Novel homozygous \textit{ADAMTS17} missense variant in Weill-Marchesani syndrome

Na Miao\textsuperscript{1}, Yao Zhang\textsuperscript{1}, Jin-Ying Liao\textsuperscript{1}, Lin Zhou\textsuperscript{1}, Ji-Cai He\textsuperscript{2}, Rong-Qin Yang\textsuperscript{2}, Xu-Yang Liu\textsuperscript{3,4}, Li Tang\textsuperscript{1}

\textsuperscript{1}Department of Ophthalmology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China
\textsuperscript{2}Department of Ophthalmology, First People’s Hospital of Liangshan Yi Autonomous Prefecture, Xichang 615306, Sichuan Province, China
\textsuperscript{3}Xiamen Eye Center, Xiamen University, Xiamen 361011, Fujian Province, China
\textsuperscript{4}Department of Ophthalmology, Shenzhen People’s Hospital, the 2nd Clinical Medical College, Jinan University, Shenzhen 518040, Guangdong Province, China

Co-first authors: Na Miao and Yao Zhang

Correspondence to: Li Tang. Department of Ophthalmology, West China Hospital of Sichuan University No.37 Guoxue Xiang, Chengdu 610041, Sichuan Province, China. tangli1a@wchscu.cn; Xu-Yang Liu. Xiamen Eye Center, Xiamen University 989 Wutong West Road, Huli District, Xiamen 361011, Fujian Province, China; Department of Ophthalmology, Shenzhen People’s Hospital, the 2nd Clinical Medical College, Jinan University, No.18, Zetian Road, Futian District, Shenzhen 518040, Guangdong Province, China. xliu1213@126.com

Received: 2022-10-31 Accepted: 2023-03-10

Abstract

\textbullet \textbf{AIM:} To explore the phenotype and genotype of Weill-Marchesani syndrome (WMS) in a Chinese family and review related literature.

\textbullet \textbf{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.

\textbullet \textbf{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 \textit{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.

\textbullet \textbf{CONCLUSION:} A novel homozygous missense variant of \textit{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 \textit{ADAMTS17} variants.

\textbullet \textbf{KEYWORDS:} Weill-Marchesani syndrome; \textit{ADAMTS17}; missense variation; molecular genetics

DOI:10.18240/ijo.2023.05.04

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 \textit{FBN1}, \textit{LTBP2}, \textit{ADAMTS10} and \textit{ADAMTS17} genes\textsuperscript{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 \textit{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 from different species 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://swissmodel.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.

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 995 Arg position of the *ADAMTS17* protein (NP_620688.2) is extremely conserved.
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 \textit{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 \textit{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)
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
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\[12,14\]. 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.


ACKNOWLEDGEMENTS

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

Weill-Marchesani syndrome

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

<table>
<thead>
<tr>
<th>Variation</th>
<th>ADAMTS17 variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases, gender</td>
<td>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)</td>
</tr>
<tr>
<td>Nationality</td>
<td>Tunisian Saudia Saudia Indian French Canadian Chinese Saudia Saudia Chinese Saudia Chinese</td>
</tr>
<tr>
<td>Age ranges (years at the time of the study)</td>
<td>Early 20s 10s Early 40s Early 20s 50s 20s 30s 10s 10s</td>
</tr>
<tr>
<td>Average diopeters (D)</td>
<td>-6.7 -9.7 -7 -10 NA NA -11.9 -10.5 -13.5</td>
</tr>
<tr>
<td>Average axial length (mm)</td>
<td>NA 22.7 22.1 22.1 NA NA 21.3 22.5 21.5</td>
</tr>
<tr>
<td>Shallow anterior chamber</td>
<td>NA 1/2 yes, 1/2 no Yes NA NA Yes Yes Yes 3/4 yes, 1/4 no Yes</td>
</tr>
<tr>
<td>Microspherophakia</td>
<td>NA Yes Yes Yes Yes Yes Yes Yes Yes</td>
</tr>
<tr>
<td>Brachydactyly</td>
<td>3/4 yes, 1/4 no No No Yes Yes Yes No No Yes</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>2/4 yes, 2/4 no No No No No No No No</td>
</tr>
<tr>
<td>Heart abnormalities</td>
<td>3/4 yes, 1/4 no NA No No No No No No No</td>
</tr>
</tbody>
</table>

REFERENCES


6 Yu XW, Kline B, Han Y, Gao Y, Fan ZG, Shi Y. Weill-Marchesani syndrome 4 caused by compound heterozygosity of a maternal submicroscopic deletion and a paternal nonsense variant in the...


16 Jeanes EC, Oliver JAC, Ricketts SL, Gould DJ, Mellersh CS. Glaucoma-causing ADAMTS17 mutations are also reproducibly associated with height in two domestic dog breeds: selection for short stature may have contributed to increased prevalence of glaucoma. Canine Genet Epidemiol 2019;6:5.

