Case report: A homozygous ADAMTSL2 missense variant causes geleophysic dysplasia with high similarity to Weill-Marchesani syndrome

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Background: Geleophysic dysplasia and Weill-Marchesani syndrome from the acromelic dysplasias group of genetic skeletal disorders share remarkable clinical and genetic overlap.

Methods: Ophthalmological, physical, radiological examinations were conducted with a female patient in her early 30s. Whole exome sequencing followed by Sanger sequencing validation was performed to identify the genetic cause.

Results: The patient, born to consanguineous Chinese parents, presented with microspherophakia, lens subluxation, high myopia, short stature, small hands and feet, stiff joints, and thickened skin. A diagnosis of Weill-Marchesani syndrome was initially made for her. However, genetic testing reveals that the patient is homozygous for the c.1966G>A (p.Gly656Ser) variant in ADAMTSL2, and that the patient's healthy mother and daughter are heterozygous for the variant. As mutations in ADAMTSL2 are known to cause autosomal recessive geleophysic dysplasia, the patient is re-diagnosed with geleophysic dysplasia in terms of her genotype and phenotype.

Conclusion: The present study describes the clinical phenotype of the homozygous ADAMTSL2 p. Gly656Ser variant, which increases our understanding of the genotype-phenotype correlation in acromelic dysplasias.

KEYWORDS
ADAMTSL2, geleophysic dysplasia, Weill-Marchesani syndrome, acromelic dysplasias, missense mutation, microspherophakia, lens subluxation, high myopia
Introduction

Geleophysic dysplasia (GD, OMIM#231050, 614185, 617899) and Weill-Marchesani syndrome (WMS, OMIM#277600, 608328, 614819, 603196) are closely related conditions in the acromelic dysplasias group according to the 2019 nosology and classification of skeletal disorders (Mortier et al., 2019). Both conditions are characterized by short stature, brachydactyly, and restricted joint mobility (Pimienta et al., 2013). Apart from the common features, GD is characteristic of a round, full ‘happy’ face and severe cardiac and/or respiratory diseases leading to a high risk of early death. The distinctive features of WMS include microphthalmia with associated lens dislocation and myopia (McInerney-Leo et al., 2016).

Genetic overlap also exists between GD and WMS. Mutations in the fibrillin1 (FBN1) gene can cause GD or WMS with autosomal dominant inheritance (Fairev et al., 2003; Le Goff et al., 2011). Mutations in ADAMTSL2 (a disintegrin and metalloproteinase with thrombospondin repeats-like 2) and LTBP3 (latent transforming growth factor β binding protein 3) are responsible for autosomal recessive and dominant GD, respectively (Le Goff et al., 2008; Allali et al., 2011). LTBP2, ADAMTS17 and ADAMTS10 are known to cause autosomal recessive WMS (Morales et al., 2009; Haji-Seyed-Javadi et al., 2012).

In an earlier study that linked missense mutations in ADAMTSL2 with autosomal recessive GD, functional assays showed that ADAMTSL2 missense mutants had reduced extracellular secretion, and that ADAMTSL2 interacted with LTBP1 (latent TGF-β-binding protein 1), a protein well-known for a storage role of latent TGF-β in the extracellular matrix. Importantly, a significant increase in total and active TGF-β in the culture medium was observed for fibroblasts derived from GD patients. These findings suggest that the GD-causing mutations in ADAMTSL2 result in a dysregulation of TGF-β signaling (Le Goff et al., 2008). The FBN1 gene, which is previously well characterized as a causative gene for Marfan syndrome, encodes the glycoprotein fibrillin-1 that forms microfibrils in extracellular matrix and act as a TGF-β modulator (Chaudhry et al., 2007). In another study of GD case series, the dominant disease-causing mutations of FBN1 were found to be concentrated in its TGF-β-binding protein-like domain 5 (TBS) and associated with microfibrillar network disorganization and enhanced TGF-β signaling in GD fibroblasts. Interestingly, ADAMTS2 was found to directly interact with FBN1 in the study (Le Goff et al., 2011). The interplays of ADAMTS superfamily members, FBN1 and LTBP5 suggest that these disease-causing genes all are involved in TGF-β pathway via directly or indirectly regulating the bioavailability of TGF-β in extracellular matrix (Le Goff and Cormier-Daire, 2012; Przyklenk et al., 2022).

Due to the great phenotypic and genetic overlap, differentiation between GD and WMS sometimes can be difficult. The present study reports a patient who carries a homozygous missense mutation in the ADAMTSL2 gene and displays a GD phenotype with high similarity to WMS.

Materials and methods

Medical ethics

The Medical Ethics Committees of Liuyang Jili Hospital (KYSZ 2022-005) and Hunan Provincial Maternal and Child Health Care Hospital approved the study. All individuals gave written informed consent to the study.

Patient and clinical examinations

A woman in her early 30s with high myopia presented to our vision center for a corrective lens prescription. She was referred for further diagnostic evaluation. Ophthalmological, physical, radiological examinations were conducted with her.

WES sequencing and data analysis

WES was conducted at Berry Genomics (Beijing, China). Briefly, Genomic DNA was extracted from 200 μL peripheral blood using a Qiagen DNA Blood Midi/Mini kit (Qiagen GmbH, Hilden, Germany) following the manufacturer’s protocol. For library construction, 50 ng DNA was fragmented to 200 bp around by enzymes. The DNA fragments were then end-repaired, and the 3′end was added 1 A base. Next, the DNA fragments were ligated with barcoded sequencing adaptors, and fragments of about 320 bp were collected by AMPure XP magnetic beads (Beckman Coulter, Brea, CA, United States). After PCR amplification, the DNA fragments were hybridized and captured by IDT primer, the DNA fragments were eluted and collected, and then subjected to PCR amplification and the purification. The prepared libraries were quantified by qPCR and size distribution were determined using an Agilent Bioanalyzer 2,100 (Agilent Technologies, Santa Clara, CA, United States). Finally, Novaseq6000 platform (Illumina, San Diego, United States), with 150 bp pair-end sequencing mode, was used for sequencing the genomic DNA. Raw image files were processed using CASAVA v1.82 for base calling and generating raw data. The sequencing reads were aligned to the human reference genome (hg19/GRCh37) using Burrows–Wheeler Aligner tool and PCR duplicates were removed by using Picard v1.57 (http://picard.sourceforge.net/), Verita Trekker® Variants Detection System by Berry Genomics and the third-party software GATK (https://software.broadinstitute.org/gatk/) were employed for variant calling. Variant annotation and interpretation were conducted by ANNOVAR (Wang et al., 2010) and the Enliven® Variants
Annotation Interpretation System authorized by Berry Genomics. The human population databases, such as gnomAD (http://gnomad.broadinstitute.org/), the 1,000 Genome Project (http://browser.1000genomes.org), dbSNP (http://www.ncbi.nlm.nih.gov/snp), and internal database (Berrybig data), and the disease and phenotype databases such as OMIM (http://www.omim.org), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), and HGMD (http://www.hgmd.org) were used for annotation.

Results

Clinical presentation

With respect to the patient, refractive errors as measured by computer optometry were as follows: right eye -13.50 DS/-1.25 DC × 110° and left eye -14.25 DS/-4.25 DC × 155°. Goldmann applanation intraocular pressure (IOP) was 41 mm Hg in both the left and right eyes. Slit-lamp examination revealed shallow anterior chamber, iridodonesis, and small, clear lens with increased thickness and inferior-nasal subluxation after pupillary dilation (Figures 1A,B). Fundus photography showed pale color of the optic papilla, cup-disc ratio of 0.5, and alteration in the fundus (Figures 1C,D). Optical coherence tomography (OCT) revealed thinning of the retinal nerve fiber layer (Supplementary Figure S1). Single field analysis revealed peripheral arcuat visual field defect at upper temporal quadrants of both eyes (Supplementary Figure S2). Ultrasound biomicroscopy (UBM) examination also suggested shallow anterior chamber, and additionally, iris pushed forward (Supplementary Figure S3). Ocular ultrasound examination showed short axial lengths (right eye 21.19 mm and left eye 21.21 mm) and no remarkable findings in the posterior segments of both eyes. On physical examination, the patient had a history of congenital heart disease and received cardiac surgery in middle childhood. She had a round face with full cheeks, upturned mouth corner, low-set ears, short stature (height 146 cm [2 SD], weight 50 kg), short neck, small hands and feet, thickened skin, stiff joints and normal intelligence (Figures 2A,B). She was born to consanguineous Chinese parents, and had mothered two children (Figure 3A). History of similar conditions in her parents and kids was denied. Serum biochemical tests were unremarkable. Digital radiography revealed short tubular bones with cone-shaped epiphysis in the feet and hands, an enlargement of cardiac shadow, and sternum closure metal wires indicative of previous surgery (Figures 2C–E). The patient was initially diagnosed as WMS based on the observed clinical symptoms, especially the ocular findings distinguishing for WMS (microspherophakia, lens subluxation, and high myopia). 0.2% bromonidine tartrate (Alphagan) and 1% brinzolamide (AZOPT) eye drops were given to relieve IOP; and the IOP was lowered to 24 mm Hg in right eye and 26 mm Hg in left eye on the third day upon hospitalization. After discharge from the hospital, Alphagan
FIGURE 2
Clinical features of the patient on physic and radiographic examinations. (A,B) Note the short hands and feet. (C,D) Digital radiography reveals short tubular bones and cone shaped epiphyses in extremities (R, right). (E) Note the enlarged cardiac shadow and sternum closure metal wires.

FIGURE 3
A pedigree of the family and Sanger sequencing results are shown. (A) The proband is indicated by a black arrow. (B) Sanger sequencing confirmed the homozygosity of ADAMTSL2 c.1966G>A (p.Gly656Ser) mutation in the proband.
and AZOPT were prescribed for daily use. The IOP was measured bimonthly and maintained at 22–23 mm Hg for both eyes.

**Genetic findings**

To genetically confirm the clinical diagnosis, the patient and her mother and daughter volunteered for genetic testing. WES revealed a homozygous ADAMTSL2 (NM_014694.4): c.1966G>A: p.Gly656Ser mutation in the patient. Sanger sequencing confirmed the homozygosity of the p. Gly656Ser variant in the patient, and the heterozygosity of the variant in the patient’s mother and daughter (Figure 3B). The variant has not been present in the ExAC, 1,000 Genomes or gnomAD database. The variant has been indexed in HGMD and classified as deleterious mutation (DM) as supported by two publications (Zhang et al., 2004; Piccolo et al., 2019). According to the ACMG guidelines, the variant is regarded as variant of uncertain significance (Rules PM2+PM3_supporting). Mutations in ADAMTSL2 have been known to cause GD. Mutations in ADAMTSL2 have been known to cause GD. Moreover, the p. Gly656Ser variant has previously been reported to cause autosomal recessive GD in compound heterozygosity with the p. Arg648Pro variant, and has a damaging effect based on *in silico* analysis (Zhang et al., 2004; Piccolo et al., 2019). In terms of the patient’s genotype and phenotype, the patient is eventually diagnosed with GD, and the homozygous ADAMTSL2 p. Gly656Ser mutation is considered as the genetic cause for the patient. Other genetic variants detected by WES but with insufficient evidence to support their pathogenicity were excluded for further analysis (Table 1).

**Discussion**

Both geleophysic dysplasia (GD) and Weill-Marchesani syndrome (WMS) belong to the acromelic dysplasias group of genetic skeletal disorders (Mortier et al., 2019). These two conditions share remarkable clinical and genetic overlap, presenting a challenge for differential diagnosis. In a previous study by Pimienta et al., a female patient with a characteristic ‘happy’ face was diagnosed with GD in early childhood. However, a rediagnosis of WMS was made in her teens based on the genetic finding of compound heterozygous mutations in ADAMTS10. Of note, her GD facial features had evolved to be atypical at reevaluation (Pimienta et al., 2013). In the present study, the patient presented to our center in her 30s and typical geleophysic facial features were not observed. Her ocular features including microspherophakia, lens subluxation, and high myopia were

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**Table 1** The variants with insufficient evidence to support their pathogenicity in whole exome sequencing for the family.

| Gene     | Chromosome location | Gene subregion | HGVS          | Mutation type | MAF             | Heterozygosity | ACMG grading | Diseases and inheritance                     |
|----------|---------------------|----------------|---------------|---------------|-----------------|----------------|--------------|---------------------------------------------|
| PKDCC    | chr2:42055393-42055393 | exon 5 | NM_138370.3: c.1222G>A: p.E408K | nonsynonymous SNV | 0.000588928 | Proband: Het; Mother: WT; Daughter: WT | VUS | Rhizomelic limb shortening with dysmorphic features, OMIM#618821, AR |
| PHE2     | chr3:190120473-190120473 | exon1 | NM_018192.4: c.259C>T: p.H87Y | nonsynonymous SNV |                          | Proband: Het; Mother: Het; Daughter: WT | VUS | High myopia with cataract and vitreoretinal degeneration, OMIM#614292, AR |
| SPARC    | chr2:151669684-151669684 | exon6 | NM_0031 18.4: c.431A>G: p.D144G | nonsynonymous SNV |                          | Proband: Het; Mother: WT; Daughter: WT | VUS | Osteogenesis imperfecta, OMIM#616507, AR |
| ESC O 2  | chr8:27776690-27776690 | exon3 | NM_0010 1740.3: c.382G>A: p.G128R | nonsynonymous SNV | 0.0069119 | Proband: Het; Mother: WT; Daughter: WT | VUS | Jaberg-Hayward syndrome, OMIM#216100, AR; Roberts-SC phocomelia syndrome, OMIM#268300, AR; Fiphyseal dysplasia multiple 4, OMIM#269004, AR |
| SLC26A2  | chr3:149981105-149981105 | exon3 | NM_000112.4: c.1512G>A: p.M504I | nonsynonymous SNV | 0.00380559 | Proband: Het; Mother: Het; Daughter: Het | VUS | Achondrogenesis, type ib, OMIM#009072, AR; De La Chapelle dysplasia, OMIM#2565050, AR; Diastrophic Dysplasia, OMIM#226000, AR; Epiphyseal dysplasia multiple 4, OMIM#226900, AR |

HGVS, human genome variation society; MAF, minor allele frequency; ACMG, american college of medical genetics and genomics; SNV, single nucleotide variation; Mother, the proband’s mother; Daughter, the proband’s daughter; Het, Heterozygous; WT, wild type; VUS, variant of uncertain significance; AR, autosomal recessive; OMIM, online mendelian inheritance in man.
arginine residue 648 are localized in the TSR3 domain. In silico analysis performed by Piccolo et al. show that the showed a less typical phenotype of the patient in our study is similar to that of the previously reported to cause autosomal recessive GD in ADAMTSL2. Both the glycine residue 656 and the compound heterozygosity with the p. Arg648Pro variant previously reported to cause autosomal recessive GD in (Piccolo et al., 2019). Both the glycine residue 656 and the arginine residue 648 are localized in the TSR3 domain. In silicon analysis performed by Piccolo et al. show that the p. Gly656Ser mutation probably has a damaging effect on the protein structure and function (Piccolo et al., 2019). In our study, the clinical features of an adult female patient with homozygous ADAMTSL2 p. Gly656Ser mutation was first described, providing new insights into the genotype-phenotype correlation of ADAMTSL2 mutations. It will be interesting to determine the potential fucosylation and secretion alterations of ADAMTSL2 Gly656Ser mutant, and further, the impact of the mutant on TGF-β pathways in future studies.

Collectively, our study has noted the clinical phenotype of a female adult patient with geleophysic dysplasia as implicated by her homozygous ADAMTSL2 p. Gly656Ser mutation. Our findings may serve as a reference for clinicians. Further analysis on posttranslational modification and secretion alterations of ADAMTSL2 Gly656Ser mutant will increase our understanding of the pathobiology of geleophysic dysplasia.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committees of Liuyang Jili Hospital (KYSZ 2022-005) and Hunan Provincial Maternal and Child Health Care Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML, YL, and HL recruited the study participants and collected the clinical data. HZ performed the sequencing analysis and interpreted the data. QP designed the study and reviewed all the data. WX wrote the manuscript draft and all authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.1014188/full#supplementary-material