· Basic Research ·

A novel compound heterozygous mutation in *ADAMTS17* identified in a Chinese family with Weill-Marchesani syndrome

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Abstract

● **AIM:** To investigate the genetic basis of Weill-Marchesani syndrome (WMS) in a Chinese family and clarify the pathogenic mechanism of novel *ADAMTS17* mutations.

● **METHODS:** Comprehensive clinical assessments and genetic analyses were performed on a Chinese family with two affected siblings. Whole-exome sequencing (WES) was conducted for the proband and other family members. Bioinformatics tools were used to evaluate the conservation, predicted pathogenicity, and structural effects of the identified *ADAMTS17* variants. In addition, protein structure modeling was applied to assess the functional impacts of the mutations.

● **RESULTS:** The proband (a 32-year-old male) and his elder sister (42y) presented typical clinical features of WMS, including short stature, brachydactyly, high myopia, ectopia lentis, and secondary glaucoma. WES identified a novel compound heterozygous mutation in *ADAMTS17*: a splicing mutation (c.451-2A>G) inherited from the father and a missense mutation (c.1043G>A; p.C348Y) inherited from the mother. The splicing mutation disrupted normal mRNA splicing and processing, leading to premature translation termination. The missense mutation, which is located in the metalloprotease catalytic domain, was predicted to abolish a critical disulfide bond, thereby impairing protein stability. Both mutations exhibited high evolutionary conservation and were predicted to be pathogenic by multiple bioinformatics algorithms.

● **CONCLUSION:** A novel compound heterozygous mutation in *ADAMTS17* is identified in this WMS-affected Chinese family, and its pathogenicity is verified *via* bioinformatics analysis and protein structural modeling. These findings are expected to facilitate the genetic diagnosis of WMS and deepen the understanding of its molecular pathogenesis.

● **KEYWORDS:** Weill-Marchesani syndrome; ADAMTS17; compound heterozygous mutation; molecular genetics; bioinformatics

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INTRODUCTION

Weill-Marchesani syndrome (WMS) is a rare genetic disorder affecting connective tissue, with symptoms typically emerging in childhood. The syndrome is characterized by short stature, carpal bone dysplasia (brachydactyly of the fingers and toes), joint stiffness, and ocular abnormalities such as microspherophakia, ectopia lentis, high myopia, and glaucoma, which may also be accompanied by cardiac anomalies[1]. These conditions can cause severe visual impairment and, in some cases, even blindness. The genetic basis of WMS is complex and heterogeneous, involving mutations in multiple genes. The most commonly associated genes include *ADAMTS10*, *FBN1*, *ADAMTS17*, and *LTBP2*. Among them, *ADAMTS10* and *ADAMTS17*, as key ADAMTS metalloproteinases, play essential roles in the formation and remodeling of the extracellular matrix (ECM). Mutations in these two genes may lead to abnormalities in fibrillin microfibril formation and function, aberrant ECM protein deposition, and potential disruptions in other signaling pathways, thereby contributing to the pathogenesis of WMS[2]. The *FBN1* gene encodes fibrillin-1, a key structural protein essential for the formation and integrity of connective tissues. Mutations in *FBN1* can disrupt the interaction between microfibrils and elastin, thereby impairing elastic fiber formation and leading to ocular, cardiovascular, and skeletal abnormalities, which are hallmark features of WMS[3]. LTBP2 is an ECM protein that plays a critical role in ECM structure and function and may influence transforming growth factor (TGF)-β activity. Mutations in LTBP2 may disrupt microfibril formation and stability, as well as lead to TGF-β signaling dysregulation, ultimately resulting in ECM structural and functional abnormalities and contributing to WMS pathogenesis[4]. Previous studies have indicated that FBN1-related WMS follows an autosomal dominant inheritance pattern, whereas ADAMTS10, ADAMTS17, and LTBP2-related WMS exhibit an autosomal recessive mode of inheritance. Here, we pinpointed a novel compound heterozygous mutation in *ADAMTS17*, comprising a splicing mutation passed down from the father and a missense mutation inherited from the mother, leading to WMS pathogenesis.

PARTICIPANTS AND METHODS

Ethical Approval This study followed the principles of the Declaration of Helsinki, and it was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No.XJTU1AF2024LSYY-270). Informed consent was obtained from all individual participants included in the study. The authors affirm that human research participants provided informed consent for publication of the images in this study.

Patients and Clinical Evaluation Detailed medical histories were collected from the patient and family members, along with comprehensive ophthalmic examinations to support the diagnosis of WMS. Ophthalmic evaluations included visual acuity assessment (Snellen chart), intraocular pressure measurement (Goldmann applanation tonometry), slit-lamp and fundoscopic examination, corneal endothelial cell counting, B-scan ultrasonography, ophthalmic biometer (IOLMaster 700), and optical coherence tomography of the optic nerve head (ONH-OCT), macula (Macular OCT), and anterior segment (AS-OCT), all performed using the Cirrus HD-OCT 5000.

WES and Sanger Validation Peripheral venous blood samples were obtained from family members for DNA extraction and genotyping. Probe hybridization technology was used to capture and enrich the exons of target genes, approximately 20 base pairs of adjacent splice regions, and the complete mitochondrial genome sequence. After quality control, high-throughput sequencing was performed on these enriched genes. Additionally, genetic validation was conducted for other family members based on the selected mutation sites.

Bioinformatics Analysis The wild-type ADAMTS17 protein sequence was retrieved from the National Center for Biotechnology Information (NCBI, https://www.ncbi.nlm.nih.gov/), and the mutated amino acids in ADAMTS17 were modified manually. The Clustal Omega online tool

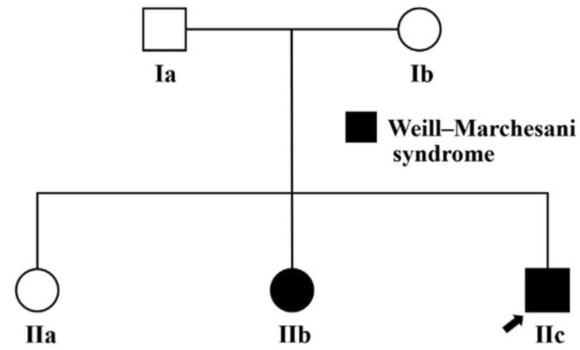

Figure 1 Pedigree of the family Individual IIc is the proband, and both IIc and his sister (IIb) are affected members of the family.

(https://www.ebi.ac.uk/jdispatcher/msa/clustalo) was used to align ADAMTS17 protein sequences from different species to determine the conservation of the mutation site. The DANN, SIFT, and PolyPhen tools were used to predict the functional impact of ADAMTS17 mutations. The three-dimensional structure of ADAMTS17 was modeled using AlphaFold (https://alphafoldserver.com/). Splicing mutation prediction was performed using the RDDC database (https://rddc.tsinghua-gd.org/). The Swiss-Model tool (https://www.swissmodel.expasy.org/) was employed for structural modeling of the mutated ADAMTS17 protein, and PyMol was used for visualization of both wild-type and mutant protein structures. The two-dimensional schematic representation of the ADAMTS17 protein was generated using Illustrator for Biological Sequences (IBS, version 2.0)[5]. The amino acid sequence of ADAMTS17 was retrieved from the NCBI database and imported into IBS. Based on the annotated functional domains obtained from the UniProt database (UniProt ID: Q8TE56; https://www.uniprot.org/), the protein structure was manually illustrated. The schematic was subsequently refined for clarity and consistency in presentation.

RESULTS

Clinical Manifestations Figure 1 illustrates the family pedigree. The 32-year-old male proband (IIc) presented on February 19, 2018, with a one-day history of acute right eye pain, blurred vision, and headache. The proband had a history of bilateral high myopia but no known family history of glaucoma. Clinical examination revealed severe visual impairment in the right eye, elevated intraocular pressure, ciliary injection, and corneal edema. The right pupil was dilated and non-reactive to light. After anterior chamber paracentesis and aqueous humor drainage, the cornea gradually became clear. The lack of the lens within the pupillary region and a normal anterior chamber depth (Figure 2A) suggested that the acute glaucoma attack was likely secondary to lens dislocation. Although the left eye had poor visual acuity, intraocular pressure was normal, the cornea was clear, and anterior chamber depth was within normal

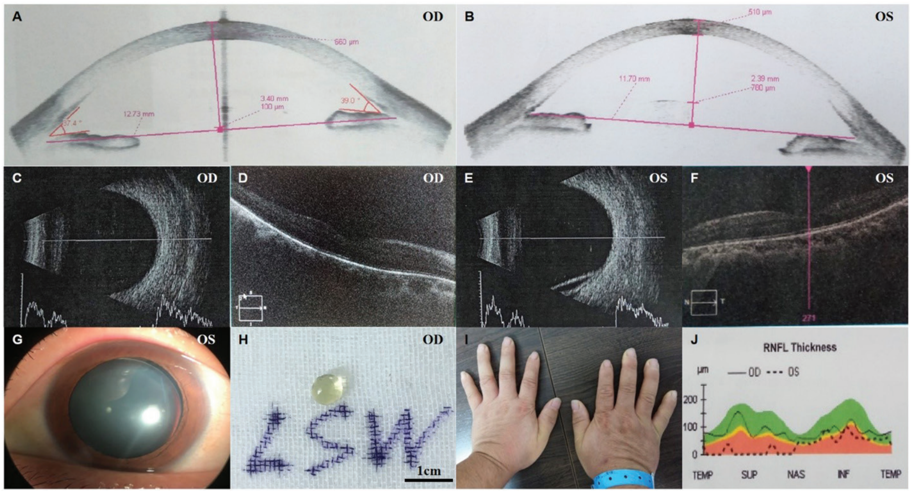

Figure 2 Main clinical findings A: AS-OCT of the proband's right eye; B: AS-OCT of the proband's left eye; C: Ultrasonography of the proband's right eye; D: Macular OCT of the proband's right eye; E: Ultrasonography of the proband's left eye; F: Macular OCT of the proband's left eye; G: Fundus photograph of the proband's left eye; H: Intraoperatively extracted lens from the proband's right eye, showing a spherical shape (diameter≈6.5 mm); I: Brachydactyly observed in the proband; J: ONH-OCT of the proband. AS-OCT: Anterior segment optical coherence tomography; ONH-OCT: Optic nerve head optical coherence tomography.

Table 1 Clinical information of patients

Characteristic	IIb	IIc (proband)
Gender	Female	Male
Age (y)	42	32
Best corrected vision (R/L)	Hand move/Hand move	Hand move/0.06
The highest intraocular pressure (R/L, mm Hg)	16/17	T+2/24
Axial length (R/L, mm)	31.09/31.03	30.63/29.68
Central corneal thickness (R/L, μm)	552/629	544/534
Anterior chamber depth (R/L, mm)	2.47/2.33	NA/3.10
Lens thickness (R/L, mm)	5.65/NA	NA/5.80
Cup/disc ratio (R/L)	NA/NA	NA/0.6
Secondary glaucoma and lens dislocation	Happened	Happened
Myopia (R/L, diopter)	NA/NA	-18.00/-18.00
Other ocular history	Choroidal Neovascularization in right eye	Retinal tear and retinal detachment in left eye
Cardiac anomalies	No	No

R: Right eye; L: Left eye; NA: Not available.

limits (Figure 2B). The pupil was responsive to light, and partial lens subluxation was observed (Figure 2G). ONH-OCT suggested optic atrophy due to chronic secondary glaucoma (Figure 2J). B-scan ultrasonography revealed excessive axial length in both eyes (Figures 2C, 2E). Fundoscopic examination revealed rhegmatogenous retinal detachment in both eyes (Figures 2D, 2F). Postoperatively, the right eye's visual acuity improved to 0.8, indicating that lens extraction effectively alleviated symptoms and suggesting a lens-related etiology. Upon inquiry, the proband's elder sister (IIb) reported experiencing progressive bilateral visual deterioration for over ten years, with a history of high myopia since childhood. Specialized ophthalmic examination revealed severe visual impairment in both eyes, with normal intraocular pressure. Both eyes exhibited lens tremors and nuclear cataracts, with spherophakic lenses. Post-dilation examination revealed partial lens subluxation exceeding 180°. Fundus examination showed a tigroid fundus, peripapillary atrophy, and an unclear foveal reflex. After bilateral lens extraction and intraocular lens implantation surgery (Figure 2H), her vision significantly improved. Clinical information is summarized in Table 1. Both the proband and his elder sister exhibited short stature and brachydactyly (Figure 2I). Based on their clinical presentation, a diagnosis of WMS was confirmed. No significant history of cardiovascular disease was reported within the family.

Genotyping WES identified a compound heterozygous mutation in *ADAMTS17* in the proband. A splicing mutation (c.451-2A>G) was identified at the 3' splice site of exon 3 in *ADAMTS17*. This variant disrupts normal mRNA splicing, potentially resulting in an aberrant or nonfunctional protein.

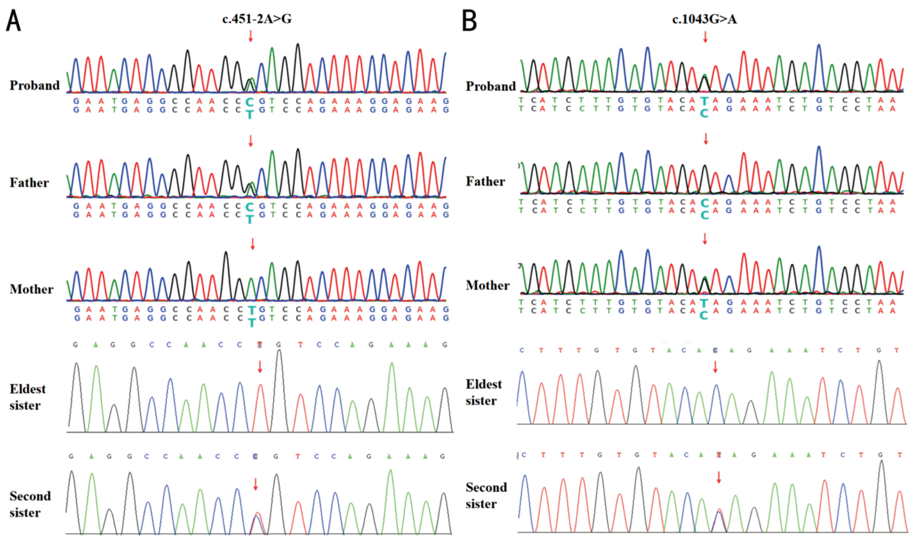

Figure 3 Sequencing chromatograms for all members of the WMS family A: Identification of the *ADAMTS17* splicing variant (c.451-2A>G) by Sanger sequencing. The proband, the father and the second sister: hemizygous variant; the mother and the eldest sister: no variant. B: Identification of the *ADAMTS17* missense variant (c.1043G>A) by Sanger sequencing. The proband, the mother and the second sister: hemizygous variant; the father and the eldest sister: no variant. WMS: Weill-Marchesani syndrome.

Furthermore, this mutation was not found in the Chigene database, the Exome Aggregation Consortium (ExAC), the 1000 Genomes Project (1000G), or the Genome Aggregation Database (gnomAD). Additionally, the variant was consistent with the clinical phenotype observed in this case. Therefore, according to the American College of Medical Genetics and Genomics (ACMG) guidelines for pathogenicity assessment, this mutation is classified as likely pathogenic. Additionally, a missense mutation (c.1043G>A) was detected in exon 7, forming a compound heterozygous mutation with c.451-2A>G. This mutation resides in the metalloproteinase catalytic domain, a region implicated in various diseases, including ocular disorders. Furthermore, this mutation was not identified in the Chigene database, ExAC, 1000G, or gnomAD. Similarly, this variant matched the clinical phenotype observed in this case. According to ACMG criteria, this variant is classified as likely pathogenic.

Sanger Sequencing Validation Sanger sequencing was conducted to further confirm our findings in the proband and his family members (Figure 3). The results confirmed that both the proband and his elder sister carried the compound heterozygous mutations c.451-2A>G and c.1043G>A in *ADAMTS17*. The proband's father carried only the c.451-2A>G mutation in *ADAMTS17*, while his mother carried only the c.1043G>A mutation. Both parents were heterozygous carriers of a single mutation and exhibited no apparent clinical symptoms. This suggests that the c.451-2A>G mutation in *ADAMTS17* was inherited from the father, while the c.1043G>A mutation was maternally inherited. The presence of both mutations in a compound heterozygous state resulted in the manifestation of WMS. In contrast, the proband's eldest sister inherited two normal alleles from her parents, harbored no mutations in *ADAMTS17*, and was classified as wild-type. These findings further substantiate that compound heterozygous mutations in *ADAMTS17* underlie WMS pathogenesis in this family.

Bioinformatics Analysis Multiple sequence alignment of ADAMTS17 across different species (Figure 4A) demonstrated that the Cys348 residue in ADAMTS17 (NP_620688.2) is highly evolutionarily conserved, including humans (*Homo sapiens*), mice (*Mus musculus*), wolverines (*Gulo gulo luscus*), groundhogs (*Marmota monax*), rabbits (*Oryctolagus cuniculus*), dolphins (*Delphinus delphis*), monkeys (*Eulemur rufifrons*), and antelopes (*Capricornis sumatraensis*). As the splicing mutation (c.451-2A>G) is located in an intronic region, conservation analysis was not applicable. DANN predicted the splicing mutation (c.451-2A>G) to be deleterious. Functional predictions using SIFT and PolyPhen indicated that the missense mutation (c.1043G>A) is deleterious. These findings support the pathogenic nature of the identified compound heterozygous mutations. RDDC database analysis predicted that the splicing mutation results in a 166-bp deletion, leading to exon skipping, a frameshift, and premature translation termination. Structural modeling using PyMol (Figure 4B) revealed that the missense mutation (c.1043G>A: p.C348Y) replaces cysteine (Cys) with tyrosine (Tyr) at position 348 (Figures 4B-a, 4B-b). This substitution is likely to disrupt a critical disulfide bond, affecting protein stability. Meanwhile, the splicing mutation (c.451-2A>G) leads to premature translation termination, resulting in a truncated protein with significant structural alterations compared to the wild-type protein (Figures 4B-c, 4B-d), severely impairing its function.

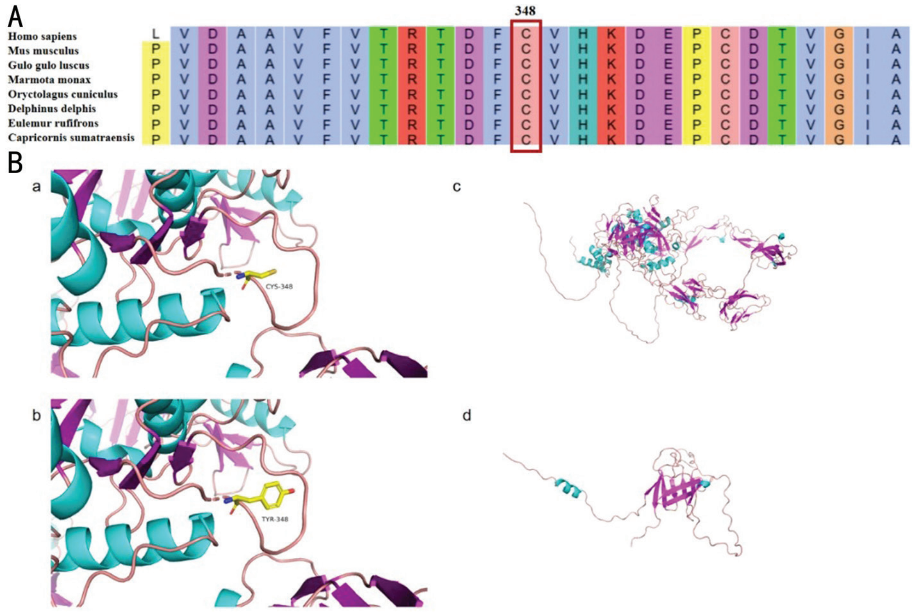

Figure 4 Bioinformatics analysis A: Multiple sequence alignment of the 348th amino acid residue (highlighted in red) across different species. B: Protein structure modeling performed using PyMOL; Ba: Structure of the 348th amino acid residue in the wild-type ADAMTS17 protein; Bb: Structure of the 348th amino acid residue in the mutant ADAMTS17 protein (c.1043G>A); Bc: Overall structure of the wild-type ADAMTS17 protein; Bd: Overall structure of the mutant ADAMTS17 protein (c.451-2A>G).

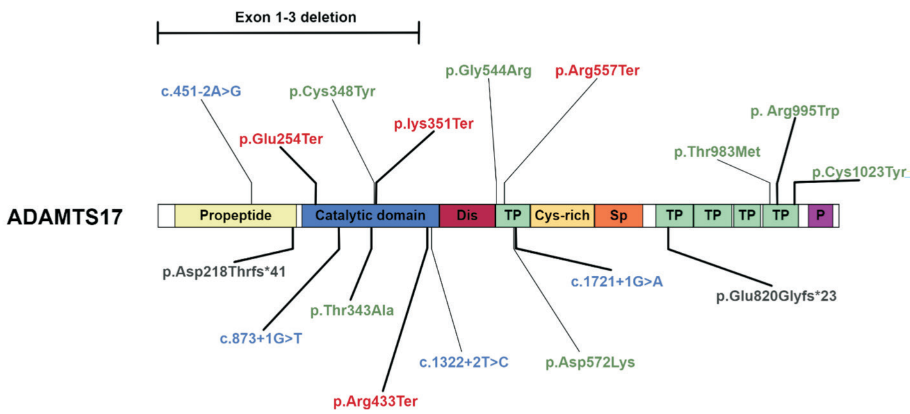

Figure 5 ADAMTS17 pathogenic variants Two-dimensional representations of proteins with pathogenic variants reported in our study and in the literature. Homozygous variants are indicated by bold lines, and compound heterozygous variants are placed at the same height. Missense, nonsense, splicing, and indel variants are highlighted in green, red, blue, and black, respectively. Dis: Disintegrin-like domain; TP: Thrombospondin type 1 repeat; Cys-rich: Cysteine-rich domain; Sp: Spacer domain; P: Protease and lacunin domain.

ADAMTS17 Pathogenic Variants Pathogenic variants in ADAMTS17 were identified in our study as well as in previously reported cases, encompassing a total of 18 variants including seven missense, four nonsense, four splicing, and three insertion/deletion (indel) variants. Among these patients, six patients carried homozygous nonsense or missense mutations, two patients had homozygous splicing mutations, four patients exhibited compound heterozygous variants (including one with a combination of missense and nonsense mutations, two with missense and splicing mutations, and one with a missense mutation on one allele while the other allele may harbor an undetected deep intronic or other gene variant), and three patients carried indel variants. These variants were distributed throughout the protein, as illustrated in Figure 5, which maps all pathogenic variants across distinct functional domains.

DISCUSSION

WMS is an uncommon genetic condition that impacts the musculoskeletal, visual, and cardiovascular systems. Individuals diagnosed with this disorder often exhibit characteristics such as reduced height, stiff joints, dense skin, eye issues (like microspherophakia and ectopia lentis), and irregularities in heart valves. Numerous previous studies have identified various mutations associated with WMS. In the *FBN1* gene, a splice site mutation (c.1327+1G>A[6]) and a missense mutation (c.2066A>G[7]) have been identified. In LTBP2, compound heterozygous mutations (c.3672delC:p.Thr1225fs and c.3542delT:p.

Table 2 Overview of clinical manifestations of known ADAMTS17 variants linked to WMS

Variants	cDNA change	Ophalmological features						Acromelic features					Cardiac anomalies valvulopathy
		Spherophakia	Ectopia lentis	Myopia	Glaucoma	Cataract	Retinal lesions	Short stature	Brachydactyly	Joint limitation	Thick skin	Pseudomuscular build	
Homozygous variants													
M	c.1027A>G	1/1	1/1	1/1	NR	1/1	1/1	1/1	1/1	0/1	1/1	1/1	0/1
	c.2983C>T	3/3	3/3	3/3	3/3	NR	NR	3/3	3/3	NR	0/3	0/3	0/3
	c.3068G>A	4/5	4/5	5/5	2/5	2/5	1/5	5/5	5/5	1/5	NR	NR	0/5
N	c.760C>T	2/2	2/2	2/2	2/2	0/2	0/2	2/2	0/2	0/2	0/2	0/2	0/2
	c.1051A>T	3/3	3/3	3/3	2/3	NR	NR	3/3	3/3	NR	NR	NR	0/3
	c.1297C>T	1/1	1/1	1/1	1/1	NR	1/1	1/1	1/1	0/1	NR	NR	0/1
S	c.1721+1G>A	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1
	c.873+1G>T	1/1	NR	1/1	1/1	1/1	1/1	1/1	1/1	0/1	NR	NR	0/1
I	c.652delG	2/2	NR	2/2	0/2	NR	NR	2/2	0/2	0/2	NR	NR	0/2
	c.2458_2459insG	4/4	4/4	4/4	4/4	0/4	0/4	4/4	0/4	0/4	0/4	0/4	0/4
	Exon 1–3 deletion[a]	4/4	4/4	3/4	1/4	1/4	1/4	4/4	3/4	2/4	NR	NR	3/4
Compound heterozygous variants													
M	c.1630G>A	1/1	1/1	1/1	1/1	NR	NR	1/1	1/1	0/1	NR	NR	0/1
N	c.1669C>T												
S	c.1322+2T>C	1/1	1/1	1/1	1/1	NR	1/1	1/1	1/1	0/1	NR	NR	0/1
M	c.1716C>G												
M	c.2948C>T	1/1	1/1	1/1	1/1	NR	NR	1/1	1/1	0/1	NR	NR	1/1
NA	Undetected												
S	c.451-2A>G	2/2	2/2	2/2	1/2	NR	2/2	2/2	2/2	NR	NR	NR	0/2
M	c.1043G>A												

[a]A 106.96 Kb deletion containing exon 1–3 regions. M: Missense mutation; N: Nonsense mutation; S: Splicing mutation; I: Indel variants; NA: Not available; NR: Not reported; WMS: Weill-Marchesani syndrome..

Met1181fs[8]) have been detected. In *ADAMTS10*, several missense mutations (c.41T>A[9], c.232T>C[10], c.1553G>A and c.2098G>T[11]) have also been described. Furthermore, a couple of mutations in *ADAMTS17* have been reported, including missense mutations (c.2983C>T[12] c.1027A>G[13], c.1630G>A, c.1716C>G, c.2948C>T[14] and c.3068G>A[15]), nonsense mutations (c.1051A>T[16], c.760C>T[11], c.1297C>T, c.1669C>T[14]), splice site mutations (c.873+1G>T[17], c.1322+2T>C[14] and c.1721+1G>A[11]), as well as indels such as c.2458_2459insG[11], c.652delG[18] and a 106.96 Kb deletion containing exon 1–3 regions[19]. Previous studies have indicated potential functional interactions among these genes. LTBP2 may regulate the interaction between LTBP1 and FBN1, thereby influencing the storage of latent TGF-β complexes on elastin-associated microfibrils, which in turn affects tissue growth and development[20]. ADAMTS10 is likely to bind to FBN1 and may facilitate its deposition in the extracellular matrix. ADAMTS17 interacts with FBN1 microfibrils without exhibiting cleavage activity toward FBN1 *in vitro*. It may regulate the formation and function of microfibrils *via* its autolytic peptides or through interactions with other ADAMTS proteins. Additionally, FBN1 microfibrils may bind ADAMTS10 and ADAMTS17 together, allowing ADAMTS17 to activate ADAMTS10[2].

ADAMTS protease family consists of structurally complex enzymes with diverse functions, potentially contributing to the development of various tissues, including cartilage, bone, skin, heart, and reproductive organs[21]. The ADAMTS family comprises 19 secreted enzymes that play a crucial role in ECM degradation and turnover. Mutations in ADAMTS2, ADAMTS10, ADAMTS13, ADAMTS17, ADAMTSL2, and ADAMTSL4 have been detected in diverse human genetic disorders[22]. WMS4 is a subtype of WMS resulting from mutations in the *ADAMTS17* gene. Compared to classic WMS, WMS4 exhibits milder cardiac involvement and primarily manifests with musculoskeletal and ocular symptoms such as short stature, brachydactyly, and ectopia lentis. *ADAMTS17* encodes a critical ADAMTS metalloproteinase that is essential for ECM formation and remodeling[13].

We discovered a previously unreported compound heterozygous mutation located in *ADAMTS17* within a Chinese family, consisting of a paternally inherited splicing mutation (c.451-2A>G) and a maternally inherited missense mutation (c.1043G>A), collectively leading to the development of WMS4. Both affected individuals in this family exhibited short stature, microspherophakia, and ectopia lentis, with no significant cardiac abnormalities, which is consistent with previous studies (Table 2). A review of our study together with previously published reports encompassing 32 patients with WMS revealed that all affected individuals presented with short stature. The prevalence of spherical lens, ectopia lentis, and high myopia was 31 of 32, whereas secondary glaucoma was documented in 21 patients. Retinal abnormalities were identified in only eight patients, comprising retinal detachment and/or retinal tears in five cases, retinal pigment epithelium (RPE) alterations in two, and retinal vascular occlusion with fibrosis in one. Notably, in families where all affected members exhibited retinal abnormalities, the associated mutations were consistently located within the catalytic domain of ADAMTS17, providing further evidence that variants in this domain may disrupt protease activity, secretion, or interactions with microfibrils[21]. Such disruptions are likely to compromise the stability of zonular fibers and the ECM, thereby affecting RPE and retinal integrity. This interpretation is consistent with findings from mouse models, which demonstrate RPE dedifferentiation and zonular fiber loss[23]. In addition, some patients presented with brachydactyly, whereas joint stiffness, thickened skin, pseudomuscular habitus, and cardiac valvular disease were documented only in rare instances.

Previous studies suggest that ADAMTS17 is strongly associated with height[24], and copy number variations (CNVs) near ADAMTS17 may influence growth and development[25]. Studies have shown that in two dog breeds, individuals carrying ADAMTS17 mutations are generally shorter than those without the mutation[26]. Moreover, ADAMTS17 knockout mice exhibit WMS-like symptoms, including short stature, brachydactyly, and thickened skin, highlighting the crucial role of ADAMTS17 in skeletal development[27]. Additionally, earlier research has demonstrated a significant link between the *ADAMTS* gene family and lens function[28]. ADAMTS17 has been shown to be expressed in various tissues, including ocular and embryonic tissues. The *ADAMTS17* gene may regulate the composition and function of microfibrils *via* FBN2, playing a role in the formation of the zonular fibers and connective tissues[29]. *ADAMTS17* mutations result in WMS-like symptoms, including short stature, lenticular myopia, microspherophakia, ectopia lentis, and secondary glaucoma, but without the typical WMS features such as joint stiffness, brachydactyly, and cardiac valve anomalies[11], which aligns with the clinical presentation of affected individuals in this family. Notably, previous studies have largely reported WMS in association with microspherophakia. The high myopia observed in WMS patients is primarily attributed to abnormal lens morphology rather than increased axial length. In contrast, most WMS patients exhibit a short axial length. However, the patients in this study exhibited increased axial length, differing from previous observations. Studies have reported that mutations in ADAMTSL4 can lead to increased axial length, possibly through mechanisms involving RPE dedifferentiation and COL18A1 upregulation[23]. ADAMTSL4 and ADAMTS17 both belong to the ADAMTS(L) protein family, and share auxiliary domains with other ADAMTS family proteins[22]. Thus, we hypothesize that ADAMTS17 may contribute to axial elongation through a similar mechanism as ADAMTSL4.

However, we acknowledge that current evidence is limited and further functional validation is required to substantiate this hypothesis. This study has several limitations. First, the sample size was small, involving only a single family with two affected individuals, which may limit the generalizability of the findings. Second, functional validation experiments were not conducted. In particular, transcriptomic analysis such as reverse transcription polymerase chain reaction (RT-PCR) or minigene assays would be required to confirm the effect of the splicing mutation (c.451-2A>G) on mRNA processing, and *in vitro* or *in vivo* functional studies are needed to clarify the impact of the missense mutation (p.C348Y) on ADAMTS17 protein stability and enzymatic activity. Nevertheless, the rarity of WMS makes single-family reports valuable, and our comprehensive bioinformatics analyses and structural modeling provide preliminary functional evidence. These investigations will be included in our future research plan, and future studies with larger cohorts and experimental validation are warranted to further confirm the pathogenic role of ADAMTS17 in WMS.

In conclusion, this study performed WES and Sanger sequencing validation in a WMS family, identifying a new compound heterozygous mutation in ADAMTS17. The pathogenicity of this mutation was further validated through bioinformatics analysis and protein structural modeling. Despite certain limitations, our findings highlight the essential role of ADAMTS17 in regulating growth and developmental processes. Furthermore, this study has contributed to a rise in the total count of documented ADAMTS17 mutations, which now stands at eighteen. These findings provide a significant foundation for further elucidating the pathophysiological mechanisms of WMS and exploring novel therapeutic strategies. Future research should incorporate a larger cohort and functional studies to further investigate mutations in other related genes and their contributions to WMS pathogenesis. Additionally, emerging therapeutic strategies, including gene therapy and targeted treatments for WMS, warrant further investigation.

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Authors' Contributions: All authors contributed to the study conception and design. Liu SW and Liu Z: Conceptualization, patient diagnosis, clinical management. Gao S (Corresponding Author): Data curation, formal analysis. Wu HY (First Author): Writing original draft. Pei C and Wu CR: Resources (providing instruments/materials).

Data Availability Statement: The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest: Wu HY, None; **Liu SW,** None; **Liu Z,** None; **Pei C,** None; **Wu CR,** None; **Gao S,** None.

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