milder hypomorphic variant leads to the Wiedemann-Rautenstrauch syndrome phenotype.[33]

Regarding non-neurologic manifestations, our findings reinforce that it is crucial to screen patients with POLR3-HLD for dental abnormalities, myopia, and short stature. The dental abnormalities are varied and can be very subtle. The lower frequency of myopia in our cohort compared with the previously reported patients with *POLR3A* or *POLR3B* variants (50% vs 87%) may be at least partly due to the fact that our patients were young. Myopia is known to progress over time in patients with POLR3-HLD and may not have started in the younger patients.

Figure 3 Pathogenic variants identified in *POLR1C* associated with POLR3-HLD



(A–B) All reported pathogenic variants and their positions within the *POLR1C* gDNA (A), with missense variants represented in green, in frame in orange, truncating in black, splice site in purple, and stop in red (B). (C) Missense variants displayed on the structure of the yeast ortholog of POLR1C (RPAC40). Variants previously identified in POLR3-HLD are represented in italic, whereas newly identified variants are shown in bold. The p.Lys295del is shown in orange. The p.Thr26Ile, p.Thr27Ala, and p.Pro30Ser variants have not been represented because they are not visible in the crystal structure of RPAC40 (PDB 5M5W).[19,20,38–40] POLR3-HLD = RNA polymerase III-related leukodystrophy.

In POLR3-HLD caused by *POLR3A* or *POLR3B* variants, brain MRI generally shows diffuse hypomyelination with relative myelin preservation of the anterolateral thalamus, optic radiation, globus pallidus, dentate nucleus, and pyramidal tracts in the posterior limb of the internal capsule.[4–6,8] In patients carrying *POLR1C* variants, the dentate nucleus appeared to be less commonly spared (55%, compared with 93% in the literature).[6] Myelin islets and hypointense medial lemniscus were seen in only 14% and 55% of our patients, respectively, however; it is important to mention that these signs are best assessed on 3T imaging.[21] Almost all of our patients exhibited thinning of the corpus callosum, regardless of their age or of the severity of supratentorial atrophy. It is therefore unlikely to represent only the result of diffuse atrophy. Alternatively, it could reflect a more severe underlying white matter involvement. This hypothesis is supported by the characteristic white matter appearance on T1 images in many of our patients, showing areas of more marked hypointensity. In our study, only few of the participants had supratentorial atrophy, which is probably in part due to the fact that they were all comparatively young.

We hypothesize that the atypical MRI characteristics of patient 20.1 could be attributable to 2 distinct conditions, as migration abnormalities have never been formally associated with POLR3-HLD.[34] Alternatively, it is possible that it represents the more severe end of the neurodevelopmental spectrum. Patient 20.2, the sister of patient 20.1, never underwent a brain MRI as she died in the neonatal period. However, she had atypical clinical features, including cardiac arrhythmias. Cardiac anomalies are reported in several animal models and a few human cases of TCS.[22,35] In addition, 3 patients were recently diagnosed with POLR1C-related

disorder in 2 large studies applying whole-exome and whole-genome sequencing to unsolved genetic cases. Their clinical presentation included cardiomegaly, long QT syndrome, and cardiomyopathy.[36,37]

In our cohort, variants were diverse and distributed across *POLR1C*. Two participants carried the p.Arg279Gln variant previously associated with TCS[16]: patient 9 (compound heterozygous with c.69+1G>A) and patient 13 (homozygous). It was initially thought that TCS and leukodystrophy disease-causing variants were distinct, leading to abnormal localization of POLR1C in the nucleolus and abnormal assembly of the RNA polymerase III, respectively.[15] However, none of the individuals carrying the TCS pathogenic variant p.Arg.279Gln showed signs of abnormal craniofacial development, raising the question whether the specific genotype combination (compound heterozygosity with p.Arg279Gln) is responsible for the presence or absence of craniofacial abnormalities, but not the p.Arg279Gln itself. Alternatively, a more complex mechanism than the previously described selective defects in POLR1 or POLR3 could be involved. We postulate that other factors, such as genetic modifiers and neonatal exposures, influence the pathophysiology POLR1C-related disorders.

This study provides a comprehensive description of POLR3-HLD caused by biallelic *POLR1C* pathogenic variants based on the largest cohort of patients to date. We present patients with both a hypomyelinating leukodystrophy and abnormal craniofacial development reminiscent of TCS, suggesting a spectrum of clinical involvement in patients with POLR1C-related disorder. These results illustrate the expansion of a known phenotype in the field of rare diseases.

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Disclosure

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Appendix Authors

Name	Location	Role	Contribution
Laurence Gauquelin, MD, FRCPC	McGill University, Montreal, Canada The Hospital for Sick Children, University of Toronto, Toronto, Canada	Co-first author	Design and conceptualized the study; acquisition of data; analyzed the data; and drafted the manuscript for intellectual content
Ferdy K. Cayami, MD	VU University Medical Center, Amsterdam, The Netherlands Center for Biomedical Research, Diponegoro University, Semarang, Indonesia	Co-first author	Designed and conceptualized the study; acquisition of data; analyzed the data; and drafted the manuscript for intellectual content
László Sztriha, MD, PhD	University of Szeged, Szeged, Hungary	Author	Acquisition of data and revised the manuscript for intellectual content
Grace Yoon, MD, FRCPC	The Hospital for Sick Children, University of Toronto, Toronto, Canada	Author	Acquisition of data and revised the manuscript for intellectual content
Luan T. Tran, MSc	McGill University, Montreal, Canada Research Institute of the McGill University Health Center, Montreal, Canada	Author	Acquisition of data and revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Role	Contribution
Julia Rankin, MD, PhD	Royal Devon and Exeter Hospital NHS Trust, Exeter, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content
Richard Webster, MBBS, MSc, FRACP	The Children's Hospital at Westmead, Westmead, New South Wales, Australia	Author	Acquisition of data and revised the manuscript for intellectual content
Heike Philippi, MD	Center of Developmental Neurology, Frankfurt, Germany	Author	Acquisition of data and revised the manuscript for intellectual content
Bart van de Warrenburg, MD, PhD	Radboud University Medical Center, Nijmegen, The Netherlands	Author	Acquisition of data and revised the manuscript for intellectual content
Dagmar Timmann, MD	Essen University Hospital, University of Duisburg-Essen, Essen, Germany	Author	Acquisition of data and revised the manuscript for intellectual content
Abhijit Dixit, MD	Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content
Claire Searle, MB ChB, MRCP	Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content
DDD Study	Wellcome Sanger Institute, Wellcome Genome Campus, Cambridge, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content
Nivedita Thakur, MD	University of Texas Health Science Center, Houston, TX	Author	Acquisition of data and revised the manuscript for intellectual content
Michael C. Kruer, MD	Phoenix Children's Hospital, Phoenix, AZ Arizona State University, Tempe, AZ	Author	Acquisition of data and revised the manuscript for intellectual content
Suvasini Sharma, MD, DM	Lady Hardinge Medical College and Associated Kalawati Saran Children's Hospital, New Delhi, India	Author	Acquisition of data and revised the manuscript for intellectual content
Adeline Vanderver, MD	Children's Hospital of Philadelphia, Philadelphia, PA University of Pennsylvania, Philadelphia, PA	Author	Acquisition of data and revised the manuscript for intellectual content
Davide Tonduti, MD, PhD	Neurological Institute C. Besta Foundation IRCCS, Milan, Italy	Author	Acquisition of data and revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Role	Contribution
Kether Guerrero, MSc	McGill University, Montreal, Canada Research Institute of the McGill University Health Center, Montreal, Canada	Author	Acquisition of data; analyzed the data; and revised the manuscript for intellectual content
François Hocke, MD (cand.)	CHU Bordeaux, Bordeaux, France	Author	Acquisition of data and revised the manuscript for intellectual content
Rosalina M.L. van Spaendonk, PhD	VU University Medical Center, Amsterdam, The Netherlands	Author	Acquisition of data and revised the manuscript for intellectual content
Eva L. Fung, MB ChB	The Chinese University of Hong Kong, Hong Kong, China	Author	Acquisition of data and revised the manuscript for intellectual content
Stefano D'Arrigo, MD	Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy	Author	Acquisition of data and revised the manuscript for intellectual content
Gessica Vasco, MD, PhD	Bambino Gesu Children's Hospital, Rome, Italy	Author	Acquisition of data and revised the manuscript for intellectual content
Isabelle Thiffault, PhD, FACMG	Children's Mercy Hospitals and Clinics, Kansas City, MO University of Missouri–Kansas City School of Medicine, Kansas City, MO	Author	Acquisition of data; revised the manuscript for intellectual content
Dmitriy M. Niyazov, MD	Ochsner for Children, New Orleans, LA	Author	Acquisition of data and revised the manuscript for intellectual content
Richard Person, PhD, FACMG	GeneDx, Gaithersburg, Maryland	Author	Acquisition of data and revised the manuscript for intellectual content
Kara Stuart Lewis, MD	Phoenix Children's Hospital, Phoenix, AZ	Author	Acquisition of data and revised the manuscript for intellectual content
Evangeline Wassmer, MD, MSc	Birmingham Children's Hospital, Birmingham, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content
Trine Prescott, MD	Telemark Hospital, Skien, Norway	Author	Acquisition of data and revised the manuscript for intellectual content
Penny Fallon, MBBS, MRCPCH	St Georges University Hospital NHS Foundation Trust, London, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content
Meriel McEntagart, MD	St Georges University Hospital NHS Foundation Trust, London, United Kingdom	Author	Acquisition of data and revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Role	Contribution
Marjo S. van der Knaap, MD, PhD	VU University Medical Center, Amsterdam, The Netherlands	Author	Acquisition of data and revised the manuscript for intellectual content
Enrico Bertini, MD	Bambino Gesu Children's Hospital, Rome, Italy	Author	Acquisition of data and revised the manuscript for intellectual content
Cyril Goizet, MD, PhD	CHU Bordeaux, Bordeaux, France	Author	Acquisition of data and revised the manuscript for intellectual content
Sébastien Fribourg, PhD	Université de Bordeaux, Bordeaux, France	Author	Acquisition of data and revised the manuscript for intellectual content
Nicole I. Wolf, MD, PhD	VU University Medical Center, Amsterdam, The Netherlands	Co-senior author	Designed and conceptualized the study; acquisition of data; analyzed the data; revised the manuscript for intellectual content; and study supervision
Geneviève Bernard, MD, MSc, FRCPC	McGill University, Montreal, Canada Research Institute of the McGill University Health Center, Montreal, Canada	Co-senior author	Designed and conceptualized the study; acquisition of data; analyzed the data; revised the manuscript for intellectual content; and study supervision

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Clinical spectrum of POLR3-related leukodystrophy caused by biallelic *POLR1C* pathogenic variants

Laurence Gauquelin, Ferdy K. Cayami, László Sztriha, et al.

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