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CLINICAL REPORT

Usher syndrome type 2A complicated with glycogen storage disease type 3 due to paternal uniparental isodisomy of chromosome 1 in a sporadic patient

Hua Wang[1] | **Liang Huo**[1] | **Yajian Wang**[2] | **Weiwei Sun**[2] | **Weiyue Gu**[2]

[1]Department of Pediatric Neurology, Shengjing Hospital of China Medical University, Shenyang, P.R. China

[2]Chigene (Beijing) Translational Medical Research Center Co., Ltd., Beijing, P.R. China

Correspondence
Hua Wang, Department of Pediatrics, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Shenyang 110004, PR China.
Email: shengjingwangh1@163.com

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Abstract

Background: The condition of uniparental disomy (UPD) occurs when an individual inherits two copies of a chromosome, or part of a chromosome, from one parent. Most cases of uniparental heterodisomy (UPhD) do not cause diseases, whereas cases of uniparental isodisomy (UPiD), while rare, may be pathogenic. Theoretically, UPiD may cause rare genetic diseases in a homozygous recessive manner.

Methods: A 4-year-old girl presented with congenital hearing loss, developmental delay, hepatomegaly, and other clinical features. She and her parents were genetically tested using trio whole exome sequencing (Trio-WES) and copy number variation sequencing (CNV-seq). In addition, we built a structural model to further examine the pathogenicity of the UPiD variants.

Results: Trio-WES identified a paternal UPiD in chromosome 1, and two homozygous pathogenic variants *AGL* c.4284T>G/p.Tyr1428* and *USH2A* c.6528T>A/p.Tyr2176* in the UPiD region. We further analyzed the pathogenicity of these two variations. The patient was diagnosed with Usher syndrome type 2A (USH2A) and glycogen storage disease type III (GSD3).

Conclusions: Our study reports a rare case of a patient carrying two pathogenic variants of different genes caused by paternal UPiD, supporting the potential application of Trio-WES in detecting and facilitating the diagnosis of UPD.

KEYWORDS

GSD3, trio whole exome sequencing, UPiD, USH2A

1 | INTRODUCTION

Uniparental disomy (UPD) refers to a condition in which both homologous chromosomes have been inherited from one parent and can present as uniparental isodisomy (UPiD), uniparental heterodisomy UPD (UPhD), or as a mix of both (UPhD/UPiD). In the case of UPhD, two different homologous chromosomes from one parent are present; however, in the case of UPiD, two identical homologous chromosomes are inherited from one parent. The general mechanisms leading to UPD include nondisjunction in meiosis I and II resulting in trisomy and

monosomy rescue, and mitotic recombination between chromatids occurring in early embryogenesis (Engel, 1980; Ledbetter & Engel, 1995; Robinson, 2000). UPD causes phenotypic abnormalities usually due to the effect of imprinted genes or homozygosity of autosomal recessive inheritance of variations.

In clinical practice, the differential diagnosis of Usher syndrome type 2A (USH2A, MIM#276901) and glycogen storage disease type III (GSD3, MIM#232400) is straight forward. The protein encoded by *USH2A* contains laminin epidermal growth factor and fibronectin III motifs that are involved in maintaining the normal function of the basal lamina and cell adhesion. *USH2A* is mainly expressed in the cochlea, eye, brain, and kidney (Eudy et al., 1998; Huang et al., 2002; Liu et al., 2007). The main phenotypes of USH2A are congenital sensorineural hearing defects and progressive retinitis pigmentation (RP). The RP in USH2A patients can be gradual or aggravated and late onset; thus, it may not be found in pediatric patients with USH2A (Eudy et al., 1998; Zahid et al., 2018). GSD3 is characterized by the AGL gene that encodes a glycogen debranching enzyme. *AGL*-related disorders result in abnormal glycogen with shortened outer chains that accumulate in the liver and muscles (GSD3 type A), or only in the liver (GSD3 type B). Patients with GSD3A, the most common form, typically have early onset hepatomegaly, hypoglycemia, and growth retardation (Endo et al., 2006); however, myasthenia gravis is much less profound in juvenile patients than in adults (Shen et al., 1996).

Patients with USH2A or GSD3 due to UPD have previously been reported and, in all cases, the UPD was paternal. However, the occurrence of these two disorders in one patient caused by UPD has never been documented. Herein, we report chromosome 1 paternal UPiD causing USH2A and GSD3 in a Chinese patient.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance and consent to participate

This study was performed in accordance with the Declaration of Helsinki Principles and was approved by the Shengjing Hospital of China Medical University (Ethics number: No. 2016-005).

2.2 | Subjects

The proband (a 4-year-old girl) and her family members were recruited from the Shengjing Hospital of China Medical University with the family consent. Written informed consent was obtained from the family and 3 ml of peripheral blood was collected from the proband and her family members.

2.3 | Genetic analysis

2.3.1 | Next-generation sequencing (NGS) and genetic data analysis

Briefly, genomic DNA was extracted from peripheral blood (2–4 ml) leukocytes using a BloodGen Midi Kit (CWBio). The purified DNA was then hybridized and enriched for whole exome sequencing (WES) according to the manufacturer's protocol. Libraries were captured using xGen Exome Research Panel, version 1.0 (Integrated DNA Technologies) and sequenced using an Illumina NovaSeq 6000 series sequencer (PE150) (Illumina). Raw image files were processed and the sequencing reads were aligned to the human reference genome (hg19) using the Burrows–Wheeler Alignment tool. The software tools GATK and ANNOVAR were used to analyze the candidate variants. A 0.5% frequency cut-off using the 1000 Genomes Project and ExAC databases was applied. The analysis of UPD was based on the general principle of H3M3, which calculates the ratio of variant homozygosity within a certain chromosome region. In our case, UPD was considered to exist when the ratio of homozygosity variants was >85%, without copy number change, and considering chromosomal regions >5 Mb. The parental origin of UPD was determined based on the genotype configurations of the parents.

For copy number variation sequencing (CNV-seq; also known as low-coverage whole genome sequencing), whole genomic DNA libraries were sequenced using the Illumina NovaSeq 6000, to a mean depth of 1×. The initial alignment and bioinformatics analysis of CNV-seq results were similar to those of WES, using self-developed software (Chigene) to analyze CNVs of 100 kb or larger and the Decipher, ClinVar, HGMD, and OMIM databases. Non-synonymous, loss-of-function, indel, duplication, splice site variants, and CNVs were taken for the identification of candidate variants.

2.3.2 | Sanger sequencing

For Sanger sequencing, the primers used were: AGL chr1:100381990–100381990 c.4284(exon32)T>G: GG3-17F TGTACTAATGCCGAGCTTATTCTG, GG3-17R CGCAC AATATCAAGACCTCAACT; USH2A chr1:216172358–216172358 c.6528(exon34)T>A: GY43-50SF AAACTTACTC CCAGCTTGATGAG, GY43-50SR-1 ATGGCAGGAGCC

ATATCACATT. The program was as follows: 95°C for 4 min, followed by 30 cycles of denaturation at 95°C for 30 s, annealing/extension temperature of (60/72) for 1 min, and a final extension of 72 for 10 min. The products were further sequenced with ABI 3730XL (Thermo Fisher Scientific).

2.3.3 | Structural modeling

Structural modeling was performed as described previously (Liu et al., 2017). Secondary structural prediction and 3D structure searching were performed using Phyre2. The x-ray crystal structures of glycogen debranching enzyme from the Candida glabrata (5d0f) were downloaded from PDB (http://www.rcsb.org/pdb/home/home.do) and the structures were visualized using PyMOL software (http://www.pymol.org/).

3 | RESULTS

3.1 | Clinical presentation

The patient was a 4-year-old girl, and she was committed in our hospital because of excessive fatigue in both lower limbs after having moderate fever for 4 days. The patient is the second child with normal parents (45-year-old father, 43-year-old mother) and with a normal older brother (17 year old). In spite of congenital deafness, she had abdominal bloating and swallowing difficulty in the neonatal period. She has no family history of the similar signs. She had cochlear implant at age of 1 year because of congenital deafness.

At the time of her commitment, physical examination showed that she had congenital hearing loss (she was living with implanted cochlear), normal pharyngeal reflex but difficulty in swallowing, delayed language development, poor learning ability, swollen liver with the lower edge 9 cm below the right costal, and visible abdominal wall varices, but no ocular conditions. At the same time, routine blood tests showed infection and mild anemia: white blood cells (WBC), 10.49 X 109/L, ratio of neutrophil count (NC), 26.70%, hemoglobin (HB), 98 g/L. Blood biochemistry showed elevated levels of creatine kinase (CK) and CK-MB that are 400 U/L and 30 U/L, respectively. Intrahepatic and intra-muscle tissue enzymatic tests showed alanine aminotransferase (ALT), 187 U/L, aspartate aminotransferase (AST), 307 U/L, triglyceride, 7.83 mmol/L, CK, 385 U/L, CK-MB, 39 U/L, lactate dehydrogenase (LDH), 478 U/L, and myoglobin (MYO), 34.1 μg/L (Table 1). The Color Doppler ultrasound examination confirmed the swelling of liver that the lower edge of liver was 9.0 cm below the right costal, and 13.4 cm obliquely protruding to the right subcostal area.

Raw corn starch therapy: corn starch 1.75 g–2.50 g/kg was mixed with drinking water and taken orally four times a day, respectively, between meals, before bed, and at night, Q6h. Three meals everyday as usual. Symptomatic treatment was performed. The patient was followed up for 8 months. After treatment, no hypoglycemia occurred in this child. The fasting blood glucose was maintained above 3.9 mmol/L (700 mg/L), lactic acid in blood was 2.0–5.0 mmol/L, and lactic acid in urinary was ≤0.6 mmol/L. Motor development: the patient can walk and ride bicycle by herself. Language development: the patient can speak 3–5 words.

3.2 | Identification of variations

Trio-WES and whole genome CNV-seq were conducted for the family using 2 mL of peripheral blood sample as described previously (Liu et al., 2017). Initially, we identified a homozygous variation NM_000642:c.4284T>G/p.Tyr1428* in *AGL*, which is associated with glycogen accumulation syndrome type 3, but the hearing abnormality could not be explained. Further analysis revealed

TABLE 1 Blood biochemistry test results of the patient

Parameters	Test value	Normal range
Creatine phosphokinase, CK	400 g/L	26–192 g/L
Lactate dehydrogenase, LDH	478 U/L	106–211 U/L
Aspartate aminotransferase, AST	307 U/L	8–38 U/L
Alanine aminotransferase, ALT	187 U/L	0–75 U/L
r-Glutamyl transferase, r-GT	470 U/L	16–73 U/L
Uric acid	420 μmol/L	155–357 umol/L
Fasting blood glucose, FBG	3.3 mmol/L	3.9–6.1 mmol/L
Triglycerides	4.83 mmol/L	0.2–2.31 mmol/L
Cholesterol	8.91 mmol/L	3.36–6.46 mmol/L
Lactate	4.6 mmol/L	0.7–2.1 mmol/L

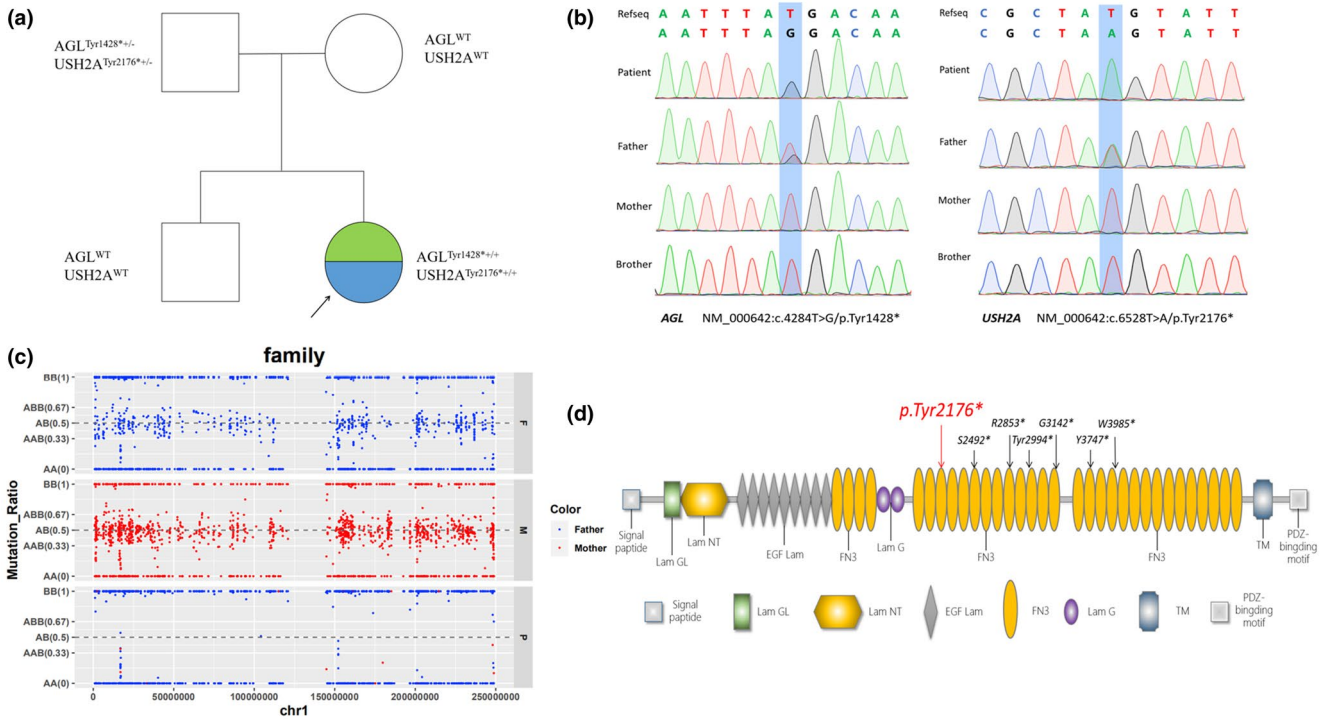

FIGURE 1 Sanger sequencing results of patients and their parents and UPD results of WES analysis. The patient is the second child of the family (a). Sanger sequencing confirmed that the patient has homozygous variations in the *AGL* gene and *USH2A* gene, and the father of the child is heterozygous, but the mother and brother of the child is wild type (b). WES analysis: UPD results showed that the patient were almost always homozygous variations (AA/BB) on chromosome 1; red indicates variations from her mother, blue indicates variations from her father (c). Our patient's variation (red) is located in the front of the USH2A protein, and the pathogenic nonsense variation (black) was submitted by multiple institutions of ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar) (d)

TABLE 2 Results of CNV test for the patient and her parents

CNV position on Chr1 (Hg19)	CNV length	Patient	Father	Mother	Annotation
660820–827685	166.87 Kb	HD	WT	WT	Frequency >1% (DGV); benign (ClinVar, Decipher)
16872446–17125658	253.21 Kb	HD	WT	WT	Benign (ClinVar, Decipher)
12853268–13052998	199.73 Kb	HL	WT	WT	Frequency >1% (DGV); pathogenicity uncertain(ClinVar, Decipher)

Abbreviations: HD, heterozygous duplication; HL, heterozygous deletion; WT, wild type.

another homozygous variation, NM_206933:c.6528T>A/p.Tyr2176*, in *USH2A*, a gene related with hearing disorders. Interestingly, both variations were heterozygous in the father and wild type in the mother, which was further confirmed by Sanger sequencing (Figure 1a,b).

Trio-WES data analysis revealed the presence of UPiD on chromosome 1, including both *AGL* and *USH2A*. The genotype in the UPiD region was inherited from the father, indicating paternal UPiD (Figure 1c). Whole genome CNV analysis showed no pathogenic changes in the copy number in the parents or the patient (Table 2).

The two variations have not been reported in any SNP database (dbSNP/1000Genomes/ExAC/ESP6500/gnomAD EAST and gnomAD), classified as pathogenic (PVS1+PS1+PM2+PP3) according to the American College of Medical Genetics guidelines (Richards et al., 2015). The USH2A p. Tyr2176* variant results in loss of function in most of the functional domain (Figure 1d). Notably, the AGL p. Tyr1428* variant is located at the C-terminus (total 1532 amino acids) which has not been reported in the literature and leads to a truncated protein possibly causing nonsense-mediated mRNA decay

(Kuzmiak & Maquat, 2006). Hogrel et al (Decostre et al., 2016) reported that a GSD3 patient carried an AGL c.4323_4324insAA/p.Gly1442fs homozygous variant and presented with symptoms including hepatomegaly, hypertrophic cardiomyopathy, and plantar flexion, which further suggests that C-terminus variants can cause disease.

3.3 | In silico analysis

In order to further predict the pathogenicity of C-terminus variation of *AGL*, our structural model of AGL shows that p.Tyr1407 constitutes the pocket involved in substrate binding (Figure 2a–c). The truncated variant could lead to pre-termination, leading to loss of about half of the binding pocket, impacting enzyme function (Figure 2d). Collectively, the structural modeling data suggest the role of this variant in the etiology of GSD3.

4 | DISCUSSION

In individuals with UPiD, both biallelic genes come from the father or mother, and the chromosomal effect can be complete or partial (segmental). At present, the reported number of patients with segmental UPiD only accounts for about 10% of the online UPD database (Erger et al., 2018). Although the proband exhibited segmental UPiD, it was almost complete UPiD (~99% paternal chr1), which also led to the majority of biallele in chr1, including the pathogenic *AGL* and *USH2A* variations carried by the father. UPD is typically diagnosed by microsatellite marker analysis or SNP array analysis. Recently, Gilissen et al. (Yauy et al., 2019) applied Exome sequencing (ES) to identify UPD in 29,723 individuals; among which, 4912 were subsequently tested by ES-Trio. The results showed that ES can detect multiple types of UPD, including segmental UPD, UPiD, and mixed UPD, and are consistent with those of previous SNP array analysis studies. In this study, we successfully identified a case of paternal UPiD by Trio-WES, which further demonstrated the potential of ES as a routine diagnostic method for UPD.

It is extremely rare for a patient to have two recessive diseases caused by UPiD. To the best of our knowledge, there is only one reported case of *USH2A* homozygous variation caused by UPD, and the patient displayed non-syndromic RP without hearing impairment (Rivolta et al., 2002). However, our patient did not exhibit RP,

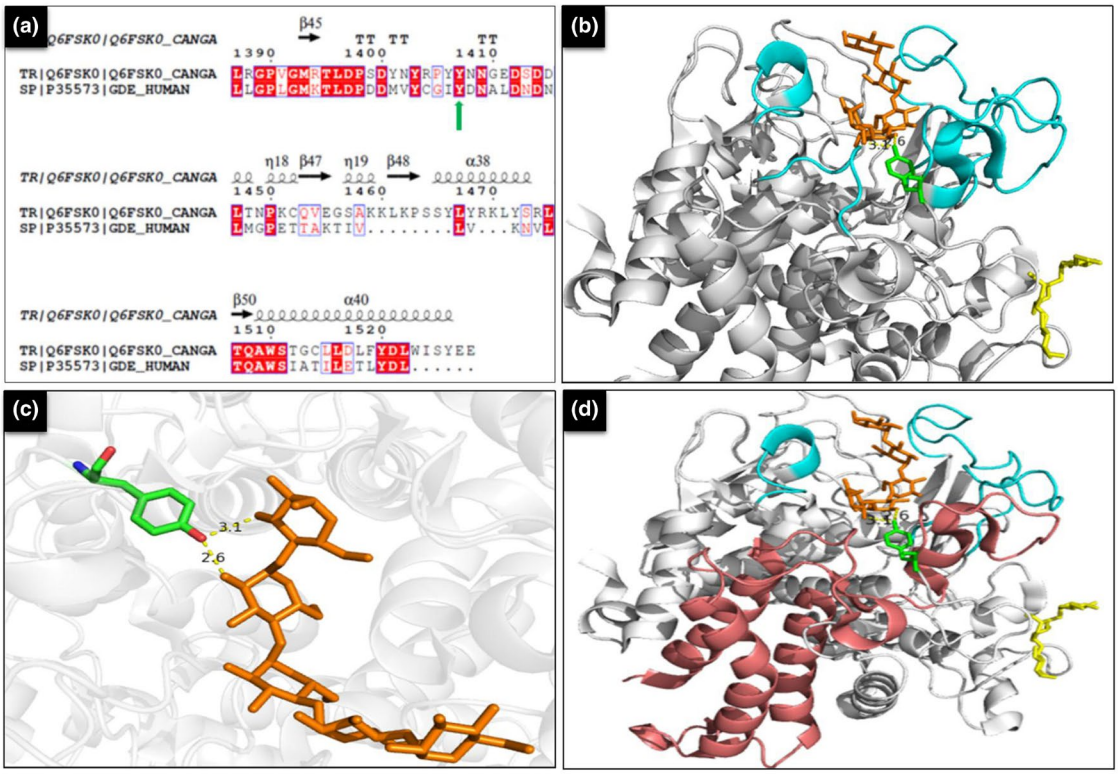

FIGURE 2 Structural modeling demonstrated that p. Tyr1428* variation in AGL is possible to be pathogenic. Human AGL and glycogen debranching enzyme from the *Candida glabrata* exhibit high homology, and p. Tyr1428 of AGL (green arrow) is aligned to p. Tyr1407 of glycogen debranching enzyme (a). The p. Tyr1407 of glycogen debranching enzyme could directly be associated with the substrate (b) and is involved in the formation of the pocket with combined substrate (blue, c). The p. Tyr1428* variant could lead to pre-termination, resulting in a protein without sequences that constitute about half of the binding pocket (d)

TABLE 3 Homozygous variants which are currently associated with OMIM disease in the LOH region on Chr1 of the patient

Gene	Location	OMIM	Nucleotide change	Nucleotide change	ACMG class	dbSNP	1000 genomes	ExAC	ESP6500	gnomAD EAST
ABCA4	1p22	153800	c.673(exon6)G>A	p.V225 M	Uncertain significance	0.000222987	0.0024	0.0039		0.0025
ABCA4	1p22	248200	c.673(exon6)G>A	p.V225 M	Uncertain significance	0.000222987	0.0024	0.0039		0.0025
ABCA4	1p22	601718	c.673(exon6)G>A	p.V225 M	Uncertain significance	0.000222987	0.0024	0.0039		0.0025
ABCA4	1p22	604116	c.673(exon6)G>A	p.V225 M	Uncertain significance	0.000222987	0.0024	0.0039		0.0025
AGL	1p21	232400	c.4284(exon32)T>G	p.Y1428X,105	Pathogenic					
AGRN	1p36.33	615120	c.3751+19(IVS22)G>A		Uncertain significance	1.59276E-05		0.0008		
AGRN	1p36.33	615120	c.5564–18(IVS32)C>T		Uncertain significance	1.59276E-05	0.0024	0.0006		
CACNA1S	1q32	170400	c.4668+44(IVS38)C>A		Uncertain significance					
CACNA1S	1q32	188580	c.4668+44(IVS38)C>A		Uncertain significance					
CACNA1S	1q32	601887	c.4668+44(IVS38)C>A		Uncertain significance					
CTPS1	1p34.1	615897	c.1411(exon15)G>A	p.A471T	Uncertain significance	0.000326516	0	0.0007	0.0001	0
FDPS	1q22	616631	c.773+42(IVS7)C>T		Uncertain significance	0.000493756	0.0072	0.0057	0.0002	0.0074
HMGCL	1p36.1-p35	246450	c.594(exon7)C>T	p.Y198Y	Uncertain significance	0.000238914	0.0048	0.0012	0.0001	0.0006
NFIA	1p31.3-p31.2	613735	c.-259(exon1)T>C		Uncertain significance					
PTPRC	1q31-q32	608971	c.3509+37(IVS31)T>C		Uncertain significance			0.0001		
PTPRC	1q31-q32	609532	c.3509+37(IVS31)T>C		Uncertain significance			0.0001		
RYR2	1q43	600996	c.*106(exon105)C>T		Uncertain significance	0.000143349				

(Continues)

TABLE 3 (Continued)

Gene	Location	OMIM	Nucleotide change	Nucleotide change	ACMG class	dbSNP	1000 genomes	ExAC	ESP6500	gnomAD EAST
RYR2	1q43	604772	c.*106(exon105)C>T		Uncertain significance	0.000143349				
SLC6A17	1p13.3	616269	c.*32(exon12)C>G		Uncertain significance	0.000127421		0.0014		0.0012
USH2A	1q41	276901	c.6528(exon34)T>A	p.Y2176X,3027	Pathogenic					
USH2A	1q41	613809	c.6528(exon34)T>A	p.Y2176X,3027	Pathogenic					

probably because she was too young. A multi-sample study on patients with *USH2A* variations revealed that the median age for night blindness (a most common symptom of RP) is 24.5 years (range 12–42 years) (Lenassi et al., 2015). Another major feature of USH2A, deafness, explains the congenital deafness observed in our patient.

The first case of GSD3 caused by UPD was reported recently for a patient with serious liver lesions and dysfunction, and developmental retardation (Ponzi et al., 2019). Similar to this case, our patient manifested typical characteristics of glycogen accumulation, such as liver enlargement and stunted growth. Although the c.4284T>G variation in *AGL* has been previously reported, pathogenesis associated with this variation was not clear (Lu et al., 2016). Structural modeling and the phenotype of our patient helped to elucidate the pathogenicity of this variation.

Moreover, analysis of the homozygous variations in all of the genes in the loss of heterozygosity region (Table 3) showed that only the *AGL* and *USH2A* variations are pathogenic. The maternal imprinting gene *DIRAS3* located on chromosome 1 may cause growth retardation (Fuke et al., 2013; Lu et al., 2016; Ponzi et al., 2019); however, the growth of our patient was normal for her age, and no variation in the gene was detected although the loss of heterozygosity region included *DIRAS*3.

After USH2A and GSD3 diagnosis, the patient was given cornmeal treatment, and symptoms improved remarkably. At 8-month follow-up, the fasting blood glucose level was above 3.9 mmol/L and blood lactate level was 2.0–5.0 mmol/L. Her liver was not enlarged. Her mobility and communication improved considerably.

As far as we know, this is the first case which UPD on chromosome 1 causes two gene pathogenic variations at the same time. Interestingly, this is also the first case in which paternal LOH caused two homozygous variations. Our case shows that two pathogenic variants on the same chromosome can cause disease at the same time, which brings enlightenment to the diagnosis of some complex phenotypes. WES can be more widely used in the field of genetic disease detection. It has shown a strong ability to identify different types of variations in the genome, including SNVs, CNVs, and UPD (Xiao et al., 2019), and can also prompt the variation of imprinted genes. Compared with single person WES, Trio-WES can further improve the recognition rate of different types of variations. Concurrently, rich exon data may reveal more findings in a retrospective analysis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

W.H and H.L conceived and documented the case; H.L, W.Y, G.W, and S.W collected the data; W.H and G.W contributed data or analysis tools, performed the analysis, and wrote the paper. All authors have read and approved the manuscript.

EHTICS STATEMENT

This study was performed with a written, informed consent of the proband's parents.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author.

ORCID

Hua Wang https://orcid.org/0000-0001-8701-0129

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