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CASE REPORT

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Genetic analysis reveals phenotypic variability in three Colombian families with dopa-responsive dystonia: novel genotype-phenotype correlations

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Abstract

Background Dopa-responsive Dystonia (DRD) due to GTP cyclohydrolase 1 (GTPCH1) deficiency is a neurogenetic disorder caused by pathogenic *GCH1* variants. Tetrahydrobiopterin (BH4) deficiency impairs dopamine synthesis in the basal ganglia, leading to childhood-onset dystonia with excellent response to levodopa.

Case presentation We report eight patients from three unrelated families with GCH1 (NM_000161.3) variants: c.142 C > T; p.(Gln48*), c.241T > C; p.(Ser81Pro), and c.607G > A; p.(Gly203Arg). Two individuals homozygous for c.142 C > T showed phenotypic discordance. Mean age at onset was 7.3 years (range: 6–12), with an average diagnostic delay of 13.4 years. All symptomatic individuals responded well to low-dose levodopa.

Discussion This is the first report to describe variable expressivity among individuals homozygous for p.(Gln48*). Previous literature has focused on heterozygous carriers with incomplete penetrance, and homozygous variability remains scarcely documented.

Conclusions Our findings expand the clinical and molecular spectrum of DRD and challenge the assumption that autosomal recessive *GCH1* variants invariably cause a severe phenotype. This report underscores the importance of family-based genetic studies, detailed pedigrees, and careful clinical surveillance of asymptomatic carriers. A low threshold for levodopa trials is warranted, even when inheritance patterns or symptom severity deviate from classical expectations. These insights are critical to improving early recognition and timely treatment.

Keywords GCH1, Dystonia, Levodopa, Genetics, Pediatrics

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Background

Dopa-responsive dystonia (DRD) due to GTP cyclohydrolase 1 (GTPCH1) deficiency is a neurogenetic disorder caused by pathogenic variants in *GCH1*, which encodes the rate-limiting enzyme in the tetrahydrobiopterin (BH4) synthesis [1]. BH4 is an essential cofactor for aromatic amino acid hydroxylases involved in catecholamines and serotonin production; its deficiency leads to impaired dopamine synthesis in the nigrostriatal pathway [1–3].

Epidemiological studies estimate the prevalence of the autosomal dominant form of DRD at 0.5–1.0 cases per million individuals [4–6]. In contrast, the recessive form is considered extremely rare, with a frequency below 1 in 1,000,000 [7] and notable geographic heterogeneity. A striking feature is the sex-related difference in penetrance: approximately 87% of female carriers exhibit clinical manifestations, compared to only 35–38% of male carriers [8].

The molecular etiology of DRD due to *GCH1* variants is characterized by two distinct Mendelian inheritance patterns with differing phenotypic correlations. The autosomal dominant (AD) form typically presents with focal or generalized dystonia exhibiting response to levodopa, incomplete penetrance influenced by sex, variable expressivity, and absence of hyperphenylalaninemia (HPA) [9]. Segregation analyses have revealed asymptomatic heterozygous carriers and identified cases arising from de novo mutations.

The autosomal recessive (AR) form is associated with a more severe neurological phenotype, including global developmental delay, complex movement disorders, and epileptic seizures, often accompanied by detectable HPA [10]. Both forms typically exhibit abnormal urinary pterin profiles and reduced monoaminergic metabolites in cerebrospinal fluid. The presence of basal HPA remains the key biochemical marker distinguishing the recessive form from the dominant variant [7].

The spectrum of *GCH1* variants has expanded significantly with the widespread adoption of next-generation sequencing technologies. According to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), a total of 691 allelic variants have been reported, including 105 classified as pathogenic and eight as likely pathogenic. The most common variant types are nonsense mutations ($n = 34$), followed by frameshift mutations ($n = 24$), splice-site mutations ($n = 21$), and missense mutations ($n = 16$). Similarly, the Franklin database (https://franklin.genoox.com/clinical-db/home) lists 583 *GCH1* variants, of which 154 are classified as pathogenic.

This article presents eight patients and their corresponding family analyses with *GCH1* pathogenic variants from three unrelated families. We describe the identified variants, characterize the observed clinical heterogeneity, outline the inheritance patterns, and highlight the notable finding of two homozygous individuals exhibiting divergent phenotypic expressivity compared with previously reported cases (Table 1).

Table 1 Clinical features, genetic findings, and results of standardized assessments in patients of the three families

Case number	Gender/ Current age	Age at symptom onset (years)	Age at diagnosis (years)	Phenotype D: Dystonia *P*: Parkinsonism O: Others	Levodopa dose response	Genotipo GCH1 (NM_000161.3)	Scales
1-III-7	M/60	20	55	D O: Dysphagia, cognitive impairment	Levodopa 125 mg Carbidopa 12.5 mg BID	c.142 C > T; p.(Gln48*)/c.142 C > T; p.(Gln48*)	UPDRS III: 37/72 points
1-IV-6	F/20	3	15	D *P*	Levodopa 125 mg Carbidopa 12.5 mg BID	c.142 C > T; p.(Gln48*)	BFM Disability: 13/30 Movement: 13.5/120
1-IV-7	M/17	-	13	-	-	c.142 C > T; p.(Gln48*)/c.142 C > T; p.(Gln48*)	-
2-III-5	F/55	-	53	-	-	c.607G > A; p.(Gly203Arg)	-
2-IV-1	F/15	4	12		Levodopa 50 mg Carbidopa 12.5 mg BID	c.607G > A; p.(Gly203Arg)	BFM Disability: 16/30 Movement: 18.5/120
2-IV-2	M/7	-	-	-	-	-	-
3-II-2	M/45	7	40	D	Levodopa 125 mg Carbidopa 12.5 mg BID	c.241T > C; p.(Ser81Pro)	UPDRS III:11
3-III-1	F/20	5	16	D	Levodopa 125 mg Carbidopa 12.5 mg BID	c.241T > C; p.(Ser81Pro)	BFM Disability: 7/30 Movement: 11.5/120
3-III-2	F/12	7	8	D	Levodopa 125 mg Carbidopa 12.5 mg BID	c.241T > C; p.(Ser81Pro)	BFM Disability: 7/30 Movement: 7.5/120

BFM Burke-Fahn-Marsden Rating Scale, *BID* Twice daily, *F* Female, *M* Male, *UPDRS* III: Unified Parkinson's Disease Rating Scale, Part III

Cases presentation

Patients and their first-degree relatives were evaluated through genetics and neurology consultations. Clinical data, physical examinations, and genealogical information were collected to construct detailed pedigrees. Symptomatic individuals were assessed using a movement disorder rating scale tailored to the predominant abnormal movement, and molecular test results were reviewed accordingly.

Informed consent was obtained from all participants. The study protocol was reviewed and approved by the institution's ethics and research committee.

Family #1

Patient 1 (IV-6/AD), the daughter of non-consanguineous parents from the same geographic region, was diagnosed with segmental dystonia at the age of 3. Next-generation sequencing (NGS) using a dystonia gene panel identified the pathogenic variant in GCH1: c.142 C > T; p.(Gln48*) in a heterozygous state, inherited from her father. Levodopa therapy was initiated, leading to notable improvements in mobility and mood. At the time of evaluation, her scores on the Burke-Fahn-Marsden (BFM) scale were 13/30 for the disability subscale (indicating mild-to-moderate functional impairment) and 13.5/120 for the motor subscale (reflecting absent or mild dystonia).

The patient's father (III-7/AR) presented with dystonia of the left foot at age 20. By age 35, he had developed rigidity in the same limb, accompanied by secondary gait disturbances, which progressed to bilateral lower limb rigidity and eventually involved the upper limbs. He reported worsening symptoms throughout the day. Over time, he also developed cognitive changes and dysphagia. Plasma phenylalanine levels were not available at the time of evaluation, and he had a normal brain MRI.

Following his daughter's diagnosis, genetic testing and a therapeutic trial with levodopa/carbidopa were conducted, resulting in marked improvement in dystonia, gait, speech, and swallowing. His MDS-UPDRS Part III (motor examination) score was 37/72, indicating moderate motor impairment. Genetic analysis identified the GCH1: c.142 C > T; p.(Gln48*) in a homozygous state, classified as pathogenic. He denied parental consanguinity and reported no other affected relatives.

Individual (IV-7/AR), the 17-year-old brother of the index case, is asymptomatic and presented with a normal physical examination. Genetic testing confirmed the familial variant GCH1: c.142 C > T; p.(Gln48*) in a homozygous state. Plasma phenylalanine levels were not available at the time of evaluation.

The mother of the index case is also asymptomatic and has an unremarkable physical examination. Genetic testing for the familial variant has not yet been performed. The pedigree of family #1 is presented in Fig. 1.

Family #2

Patient 2 (IV-1/AD) is a female who developed symptoms at 4 years of age, presenting with progressive dystonia of the lower limbs. Trio whole exome sequencing identified the heterozygous pathogenic variant *GCH1*: c.607G > A; p.(Gly203Arg), inherited from her mother.

Following the diagnosis of DRD, treatment was initiated, resulting in dystonia improvement and a reduction in dysphagia. The BFM rating scale showed a disability score of 16/30 (indicating moderate functional impairment) and a motor score of 18.5/120 (suggesting absent or mild dystonia).

The patient's mother (III-5/AD) was asymptomatic and had a normal neurological examination. The patient's 7-year-old brother (IV-2), also asymptomatic, was recommended for genetic testing; results are currently pending. No additional affected individuals were identified in the family. The pedigree of family #2 is presented in Fig. 2.

Family #3

Patient 4 (III-2/AD), currently 12 years old, presented at age 7 with dystonia affecting the right hemibody, which progressively generalized to involve all four limbs, predominantly the lower extremities, leading to gait impairment and subsequent Parkinsonian features. Complementary investigations, including brain MRI, revealed no structural abnormalities. Trio whole-exome sequencing identified the heterozygous variant c.607G > A; p.(Gly203Arg) in *GCH1*, classified as a variant of uncertain significance, inherited from her mother.

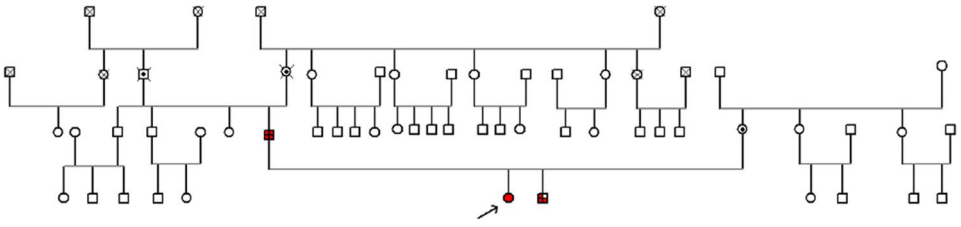

Fig. 1 Pedigree of family # 1. Pedigree legends: Males are represented by squares, females by circles, and deceased individuals by a cross. Symptomatic homozygous. Symptomatic heterozygous. Asymptomatic homozygous. Asymptomatic heterozygous

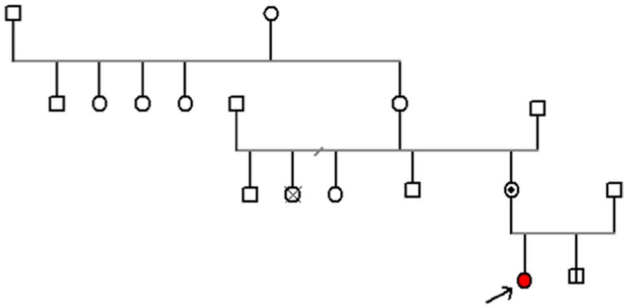

Fig. 2 Pedigree of family #2. Pedigree legends: Males are represented by squares, females by circles, and deceased individuals by a cross. Symptomatic homozygous. Symptomatic heterozygous. Asymptomatic homozygous. Asymptomatic heterozygous

The mother (II-2/AD) reported symptom onset at age 7, initially presenting with progressive dystonia, predominantly affecting the left upper limb and worsening in the afternoon, associated with pain. By age 8, she had been diagnosed with mixed cerebral palsy (spastic-dyskinetic type) and underwent multiple orthopedic surgeries. Despite initial improvement, symptoms recurred. At age 25, she developed rigidity.

Motor assessment using the MDS-UPDRS Part III yielded a score of 11, indicating mild motor impairment, with minimal rigidity and bradykinesia predominantly affecting the left hemibody. Treatment with levodopa (125 mg) and carbidopa (12.5 mg) every 12 h resulted in adequate symptom control.

Following the diagnosis of patient 4 (III-2/AD), genetic evaluation was performed in her older sister, patient 3 (III-1/AD). This individual, currently 17 years old, began experiencing lower limb dystonia at age 7. Unlike her sister, the condition remained stable over time, causing only mild limitations in sports activities without affecting daily functioning. Treatment with levodopa/carbidopa was initiated, resulting in improved physical performance.

Both sisters exhibited dystonia as the predominant movement disorder, as assessed by the BFM scale. Disability subscale scores were 7/30 in both cases, indicating minimal or no functional impairment. Movement subscale scores were 11.5/120 for patient 3 and 7.5/120 for patient 4, consistent with absent or mild dystonia.

The pedigree of family #3 is presented in Fig. 3.

Discussion

We present a case series of eight patients from three unrelated families, all with clinical features and molecular confirmation of dopa-responsive dystonia due to *GCH1* variants. The predominant clinical presentation was childhood-onset dystonia affecting the lower limbs, with a mean age at onset of 7.6 years. Diurnal fluctuation of symptoms and subsequent development of Parkinsonian features were also commonly observed. All symptomatic patients responded favorably to low-dose levodopa, with significant improvement in functional scores and no emergence of motor complications during follow-up (mean duration: 2.8 years). The phenotypic features and corresponding genetic variants are summarized in Table 1.

In Family 1, the GCH1: c.142 C > T; p.(Gln48*) located in exon 1, was identified. Although absent from population databases, it has been previously reported in individuals with autosomal dominant dystonia—specifically, in eight members of the same Korean family [11, 12]. Five of them presented with gait disturbances that worsened toward the evening due to dystonia of the lower limbs, with complete or partial resolution of the dystonia following levodopa treatment. One of the affected individuals also exhibited Parkinsonism. The age of symptom onset was 5 years. There were three asymptomatic carriers.

To date, no cases of affected individuals homozygous for this variant have been described in the literature.

Recently, the phenotypic spectrum of autosomal recessive *GCH1* deficiency has been expanded through a comprehensive analysis of 45 patients, proposing three distinct clinical phenotypes [13]. Phenotype A corresponds to a severe early infantile encephalopathy with neonatal or early-onset presentation, characterized by failure to thrive, developmental arrest, hypokinesia, oculogyric crises, and frequently associated hyperphenylalaninemia. Phenotype B presents as an early-onset neurodevelopmental disorder with dystonia-parkinsonism, emerging after initially normal development and characterized by motor stagnation, irritability, and

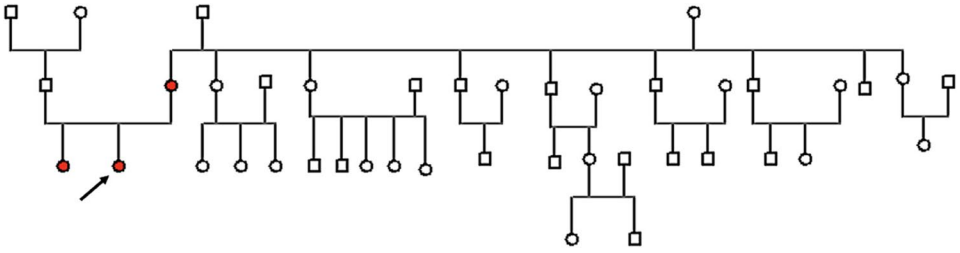

Fig. 3 Pedigree of family #3. Pedigree legends:Males are represented by squares, females by circles, and deceased individuals by a cross. Symptomatic homozygous. Symptomatic heterozygous. Asymptomatic homozygous. Asymptomatic heterozygous

progressive dystonia, typically with preserved cognition. Phenotype C reflects the classic presentation of DOPA-responsive dystonia with later onset (ranging from 2 to 39 years) and characteristic diurnal symptom fluctuation.

This phenotypic stratification delineates a severity gradient that appears to correlate with biochemical patterns (enzymatic defects) and the severity of genetic variants.

In family 1, c.142 C > T; p.(Gln48*) nonsense mutation introduces a premature stop codon at position 48, likely resulting in loss of protein function through nonsense-mediated mRNA decay or truncated, nonfunctional protein. There is strong evidence supporting a loss-of-function mechanism of the gene in disease. MutationTaster/CADD is expected to indicate a high impact.

Remarkably, affected individuals exhibited allelic heterogeneity, with both autosomal dominant and recessive inheritance patterns, and notable phenotypic variability. Both the index case (heterozygous) and her father (homozygous) presented with lower limb dystonia. However, symptom onset differed significantly: the index case showed earlier onset despite being heterozygous, possibly reflecting sex-related predisposition. The father had a later onset of movement symptoms, which is atypical given that recessive forms generally present in early infancy. Notably, the index case's brother, also homozygous for the variant, remained asymptomatic at 17 years of age; however, a longitudinal follow-up will be undertaken, as his homozygous father developed the first symptoms later in life (20 years of age). Notably, there are phenotypical similarities between cases of DRD and early-onset Parkinson´s Disease (EOPD), when patients present with prominent parkinsonian features (as the homozygous father), in which clinical differentiation can be challenging, given that some EOPD patients can show early dystonia, preceding the emergence of parkinsonian symptoms [14]. Functional studies, such as DaTSCAN, can be a valuable tool for evaluating the nigrostriatal pathway and differentiating degenerative changes expected in EOPD from those absent in patients with DRD [15].

Regarding individual IV-II, being homozygous for the familial variant, it is essential to perform segregation analysis of the variant in the mother. Other potential mechanisms, such as uniparental disomy, could be considered; however, to date, no reports in the literature describe this mechanism for this condition. The absence of maternal genetic testing is regarded as a limitation of the study.

Incomplete penetrance and variable expressivity have been reported in this condition. Since segregation analysis could not be performed in all at-risk relatives, it is not possible to calculate penetrance within the families. As for the explanations for its low penetrance, it has been postulated that, at the molecular level, the basal activity of GTP-cyclohydrolase I is higher in males than in females, resulting in greater functional enzymatic activity [16]. Furukawa et al. evaluated the influence of sex on GCH1 penetrance and did not observe a significant difference depending on whether the variant was inherited from the father or the mother. Additionally, they reported a substantial number of de novo variants, unlike our patients, in whom the variant was inherited from a parent in all cases.

Incomplete penetrance, influenced by sex, has been associated with possible hormonal factors [17], but environmental factors, modifier genes, and epigenetic mechanisms that alter the phenotype may also play a role. Further studies are needed to elucidate the underlying causes.

In Family 2, the *GCH1*: c.607G > A; p.(Gly203Arg) was initially reported in a British patient [18]. In vitro studies demonstrate that this variant markedly reduces enzymatic activity to less than 6% of control levels, likely due to conformational alterations and a potential dominant-negative effect [19]. There was a family described with four affected female members: three presented with childhood-onset lower limb dystonia, comparable to the case in our study, while one individual developed Parkinsonian features—tremor, rigidity, and bradykinesia—at 65 years of age, without dystonia [20]. Gly203 is a conserved position. In silico prediction (expect deleterious SIFT/REVEL7 BayesDel/,alphamisensse, probably damaging PolyPhen).

In Family 3, the *GCH1*: c.241T > C; p.(Ser81Pro) was initially classified as a variant of uncertain significance, given its absence from population databases despite being located within a known mutational hotspot. However, it is currently considered likely pathogenic based on prior reports. Two female patients from the same family were described presenting with tremor and bradykinesia [20]. Another study [21] documented three individuals carrying this variant: one with dopa-responsive dystonia—clinically comparable to the three patients described in our cohort—one with Parkinsonism, and one asymptomatic. Functional studies have demonstrated that serine at position 81 plays a critical role in enzymatic activation [22], supporting a high probability of functional impairment associated with this substitution. Importantly, Ser81 has been implicated as a phosphorylation/regulatory residue in GCH1, and substitutions to proline may disrupt local structure and phosphorylation-dependent regulation. In silico tools like Revel/mutationTaster/BayesDel/alphamisensse predict likely to be damaging.

Our study underscores the persistent challenge of diagnosing and correlating genotype with phenotype in DRD due to GTPCH1 deficiency, despite significant advances in its molecular characterization. The observed clinical

variability and incomplete penetrance can lead to delayed or incorrect diagnoses, reinforcing the importance of considering DRD in the differential diagnosis of conditions that mimic cerebral palsy—illustrated by the case of the mother in Family 3.

Furthermore, the presence of atypical phenotypes and late-onset forms complicates diagnostic pathways, underscoring the need for regular monitoring of asymptomatic individuals carrying *GCH1* variants. This is particularly relevant given reports of late-onset Parkinsonian manifestations, likely reflecting variable expressivity. Functional characterization of specific variants may provide further insight into this clinical heterogeneity, and future research should explore the potential roles of genetic modifiers and hormonal influences.

Our findings highlight the critical role of family history and pedigree analysis in the diagnostic evaluation of DOPA-responsive dystonia. In Families 1 and 3, parental diagnoses were established late despite prior symptomatic presentations, reflecting missed diagnostic opportunities. A striking observation in our cohort was the prolonged interval between symptom onset and molecular confirmation, with a mean delay of 13.4 years (range: 1–42 years). This delay was particularly pronounced in the parental generation (mean: 27.3 years), compared to a substantially shorter interval in offspring (mean: 4.2 years), emphasizing the value of early clinical suspicion and the use of segregation studies. Adopting a family-centered diagnostic strategy significantly reduced diagnostic complexity, enabled timely treatment initiation, and facilitated appropriate genetic counseling.

Our study has multiple limitations: we lacked access to cerebrospinal fluid biochemical evaluations, including homovanillic acid, 5-hydroxyindoleacetic acid, neopterin, biopterin, and tetrahydrobiopterin, to strengthen the biochemical analysis. It was not possible to measure plasma phenylalanine levels in our subjects with homozygous variants, nor segregation studies in individuals, such as III-24 in family 1, to explain the homozygous mechanisms. Furthermore, the number of individuals tested did not allow us to estimate the penetrance of the variants in the families described. We were unable to do functional studies to evaluate the impact of the variant on protein function.

Conclusions

The systematic analysis of patient series with DOPA-responsive dystonia due to GTPCH1 deficiency is essential for expanding the clinical and genetic understanding of this disorder. Detailed characterization of patients' clinical features, treatment responses, and molecular findings provides critical insights to improve diagnostic accuracy and therapeutic management. Through this study, we contribute novel variants to existing databases, enhance the current understanding of genotype–phenotype correlations and clinical variability, and aim to support the future expansion of pedigrees and regional variant registries relevant to this condition.

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The authors declare that there are no additional disclosures to report.

Authors' contributions
Author 1: 1 A,1B,1 C,2 A,2B,2 A,3 A,3BAuthor 2:
1 A,1B,1 C,2 A,2B,2 A,3 A,3BAuthor 3: 1 A,1B,1 C,2 A,2B,2 A,3 A,3BAuthor 4:
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Data availability
All of the reported variants have been previously described in the literature and are included in the ClinVar database.All variants of the GCH1 gene are reported using the transcript: NM_000161.3Family 1: Variant: c.142 C> T (p.Gln48Ter)· ClinVar Variation ID: 9288 Accession: VCV000009288.8Family 2: c.607G> A (p.Gly203Arg)· ClinVar Variation ID: 381665 Accession: VCV000381665.12Family 3: c.241T> C· ClinVar Variation ID: 1463233 Accession: VCV001463233.7.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Instituto Roosevelt approved this study. Written informed consent was obtained from all patients or their legal guardians (in the case of minors, individuals younger than 18) for participation and publication of their clinical details, along with figures, in this study.
We confirm that we have read the Journal's position on ethical publication and affirm that this work is consistent with those guidelines.
The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
The study was conducted in accordance with the principles of the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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