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Distinguishing severe phenotypes associated with pathogenic variants in *POLR3A*

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Abstract

A recent report by Majethia and Girisha described a patient with biallelic pathogenic variants in *POLR3A* and Wiedemann-Rautenstrauch syndrome. In this correspondence, we compare the features of this patient to that of a cohort of patients with severe POLR3-related leukodystrophy and a similar genotype and clinical course. We comment on the phenotyping and classification of POLR3-related disorders.

To the editor:

We read with great interest the recent publication by Majethia and Girisha, titled "Wiedemann-Rautenstrauch syndrome in an Indian patient with biallelic pathogenic variants in *POLR3A*" (Majethia & Girisha, 2021). This case report provided a detailed description of a patient with variants in *POLR3A* (OMIM: 614258; NM_007055.4: c.1771-7C>G and c.2005C>T; p.Arg669*). We appreciate the thorough report of this patient and commend the authors for this work. After reviewing the phenotypic description of the patient, we would like to comment on the classification of POLR3-related disorders by comparing the clinical

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Author Contributions

All authors participated in the design, analysis, and interpretation of the work, as well as drafting the manuscript. All authors critically revised and reviewed the final version of the manuscript.

features of the reported patient to those of patients with a severe form of POLR3-related hypomyelinating leukodystrophy (POLR3-HLD).

In a recent study, we reported a cohort of six patients with a more severe phenotype compared to that typically seen in POLR3-HLD (OMIM: 607694) and a specific genotype (Perrier et al., 2020). This genotype includes the *POLR3A* splicing variant c.1771-7C>G on one allele, and on the other, a *POLR3A* variant leading to a truncated protein (i.e. nonsense variant or frameshift deletion) (Perrier et al., 2020). Likewise, the patient published by Majethia and Girisha also harbours this combination of variants (i.e. c.1771-7C>G and c.2005C>T; p.Arg669*). It was this similarity, along with the similarities in clinical course that led us to further consider the features of this patient compared to those with the severe form of POLR3-HLD.

In table 1, we present a comparison between the clinical features of the patient reported by Majethia and Girisha, our cohort of patients with a severe POLR3-HLD phenotype, and five published studies of other cohorts of patients with Wiedemann-Rautenstrauch syndrome (WRS; OMIM: 264090) caused by biallelic pathogenic variants in *POLR3A* (Jay et al., 2016; Lessel et al., 2018; Paolacci et al., 2018; Temel et al., 2020; Wambach et al., 2018). Notably, the patient reported by Majethia and Girisha was born at term with a normal weight, similar to the patients with severe POLR3-HLD, whereas in patients with WRS, intrauterine growth retardation and low birth weight are common. The clinical course of the patient was similar to those with severe POLR3-HLD, involving failure to thrive and recurrent respiratory issues. The patient also had laryngomalacia, which was reported in three out of six patients with severe POLR3-HLD. Most importantly, the patient reported by Majethia and Girisha appeared to have prominent neurological manifestations, with developmental regression, movement disorders, and upper motor neuron signs on examination. There was loss of motor skills, and walking was never achieved. Neurological features, when present, are not typically prominent in patients with WRS. Dystonia was reported in the patient described by Majethia and Girisha, a feature seen in all patients with severe POLR3-HLD, but not usually in WRS. The patient succumbed to an early death at 1.5 years of age. In patients with POLR3-related disorders, the age of premature death can range from shortly after birth to childhood or adulthood, depending the severity of the disease. Several patients with severe POLR3-HLD passed at an early age (4/6 before age 3) (Perrier et al., 2020). In the studied cohorts of patients with WRS, there was variance as to whether patients succumbed to an early death. The first patient described in the literature with WRS and biallelic pathogenic variants in *POLR3A* passed during infancy, at age 7 months (Jay et al., 2016). In three other publications of patients with WRS and published data on current age (Lessel et al., 2018; Temel et al., 2020; Wambach et al., 2018), all were living at the time of publication (11 patients; age range 11 months to 21 years). In the cohort study by Paolacci et al. (2018), the age of death was not listed for all patients, however some were previously published and noted to be deceased, including two females who passed in early to late adolescence (Paolacci et al., 2017; Rautenstrauch & Snigula, 1977), and several patients who passed at various ages ranging from days to months after birth [specifically, four patients within the first two weeks of life (G. Arboleda, Morales, Quintero, & Arboleda, 2011; H. Arboleda, Quintero, & Yunis, 1997; Morales et al., 2009),

one patient after 1.5 months (G. Arboleda et al., 2011), and one patient after 6 months (H. Arboleda et al., 1997)].

WRS typically presents in the neonatal period. Individuals are known to have characteristic facial features, including a triangular face with a prominent forehead, visible scalp veins, and sparse scalp hair (Paolacci et al., 2017). The patient reported by Majethia and Girisha did not have these facial characteristics early on, but a triangular face was only noticed around the age of 15 months, when the child had lost a significant amount of weight and has become cachectic. Contractures are also common in individuals with WRS, however the reported patient was not known for joint abnormalities. Another typical feature of WRS is lipodystrophy with localized fat deposits usually over the iliac region. The reported patient had decreased subcutaneous fat, without deposits noted in the description. Our patients with severe POLR3-HLD did not have notable facial dysmorphia or a progeroid appearance, and POLR3-HLD is not typically associated with joint abnormalities or unusual fat distribution.

Dental abnormalities appear to be common and diverse across each described phenotype. The presence of dental abnormalities between patients with different *POLR3A* genotypes and broad phenotypes is an interesting concept that exemplifies the importance of proper POLR3A protein abundance/function in the development of specific tissues.

POLR3-HLD can be associated with atypical MRI findings, without frank hypomyelination (Azmanov et al., 2016; Harting et al., 2020; Hiraide et al., 2020; La Piana et al., 2016; Perrier et al., 2020; Wu et al., 2019). The brain MRI pattern of published patients with the c.1771-7C>G variant (whether homozygous or in trans with another variant) is specific, and distinct from the typical POLR3-HLD imaging pattern (Harting et al., 2020; Perrier et al., 2020). In the cohort of patients with a severe POLR3-HLD phenotype (and a similar genotype to the patient reported by Majethia and Girisha), all had insufficient myelin deposition not meeting the criteria for true hypomyelination, as well as additional findings including progressive abnormalities of the basal ganglia and thalami (sometimes only seen on repeat imaging) (Perrier et al., 2020).

A recent cohort study by Harting et al. also reported the combination of the c.1771-7C>G variant with an additional splicing, missense, or synonymous variant (Harting et al., 2020). Phenotypes of patients in this cohort ranged from severe (with similar features to those in our severe POLR3-HLD cohort) to a milder presentation. However, all patients had a specific MRI pattern involving striatal abnormalities, without frank hypomyelination (Harting et al., 2020). In other cohorts of patients with the adjacent c.1771-6C>G variant, whether homozygous or compound heterozygous with another variant in trans, striatal involvement was also evident on MRI (Azmanov et al., 2016; Hiraide et al., 2020; Wu et al., 2019). Thus, it would be interesting to review the MRI of the patient reported by Majethia and Girisha specifically for abnormalities of the basal ganglia and thalami, as well as for subtle evidence of insufficient myelin deposition. Moreover, it should be noted that although this MRI pattern appears to correlate to the genotype, it is possible that these abnormalities could have only been detected later, on repeat imaging, and were not evident on a single MRI obtained at 8 months.

As we mention above, genotypically, the patient described by Majethia and Girisha harboured similar *POLR3A* variants to those associated with the severe POLR3-HLD phenotype (c.1771-7C>G in addition to a nonsense variant). In this case, the nonsense variant (c.2005C>T; p.Arg669*) has also been reported in one patient with WRS (in combination with the splicing variant c.3337-11T>C) (Wambach et al., 2018). This patient was 20 years old at the time of publication and had typical facial features associated with WRS, as well as contractures and frank generalized lipodystrophy. She had recurrent pneumonias and dysphagia. She also had cerebellar signs and intention tremors, and lost the ability to walk at 9 years of age.

These similarities are interesting and support the question of whether it is a dose-dependent amount of functional POLR3A that causes specific phenotypes, or the presence of specific variants. Indeed, the phenotypic variability associated with pathogenic variants in *POLR3A* is complex, and before distinct correlations can be formed, studies on additional patients with a similar genotype would be necessary, together with functional studies.

In conclusion, we thank Majethia and Girisha for their report of this patient and contribution to the literature on patients with biallelic pathogenic variants in *POLR3A*. While we highlight the similarities to patients with severe POLR3-HLD, as well as the differences in phenotype between this patient and those with WRS, we acknowledge that intermediate phenotypes of POLR3-related disorders may exist. Phenotypic diversity is broad in disorders associated with pathogenic variants in RNA polymerase III subunits, ranging from extremely mild to very severe. As researchers and clinicians move forward to characterize these disorders, detailed phenotyping and systematic classification of disorders are of importance for genotype-phenotype correlations to be established, knowledge of disease progression in a clinical setting, and potential therapeutic interventions.

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Conflict of Interest Statement

Geneviève Bernard has no relevant conflict of interests. She is/was a consultant for Passage Bio Inc and Ionis. She serves on the scientific advisory board of the Pelizaeus-Merzbacher Foundation and is the Chair of the Medical Advisory Board of the United Leukodystrophy Foundation. She has received an unrestricted educational grant from Takeda (2021). In the last 2 years, Dr Bernard received research grants from the Canadian Institutes for Health Research (project grant 426534 and 201610PJT-377869), Montreal Children's Foundation, Fondation Les Amis d'Elliot, Pelizaeus-Merzbacher Disease Foundation, Foundation of Stars, Healthy Brains Healthy Lives, Fondation

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Data Availability Statement

Data sharing is not applicable to this correspondence as discussion is based on previously published articles.

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Table 1.

Comparison of phenotypic and genotypic features of the patient reported by Majethia and Girisha (2021), the cohort of patients with severe POLR3-HLD (Perrier et al. 2020), and five published studies of patients with WRS (Jay et al. 2016, Wambach et al. 2018, Lessel et al. 2018, Paolacci et al. 2018, Temel et al. 2020).

	Majethia et al. 2021 Am J Med Genet A	**Perrier et al. 2020 Neurol Genet**	**Jay et al. 2016 Am J Med Genet A**	**Wambach et al. 2018 Am J Hum Genet**	**Lessel et al. 2018 Hum Genet**	**Paolacci et al. 2018 J Med Genet**	**Temel et al. 2020 Eur J Hum Genet**
Phenotype	**? Severe POLR3-related leukodystrophy**	**Severe POLR3-related leukodystrophy**	**Wiedemann-Rautenstrauch syndrome**	**Wiedemann-Rautenstrauch syndrome**	**Wiedemann-Rautenstrauch syndrome**	**Wiedemann-Rautenstrauch syndrome**	**Wiedemann-Rautenstrauch syndrome**
Pre-natal Growth	Normal pregnancy	Unremarkable	Intrauterine growth restriction (1/1)	Intrauterine growth restriction (6/7)	Intrauterine growth restriction (3/3)	Length at birth <P3 (3/12)	Length 8 days after birth <P3 (1/1)
Birth weight	Normal weight	Normal weight (6/6)	Low birth weight (1/1)	Low birth weight (6/7)	Low birth weight (3/3)	Low birth weight (11/14)	Low birth weight (1/1)
Age of death	Death at 1.5 years	Death before age 3 years (4/6)	Death at 7 months (1/1)	Currently living at time of publication (ages 2–21 years) (7/7)	Currently living at time of publication (ages 11 months–12 years) (3/3)	Death within first 6 months (6/15) Death in early-late adolescence (2/15) Age of death not reported (7/15)	Currently living at time of publication (age 6 years) (1/1)
Physical Appearance	Triangular face at 15 months	No notable dysmorphia	i) Triangular face ii) Alopecia iii) Prominent forehead veins iv) Low set malformed ears (1/1)	i) Triangular face (5/7) ii) Sparse scalp hair (5/7) iii) Prominent forehead veins (6/6) iv) Low set ears (5/7)	i) Triangular face (3/3) ii) Sparse scalp hair (2/3) iii) Prominent scalp veins (3/3) iv) Thin/translucent skin (3/3)	i) Triangular face (13/14) ii) Sparse scalp hair (13/13) iii) Prominent scalp veins (13/13) iv) Thin/translucent skin (14/14)	i) Triangular face ii) Alopecia iii) Prominent scalp veins iv) Low set ears (1/1)
Fat distribution	Decreased subcutaneous fat Fat accumulation not reported	Unremarkable	Decreased subcutaneous fat (1/1)	Lipodystrophy (6/7) Localized fat accumulation (5/7)	Lipodystrophy (3/3) Fat accumulation not reported	Lipodystrophy (14/14) Localized fat accumulation (6/11)	Local lipoatrophy (1/1)
Dental Abnormalities	Anodontia	Delayed dentition (3/6)	Natal teeth (1/1)	Delayed dentition/ Hypodontia (4/7) Natal teeth (5/6)	Delayed dentition/ Oligodontia (2/2) Natal teeth (1/3)	Delayed dentition/ Hypodontia (8/8) Natal teeth (13/14)	Delayed dentition, natal teeth (1/1)
Neurological and Movement Abnormalities	Increased muscle tone in lower limbs, ankle clonus, bilateral cortical thumbs, dystonia, walking not achieved	Axial hypotonia and upper motor neuron signs (spasticity and/or hyperreflexia) (5/6), dystonia/ chorea, walking not achieved (6/6)	Abnormalities not reported (1/1)	Ability to walk/ walk with assistance (6/7) Tremor, cerebellar signs, inability to walk (1/7)	Ability to walk (2/2)	Tremor (2/8) Hypertonia (8/13) Ataxia or hypotonia (3/12)	Developmental delay (1/1)
MRI features	None reported	Basal ganglia and thalami abnormalities, insufficient	MRI not performed (1/1)	MRI normal (1/7) MRI not available (6/7)	Agenesis of corpus callosum (1/1) MRI	No hypomyelination (4/4) MRI not	None reported (1/1)

	Majethia et al. 2021 Am J Med Genet A	**Perrier et al. 2020 Neurol Genet**	**Jay et al. 2016 Am J Med Genet A**	**Wambach et al. 2018 Am J Hum Genet**	**Lessel et al. 2018 Hum Genet**	**Paolacci et al. 2018 J Med Genet**	**Temel et al. 2020 Eur J Hum Genet**
		myelin deposition (6/6)			not available/ reported (2/3)	available/ reported (11/15)	
Genotype (Variants in *POLR3A* NM_007055.3)	**Present report:** Allele 1: c.1771−7C>G Allele 2: c.2005C>T (p.Arg669*)	**6/6 Patients:** Allele 1: c.1771−7C>G Allele 2: Nonsense variant or frameshift deletion	**1/1 Patient:** Allele 1: c.1909+18G>A Allele 2: c.2617C>T (p.Arg873*)	**6/7 Patients:** Allele 1: c.3337−5T>A or c.3337−11T>C Allele 2: Additional splicing or nonsense variant **1/7 Patients:** Allele 1: c.3G>T (p.Met1?) Allele 2: c.*18 C>T	**2/3 Patients:** Alelle 1: c.3337−5T>A Allele 2: Additional splicing or nonsense variant **1/3 Patients:** Allele 1: c.3G>T (p.Met1?) Allele 2: Unidentified	**5/15 Patients:** Allele 1: c.1909+18G>A or c.1909+22G>A & c.3337−11T>C Allele 2: Additional splicing or missense or synonymous variant **2/15 Patients:** Allele 1: c.*18C>T Allele 2: c.3G>T (p.Met1?) or c.4003G>A (p.Gly1335Arg) **8/15 Patients:** Allele 1: Missense or Frameshift deletion Allele 2: Unidentified (ex12–15 del identified in one patient)	**1/1 Patient:** Allele 1: c.3337−11T>C Allele 2: c.3568C>T, (p.Gln1190*)