



Original Article

The Impact of RNA Polymerase III–Related Leukodystrophy on Nonaffected Family Members: A Qualitative Study



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ARTICLE INFO

Article history:

Received 27 August 2025

Accepted 10 December 2025

Available online 16 December 2025

ABSTRACT

Background: RNA polymerase III–related hypomyelinating leukodystrophy (POLR3-HLD) is a rare, neurodegenerative, brain white matter disorder characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism. Due to the complex and progressive nature of this disorder, parents and siblings of patients face many potential challenges and stressors. We, therefore, sought to explore

This study was supported by the Montreal Children's Hospital Foundation (Estate of Daphne Dale Townsend) and the Fondation Les Amis d'Elliot. AL has received the RI-MUHC Desjardins Studentship Award in Child Health Research from the McGill University Health Centre Research Institute (MUHC-RI) (2023) and the Integrated Program in Neuroscience (IPN) Internal Student Award from McGill University (2023–2024). EB and FN are supported by a Ricerca Corrente grant from the Italian Ministry of Health and by a grant from the Pelizaeus-Merzbacher Foundation. EB and FN are members of the European Reference Network for Rare Neurological Diseases, Project ID No 739510. AV is funded by the RDCRN at NCATS and NINDS (U54TR002823) and the Kamens Chair in Translational Neurotherapeutics. GB has received the Clinical Research Scholar Junior 1 Award from the Fonds de Recherche du Québec-Santé (FRQS) (2012–2016), the New

Investigator Salary Award from the Canadian Institutes of Health Research (CIHR) (2017–2022), the Clinical Research Scholar Senior Award from the FRQS (2022–2025), and the Chercheur de Mérite Award from the FRQS (2025–2029). All other authors did not receive any financial support relevant to this article. The Montreal Children's Hospital Foundation and the Fondation Les Amis d'Elliot had no role in the design and conduct of the study.

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Keywords:

POLR3-related Leukodystrophy
Thematic analysis
Burden of disease
Rare disease
Parents and caregivers
Impact on siblings

parents' and siblings' experiences to understand their specific needs and identify modifiable factors to limit familial burden and improve their quality of life.

Methods: We conducted semistructured interviews with parents and siblings of patients with POLR3-HLD. Interview questions focused on the financial, emotional, and psychosocial impacts on parents, as well as siblings' relationship with their affected sibling and the psychosocial impacts they may have experienced. All interviews were recorded, transcribed, and analyzed using reflexive thematic analysis. Through the coding process, themes surrounding the impact on and experiences of parents and siblings were developed.

Results: Nineteen semistructured interviews with 24 parents and nine interviews with 9 siblings were completed between March and October 2023 and February and May 2024, respectively. Four themes from parent interviews included extensive caregiver burden, emotional and psychosocial challenges, the importance of parental self-health, and comfort in the leukodystrophy community. Three themes from sibling interviews included the spectrum of emotional impacts, limited knowledge about POLR3-HLD, and adapting to their sibling's needs.

Conclusions: This study provides a comprehensive understanding of the family experience, identifying the common challenges and specific needs of parents and siblings, highlighting areas of improvement in the global care offered to this vulnerable patient population.

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Introduction

RNA polymerase III-related hypomyelinating leukodystrophy (POLR3-HLD; Mendelian Inheritance in Man [MIM]: 607694, 614381, 616494, 619310), also known as 4H leukodystrophy, is a rare, inherited, and progressive white matter disorder,^{1–4} characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism.^{1,5} Patients with POLR3-HLD can experience neurological characteristics such as developmental delay and regression,^{5,6} motor dysfunction (with predominant cerebellar features),^{5–8} and cognitive impairment,^{5,6,8} and non-neurological manifestations, including dental,^{6,9} ocular,⁸ and endocrine system involvement.¹⁰

The rare and progressive nature of POLR3-HLD, along with the complex care needs of affected patients, can place immense stress, responsibility, and psychosocial challenges on parents.^{11–14} Navigating the uncertainty and decline of their child(ren)'s health while confronted by a perceived lack of understanding and support¹⁵ can leave parents feeling overwhelmed and isolated.^{14,16–20} Siblings of patients with POLR3-HLD, as seen in other rare diseases (RDs),^{21–25} may be equally impacted, experiencing emotional confusion in trying to comprehend and adjust to the realities of this disease. They may also face limitations in their own lives, as they are called to take on extra responsibilities in supporting their affected family member.²⁴

Previous work using quantitative methods have explored stress and quality of life of parents of patients with diverse leukodystrophies (LDs)^{26,27} and parental stress and coping mechanisms in POLR3-HLD.²⁸ A qualitative research approach, however, is necessary to uncover more nuanced insights, increasing the depth and understanding of families' experiences.^{29–31} Building on our prior qualitative study of parents' experiences within the health care system,¹⁵ the present study examines the broader psychosocial and familial dimensions of living with a child with POLR3-HLD. We therefore chose to explore the experiences of parents and siblings of patients with POLR3-HLD through in-depth qualitative interviews to understand families' specific needs and identify modifiable factors to limit familial burden and improve quality of life.

Materials and Methods*Study design*

In-depth, semistructured interviews were completed with parents and siblings of patients with POLR3-HLD. This study was

approved by the Research Ethics Board of the McGill University Health Centre Research Institute (2020-6222).

Participants

Using purposive sampling,^{29,32,33} we recruited 24 parents and 9 siblings from the McGill University Health Centre Research Institute Research Ethics Board–approved MyeliNeuroGene Biobank (2019-4972). We utilized the MyeliNeuroGene laboratory social media to aid participation and recruitment. Eligibility criteria included the following: (1) being a parent or sibling of a patient with POLR3-HLD, (2) being a sibling of at least 5 years old, (3) being fluent in English or French, and (4) being able to come to the Montreal Children's Hospital or to be reached virtually for the interview. The parent participants in this study were the same as those who participated in a previous study exploring health care experiences.¹⁵ Questions regarding both research topics were covered in the same interviews. The present study focuses on distinct research questions and themes addressing the personal and family-level impacts of caring for a child with POLR3-HLD and additionally integrates the perspectives of unaffected siblings. All parents were contacted directly, while siblings were contacted via their parents by email. They were informed about the study and gave written consent/assent.

Interview guides

Two semistructured interview guides specific to either parents or siblings of patients with POLR3-HLD were used ([Supplemental Material](#)). The interview guide for parents was developed in English and translated into French by the research team. It focused on the financial, emotional, and psychosocial impacts on parents and their existing support networks. The interview guide for siblings was adapted from the questionnaire: "Impact of Disease Inventory in VWM: Questionnaire for Siblings", developed by a subgroup of The Vanishing White Matter Consortium, and recently used in this population.²⁵ Any modifications were completed in English and translated into French. Interview questions focused on siblings' relationships with and perceptions of their affected sibling, the care they provided for them, and the psychosocial impacts they may have experienced. A mother and a 9-year-old daughter from a single family affected by a phenotypically similar HLD, Pelizaeus-Merzbacher-like Disease pilot-tested the two interview guides. No modifications were recommended for the interview guide for parents. Their feedback helped tailor the sibling guide to better

suit young children. Revisions included more rapport-building questions and prompts about friendships, family relationships, and hospital experiences.

Researchers and roles of the researchers

The research team consisted of a graduate student (A.L.), a medical student (K.-A.T.), pediatric neurology resident (P.A.Y.), graduate students (A.C., R.v.V.), an international group of clinician experts in LDs (E.B., F.N., D.P., S.V., S.K., D.Re., D.G.M., M.K., D.D.A.P., A.V., M.v.d.K.), and was supervised by an expert in qualitative health research (M.M.) and a pediatric neurologist and clinician-scientist specialized in LDs (G.B.). This multidisciplinary composition provided complementary expertise in clinical care, psychosocial research, and qualitative methodology, strengthening the rigor of the analysis.

The study was approached through a reflexive qualitative lens, acknowledging that the researchers' backgrounds and experiences informed data generation and interpretation. A.L. had been working within a clinical research program focused on LDs, providing familiarity with the patient population and research context, while K.-A.T. contributed a medical student perspective. Their engagement, under the guidance of M.M. and G.B. fostered balanced reflection throughout the study. Regular discussions among the team supported reflexivity and ensured that the analysis remained grounded in participants' lived experiences.

Data collection

A sociodemographic questionnaire was filled out by parents before the study interview. Semistructured interviews occurred with parents and siblings virtually or in person at the Montreal Children's Hospital. Parents participated alone or together, based on preference, with responses analyzed individually. Separate interviews were held for siblings from the same family. A.L. or K.-A.T. recorded all interviews, transcribed them verbatim, and reviewed for accuracy. Recruitment for this study continued until data saturation was reached.^{29,32}

Data analysis

Reflexive thematic analysis (TA) was conducted to identify patterns of meaning related to the caregiving experiences and personal impacts reported by parents and siblings.^{34–36} Reflexive TA is an approach used to systematically identify and interpret patterns within qualitative data while recognizing the active role of the researcher in meaning-making.³⁶ It was selected as the most appropriate method for exploring shared experiences across participants, rather than generating theory or focusing on individual phenomenology, such as in grounded theory or interpretative phenomenological analysis.³⁶ Interview transcripts were deidentified and uploaded to NVivo 14³⁷ for data management and coding. Transcripts were independently coded by A.L. and K.-A.T., with discussions held after every two to three interviews to review code development and analytic reflections. An inductive approach was employed to generate both semantic and latent codes. Themes were subsequently developed by A.L. by identifying patterns across the dataset. The analysis followed a fully qualitative ('Big Q') framework, consistent with guidance advising against the application of statistical analyses in reflexive TA.³⁶ In line with a relativist ontology (which assumes that meaning is subjective and shaped by context) and constructionist epistemology (which views knowledge as coconstructed between researchers and participants), the analysis aimed to provide a rich, though partial,

interpretation of participants' experiences,^{36,38} emphasizing individual meaning-making over postpositivist quantification.

Results

Semistructured interviews were completed with 24 parents (14 individual, 5 pairs) and 9 siblings of patients with POLR3-HLD between March 2023 and May 2024. Parent interviews lasted between 30 and 120 minutes, and sibling interviews between 17 and 41 minutes. The nine siblings interviewed were from families in which parent(s) were also part of this study. Demographic characteristics of parent and sibling participants can be found in [Table 1](#) and [Table 2](#), respectively.

Parents and siblings of patients with POLR3-HLD each have unique experiences in the care journey of their loved one(s). As such, four themes were developed for parents and three themes for siblings, highlighting the impacts they face as family members of patients with POLR3-HLD. Parental themes included (1) extensive caregiver burden, (2) emotional and psychosocial challenges, (3) the importance of parental self-health, and (4) comfort in the leukodystrophy community. Sibling themes included (1) the spectrum of emotional impact, (2) limited knowledge about POLR3-HLD, and (3) adapting to their sibling's needs. Representative quotes from parental and sibling themes are presented in [Table 3](#) and [Table 4](#), respectively.

Parental themes

Theme 1: extensive caregiver burden

Parents of patients with POLR3-HLD spent extensive time providing care and accessing health care for their child(ren) which impacted many facets of their lives. Parents recalled having to alter their career progression, unable to dedicate themselves to the same extent to their work. As such, many were required to adjust, reduce, or halt their working hours. Some parents also cited difficulty in finding understanding and flexible employers, placing additional pressure on their lives. They also discussed having to frequently refuse promotions, prioritizing stability over personal and financial gain for their families.

These shifts in working income, coupled with the health care needs of their child(ren), often placed a heavy financial burden on families. Parents highlighted the substantial expenses associated with accessing specialized care and adaptable equipment for their child(ren), which few could afford without assistance. While many described these changes as burdensome, some parents reflected on how these experiences motivated them to pursue greater financial stability and plan more intentionally for their families' future.

The unique situation in which parents found themselves, as caregivers to children with POLR3-HLD, often altered their interpersonal relationships. Many parents recalled the additional stress on their marriages/partnerships, in having to navigate this journey together. While this strengthened many relationships, some did not survive the weight of this disease. Large impacts were also felt regarding their relations with friends and family. Parents faced difficulty in maintaining relationships with others due to the time constraints on their personal lives. They also often perceived a lack of understanding and support from those around them and feared becoming overbearing and a burden on others.

Theme 2: emotional and psychosocial challenges

In addition to these external impacts, parents experienced many emotional challenges in accepting and living with their child(ren)'s diagnosis. They described seeing their child(ren) struggle as extremely difficult. Before a diagnosis, parents felt

TABLE 1.
Summary of Parent and Patient Characteristics

Parent Characteristics	Total (n = 24)*	%
Parent sex		
Female	18	75
Male	6	25
Preferred language (n = 19)		
English	17	89
French	2	11
Continent of residence (n = 19)		
North America	12	63
Europe	4	21
South America	2	11
Africa	1	5
Household income (CAD) (n = 19)		
Less than 50,000	4	21
Between 50,000-99,000	4	21
Between 100,000-149,000	3	16
Between 150,000-199,000	3	16
Above 200,000	3	16
Unanswered	2	11
Marital status (n = 19)		
Married	14	74
Single	2	11
Divorced	1	5
Living common law	2	11
Employment status		
Employed	18	75
Unemployed	5	21
Retired	1	4
Region of origin		
North American	3	13
British Isles	2	8
Northern European	9	38
Southern European	2	8
Western European	3	13
Eastern European	2	8
Other European	1	4
Latin, Central, South American	4	17
Caribbean	2	8
Arab	1	4
French Canadian	2	8
Unanswered	1	4
Number of affected children (n = 19)		
1	16	84
2	3	16
	Total (n = 22)	%
Patient sex		
Female	12	55
Male	10	45
Patient age (years)†		
1-4	3	14
5-9	9	41
10-19	6	27
20-34	4	18
Time since molecular diagnosis (years)†		
0-5	13	59
6-10	4	18
11-15	4	18
16-20	1	5

Abbreviations:

CAD = Canadian dollar

POLR3-HLD = RNA polymerase III-related hypomyelinating leukodystrophy

This table summarizes parental and patient demographic characteristics, including parents' sex, preferred language, continent of residence, household income, marital status, employment status, region of origin, number of children with POLR3-HLD, and the sex, age, and years since molecular diagnosis of the patient(s).

* Demographic values are represented as a function of total parent participants (n = 24) or total qualitative interviews (n = 19).

† Patients' ages and time since diagnosis in years are those at the time of the interviews.

confused and worried, fearing the worst, yet hoping for the best. Unfortunately, a diagnosis only provided temporary comfort as they were met with a new reality; their child had a rare,

TABLE 2.
Summary of Sibling and Patient Characteristics

Sibling Characteristics	Total (n = 9)	%
Sibling sex		
Female	6	67
Male	3	33
Sibling age		
5-14	4	44
15-24	1	11
25-37	4	44
Age in relation to affected sibling		
Older	6	67
Younger	3	33
Preferred language		
English	7	78
French	2	22
Continent of residence		
North America	5	56
Central America	1	11
South America	1	11
Europe	2	22
Number of affected siblings		
1	9	100
2	0	0
Total number of children/siblings in family		
2	1	11
3	6	67
4	2	22
Patient characteristics	Total (n = 5)	%
Patient sex		
Female	5	100
Male	0	0
Patient age (years)*		
7-14	3	60
15-24	0	0
25-34	2	40
Time since molecular diagnosis (years)*		
0-5	1	20
6-10	2	40
11-15	1	20
16-20	1	20

Abbreviation:

POLR3-HLD = RNA polymerase III-related hypomyelinating leukodystrophy

This table summarizes sibling and patient demographic characteristics, including siblings' sex, age, age in relation to sibling with POLR3-HLD, preferred language, continent of residence, number of siblings with POLR3-HLD, the total number of children within their family, and the sex, age, and years since molecular diagnosis of the patient(s).

* Patients' ages and time since diagnosis in years are those at the time of the interviews.

neurodegenerative disorder, and they felt little knowledge or support was available to them. This unknown was described as the most difficult part. The absence of answers, predictions, or outlooks was both exceptionally difficult and mind-consuming for many. As such, parents lived their lives on an emotional rollercoaster. In a constant state of worry, they grieved their child(ren) with each decline, unsure how far it would go.

Parents were often confronted with a profound sense of helplessness, wanting to do all they could for their child(ren). The scarcity and/or difficulty accessing available treatments, therapies, and perceived limited understanding of health care practitioners, provoked internal conflict among parents. They often questioned the adequacy of their efforts, adding a layer of guilt to their already heavy burden. They wondered whether they were doing enough for their child(ren); could more be done for research, how much therapy was enough therapy, and what was the best use of their time? These questions ran endlessly throughout their minds. Unknowing when and how POLR3-HLD would progress, parents felt they were in a "race against time", fighting to do the most they

TABLE 3.
Parental Themes and Representative Quotes

Themes	Quotes*
Extensive caregiver burden	
Choosing care over career	"Before, I was very focused on my career and on my work, but things changed completely, and this is now a secondary aspect of my life. The priority now is my family and my children." (Parent 2B)
The financial weight of caregiving	"I mean, yes. The fact that I can't go back to, or I haven't gone back to work is huge. Not that you know we're suffering, per se, but it's just a huge hit to our house. [...] It's just added stress, you know, can I go back to work? Can I bring in income? I don't know. I would say that's just kind of our biggest issue in this house, that the income level has dropped quite significantly, and my husband's job is connected to the economy, and the economy has gone down." (Parent 6)
Social isolation in the face of caregiving	"I mean, we won't ever have a situation where we don't have to either bring her with us or ensure somebody's with her. So, it's not as easy to do things or to accept invitations to do things. There's a lot more planning involved. It's just always going to be that way. It's not going to change." (Parent 7)
Emotional and psychosocial challenges	
Fear of the unknown	"We just don't have an option. We don't have an option for things to be different at all. [...] I worry about time. [...] It's anxiety provoking to think about time. So, yeah, we try to get things done with her and do as much as we can, create the most memories that we can because we just don't know. [...] The unknown is scary and anxiety-provoking." (Parent 9A)
Internal conflict	"Then once the diagnosis is in, it's like okay, it's okay, I don't feel guilty anymore, but now I feel guilty about everything. [...] I feel guilty for everything I'm not doing with him, for everything I'm not doing with my daughter, for everything I'm not doing for research, for everything I'm not doing to fight for other people's health care. [...] It's a guilt trip that's been going on for 16 years, then during COVID it was really intense." (Parent 14B)
The importance of parental self-health	
Maintaining one's own health	"Well, it's funny to have this question and it's actually good to have this question. So, we had to pass a lot of time until someone actually asked; 'okay guys, we know about your child, but how are you?' Everybody was so busy with what was happening with our daughter and of course, we are busy with that as well and we don't think about ourselves, but we have to be in good mental and physical health to be able to support our child, because if we don't take care of ourselves, it's not going to be good for her." (Parent 17)
Life outside of caregiving	"Yeah, because it (work) is not my top priority, so it's just enough to keep my hand in it and when I'm there it's actually a really nice distraction, especially when he was really little. When I go to work, I mean you cannot think about anything but work, and it was kind of a nice distraction to forget, and it also reminds you to balance. When you do it every day, all the time, you have nothing to compare it to, so, I don't know. It kind of keeps things balanced." (Parent 3)
Comfort in the leukodystrophy community	
Importance of community support	"But probably the best support is people I've never met in person, which are the families that deal with this, the 4H families. That Facebook group that we have is a great place because we can all confide and compare stories. Like day-to-day, like the emotional stuff, I feel kind of isolated, but I have that network through Facebook with those other families which helps." (Parent 4)
Leukodystrophy Foundations	"I really, really like that they kind of keep you updated on the research as best as possible, even though there's not a whole lot of research. They keep you up to date on every little detail, which has been really nice, just so you feel like we are moving forward, even if it's at a snail's pace. So that's been really, really nice. And again, if I have any questions, I mean, I know there's not a whole lot of answers, but for any questions, they can either say yes, here's the answer to your question, or have you thought about messaging so and so because they might have an answer to your question. So that's been nice." (Parent 11)

Abbreviation:

POLR3-HLD = RNA polymerase III-related hypomyelinating leukodystrophy

This table provides representative quotes from the interviews with parents of patients with POLR3-HLD.

* Some quotes have been translated from French to English, and all have been edited for clarity.

could with every moment. Some parents acknowledged the weight of their efforts within the constraints of available resources and information. While this did not alleviate their doubts, it offered some degree of emotional relief.

Theme 3: the importance of parental self-health

Amid the overwhelming responsibilities of caring for a child with POLR3-HLD, parents recognized the importance of maintaining their own health and well-being. Although their child(ren) remained the top priority, parents emphasized that maintaining their own health was essential to providing the best possible care. Many parents described the benefits of regular exercise, healthy eating, and participating in therapy to manage the emotional weight of their situation. Unfortunately, in dedicating themselves wholeheartedly to caring for their child(ren), parents often neglected their own needs. This also extended to their health care. Many parents mentioned that they often failed to attend their primary care and dental visits, a sharp contrast to the multitude of clinical and therapy appointments for their child(ren).

Parents voiced that finding some balance is crucial. They often felt as though they were only living for their child(ren) and had no life of their own outside of caretaking. For those who still worked, this became somewhat of an escape. It provided parents with an identity outside of caretaking and a distraction from the overbearing responsibilities of their lives. Parents also discussed that, although difficult, time spent for themselves and with their friends

was greatly beneficial. Ultimately, parents acknowledged accepting their circumstances as the only path forward to focus on living the best lives for themselves and their child(ren).

Theme 4: comfort in the leukodystrophy community

Parents expressed the great comfort they found in the community of parents and families of patients with POLR3-HLD. Much emphasis was placed on the deep understanding found among parents. Due to their unique and shared experiences, parents felt understood and supported rather than isolated in their struggles. Parents also served as an invaluable resource for one another, offering emotional support and practical advice. They were often described as the "best guides", sharing invaluable recommendations and guidance to families with a new diagnosis. In providing these parents with a roadmap, they were better equipped on what to expect and the most effective ways to navigate the complexities of caring for a child with POLR3-HLD.

LD foundations also played a crucial role in fostering this supportive network. Parents described their benefit of bringing together the global POLR3-HLD community and bridging the gap between patients and LD specialists. They also provided families with accurate and up-to-date information, offering some hope amid the uncertainty. Parents greatly appreciated the support provided by these organizations and described feeling empowered, knowing that dedicated advocates were fighting alongside them.

TABLE 4.
Sibling Themes and Representative Quotes

Themes	Quotes*
The spectrum of emotional impacts	
The normalcy of 4H	“Oh, I don't think I can remember like, a specific moment. I feel like I just remember at first, we thought it was cerebellar ataxia. So, you know, I just remember that whole kind of scenario of like 'okay well, because of her cerebellar ataxia she can't walk straight, and you know, she's going to have to try a walker out, she has growth medicine, this, this, this, and this'. I was like 'okay like, whatever this thing is, you know, it's fine'. And then eventually, when they went to, I think maybe it was Philadelphia or something, they had found out she had 4H leukodystrophy or something like that. Then I was just kind of like, 'okay, well instead of this is, it's actually this'. So, it didn't really change anything, but I can't remember like when I noticed.” (Sibling 8)
Difficulty in accepting 4H	“And personally, I've never really accepted the disease [...] I've always had trouble accepting it because my role as the big brother is to protect my sisters. And I've felt a bit like my parents, in that we're dealing with something, and we don't have the tools, and we don't know what to do. It's that there's this thing, but what can we do to meet her needs, and all that. And we don't, so it's very hard for me to accept it, because I feel totally powerless because I don't know what to do, and there's nothing I can do. So, it took me over 20 years to finally understand that there's nothing I can do.” (Sibling 6)
Limited knowledge about POLR3-HLD	
Siblings limited knowledge	“I don't know if I have that much knowledge as my mother. My mother basically knows everything about it. I know what a leukodystrophy is. I know the type of leukodystrophy she has. When people ask me to explain, I do the basics. It's a leukodystrophy. I state 4H, what each H stands for. My sibling doesn't have one of the Hs. That is the one with the teeth. But I can manage in a basic way to explain what it is.” (Sibling 3)
Coping and avoidance	So, I prefer to be in denial. To leave this mental burden of understanding why the illness, this and that, to my parents, and then me to live a little bit with my state of health as we go along, what we have to... what we have to be vigilant about. What should we do and what shouldn't we do? (Sibling 6)
Adapting to their sibling's needs	
Care provided by siblings	“Oh no, we always make time for her, when she's at home with my parents, we make a schedule for her. If she wants to go for a walk, we all get dressed, put her in a wheelchair, and off we go. If she doesn't feel like it, well, that's okay, we'll stay at home. No, no, we really adapt to her and what she wants.” (Sibling 7)
Adapting to a new normal	“I'm going to be truly honest, there are moments where I get a little bit anxious and a little bit, I don't know, aggressive. I lose my patience because when you tell her something, she has so much delay that maybe I don't know, after 10 minutes, she replies to a conversation that you were having 10 minutes before. And so, it's very difficult to follow, and imagine when you ask like, 'raise your hand,' and raise your hand never comes, and then you're sitting there like, maybe I have to go to a meeting. So, yeah, I think there's a lot of work from my side to be done, but this is when I had my Eureka moment. I mean things started accommodating in my brain and I said 'okay, we have a problem, and we need to help'. I will try to help as much as possible and my relationship with her actually changed.” (Sibling 9)

Abbreviation:

POLR3-HLD = RNA polymerase III-related hypomyelinating leukodystrophy

This table provides representative quotes from the interviews with siblings of patients with POLR3-HLD.

* Some quotes have been translated from French to English, and all have been edited for clarity.

Sibling themes

Theme 1: the spectrum of emotional impacts

The emotional impacts experienced by siblings of patients with POLR3-HLD were observed to exist on a spectrum. Younger siblings often adopted a more casual attitude toward the disorder, as their sibling's diagnosis occurred early in life and became part of their everyday reality. While they did feel “sad” about their sibling's condition, they described it as a natural part of their family dynamic, rather than a source of profound distress. In contrast, for some families where the disease onset occurred later in the patient's life, the diagnosis was more disruptive for siblings. As siblings matured and gained a deeper understanding of the implications of POLR3-HLD, they shared similar emotional pain and uncertainty as their parents. Similarly, older siblings discussed their fear of the unknown, unsure of their sibling's future. They also described the difficulty in witnessing the gradual decline of their sibling's condition, which added an additional layer of distress.

Theme 2: limited knowledge about POLR3-HLD

The general knowledge and understanding of POLR3-HLD was limited among siblings, even among those who were older in age. They often described the general symptoms seen and some details about their afflicted sibling's condition but had little comprehension of its progression or long-term implications. Among those who were older, many either adopted a “leave it to the parents” attitude or felt constrained in their involvement due to parental control over care and decision-making. Siblings described their limited attendance at clinical and therapy appointments, choosing instead to focus on their own activities. This limited understanding appeared to compound the emotional uncertainty they

experienced. Siblings often had even fewer answers than their parents did and so faced additional difficulties in coping.

Theme 3: adapting to their Sibling's needs

Siblings shared different ways in which they adapted to their affected sibling's needs including the physical, social, and emotional support they provided. They often discussed their role in physical caretaking, helping their sibling with their daily needs and providing needed support to their parents. Interestingly, this did not often interfere with their personal lives; siblings described their continued participation in work and extracurricular activities. This attests to parents' active efforts to maintain a sense of normalcy within the home and ensure their nonaffected child(ren) still felt prioritized and supported. Older siblings also highlighted the heightened awareness of their sibling's functional and cognitive limitations. They described how their relationships have changed with time, the things they wish they could do with their sibling, and how they have learned to adapt to this new normal. In discussing their family dynamic, siblings mentioned having to offer more grace to their affected sibling compared to their non-affected siblings. Some siblings cited the challenges they faced in finding patience and understanding and admitted to frustration at times. Even so, they spoke of consciously adapting their interactions and expectations to better support their sibling's evolving needs.

Discussion

This study provides unique insights into the lived experience of parents and siblings of patients with POLR3-HLD through qualitative methods. The care experiences and disease burden of families of children with RDs are limited among existing

literature^{25,39–41} and are currently absent for this patient population.

Parents of children with RDs play a multifaceted role; the demanding nature of these complex and progressive disorders is exacerbated by a challenging health care landscape^{15,16} and little available support due to their rarity.^{14,17} As such, parents described the many challenges they faced in their lives. Consistent with previous research, parents experienced alterations to their employment status. Pelentsov et al.,⁴¹ 2016 revealed that 38% of RD parents reduced their working hours, and 34% stopped working altogether. This loss of income is often compounded by the high cost of RD care, creating much financial difficulty for families.⁴² Parents also experienced isolation from friends and family, citing an apparent disconnect with those around them. The limited awareness and understanding of RDs make meaningful connections difficult.⁴¹ Confronted with a perceived lack of understanding and support,⁴¹ parents often distanced themselves, limiting interactions with those around them.^{41,43} They were often left to battle this uncertainty and great stress on their own. Parents experienced emotional turmoil regarding their child(ren)'s limitations and deteriorating condition. The “unknown” as described by parents in our cohort, is a shared sentiment among parents of children with RDs, leading to much anxiety,^{11,41,44–46} frustration, and guilt.^{41,47}

In discussing these challenges, parents acknowledged the need to better prioritize their self-health. They often experienced personal neglect in pursuit of care for their child(ren), however, discussed the importance of maintaining their physical and mental health. Parents also highlighted the importance of taking time for themselves. Being a caretaker of a child with POLR3-HLD can be all-consuming, and so having a life outside of caretaking provided some relief and helped them to find peace in their circumstances. Previous research has identified social support from peers and participation in daily life as important coping mechanisms used by parents of children with RDs.^{48–52} Parents, however, expressed uncertainty about relying on this support, often fearing that others may not understand their situation or their child(ren)'s specific care needs.⁵⁰ As such, parents described the benefit of specific support from members of the LD community. Sharing similar experiences, these families helped one another to feel heard, understood, and supported. In a recent study, parents of children with RDs highlighted the critical role of peer support in coping with daily challenges.⁵³ POLR3-HLD and LD foundations also played a vital role in parents' lives. In connecting individuals across the world, these RD organizations help mitigate feelings of isolation. They also help synthesize important information and scientific advances often difficult for RD families to find.^{54,55}

The experiences of siblings of patients with POLR3-HLD appeared to vary by age. Younger siblings generally appeared less emotionally impacted compared to their older counterparts, demonstrating a casual acceptance of their sibling's condition. This likely stemmed from their lack of prior experience with anything different; the disorder had been present for as long as they could remember. This difference is consistent with previous research. Haukeland et al.⁵⁶ 2015, reports complex and often contradictory emotional responses among siblings, leading to both positive and negative emotional experiences. These differences in emotional impact and normalization reflect both the developmental stage and age of unaffected siblings at the time of diagnosis: younger siblings, who experienced the diagnosis early in life, often knew only life with an affected sibling, whereas older siblings recalled a clearer ‘before and after,’ having witnessed the progression and later diagnosis.

In addition to emotional responses, siblings also presented with limited knowledge about POLR3-HLD. Unfortunately, due to the

lack of available information about RDs, this is not uncommon.^{57–59} In our cohort, some siblings described distancing themselves by choice or feeling obligated to do so due to “overprotective” parents who sought to shield them from the medical aspects of their sibling's condition. Consistent with findings from other RD populations, the additional responsibilities of siblings of children with RDs²⁴ were represented in our interviews. Siblings recognized their affected sibling's needs and wanted to help. They described the physical support they provided daily and the social and emotional ways in which they adapted to their sibling's needs but did not face limitations in their personal lives. Parents appeared to support their unaffected child(ren)'s endeavors, allowing them to live their lives with minimal disruption.

Overall, siblings of patients with POLR3-HLD experienced emotional hardship but demonstrated important ways in which they cope with their situations. The perspectives of both older and younger siblings underscore the importance of considering age-related differences when assessing the sibling experience. Tailored supports that reflect these differences are essential to better meet the needs of siblings across developmental stages.

While many of the emotional, informational, and relational challenges identified in this study align with findings from other RDs, the present work extends this literature by situating these experiences within the context of POLR3-HLD. By integrating the perspectives of both parents and siblings, this study offers a more comprehensive view of family burden and adaptations. These results highlight how shared family processes, such as normalization, emotional containment, and evolving understanding of disease, shape individual well-being and underscore the critical need for comprehensive and phased support systems for parents and siblings of patients with POLR3-HLD. Several key recommendations can therefore guide leukodystrophy care teams to better support families (Box 1). Support at the time of diagnosis is especially critical, yet too often, parents were left with little to no information or guidance, leaving them feeling unprepared and anxious. Psychological support should be offered immediately following diagnosis by a social worker or psychologist to help families process the emotional impact of this news. In parallel, genetic counseling should be routinely offered and available to support families in understanding the implications of the diagnosis.^{60,61} A follow-up appointment within one to 4 weeks would provide families with time to reflect on this information, help address any unanswered questions, and support informed decision-making about their child(ren)'s care and future.^{60,62}

In addition, standardized, easy-to-access information such as digital resources and/or informational booklets should be available to families at the time of diagnosis and updated as new research emerges.^{62,63} This is a key area where improved collaboration between clinicians and LD foundations and advocacy organizations could help bridge persistent information gaps. Foundations play an essential role in curating disease-specific educational materials, connecting families with expert clinicians, and providing guidance on navigating complex care pathways.^{64,65} Strengthening these partnerships could enhance the dissemination of accurate, up-to-date information and ensure that families receive ongoing support beyond the clinical setting.

Finally, structured medium-to long-term support is crucial in alleviating the ongoing burden faced by parents. Both social workers and care coordinators could play important and distinct roles. Social workers can help address persistent psychosocial needs, assist with access to financial and respite services, and offer counselling to support family relationships. Meanwhile a care coordinator could assist families by managing the organization of care, facilitating appointments, and acting as a liaison between health care practitioners and family. A recent study highlighted

Box 1**Recommendations for Supporting Families Affected by POLR3-Related Leukodystrophy**

Area of Support	Recommendations
Communication and guidance at diagnosis	Provide clear, structured information at diagnosis; schedule a follow-up visit within 1-4 weeks to address emerging questions and guide care planning.
Psychological and genetic counselling	Offer access to a psychologist or social worker for emotional processing and to a genetic counselor to explain diagnostic implications for the family.
Accessible information resources	Develop and maintain up-to-date digital or print materials for families, in collaboration with LD foundations and advocacy organizations.
Ongoing care coordination	Integrate a dedicated care coordinator to assist with appointments, referrals, and communication among multidisciplinary providers.
Parental and family well-being	Facilitate long-term psychosocial follow-up through social work and respite services to help parents manage chronic strain and maintain self-care.
Sibling support	Provide age-appropriate information and access to RD-specific sibling support programs or peer groups to mitigate isolation and promote understanding.

Abbreviation:
POLR3-HLD = RNA polymerase III-related hypomyelinating leukodystrophy. This box summarizes practical recommendations derived from the study findings on how leukodystrophy care teams can support parents and siblings of patients with POLR3-HLD. Recommendations were informed by the qualitative interviews and synthesized by the research team.

the many psychosocial information needs of parents of children with RDs, including navigating the health care system, coping with family strain, and managing daily life.⁶⁶ Respite care services, including in-home respite care, specialized education programs, or peer support networks should also be more widely available and accessible. This ongoing and personalized support would provide families with necessary relief and enable them to attend to their own self-care needs.

Siblings too face unique challenges navigating this RD and so require more robust support systems to help them cope. By better informing parents about POLR3-HLD, we can empower them to provide more comprehensive support and guidance to their unaffected children. The availability of psychologists and social workers specialized in RD family support can facilitate this and help parents to better navigate this journey with their families. In addition, just as the broader LD community has been a vital resource for parents, similar initiatives targeting the needs of siblings can help mitigate the emotional and social impacts they experience. Tailored knowledge translation efforts, such as informational booklets and structured programs, can also help siblings better understand the condition. Similarly, engaging siblings in RD foundations and RD sibling support groups may further strengthen their connection to the broader RD community, providing valuable support and camaraderie. It is especially important to understand and prioritize siblings' needs and engage them in developing these initiatives.

The inclusion of both parents and siblings of children with POLR3-HLD provided a comprehensive understanding of the family experience and is a major strength of this study. However, there are also limitations. Differences in participant reservation/

willingness to discuss sensitive topics may have occurred, limiting the comprehensive understanding of participants' experiences. Parents may not have felt comfortable sharing all their struggles to avoid being perceived negatively. Although many efforts were made to ensure comfort, the limited understanding and reservation of younger siblings may have restricted their openness. This may partly explain the divergence in experiences and responses between younger and older siblings. Unfortunately, these challenges can arise with qualitative studies, and so the use of in-person interviews in the future may help alleviate this.

Conclusions

Families of patients with POLR3-HLD demonstrate great dedication for their affected member and experience emotional turmoil surrounding the uncertainty of their loved one's condition. These findings highlight the emotional and practical support needs and the importance of greater knowledge and awareness of POLR3-HLD to better equip parents and siblings on their care journeys.

Declaration of competing interest

Dr. Bertini is a consultant for Roche, Orchard Therapeutics, Biogen, PTC, and Pfizer. He is a site investigator for for the Alexander's disease trial of Ionis (2021-present). He serves on the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation and the European Leukodystrophy Association and is a member of the Vanishing White Matter Consortium. He is on the editorial board of Neuromuscular Disorders. Dr. Keller is/was a consultant for Veristat, LLC (2021), Orchard Therapeutics (2023), and the Applied Therapeutics (2024). She was also an ad hoc consultant for the FDA Cellular, Tissue and Gene Therapeutics Committee. She is/was a site investigator for the Alexander's disease trial of Ionis (2021-present) and the Pelizaeus-Merzbacher Disease trial of Ionis (2024-present). She serves on the Board of Directors for the United Leukodystrophy Foundation. She is the site PI for the NIH-funded GLIA-CTN (2019-present) and the Aicardi Goutières Syndrome outcomes study. Dr. Vanderver receives Grant and in-kind support for translational research without personal compensation from Affinia, Biogen, Boehringer Ingelheim, Eli Lilly, Illumina, Ionis, Homology, Myrtelle, Orchard therapeutics, Passage Bio, Sana, Sanofi, Synaptixbio, and Takeda. Dr. Bernard is/was a consultant for Calico (2023-present), Orchard Therapeutics (2023), Passage Bio Inc (2020-2022), and Ionis (2019). She leads two investigator-initiated N=1 trials using Fosigotifator from Calico. She is/was a site investigator for the Vanishing White Matter trial of Calico (2025-present), Alexander's disease trial of Ionis (2021-present), Metachromatic leukodystrophy of Shire/Takeda (2020-2021), Krabbe (2021-2023) and GM1 gene therapy trials of Passage Bio (2021-2024), GM1 natural history study from the University of Pennsylvania sponsored by Passage Bio (2021-present) and Adrenoleukodystrophy/Hematopoietic stem cell transplantation natural history study of Bluebird Bio (2019), a site sub-investigator for the MPS II gene therapy trial of Regenxbio (2021-present) and the MPS II clinical trial of Denali (2022-present). She has received unrestricted educational grants from Takeda (2021-2022). She serves on the scientific advisory board of the Pelizaeus-Merzbacher Foundation, the Yaya Foundation Scientific and Clinical Advisory Council, and the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation. She is a member of the Vanishing White Matter Consortium, the H-ABC Clinical Advisory Board, MLC Clinical Expert Consortium and the Chair of the POLR3-related (4H) Leukodystrophy Consortium. She is on the editorial boards of Neurology Genetics,

Frontiers in Neurology – Neurogenetics, and Journal of Medical Genetics. All other authors have no conflicts of interest relevant to this article to disclose.

Acknowledgments

The authors thank all the parents and siblings of patients with POLR3-HLD who participated in this study. It was an honor to discuss your experiences and to share your stories.

Author contributions: A.L.: Writing – review and editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. K.-A.T.: Writing – review and editing, Validation, Methodology, Investigation, Formal Analysis, Data Curation. P.A.Y.: Writing – review and editing, Methodology. A.C.: Writing – review and editing, Methodology. R.v.V.: Writing – review and editing, Methodology. E.B.: Writing – review and editing, Resources. F.N.: Writing – review and editing, Resources. D.P.: Writing – review and editing, Resources. S.V.: Writing – review and editing, Resources. S.K.: Writing – review and editing, Resources. D.Re.: Writing – review and editing, Resources. D.G.M.: Writing – review and editing, Resources. M.K.: Writing – review and editing, Resources. D.D.A.P.: Writing – review and editing, Resources. A.V.: Writing – review and editing, Resources. M.v.d.K.: Writing – review and editing, Methodology. M.M.: Writing – review and editing, Supervision, Project administration, Methodology, Conceptualization. G.B.: Writing – review and editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pediatrneurol.2025.12.004>.

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