Deep Insight Section

The vagaries of non-traditional mendelian recessive inheritance in uniparental disomy: AA x Aa = aa!

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A situation of Non-Traditional Mendelian Inheritance is achieved whenever an exceptional mode of recessive transmission, distinctly alien to the usual pattern, leads paradoxically to a similar phenotype.

**Example:**

\[
\begin{align*}
AA \times Aa &= aa \\
Aa \times Aa &= aa \\
\end{align*}
\]

**Laws and Out-Laws in Mendelian Recessive Inheritance**

Two basic traditional tenets of the Mendelian Laws of Inheritance are the segregation (separation) and the independent assortment of alleles.

In the Non-Traditional Mode of Mendelian Inheritance, the non-congruent path of transmission usually resorts to a stratagem, the meiotic mis-segregation of alleles followed by a revised assortment at mitosis. Both steps may end-up in the uniparental transmission of allele pairs while euploidy is maintained, a situation referred to as Uniparental Disomy.

**Examples of Non-Traditional Mendelian Inheritance causing genetic harm through UPD**

1) duplication of a same dominant mutant (must often be lethal)
2) duplication of the same recessive mutant
3) overdose of the duplicated active domain of a parentally imprinted area
4) loss of a singly active domain of a parentally imprinted area
5) combination of 3) and 4)
6) combination of 2) with 3) or 4) or 5) - quite rare

**What is Uniparental Disomy (UPD)?**

UPD is the occult presence of a chromosome pair inherited from only the mother or father in a diploid conceptus (or cell-line).

**How does UPD come about?**

A two-step twist of chromosomal inheritance (usually one step occurring at meiosis, the other at mitosis) leads to a diploid state with one pair issued from one parent only.

**What is the meiotic error leading to UPD?**

The usual meiotic process entails the same one that leads to zygotic trisomy or monosomy (i.e. MeI or MEII non-segregation).

**What is the mitotic step superseding the meiotic one and resulting in UPD?**

An early somatic error, namely a mitotic non-disjunction or a chromosome lag restoring diploidy.

**What is the end-result of the two-step process leading to UPD?**

- Trisomy rescue by loss of one or the other member of the uniparental pair, (thus restoring the biparental parity) or by the loss of the normally inherited chromosome (leaving in place the monoparental pair).
- Monosomy duplication (always resulting in a monoparental pair).

**What may be the broad genetic make-up of the uniparental pair?**

The overall content of the pair be one of isodisomy (i.e. both members are a carbon copy of one over the other) with complete allelic sameness as seen in the process resulting of mitotic monosomy duplication...
...or one of heterodisomy (non-identical allelism between homologous members) as may occur for the complete lack of crossing-over of two homologues failing MeI segregation. Aside from these extreme examples, the UPD content resulting from meiotic non-segregation is often a mix-pot of iso- and heterodisomy.

Definition of isodisomy
The homoallelic duplication of a chromosome or a chromosome segment in one pair of a diploid individual or in a 2n cell-line or a 2n cell is called isodisomy.

NOn-TRAditional Mendelian Inheritance (NOTRAMI)
Conditions for the occurrence of an isodisomic recessive trait:
1) Inheritance of a UPD pair showing duplication of a same chromosome or duplication of chromosome segments shared by homologues as a result of crossing over.
2) Presence of a locus with a recessive mutant on that chromosome or segment.

What can bring about duplication of a same segment (isodisomy) in a uniparentally inherited pair:
1) Transmission at normal MeII of a pair including the two same crossed-over segments derived from a tetravalent, which failed MeI segregation.
2) Transmission of the non-crossed-over segment of the chromatids of a reduplicated chromosome, which failed MeII segregation.
3) The mitotic non-disjunction of a reduplicated monosomic member.
Note: the centromeric and juxta-centromeric areas of a tetravalent do not cross-over and stay heterodisomic. As a result, the above areas of a MeII reduplicated chromosome remain isodisomic. The typing of these areas with appropriate polymorphisms allows to distinguish between MeI and MeII non-disjunction but not between MeII and mitotic non-disjunction.

Reduction to homozygosity by isodisomy formation
Depending on the dual meiotic-mitotic comedy of errors, an F1 individual can become homozygous for a recessive allele, if this allele gets duplicated in a uniparental pair. Thus, the singly heterozygous partner of a couple (Aa) can sire a homozygous child (aa) by "reduction to homozygosity" as shown below:

\[
\begin{align*}
AA \times Aa^* & = aa^{**} \\
\text{SCHEMATIC REPRESENTATION OF THE PRIMARY AND SECONDARY MECHANISMS OF FORMATION OF A UNIPARENTAL PAIR} & \\
1) \text{Gamete complementation} & \\
A1A2 \times A3a & = \text{two meiotic errors} \\
0 & = \text{nullisomy} \\
+ a & = aa \\
\text{Result} & \\
2) \text{Trisomy rescue} & \\
A1A2 \times A3a & = \text{meiotic error} \\
A1a & = \text{trisomy} \\
\text{mitotic error} & = \text{deletion} \\
A1 & = aa & \\
3) \text{Monosomy duplication} & \\
A1A2 \times A3a & = \text{meiotic error} \\
A1 & = 0 & = \text{nullisomy} \\
\text{mitotic error} & = \text{duplication} \\
\end{align*}
\]

In these examples, it may be considered the symbol of a chromosome carrying a clinically significant recessive allele.

Specific factors potentially favoring complementation of aneuploid gametes *
a) A high frequency of germ cell aneuploidy targeting a same homologous member chromosome in both sexes causing a number of gametes to be either disomic or nullisomic for that chromosome (scarce evidence).
b) Presence in both parents of a balanced translocation involving a same homologous member favoring unbalanced segregation of the translocated partner in the germ cells in a complementary pattern (some very suggestive evidence).
(*Probably the least common pathway to UPD)
Sometime the UPD does not involve the whole of a chromosome and remains confined to a segment of a pair as it arises from a somatic crossing over between two homologous non-sister chromatids. When interstitial, the segmental UPD results from two symmetrical breaks, which are shown below as the...
result of an "interchromatid kiss"! Mitotic segregation of the duplicated chromosomes, thereafter leads to mosaicism with one native and one reshuffled balanced cell line.

**SEGMENTAL UNIPARENTAL DISOMY**

In other instances the segmental UPD is terminal and results from a single symmetrical break in each of two homologous non-sister chromatids, as seen below. Mosaicism involving two somatic cell types also results from this.

**INSTANCES OF SEGMENTAL UNIPARENTAL DISOMIES (Terminal or interstitial)**

<table>
<thead>
<tr>
<th>Chrom. segment</th>
<th>Condition</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (q21q22)</td>
<td>Ablotipheinemia</td>
<td>&quot;Yang XP et al 1999&quot;</td>
</tr>
<tr>
<td>4 (p13p14)</td>
<td>Ellis van Creveld</td>
<td>&quot;Thomas SW et al 2001&quot;</td>
</tr>
<tr>
<td>6 (p21.3)</td>
<td>Steroid-21 hydroxylase deficiency</td>
<td>&quot;Lopez-Outtoner et al 1995&quot;</td>
</tr>
<tr>
<td>6 (p24pter)</td>
<td>Neonatal diabetes mittus</td>
<td>&quot;Das S et al 2000&quot;</td>
</tr>
<tr>
<td>7 (q31qter)</td>
<td>Silver-Russell Syndrome</td>
<td>&quot;Henneke K et al 2001&quot;</td>
</tr>
<tr>
<td>7 (p15pter)</td>
<td>&quot;&quot;</td>
<td>&quot;Eggermann T et al 2004&quot;</td>
</tr>
<tr>
<td>11 (q13pter)*</td>
<td>Short dysmorphic female</td>
<td>&quot;Kozaitis D et al 2001&quot;</td>
</tr>
<tr>
<td>11 (p13p13)</td>
<td>Wiedemann-Beckwith</td>
<td>&quot;Henry L et al 1999&quot;</td>
</tr>
<tr>
<td>14(q23p24.2)</td>
<td>Maternal UPD 14</td>
<td>&quot;Martin RA et al 1999&quot;</td>
</tr>
<tr>
<td>14 (q12q25.3)</td>
<td>&quot;&quot;</td>
<td>&quot;Eggermann T et al 2001&quot;</td>
</tr>
<tr>
<td>14 (q12q12)</td>
<td>Maternal &quot; 16 &quot;</td>
<td>&quot;Coster RJ et al 2002&quot;</td>
</tr>
<tr>
<td>28 (q)</td>
<td>PTH resistance</td>
<td>&quot;Ensminger M et al 2001&quot;</td>
</tr>
</tbody>
</table>

* With partial triosity

On the slide below are presented examples of both types of segmental UPD, terminal or interstitial, as found for various chromosomes, 4, 6, 7, 11, 14 and 20. Some were discovered because of reduction to homozygosity causing recessive traits, while others involved imprinted domains and disrupted them.
Uniparental disomies for chromosome 1 as a cause of recessive phenotypes.

<table>
<thead>
<tr>
<th>Origin</th>
<th>cause</th>
<th>Phenotype</th>
<th>Author et al</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Me I</td>
<td>H-JEB</td>
<td>Puliddlens</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Me I</td>
<td>Diabetes&lt;</td>
<td>Field</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Me H</td>
<td>MSD type 2&lt;</td>
<td>Liebh</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>Cherubin-Hyogoishi</td>
<td>Daufoury-Lajeunais</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>MCA</td>
<td>Hefslberger</td>
<td>2001</td>
</tr>
<tr>
<td>Paternal</td>
<td>Me I</td>
<td>Usher</td>
<td>Rivolta</td>
<td>2002</td>
</tr>
<tr>
<td></td>
<td>Me H</td>
<td>Pyeunostrostis</td>
<td>Geib</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>SHCA</td>
<td>Chen</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>H-JEB</td>
<td>Takizawa</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>CIPA + TRKA</td>
<td>Minn</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>CIPA</td>
<td>Inus</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>mono. dupl</td>
<td>Refusal dystrophy</td>
<td>Thomson</td>
<td>2002</td>
</tr>
</tbody>
</table>

* unexplained by the UPD condition.
** mother and father homozygous normal at the MSD locus. Me II non-disjunction duplicated a prenatal mutation which was then homozygously transmitted as a maternal UPD.

Aneuploid mode and mood of chromosomes:
The results for chromosome 1 UPD's emphasize the major role of maternal meioses errors causing gamete nullisomy and disomy in cases of either maternal or parental UPD1 (8 cases). Paternal meioses errors also account for 4 cases.

The perfect culprit for Non-Traditional Mendelian Inheritance in UPD
-A chromosome from a disomic or nullisomic ovum responsible after fertilization for trisomies or monosomies respectively liable to rescue by mitotic deletion or duplication.
-A large member of the set.
-A member carrying a locus with a common mutation or an imprinted domain.

Factors influencing the chance occurrence of trisomy rescue
a) The relatively large pool size of the trisomy liable to rescue (i.e. 16, 15, 21, 22, X).
b) The factors modulating the size and nature of such a pool:
- the aneuploid mode and mood of specific chromosome members
- maternal age
- abnormal segregation of common centric fusions
- etc...

At meiosis, what affects the occurrence and genetic content of the non-disjoined pair?
- Some ill-understood specific factors of the chromosome member implicated which I have just called the aneuploid mode and mood of that particular chromosome.
- Recombination which may stay normal or be perturbed in the process.

The variable aneuploid mode and mood at the origin of numerical abnormalities of different chromosome numbers of the set
- Great difference in the incidence of trisomy for different chromosomes *
- Variable association with increased parental (maternal) age *
- Absence of all monosomies except for the X chromosome *
- Differential selection and survival at different stages of pregnancy *
- Different frequencies of non-disjunction among different chromosomes *


Aneuploid mode and mood of some clinically significant chromosomes
The vagaries of non-traditional mendelian recessive inheritance in uniparental disomy: \( AA \times Aa = aa \)

Engel E

Possible end-points of the various factors affecting transition to isodisomy in the formation of uniparental pairs

1) Some mechanisms rule out or lower the chances of a transition from hetero- to isodisomy and minimize the risks of transmission of a recessive allele.
2) Other mechanisms carry-out a higher to much higher risk of isodisomy along with an increased chance of homozygosity for a recessive allele.

NOTRAMI

What suppresses or lowers the risk of isodisomy as a cause of reduction to homozygosity in UPD?
1) an MeI nulli-chiasmate or pauci-chiasmate synapsis (i.e. an absolute or relative recombination failure of homologues) followed by MeI non-segregation and normal MeII separation.
2) an MeI failure of synapsis (i.e. the lack of homologous pairing) followed by the same pole migration of the two resulting univalent an normal MeII separation.

### Conclusion:

Except for the 45,X, most cases are of maternal origin, the meiotic stage of non-disjunction is variable for different numbers (from 100% MeI to 66% MeII) and the lethality rate quite disparate.

<table>
<thead>
<tr>
<th>Chr No</th>
<th>Spont. abort. frequency</th>
<th>Parental origin</th>
<th>Mel MeII</th>
</tr>
</thead>
<tbody>
<tr>
<td>+16</td>
<td>7.5%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>+18</td>
<td>1.1%</td>
<td>95%</td>
<td>%</td>
</tr>
<tr>
<td>+13</td>
<td>1.1%</td>
<td>90%</td>
<td>%</td>
</tr>
<tr>
<td>+X (xxx or xxy)</td>
<td>0.3%</td>
<td>90-100</td>
<td>%</td>
</tr>
<tr>
<td>-X</td>
<td>8.6%</td>
<td>20%</td>
<td>-</td>
</tr>
</tbody>
</table>

### Absence of transition from hetero- to isodisomy in pairs resulting from multi-chiasmate MeI non-segregation errors

On the following few slides, we show some specific examples of the role of the aneuploid mechanisms on the production of UPD for chromosomes 21, 1, 7 and 15:
**Aneuploid mode and mood of specific chromosomes**

**Chromosome 21**

**ETIOLOGIES OF TRISOMY 21**

**AS A RAW MATERIAL FOR TRISOMY RESCUE**

Frequency is 1 : 700

Maternal cases 86 % : 3/4 though M1 mat. non-segr.

: 1/4 through M1 mat. non-segr.

Paternal cases 9 % : 1/2 through M1 pat. non-segr.

: 1/2 through M1 pat. non-segr.

5 % : through mitotic non-disjunction

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**Aneuploid mode and mood of chromosomes**

**Chromosome 21**

**MIS-SEGREGATING MATERNAL PAIRS IN TRISOMY 21:**

**SYNAPSIS AND CHIASMA FORMATION**

<table>
<thead>
<tr>
<th>MECHANISMS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 homologues fail to pair or recombine</td>
<td>complete heterodisomy</td>
</tr>
<tr>
<td>M1 non-disjunction involves increased</td>
<td>more extensive hetero- or isodisomy</td>
</tr>
<tr>
<td>21q proximal recombination at M1</td>
<td>depending on chromosomal assortment</td>
</tr>
</tbody>
</table>

Conclusion

the major mechanism causing trisomy 21 also impairs transition from heterodisomy to isodisomy. Therefore, UPD 21 heterodisomy is the most likely outcome in rescue, limiting the risk of a recessive trait through reduction to homozygosity of that chromosome.

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**Aneuploid mode and mood of chromosomes**

**Chromosome 21**

**MITOTIC CONTRIBUTION TO THE ETIOLOGY OF TRISOMY 21**

- Only 5% of all cases

- All non-disjointed pairs with no identical content (isodisomnic)

- But, in a situation of so-called rescue, only one in three of the derived UPD pairs is statistically liable to become isodisomnic.

**CONCLUSION**

Small chance only of a transition to isodisomy for number 21 in UPD.

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*From Yoon P.W. et al., AJHG 1996, 58: 628-633*

*From Lamb NE et al., Nat. Genet. 1996, 14 : 490-495*
The vagaries of non-traditional mendelian recessive inheritance in uniparental disomy: AA x Aa = aa

**Chromosome 1**

**UNIPARENTAL DISOMY FOR CHROMOSOME 1**

**MECHANISMS OF FORMATION OF 12 KNOWN CASES**

**MATERNAL CASES**: Mel non-disjunction: 2 cases
Mell non-disjunction: 1 case
Mitotic duplication: 2 cases
(rescue from paternal nullisomy)

**PATERNAL CASES**: Mitotic duplication: 5 cases
(rescue from maternal nullisomy)
Mel non-disjunction: 1 case
Mell non-disjunction: 1 case

**CONCLUSION**: The main underlying mechanism implies rescue from 8 maternal meiotic accidents causing disomies (3 cases) or nullisomies (5 cases).

*From Engel E (1992), Hum Mol Genet 1: 1127* - 1132

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**Chromosome 7**

**UPD PATTERNS OF RESCUE AND TRANSITION TO HOMOZYGOSITY FOR CHROMOSOME 7**

**Maternal UPD 7**: Maternal meiotic errors with heterodisomy: 12
 causative chromosome recovery/mitotic loss of the paternal chromosome.
Maternal meiotic rescue with isodisomy: 11
(compensating for paternal gametic nullisomy).

**Paternal UPD 7**: Paternal meiotic rescue with isodisomy
(making up for maternal nullisomy).

**CONCLUSION**
Role for meiotic non-disjunction and monosomy duplication in both sexes with a greater liability to recessive traits such as CF


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**Chromosome 15**

**LEVEL OF TRANSITION FROM HETERO- TO ISODISOMY IN CASES WITH MATERNAL PAIR 15 NON-DISJUNCTION**

<table>
<thead>
<tr>
<th>Type of error</th>
<th>Interference with recombination</th>
<th>transition to isodisomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mel</td>
<td>75%</td>
<td>20% multi-chiasmata</td>
</tr>
<tr>
<td>Mell</td>
<td>15%</td>
<td>?</td>
</tr>
<tr>
<td>Mitotic</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

*From Robinson WP et al Hum Mol Genet 1998. 7: 1011-1019*
Summary

1) Presence of a uniparental pair in a diploid genome (UPD) results from an aberrant mode of transmission separate from Traditional Mendelian Inheritance. Instead of the classic tenets of allele segregation and independent assortment, an abnormal and complex pattern of segregation leads to this unusual unilateral assortment of alleles in the offspring.

2) The phenotype effect of this odd transmission then depends on the character -normal, mutant or imprinted- of the mis-assorted gene(s).

3) In the case of recessive inheritance, a singly heterozygous parent may sire a homozygous affected child. This will occur when the uniparental pair is homoallelic (isodisomy).

4) Isodisomy in uniparental pairs depends on various factors such as the aneuploid ways and means of the chromosome number involved, the recombination process, the meiotic disjunctonal pattern and the postzygotic mitotic adjustment of the chromosomes which all concur in shaping the end-product of the uniparental pair and its genetic impact.

5) To this day, some thirty different recessive phenotypes have been traced once or a few times to the presence of uniparental pairs. The good thing about the uniparental inheritance of recessive traits is that their risk of recurrence is almost nil.

Illustrations by Mr Jean-Claude Malgouyres

This article should be referenced as such: