Case Report

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Case Report: Chung-Jansen Syndrome Associated with a Novel PHIP Deletion and Lysosomal Storage–Like Features

Milena Greczan [1,*], Izabela Mendrek [2], Agnieszka Janiec [1] and Agnieszka Ługowska [3]

[1] Department of Pediatrics, Nutrition and Metabolic Diseases, Children's Memorial Health Institute, Warsaw, Poland

[2] Department of Medical Genetics, Children's Memorial Health Institute, Warsaw, Poland

[3] Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland

* Correspondence: m.greczan@ipczd.pl

Abstract

Background: Chung–Jansen syndrome (CHUJANS, OMIM #617991) is a rare neurodevelopmental disorder caused by heterozygous pathogenic variants in the *PHIP* gene. Core clinical features include developmental delay, intellectual disability, behavioral abnormalities, childhood-onset overweight or obesity and dysmorphic features. **Case presentation:** We report a case of a girl diagnosed with CHUJANS, who presented with global developmental delay, hypotonia, minor facial anomalies, and early failure to thrive followed by childhood-onset obesity. Biochemical and radiological investigations revealed abnormalities suggestive of a lysosomal storage disorder (LSD), including persistent urinary glycosaminoglycan excretion, transiently decreased lysosomal enzyme activities, and dysostosis multiplex–like skeletal features. Comprehensive genetic testing excluded primary and secondary LSDs and identified a novel de novo heterozygous in-frame deletion in *PHIP*, classified as an ACMG class IV/V variant. Longitudinal follow-up demonstrated gradual developmental progress with emerging behavioral difficulties and progressive nephromegaly. **Conclusion:** This case report describes a novel de novo *PHIP* in-frame deletion associated with a typical CHUJANS syndrome phenotype and additional LSD–like features not previously reported in this condition; whether these findings are secondary to PHIP dysfunction or represent an independent process remains unclear and warrants further investigation.

Keywords: Chung-Jansen syndrome; CHUJANS; *PHIP*; mucopolysaccharidosis; dysostosis multiplex; case report

1. Introduction

CHUJANS is a rare disorder, most commonly resulting from a *de novo* heterozygous variant in the *PHIP* gene [1].

PHIP encodes two protein isoforms: the full-length Pleckstrin Homology Domain Interacting Protein (PHIP) and a shorter isoform lacking the C-terminal region, known as Neuronal Differentiation–Related Protein (NDRP) [2]. PHIP contains in its structure eight WD40 repeats, that form a β-propeller architecture and serve as a scaffold for protein–protein interactions, as well as two bromodomains, an insulin receptor substrate-1 (IRS-1) domain, a nuclear localization signal, and a pleckstrin homology (PH) domain–binding region [1–3]. PHIP functions as a substrate receptor of the CRL4 ubiquitin ligase complex and plays a role in ubiquitin-mediated protein degradation, replication fork stability, maintenance of genome integrity, and epigenetic regulation [3,4]. It is also involved in insulin-mediated signaling and the leptin–melanocortin pathway, providing a plausible biological basis for the overweight and obesity phenotype observed in affected individuals [3]. Although current knowledge regarding the shorter isoform, NDRP, remains limited, available data

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indicate that it may contribute to normal neurodevelopment. Based on current evidence, CHUJANS syndrome is considered to result from PHIP/DCAF14 disruption caused by *PHIP* haploinsufficiency [5].

The syndrome was first described in 2016 year by Webster et al., however the first patient with a variant in *PHIP* gene and symptoms matching CHUJANS was described in 2012 year by deLigt et al. [5,6]. Since its initial description, more than 100 individuals with *PHIP*-related disease have been reported, with an estimated 400 diagnosed worldwide (according to the patients' association website chungjansensyndrome.eu) [2,7,8]. The true incidence of CHUJANS is currently unknown; however, based on the limited number of reported cases and available cohort data, it is considered an ultra-rare neurodevelopmental disorder [2,7,8].

To date, a substantial number of *PHIP* variants have been catalogued in public databases. According to VarSome—which integrates data from UniProt, ClinVar, LOVD, MitoMap, and the published literature—over 1,000 *PHIP* variants have been classified, including approximately 190 variants interpreted as pathogenic or likely pathogenic under ACMG/AMP criteria. The majority of pathogenic and likely pathogenic variants represent loss-of-function changes, such as nonsense, frameshift, and splice-site variants, whereas missense variants constitute the largest group overall, but are predominantly classified as variants of uncertain significance [1,2,6]. In-frame deletions affecting functionally important domains of *PHIP* are rare, and their clinical interpretation remains challenging due to limited functional data and scarce genotype–phenotype correlations [2].

Clinically, CHUJANS is characterized by global developmental delay (DD) or intellectual disability (ID), behavioral abnormalities such as autistic traits, attention deficit, aggression, anxiety and social disinhibition, and a distinctive growth trajectory with childhood-onset overweight or obesity [2,6,7]. Additional features may include hypotonia, balance disturbances, hearing or visual impairment, constipation, and endocrine abnormalities [7]. Facial minor anomalies—such as thick arched eyebrows, synophrys, almond-shaped eyes, upturned nose, large ears with fleshy earlobes, as well as other mild dysmorphic features (tapered fingers, fifth finger clinodactyly, second and third toes cutaneus syndactyly) are commonly reported [1,2,6,7]. Congenital anomalies of the kidney and urinary tract (CAKUT) have also been described, whereas systemic metabolic involvement, including lysosomal dysfunction, is not regarded as a feature of the syndrome [15].

There is no specific treatment for PHIP deficiency; management remains supportive and multidisciplinary, including early developmental interventions (physical, speech, occupational therapy), behavioral/psychiatric evaluation and monitoring for obesity, endocrinology, audiology and vision.

Given that PHIP dysfunction leads to impairment of ubiquitin-dependent intracellular trafficking, protein turnover and transcriptional dysregulation, it may have broader cellular consequences, including autophagy-lysosomal axis disruption [5]. However, the potential contribution of PHIP dysfunction to lysosomal or metabolic pathways has not been investigated.

Here, we describe a child with clinical features consistent with CHUJANS and a novel *de novo* in-frame deletion in *PHIP*, who additionally exhibited biochemical and skeletal findings suggestive of LSD-like disturbance.

2. Detailed Case Description

2.1. Demographic, Prenatal, and Family History

The patient is a girl, the second child of non-consanguineous parents. She was born at term from uncomplicated pregnancy by spontaneous vaginal delivery, with a birth weight of 3560 g (appropriate for gestational age), a length of 52 cm, and a head circumference of 34 cm. Family history was unremarkable for neurodevelopmental, metabolic or genetic disorders. The patient lives with both parents and an older sister, does not attend daycare and receives early developmental intervention services.

 doi:10.20944/preprints202602.1583.v1

2.2. Early Development and Medical History

Neonatal adaptation was normal except for abnormal distortion-product otoacoustic emissions (DPOAE) screening, with subsequent confirmation of left-sided sensorineural hearing impairment. Early infancy was notable for recurrent urinary tract infections (UTIs). Feeding and early postnatal weight gain were initially appropriate. During the first year of life, DD, generalized hypotonia, and poor weight gain became evident, prompting further diagnostic evaluation.

2.3. Clinical Findings and Physical Examination

At 19 months, physical examination revealed global DD, marked hypotonia, and facial minor anomalies, including thick arched eyebrows with synophrys, almond-shaped upslanting palpebral fissures, thick eyelashes, a short, upturned nose, narrow nasal alae, and a pointed chin. Additional findings included shortened lingual frenulum, fleshy earlobes, tapering fingers with mild clinodactyly of the fourth and fifth digits, and mild bilateral syndactyly of the second and third toes. Developmentally, the child was able to sit independently but could not stand even with support and used only a few single words. Anthropometric assessment demonstrated underweight status with relatively preserved body length, narrow shoulders, reduced chest circumference, and shortened lower limbs. Chronic constipation was present.

2.4. Diagnostic Investigations

Brain and spinal cord magnetic resonance imaging with spectroscopy (MRI with MRS) revealed no abnormalities. Transthoracic echocardiography (ECHO) and resting electrocardiography (ECG) demonstrated normal cardiac anatomy and function. Ophthalmological evaluation was unremarkable. Endocrine assessment, including thyroid function, cortisol, growth hormone, insulin-like growth factor 1, and parathyroid hormone levels, showed no abnormalities. Urine organic acid analysis, plasma amino acid, acylcarnitine profiles in dried blood spot and serum transferrin isofocusing were all normal.

Abdominal ultrasonography (aUSG) demonstrated borderline splenomegaly and bilateral renal pelvic dilatation. Subsequent urological evaluation, including cystometrogram and voiding cystourethrography, was normal. Detailed diagnostic tests results are presented in Supplementary Materials, Table S1.

2.5. Lysosomal and Metabolic Investigations

Given the coexistence of DD, facial minor anomalies, and organomegaly, diagnostic evaluation for LSDs was initiated. Urinary GAG electrophoresis demonstrated persistent heparan sulfate excretion, with subsequent appearance of dermatan sulfate. Semiquantitative turbidity with cetylpyridinium chloride (CPC) testing repeatedly yielded elevated values. Enzymatic analysis using the fluorogenic derivatives of 4-methylumbelliferone as substrates demonstrated decreased activities of heparan sulfate sulfatase (MPS IIIA), α -glucosaminide N-acetyltransferase (MPS IIIC), S-glucosamine sulfatase activity (MPS IIID), slightly decreased activity of iduronate sulfatase (MPS II) and total β-glucosaminidase, with normal activity of the control enzyme - β-galactosidase. Urinary oligosaccharides and chitotriosidase activity were normal (Table 1).

Table 1. Lysosomal Diagnostic Studies.

Test name and reference range	19 months	22 months	4 years 1st test	4 years 2nd control test
Urinary GAG electrophoresis Normal: chondroitin sulfate or no bands	Chondroitin sulfate, Heparan sulfate (subtle band) ---------- Abnormal, suggestive of MPS	Chondroitin sulfate, Heparan sulfate (subtle band) ---------- Abnormal, suggestive of MPS	Chondroitin sulfate, Heparan sulfate (subtle band) ---------- Abnormal, suggestive of MPS	Chondroitin sulfate, Heparan sulfate (subtle band), Dermatan sulfate (subtle band) ----------

 doi:10.20944/preprints202602.1583.v1

				Abnormal, suggestive of MPS
Semiquantitative turbidity test (STT) (mg/g creatinine) Reference range: 116 +/- 70	235 ---------- Elevated, suggestive of MPS	206 ---------- Elevated, suggestive of MPS	559 ---------- Elevated, suggestive of MPS	183 ---------- upper normal limit, suggestive of MPS
Lysosomal enzymatic studies				
Heparan sulfate sulfatase activity (MPS IIIA) (nmol/mg protein/18h) Reference range: 4.1 +/- 1.4	1.1 ---------- Decreased to 40% of LNL	1.3 ---------- Decreased to 48% of LNL	3.52 ---------- Normal	-
α -glucosaminidase activity (MPS IIIB) (nmol/ml/42h) Reference range: 464-2490	1341 ---------- Normal	1194 ---------- Normal	-	-
α -glucosaminide N-acetyltransferase	6,5	-	15,4	-

GAG – glycosaminoglycans, MPS – muopolysaccharidosis, LNL – lower normal limit.

Skeletal radiographs revealed changes resembling dysostosis multiplex, including a J-shaped sella turcica, *coxa valga*, irregular contours of the distal radial metaphyses, and bilateral hip subluxation (Figure 1); however, several hallmark features of classical dysostosis multiplex, were absent (Table 2).

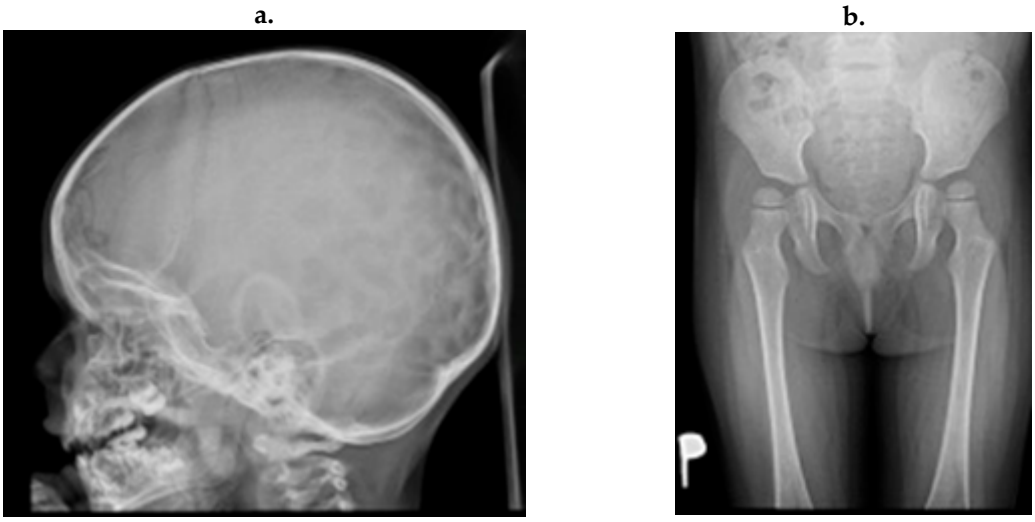

Figure 1. Skeletal X-ray at the age of 19 months: 2a. J-shaped sella turcica, 2b. bilateral coxa valga with signs of hip joint subluxation.

Table 2. Classical radiological features of dysostosis multiplex and findings observed in the present case.

Skeletal region	Typical features of dysostosis multiplex	Findings in the presented patient
Skull	J-shaped sella turcica, thickened calvaria	J-shaped sella turcica present
Spine	Platyspondyly, anterior vertebral beaking, kyphosis or scoliosis	Not observed

 doi:10.20944/preprints202602.1583.v1

Thorax	Oar-shaped ribs, narrowed thoracic cage	Not observed
Pelvis	Flared iliac wings, shallow acetabula	Coxa valga, bilateral hip subluxation
Long bones	Shortened diaphyses, irregular metaphyses	Irregular contours of distal radial metaphyses
Hands	Proximally pointed metacarpals, short and broad phalanges	Not observed
Lower limbs	Genu valgum, joint stiffness	Genu valgum present
Overall skeletal growth	Short stature, disproportional skeletal development	Normal height with disproportionate skeletal features

2.6. Genetic Testing

Initial next-generation sequencing (NGS) panel testing for RASopathies and Cornelia de Lange syndrome and targeted *SGSH* sequencing revealed no pathogenic or likely pathogenic variants consistent with the phenotype. Array comparative genomic hybridization (aCGH) yielded normal results.

Exome sequencing (ES) (GRCh38, mean coverage 20x–98.1%) identified a novel heterozygous in-frame deletion in *PHIP* c.[1529_1546del], p.(Glu510_Gly515del). This variant and its *de novo* origin was confirmed by Sanger sequencing of the patient and her parents. The nomenclature of molecular variant follows the Human Genome Variation Society guidelines (HGVS, http://varnomen.hgvs.org/) using MANE select human *PHIP* reference sequence: NM_017934.7 (for cDNA) and NP_060404.4 (for protein). The variant was absent from population databases, including gnomAD and affected a highly conserved region within the WD40/YVTN-like repeat domain/PH-interacting protein (Conservation PhyloP100 score: 9.46). Notably, a pathogenic missense variant affecting one of these residues (c.1541A>G, p.(His514Arg)) has been reported previously in ClinVar. According to ACMG criteria (PM1, PM2, PM5, PS2, PP3), the variant was classified as ACMG class IV/V. Due to the size of the variant (18-nucleotide in-frame deletion), several commonly used in silico predictors were not applicable to this type of sequence change. Therefore, pathogenicity assessment was supported using designed to evaluate larger in-frame deletions in silico algorithm MutationTaster, which qualified this variant as likely pathogenic. No additional variants of potential clinical relevance were identified.

2.7. Clinical Course and Follow-Up

Developmental progress was gradual. The patient achieved supported standing at 22 months and independent walking at 2.5 years of age, with a broad-based gait with balance disturbances during rapid directional changes. Speech development remained delayed. All previously present facial anomalies and other dysmorphic features became more evident (Figure 2). On neurological assessment hyperreflexia, bilateral Babinski sign and bilateral *genu valgum* were found. Behavioral features included irritability, social disinhibition, and sleep disturbances. Throughout the observation period, follow-up urinary GAGs excretion showed a persistent presence of a heparan sulfate band and an additional dermatan sulfate band in the most recent analysis. The results of a semiquantitative turbidity test remained elevated, while control lysosomal enzyme activities, initially decreased at 19 and 22 months of age, had normalized by the most recent follow-up visit at 4 years.

Follow-up aUSG revealed progressive nephromegaly without evidence of functional renal impairment, without other organomegaly. Cardiac ECHO as well as ophtalmological evaluation remained normal. Growth trajectory evolved from early failure to thrive to overweight by 4 years of age (body mass index >99th percentile), with normal height and head circumference. At the most recent follow-up, the patient remained clinically stable, with preserved organ function and ongoing developmental support.

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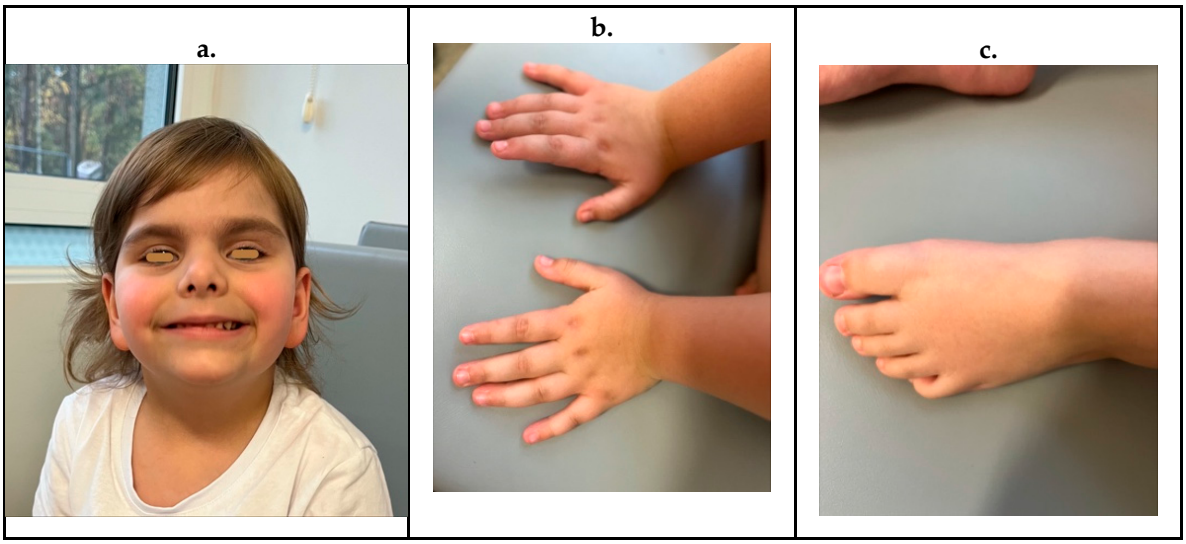

Figure 2. Patient's dysmorphic features at the age of 4 years 1a. Facial dysmorphy: thick, arched eyebrows with synophrys, almond-shaped, slightly upward-slanting eyes with thick eyelashes, short, upturned nose with narrow nasal alae, pointed chin, large ears with fleshy earlobes. **1b.** Tapering fingers, mild 4th and 5th finger clinodactyly. **1c.** Mild cutaneus 2-nd and 3-rd toe syndactyly.

Written informed consent was obtained from the patient's legal guardians for publication of this images.

2.8. Therapeutic Interventions

Due to persistent failure to thrive and a short lingual frenulum, a frenotomy was performed at 19 months of age, resulting in sustained improvement in feeding and oral intake. Concurrently, prophylactic treatment for chronic constipation (macrogols) and recurrent UTIs (furazidin) was initiated. Following the introduction of these interventions, no further UTI were reported. The patient has remained under multidisciplinary care, including speech therapy, physical rehabilitation, and regular neurological and psychological follow-up. Ongoing nephrological supervision has been provided due to progressively increasing kidney size observed on follow-up imaging, although renal function has remained preserved. Additionally, the patient is followed by a dietitian to monitor growth parameters and manage the evolving pattern of weight.

4. Discussion

In this report, we present a patient with a novel *de novo* in-frame deletion in the *PHIP* gene, identified during diagnostic ES. Based on in silico analysis using MutationTaster, the variant was predicted to be likely pathogenic. Applying ACMG/AMP criteria, including its *de novo* occurrence, absence from population databases, and location within a conserved and functionally relevant WD40 domain encompassing an amino acid residue previously affected by a pathogenic missense variant, the variant was classified as an ACMG class IV/V. At the molecular level, interpretation of the identified in-frame deletion can be informed by the structural organization of PHIP. WD40/YVTN repeat domains adopt a β-propeller architecture in which each repeat contributes to a single structural "blade," forming a platform for protein–protein interactions [20]. Alterations affecting the length of individual repeats, such as in-frame deletions, may influence local blade architecture and potentially affect domain conformation or interaction capacity [20]. Despite suggested classification and structural considerations, the lack of functional validation necessitates cautious interpretation of its pathogenic relevance. However, the patient described in this report presented with a clinical phenotype highly consistent with CHUJANS, including characteristic facial anomalies and minor dysmorphic features, global developmental delay, hypotonia, balance disturbances, behavioral abnormalities and a distinctive growth trajectory with childhood-onset overweight. These features

 doi:10.20944/preprints202602.1583.v1

are well aligned with previously published CHUJANS cohorts and support the clinical relevance of the identified novel *PHIP* variant [4,7].

Interestingly, in addition to these core CHUJANS manifestations, the patient exhibited biochemical abnormalities suggestive of LSD-like dysfunction, including persistent urinary GAG excretion and transient reduction in lysosomal enzyme activities. Such symptoms have not been described to date; however, the available literature also does not indicate whether the reported patients were evaluated in this regard. Moreover, beyond biochemical findings, subtle organ-level LSD-like manifestations, including progressive nephromegaly and skeletal abnormalities resembling dysostosis multiplex, were present in our patient. Regarding the urinary system, CAKUT has been reported to date, and was also initially observed in our patient (mild pelvicalyceal dilatation); however, renal enlargement has never been described [15]. Hypothetically persistent urinary excretion of heparan and dermatan sulfate could reflect subclinical accumulation within renal tubular cells, whereas altered lysosomal GAG handling in bone and cartilage could contribute to the observed skeletal changes. These manifestations conceptually resemble features of secondary lysosomal disorders, such as mucopolysaccharidosis-plus syndrome (MPSPS, OMIM #617303), although the clinical severity and progression in our patient were substantially milder [16,18,19].

As LSD-like findings are not considered defining features of CHUJANS, their presence necessitates cautious interpretation. In the absence of functional validation, a direct causal relationship between the identified *PHIP* variant and the LSD–like abnormalities cannot be conclusively established, and alternative explanations must therefore be considered. These include secondary metabolic disturbances, preanalytical variability in biochemical assays, or the presence of an additional undetected genetic condition. However, the persistence of abnormal urinary GAG excretion and associated biochemical findings across multiple independently collected samples over more than two years of follow-up argues against a purely preanalytical or transient laboratory artifact. Recurrent UTIs are known to cause false-positive or transient elevations of urinary GAGs; nevertheless, this explanation is unlikely in the present case, as infections resolved early in life and routine urinalyses obtained concurrently with GAG measurements remained normal [13,14]. Furthermore, limitations inherent to exome sequencing—particularly reduced sensitivity for deep intronic, regulatory, or structural variants—must be acknowledged and further support a cautious and conservative interpretative approach.

However, a biologically plausible link between PHIP dysfunction and secondary lysosomal abnormalities can be proposed. PHIP functions as a substrate receptor of the CRL4 ubiquitin ligase complex and participates in ubiquitin-mediated protein regulation and intracellular trafficking. Ubiquitination serves, among other functions, as a key signal for targeting proteins to the lysosome for degradation [9–11]. Partial disruption of ubiquitin-dependent trafficking pathways may therefore indirectly impair endosomal–lysosomal homeostasis without resulting in a primary lysosomal enzyme deficiency. Interestingly, our patients biochemical profile was characterized by selective abnormalities in GAG metabolism—predominantly involving heparan sulfate, with later emergence of dermatan sulfate—while urinary oligosaccharides and chitotriosidase activity remained normal. This pattern likely reflects differences in degradation pathways and may support discussed hypothesis. GAGs are long, highly sulfated polysaccharides requiring coordinated lysosomal enzymatic cascades and precise intracellular trafficking for complete degradation, rendering them particularly vulnerable to partial disturbances in lysosomal homeostasis. Especially heparan sulfate metabolism is tightly linked to cellular signaling and endocytosis pathways that depend on ubiquitin-mediated trafficking. In contrast, oligosaccharides are shorter and degraded through more redundant metabolic routes, which may explain their preserved metabolism in this patient. Similar patterns of secondary lysosomal involvement have been described in genetic disorders not primarily classified as LSD [12,16]. The persistence of abnormal urinary GAG excretion despite normalization of lysosomal enzyme activities further supports the interpretation of a secondary rather than primary lysosomal disturbance. At this interface between ubiquitin-mediated trafficking and lysosomal metabolism, PHIP dysfunction may intersect with pathways involved in GAG processing, although

 doi:10.20944/preprints202602.1583.v1

this relationship has not been systematically investigated. Furthermore, PHIP role in replication fork stability, genome integrity and epigenetic regulation can affect proper genes expression, including those involved in lysosomal biogenesis and metabolic regulation [2,3,10,16].

In summary, this case highlights the phenotypic complexity of *PHIP*-related Chung–Jansen syndrome and underscores the diagnostic challenges posed by overlapping neurodevelopmental, metabolic, and dysmorphic features. Although the identified *PHIP* in- frame deletion is consistent with the clinical diagnosis of CHUJANS, the accompanying LSD–like findings cannot be definitively attributed to *PHIP* dysfunction and should be interpreted with caution. Nevertheless, the recurrent and persistent nature of biochemical abnormalities suggests a non-random association that warrants attention. Recognition of such atypical findings may help avoid misdiagnosis as a primary LSD and emphasizes the importance of integrated genomic, biochemical, and longitudinal clinical assessment. Further studies incorporating functional analyses and systematic evaluation of lysosomal biomarkers in larger CHUJANS cohorts will be essential to clarify whether secondary lysosomal disturbances represent a recurring modifier of *PHIP* haploinsufficiency or reflect individual, coincidental findings.

6. Conclusions

We report a case of CHUJANS associated with a novel *de novo* in-frame deletion in the *PHIP* gene. Although a causal relationship between the *PHIP* variant and additional LSD-like findings cannot be established, this case underscores the importance of careful interpretation of atypical metabolic features in patients with neurodevelopmental syndromes. Further functional and cohort-based studies are required to clarify whether such abnormalities represent secondary manifestations of *PHIP* haploinsufficiency or individual variability.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org; Table S1: Timeline; Table S2: Diagnostics.

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Informed Consent Statement: Written informed consent has been obtained from the patients' legal guardians to publish this paper and any potentially identifiable images or data included in this article.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflicts of Interest: The authors declare no conflicts of interest.

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