RESEARCH PAPER

Genetically Confirmed Weill–Marchesani Syndrome Type 4 With Bilateral Ectopia Lentis and Glaucomatous Changes in a 12-Year-Old Male: A Comprehensive Environmental and Clinical Analysis

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ABSTRACT
Background: Weill–Marchesani Syndrome Type 4 (WMS4) is an uncommon connective tissue disorder caused by pathogenic variants in the ADAMTS17 gene. It predominantly affects the ocular system but may also involve cardiovascular, skeletal, and neurological components. Although primarily a genetic condition, environmental factors—including maternal nutrition, teratogenic exposure, and epigenetic modifiers—may alter phenotypic expression.
Case Presentation: A 12-year-old male presented with gradual, painless bilateral defective vision. Ocular examination revealed superior-nasal lens subluxation, optic disc cupping, and characteristic visual field defects. Systemic evaluations showed trivial tricuspid regurgitation and EEG evidence of epileptiform discharges. Genetic analysis confirmed a homozygous likely pathogenic variant in ADAMTS17 consistent with WMS4, and a heterozygous NR2E3 variant associated with enhanced S-cone syndrome without clinical manifestation.
Management: The patient was started on topical dorzolamide–timolol for intraocular pressure control and was advised multidisciplinary follow-up.
Conclusion: This case highlights the complexity of WMS4 and the importance of early ocular screening, genetic diagnosis, and awareness of environmental modifiers that may influence phenotypic severity.
Keywords:Weill–Marchesani Syndrome; ADAMTS17; Ectopia Lentis; Lens subluxation; Pediatric ophthalmology; Environmental modifiers; Genetic disorders; Case report...
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INTRODUCTION

Weill–Marchesani Syndrome (WMS) is a rare connective tissue disorder characterized by microspherophakia, lens subluxation, short stature, and brachydactyly. Among its subtypes, Weill–Marchesani Syndrome Type 4 (WMS4) is caused by homozygous pathogenic variants in the *ADAMTS17* gene, which plays an essential role in extracellular matrix organization and zonular fiber stability. Disruption of this protein predisposes affected individuals to ectopia lentis, most typically in a superior or superonasal direction (1,2). Secondary complications such as pupillary block and glaucoma significantly contribute to visual

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morbidity, emphasizing the need for early identification and treatment.

Although genetically determined, variability in disease expression among WMS4 patients suggests modifying influences from the environment, including maternal nutrition, oxidative stress, endocrine disruptor exposure, and socio-cultural factors such as consanguinity (3,4). Consanguineous marriages increase the likelihood of homozygosity for recessive pathogenic variants, making them an important environment-linked factor that shapes disease patterns in certain populations. Environmental ophthalmology is an emerging field that examines these interactions between genetics and environmental exposures during critical developmental windows. The present case describes a child with genetically confirmed WMS4, highlighting classical ocular findings, systemic evaluation results, EEG abnormalities, and environmental factors. This case underscores the importance of integrating clinical, genetic, and environmental perspectives to understand the full spectrum of WMS4.

This case is unique due to the presence of early glaucomatous optic neuropathy despite borderline intraocular pressure levels, along with associated epileptiform activity and a heterozygous NR2E3 mutation without phenotypic expression. The inclusion of environmental and socio-cultural factors further distinguishes this case by highlighting genotype–phenotype variability.

Case Presentation

A 12-year-old male presented with gradual, painless bilateral defective vision over several months. No photophobia, glare, floaters, flashes, or halos were reported. There was no history of trauma, ocular surgery, or systemic illness. The child was born via LSCS with a birth weight above 2.5 kg, cried immediately after birth, and did not require neonatal intensive care. Family history revealed consanguinity. His diet, sleep, and bowel and bladder habits were normal. He exhibited normal-variant short stature and brachydactyly.

Ocular examination revealed full extraocular movements and orthophoria. Anterior segment evaluation noted bilateral superonasal lens subluxation, persistent pupillary membrane, and Grade 3 vitreous haze. Intraocular pressures measured 20 mmHg in both eyes but interpretation required caution due to markedly increased central corneal thickness (637 µm OD and 612 µm OS). Axial lengths were normal. Fundus evaluation showed optic disc cupping of 0.8:1 with corresponding retinal nerve fiber layer thinning. Visual field testing demonstrated inferior arcuate and Seidel's scotomas in the right eye and double arcuate scotomas in the left eye. Systemic evaluation revealed no overt syndromic features apart from short stature. Echocardiography revealed situs solitus, trivial tricuspid regurgitation, intact septae, and normal cardiac function. EEG showed epileptiform activity. Genetic testing confirmed a homozygous likely pathogenic *ADAMTS17* variant diagnostic of WMS4 and a heterozygous *NR2E3* pathogenic variant without clinical phenotype. The patient was diagnosed with WMS4 and started on dorzolamide–timolol combination therapy. The family received genetic counseling.

Results

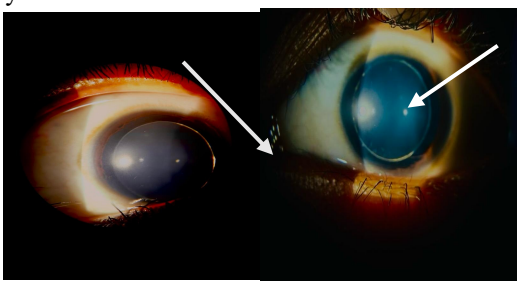
The patient showed prominent ophthalmic abnormalities consistent with WMS4, including bilateral superonasal lens subluxation, increased corneal thickness, optic nerve cupping, and visual field loss. Table 1 summarizes these ocular findings.

Table 1. Ocular Findings of the Patient

Parameter	Right Eye	Left Eye
Lens position	Superonasal subluxation	Superonasal subluxation
Intraocular pressure	20 mmHg	20 mmHg
Central corneal thickness	637 µm	612 µm
Axial length	21.7 mm	22.0 mm
Optic disc cupping	0.8:1	0.8:1
RNFL thinning	Superior & inferior	Superior, inferior & temporal
Visual field defects	Inferior arcuate & Seidel's scotoma	Double arcuate scotomas
Additional findings	Persistent pupillary membrane, VH Grade 3	Persistent pupillary membrane, VH Grade 3

Table 1 summarizes the detailed ocular findings of the patient and highlights the classical ophthalmic manifestations of Weill–Marchesani Syndrome Type 4. The bilateral superonasal lens subluxation reflects the hallmark zonular instability associated with *ADAMTS17* dysfunction. Although intraocular pressure measurements were within the upper-normal range, their interpretation is limited by the significantly increased central corneal thickness, which can lead to underestimation of true pressure. Optic disc cupping and RNFL thinning were evident, with corresponding visual field defects indicative of early glaucomatous neuropathy. Additional anterior segment observations such as persistent pupillary membrane and vitreous haze further support the diagnosis of a connective tissue–related lens pathology.

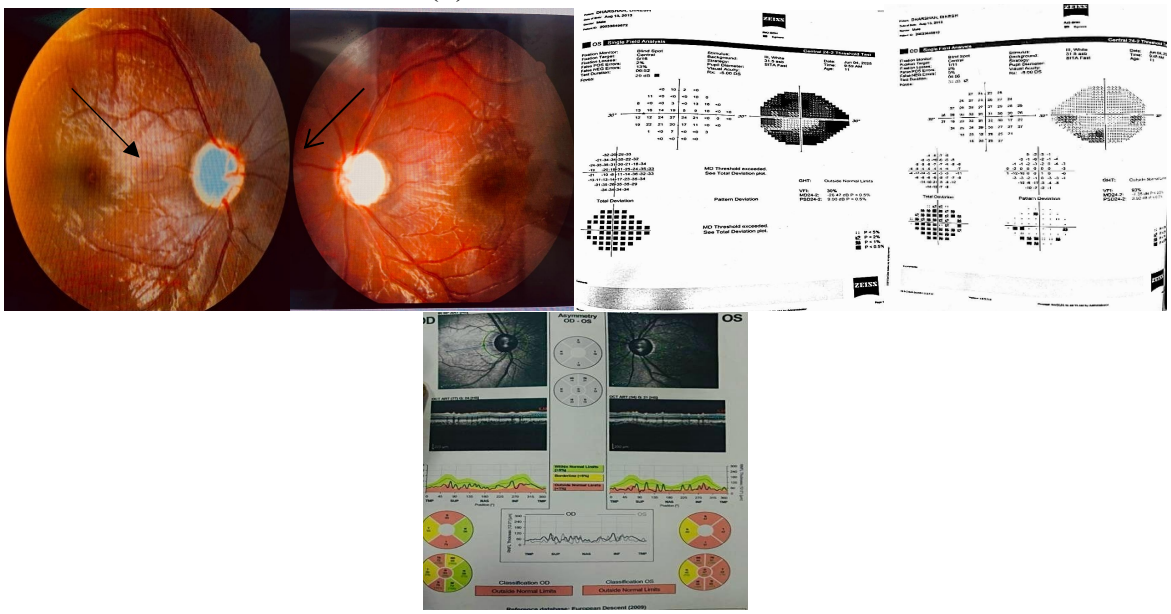
Figure 1. Slit-lamp photograph showing bilateral superonasal lens subluxation (white arrow) with zonular weakness. Persistent pupillary membrane is also noted .



OD: Right eye; **OS:** Left eye.

Figure 2. Fundus photograph demonstrating optic disc cupping (cup–disc ratio ~0.8:1) with thinning of the neuroretinal rim suggestive of glaucomatous optic neuropathy (A)and visual field defects(B),OCT-RNFL shows thinning in both eyes(C).

(A)FUNDUS PHOTOGRAPHY **(B)PERIMETRY**



(C)OCT -RNFL

Figure 3. Brachydactyly-normal variant short stature

Systemic and genetic assessment revealed abnormalities significant for diagnosis and prognosis. These are summarized in Table 2.

Table 2. Systemic and Genetic Findings

Domain	**Findings**
Birth history	LSCS, birth weight >2.5 kg, no NICU stay
Growth pattern	Normal-variant short stature
Cardiovascular evaluation	Situs solitus, levocardia, trivial TR, LVEF 67%, no structural defects
Neurological evaluation	EEG with lateral sharp & slow waves (epileptiform activity)
Musculoskeletal	Brachydactyly, no joint stiffness
Genetic mutations	Homozygous *ADAMTS17* (WMS4), heterozygous *NR2E3* (ESCS carrier)

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Environmental/socio-cultural factor	Positive history of consanguinity

Table 2 presents the systemic and genetic characteristics of the patient, demonstrating the broader clinical context of WMS4. Birth and growth patterns were normal except for short stature, consistent with reported phenotypes. Cardiovascular evaluation revealed only trivial tricuspid regurgitation, supporting the known limited cardiac involvement in WMS4. EEG findings of epileptiform discharges suggest potential neurological associations or additional genetic modifiers. The homozygous *ADAMTS17* mutation confirms Weill–Marchesani Syndrome Type 4, while the heterozygous *NR2E3* variant indicates carrier status for Enhanced S-Cone Syndrome without phenotypic expression. The presence of consanguinity highlights a key environmental–cultural factor contributing to autosomal recessive disease occurrence.

Discussion

This case demonstrates the characteristic ocular and systemic features associated with Weill–Marchesani Syndrome Type 4, emphasizing the role of *ADAMTS17* mutations in zonular weakness leading to superonasal lens subluxation (1,2). The patient showed early glaucomatous damage with optic disc cupping and visual field defects despite only mildly elevated IOP readings, which were likely underestimated due to markedly thick corneas (3). This highlights the importance of careful interpretation of IOP in pediatric patients with connective tissue disorders.

The severity of ocular findings and the presence of neurological abnormalities suggest potential modifying influences beyond the primary mutation. Environmental, epigenetic, and socio-cultural factors may impact phenotypic expression, particularly in populations with high consanguinity rates. Consanguinity increases homozygosity for recessive pathogenic variants and remains an important environmental–social determinant of genetic disease distribution (3). Emerging research also suggests that environmental exposures—including oxidative stress, micronutrient deficiencies, and endocrine-disrupting chemicals—may influence extracellular matrix homeostasis and connective tissue development, potentially altering disease manifestation or progression (4).

The normal cardiac findings are consistent with prior studies showing less cardiovascular involvement in WMS4 compared to other connective tissue disorders. The incidental finding of epileptiform activity raises questions about broader multisystem involvement or additional genetic interactions. A multidisciplinary approach is essential for management, including ophthalmology, clinical genetics, cardiology, and neurology. Early diagnosis, regular intraocular pressure monitoring, and timely intervention for lens subluxation and glaucoma are critical to preserving vision.

Conclusion

This case highlights the classical ocular features, systemic characteristics, and genetic confirmation of Weill–Marchesani Syndrome Type 4 in a 12-year-old male. The interplay between genetic mutations and environmental influences—including consanguinity—likely contributed to the disease expression. Early detection and comprehensive evaluation are essential to minimize the risk of irreversible visual loss. This case reinforces the importance of integrating environmental and genetic perspectives in the diagnosis and management of rare pediatric ophthalmic disorders.

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