Novel mutations of POLR3A Gene caused hypomyelinating leukodystrophy type 7 (HLD7) in a Chinese family: a Case Report

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Case report

Keywords: hypomyelinating leukodystrophy type 7(HLD7); POLR3A gene; polytrichia; bronchodysplasia

Posted Date: June 25th, 2019

DOI: https://doi.org/10.21203/rs.2.10640/v1

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Version of Record: A version of this preprint was published on August 22nd, 2019. See the published version at https://doi.org/10.1186/s12887-019-1656-7.
Abstract

Background Hypomyelinating leukodystrophy 7 (HLD7) is an autosomal recessive neurodegenerative disorder characterized by childhood onset of progressive motor decline that manifests as spasticity, ataxia, tremor, and cerebellar symptoms, as well as mild cognitive regression and hypodontia. HLD7 belongs to the family of RNA polymerase III-related leukodystrophy, which are caused by biallelic mutations in the POLR3A or POLR3B gene. Case presentation In this study, we report a female child with HLD7 manifesting as cognitive decline, moderate dysarthria, intellectual disability, cerebellar syndrome, short stature, dysphagia, hypodontia, and aberrant brain imaging. Interestingly, polytrichia and bronchodysplasia were first observed in the HLD7 patient. Medical exome sequencing with high coverage depth was employed to identify potential genetic variants in the patient. Novel compound heterozygous mutations of the POLR3A gene, c.1771-6C>G and c.2611del (p.M871Cfs*8), were detected. One of them is an uncommon splice site mutation, and this is the first report of this mutation in a Chinese family. The father was determined to be a heterozygous carrier of the c.2611del (p.M871Cfs*8) mutation and the mother a heterozygous carrier of the c.1771-6C>G mutation. Conclusion The patient’s newly emerged clinical features and mutations provide useful information for further exploration of genotype-phenotype correlations of HLD7.

Background

Hypomyelinating leukodystrophy 7 (HLD7), also known as hypomyelination, hypodontia, and hypogonadotropic hypogonadism (4H) syndrome, is a rare autosomal recessive disorder [1]. Clinical manifestations include progressive cerebellar dysfunction, vertebral body system obstacle, dystonia, cramps, cognitive impairment, and dysarthria. Dental abnormalities (i.e., tooth delay, tooth agenesis, fewer teeth, and abnormal tooth form and arrangement), short stature, dysphagia, endocrine abnormalities such as retardation and no adolescence, and progressive eye abnormalities such as myopia and optic atrophy are also possible [2]. Myopia is seen in almost all patients and short stature occurs in 50% of patients with HLD7. However, dental issues, difficulty swallowing, endocrine features, and aberrant tooth and hormonal abnormalities are not always present [1]. Systematic magnetic resonance imaging (MRI) revealed that the combination of hypomyelination with relative T2 hypointensity of the ventrolateral thalamus, optic radiation, globus pallidus, dentate nucleus, cerebellar atrophy, and thinning of the corpus callosum indicate HLD7. MRI characteristics are the main supporting evidence for diagnosis of HLD7, especially if classic non-neurological features are absent [1, 3, 4].

HLD7 belongs to the family of Pol III-related leukodystrophy caused by biallelic mutations in the POLR3A gene on chromosome 10q22 or the POLR3B gene on chromosome 12q23, which are inherited in an autosomal recessive manner. These genes are responsible for encoding the two largest subunits of RNA polymerase III (Pol III), which has been hypothesized to be crucial for the synthesis of small RNAs, such as 5SrRNA and transfer RNAs (tRNAs). Many genetic factors, especially biallelic mutations in POLR3A (OMIM: 614258) or POLR3B (OMIM: 614366), have been reported in this hereditary disease [5–8]. Mutations in these genes cause abnormal tRNA and non-coding RNA transcription in a cell type and
growth state dependent manner, and can impact cellular growth, differentiation, and apoptosis [5, 9]. Patients with POLR3A mutations have a more severe disease course and an unfavorable prognosis compared to cases with POLR3B mutations. Bernard et al. hypothesized that POLR3A mutations lead to dysregulation of Pol III and its targets, resulting in decreased expression of certain tRNAs during development and impaired protein synthesis [7]. Previous studies have shown that 14 recessive mutations in the POLR3A gene were found in 19 French-Canadian, Caucasian, and Syrian individuals [7]. However, cases among the Chinese population are still unclear. Most published mutations of POLR3A associated with HLD7 or 4H syndrome [1, 3, 4, 6–8, 10] have focused on mutations that cause a change of amino acid; studies of splice site mutations and copy number variants are rare. In the present study, we report a female patient with a novel compound heterozygous mutation with an uncommon splice site mutation, c.1771-6C>G and c.2611del of POLR3A. Our study will broaden our knowledge of mutations associated with HLD7 and contribute to the further study of genotype-phenotype correlations of HLD7.

Case Presentation

A girl aged 2.5 years was admitted to the intensive care unit of our hospital because of severe pneumonia for hyper-breath and poor appetite for 2 days, with aggravated symptoms for a half-day period. She had a history of recurrent pneumonia and was the first birth of the parents with full-term normal delivery and a birth weight of 3,00 g. There was no history of asphyxia and injury in the parturition period. Her previous medical history included febrile seizures on several occasions. The patient was of short stature with a height of 80 cm (<-3SD), consistent with the short stature seen in 50% of cases, while nutrition and development were within a normal range with a body weight of 15 kg (+1SD). Cognitive decline, dystonia, nystagmus, dysarthria, and movement disability were apparent. The striking observation is dysphagia. Gastro-esophageal reflux often occurs with tube feeding, indicating decreased visceral smooth muscle mobility. Body examination indicated nystagmus, hypodontia, polytrichia (Fig. 1A and B), ataxia, and spastic paralysis of the upper and lower limbs. Brain MRI showed the extra cerebral space widening at 6 months of age (Fig. 1 C). In addition, at 11 months, further frontotemporal space widening was apparent, as was loss of white matter and hypomyelination of white matter in the anterior angle of the bilateral posterior ventricle (Fig. 1D–F). Laboratory examination indicated that plasma ammonia, lactate, serum antibody tests for toxoplasma, rubella virus, cytomegalovirus, and herpes simplex virus (TORCH), vitamin B, trace elements, creatine kinase, and thyroid function were normal. Electroencephalogram and electrocardiogram results were negative. The value of auditory brain-stem responses was greater than the threshold line (50 dbnml) (Table 1). Chest X-ray showed bilateral lung inflammation. Because of recurrent pneumonia, tracheobronchoscopy was performed and an orifice of the right middle bronchus was found to be absent (Fig. 1 G), which was first observed in HLD7. Genetic metabolic screening of blood and urine were performed twice and parameters were determined to be within normal range. The results of the abdomen ultrasound examination were negative. Fundus examination was normal without optic atrophy and cataract. Visual acuity was also measured and no myopia was found. The endocrinal profile was not detected because the patient was too young; data regarding motor conduction velocity was also not available. Conventional karyotype analysis revealed a normal 46 XX karyotype.
To achieve an accurate genetic diagnosis, medical exome sequencing was carried out with a Trio sample strategy. A peripheral blood sample was collected from the proband and her parents and genomic DNA was isolated using the High Pure PCR Template Preparation Kit (Roche, Basel, Switzerland) according to the manufacturer's instructions. The medical exome including coding regions and known pathogenic non-coding regions of over 4,000 disease-related genes was captured before next-generation sequencing (Amcare Genomic Laboratory, Guangzhou, China). The potential pathogenic variants were filtered by bioinformatics analysis as described previously [11]. Sequencing of 50,902 genomic regions spread over 8,591,731 bp with an average coverage of 274 +/- 164× was obtained; the coverage of 99.4% of the sequenced regions exceeded 10× and the coverage of 99.2% of the sequenced regions exceeded 20×. Further analysis revealed two novel mutations of \textit{POLR3A} in the patient: c.1771-6C>G (NM_007055) adjacent to the mRNA splicing site and c.2611del, which results in early termination of translation (p.M871Cfs*8). The c.1771-6C>G mutation occurs at very low frequency in the population (< 0.001), while the c.2611del mutation is not listed in 1000 Genomes (The 1000 Genome Project Consortium) or The Genome Aggregation Database (gnomAD, Broad Institute). Co-segregation analysis confirmed that the two mutations were inherited from the heterozygous parents of the proband. The father was determined to be the carrier of the c.2611del (p.M871Cfs*8) mutation and the mother was determined to be the carrier of the c.1771-6C>G mutation. Collectively, we identified novel compound heterozygous mutations of the \textit{POLR3A} gene that caused HLD7 in the patient combined with the clinical presentation, MRI brain pattern, and medical exome sequencing (Figs. 1 and 2).

\textbf{Discussion And Conclusions}

HLD7 is an autosomal recessive neurodegenerative disorder characterized by childhood onset of progressive motor decline that manifests as spasticity, ataxia, tremor, and cerebellar symptoms, as well as mild cognitive regression. Other features include hypodontia or oligodontia and hypogonadotropic hypogonadism. Initially POLR3-related leukodystrophy were included originally, such as 4H; ataxia, delayed dentition, and hypomyelination (ADDH); leukodystrophy with oligodontia (LO); tremor-ataxia with central hypomyelination (TACH); and hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCACH) syndromes, because of different clinical phenotypes. They are now known as the same entity and referred to as POLR3-related leukodystrophy, and also known as 4H leukodystrophy because they have phenotypes in common and the same molecular foundation, which are commonly caused by mutations in \textit{POLR3A}, \textit{POLR3B}, and \textit{POLR1C} [7, 8, 12–14]. Patients exhibit a wide range of severities and onset time ranges from the neonatal period to late childhood. Mean age with gross motor delay or regression of the majority is before 6 years. Ten percent of the patients had an onset of beyond 10 years [1, 15].

In this study, we present a female child from the southern district of China who displayed severe neurological manifestations. Before 1 year of age, she presented with reduced motor ability, and then started to show prominent cerebellar signs, including nystagmus, motor ataxia, dysarthria, and spastic paralysis of the upper and lower limbs. Delayed dentition and development figures, prominent body hair, and hypertonia of both the upper and lower limbs were also observed. She had not attained complete
head control and required assistance to sit. To date, she is two and a half years of age, does not have ambulation ability, and is bedridden. Brain MRI indicated loss of white matter and hypomyelination of white matter in the anterior angle of the bilateral posterior ventricle. Since hypomyelination is a nonspecific finding that affects patients, brain MRI of approximately one-third of patients with hypomyelination did not result in a definitive diagnosis [16]. The identification of further clinical and genetic characteristics will be fundamental for the classification of this group of diseases [17]. Therefore, we performed medical exome sequencing and found novel compound heterozygous mutations of the POLR3A gene. We therefore concluded the diagnosis and identified the compound heterozygous variants as the causative variants for the disease in this patient. It is noteworthy that this disease has mostly been reported in European populations, including French-Canadian, Caucasian, and Syrian individuals [1, 4]. Occasional cases have been reported in the Indian population [18–20]. However, this is the first case reported in a Chinese family.

POLR3-related leukodystrophy is a hypomyelinating leukodystrophy characterized by neurological (cerebellar, extrapyramidal, pyramidal, and cognitive) and non-neurologic (dental, endocrine, and ocular) features. Neurological impairment of our case started in the infantile period with marked hypotonia, global developmental delay, and congenital ataxia. Although cerebellar signs of this case became progressively obvious, cerebellar atrophy was not observed, which may be due to the young age. Previous studies have found that cerebellar anomalies were more severe in patients with POLR3B defects while the pattern of hypomyelinization was more evident in the MRI of patients with POLR3A mutations [1, 3]. This may be another explanation for our case. Other than neurological symptoms, patients also show extra neurologic symptoms, including hypodontia with abnormal tooth eruption shape, hypogonadotropic hypogonadism, myopia, and short stature. Our patient also showed classical extraneurologic features, characterized by hypodontia with delayed tooth eruption and short stature. She also displayed polytrichia, an atypical feature of HLD7, which may be due to aberrant gonadal function or other reasons; gonadal function was not assessed. Hypogonadotropic hypogonadism was not detected because she was too young. Previous studies have also shown that the syndrome may or may not be associated with hypodontia and/or hypogonadotrophic hypogonadism in many cases [6, 7]. She did not show myopia and optic atrophy; this is inconsistent with most cases, which are usually accompanied by myopia [1]. Her dysphagia phenotype was striking, which is rare. She had obvious difficulty with tube feeding and forceful vomiting occurred frequently. This is likely due to the incoordination of swallowing of cerebellar syndrome, or due to other unpredictable reasons. Bronchodysplasia is another feature first observed in HLD7, suggesting that it was not recognized previously in the HLD7 spectrum. Thus, in addition to the classical extraneurological features, abnormal body hair and visceral smooth muscle features should be carefully looked for in patients with POLR3-related disorders. Our case presented with severe manifestation at early onset and diverse manifestations among those of patients with Pol III-related leukodystrophy, which may be a result of the genotype identified in this patient; further analysis is necessary.

POLR3A, POLR3B, and POLR1C mutations are associated with Pol III-related leukodystrophies. The former two genes encode the two largest subunits of Pol III, which is composed of 17 subunits, while
defects in the POLR1C gene impair assembly and nuclear import of POLR3 and thereby lead to decreased binding to its target genes [5]. Pol III transcribes a series of small non-coding RNAs (i.e., tRNAs, 5S RNA, 7S RNA, U6 RNA), which participate in the regulation of vital cellular processes, such as transcription, RNA processing, and translation [9], leading to a series of neuronal and non-neurological features. There are 62 pathogenic variants associated with POLR3-related leukodystrophy, and 14 different mutations in the POLR3A gene have been reported to be associated with 4H syndrome patients [7, 10]. To date, most of the identified mutations are point mutations in the codon region; however, non-coding DNA variants are suspected to account for a substantial portion of undiscovered causes of rare diseases [21]. Minnerop et al. identified mutations in deep intronic regions of POLR3A as a common cause of hereditary spastic paraplegia and cerebellar ataxia, and > 80% of POLR3A mutation carriers presented the same deep intronic mutation (c.1909+22G>A), which leads to a novel, distinct, uniform, and severe phenotype [22]. Jay AM et al. also reported alteration of mRNA splicing in POLR3A causing neonatal progeroid syndrome with severe clinical manifestations [23]. In this study, we identified the c.1771-6C>G (NM_007055) mutation adjacent to the mRNA splice site demonstrating that exploring non-coding genomic regions was helpful in revealing the causes of related hereditary diseases.

The complexity of clinical phenotypes and the heterogeneity of genotypes raise new challenges in genetic diagnoses. In the present study, medical exome sequencing was used to explore the possible genetic defects resulting in the disease of the patient. Compared to whole genome and whole exome sequencing, medical exome sequencing focuses on clinical interpretable regions of genes; less variants of uncertain significance in medical exome sequencing greatly improve the diagnostic yield and increase the coverage depth of sequencing, improving the accuracy of sequencing and broadening the spectrum of variants. In the present study, we identified novel heterozygous mutations of POLR3A that caused HLD7 disease for the first time in a Chinese family. This study will further our understanding of the molecular mechanisms of HLD7 and contribute to further analysis of phenotype–genotype correlations of related disorders.

**Abbreviations**

HLD7, Hypomyelinating leukodystrophy 7; MRI, magnetic resonance imaging; TORCH, serum antibody tests for toxoplasma, rubella virus, cytomegalovirus, and herpes simplex virus; ADDH, ataxia, delayed dentition, and hypomyelination; LO, leukodystrophy with oligodontia; TACH, tremor-ataxia with central hypomyelination; HCACH, hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum.

**Declarations**

Ethics approval and consent to participate

Ethical approval for this study was obtained from the local ethics committee. Informed consent informed consent was obtained from the patient’s parents.
Consent for publication

The guardians have written informed consent to publish this information and the proof of consent can be requested at any time.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author (Haitao Lv) on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

Design of the study and collection, analysis, and interpretation of data and in writing the manuscript were funded by Suzhou Science and Technology Development Project (project code SYS 201757) and Natural science fund for colleges and universities of Jiangsu Province (project code 18KJB320022).

Authors’ contributions

SW: Designed the research, analyzed the data and drafted the manuscript;

ZB: Participated in analyzing the part of data;

XD: Collected clinical data;

HC, Daoping Yang and Jun Hua: Participated in the communicate with patients’ guardians;
LZ: Collected clinical data;

HL: Participated to the in discussion and interpretation of the data and results, involved in the critical revision of this manuscript and take the primary responsibility of this research;

All authors have read and approved this manuscript and ensure that this is the case.

Acknowledgements

Not applicable.

References

1. Wolf NI, Vanderver A, van Spaendonk RM, Schiffmann R, Brais B, Bugiani M, Sistermans E, Catsman-Berrevoets C, Kros JM, Pinto PS et al. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. Neurology 2014, 83(21):1898-1905.

2. Bernard G, Vanderver A: POLR3-Related Leukodystrophy. In: GeneReviews((R)). edn. Edited by Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A. Seattle (WA); 1993.

3. Takanashi J, Osaka H, Saitsu H, Sasaki M, Mori H, Shibayama H, Tanaka M, Nomura Y, Terao Y, Inoue K et al: Different patterns of cerebellar abnormality and hypomyelination between POLR3A and POLR3B mutations. Brain & development 2014, 36(3):259-263.

4. Daoud H, Tetreault M, Gibson W, Guerrero K, Cohen A, Gburek-Augustat J, Synofzik M, Brais B, Stevens CA, Sanchez-Carpintero R et al: Mutations in POLR3A and POLR3B are a major cause of hypomyelinating leukodystrophies with or without dental abnormalities and/or hypogonadotropic hypogonadism. Journal of medical genetics 2013, 50(3):194-197.

5. Tewari VV, Mehta R, Sreedor CM, Tewari K, Mohammad A, Gupta N, Gulati S, Kabra M: A novel homozygous mutation in POLR3A gene causing 4H syndrome: a case report. BMC pediatrics 2018, 18(1):126.

6. Thiffault I, Wolf NI, Forget D, Guerrero K, Tran LT, Choquet K, Lavallee-Adam M, Poitras C, Brais B, Yoon G et al: Recessive mutations in POLR1C cause a leukodystrophy by impairing biogenesis of RNA polymerase III. Nature communications 2015, 6:7623.

7. Saitsu H, Osaka H, Sasaki M, Takanashi J, Hamada K, Yamashita A, Shibayama H, Shiina M, Kondo Y, Nishiyama K et al: Mutations in POLR3A and POLR3B encoding RNA Polymerase III subunits cause an autosomal-recessive hypomyelinating leukoencephalopathy. American journal of human genetics 2011, 89(5):644-651.

8. Bernard G, Chouery E, Putorti ML, Tetreault M, Takanohashi A, Carosso G, Clement I, Boespflug-Tanguy O, Rodriguez D, Delague V et al: Mutations of POLR3A encoding a catalytic subunit of RNA
polymerase Pol III cause a recessive hypomyelinating leukodystrophy. *American journal of human genetics* 2011, 89(3):415-423.

9. Potic A, Brais B, Choquet K, Schiffmann R, Bernard G: **4H syndrome with late-onset growth hormone deficiency caused by POLR3A mutations.** *Archives of neurology* 2012, 69(7):920-923.

10. Dumay-Odelot H, Durrieu-Gaillard S, Da Silva D, Roeder RG, Teichmann M: **Cell growth- and differentiation-dependent regulation of RNA polymerase III transcription.** *Cell cycle* 2010, 9(18):3687-3699.

11. Azmanov DN, Siira SJ, Chamova T, Kaprelyan A, Guergueltcheva V, Shearwood AJ, Liu G, Morar B, Rackham O, Bynevelt M et al: **Transcriptome-wide effects of a POLR3A gene mutation in patients with an unusual phenotype of striatal involvement.** *Human molecular genetics* 2016, 25(19):4302-4314.

12. Tetreault M, Choquet K, Orcesi S, Tonduti D, Balottin U, Teichmann M, Fribourg S, Schiffmann R, Brais B, Vanderver A et al: **Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy.** *American journal of human genetics* 2011, 89(5):652-655.

13. Hennekam RC: **What to call a syndrome.** *American journal of medical genetics Part A* 2007, 143A(10):1021-1024.

14. 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.** *Pediatric dentistry* 2010, 32(5):386-392.

15. La Piana R, Cayami FK, Tran LT, Guerrero K, van Spaendonk R, Ounap K, Pajusalu S, Haack T, Wassmer E, Timmann D et al: **Diffuse hypomyelination is not obligate for POLR3-related disorders.** *Neurology* 2016, 86(17):1622-1626.

16. Jiang Y, Pan J, Guo D, Zhang W, Xie J, Fang Z, Guo C, Fang Q, Jiang W, Guo Y: **Two novel mutations in the PPIB gene cause a rare pedigree of osteogenesis imperfecta type IX.** *Clinica chimica acta; international journal of clinical chemistry* 2017, 469:111-118.

17. Schiffmann R, van der Knaap MS: **Invited article: an MRI-based approach to the diagnosis of white matter disorders.** *Neurology* 2009, 72(8):750-759.

18. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kemytsky A, Garimella K, Altshuler D, Gabriel S, Daly M et al: **The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data.** *Genome research* 2010, 20(9):1297-1303.

19. Jauhari P, Sahu JK, Singhi P, Dayal D, Khandelwal N: **An Indian boy with a novel leukodystrophy: 4H syndrome.** *Journal of child neurology* 2014, 29(1):135-138.

20. Muthusamy K, Sudhakar SV, Yoganathan S, Thomas MM, Alexander M: **Hypomyelination, Hypodontia, Hypogonadotropic Hypogonadism (4H) Syndrome With Vertebral Anomalies: A Novel Association.** *Journal of child neurology* 2015, 30(7):937-941.

21. Baralle D, Buratti E: **RNA splicing in human disease and in the clinic.** *Clinical science* 2017, 131(5):355-368.
22. Minnerop M, Kurzwelly D, Wagner H, Soehn AS, Reichbauer J, Tao F, Rattay TW, Peitz M, Rehbach K, Giorgetti A et al: Hypomorphic mutations in POLR3A are a frequent cause of sporadic and recessive spastic ataxia. Brain: a journal of neurology 2017, 140(6):1561-1578.

23. Jay AM, Conway RL, Thiffault I, Saunders C, Farrow E, Adams J, Toriello HV: Neonatal progeriod syndrome associated with biallelic truncating variants in POLR3A. American journal of medical genetics Part A 2016, 170(12):3343-3346.

Tables

Table 1 Laboratory results

| Test                                      | Results                                      |
|-------------------------------------------|----------------------------------------------|
| Chromosome karyotype                      | 46 XX, normal                                |
| Plasma ammonia                            | Normal                                       |
| Lactate                                   | Normal                                       |
| TORCH                                     | Negative                                     |
| Genetic Metabolic Screening               | Negative                                     |
| Electroencephalogram EEG                  | Normal                                       |
| Auditory brain-stem responses, ABR        | Over than threshold(50dbnml)                 |
| Vitamin B                                 | Normal                                       |
| Trace elements                            | Normal                                       |
| Creatine kinase                           | Normal                                       |
| Thyroid function                          | Normal                                       |

Figures
Figure 1

Clinical pictures of this patient. A: Tooth delay or tooth agenesis was found at the age of 2 years and 6 months old; B: Body examination indicated manifestation of polytrichia; C: Brain MRI showed the extra cerebral space widening at six months old; D-F: Frontotemporal space widening, white matter vanishing and hypomyelination of white matter in the anterior angle of the bilateral posterior ventricle at the age of eleven months. G: Fiberoptic bronchoscopy presented the absence of right middle bronchus orifice.
Figure 2

Identification of novel POLR3A mutations in the family by next-generation sequencing.

Supplementary Files

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