DOI: 10.4274/jcrpe.galenos.2023.2023-1-15

Case report

The First Case of 4H Syndrome with Type 1 Diabetes Mellitus

Running Head: 4H Syndrome with Type 1 Diabetes Mellitus

Gonul Buyukyilmaz[1], Busra Erozan Cavdarlı[2], Keziban Toksoy Adiguzel[1], Mehmet Adiguzel[3], Cigdem Seher Kasapkara[4], Fatih Gurbuz[1], Mehmet Boyraz[1], Esra Gurkas[5]
[1]Department of Pediatric Endocrinology, Ankara City Hospital, Ankara, Turkey
[2]Department of Medical Genetics, Ankara City Hospital, Ankara, Turkey
[3]Department of Radiology, Ankara University School of Medicine, Ankara, Turkey
[4]Department of Pediatric Metabolism and Nutrition, Ankara Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey
[5]Department of Pediatric Neurology, Ankara Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey

What is already known on this topic?
4H syndrome is a rare autosomal recessive disorder characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism. Biallelic pathogenic variants in *POLR3A, POLR3B, POLR1C*, and *POLR3K* gene cause 4H syndrome. There is no obvious genotype/phenotype correlation. In addition to the 3 classic features, patients may present with other system involvements.

What this study adds?
We report two siblings with bi-allelic pathogenic variants of the *POLR3A* gene. This is the first case of 4H syndrome accompanied by type 1 DM in the literature. It is not exactly known whether this is coincidental or the expansion of the phenotype.

ABSTRACT
4H syndrome is a rare progressive hypomyelinating leukodystrophy. Hypomyelination, hypodontia, and hypogonadotropic hypogonadism are the 3 classic features of 4H syndrome. Biallelic pathogenic variants in *POLR3A, POLR3B, POLR1C*, and *POLR3K* gene cause 4H leukodystrophy. Herein, we present clinical features in two siblings with 4H syndrome. The first patient (16 years) presented hypogonadotropic hypogonadism, euthyroid Hashimoto's thyroiditis and type 1 diabetes mellitus. The second patient (13.5 years) showed normal physical, biochemical and hormonal examination at presentation. It was learned that he was followed up for epilepsy between the ages of 6 months and 6 years, his epilepsy medication was discontinued at the age of 6, and he did not have seizure again. T2-weighted magnetic resonance images showed increased signal intensity secondary to hypomyelination in both patients. They were subsequently found to have homozygous mutation in the *POLR3A* gene. 4H syndrome may present with neurological and non-neurological findings in addition to classic features of 4H syndrome. Progressive neurological deterioration may occur and endocrine dysfunction may be progressive. Although multiple endocrine abnormalities associated with this disorder have been reported to date, case accompanied by type 1 DM has not been seen in the literature. We do not know exactly whether this is coincidental or the expansion of the phenotype. So that reporting such cases helps to determine the appropriate genotype–phenotype correlations in patients.
Keywords: 4H leukodystrophy; *POLR3A*, hypogonadotropic hypogonadism, type 1 diabetes mellitus.

Gönül Büyükyılmaz, MD, Ankara City Hospital Department of Pediatric Endocrinology
06000; Ankara, Turkey
gonulgulal@hotmail.com
+905064596008
0000-0001-7888-7295
26.01.2023
28.02.2023

Published: 27.03.2023

INTRODUCTION
Leukodystrophies constitute a heterogeneous, rare inherited group of diseases that mainly affect the white matter of the central nervous system (1). The clinical signs of the disease are generally nonspecific and may occur at different ages, from the neonatal period to late adulthood (2). Patients may present with non-neurological findings as well as the neurological findings. Non-neurological symptoms can be used to categorize leukodystrophies more accurately (3). Ophthalmological, dental, musculoskeletal, gastrointestinal, and skin problems have also been reported in addition to the endocrine problems, such as adrenal insufficiency, hypogonadism, hypothyroidism, growth hormone (GH) deficiency, and ovarian insufficiency (2). 4H syndrome inherited in an autosomal recessive manner is a rare progressive hypomyelinating leukodystrophy. It was first described in 2006 by Timmons et al. and is characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism (4). Its clinical course is highly variable. In addition to cases with severe neurological signs, some cases presenting only with idiopathic hypogonadotropic hypogonadism in late adolescence have also been reported (5, 6). While the most common endocrine abnormalities in 4H syndrome have been reported as hypogonadotropic hypogonadism, herein, we present two siblings, one of them with 4H syndrome accompanied by diabetes mellitus (DM), that has not been defined previously in literature and the other 4H syndrome with a milder phenotype.

CASE PRESENTATION
Case 1
A 16-year-old Turkish female (II-1) was referred to our hospital with the complaint of secondary amenorrhea. After menstrual bleeding twice with an interval of 1 month at the age of 13.5 years, she didn't have menstrual bleeding again. Patient was born as a term baby, with a birth weight of 4750 g, from a first-degree consanguineous marriage. Her neuromotor development was consistent with her peers. She started to walk at the age of 10 months, walked without support by 12 months of age, started speaking single meaningful words by 12 months of age and spoke in short sentences by 2 years of age. After the age of 12, she could not continue school due to the gradual decrease in her academic success and the increase in forgetfulness.
When she applied to endocrinology department, her body weight was measured as 50.7 kg (-0.88 standard deviation score (SDS)), height was 161.1 cm (-0.22 SDS), and body mass index was 19.5 kg/m² (-0.8 SDS). Other systemic and detailed neurological examinations of the patient with Tanner stage 5 were normal. The laboratory examination results were found to be compatible with impaired fasting glucose, impaired glucose tolerance, euthyroid Hashimoto's thyroiditis, and hypogonadotropic hypogonodism (Table 1).

The patient, whose antibody levels for type 1 DM were found to be positive, was initially planned to be followed-up without insulin by adjusting her diet. On brain magnetic resonance imaging (MRI) ; pathological hyperintensity on T2-weighted images secondary to hypomyelination was seen in periventricular white matter and centrum semiovale (Figure 1). Mild atrophy of the cerebrum, cerebellum, and corpus callosum was also detected. Metabolic investigations involving very long-chain fatty acids, free carnitine, urinary organic acids, urinary and plasma amino acids, lactic and pyruvic acids, arylsulfatase A, b-galactocerebroside and total hexosaminidase were normal. Since our patient did not have findings such as fatty and oily stools, diarrhea, gas, bloating, abdominal pain, unexplained weight loss, no evaluation was made in terms of pancreatic exocrine functions. Her psychometric evaluation with the Wechsler Intelligence Scale showed that her IQ score was 70-79. There were no signs of hypo-oligodontia, or any other dental anomaly. Ophthalmic examination showed no abnormality. It was considered to possibly be 4H syndrome due to the presence of hypogonadotropic hypogonadism and hypomyelination.

In genetic analyses, genomic DNA was extracted from the patient's peripheral blood lymphocytes (QIAGEN Inc., Hilden, Germany) by obtaining an informed consent form from the patient's parents. All 31 exons and exon-intron boundaries of the *POLR3A*(NM_007055.4) gene were analyzed with the Next Generation Sequencing (NGS) system according to manufacturers' instructions (Myseq, Illumina Inc., San Diego, CA, USA). The homozygous c.2005C>G (p.R669G) (p.Arg669Gly) missense variant on exon 15 of the *POLR3A* gene was detected and evaluated as likely pathogenic according to the guidelines. The variant did not found in any healthy population (GnomAD) and in-silico analyzing tools have pathogenic predictions about it. The variant was reported previously and registered as a disease-causing variant in the Human Genome Variation Database (CM1411442). Segregation analyses of the variant were performed with QIAseq® FX DNA Library Kit (Qiagen, Hilden, Germany) in all of the family members and the results are visualized in Figure 2.

In the follow-up after 3 months, her fasting plasma glucose level measured 400 mg/dL, while her insulin was 3 mU/L, c peptide was 0.1 µg/L, and HbA1c was 10%; therefore, intensive insulin therapy was started.

Case 2

The younger brother of the proband was evaluated at age 13.5 years (II-3). Body weight was measured as 57.4 kg (-1.2 SDS), height was measured 167 cm (0.65 SDS). Between the ages of 6 months and 6 years, he was followed with the diagnosis of epilepsy in another hospital. MRI and electroencephalography (EEG) findings of that period could not be reached. Epilepsy treatment was completed at the age of 6 years and he did not have epileptic seizures afterward. We were able to reach the MRI findings of 7 years old, at the oldest date. Increased signal intensity was also detected in the MRI at that time. However, since the diagnosis was unknown, further investigation was recommended in terms of metabolic disease or hypoxic ischemic encephalopathy. It was learned that his school success was good and he had a problem of forgetfulness. IQ score was found 68 by Wechsler Intelligence Scale. He was in Tanner stage 3-4. The patient's biochemical and hormonal examinations were evaluated as normal and were shown in Table 1. EEG monitoring was normal. T2-weighted images showed increased signal intensity secondary to hypomyelination in bilateral periventricular white matter (Figure 1). The same homozygous missense variant as in his sister was confirmed with genetic testing. Consanguineous parents of siblings were also found as heterozygous carriers.

DISCUSSION

RNA polymerase III (POLR3) related leukodystrophy, also known as 4H leukodystrophy are the 2 terms accepted for 5 overlapping clinical phenotypes described previously, which comprise 1) hypomyelination, hypodontia, hypogonadotropic hypogonadism (4H syndrome); 2) ataxia, delayed dentition, and hypomyelination; 3) tremor-ataxia with central hypomyelination, 4) leukodystrophy with oligodontia; and 5) hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (7). It is found that biallelic pathogenic variants in *POLR3A, POLR3B, POLR1C*, and *POLR3K* gene cause 4H leukodystrophy (8-10). Mutations in these genes either disturb the proper assembly of the RNA polymerase III enzyme or impair its ability to bind to DNA (12-14). Disruption of this function is very important for the maintenance and development of myelin, which can affect the development and function of many parts of the body (13). However, the molecular basis of the pathophysiology of the disease is not fully understood. It remains a mystery how mutations in POLR3 lead to disorders with clinical features largely restricted to the central nervous system, and a few other tissues, all of which originate from neural crest cells (14). The mutations are spread throughout the gene and there is no obvious genotype/phenotype correlation.

Classical clinical findings with typical brain MRI features are helpful in addressing the diagnosis of 4H leukodystrophy. While hypomyelination, hypodontia, and hypogonadotropic hypogonadism are the 3 classic features of 4H leukodystrophy; patients may also present with neurological findings, such as ataxia, dysarthria, dysmetria, tremor, eye movement abnormalities and non-neurological features include cataract, progressive myopia, dental abnormalities, endocrine abnormalities (6, 11, 15, 16). Diagnostic MRI findings include cerebellar atrophy, progressive thinning of the corpus callosum, and high-intensity areas in the white matter on the T2-weighted images (17, 18). The disease progress insidiously and may result in death.

In a study examining the endocrine problems of 150 patients with 4H leukodystrophy, delayed puberty and short stature were found to be the most common endocrine problems. Most of the patients who underwent Luteinizing hormone releasing hormone (LHRH) stimulation test had abnormally low levels of LH and FSH. Also, immunohistochemical analysis of the anterior pituitary gland in the same study revealed that there was no immunostaining of anti-FSH and anti-LH antibodies. All of them emphasized that the hypogonadism was hypophyseal. A delay in puberty was detected more frequently in patients with *POLR3A* gene mutation, which was stated to be followed by *POLR3B*. Patients with 4H leukodystrophy have short stature compared to the general population. So that growth and height should be evaluated at least once a year. In 41% of patients, prolactin levels were found to be abnormal (elevated (18%) or deficient (23%) levels). Hypothyroidism was reported in 4% of patients. No problems were detected in the cortisol axis (11).

In the cases (II-1) and (II-3) have mild neurological manifestations. Patients are able to walk independently. They have no cerebellar, pyramidal and extrapyramidal signs. Cognition began to deteriorate slowly after 12 years old, but language comprehension and nonverbal communication are preserved until now. As we know, *POLR3A* mutations trend to a more severe disease course compared to *POLR3B* mutations, but the disease starts slightly later in *POLR3A*-mutated patients in contrast to *POLR3B*-mutated patients (6). From our country, a 38-year-old Turkish male patient with *POLR3A* gene was reported. His first neurological complaints started at the age of 25. Signs of endocrine dysfunction and dental anomaly was not detected (19). Our patients with *POLR3A* mutation has an exceptionally mild clinical course. Dental abnormalities aren't present in our patients. In addition to hypogonadotropic hypogonadism; hypoprolactinemia, type 1 DM and thyroid Hashimoto's thyroiditis were detected in the sister. Other anterior pituitary hormones were found to be normal. It was found that there was no one with type 1 DM in the patient's family, and the autoimmune thyroid antibodies of the parents were negative. To date, more than 100 patients have been reported to have *POLR3A, POLR3B* mutations in the literature. As far as could be seen, this is the first case of 4H syndrome accompanied by type 1 DM in the literature. It is not exactly known whether this is coincidental. In the literature, no relation was found between the *POLR3A* gene and pancreas.

In conclusıon we are still far from understanding the pathogenesis of 4H leukodystrophy. It is great importance for radiologists, endocrinologists and neurologists to recognize the clinical and imaging characteristics of this disorder. The present patient showed not only hypogonadotropic hyogonadism but also some of other endocrine disorders. Reporting such cases will contribute to the genotype-phenotype relationship of the disease.

Acknowledgment

None

Compliance with Ethical Statements

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: There is no funding source.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.
All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contribution

- Gonul Buyukyilmaz, Keziban Toksoy Adiguzel, Mehmet Adiguzel, Busra Erozan Cavdarlı were responsible for data collection and drafted the initial manuscript, substantial contributions to the conception and design of the work.
- Gonul Buyukyilmaz, Fatih Gurbuz, Busra Erozan Cavdarlı, Cigdem Seher Kasapkara, Esra Gurkas were responsible for drafting the work or revising it critically for important intellectual content.
- Gonul Buyukyilmaz, Keziban Toksoy Adıguzel, Fatih Gurbuz, Busra Erozan Cavdarlı, Mehmet Boyraz, Cigdem Seher Kasapkara, Esra Gurkas were responsible for final approval of the version to be published

References

1. van der Knaap MS, Bugiani M. Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms. Acta Neuropathol. 2017;134(3):351-82.
2. Ashrafi MR, Amanat M, Garshasbi M, Kameli R, Nilipour Y, Heidari M, Rezaei Z, Tavasoli AR. An update on clinical, pathological, diagnostic, and therapeutic perspectives of childhood leukodystrophies. Expert Rev Neurother. 2020;20(1):65-84.
3. Steenweg ME, Vanderver A, Blaser S, Bizzi A, de Koning TJ, Mancini GM, van Wieringen WN, Barkhof F, Wolf NI, van der Knaap MS. Magnetic resonance imaging pattern recognition in hypomyelinating disorders. Brain. 2010;133(10):2971-82.
4. Timmons M, Tsokos M, Asab MA, Seminara SB, Zirzow GC, Kaneski CR, Heiss JD, van der Knaap MS, Vanier MT, Schiffmann R, Wong K. Peripheral and central hypomyelination with hypogonadotropic hypogonadism and hypodontia. Neurology. 2006;67(11):2066-9.
5. Verberne EA, Dalen Meurs L, Wolf NI, van Haelst MM. 4H leukodystrophy caused by a homozygous POLR3B mutation: Further delineation of the phenotype. Am J Med Genet A. 2020;182(7):1776-9.
6. Wolf NI, Vanderver A, van Spaendonk RM, Schiffmann R, Brais B, Bugiani M, Sistermans E, Catsman-Berrevoets C, Kros JM, Pinto PS, Pohl D, Tirupathi S, Strømme P, de Grauw T, Fribourg S, Demos M, Pizzino A, Naidu S, Guerrero K, van der Knaap MS, Bernard G. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. Neurology. 2014;83(21):1898-905.
7. Bernard G, Vanderver A. POLR3-Related Leukodystrophy. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle
Copyright © 1993-2022, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
8. Bernard G, Chouery E, Putorti ML, Tétreault M, Takanohashi A, Carosso G, Clément I, Boespflug-Tanguy O, Rodriguez D, Delague V, Abou Ghoch J, Jalkh N, Dorboz I, Fribourg S, Teichmann M, Megarbane A, Schiffmann R, Vanderver A, Brais B. Mutations of POLR3A encoding a catalytic subunit of RNA polymerase Pol III cause a recessive hypomyelinating leukodystrophy. Am J Hum Genet. 2011;89(3):415-23.
9. Dorboz I, Dumay-Odelot H, Boussaid K, Bouyacoub Y, Barreau P, Samaan S, Jmel H, Eymard-Pierre E, Cances C, Bar C, Poulat AL, Rousselle C, Renaldo F, Elmaleh-Bergès M, Teichmann M, Boespflug-Tanguy O. Mutation in POLR3K causes hypomyelinating leukodystrophy and abnormal ribosomal RNA regulation. Neurol Genet. 2018;4(6):e289.
10. Saitsu H, Osaka H, Sasaki M, Takanashi J, Hamada K, Yamashita A, Shibayama H, Shiina M, Kondo Y, Nishiyama K, Tsurusaki Y, Miyake N, Doi H, Ogata K, Inoue K, Matsumoto N. Mutations in POLR3A and POLR3B encoding RNA Polymerase III subunits cause an autosomal-recessive hypomyelinating leukoencephalopathy. Am J Hum Genet. 2011;89(5):644-51.
11. Pelletier F, Perrier S, Cayami FK, Mirchi A, Saikali S, Tran LT, Ulrick N, Guerrero K, Rampakakis E, van Spaendonk RML, Naidu S, Pohl D, Gibson WT, Demos M, Goizet C, Tejera-Martin I, Potic A, Fogel BL, Brais B, Sylvain M, Sébire G, Lourenço CM, Bonkowsky JL, Catsman-Berrevoets C, Pinto PS, Tirupathi S, Strømme P, de Grauw T, Gieruszczak-Bialek D, Krägeloh-Mann I, Mierzewska H, Philippi H, Rankin J, Atik T, Banwell B, Benko WS, Blaschek A, Bley A, Boltshauser E, Bratkovic D, Brozova K, Cimas I, Clough C, Corenblum B, Dinopoulos A, Dolan G, Faletra F, Fernandez R, Fletcher J, Garcia Garcia ME, Gasparini P, Gburek-Augustat J, Gonzalez Moron D, Hamati A, Harting I, Hertzberg C, Hill A, Hobson GM, Innes AM, Kauffman M, Kirwin SM, Kluger G, Kolditz P, Kotzaeridou U, La Piana R, Liston E, McClintock W, McEntagart M, McKenzie F, Melançon S, Misbahuddin A, Suri M, Monton FI, Moutton S, Murphy RPJ, Nickel M, Onay H, Orcesi S, Özkınay F, Patzer S, Pedro H, Pekic S, Pineda Marfa M, Pizzino A, Plecko B, Poll-The BT, Popovic V, Rating D, Rioux MF, Rodriguez Espinosa N, Ronan A, Ostergaard JR, Rossignol E, Sanchez-Carpintero R, Schossig A, Senbil N, Sønderberg Roos LK, Stevens CA, Synofzik M, Sztriha L, Tibussek D, Timmann D, Tonduti D, van de Warrenburg BP, Vázquez-López M, Venkateswaran S, Wasling P, Wassmer E, Webster RI, Wiegand G, Yoon G, Rotteveel J, Schiffmann R, van der Knaap MS, Vanderver A, Martos-Moreno G, Polychronakos C, Wolf NI, Bernard G. Endocrine and Growth Abnormalities in 4H Leukodystrophy Caused by Variants in POLR3A, POLR3B, and POLR1C. J Clin Endocrinol Metab. 2021;106(2):e660-e74.
12. Dieci G, Fiorino G, Castelnuovo M, Teichmann M, Pagano A. The expanding RNA polymerase III transcriptome. Trends Genet. 2007;23(12):614-22.
13. Azmanov DN, Siira SJ, Chamova T, Kaprelyan A, Guergueltcheva V, Shearwood AJ, Liu G, Morar B, Rackham O, Bynevelt M, Grudkova M, Kamenov Z, Svechtarov V, Tournev I, Kalaydjieva L, Filipovska A. Transcriptome-wide effects of a POLR3A gene mutation in patients with an unusual phenotype of striatal involvement. Hum Mol Genet. 2016;25(19):4302-14.
14. Lata E, Choquet K, Sagliocco F, Brais B, Bernard G, Teichmann M. RNA Polymerase III Subunit Mutations in Genetic Diseases. Front Mol Biosci. 2021;8:696438.
15. Sato I, Onuma A, Goto N, Sakai F, Fujiwara I, Uematsu M, Osaka H, Okahashi S, Nonaka I, Tanaka S, Haginoya K. A case with central and peripheral hypomyelination with hypogonadotropic hypogonadism and hypodontia (4H syndrome) plus cataract. J Neurol Sci. 2011;300(1-2):179-81.
16. Wolff A, Koch MJ, Benzinger S, van Waes H, Wolf NI, Boltshauser E, Luder HU. Rare dental peculiarities associated with the hypomyelinating leukoencephalopathy 4H syndrome/ADDH. Pediatr Dent. 2010;32(5):386-92.
17. La Piana R, Tonduti D, Gordish Dressman H, Schmidt JL, Murnick J, Brais B, Bernard G, Vanderver A. Brain magnetic resonance imaging (MRI) pattern recognition in Pol III-related leukodystrophies. J Child Neurol. 2014;29(2):214-20.
18. Wang C, Wang S, Xie H, Yang S. Clinical and imaging characteristics of 4H syndrome: A case report. CNS Neurosci Ther. 2022;28(3):458-60.
19. Uygun Ö, Gündüz T, Eraksoy M, Kürtüncü M. Adult-onset 4H leukodystrophy: a case presentation and review of the literature. Acta Neurol Belg. 2020;120(6):1461-2.

Table 1: The laboratory findings of siblings

	Case 1	Case 2	Reference ranges
Fasting plasma glucose (mg/dL)	104	73	<100
2. hour glucose during an OGTT (mg/dL)	142	NA	<140
Fasting insulin (mU/L)	14.4	6.7	3-25
2. hour insulin (mU/L)	36.6	NA	22-79
C peptide (µg/L)	1.1	1.1	0.8–3.8
HbA1c (%)	5.6	5.4	<5.7
Anti-GAD (IU/mL)	61.2	5.7	<17
ICA (U/mL)	54.9	3.8	<28
FSH (U/L)	4.6	6.1	
LH (U/L)	0.5	2.8	
Estradiol (ng/L)	<11.8		11.8-36.6
Testosterone (ug/L)		1.51	0.23-7.42
LHRH peak LH (U/L)	3.6	NA	
TSH (mU/L)	1.6	3.3	0.5–4.9
fT4 (ng/dL)	1.09	1.01	0.83-1.43
Anti TG (IU/mL)	31.1	<1.3	<4.5
Anti TPO (U/mL)	32	<28	<60
ACTH (pg/mL)	14	16	<46
Cortisol (µg/dL)	10	11	5.2-22
Prolactin (µg/L)	2.3	4.8	4.[illegible]

OGTT: Oral glucose tolerance test; Anti-GAD: Glutamic acid decarboxylase antibody; ICA: Islet cell antibody; TSH: Thyroid stimulating hormone; HbA1c: Hemoglobin A1c; Anti TG: Anti thyroglobulin; Anti TPO: Anti-thyroid peroxidase, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, LHRH: Luteinizing-hormone releasing hormone; ACTH: Adrenocorticotropic hormone, NA: Not available

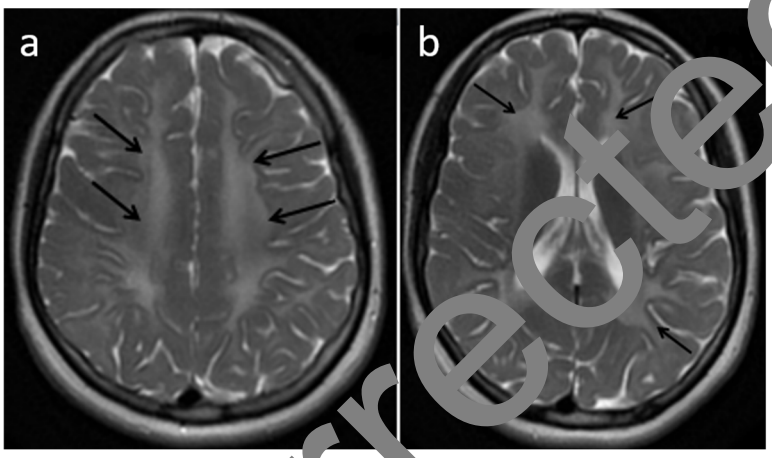

Figure 1. On axial T2-weighted MR images, hyperintense areas (black arrows) secondary to hypomyelination are seen in bilateral centrum semiovale (a) and periventricular white matter (b).

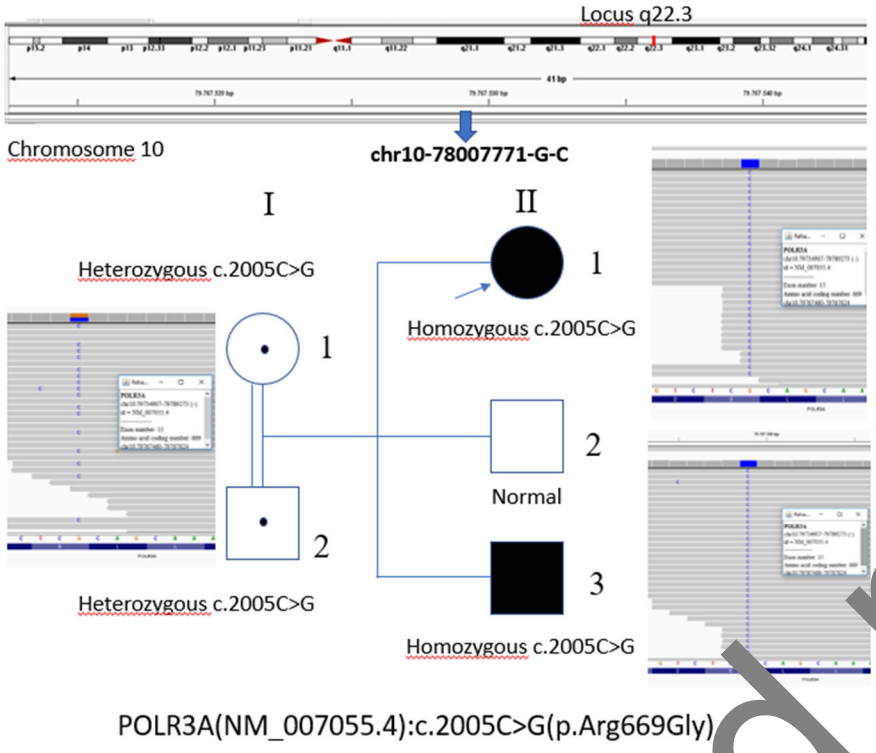

Figure 2. Schematic presentation of the genomic locus of the POLR3A gene on chromosome 10, and the results of segregation analysis of POLR3A gene c.2005C>G variant on the pedigree of the family.

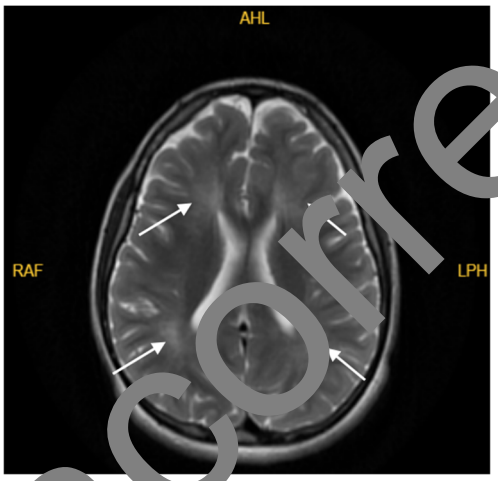

Figure 3. Axial T2-weighted MR image shows (white arrows) increased signal intensity secondary to hypomyelination in bilateral periventricular white matter.