

Review

Uniparental disomy as a cause of pediatric endocrine disorders

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Abstract. Uniparental disomy (UPD) refers to a condition in which two homologous chromosomes or chromosomal regions are inherited from one parent. Recent studies have shown that UPD is not rare among the general population, arising from trisomy rescue, gamete complementation, and other mechanisms. Although UPD is not necessarily pathogenic, it can lead to various disease phenotypes by causing imprinting disorders or by unmasking autosomal recessive mutations. Notably, known UPD-mediated autosomal recessive disorders include congenital adrenal hyperplasia due to 21-hydroxylase deficiency, 11 β -hydroxylase deficiency, and 3 β -hydroxysteroid dehydrogenase deficiency. In addition, UPD can occur in combination with additional cytogenetic abnormalities that may affect growth and development. Therefore, UPD represents a clinically important condition that accounts for a certain percentage of the etiology of growth failure and endocrine abnormalities. Although UPD is barely detectable by standard karyotyping or sequence analyses, it can be screened by single nucleotide polymorphism- and microsatellite-genotyping of patients and their parents, or by DNA methylation analysis of the patients. This mini-review introduces the underlying mechanisms and phenotypic consequences of UPD in association with pediatric endocrine disorders.

Key words: DNA methylation, growth failure, imprinting, uniparental disomy, unmasked autosomal recessive mutation

Introduction

Uniparental disomy (UPD) refers to a type of chromosomal variation in which two homologous chromosomes or chromosomal

regions are inherited from one parent (1). UPD includes uniparental heterodisomy and uniparental isodisomy. Patients with uniparental heterodisomy inherit two different alleles from one parent, whereas those with uniparental isodisomy carry two identical copies of one allele from either the mother or the father. Moreover, a substantial percentage of UPD patients harbor a combination of heterodisomy and isodisomy. Notably, isodisomy can unmask autosomal recessive mutations.

Currently, UPD is a hot topic in the fields of human genetics and reproductive medicine. Recent studies have shown that UPD is present in nearly 1 of 3,500 live births (2). Although UPD is not necessarily pathogenic, it can result

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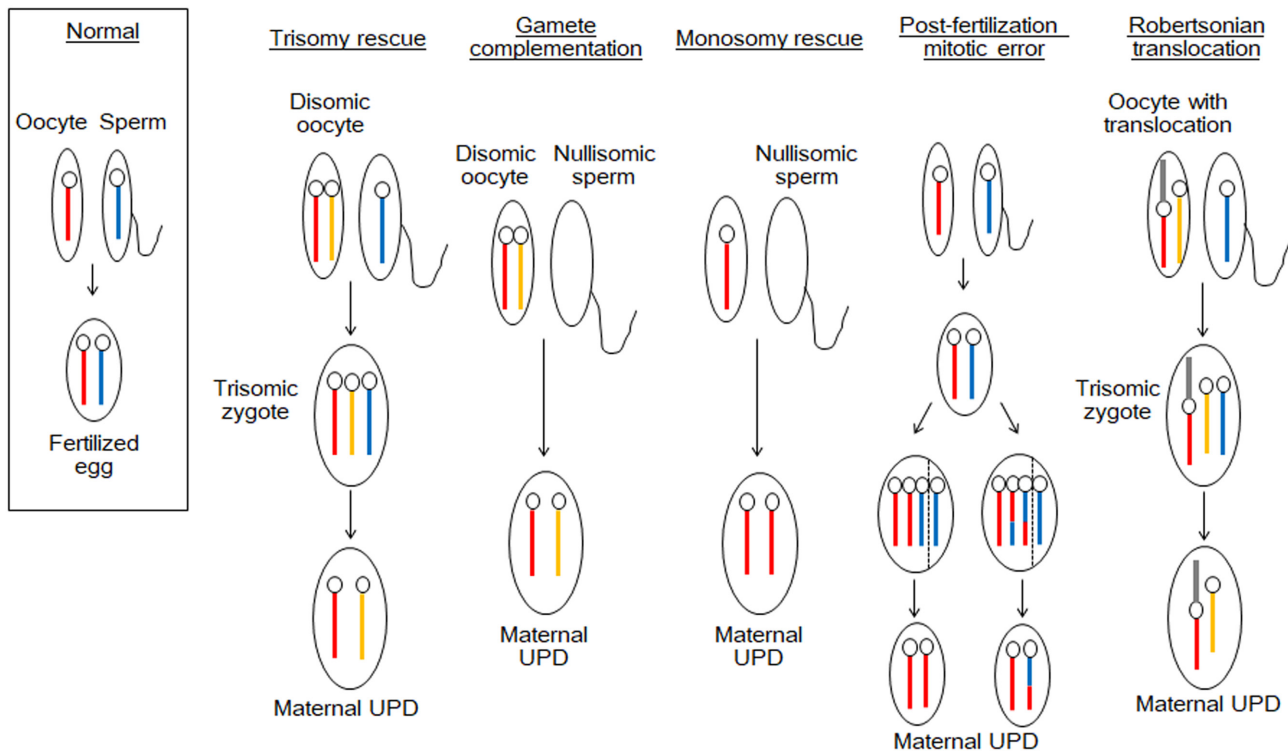


Fig. 1. Schema of the mechanisms underlying maternal uniparental disomy (UPD). The blue bars denote the chromosomes of the father, and the red and yellow bars indicate the homologous chromosomes of the mother. The gray bars depict the translocated chromosomes of the mother. These mechanisms are also applicable to paternal UPD.

in imprinting disorders and autosomal recessive disorders. Moreover, UPD can be accompanied by additional cytogenetic abnormalities. UPD plays certain roles in the development of various diseases including pediatric endocrine disorders. In this mini-review, we introduce the underlying mechanisms and phenotypic consequences of UPD.

Mechanisms Leading to UPD

UPD is caused by various mechanisms such as trisomy rescue, gamete complementation, monosomy rescue, and post-fertilization mitotic error (3). Fig. 1 shows a schema of the development of maternal UPD. Paternal UPD also occurs through the same mechanisms. Trisomy rescue results from fertilization of a disomic oocyte and a normal sperm. Subsequently, one of the

supernumerary chromosomes in the trisomic zygote is eliminated to restore the normal chromosomal number. Theoretically, this process creates maternal UPD at a rate of 33%, when the paternally derived chromosome is lost. Gamete complementation is a rare condition caused by fertilization of a disomic oocyte and a nullisomic sperm. Monosomy rescue results from fertilization of a normal oocyte and a nullisomic sperm, and subsequent amplification of the maternally derived chromosome. Post-fertilization mitotic errors are caused by chromosomal mis-segregation that occurs after the formation of a normal zygote. In addition, non-homologous Robertsonian translocation can also lead to UPD.

Notably, disomic oocytes that serve as the source of trisomy rescue and gamete complementation are created through meiotic errors during oogenesis. Specifically,

nondisjunction of two homologous chromosomes or the premature separation of sister chromatids underlies disomy in oocytes. Since the frequency of such meiotic errors is known to increase with age (4), advanced maternal age appears to be a risk factor of UPD in the offspring (5, 6).

UPD and Diseases

Patients with UPD usually retain the normal genomic structures of all chromosomes; therefore, they have a normal gene dosage. Consistent with this, recent studies have identified UPD in several phenotypically normal individuals (summarized in the UPD source, <http://upd-tl.com/upd.html>). However, UPD can exert negative effects on human health in the following situations: 1) when an imprinted gene(s) of functional importance is located in the UPD region(s), 2) when a heterozygous autosomal recessive mutation is unmasked by uniparental isodisomy, and 3) when the UPD is accompanied by other cytogenetic abnormalities, such as mosaicism with an abnormal cell lineage or small supernumerary marker chromosomes.

To date, UPD has been documented for almost all human chromosomes. The information of previously reported cases is shown in the UPD database (<http://upd-tl.com/upd.html>). Table 1 shows an overview of the phenotypic data of various UPDs based on this database. The phenotypes of affected individuals varied from an apparently normal phenotype to specific malformation syndromes.

Imprinting Disorders and UPD

The human genome encompasses more than 100 imprinted genes. These genes show monoallelic expression depending on the parental origin and are classified into maternally expressed genes (MEGs) and paternally expressed genes (PEGs). When an imprinted gene is located on a chromosome or chromosomal region of UPD, the expression level of the gene

is altered, reflecting the parental origin of the chromosome. For example, maternal UPD results in overexpression and downregulation of *MEGs* and *PEGs* on the chromosome, respectively. The aberrant expression or function of some imprinted genes has been implicated in the development of imprinting disorders (for a review, see <http://www.geneimprint.com/site/genes-by-species>). UPD is known as the major cause of imprinting disorders, although such disorders can also be caused by epimutations, genomic rearrangements, and mutations in the imprinted genes. The contribution of each molecular abnormality to the etiology varies among imprinting disorders.

Known imprinting disorders include Silver-Russell syndrome, Temple syndrome, Prader-Willi syndrome, transient neonatal diabetes mellitus, Beckwith-Wiedemann syndrome, Kagami-Ogata syndrome, Angelman syndrome, and pseudohypoparathyroidism (Table 2). In addition, the concept of imprinting disorders is still expanding (Table 2) (7). For example, the maternal UPD of chromosome 6 [UPD(6)mat], UPD(16)mat, and UPD(20)mat have been detected in patients with growth failure (8–11). Furthermore, paternally derived mutations in *MKRN3*, a *PEG* on chromosome 15q, have recently been reported as a genetic cause of precocious puberty (12). Likewise, mutations in *CDKN1C*, a *MEG* on 11p, were shown to underlie IMAGE syndrome characterized by skeletal and adrenal abnormalities, as well as Silver-Russell syndrome characterized by growth failure (13, 14). Moreover, some imprinting disorders may remain unrecognized. In fact, several imprinted genes could be hidden in the human genome, although the apparently normal phenotypes of individuals with UPD for chromosomes 13 and 22 indicate the absence of clinically important imprinted genes on these chromosomes.

It is worth mentioning that growth failure is a common feature of most imprinting disorders. Patients with imprinting disorders often present with intrauterine growth retardation,

Table 1 Overview of uniparental disomy (UPD) cases in the UPD database

Chromosome	Maternal UPD		Paternal UPD	
	No. of cases with a normal phenotype ^a	No. of cases with phenotypic abnormalities ^b (Phenotype)	No. of cases with a normal phenotype ^a	No. of cases with phenotypic abnormalities ^b (Phenotype)
1	1	1 (autism)	4	1 (short stature and dysmorphic features)
2	3	1 (hypospadias, developmental delay)	3	1 (severe intellectual disability, dysmorphic features)
3	0	0	1	0
4	3	1 (major depressive disorder), 1 (mild intellectual disability)	0	1 (renal anomalies, dysmorphic features)
5	0	0	0	1 (developmental delay, macrocrania, hypospadias)
6	0	5 (IUGR)	0	Many (<u>transient neonatal diabetes mellitus</u>)
7	0	Many (<u>Silver-Russell syndrome</u>)	0	1 (overgrowth) ^c
8	1	1 (dysmorphic features), 1 (developmental delay)	0	0
9	0	1 (IgA nephropathy, hypothyroidism, short stature), 1 (heart disease, developmental delay)	0	0
10	1	0	0	0
11	0	4 (<u>Silver-Russell syndrome</u>)	0	Many (<u>Beckwith-Wiedemann syndrome</u>)
12	1	0	0	0
13	3	0	4	0
14	0	Many (<u>Temple syndrome</u>)	0	Many (<u>Kagami-Ogata syndrome</u>)
15	0	Many (<u>Prader-Willi syndrome</u>)	0	Many (<u>Angelman syndrome</u>)
16	1	Many (IUGR)	0	0
17	1	1 (seizures, developmental delay)	1	0
18	1	0	2	1 (delayed speech, overlapping 4th finger)
19	0	0	0	0
20	0	Many (IUGR, feeding problems, hypotonia)	1	Many (<u>pseudohypoparathyroidism</u>)
21	4	2 (developmental delay)	3	0
22	7	0	2	0
X	0	0	1	1 (developmental delay, hypotonia, short stature)
Y	0	0	0	0

The contents of this table are based on the data of the UPD database (<http://upd-tl.com/upd.html>). Numbers in the parentheses indicate the numbers of cases submitted to the UPD database. Well-established imprinting disorders are underlined. IUGR; intrauterine growth restriction. ^a The number of cases without apparent clinical features. These individuals include those with balanced translocations, small supernumerary marker chromosomes, or other chromosomal imbalances. ^b The number of cases with clinically discernible phenotypic abnormalities. Patients with abnormal karyotype or apparent monogenic disorders are excluded. We excluded the cases in whom the information of phenotypes during post-natal period were not available. ^c Nakamura *et al.* (ref. 16).

Table 2 Imprinting disorders associated with uniparental disomy (UPD)

Imprinting disorder	Estimated prevalence	OMIM ^a	Disease-associated locus	Type of UPD	Frequencies of UPD ^b	Salient clinical features
Transient neonatal diabetes mellitus	1/300,000	601410	6q24	UPD(6)pat	40%	IUGR, transient diabetes in early infancy, hyperglycemia without ketoacidosis, macroglossia, omphalocele, hypotonia
UPD(6)mat	Unknown	–	Chromosome 6	UPD(6)mat	100%	IUGR, preterm delivery
Silver-Russell syndrome	1/75,000-1/100,000	180860	7p11.2 11p15	UPD(7)mat UPD(11p15)mat	~10% single case	IUGR/PNGR, macrocephaly at birth, hemihypotrophy, prominent forehead, triangular face, feeding difficulties, clinodactyly
Beckwith-Wiedemann syndrome	1/15,000	130650	11p15	UPD(11p15)pat	~20%	Pre- and postnatal overgrowth, organomegaly, macroglossia, omphalocele, neonatal hypoglycemia, hemihypertrophy, increased tumor risk
Kagami-Ogata syndrome	Unknown	608149	14q32	UPD(14)pat	65%	IUGR, polyhydramnion, abdominal and thoracic wall defects, bell-shaped thorax, coat-hanger ribs
Temple syndrome	Unknown	616222	14q32	UPD(14)mat	78%	IUGR/PNGR, neonatal hypotonia, feeding difficulties in infancy, truncal obesity, scoliosis, precocious puberty, small feet and hands
Prader-Willi syndrome	1/25,000-1/10,000	176270	15q11-q13	UPD(15)mat	< 30%	PNGR, intellectual disabilities, neonatal hypotonia, hypogonadism, obesity/hyperphagia
Angelman syndrome	1/20,000-1/12,000	105830	15q11-q13	UPD(15)pat	1–3%	intellectual disabilities, microcephaly, severe speech impairment, unmotivated laughing, ataxia, seizures, scoliosis
UPD(16)mat	Unknown	–	Chromosome 16	UPD(16)mat, often associated with chromosomal aberrations	100%	IUGR
Pseudohypoparathyroidism	Unknown	103580	20q13.32	UPD(20)pat	2.5%	Resistance to PTH and other hormones, Albright hereditary osteodystrophy, subcutaneous ossifications, feeding difficulties, abnormal growth patterns
UPD(20)mat syndrome	Unknown	–	Chromosome 20	UPD(20)mat	100%	IUGR/PNGR, feeding difficulties

Based the data by Eggermann (ref 5). IUGR; intrauterine growth retardation, PNGR; postnatal growth retardation. ^a Online Mendelian inheritance in man (<https://www.ncbi.nlm.nih.gov/omim/?term=>). ^b Frequencies of UPD among cases with the imprinting disorder.

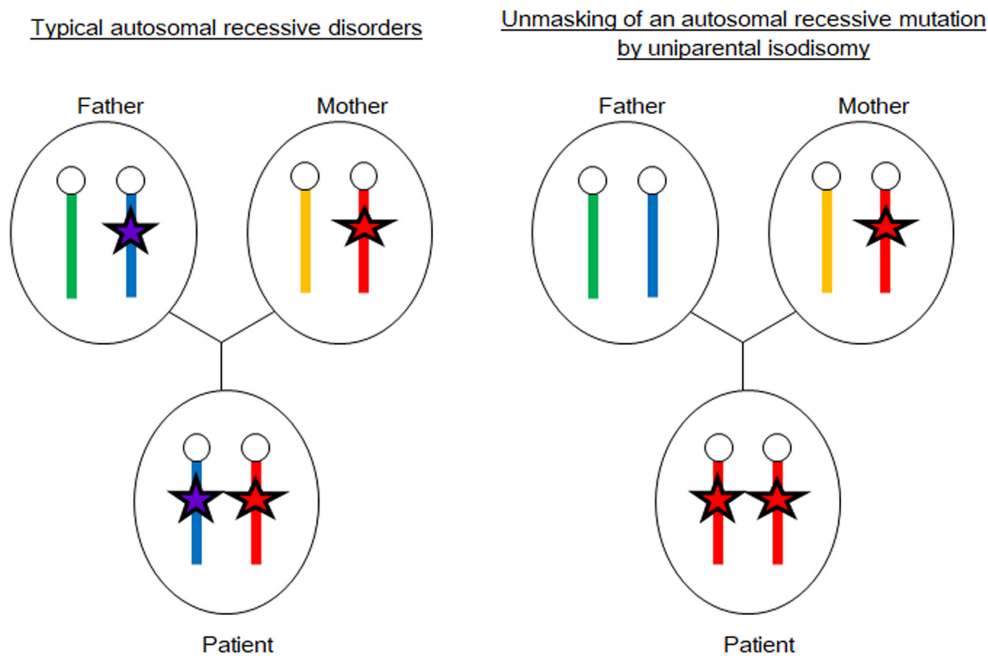


Fig. 2. Unmasking of an autosomal recessive mutation by uniparental isodisomy. The left panel shows a typical autosomal recessive disorder caused by homozygous or compound heterozygous mutations (red and purple stars) transmitted from both parents. The right panel shows an example of autosomal recessive disorders caused by maternal isodisomy encompassing a heterozygous mutation (red stars).

short stature, and/or poor weight gain. Recent studies have shown that UPD can also lead to prenatal and/or postnatal growth failure without additional clinical features (15). On the other hand, overgrowth has also been reported as a clinical manifestation of some imprinting disorders (4, 16). These phenotypes are consistent with the critical roles of imprinted genes in the regulation of cell proliferation and differentiation. Furthermore, imprinting disorders frequently involve endocrinological manifestations. For example, transient neonatal diabetes mellitus due to aberrant expression of *PLAGL1* at 6q24, and pseudohypoparathyroidism due to aberrant DNA methylation of the *GNAS* loci at 20q13 represent unique endocrine disorders (17, 18). Moreover, pubertal disorders are frequently seen in patients with Temple syndrome or Prader-Willi syndrome (19, 20). Collectively, imprinting disorders are clinically important conditions, particularly in pediatric endocrinology clinics.

Autosomal Recessive Disorders and UPD

Usually, patients with autosomal recessive disorders inherit pathogenic mutations from both parents. Thus, the patients are homozygous or compound heterozygous for the mutation, and both parents are heterozygous. However, uniparental isodisomy can lead to autosomal recessive disorders in the presence of one non-carrier parent. As shown in Fig. 2, uniparental isodisomy can unmask heterozygous pathogenic mutations on the disomic chromosomes. The UPD review site (<http://upd-tl.com/upd.html>) shows several examples of monogenic disorders, including pediatric endocrine disorders, caused by unmasked autosomal recessive mutations. Moreover, recent studies have revealed that some patients with 21-hydroxylase deficiency (21OHD), the most common form of congenital adrenal hyperplasia (CAH), were born to families in which one of the parents is a carrier of a disease-causing mutation and the other is a

non-carrier (21). In these cases, the disorder was caused by uniparental isodisomy of chromosome 6 or *de novo* mutations in *CYP21A2*. Finkelstein *et al.* examined a large cohort of 21OHD patients and identified UPD(6) and *de novo* mutations in 0.9% and 1.9% of the subjects, respectively (22). Similarly, other forms of CAH, namely, 11 β -hydroxylase deficiency or 3 β -hydroxysteroid dehydrogenase deficiency, were also shown to be caused by pathogenic mutations unmasked by uniparental isodisomy (23, 24).

These findings suggest that UPD should be considered a possible cause of autosomal recessive disorders, particularly when a patient harbors a rare homozygous mutation despite being born to non-consanguineous parents. This notion is important for genetic counseling because the recurrence risk of autosomal recessive disorders is 25% in most cases and negligible when the disease is associated with UPD. Therefore, the carrier status of parents should be examined before genetic counseling of families with autosomal recessive disorders.

UPD Combined with Other Cytogenetic Abnormalities

UPD occurs either alone or in combination with other cytogenetic abnormalities such as mosaicism with abnormal cell lineages or small supernumerary marker chromosomes (25–27). For example, UPD due to trisomy rescue can be associated with trisomy mosaicism depending on the timing of trisomy rescue during embryogenesis. In addition, small supernumerary marker chromosomes may be formed during the trisomy rescue process. Indeed, there have been several reports on mosaicism of UPD cells and trisomy cells and/or supernumerary marker chromosomes. The presence of abnormal cell lineages or supernumerary marker chromosomes may affect clinical manifestations of UPD patients, even when the UPD itself has no deleterious effects on the phenotype. On the other hand, it has been reported that additional

cytogenetic abnormalities can occasionally rescue the severity of phenotypes of UPD patients (28).

UPD in Clinical Practice

In most cases, UPD occurs by chance. The frequency of UPD was estimated to be approximately 1 in 3,500 live births (2), while in cases with nonhomologous Robertsonian translocation it is as high as ~0.6–0.8% (29). Since advanced maternal age is associated with the risk of UPD (6, 7), and the average age of child bearing is continuously increasing in many countries (data from Japan, USA, and EU are available at <http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei16/index.html>, https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_01_tables.pdf and <http://ec.europa.eu/eurostat/web/population-demography-migration-projections/births-fertility-data/database>, respectively), the frequency of UPD may increase in the future.

Notably, UPD is barely detectable by karyotyping or copy-number analyses unless it is combined with other cytogenetic abnormalities. Standard sequencing is also inadequate for identifying UPD. Thus, specific techniques are required for the molecular diagnosis of UPD (30, 31). Single nucleotide polymorphism (SNP)-genotyping or microsatellite analyses using the DNA samples of the patients and their parents are useful tools to detect UPD. Furthermore, comparative genomic hybridization (CGH) using SNP plus CGH arrays is a powerful method to screen uniparental isodisomy in the entire genome. Various methods, such as pyrosequencing, methylation-specific PCR, and combined bisulfite restriction analysis, are utilized to detect DNA methylation abnormalities.

Conclusions

Accumulating evidence suggests that UPD occurs in approximately 1 in 3,500 live births (2). UPD plays certain roles in the development of growth failure and endocrine abnormalities;

therefore, it is a clinically important condition in the field of pediatric endocrinology. SNP- or microsatellite-genotyping or DNA methylation analyses are useful to diagnose patients with UPD.

Conflict of interest: The authors declare no conflict of interest.

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