• Basic Research •

Novel homozygous *ADAMTS17* missense variant in Weill-Marchesani syndrome

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Abstract

● **AIM:** To explore the phenotype and genotype of Weill-Marchesani syndrome (WMS) in a Chinese family and review related literature.

● **METHODS:** Three WMS patients and other unaffected individuals in this family with a history of consanguineous marriage were included in this study. Medical history, comprehensive ophthalmic examinations, and systemic evaluation, as well as whole exome and Sanger sequencing of specific genomic regions, were performed.

● **RESULTS:** The three affected siblings presented with short stature, brachydactyly and ocular disorders, including very shallow anterior chamber, high myopia, microspherophakia lens subluxation with stretched zonules and glaucoma. Genetic analysis verified a homozygous missense mutation (c.2983C>T: p. Arg995Trp) in *ADAMTS17*, which was correlated with the diseases in this family, indicating an autosomal recessive inherited manner of WMS. This review aims to summarize the mutation sites of WMS genes, so as to prevent the disease and better guide clinical diagnosis and treatment.

● **CONCLUSION:** A novel homozygous missense variant of *ADAMTS17* is identified in a WMS family with a history of consanguineous marriage. Our study expands the range of mutations associated with WMS and deepens our understanding of pathology in disease associated with *ADAMTS17* variants.

● **KEYWORDS:** Weill-Marchesani syndrome; *ADAMTS17*; missense variation; molecular genetics

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INTRODUCTION

Weill-Marchesani syndrome (WMS) is a rare hereditary connective tissue disease characterized by ocular problems, including microspherophakia, ectopia lentis, high myopia, and secondary glaucoma. Other symptoms include short stature, brachydactyly, joint stiffness, and occasional cardiac defects. The syndrome usually involves a family history or a history of consanguinity between parents or close relatives. WMS can show autosomal dominant or autosomal recessive inheritance. The most common pathogenic genes linked to WMS are the *FBN1, LTBP2, ADAMTS10 and ADAMTS17* genes[1-8]. Regardless of which of these genes is varied in WMS patients, the disease features appear to be similar. Here, we report a new homozygous variation in *ADAMTS17* (MIM*607511, ADAM metallopeptidase with thrombospondin type 1 motif, 17) leading to autosomal recessive WMS in a Chinese family.

SUBJECTS AND METHODS

Ethical Approval This study followed the principles of the Declaration of Helsinki, and it was approved by the Ethics Committee of West China Hospital of Sichuan University

(2019, No.53). All subjects fully understood the purpose of the study and provided written informed consent.

Patient Ascertainment and Clinical Assessment The proband and other family members were invited to our hospital for a detailed medical history inquiry and complete physical and ophthalmic examination, including height measurement, ECG, hands and feet X-ray, cardiac ocular ultrasound, best-corrected visual acuity testing, intraocular pressure (IOP) measurement (Goldmann tonometry), slit lamp examination, fundus examination, gonioscopy, ultrasound biomicroscopy (UBM), corneal endothelial cell count, B-ultrasound, ocular biometry measurement, visual field and anterior segment-optical coherence tomography (AS-OCT, Cirrus HD-OCT 4000) testing.

Whole-Exome Sequencing and SANGER Sequencing Peripheral venous blood (3 mL) was collected from each family member for DNA extraction and genotyping. The exons and adjacent splicing regions (approximately 20 base pairs) of the target gene and the full length of the mitochondrial genome were captured and enriched by probe hybridization. The enriched genes were quality controlled and sequenced using a high-throughput sequencer. According to the selected mutation sites, the consolation of other family members was verified.

Bioinformatic Analysis Sequences of the wild-type *ADAMTS17* gene and encoded protein were downloaded from the National Center for Biotechnology Information (NCBI, https://www.ncbi.nlm.nih.gov/), and mutated amino acids in the *ADAMTS17* protein were changed manually. The online Cobalt tool (https://www.ncbi.nlm.nih.gov/tools/cobalt) was used to align *ADAMTS17* proteins from different species to determine whether a mutated position was conserved. The potential functional implications of *ADAMTS17* mutations were predicted using PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://provean.jcvi.org/). The structures of mutant *ADAMTS17* proteins were modeled based on homology with the wild-type protein in PyMOL (https://swiss-model.expasy.org).

RESULTS

Family Characteristics This case study involved a family of nine members, all Han Chinese, from three generations identified at West China Hospital of Sichuan University. Three of the individuals were diagnosed with WMS, including one male (IV-3) and two females (IV-2 and IV-5; Figure 1). The proband was a 22-year-old patient IV-3, who was referred to our clinic with complaints of decreased vision accompanied frequently by eye soreness in both eyes for 5y. He was diagnosed with bilateral secondary angle-closure glaucoma. His sister IV-5 had high myopia in both eyes that was not corrected by glasses and complained of eye soreness after reading for long periods. The other sister, IV-2, had poor visual acuity but never visited the hospital before. Their parents (III-1 and III-2) were in consanguineous marriage. The inheritance pattern of WMS in this family was autosomal recessive. The family pedigree is depicted in Figure 1.

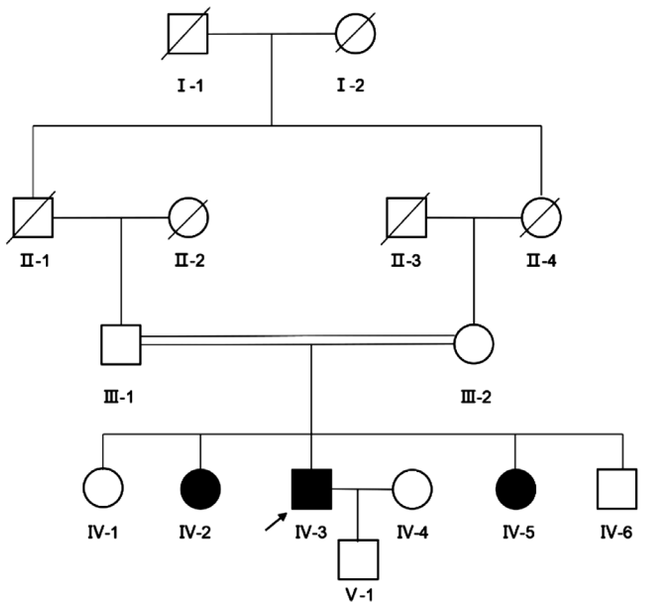

Figure 1 Pedigree showing inheritance of WMS in a Han Chinese family with a history of consanguineous marriages Black identifies individuals diagnosed with the syndrome. The arrow marks the proband, IV-3. WMS: Weill-Marchesani syndrome.

The height of the three affected siblings was significantly lower than that of other family members. The other systemic abnormalities included brachydactyly but had no anomalies in the cardiovascular system (Table 1, Figure 2). Ophthalmic examination revealed high myopia, a very shallow anterior chamber, microspherophakia with stretched zonules, lens subluxation and angle closure glaucoma (Figure 3). Their clinical findings are summarized in Table 1. Based on these findings, the proband and his sister (IV-5) underwent surgeries for removal of the dislocated lens and implantation of an intraocular lens (IOL). Capsular bag stabilization was accomplished with capsular hooks during the procedure, and a capsular tension ring was inserted prior to IOL implantation in the capsular bag. Following surgery, visual acuity significantly improved, and the IOP was normalized with a stable, deepened anterior chamber.

Genotyping A homozygous missense variation c.2983C>Tp.Arg995Trp) was detected in the *ADAMTS17* gene in all members of the family with the disease. Individuals III-1, III-2, IV-1, IV-6, and V-1 were heterozygous for the same mutation. One individual was homozygous for the wild-type allele. This mutation changed C2983 to T in the cDNA, resulting in an Arg995Trp substitution in the protein (Figure 4).

Bioinformatics Analysis The 995Arg position of the *ADAMTS17* protein (NP_620688.2) is extremely conserved

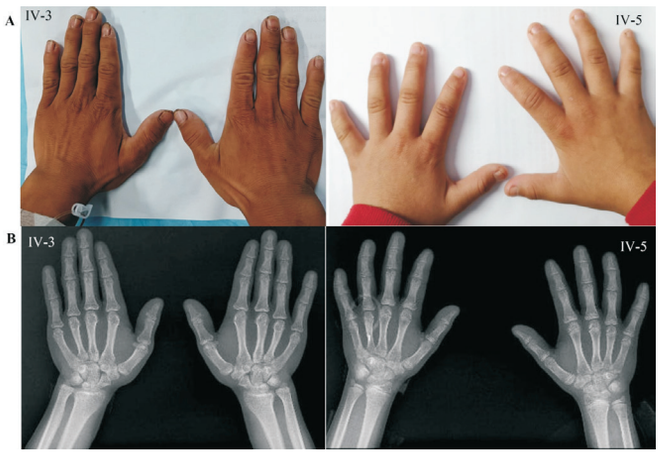

Figure 2 Clinical features of patients A: Images of the hands of proband IV-3 and sister IV-5 showing short fingers; B: X-ray of both hands showing a shorter phalanx normal joint.

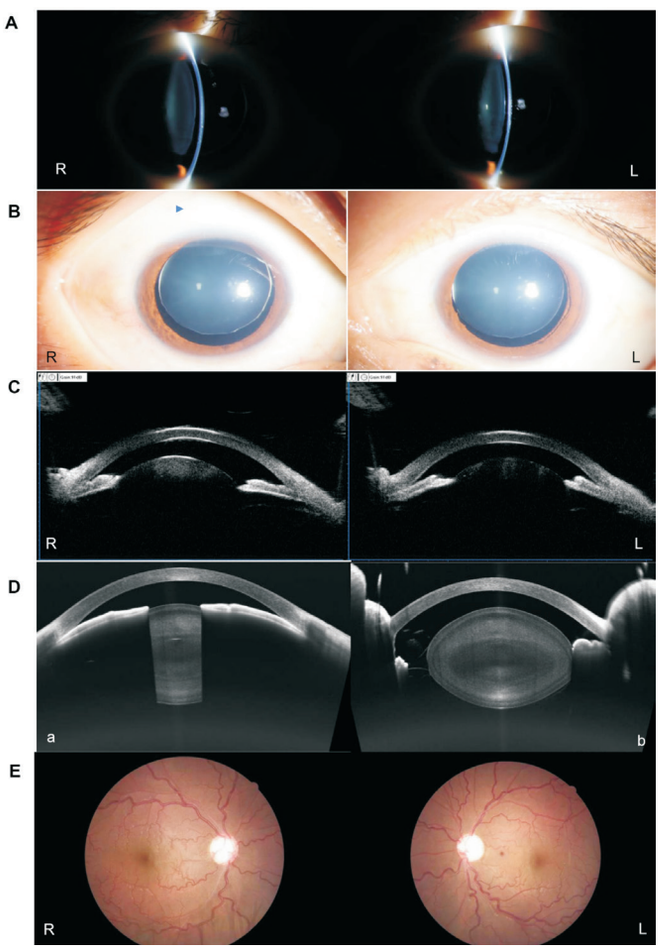

Figure 3 Ophthalmological characterization of the proband (IV-3) A: Slit-lamp examination revealed a very shallow anterior chamber in both eyes; B: Anterior segment photographs, after dilatation of the pupil, showing a small spherical lens and a gold ring, which was caused by the reflection of light from the 360° periphery of the small crystalline globular lens with stretched zonules, resulting in the subluxation of the lens; C: UBM showed a shallow anterior chamber in both eyes, a forward-shifted lens iris, and a spherical anterior surface on the lens; D: The AS-OCT, before (a) and after (b) dilatation of the pupil (left eye), showed a very shallow anterior chamber and a subluxated small spherical lens, and the zonules were still not relinquished; E: Fundoscopy showed advanced glaucomatous cupping in both eyes.

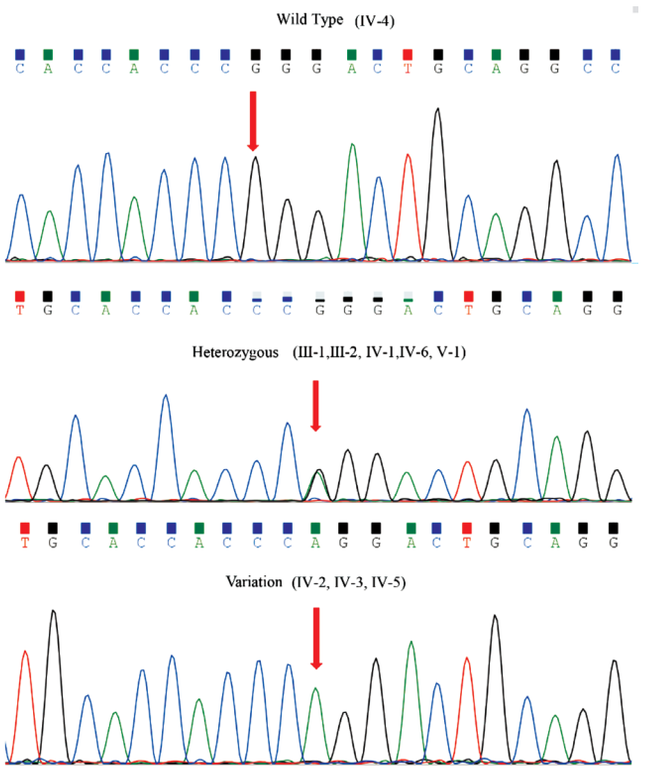

Figure 4 Partial sequencing of the *ADAMTS17* gene in WMS patients of the family A homozygous missense mutation (c.2983C>T: p.Arg995Trp, red arrow) was found in the *ADAMTS17* gene of all patients in this family. WMS: Weill-Marchesani syndrome.

among different species, such as humans (Homo sapiens), mice (Mus musculus), zebrafish (Danio rerio), frogs (Xenopus tropicalis), rhesus monkeys (Macaca mulatta), rats (Rattus norvegicus), chickens (Gallus gallus), goats (Capra hircus), rabbits (Oryctolagus cuniculus) and hamsters (Cricetulus griseus), according to the alignment of protein sequences shown in Figure 5. The PolyPhen-2 analysis results showed that the missense *ADAMTS17* variant (c.2983C>T: p.Arg995Trp) was predicted to be PROBABLY DAMAGING with a score of 1000. The PROVEAN score was -4.928, deleterious, according to the PROVEAN prediction results. Two protein functional prediction tools obtained the same harmful results, indicating that this variant should be pathogenic. Furthermore, the structural prediction results of PyMOL showed that there might be no large structural change between the mutated and wild-type ADAMTS17 proteins. However, the charged and hydrophobic status should be changed at the 995 position, as shown by the black arrows in Figure 5.

DISCUSSION

In this study, we identified a novel homozygous *ADAMTS17* missense variant (c.2983C>T: p.Arg995Trp) associated with WMS. Three of nine siblings in the family were diagnosed with WMS.

The proband and his two affected sisters presented with angle closure glaucoma. The proband and one of his sisters (IV-2)

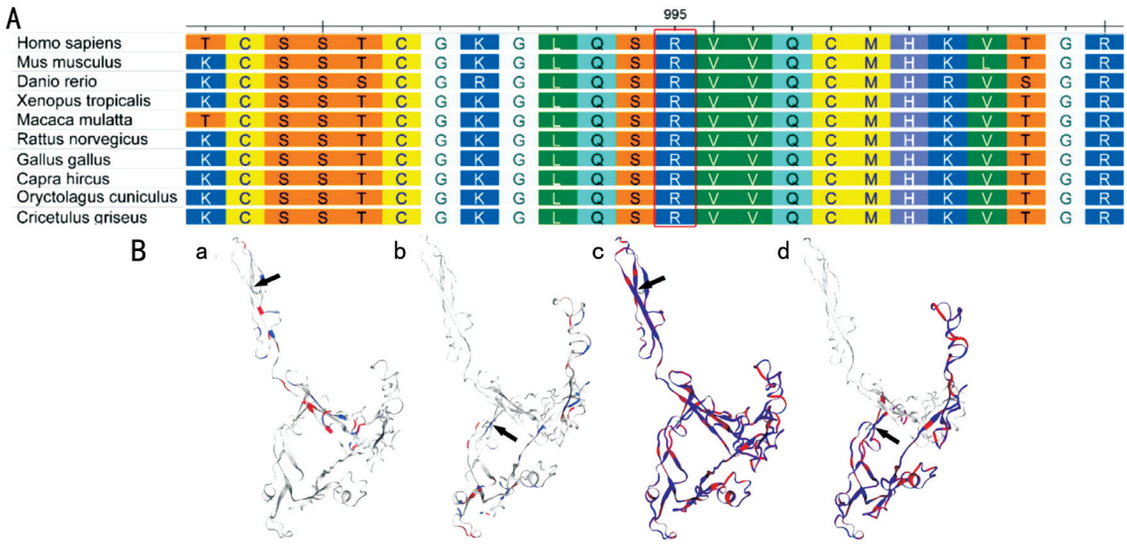

Figure 5 Bioinformatics analysis A: Protein sequence alignment at the 995 position (red box) among different species; B: Structural modeling by PyMOL showing charged and hydrophobic status. a: Charged wild type; b: Charged mutated protein; c: Hydrophobic wild type; d: Hydrophobic mutated; Black arrow: Mutated position.

Table 1 Clinical features of the affected individuals in the family

Characteristic	IV-3 (proband)	IV-2	IV-5
Gender	Male	Female	Female
Age ranges (y)	Early 20s	Early 30s	10s
Best corrected visual acuity (R/L)	0.15/0.4	Counting figures/counting figures	0.5/0.4
The highest intraocular pressure (R/L, mm Hg)	45/43	38/36	27/28
Axial length (R/L, mm)	22.35/22.07	NA	20.71/20.87
Anterior chamber of depth (R/L, mm)	1.46/1.30	NA	1.52/1.48
Cup disc ratio (R/L)	0.9/0.9	1.0/1.0	0.5/0.5
Myopia (R/L, diopter)	-16.0/-15.0	-13.0/-13.5	-11.0/-12.0
Other ocular history	Blurred vision and soreness	NA	Soreness after reading for long periods
Height (cm)	150	130	128
Brachydactyly	Yes	Yes	Yes
Cardiac anomalies	No	No	No
Joint stiffness[a]	No	No	No

L: Left eye; NA: Not available; R: Right eye. [a]Based on the ability to make a fist.

showed optic atrophy. Another sister (IV-5) did not exhibit obvious optic atrophy. The reason for the inconspicuous optic atrophy was that she was the youngest and had a short onset time.

To prevent further injury of the optic nerve and improve visual acuity, two affected individuals (proband and IV-5) underwent surgeries to remove the dislocated lens and implant the IOL. In this case, to remove the lens more safely and with less risk of further zonular damage, iris retractors were used to temporarily support and stabilize the capsular bag; then, a capsular tension ring was inserted prior to IOL implantation in the bag. The surgeries were uneventful, and the patients were doing well.

Pathogenic *ADAMTS17* variants were first reported in 2009[3]. To date, eight variations in the human *ADAMTS17* gene have been reported, including a nonsense mutation (c.1051A>T), a missense mutation (c.760C>T), c.1027A>G, splice-site mutations (c.873+1G>T and c.1721+1G>A), indels (including c.2458_2459insG, c.652delG and a 106.96 Kb deletion containing exon 1–3 regions. Our study increases the number of variations of this gene to nine (Table 2)[1,3,9-12].

None of the three individuals with WMS in our study showed joint stiffness or cardiac abnormalities, consistent with the lack of such symptoms in other reports of WMS associated with *ADAMTS17* variants (Table 2). Review the literature, all the patients had ocular abnormalities and short stature, but only a few patients had brachydactyly, joint stiffness, and cardiac abnormalities. Cardiac abnormalities were reported in only 3 of 18 patients. One of the patients had concomitant tachycardia, mitral valve dysplasia, and cardiomyopathy, and two patients had mitral valve dysplasia[9] Our study adds to

Table 2 Summary of clinical phenotypes of known *ADAMTS17* variations linked to WMS

Variation	*ADAMTS17* variations								
	106.96-kb deletion[9]	c.652 delG[10]	c.760 C>T[3]	c.873+1 G>T[11]	c.1027 A>G[12]	c.1051 A>T[1]	c.1721+1 G>A[3]	c.2458_2459insG[3]	c.2983C>T
No. of cases, gender	4, F(4)	2, F(1), M(1)	2, F(2)	1, F(1)	1, F(1)	3, F(2), M(1)	1, M(1)	4, F(2), M(2)	3, F(2), M(1)
Nationality	Tunisian	Saudi	Saudi	Indian	French Canadian	Chinese	Saudi	Saudi	Chinese
Age ranges (years at the time of the study)	Early 20s	10s	Early 40s	Early 20s	50s	20s	30s	10s	10s
Average diopters (D)	-6.7	-9.7	-7	-10	NA	NA	-11.9	-10.5	-13.5
Average axial length (mm)	NA	22.7	21.2	22.1	NA	NA	21.3	22.5	21.5
Shallow anterior chamber	NA	1/2 yes, 1/2 no	Yes	NA	NA	Yes	Yes	3/4 yes, 1/4 no	Yes
Microspherophakia	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brachydactyly	3/4 yes, 1/4 no	No	No	Yes	Yes	Yes	No	No	Yes
Joint stiffness	2/4 yes, 2/4 no	No	No	No	No	NA	No	No	No
Heart abnormalities	3/4 yes, 1/4 no	NA	No	No	No	No	No	No	No

F: Female; M: Male; NA: Not available.

the range of *ADAMTS17* polymorphisms in humans (Table 2). Further studies should examine whether WMS associated with *ADAMTS17* variants represents a different subtype of the disease or simply a milder manifestation of the typical disease phenotype.

ADAMTS17, located at position 15q26.3 (MIM 613195), encodes a member of the ADAMTS family of secreted metalloproteases, which are involved in extracellular matrix (ECM) formation, remodeling and degradation[13]. *ADAMTS17*, which in the eye is expressed mainly near the crystal epithelium, appears to promote ECM formation, especially the assembly of fibrillin microfibrils[2,11]. *ADAMTS17* appears to stabilize zonular microfibrils[14]; therefore, deficiency in the protein may destabilize microfibrils, causing abnormalities in the lens zonule[12,14]. Consistent with this idea, polymorphisms in *ADAMTS17* have been linked to primary open angle glaucoma and ectopia lentis in dogs[15-16]. Future studies should explore the role of *ADAMTS17* polymorphisms in the pathogenesis of WMS.

Short stature is a distinct feature of WMS, and *ADAMTS17* polymorphism in humans was linked to height[17], as have variations in copy number at a locus near this gene[18-19]. *ADAMTS17* polymorphism has also been linked to height in dogs[15-16], suggesting that *ADAMTS17* plays an important role in normal growth and development.

In this study, we analyzed the gene variation in the adjacent splicing region of the whole exome of the proband and revealed a homozygous missense variant c.2983C > T: p. Arg995Trp on the *ADAMTS17* gene, which segregated with the phenotype in the pedigree. This variant site is in three TSP1 repeats, which may destabilize zonules by affecting ECM and microfibril assembly, causing zonular abnormalities, spherical crystals, or crystal subluxation.

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