

CASE REPORT

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Clinical features associated with maternal uniparental disomy for chromosome 6

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Abstract

Background Maternal uniparental disomy for chromosome 6 (upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat) has been previously reported to cause intrauterine growth restriction (IUGR), but the specific clinical phenotype has not been defined. Based on clinical data from two new cases and patients from the literature, specific phenotypes and mechanisms will be discussed further.

Case presentation : In case 1, a maternal isodisomy mixed with a heterodisomy was found on chromosome 6, including a regional absence of heterozygosity between 6q23.3 and 6q27. In case 2, a homozygous *SCUBE3* mutation and upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat, involving the 6p21.1–25.1 region were found. Clinical data related to upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat were also reviewed. Of all the 21 reported cases with upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat (including our 2 cases), 18 (85.7%) presented IUGR.

Conclusions The phenotypes of the two newly identified patients with upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat further suggest that IUGR is associated with upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat and case 2 is the first reported upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat patient with a homozygous *SCUBE3* gene mutation. However, the specific phenotypes involved in upd(Cajaiba MM, Witchel S, Madan-Khetarpal S, Hoover J, Hoffner L, Macpherson T, et al. Prenatal diagnosis of trisomy 6 rescue resulting in paternal UPD6 with novel placental findings. *Am J Med Genet Part A.* 2011;155 A(8):1996–2002.)mat and the related mechanisms need to be further studied.

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Keywords Failure to thrive, Intrauterine growth restriction, Uniparental disomy, maternal, Chromosome 6, *SCUBE3*

Background

Uniparental disomy (UPD), first reported by Engel in 1980 [1], is defined as the inheritance of both copies of genetic material from one parent and can be classified into isodisomy and heterodisomy based on the underlying mechanism. In uniparental heterodisomy, a child inherits both alleles from a single parent while a single parental allele is duplicated in uniparental isodisomy [2]. Heterodisomy and isodisomy can occur on the same chromosome, making it difficult to distinguish them. UPD usually arises through meiotic non-disjunction with mitotic correction or gametic complementation [3].

If the UPD affects a chromosome harboring imprinted genes, it can result in an imprinting disorder. Imprinted genes tend to cluster, and the imprinting control is often not restricted to a single gene at an imprinted locus but affects the expression of several factors. The clinical outcome in the case of microduplications or microdeletions is influenced by the size, the breakpoint positions, and the parental inheritance of the imbalance as well as by the imprinting status of the affected genes [4]. Furthermore, there is the potential risk of homozygosity of an autosomal-recessive mutation in the case of uniparental isodisomy. In this case, homozygous mutations can be detected in the patient. And one parent is heterozygous for the mutant vector, while the other parent is homozygous for the wild-type allele. A third pathobiological mechanism can be delineated from UPD formation mechanisms: uniparental heterodisomy may be the result of a trisomic rescue [5].

The phenotype of paternal UPD6 (upd [6]pat) results from the biallelic expression of the maternally imprinted, paternally expressed *PLAGL1* and *HYMAI* genes and includes transient neonatal diabetes mellitus, intrauterine growth restriction (IUGR), macroglossia, and minor anomalies [6].

The first reported maternal uniparental disomy for chromosome 6 (upd [6]mat) was found in kidney transplant patients in 1996 [7]. However, upd [6]mat is extremely rare, with only about 20 cases reported so far. Its exact phenotype and associated mechanisms are still unknown, with IUGR being the most common phenotype in the patients reported. Herein, we report 2 upd [6]mat pediatric patients presented with IUGR to highlight the specific phenotype and mechanism of upd [6]mat.

Case presentation

Clinical report

Case 1 is a 6 years and 8 months boy admitted to our hospital as growth retardation. He was the second child of his non-consanguineous marriage parents. He was

born by cesarean section at 32 weeks gestation with a birth weight of 1.3 kg. After birth, he had feeding difficulties and had a gastrostomy at the age of 1 year. He started walking and talking when he was one year old, and neither his intellectual nor physical ability significantly regressed. Additionally, he had allergic rhinitis. When he was six and a half years old, his bone age was about nine years. The insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone were 250 ng/ml and 2.92 μ mol/L, respectively. The adrenal routine scan showed no obvious abnormalities in local hospital. His 8-year-old brother was 129 cm tall. His mother is 158 cm tall, while his father is 160 cm. The heights of the paternal grandmother and grandfather are 156 cm and 167 cm, respectively. The maternal grandmother is 156 cm tall and the maternal grandfather is 168 cm tall.

Physical examination revealed a weight of 24 kg and a height of 117 cm (-2SD-1SD). He was found to have strange body hair, penetrating hands, and a high palatal arch despite having a uniform figure and appearance. His cardiopulmonary auscultation revealed no abnormalities. The bilateral testicular stage was G1 and the pubic hair stage was Ph1.

The basic luteinizing hormone was 0.12 IU/l, follicle-stimulating hormone was 1.14 IU/l, prolactin was 153.4 mIU/l, testosterone was lower than 0.45 nmol/l and human chorionic gonadotropin was lower than 1.2 IU/l. Adrenocorticotrophic hormone (ACTH) stimulation test showed the cortisol levels of 13.6, 27.6, 28.2, and 32.4 μ g/dl, respectively (basic normal range, 5–25 μ g/dl), dehydroepiandrosterone sulfate levels of 224, 208, 234 and 241 ng/ml (basic normal range for prepubertal children, <80.1 ng/ml), the 17 α -hydroxyprogesterone levels of 1.1, 2, 1.8 and 1.2 ng/ml, respectively (basic normal range, <11.58 ng/ml), and testosterone levels of 0.47, 0.57, 0.62 and 0.58 nmol/l at 0, 30, 60 and 90 min. The fasting blood glucose was 5.59 mmol/L and the insulin was 95.6 pmol/L. Testicular echo was found on the left scrotum scan (1.7 cm \times 1.0 cm \times 0.8 cm), and on the right scrotum scan (1.8 cm \times 1.1 cm \times 0.8 cm). Blood gases, thyroid function, magnetic resonance imaging (MRI) of the pituitary, electrocardiogram, and abdominal ultrasound were unremarkable.

Case, a 9-year-old girl, presented to our unit because of growth retardation and poor response to recombinant human growth hormone (rhGH) treatment. She was the first child of her non-consanguineous marriage parents. She was born by cesarean section at 36 weeks gestation with a birth weight of 1.2 kg. she had normal development milestones without significant abnormal intelligence. However, growth retardation was noted with

a height of 118.6 cm (-2SD-1SD) at the age of 8. Bone age showed 8 carpal osteogenesis, ulnar shaft protrusion, and sesamoid bone present, which implied about 10.5 years old. Growth hormone (GH) stimulation test showed a peak GH of 18.39 ng/ml and an IGF-1 of 266 ng/ml in the local hospital. The basic luteinizing hormone, follicle-stimulating hormone, testosterone, human chorionic gonadotropin, and 17 α -hydroxyprogesterone levels were within the normal range for prepubertal children. Liver or kidney function, thyroid function, MRI of the pituitary, and abdominal ultrasound were unremarkable. Small for gestational age (SGA) was regarded and rhGH was administered. The dose of rhGH was gradually increased from the initial 2.5U to 4U (about 0.19 U/kg). However, her height was poor increased with about 2 cm in 6 months. The mother's second fetus was aborted because of the deformity (without detail data). Her father is 168 cm tall and her mother is 155 cm tall. The maternal grandmother's height is 140 cm.

Physical examination revealed a height of 124.5 cm (-2SD-1SD) and a weight of 21.1 kg (-2SD-1SD). She has a well-proportioned figure and no distinctive features were noted. Her cardiopulmonary auscultation revealed no abnormalities. The breast stage was B1 and the pubic hair stage was Ph1.

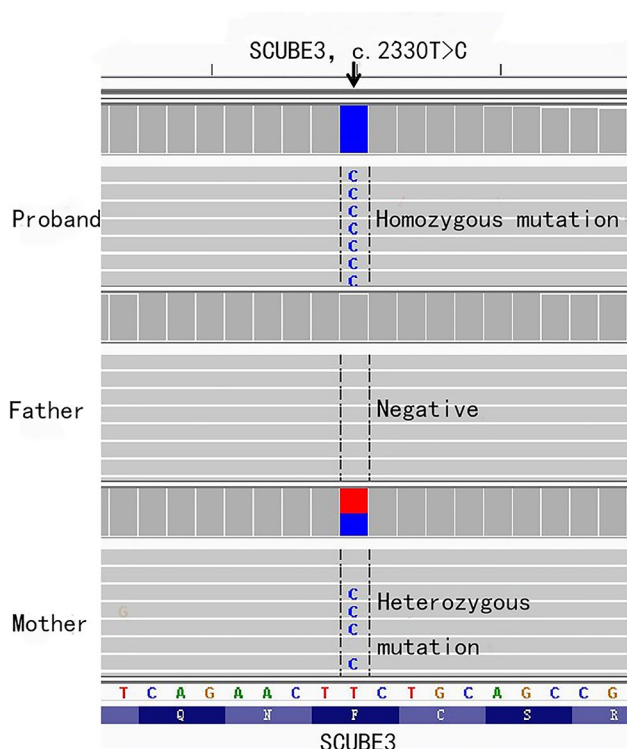


Fig. 1 The next generation sequencing results of the case 2 and parents: the top is the proband's, the middle is the father's, and the bottom is the mother's

Genetic testing

In case 1, genetic testing is done because parents want to know why their children lag behind their peers. chromosomal microarray analysis (CMA) and whole exome sequencing (WES) were performed, and *CYP21A2* gene rearrangement was detected to further exclude adrenocortical hyperplasia as well. WES was performed for case 2 genetic testing was carried out as growth retardation and poor response of rhGH. The sequencing results were analyzed by bioinformatics and interpreted by pedigree genetics.

Results of genetic testing

In case 1, no copy number changes were identified by CMA analysis. However, the single nucleotide polymorphism (SNP) component of this assay identified 2 large regions of the absence of heterozygosity (AOH) on chromosome 6, including a 55 Mb in 6p21.2q15 (37 496 966-92 651 403) region and a 34 Mb 6q23.3q27 (136 295 353-170 903 114) region. At least 199 genes were enrolled in this region, which includes the imprinted region. The presence of a large region of AOH on an imprinted chromosome may be indicative of UPD6. The trio-WES data showed a UPD6, which originated from his mother. This suggested a uniparental isodisomy mixed with a uniparental heterodisomy. No rearrangements or hot spot mutations were detected in the *CYP21A2* gene.

A homozygous missense variant c.2330T>C (p. Phe-777Ser) in the exon 18 of the *SCUBE3* gene was found in case 2. It was noted that a similar heterozygous variant was found in her mother but not in her father (Fig. 1). Deep data mining analysis showed that the SNPs in the 6 318 921-42 236 498 of the 6p21.1-25.1 region (about 36 Mb) were homozygous and inherited from the mother with normal signal intensity, which suggested the mUPD in this region and the homozygous variant detected in this patient was associated with upd [6]mat.

Following-up

Case 1 has been taking 3.5 U (about 0.19 U/kg) of rhGH powder daily for about 4 months and has gained about 3 cm in height. Case 2 discontinued rhGH treatment because of poor response to the rhGH treatment.

Literature review

In PubMed and Wangfang Date, articles related to upd [6]mat are retrieved by searching for keywords "maternal uniparental disomy chromosome 6" or "mat UPD6" or "upd [6]mat" till July 30, 2022.

Only 21 cases (including our 2 cases) have been reported. Although phenotype was different in different cases, IUGR was present in 18 of 21 cases (85.7%) and postnatal short stature was present in 11 cases (52.4%), as showed Table 1 [4, 7-22].

Discussion and conclusions

UPD is a rare event that can lead to disease phenotypes through different mechanisms: genomic imprinting, mosaics, or uncovering autosomal recessive genetic variants [5]. Due to the rarity of upd [6]mat, its mechanism and phenotype are not well understood.

One of the possible mechanisms by which upd [6]mat contributes to the phenotype is the disturbance of imprinted genes. Disturbances of imprinting genes are known to cause abnormalities in fetal growth and placental function [23, 24]. Of the 21 reported upd [6]mat patients, 18 had IUGR. IUGR may be the specific phenotype of upd [6]mat and the occurrence of IUGR in upd [6]mat patients is most likely caused by the disorder of the imprinted gene. Genetic detection of case 1 revealed the presence of upd [6]mat, mainly involving 6q23.3q27, which contains the imprinted genes *HYMAI* and *PLAGL1* (at 6q24). The patient presents with IUGR and short stature. In upd [6]mat, the overexpression of imprinted genes *PLAGL1* and *HYMAI* lead to IUGR and other specific clinical phenotypes, while in case 1, the absence of imprinted genes also indicates IUGR. We hypothesized that not imprinted genes *HYMAI* and *PLAGL1*, but other imprinted genes on chromosome 6 are responsible for IUGR in case 1. The effect of *IGF2R* (at 6q25.3) methylation on intrauterine growth and upd [6]mat has been reported [14]. *PRIM2*, *PXDC1*, and other imprinted genes on chromosome 6 can be further investigated.

Upd [6]mat can also lead to phenotypes by uncovering homozygous mutations in autosomal recessive genes. Case 2 has an autosomal recessive disorder caused by upd [6]mat, which is the first reported case of upd [6]mat with *SCUBE3* mutation. The *SCUBE3* gene is highly expressed in primary osteoblasts and long bones and is localized on human chromosome 6p21.3 [25]. *SCUBE3* loss-of-function causes a recognizable recessive developmental disorder. The common clinical manifestations of homozygous *SCUBE3* mutations are short stature, facial deformities, and skeletal abnormalities with or without cardiac abnormalities [26]. A homozygous missense variant c.2330T>C (p.Phe777Ser) in exon18 of the *SCUBE3* gene was found in case 2. It was noted that a similar heterozygous variant was found in her mother but not in her father. The patient presented with IUGR, further suggesting that upd [6]mat is associated with IUGR and may be due to an autosomal recessive disorder caused by upd [6]mat. Case 2 showed short stature, but no facial deformity or skeletal abnormality was found on physical examination, and the presence of cardiac abnormality requires further examination.

Upd [6]mat can be found in the mechanism exploration of some rare diseases, such as Silver-Russell syndrome [5]. There are also some patients with upd [6]mat whose phenotype does not appear abnormal and are ignored [20]. Due to the limitation of the number of upd [6]mat cases, the mechanism by which it leads to the phenotype

Table 1 Overview on the upd [6]mat patients reported in the literature

Ref.	Sex	Placenta	Birth at	IUGR	Reported Hetero-/Isodisomy	Failure to thrive	Monogenic mutation
[7]	M	NR	At term	Yes	Isodisomy	Yes	---
[8]	F	Normal	At term	Yes	Isodisomy	NR	<i>CYP21</i>
[9]	M	Normal	23w	No	Heterodisomy	NR	---
[10]	M	NR	36w	Yes	Isodisomy	Yes	<i>CYP21</i>
[11]	M	NR	At term	No	Isodisomy	Yes	<i>MOCS1</i>
[12]	M	NR	At term	No	Heterodisomy	NR	---
[13]	M	NR	36w	Yes	Hetero-/Isodisomy	Yes	<i>CUL7</i>
[14]	F	Small	35w	Yes	Isodisomy	Yes	---
[4]	F	NR	34w	Yes	Heterodisomy	Yes	---
[15]	NR	NR	NR	Yes	Isodisomy	NR	<i>TULP1</i>
[16]	F	NR	29w	Yes	Isodisomy	No	---
[17]	M	Placental dysfunction	28w	Yes	Isodisomy	Yes	---
[19]	F	NR	34w	Yes	Heterodisomy	NR	---
[19]	F	NR	32w	Yes	Heterodisomy	NR	---
[18]	F	Placental dysfunction	27 + 6w	Yes	Hetero-/Isodisomy	Yes	---
[18]	M	NR	30w	Yes	Hetero-/Isodisomy	NR	<i>CYP21</i>
[20]	F	NR	32w	Yes	Isodisomy	Yes	---
[21]	NR	NR	At term	Yes	Isodisomy	NR	<i>TULP1</i>
[22]	M	NR	At term	Yes	Isodisomy	NR	<i>IFNGR1</i>
Case1	M	NR	32w	Yes	Hetero-/Isodisomy	Yes	---
Case2	F	NR	36w	Yes	Isodisomy	Yes	<i>SCUBE3</i>

NR, not reported; w, week

Hetero-/Isodisomy: this discrimination only refers to the regions which have been analysed

is unclear. At present, more related cases need to be found, and the specific phenotype and mechanism that lead to them of upd [6]mat should be actively explored.

In conclusion, our patients further provided evidence that upd [6]mat is associated with IUGR and we report the first upd [6]mat patient with *SCUBE3* mutation. Further understanding of the specific phenotype of upd [6]mat and exploring its pathogenesis will not only facilitate the detection of upd [6]mat patients and early treatment but also help to expand the mutation spectrum and pathogenesis of various rare diseases, which will help to carry out genetic counseling and reduce the incidence of the disease.

Abbreviations

UPD	Uniparental disomy
UPD6	Uniparental disomy for chromosome 6
upd(6)mat	Maternal uniparental disomy for chromosome 6
upd(6)pat	Paternal UPD6 uniparental disomy for chromosome 6
IUGR	Intrauterine growth restriction
CMA	Chromosomal microarray analysis
WES	Whole exome sequencing
SNP	Single nucleotide polymorphism
IGF-1	Insulin-like growth factor 1
MRI	Magnetic resonance imaging
GH	Growth hormone
rhGH	Recombinant human growth hormone
AOH	Absence of heterozygosity
ACTH	Adrenocorticotropic hormone

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Author contributions

Chao-Chun Zou conceptualized the study. Jing-Wen Li and Yan-Jie Qian drafted the initial manuscript. Shao-Jia Mao, Yun-Qi Chao, Yi-Fang Qin, Chen-Xi Hu and Zheng-Lan Li polished and revised the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Our cases have been approved for research by the Medical Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine, under review number 2022-IRB-255.

Consent for publication

The consent of their parents or legal guardians has been obtained.

Competing interests

The authors declare no competing interests.

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