

Uniparental Disomy

【Abstract】

Uniparental disomy (UPD) is a unique phenomenon when an individual receives both copies of a homologous chromosome pair from one parent only and no copies from the other parent. Typically, a person should receive one copy from each parent. UPD is usually a sporadic event as a result of errors in sperm/egg formation or in early embryonic/fetal development.

UPD is not associated with gains or losses of chromosomal segments or genes. However, UPD occurring at chromosomes carrying imprinting genes can lead to clinically pathogenic syndromes as imprinting genes rely on bi-parental inheritance to ensure proper expression and function.

A case example of UPD disorder is presented—a 3-year-old female with motor and speech delays, social pervasive developmental delay and abnormal eye movement, who has complete UPD of chromosome #15 [UPD(15)] detected by using a microarray platform with single nucleotide polymorphism (SNP) probes. UPD(15) can be associated with Angelman syndrome, which was consistent with the clinical phenotype observed in this female child. **Counseling points related to this case are discussed. The concept of UPD and known UPD disorders, as well as a short overview of Angelman syndrome are also included.**

【Case Example】

Tiffany is three years old. She is delayed in her motor and speech skills. She also has behavioral issues of pervasive development delay. Her eye movement is also concerning. Tiffany's parents are concerned and brought her to get evaluated by a pediatric neurologist. Besides wanting to understand how to best care for their daughter, Tiffany's parents are also curious as to why Tiffany has such challenges.

Based on Tiffany's clinical findings, the neurologist suspected Tiffany may have an underlying congenital genetic abnormality. After discussion with the family, a microarray array with SNP probes (SNP array) was elected and performed. Identification of the underlying cause for Tiffany's health issues not only provides Tiffany's family with an answer, but can also help the medical team understand her disease prognosis, treatment options, and potential other complications. Furthermore, whether Tiffany's issues are hereditary can be clarified once a disease-causing reason is found. Recurrence risk as well as reproductive testing options can be provided to Tiffany's

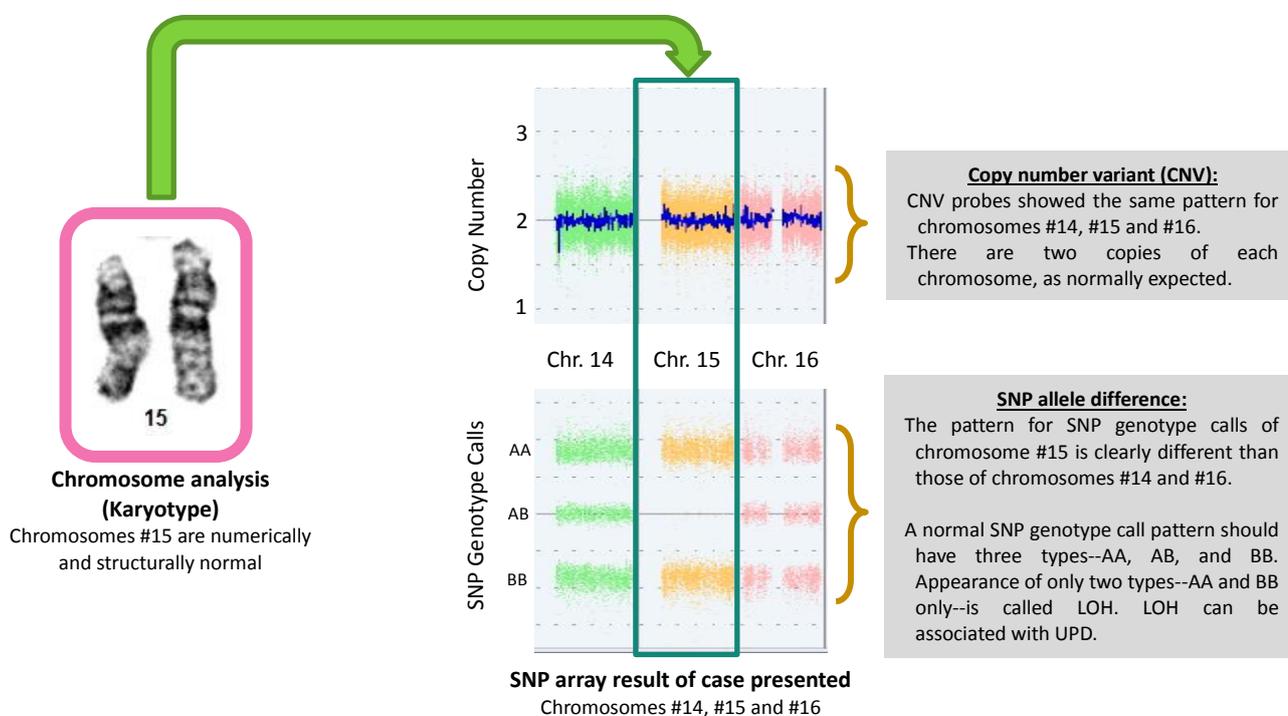
relatives to prevent birth of another child having to experience the same difficulties as Tiffany.

Tiffany's SNP array showed interesting results. There were no gains or losses of chromosomal segments; however, a loss of heterozygosity (LOH) of the entire chromosome #15 was present. This is consistent with uniparental disomy (UPD) of chromosome #15.

If both chromosome #15 are inherited from the mother only, it is called maternal UPD(15). Maternal UPD(15) is associated with Prader-Willi syndrome. On the other hand, paternal UPD(15), when both chromosome #15 are inherited from the father, can lead to Angelman syndrome (AS).

Based on Tiffany's SNP array result of LOH alone, it is not possible to distinguish between maternal and paternal UPD(15). Further testing is needed, such as comparing Tiffany's SNP array result with both of her parents' SNP array results, or using a different testing platform to assess parent-specific methylation patterns.

The clinical presentation of Prader-Willi syndrome and AS is quite different. Based on clinical evaluation, Tiffany's symptoms are consistent with that of AS. Finding out the underlying cause of Tiffany's clinical issues allows her medical team as well as her family to provide her with the best care she deserves.



【Counseling Discussion】

1. Often times, a cure may still not be available for a child with congenital anomalies and/or developmental delays even after an underlying cause of the abnormalities is identified. However, understanding the underlying cause is still important not only to provide an answer, but also to better understand the child's prognosis, treatment options and prevent other complications. Identifying a cause also clarifies the recurrence risk and the appropriate reproductive testing options for at-risk family members.
2. The presenting clinical features of many genetic disorders are often similar and overlap with one another. Sometimes, it is quite challenging to pinpoint one specific genetic disorder as the working diagnosis. Selecting a genetic test that only screens for one genetic condition may not be an easy, effective and/or cost-saving option.
3. Practice guideline released by the American College of Medical Genetics in 2010 had recommended microarray to be the first-line test in the initial postnatal evaluation of individuals with 1) multiple anomalies not specific to a well-delineated genetic syndrome, 2) apparently non-syndromic developmental delay/intellectual disability and 3) autism spectrum disorders.
4. Compared to G-banding chromosome analysis, microarray test allows simultaneous evaluation of gains and losses of not only large chromosomal segments but also small chromosomal pieces beyond those detectable by G-banding, i.e. microdeletions and microduplications. Microarray platforms that include SNP probes can additionally screen for UPD disorders.
5. Genotype calls can be inferred using data readings provided by the SNP probes. This evaluates the presence of LOH status, which can be associated with UPD disorders.
 - With SNP probes, it is possible to infer whether the genotype at a chromosome position is AA, AB or BB.
 - If a large chromosomal region shows only homozygous "AA" or "BB" genotypes without mixed of *heterozygous* "AB" genotype, then it is called a region of "loss of *heterozygosity*" (LOH).
 - LOH is neither associated with changes in the number or the structure of the chromosomes, nor directly pathogenic and disease-causing.
 - Reasons for LOH:
 - 1) Biparental inheritance: The chromosome pair was inherited as expected—one chromosome from the father and one from the mother, and the fetus/child

coincidentally received identical genotypes from both parents. This generally does not directly lead to clinically abnormal disorders, though the risk for recessive disorders may be increased.

2) Uniparental inheritance: Both chromosomes of a homologous pair were inherited from a single parent only (meaning the two chromosomes of the same number came from only one parent). Clinically, this may lead to UPD disorders and abnormal symptoms.

6. **UPD of specific chromosomes is associated with clinical abnormality.**

- UPD occurring at chromosomes carrying imprinting genes will lead to abnormal growth and development due to disruption of normal gene expression and function.

7. **UPD disorders are mostly sporadic. The recurrence risk for sibling of an affected individual is low.**

8. **Having an abnormal microarray results does not always mean the chromosome analysis result will be abnormal as well.**

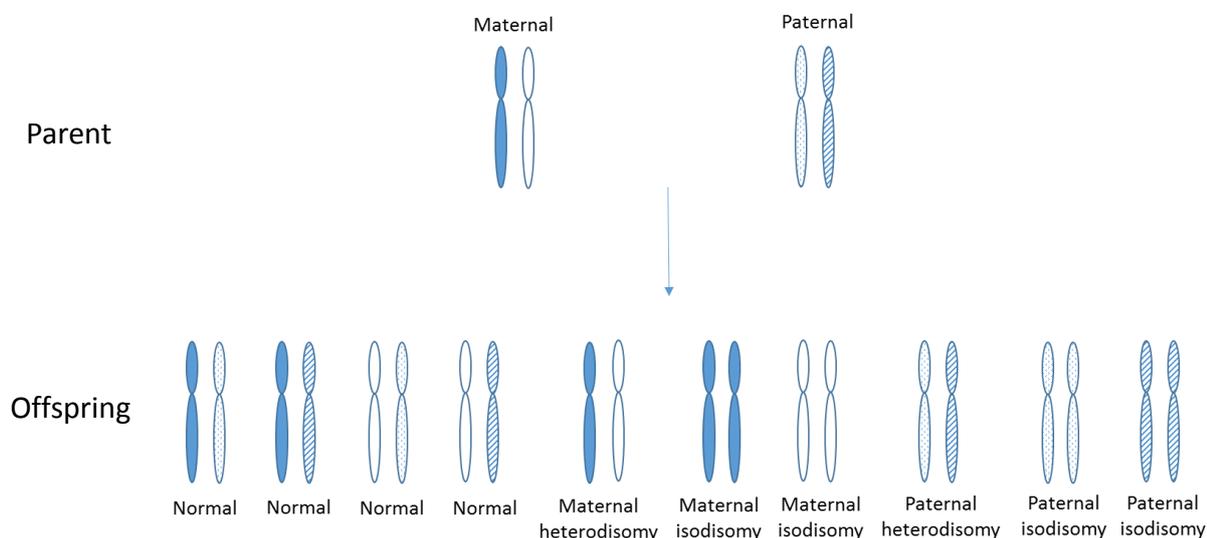
- Different genetic testing methodology evaluates different types of genetic changes. Every testing methodology and platform has its own advantages and disadvantages as well as applicable situation.
- Because UPD will not cause numerical or structural changes in chromosomal segments and genes, testing platforms that only evaluate such variations, such as G-banding chromosome analysis or microarray without SNP probes, would not be able to detect UPD disorders.



Uniparental Disomy

Typically, a pair of homologous chromosomes should be inherited from both parents, i.e. one chromosome from the father and one from the mother. **When a person receives both copies of a homologous chromosome pair from one parent only and no copies from the other parent, then it is called “UPD”.** UPD can involve an entire chromosome or just part of a chromosome. **Paternal UPD implies both copies of chromosomes are from the father only, i.e. no copy from the mother; whereas maternal UPD refers to when both copies are from the mother, i.e. no copy from the father.**

UPD can be further categorized into uniparental isodisomy or uniparental heterodisomy (see diagram below). Both subtypes can cause clinical pathogenicity.



Possible mechanisms leading to UPD:

1. **Trisomy rescue:** An embryo containing three copies of a chromosome (trisomy) and subsequently loses one of the three chromosomes through self-rescue
2. **Monosomy rescue:** An embryo containing only one copy of a chromosome (monosomy) and subsequent duplication of this chromosome occurs through self-rescue
3. **Gamete complementation:** Fertilization between a gamete with two copies of the same chromosome and a gamete with no copies of that particular chromosome
4. **Postzygotic/Post-fertilization error:** Meiotic errors of an embryo originally with disomy chromosomes

Molecular methodologies to detect UPD:

- Polymorphic microsatellite markers
- Methylation-specific PCR
- Methylation-specific MLPA
- Microarray with SNP probes

UPD-related disorders:

Most of the human genes are not dependent on which parent we inherited them from; therefore, as long as the copy number and the function of the genes are correct, they will generally perform properly as expected. However, **there are some genes in which their functions**

and expressions vary depending on the parental origin. They are called the “imprinting genes”. For these imprinting genes, biparental inheritance—inheriting one copy from the mother and one from the father—is very crucial to ensure proper growth and development of the person.

Only a few chromosomes are currently known to contain imprinting genes. UPD of these chromosomes results in the lack of bi-parental inheritance of imprinting genes and will lead to abnormal physical and/or mental development.

The table below shows known UPD chromosomes associated with imprinting disorder.

UPD Chromosome	Imprinted Locus	Maternal vs Paternal UPD	Associated Disorder	Major Clinical Features	Known/Proposed Dysregulated Gene(s)
6	q24	Paternal	Diabetes Mellitus, 6q24-related Transient Neonatal ⁵²	Intrauterine growth retardation, neonatal hyperglycemia	<i>PLAG1, HYMAI</i>
7	p11.2-p12 and q32.2	Maternal	Russell-Silver syndrome ⁵³	Intrauterine and postnatal growth retardation, triangular facies	<i>GRB10, MEST</i>
11	p15.5	Paternal (segmental)	Beckwith-Wiedemann syndrome ⁵⁴	Macrosomia, macroglossia, visceromegaly, omphalocele	<i>IGF2, H19, CDKN1C, KCNQ1, KCNQ10T1</i>
		Maternal	Russell-Silver syndrome ⁵⁵	Intrauterine and postnatal growth retardation, triangular facies	<i>IGF2, H19, CDKN1C, KCNQ1, KCNQ10T1</i>
14	q32.2	Maternal	Maternal UPD14 syndrome ⁵⁶⁻⁵⁸	Precocious puberty, hypotonia, joint laxity	<i>RTL1, DLK1</i>
		Paternal	Paternal UPD14 syndrome ⁵⁶⁻⁵⁹	Skeletal abnormalities, joint contractures, intellectual disability	<i>RTL1, DLK1</i>
15	q11-q13	Paternal	Angelman syndrome ⁶⁰	Severe intellectual disability, speech impairment	<i>UBE3A</i>
		Maternal	Prader-Willi syndrome ⁶¹	Hypotonia, hypogonadism, obesity	<i>SNRPN, MKRN, MAGEL2, NDN, U5snoRNAs</i>
20	q13.3	Paternal	Pseudohypoparathyroidism type 1b ^{62,63}	Neonatal hyperbilirubinemia, parathyroid hormone resistance	<i>GNAS</i>

Reference: Kearney (2011)

【Reference】

- Kearney HM, Kearney JB, Conlin LK. Diagnostic implications of excessive homozygosity detected by SNP-based microarrays: consanguinity, uniparental disomy, and recessive single-gene mutations. *Clin Lab Med.* 2011 Dec;31(4):595-613.
- Liehr, T. What is uniparental disomy (UPD)? [online] Oxford Gene Technology 2013. [cited 2017 Aug 30]. Available from: http://www.ogt.co.uk/cytosure_whatisUPD.html.
- Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* 2010 Nov;12(11):742-5.
- Yamazawa K, Ogata T, Ferguson-Smith AC. Uniparental disomy and human disease: an overview. *Am J Med Genet C Semin Med Genet.* 2010 Aug 15;154C(3):329-34.



【 Angelman Syndrome 】

【 Clinical Features 】

Most affected patients do not show obvious abnormalities during newborn periods. Birth weight and head circumference are within normal range. Some patients may have feeding or sucking difficulties and/or hypotonia. Developmental delays are usually first noted at around six months of age; however, the unique clinical features of AS typically many not manifest until after one year of age. For some, it can take several years before the correct clinical diagnosis is made. Life span data is limited, though it appears to be nearly normal.

Common clinical features:

- Severe developmental delay or intellectual disability
- Severe speech disability and limited verbal language skills
- Gait ataxia and/or tremulousness of the limbs, the average child with AS walks between 2.5-6 years of age
- Inappropriate happy demeanor: frequent laughing , smiling, and excitability
- Microcephaly
- Seizures, typically occurring between ages one and three years



Reference: GeneReviews

【 Management 】

- Symptom-oriented management
- Physical therapy, occupational therapy, and speech therapy with emphasis on nonverbal communication methods
- Anti-epileptic medication, such as vigabatrin, tigabine and carbamazepine, should be avoided as they may exacerbate seizures

【 Prevalence 】

1/12,000 - 1/24,000

【 Angelman Syndrome 】

【 Disease-causing Genetic Mechanism 】

Abnormality at the q11.2q13 region of chromosome #15

Mechanism	% of Affected Patients
15q11.2q13 5Mb – 7Mb deletion	65-75%
UBE3A gene mutation	11%
Paternal UPD	3-7%
Imprinting defect in the imprinting center	3%
Chromosomal translocation-related changes	< 1%
Others – unknown mechanism	10-15%

【 Inheritance Pattern 】

Dependent on the underlying disease-causing mechanism of the affected family member;
Recurrence risk can range from <1% to nearly 100%

【 Genetic Testing 】

Different genetics mechanism requires different molecular methodology to detect, such as methylation testing, UPD testing, microarray, FISH, gene sequencing and etc.

【 Genetic Counseling 】

Prenatal

1. Most affected fetuses do not have ultrasound anomalies.
2. Routine chromosomal analysis (karyotype) is difficult in detecting AS.
3. Some of the new non-invasive prenatal tests (using cell-free DNA derived from placenta for analysis) can detect deletion-type AS. Those with SNP-based analytical platform can also detect UPD-type AS. These cell-free DNA tests are screening test only. Women whose pregnancies are found to be at increased risks for AS through these tests should be offered follow-up diagnostic tests to clarify true fetal genetic status.
4. Microarray can detect deletion-type AS. Array platforms that include SNP probes can additionally screen for some UPD-type AS.
5. Because of the various genetic mechanism leading to AS and because not all disease-causing mechanism are yet known, routine prenatal testing cannot rule out all cases of AS to guarantee an unaffected child.

【 Angelman Syndrome 】

Pediatrics

1. Most affected patients do not show obvious abnormalities during newborn periods. Birth weights and head circumferences are usually within normal range. Some patients may have feeding or sucking difficulties and/or hypotonia.
2. Developmental delays may be first noted at around six months of age; however, the unique clinical features of AS typically become apparent after one year of age. For some patients, it can take several years before the correct clinical diagnosis is made. Data on life span is limited, though it appears to be nearly normal.
3. If clinical features are highly suspicious of AS, targeted AS testing can be considered to rule out this disorder. However, because not all disease-causing mechanism are fully known, about 10% of patients with a clinical diagnosis of AS will not have an identifiable genetic change.
4. If the clinical features do not obviously suggest AS and/or possibly overlap with many other conditions, microarray test can be considered to comprehensively assess numerical abnormalities of all the chromosomes while rule out most cases of AS at the same time.
5. If AS is confirmed, care and management from multi-disciplinary specialties can assist the patient in achieving his/her greatest potential. Anti-epileptic medication, such as vigabatrin, tigabine and carbamazepine, should be avoided as they may exacerbate seizures.

【 Extended Reading and Reference 】

- ◆ GeneReviews – Angelman Syndrome [Cited 2017 Aug 30]
<https://www.ncbi.nlm.nih.gov/books/NBK1144/>
- ◆ Genetics Home Reference – Angelman Syndrome
<https://ghr.nlm.nih.gov/condition/angelman-syndrome>



Do you have any questions related to genetic counseling?
What topics would you like the GGA Genetic Counseling
Newsletter to discuss?

Your suggestions are greatly appreciated so we can
further improve our newsletter!

Email address of the GGA Genetic Counseling Team

GCSupport@gga.asia