

Clinical spectrum of 4H leukodystrophy caused by *POLR3A* and *POLR3B* mutations

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Supplemental data
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ABSTRACT

Objective: To study the clinical and radiologic spectrum and genotype-phenotype correlation of 4H (hypomyelination, hypodontia, hypogonadotropic hypogonadism) leukodystrophy caused by mutations in *POLR3A* or *POLR3B*.

Methods: We performed a multinational cross-sectional observational study of the clinical, radiologic, and molecular characteristics of 105 mutation-proven cases.

Results: The majority of patients presented before 6 years with gross motor delay or regression. Ten percent had an onset beyond 10 years. The disease course was milder in patients with *POLR3B* than in patients with *POLR3A* mutations. Other than the typical neurologic, dental, and endocrine features, myopia was seen in almost all and short stature in 50%. Dental and hormonal findings were not invariably present. Mutations in *POLR3A* and *POLR3B* were distributed throughout the genes. Except for French Canadian patients, patients from European backgrounds were more likely to have *POLR3B* mutations than other populations. Most patients carried the common c.1568T>A *POLR3B* mutation on one allele, homozygosity for which causes a mild phenotype. Systematic MRI review revealed that the combination of hypomyelination with relative T2 hypointensity of the ventrolateral thalamus, optic radiation, globus pallidus, and dentate nucleus, cerebellar atrophy, and thinning of the corpus callosum suggests the diagnosis.

Conclusions: 4H is a well-recognizable clinical entity if all features are present. Mutations in *POLR3A* are associated with a more severe clinical course. MRI characteristics are helpful in addressing the diagnosis, especially if patients lack the cardinal non-neurologic features.

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GLOSSARY

4H = 4H leukodystrophy; **ADDH** = ataxia, delayed dentition, and hypomyelination; **TACH** = tremor-ataxia with central hypomyelination.

4H leukodystrophy (4H) (HLD7, OMIM 607694 and HLD8, OMIM 614381) is typically characterized by the triad of hypomyelination, hypodontia, and hypogonadotropic hypogonadism. It was first identified in 4 children too young for the assessment of pubertal development. Clinical hallmarks were early-onset ataxia, delayed dentition, and hypomyelination (ADDH).¹ Four adult patients with milder neurologic signs and hypogonadotropic hypogonadism were described shortly thereafter,² and it soon became clear that they all had the same entity.³

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Additional signs such as severe myopia and small stature emerged, but patient numbers were too small to confirm that they are typical of 4H.³ Several years later, tremor-ataxia with central hypomyelination (TACH) was described in French Canadian patients⁴ and mapped to 10q22.3–10q23.31 with subsequent identification of the responsible gene, *POLR3A*, coding for the largest subunit of RNA polymerase III.⁵ Mutations in *POLR3A* and *POLR3B*, encoding another subunit of this polymerase, were then shown to also cause 4H, as well as 2 other entities: “hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum,” and “leukodystrophy with oligodontia.”^{6–8} The name Pol III-related leukodystrophies has been suggested in order to include all the variations described above. As the term 4H encompasses the non-neurologic symptoms and is therefore clinically helpful for the diagnosis, we chose to refer to the condition as 4H leukodystrophy in this article.

We report the clinical, molecular, and radiologic characteristics of 105 patients with mutation-proven 4H leukodystrophy.

METHODS Patients. A cross-sectional observational study was performed including 105 patients (table 1) with 4H leukodystrophy present in the white matter disorders database of the Centre for Childhood White Matter Disorders, VU University Medical Centre, Amsterdam, the Netherlands; the Montreal Children’s Hospital of the McGill University Health Center, Canada; and the Myelin Disorders Bioregistry Project at Children’s National Medical Center, Washington, DC. Clinical questionnaires were completed by the referring physician or family, supplemented by information from medical records. Thirty-six patients were seen by N.I.W. (19), A.V. (8), or G.B. (9). Some of the patients had already been published when delineating the clinical entity or describing the genetic basis of the disease (table e-1 on the *Neurology*[®] Web site at Neurology.org). Patients were initially recruited when noted to have hypomyelination and dental abnormalities, later on the basis of typical MRI abnormalities.

Standard protocol approvals, registrations, and patient consents. We received approval from the ethical standards committee for our research on patients with leukoencephalopathies, and written informed consent was obtained from the guardians.

Mutation analysis. Mutation analysis of *POLR3A* and *POLR3B* was performed in Amsterdam and Montreal, except for 5 patients, who were diagnosed in clinical laboratories (4H-41, 4H-42, 4H-43, 4H-104, and 4H-105), and 2 patients (4H-37 and 4H-38) using whole exome sequencing, followed by Sanger sequencing.

MRI. The latest available MRI was analyzed for this study. MRI was unavailable for 4 patients and in 5 patients, not all items could be scored due to insufficient quality of the MRI. MRIs were evaluated according to a previously published protocol⁹ by either N.I.W. or G.B. For hypomyelination, previously defined MRI criteria were applied.¹⁰ Studies typically included sagittal T1-weighted and axial T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images.

Pathology. Six-micrometer-thick formalin-fixed paraffin-embedded tissue sections of the brain of patient 4H-92, who had died of pneumonia at age 14 years, were deparaffinized and stained according to standard protocols (supplemental data).

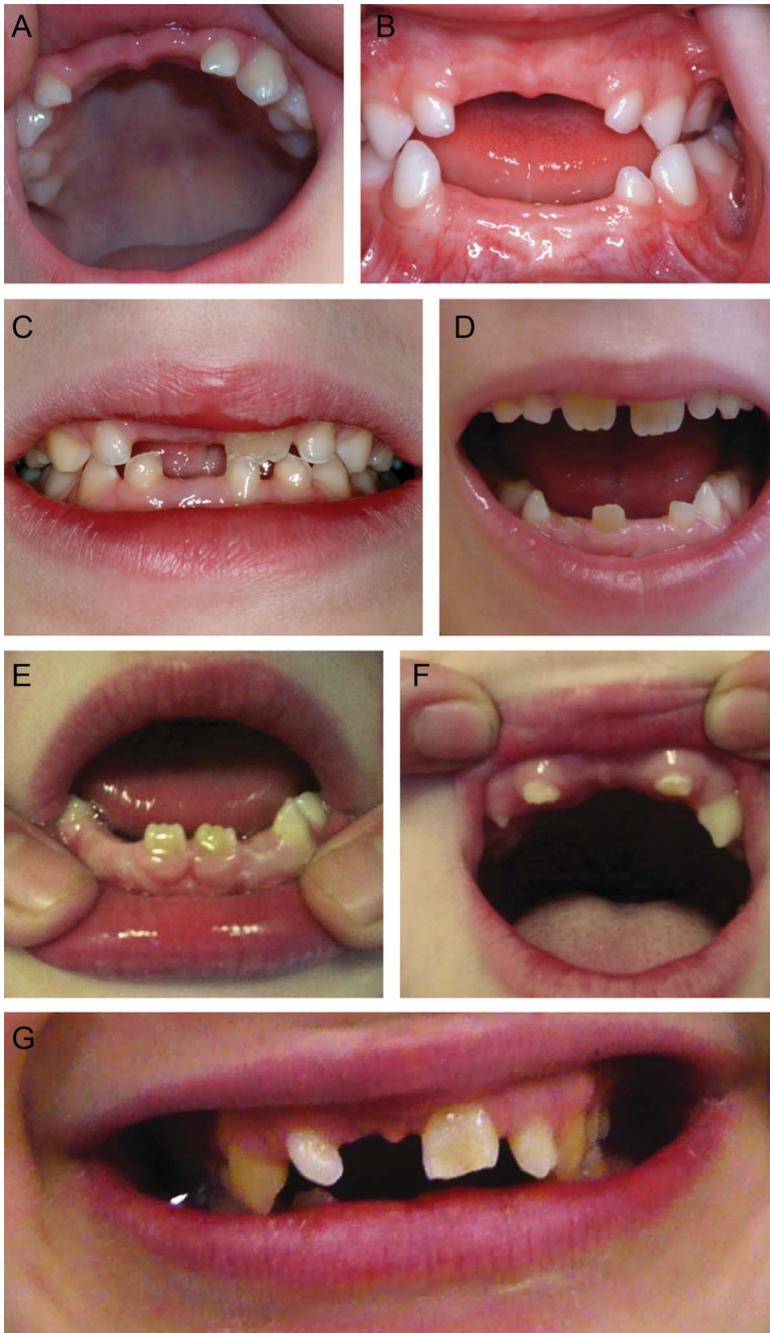
RESULTS Molecular data. Of the 105 patients, 43 had mutations in *POLR3A* and 62 in *POLR3B* (table e-1 and figure e-1). Most patients of French Canadian descent carried the c.2015G>A mutation in *POLR3A* in a homozygous or heterozygous state. Only one patient without French Canadian descent was heterozygous for this mutation. Patients with Mediterranean ancestry mostly carried mutations in *POLR3A*. With the exception of French Canadian patients, patients of European descent were much more likely to have mutations in *POLR3B* (53/62 cases). A total of 51 of 62 patients were compound heterozygous for c.1568T>A in *POLR3B*. Surprisingly, only one sibling pair was homozygous for this mutation, although the carrier frequency is estimated to be 0.5%.⁸ The combination c.1568T>A and c.2084-6A>G was present in 5 patients, c.1568T>A and c.2570+1G>A in 4. Nonsense mutations were rare and never homozygous. In 4 families, a second mutation could not be ascertained. Six additional patients with typical clinical and radiologic features of 4H syndrome were negative for mutations in both genes and were not included in the further analysis.

Neurologic signs. In about half of the patients (52%; 54/103), development was delayed. This was usually noted between the age of 1 and 2 years. Nineteen children (17%) were never able to walk independently (4 with *POLR3A*, 15 with *POLR3B* mutations). If unsupported walking was possible, it was usually achieved before age 2 years. There were 10/105 (10%) patients presenting late, after age 10 years. Only one patient, a 21-year-old woman diagnosed at age 16 years when she developed optic neuritis, had no cerebellar signs. Many patients had severe intention

Table 1 Demographic data on our patient cohort

	All patients	<i>POLR3A</i>	<i>POLR3B</i>
Number of patients	105	43	62
Male:female	52:53	20:23	32:30
Age at time of the study, y	1–40	3–40	1–40
Median age, y	18	20	16
Age at last MRI	15 mo–39 y	2–36 y	1–39 y
Median age at last MRI, y	11	13	10

Figure 1 Typical dental abnormalities



In the 2 youngest children (A: 4H-70, age 3 years; B: 4H-51, age 4 years), the most typical abnormality is the lack of the upper median deciduous incisors. In patient 4H-47 (age 7 years [C] and age 8 years [D]), the deciduous maxillary median incisors never erupted, but the permanent incisors did. In patient 4H-55, age 9 years (E, F), these teeth are still absent, and the permanent lower median incisors have only recently erupted. (G) In patient 4H-93 (age 19 years), the right upper median incisor never erupted. The right lateral median incisor is still a deciduous tooth, as is the left maxillary canine.

tremor and dysmetria; in others, gait ataxia was evident, whereas appendicular ataxia was mild. Abnormal smooth pursuit and gaze-evoked nystagmus were present in most patients. Limitation of vertical gaze was present in 18/91 (20%) patients for whom the information was available, and this was often an early sign. Pyramidal signs were usually absent in young children and developed slowly in

older patients. Extrapyramidal signs, typically dystonia, were prominent in only a few patients. Wheelchair dependence was usually delayed and occurred from the end of the first decade (mean age of 14 years), but half of the patients (48%, 26/54) were ambulatory as adults. The main limitation to walking was ataxia. Expressive language and swallowing deteriorated over time as well.

Cognition varied widely, from normal cognitive abilities in some patients to learning difficulties or mild to moderate intellectual disability in most. Cognition usually deteriorated slowly in the second decade, but language comprehension and nonverbal communication were present until late. Epilepsy was infrequent (present in 19/99 [19%] patients for whom the information is available), and usually well-controlled with medication. Neurologic deterioration with infections was present in half (42/37, 53%), with not all children regaining their previous level. Eight patients, only one of whom carried mutations in *POLR3B*, died due to disease progression, the youngest at age 8 years, the oldest at age 36 years.

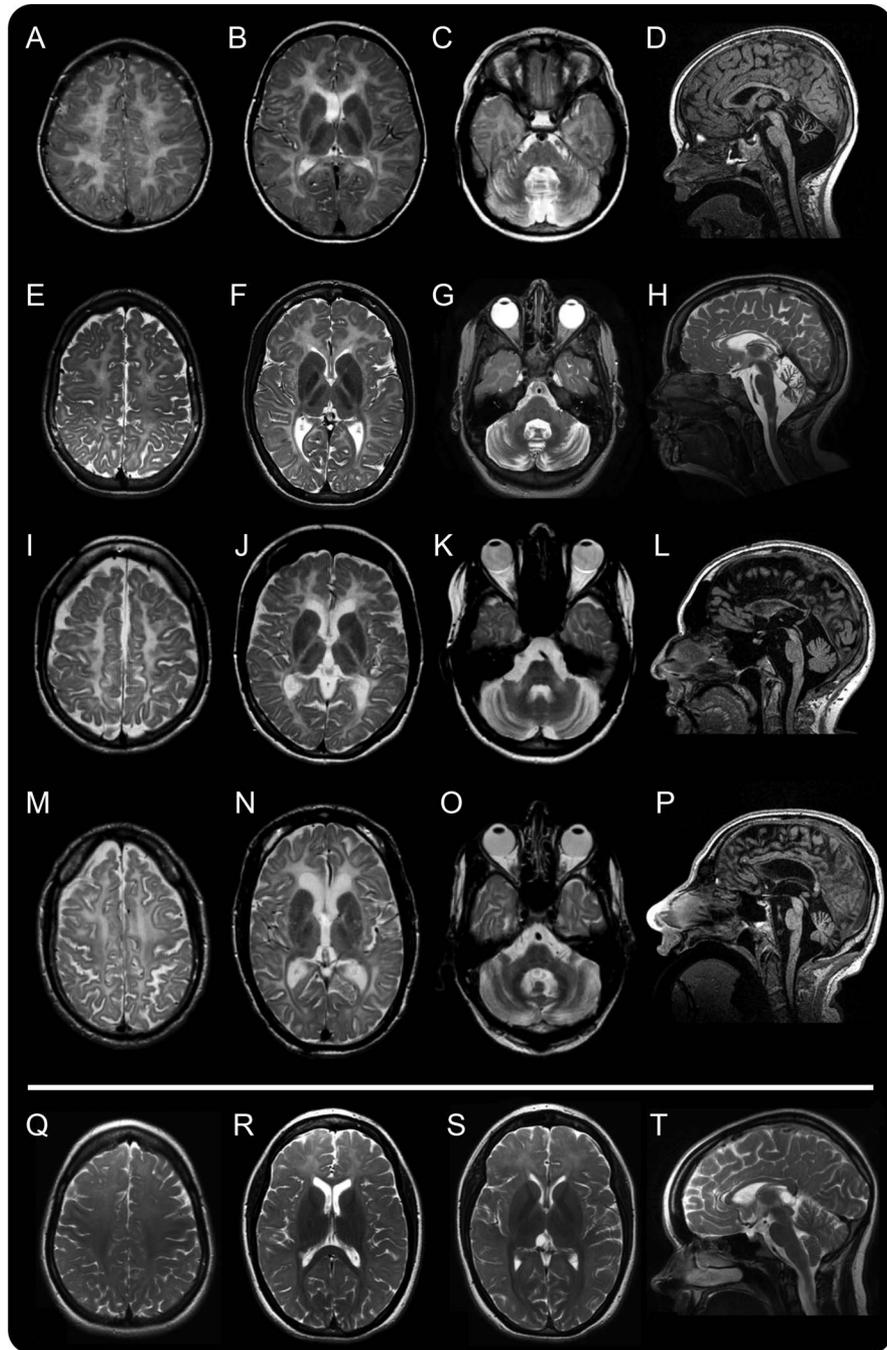
Non-neurologic manifestations. Dental abnormalities were present in 88/101 patients for which the information was available (87%). Natal teeth were present in 18/94 (19%). Delayed dentition with abnormal order of deciduous tooth eruption was reported in 65/91 (71%), with the upper median incisors erupting late or not at all. Hypodontia was present in 71/98 (72%) (figure 1).

Delayed puberty was defined as absence of pubertal development after age 14 (girls) or 16 years (boys). Thirty-seven patients were too young to assess pubertal development. Delayed puberty or primary amenorrhea was present in 27/33 patients with *POLR3A* (81%) and 20/29 patients (69%) with *POLR3B* mutations.

The majority of patients (73/84, 87%) had myopia, often pronounced, and usually progressive. Optic atrophy was present in older patients and is probably more frequent than reported here, as not all patients were assessed for it. Cataracts were seen in only 3 patients, including 1 sibling pair. About half of the patients had short stature (47/91, 51%); this was slightly more frequent in children with onset before 3 years. Growth hormone deficiency was confirmed in 5 of 10 patients tested and might be more common, as many patients were not investigated for this. Several patients were tested for hypothyroidism with normal results. Three patients had mild osteopetrosis detected by chance on routine hip X-rays.¹¹ In one of these patients, hip X-ray results had normalized at age 18 years.

MRI findings. Hypomyelination was invariably present with myelination of the optic radiation seen in almost all patients (93/97; 95%). A small T2

Figure 2 MRI changes with age



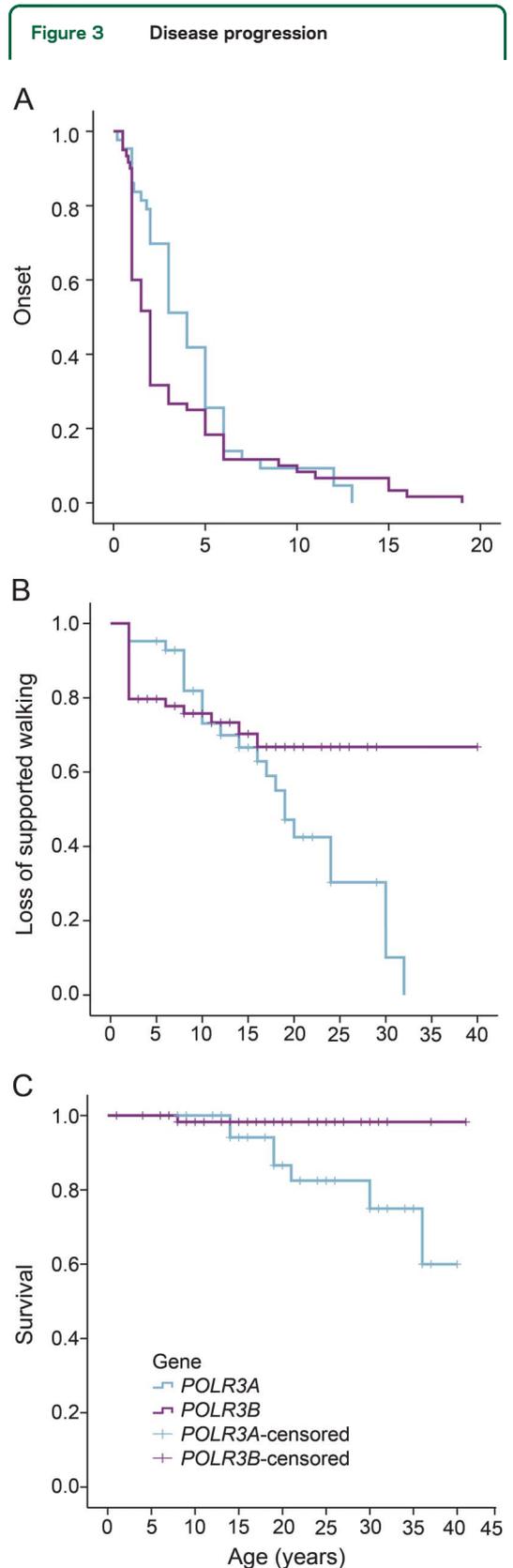
MRI of 4 patients with 4H syndrome at 6 (A-D, patient 4H-52, row 1), 12 (E-H, patient 4H-53, row 2), 23 (I-L, patient 4H-58, row 3), and 40 (M-P, patient 4H-94, row 4) years of age. The axial T2-weighted images all show diffusely elevated white matter signal, less hyperintense than CSF, consistent with hypomyelination. The signal of the optic radiations is hypointense, indicating myelination. In the youngest patient, there is a small hypointense dot in the posterior limb of the internal capsule (B). All patients show a relatively hypointense signal of the ventrolateral thalamus. The corpus callosum becomes thinner with age (sagittal T1 images, A, L, P, and sagittal T2 image, H). The sagittal images also demonstrate cerebellar atrophy. White matter signal of the middle cerebellar peduncles and the cerebellar white matter is too high on the T2-weighted images; the dentate nucleus appears hypointense as well as the dorsal tegmentum (C, G, K, O). (Q-T) MRI of patient 4H-45 homozygous for c.1586T>A (*POLR3B*) at age 16 years. Myelination of the perirolandic cortex and the parieto-occipital white matter is relatively good on these axial T2-weighted images, compared to the frontal white matter (Q, R, S). The splenium and the anterior limb of the internal capsule (R) as well as the optic radiations (S) are well-myelinated. There is a small lesion in the right optic radiation (R). No cerebellar atrophy is seen on the sagittal T1-weighted image (T).

hypointense dot in the posterior limb of the internal capsule was seen in 42/60 (70%) patients with *POLR3B*, but only 5/37 (13%) patients with *POLR3A* mutations. Relative T2 hypointensities (relative myelin preservation) of the ventrolateral thalamus (88/97; 91%) and the dentate nucleus (90/97; 93%) were also characteristic (figure 2). Supratentorial atrophy was invariably present in the adult patients but rarely seen before age 10 years. A thin corpus callosum was present in all patients examined beyond 17 years, reflecting generalized atrophy and white matter loss. In children younger than 10 years, thinning of the corpus callosum was more frequent with *POLR3A* (10/12) than *POLR3B* (14/26) mutations. In 8 patients, a small cyst was seen in the splenium. Cerebellar atrophy was present in all *POLR3B* patients except for one 3-year-old girl; it was absent in 8 patients with mutations in *POLR3A* (2–12 years at MRI) (figure e-2).

Relation between genotype and phenotype. Patients with *POLR3A* had, in general, more severe disease than patients with *POLR3B* mutations, despite the fact that disease onset was slightly earlier in the latter group (4.3 years vs 3.4 years). This is reflected in both age at loss of supported walking and survival (figure 3).

In French Canadian patients with homozygosity for c.2015G>A in *POLR3A*, age at onset was usually in infancy or early childhood, except for one patient with a milder disease course and onset at 5 years. There were several patients with a similar combination of *POLR3B* mutations: c.1568T>A with c.2084-6A>G and c.1568T>A with c.2570+1G>A. One patient compound heterozygous for c.2084-6A>G and c.1568T>A presented late (at 15 years with delayed puberty), while the presentation of the other patients with this combination was early. The 2 siblings homozygous for c.1568T>A had an exceptionally mild clinical course, the older of the 2 having no neurologic signs at age 21 years. On brain MRI, myelination was much better in the latter 2 patients, especially in the parieto-occipital white matter, than in the other patients (figure 2, Q–S). Only 1 out of 12 sibpairs showed significant intrafamilial variability, with a very mildly affected and a severely affected sibling.

Pathology. Gross examination of the brain of a 14-year-old girl (4H-92; homozygous for c.1797G>C/p.Gln599His in *POLR3A*) showed diffuse white matter atrophy with thin corpus callosum and enlarged lateral ventricles. The white matter was non-homogeneously discolored, also involving U-fibers, commissures, and capsules. Histologic analysis revealed variable white matter rarefaction, lack of myelin, and reduced numbers of oligodendrocytes with



Cumulative probability of age at onset, age at wheelchair dependence, and age at death in our patients' cohort. (A) Age at onset of the patients according to the mutated gene. Patients with *POLR3B* mutations have an earlier disease onset than patients with *POLR3A* mutations. Cumulative probability of (B) age at wheelchair dependence and (C) death in our patients' cohort.

better preservation of the perivascular myelin in the centrum semiovale (figure e-3). The degree of axonal loss was proportional to the myelin involvement. Foamy macrophages were seen clustering around small blood vessels. Microglial activation was mild. Neurons showed neither mineralization in the cortex (as seen in another patient¹²) nor iron accumulation in the globus pallidus. The cerebellar folia were mildly atrophic with some loss of granular neurons and, in places, of Purkinje cells. There was nonhomogeneous lack of myelin in the deeper cerebellar white matter, with relative sparing of the hilus of the dentate nucleus.

Analysis of the sural nerve of the same patient showed mild lack of myelin. The ovaries appeared normal apart from a slightly reduced number of oocytes. Immunohistochemical analysis of the pituitary gland for follicle-stimulating hormone, luteinizing hormone, growth hormone, and prolactin showed no abnormalities.

DISCUSSION From our dataset concerning a cohort of 105 mutation-proven cases, it is evident that 4H is an insidiously progressive disorder with declining motor function due to increasing ataxia, sometimes with episodes of faster deterioration triggered by minor infections. Albeit not formally evaluated, cognition remains relatively spared until late. 4H leukodystrophy comes with a spectrum of disease severity. At the severe end, affected children do not achieve independent walking and have mild to moderate intellectual disability. At the milder end of the spectrum, patients present after age 5 years with learning difficulties and motor clumsiness. Exceptionally, patients become symptomatic only in late adolescence or early adulthood. It is likely that this late-onset group represents an underestimation, since clinical presentation of this age group is mild, with one family even diagnosed by chance.

In general, patients with *POLR3A* mutations are more severely affected than patients with *POLR3B* mutations with faster regression and shorter life expectancy. Strikingly, the disease starts slightly later in *POLR3A*-mutated patients and, in contrast to *POLR3B*-mutated patients, most *POLR3A*-mutated patients achieve independent walking. Homozygosity for the common c.1568T>A *POLR3B* mutation, which we found much less often than expected given the estimated carrier frequency,⁸ causes a mild clinical presentation. Considerable intrafamilial variability is rare, seen in only 1 of the 12 sibling pairs. All these findings suggest that there is a genotype–phenotype correlation, but due to the numerous private mutations we could not confirm such a relationship.

The characteristic dental abnormalities—natal teeth, delayed dentition, abnormal order of teeth

eruption, hypodontia—are present in two-thirds of the patients and as such are not obligatory for the diagnosis. The same is true for hypogonadotropic hypogonadism, which is absent in a quarter of the patients. When all features are present, the likelihood for finding mutations in either *POLR3A* or *POLR3B* is high, although the small number of mutation-negative cases opens the possibility of additional responsible genes. As our study initially only included patients with all features present, the proportion of patients with neither abnormal puberty nor dental abnormalities might be higher. Our study has made clear that the disturbance of pubertal development itself is also variable. Several female patients had normal breast development but primary amenorrhea. One patient did not respond to pulsatile GnRH, suggesting that delayed puberty might be secondary to a defect in the GnRH receptor or in gonadotropin bioactivity.¹³ Endocrine abnormalities not only include hypogonadotropic hypogonadism, but in a small number of patients also growth hormone deficiency. The latter might be more common as the majority of patients, even in the large group with short stature, were never evaluated for growth hormone deficiency. Almost all patients have myopia, usually progressive and severe.

An important question is how to reach a diagnosis in the absence of dental and endocrine abnormalities. Brain MRI pattern recognition proves an excellent means to facilitate this. Hypomyelination in combination with cerebellar atrophy, relative T2 hypointensity of the ventrolateral thalamus, and myelination of the pyramidal tracts within the posterior limb of the internal capsule, dentate nuclei, and the optic radiation are present in most patients and suggest the diagnosis.^{10,14} The corpus callosum is usually normal in young children, but invariably thin in adults, reflecting slowly progressive cerebral white matter volume loss. Interestingly, although it was considered as one of the essential radiologic findings,¹⁰ cerebellar atrophy is absent or mild in a substantial number of patients with *POLR3A* mutations, confirming the results from a previous small study on 6 patients.¹⁵

We are still far from understanding the pathogenesis of 4H leukodystrophy. The combination of hypomyelination with the peculiar dental anomalies remains enigmatic. As a few patients show signs of osteosclerosis,¹¹ we hypothesize that a defect of osteoclasts is at the basis of the dentition abnormalities by preventing normal tooth eruption, which necessitates local bone resorption. Regarding the white matter abnormalities, it emerges that defects of proteins essential for RNA synthesis—RNA polymerase III in 4H leukodystrophy, cytoplasmic aspartyl tRNA synthetase in hypomyelination with brainstem involvement and leg spasticity¹⁶—cause hypomyelination, but the

underlying mechanism is unresolved. Which cell type is primarily affected in 4H leukodystrophy, the oligodendrocytes providing the myelin sheath or the neurons whose axonal integrity is essential to induce myelination, remains unclear. Histopathology results with widespread axonal damage and, in the cerebellum, Purkinje cell loss and axonal and dendritic swellings, point to an important neuroaxonal involvement. However, all end-stage brain disorders, including white matter disorders, involve neurons without necessarily providing clues for the initial problem. This is true even for the prototypic oligodendrocyte disorder Pelizaeus-Merzbacher disease, in which the gene coding for proteolipid protein 1 is mutated, and where neuroaxonal degeneration is a feature of late disease.¹⁷ The fact that, in 4H leukodystrophy, clinical presentation is comparatively mild in many patients during the first years of life and the subsequent disease progression slow opens the possibility of intervention once its pathogenesis has been elucidated.

AUTHOR CONTRIBUTIONS

Nicole I. Wolf: designed and supervised the study, collected data, wrote the first draft of the article. Adeline Vanderver: collected patient and MRI data, reviewed the article. Rosalina M.L. van Spaendonk: responsible for molecular genetic analysis of a large part of the patients, reviewed the article. Raphael Schiffmann: collected patient and MRI data, reviewed the article. Bernard Brais: collected patient and MRI data, reviewed the article. Marianna Bugiani: performed additional histopathologic stainings, wrote part of the article. Erik Sistermans: collected mutation data, reviewed the article. Coriene Catsman-Berrevoets: collected patient and MRI data, reviewed the article. Johan M Kros: performed the autopsy on one patient, reviewed the article. Pedro Soares Pinto: collected patient and MRI data, reviewed the article. Daniela Pohl: collected patient and MRI data, reviewed the article. Sandya Tirupathi: collected patient and MRI data, reviewed the article. Petter Strømme: collected patient and MRI data, reviewed the article. Ton de Grauw: collected patient and MRI data, reviewed the article. Sébastien Fribourg: analyzed molecular data. Michelle Demos: collected patient and MRI data, reviewed the article. Amy Pizzino: collected patient and MRI data, reviewed the article. Sakubai Naidu: collected patient and MRI data, reviewed the article. Kether Guerrero: responsible for molecular genetic analysis of a large part of the patients, reviewed the article. Marjo S van der Knaap: collected patient and MRI data, reviewed the article. Geneviève Bernard: designed and supervised the study, collected data, reviewed the article.

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DISCLOSURE

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Clinical spectrum of 4H leukodystrophy caused by *POLR3A* and *POLR3B* mutations

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