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REVIEW

A fascination with chromosome rescue in uniparental disomy: Mendelian recessive outlaws and imprinting copyrights infringements

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With uniparental disomy (UPD), the presence in a diploid genome of a chromosome pair derived from one genitor carries two main types of developmental risk: the inheritance of a recessive trait or the occurrence of an imprinting disorder. When the uniparentally derived pair carries two homozygous sequences (isodisomy) with a duplicated mutant, this 'reduction to homozygosity' determines a recessive phenotype solely inherited from one heterozygote. Thus far, some 40 examples of such recessive trait transmission have been reported in the medical literature and, among the current 32 known types of UPDs, UPD of chromosomes 1, 2, and 7 have contributed to the larger contingent of these conditions. Being at variance with the traditional mode of transmission, they constitute a group of 'Mendelian outlaws'. Several imprinted chromosome domains and loci have been, for a large part, identified through different UPDs. Thus, disomies for paternal 6, maternal 7, paternal 11, paternal and maternal 14 and 15, maternal 20 (and paternal 20q) and possibly maternal 16 cause as many syndromes, as at the biological level the loss or duplication of monoparentally expressed allele sequences constitutes 'imprinting rights infringements'. The above pitfalls represent the price to pay when, instead of a Mendelian even segregation and independent assortment of the chromosomes, the fertilized product with a nondisjunctional meiotic error undergoes correction (for unknown or fortuitous reasons) through a mitotic adjustment as a means to restore euploidy, thereby resulting in UPD. Happily enough, UPDs leading to the healthy rescue from some chromosomal mishaps also exist.
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Part 1
Preamble

Mendelian recessive outlaws are traits inherited outside the undisputed Mendel laws, which are the even segregation and independent assortment of alleles in germ cells. In uniparental disomy (UPD), by contrast, the meiotic mis-segregation of alleles on a chromosome pair is followed, in general, by a revised early mitotic balancing reassortment. Such a reassortment, to be conducive to UPD, resorts to the loss of the normally inherited member of a trisomy or, more rarely, to the duplication of the lone member of a monosomy. If all ends well, the euploid status is restored but one of the 23 pairs lacks the other parent's partner. In rarer situations, instead of a dual, that is meiotic and mitotic compensating mistake, two meiotic errors, one in the fertilizing germ cell of each sex, complement each other. Although hypothetical, the latter probability

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served as the basis of the UPD concept, by taking into account the high rate of gametal aneuploidy in humans.

Introduction

In situations of grief, people who consult genetic clinics deserve as much truth and solace as relevant scientific information permits. When in consultation with couples suffering from repeated pregnancy loss, I found that the would-be parents were relieved to learn that fully half of first trimester miscarriages are the result of a chromosomal aberration incompatible with life or with normal development. Sitting around the table with a karyotype at hand, I would then unwearyingly, time and again, spell out the nature of such random mishaps, one-fifth being found to be 45,X; one-half with a trisomy, chiefly for chromosomes 16, 15, 21 and 22; some others with polyploidy, all nearly lethal except for a contingent of trisomies 21 and a few 45,X.

So often had I heard myself telling the habitual-aborters consulting me about this high incidence of certain anomalies in their type of problem that, in the end, a question dawned on me: what if, at fertilization, on occasion, a gamete with a disomy would meet one with a nullisomy for a same chromosome? Meiotic nondisjunction, whether it occurs in the ovary or in the testis, should produce complementary germ cells, one nullisomic and the other disomic for the chromosome in question. It follows that two abnormal germ cells, aneuploid for the same chromosome, might occasionally complement each other at fertilization. If viable, defective but complementary gametes could then, by chance, fertilize one another and proceed towards development with one of the 23 chromosome pairs derived from one parent. With this in mind, I called UPD this presumed and occult presence of a pair inherited from only the mother or father, in a diploid conceptus.[1]

For a long time, the above thoughts fascinated me and haunted my sleep. So much so that in the end, one evening in June 1979, a Saturday night, I sat home at my dining room table to tell that story. However, no need then for any handy reprint, since abortion studies alone, among them the work of Hassold *et al*,[2] were to serve as the groundwork of this early summer dream. It so happened that, at the end of that night, on Sunday, I was still sitting at that table, putting the final dot on an initial draft. Months later, after the due process of peer review, the final draft would be downsized to the point that the thrust of the remaining idea was that complementary errors could result in a seemingly euploid, normal zygote, with one whole pair derived from one parent (UPD). Such a pair could potentially carry lots of homozygous sequences (a case of so-called isodisomy), depending on the rate and level of crossing over and the meiotic stage at which mis-segregation had occurred. If so, by inheriting a (paternal) XY pair, male-to-male transmission of an X-linked mutant could happen; duplication of an autosomal recessive allele could cause a trait to be inherited from a single carrier parent and so on (see below). I dismissed the thought that, besides complementation, the secondary loss, at mitosis, of the normally inherited member of a trisomy would also result in a pattern of diploidy including a uniparental pair because, in most instances, this should have led, in my view, to a detectable mosaic pattern. Such a mechanism, however, later proved to be true, with the aneuploid cell line apparently often confined to the placenta and somatically undetected or inexistent (confined placental mosaicism, CPM).[3]

Another thought that was initially put down in the draft was obscurely present in my mind. In hindsight, I realize that it was implicitly relying on the notion of genomic imprinting, at that time totally alien to my mind. As is now well known, the process of genomic imprinting ends up in a selectively biased expression of maternal or paternal alleles at some loci or domains of the offspring genome. This evidence stemmed from the work of Lyon,[4] Searle and Beechey[5] and was indeed known from publications in 'mouse language'. Thus, in 1978, one could read the following apodictical statement:[5] 'The possibility that haploid expression of particular maternal or paternal genes is important for normal mouse development is discussed'. However, I was not then personally conversant with that murine language and I remained basically ignorant of the above notion. Yet, I had my own questions regarding the somatic effects of a pair of parental chromosomes not properly channelled to a zygote. Sex has always fascinated me and I was then wondering what could developmentally occur were a boy to get his X, as well as the Y chromosome from his father. Or a girl, her X pair from only her father. It had also occurred to me, and I had referred to it in my initial drafts that, maybe, an ultimately undue process of uniparental autosomal transmission might account as well for some not yet explained idiopathic syndromes, for instance the Cornelia-de-Lange syndrome, whose mode of transmission was then so poorly understood. However,, at the time, I did remove this statement from the article, as a Reviewer objected that the condition did not result from a pair of recessive alleles and also because I found myself unable to process the proposed thought into a scientifically referenced statement. Yes, indeed, Professor ten Kate, there also is fascination in being a reviewer of a scientific article for a noted journal!

Publication of the UPD article

Once masterly edited by John Opitz, and accepted after a long wait for publication in the American Journal of Medical Genetics in 1980, the paper[1] slept on a shelf for

several years, for want of the molecular developments which would make it possible to tell the parental origin of the chromosomes from their DNA polymorphisms. Some of the main techniques now in use have been reviewed in our book.[6]

The broad features of a genotype with UPD are as follows:

(1) It has 46 chromosomes which can be sorted out in 23 normal looking pairs, baring a translocation;
(2) 22 of the 23 pairs have been inherited normally;
(3) One pair has been derived from one parent only;
(4) This exceptional pair may result from three main mechanisms, namely:
   (a) trisomy rescue, through early mitotic loss of one of the three chromosomes;
   (b) monosomy duplication, through doubling of the lone chromosome of a monosomy;
   (c) gamete complementation, when a germ cell, by chance, has the surplus of what lacks in the other;
(5) Alleles at the uniparental loci may all be heterozygous (heterodisomy), homozygous (isodisomy) or a mix of both, depending on the nondisjunctional mechanisms and the mode of chromosome reassortment restoring the $2n$ state;
(6) Segmental UPD involving only some part of a chromosome pair can occur as a result of equal somatic crossing over.

UPD types currently documented

The first clinically recognized case of UPD was presented at the 1987 ASHG annual meeting, published in 1988 by Arthur Beaudet's group[7] and commented upon in an editorial.[8] This was the story of a mentally normal 16-year-old girl, menarch at 14, who measured only 130 cm, with some physical asymmetry suggestive of the Silver–Russell syndrome. She suffered from cystic fibrosis, although the father was homozygous for alleles distinct from hers on chromosome 7. The use of a number of RFLPs and centromeric alphoid probes for number 7 confirmed an absence of paternal alleles and showed full homozygosity of the patient's DNA. In short, '…the uniparental origin of the centromere, the lack of heterozygosity and failure to demonstrate mosaicism led to the conclusion that there had been duplication of a maternal chromosome 7 in a monosomic conception' of biologically unquestionable parentage. This first report of a case considered as most exceptional[8] was to be followed by a number of others dealing with this and a number of other chromosome pairs as well.

In theory, uniparental derivation of an entire chromosome pair offers a chance of 47 possibilities made of the 22 autosomes and X in each sex plus the XY paternal duplet. From the 1987 to 1988 period that started with the Spence *et al*,[7] initial publication and a remarkable case of Créau-Goldberg *et al*,[9] some three to six new types of UPDs were biannually described until 1997–1998, comprising from two to four paternal and/or one to five maternal ones (Figure 1 and Table 1). In all, they represent the 32

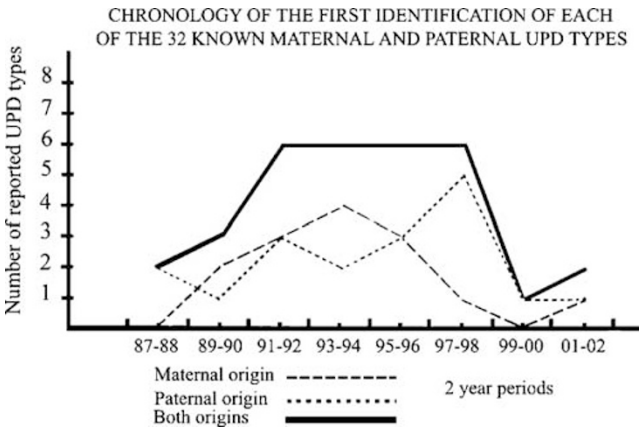

Figure 1 Chronology of the first identification of each of the 32 known maternal and paternal UPD types.

Table 1 Timing of the first identification of each known type of UPD

Year	*Type*	*References*
1987	21 mat	Créau-Goldberg *et al*[9]
1988	7 mat	Spence *et al*[7]
1989	15 mat	Nicholls *et al*[10]
1989	XY	Vidaud *et al*[11]
1990	6 pat	Welch *et al*[12]
1991	11 pat	Grundy *et al*[13]
1991	4 mat	Lindenbaum *et al*[14]
1991	14 mat	Temple *et al*[15]
1991	14 pat	Wang *et al*[16]
1991	15 pat	Malcolm *et al*[17]
1992	16 mat	Bennett *et al*[18]
1993	21 pat	Blouin *et al*[19]
1993	16 pat	N'go *et al*[20]
1994	22 mat	Schinzel *et al*[21]
1994	5 pat	Brzustowicz *et al*[22]
1994	7 pat	Höglund *et al*[23]
1994	13 mat	Slater *et al*[24]
1995	13 pat	Slater *et al*[25]
1995	2 mat	Harrison *et al*[26]
1995	10 mat	Jones *et al*[27]
1995	22 pat	Miny *et al*[28]
1996	8 pat	Benlian *et al*[29]
1996	6 mat	Van Den Berg-Loonen *et al*[30]
1997	1 mat	Pulkkinen *et al*[31]
1997	8 mat	Piantanida *et al*[32]
1997	9 mat	Sulisalo *et al*[33]
1997	X mat	Quan *et al*[34]
1998	1 pat	Gelb *et al*[35]
1999	20 mat	Chudoba *et al*[36]
1999	17 mat	Genuardi *et al*[37]
2000	2 pat	Thomson *et al*[38]
2002	12 mat	Von Eggling *et al*[39]

Table 2 Types and frequencies of maternal or paternal UPDs in the clinical field

(A) 18 Known maternal types					
	1[a]	2[a]	4	6	7[b]
	8	9	10	12	13
	14[b]	15[b]	16[b]	17	20
	21	22			X
(B) 14 Known paternal types					
	1[a]	2[a]	5	6[b]	7[a]
	8	11	13	14	15[b]
	16	21	22		XY
(C) Five unknown maternal types					
	3	5	11	18	19
(D) 10 Unknown paternal types					
	3	4	9	10	12
	17	18	19	20	X

[a]Less common.
[b]Relatively common.
All other reported types are rare or exceptional.
Undetected:
- from the mother 5, 11
- from the father 4, 9, 10, 12, 17, 20, X
- from both parents 3, 18, 19.

(out of 47) known examples of their type for a whole pair (holo-uniparental disomy) as opposed to the untold number of biparental pairs having acquired a mono-parental segment (see below).

Table 2 displays the chromosome pairs with UPD, identified or not yet identified in either sex, and gives a rough estimate of the relative clinical frequencies for the various pairs involved.

Reduction to homozygosity: the 'Mendelian outlaws'!

These outlaws are a by-product of isodisomy and will only cause trouble when one parental duplicated allele is a mutant. In heterodisomy, the whole length or a portion of a uniparentally inherited pair is heterozygous. In isodisomy, the loci of both pair members are homozygous on the entire length or on a part of the pair. At the extremes, complete heterodisomy will occur when one parental pair, not reshuffled by crossing over (nulli-chiasmatic) and nondisjoined at the first meiotic division, is inherited as such, after a normal meiosis 2. In wholesale isodisomy, meiosis 2 nondisjunction of a meiosis 1 (me1) nulli-chiasmatic pair, as well as the duplication of a monosomic chromosome at early mitosis, may cause both members to be carbon copies of each other. If so, all loci of such pairs are homoallelic, homozygous and thus isodisomic. Ruling out the above mechanisms, a number of uniparental pairs are a mix of hetero- and iso-disomy segments. In any event, as crossing over does not take place in juxta-centromeric areas, the latter remain heterodisomic in UPD pairs nondisjoined at me1 and isodisomic in pairs not disjoined at meiosis 2 (me2), which allows them to be distinguished from each other. It is thus obvious that the genotypic risk of isodisomy is the transmission of a clinically significant mutant allele on a duplicated chromosome or chromosome segment. As a result, some 40 examples of homozygosity for a recessive mutant present in only one parent have been published in medical literature and are presented in chromosome numerical order in Table 3.

It can be seen that isodisomy as a cause for homozygosity of a recessive mutant is less rare for numbers 1, 7 and 2. With respect to chromosome 1, five maternal and eight paternal such instances are on record. Chromosome 7 provides six examples of clinically significant reduction to homozygosity – four maternal, two paternal. As to chromosome 2, it is seen five times, caused by two maternal and three paternal UPDs. Most other examples of such intimidating recessive outlaws are singular! Their high recurrence on chromosome 1 is fascinating because one hardly knows of a single case of trisomy 1 among first trimester abortuses so that all such derived number 1 disomies must result from a very early rescue of almost unviable conceptuses, as is notoriously the case for nearly all monosomic ones as well, hardly seen in abortion products, with an exception for some X monosomies.

In general, one might presume that, with a higher number of loci, the larger chromosomes such as 1 and 2, in isodisomy, contribute to a commensurate display of their recessive mutations. Yet, one remains puzzled by the very fact that the (nonsense!) mutations of the LAMB3 locus on chromosome 1q32.2, encoding the subunit polypeptide gamma 2 of lamin 5, account for three of the 13 recorded instances of reduction to homozygosity of that member![31,45,48] The relatively high incidence of cystic fibrosis, for which four of six UPDs seven are responsible[7,55–57] may be biased as a result of the many segregation studies carried out for counselling in CF families, increasing the chances of detecting such events. All these disparate remarks point to the fact that the nondisjunctional meiotic mechanisms, central to the occurrence of the isodisomy process, vary strongly among the different chromosome members as shown for some on Table 4, inspired from Jacobs and Hassold.[64]

Suffice it to say that key differences exist in the ways our chromosomes may go astray. Thus, so common among early abortuses, trisomies 16 feature an exclusive, almost totalitarian display of ovarian me1 errors. In contrast, trisomies 18 are not always of maternal origin and are caused, in the majority, by an me2 nondisjunction (reviewed by Jacobs and Hassold[64]). The implications for UPD16 may be straightforward: the noted frequency of trisomy 16, its unique and constant maternal origin, and the reduced recombination going along with me1-generated disomies[64] should explain the relatively high frequency of UPD16 mat void of isodisomy (reviewed by

Table 3 Uniparental isodisomy: reduction to homozygosity leading to recessive disorders

Recessive disorders	*UPD type*	*References*
Functional epidermolysis bullosa, herlitz type	1 mat	Pulkkinen *et al*[31]
Diabetes mellitus, type I	1 mat	Field *et al*[40]
Chediak–Higashi syndrome	1 mat	Dufourcq-Lagelouse *et al*[41]
Maple syrup disease, type 2	1 mat	Lebo *et al*[42]
MCA (multiple congenital anomaly)	1 mat	Rothlisberger *et al*[43]
Pycnodysostosis	1 pat	Gelb *et al*[35]
MiCA	1 pat	Chen *et al*[44]
Functional epidermolysis bullosa, Herlitz type	1 pat	Takizawa *et al*[45]
Congenital insensitivity to pain anhydrosis (CIPA)	1 pat	Miura *et al*[46]
CIPA+pyruvate kinase deficiency	1 pat	Indo *et al*[47]
Junctional epidermolysis bullosa, Herlitz type	1 pat	Fassihi *et al*[48]
Retinal dystrophy	1 pat	Thomson *et al*[38]
Usher syndrome type A2	1 pat	Rivolta *et al*[49]
Trifunctional protein deficiency	2 mat	Spiekerkoetter *et al*[50]
Pseudohermaphroditism (5α reductase deficiency)	2 pat	Chavez *et al*[51]
Retinal distrophy	2 pat	Thomson *et al*[38]
Crigler–Najjar, type I	2 pat	Petit *et al*[52]
Congenital afibrinogenaemia	4 mat	Spena *et al*[53]
Spinal muscular atrophy, type 3, Juvenile	5 pat	Brzustowicz *et al*[22]
Congenital adrenal hyperplasia	6 mat	Spiro *et al*[54]
Cystic fibrosis	7 mat	Spence *et al*[7]
Cystic fibrosis	7 mat	Voss *et al*[55]
Osteogenesis imperfecta (COL1A2)	7 mat	Spotila *et al*[56]
Cystic fibrosis	7 mat	Hehr *et al*[57]
Congenital chloride diarrhoea	7 pat	Höglund *et al*[23]
Cystic fibrosis and kartagener syndrome	7 pat	Pan *et al*[58]
Chylomicronemia familial	8 pat	Benlian *et al*[29]
Hair–cartilage syndrome	9 mat	Sulisalo *et al*[33]
Leigh syndrome	9 mat	Tiranti *et al*[59]
Beta thalassemia major	11 pat	Beldjord *et al*[60]
Prelingual hearing impairment (Connexin26)	13 mat	Alvarez *et al*[61]
Complete congenital achromatopsia (rod monochr.)	14 mat	Pentao *et al*[62]
Bloom syndrome (with PWS)	15 mat	Woodage *et al*[63]
Hydrops fetalis alpha-thalassemia	16 pat	N'go *et al*[20]
Duchenne muscular distrophy	X mat	Quan *et al*[34]
Hemophilia A	XY	Vidaud *et al*[11]

Table 4 Aneuploid mechanisms affecting some clinically important chromosome pairs

Chr. no.	*Spont. abort. frequency (%)*	*Parental origin maternal (%)*	*MeI (%)*	*MeII (%)*
+16	7.5	100	100	—
+18	1.1	95	1/3	2/3
+13	1.1	90	2/3	1/3
+X (xxx or xxy)	0.3	90–100	7/10	2/10
−X	8.6	20	—	—

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

Engel and Antonarakis[6]). And, UPD16pat[20,65] should mainly and perhaps constantly be the rare by-product of maternal 16 meiotic nullisomy. If so, holo-isodisomy would prevail by early mitotic duplication of the lone paternal 16 and could carry the risk of homozygosity for recessive mutants.[20]

A somewhat similar commentary could hold true for the UPD's 21 derived from a trisomy 21 where the trend seems as follows: the risk of isodisomy is lowered and the chance of heterodisomy maintained if a lack or a dearth of crossing over recombination is a cause for me1 nondisjunction, as is indeed the case[66]; such a risk is lessened as well if a (proximal) increase in recombination at me1 favours me2 nondisjunction, which has also been well documented.[67] We see therefore that the mood of chromosome 21, in pathology, is against isodisomic deviancy and does not at all favour the works of 'recessive outlaws'! In addition, UPD21 is clinically innocuous at the difference of UPD16 mat (reviewed by Engel and Antonarakis[6]) and the pair presents a relatively small number of genes up for recessive

mutations. Detecting UPD21 with present means will thus remain quite hard, except in cases where an isochromosome 21, *de novo* or transmitted, calls attention to it.[9] A different pattern of conversion to UPD is seen for other chromosome members of somewhat different pathologic behaviour. Our review of the situation in UPD1, maternal or paternal, emphasizes again the major role of maternal meiosis errors. This is no surprise since most known cases have been uncovered on the basis of a reduction to homozygosity leading mainly to recessive traits (Table 3).

From this clinically biased sample, it would appear that the chromosome1 Mendelian outlaws stem not only from the rescue of trisomies caused by maternal meiotic nondisjunction[31,40,42] but also from maternal nullisomies complemented by paternal monosomy duplications,[38,44–47] a mechanism much rarer for chromosomes 18 and 21, as already discussed. Besides, a paternal meiotic involvement at the origin of these cases is also rather surprising, with 2*n* genotypes presumably arising from the correction of paternally induced trisomies[35,49] or from mitotic complementations of the monosomies resulting from a meiotic loss of the paternal member.[41,43]

A survey of and a personal contribution to published maternal UPD7 cases[68] produced as many cases of heterodisomy after presumed maternal trisomy rescue (12) as cases of holo-isodisomy (11). In my view, although other mechanisms may be considered, the isodisomy group is best explained by maternal complementation of paternal gamete nullisomy. If so, one should also assume that paternal germ cells with chromosome 7 nondisjunction and disomy are as numerous as their nullisomic counterparts and will contribute to trisomy 7 conceptuses, which they may well do, although survival to birth is nil.[64] Cases of paternal UPD7 appear rarely in medical literature and may show isodisomy, to make up for maternal nullisomy. The redundance of isodisomy among UPD7 pairs, the size of the chromosome, the presence of a CF mutation on one for every 40–50 such members and the contribution of maternal UPD7 to the Silver–Russell phenotype all guarantee that this UPD will be relatively frequently met in the clinical field when looked for in the laboratory.

As a final example, we shall also trace some of the pathologic features of chromosome 15 aneuploidy to examine their bearing on the allelic assortment of the uniparental derivatives. Trisomies 15 are not so uncommon in spontaneous abortuses, being next in frequency to trisomies 16, 21 and 22.[64] They are sublethal. Three-quarters of them result from maternal me1 nonsegregation events and, as for chromosome 21, are aided by a lack or a dearth of recombination. Close to 10% are of mitotic origin,[69] so that roughly one-third, or 3% of all 15 trisomies may contribute to maternal or paternal isodisomy with the implied risk of a recessive trait from a mutant. Given the high contribution of maternal meiotic nondisjunction to trisomy 15, most detected rescues will have to represent cases of maternal UPD. It is not therefore surprising that quite a few cases of Prader–Willi syndrome (PWS), caused by the deficit of a paternal 15 imprinted domain, come from this relatively common disomy. Cases of paternal UPD15 are much rarer and result in the Angelman syndrome (AS), owing to the deficit of a maternally active domain on that number. As seen for other members, mitotic duplication of a paternal chromosome is a palliative for a maternal nullisomy owing to a meiotic loss; it is conducive to isodisomy and can cause, as such, a reduction to homozygosity of any present recessive allele. Some cases of UPD15 also occur from a rescued paternal 15 trisomy caused by an me1 error but, all in all, 75–80% UPD15 pat stem from a mitotic segregation error or from a centromeric misdivision with isochromosome formation. Thus, quite evidently, most holo-isodisomies for chromosome 15 are paternal in origin, leading potentially to a recessive trait, aside from causing AS.

The point of this discussion of the ways and means by which chromosomes 1, 21, 7 and 15, taken as examples, behave in pathology is to show that, in the process, their 'skin changes' from hetero- to iso-disomy – should UPD occur – depend highly on the chromosome at stake and reflect both the mode of formation involved and, oddly enough, something of the very essence of the particular chromosome involved. This implies that, under the circumstances, some chromosome individuals are much more prone than others to breed Mendelian outlaws. It is hard therefore to state the level of contribution of the various uniparental pairs to the overall occurrence of recessive disorders. As an indication, among some series of recessive conditions studied, such an aetiology was found in one of 61 cases of junctional epidermolysis bullosa of Herlitz, nearly 2%,[31] in one of 55 cases of cystic fibrosis, again 2%[55] and in two of 54 cases of cartilage–hair hypoplasia, about 4%.[33]

Segmental UPD

Cases with this type of defect are difficult to expose, as a segment only of an otherwise biparental pair is affected. This segment may be terminal or interstitial and results from a balanced somatic crossing over. A terminal exchange occurs with one single symmetrical break, whereas, when interstitial, the balanced homologous exchange requires two such breaks. The reasons for these types of somatic reshuffling are unknown and hot spots to this effect must exist. Once such a remodelling has happened, a mosaic chromosomal state is achieved with the simultaneous presence of the initial genotype and the genotypes of the two new reciprocal clones issued from the balanced interchange. The archetype of a relatively frequent somatic, mitotic interchange is to be seen in the terminal uniparental paternal segment at or close to 11p15.5, a hallmark in a proportion of patients with the

Table 5 Instances of segmental uniparental disomies (terminal or interstitial)

Chromosomes	*Segment*	*Conditions*	*Authors*
1 mat	1p11.2-qter	Progeria type Hutchinson–Gilford	Erikson *et al*[71]
1 mat or pat	1q22-qter	Progeria type Hutchinson–Gilford	Erikson *et al*[71]
2 mat	2q37.3	Iary Xxaluria-type I	Chevalier-Porst *et al*[72]
4 mat	4q21–35	A-Beta Lipoproteinemia	Yang *et al*[73]
4 mat	4pter	Ellis–van Creveld syndrome	Tomson *et al*[74]
6 pat	6p	21 Hydroxylase deficiency	Lopez-Gutierrez *et al*[75]
6 pat	6q24-qter	TNDM	Das *et al*[76]
7 mat	7q31-qtr	Silver–Russel syndrome	Hannula *et al*[77]
7 mat	7q31-qtr	Silver–Russel syndrome	Eggermann *et al*[78]
11 pat	11p15.5	Wiedemann–Beckwith syndrome	Henry *et al*[70]
11 mat	11q13-qter	Multiple anomalies	Kotzot *et al*[79]
14 pat	14q12-qter	Pat14 Disomy syndrome	Towner *et al*[80]
15 mat	15q proximal	Prader–Willi syndrome	Nazarrenko *et al*[81]
20 pat	20q	Parathormone resistance	Bastepe *et al*[82]

Wiedemann–Beckwith syndrome (WBS).[70] Oddly enough, in this case, the maternal 11p15.5 homologous segment, as the counterpart of this exchange, has not been identified and may well be selected against from the tissues and organs in development. So intriguing is the underlying cause of the exchange that, as a rule, tissues of only one of identical twins will undergo this change in early gestation and suffer from the WBS.

Table 5 lists clinical instances of reported segmental UPDs in congenital disorders. Just like complete uniparental pairs, partial ones may be responsible for recessive traits or for various imprinting syndromes. Segmental UPD research probably has a great future as it occasionally happens in association with another holo-disomic UPD pair within a same genome[83,84] or with some other rearrangements,[85] and as a part of the clonal evolution of malignancies.[86–88] A full review of these instances would be beyond the scope of this article.

Part 2

Genomic imprinting amounts to a silencing of the expression of certain genes or domains through a reversible methylation process and other secondary biochemical changes of the DNA blueprint, as a mark of the parental sex. The end result is a functional hemizygosity (maternal or paternal) for the loci of some domains. 'Imprinting copyrights infringements' are lawless acts of nature whereby allelic expression contravenes the expected course of the conventional biological printing press medium! The complex normal printing machine is under the control of an imprinting centre and a relaxation of the imprint normally occurs in early gametogenesis, to be selectively reinstated afterwards as a function of the parental sex, according to some prescribed developmental timing for different tissues and organs. The chromosomal by-pass of one of the two parental channels of transmission in UPD perturbs the above functional adjustments of allelic expression where relevant. In such cases, the presence of a second homologue from the same genitor is no substitute for that missing from the other genitor, as far as the specifically imprinted domains are concerned.

Besides reduction to homozygosity, the genotypic risk of carrying UPD pairs with imprinted domains results from the eventual loss or duplication of allelic expression by the offspring. Just as had happened with the first clinical report of UPD7, the interest in the subject matter took another turn with the report of the first case of UPD as an imprinting disorder.[10] This initial observation was that connecting UPD15 mat to the PWS.

The fascination for the genetics of UPD grew further with this and other reports confirming an intimate link between certain pairs and disturbances of the ordinances of genomic imprinting. It had been known for some years that a tiny deletion in 15q11–q13 was a frequent cause of PWS.[89] Sometime later, it appeared that such a deletion would cause two distinct syndromes, AS *versus* PWS, when affecting, respectively, the maternal or paternal chromosome 15.[90] It was now being seen that the paternal counterpart for UPD15 mat also confirmed this dichotomy, by causing AS, not PWS. In short, a second maternal or paternal 15 in a pair could not substitute for the missing partner! Undoubtedly, even intact, chromosomes 15 mat and 15 pat did not express the same genetic message: they thus were imprinted and the hemizygously expressed domain must also lie in the area where the deletion could occur and cause a similar damage. We now know that chromosome 15 has two adjacent imprinted domains, one of several complex expressed alleles on paternal 15, the other more distal with active alleles on the maternal contiguous sequence. With time it would be learned that the lack of expression of paternal alleles in UPD15 mat accounted for some 25% of PWS cases, whereas UPD, as a rule with isodisomy, for the paternal 15 segment at

Table 6 UPD pairs clinically harmful through a genomic imprinting disturbance

UPD type	*Syndrome*
Certain	
Paternal 6	Neonatal diabetes (transient)[91]
Maternal 7	Silver–Russell[92]
Paternal 11	Wiedemann–Beckwith[70]
Maternal 14	Growth failure, early puberty[15,93]
Paternal 14	Dwarfism, rib cage hypoplasia[16]
Maternal 15	Prader–Willi[10]
Paternal 15	Angelman[17]
Maternal 20	Growth failure, hyperactivity[36]
Probable	
Maternal 16	Growth failure, CHD, IA, etc.[94,95]

q11–q13, accounts for about 2% of AS only.[6] After these essential findings, other UPD pairs or segments causing various imprinted syndromes were documented, and the main ones shown on Table 6.

These various pairs appear to delineate two types of situations, one where other genomic alterations may also cause the condition, and another type in which the newly identified UPDs point to syndromes until then not recognized, as is seen for the maternal and paternal variants of UPD14 and maternal UPD16.

As shown on Table 6, today nine full-blown UPDs cause 'imprinting copyrights infringements'. Wholesale UPD20 mat and (segmental) 20q pat specifically alter the activities of the Neuronatin[96] and GNAS[97] alleles, respectively, paternally and maternally expressed. Curiously, at the difference of other chromosomes such as maternal and paternal 15 or paternal 11, etc., the imprinted genes of chromosome 20 are not part of domains and represent isolated exceptions amidst biparentally active loci, the so-called microimprinting.[96]

On Table 7 are shown the frequencies of UPD contributing to the aetiologies of these syndromes.

The approximate population frequencies of UPD pairs in the aetiology of major imprinted syndromes are detailed in Table 8.

Making some assumptions, an approximate population frequency of UPD as an aetiology of major imprinted syndromes is presented. As an example, let us refer to the PWS phenotype, which is in general viable and may know a clinical frequency of one in 20 000 live births. Considering that maternal UPD15 serves as an aetiology for some 25% of the cases, one may infer that this maternal UPD occurs around once every 80 000 live births. The same type of calculation can also help to approach an estimate for several other UPDs, at the origin of a proportion of syndromic conditions of rather well-documented frequencies.

It would be beyond the scope of this clinical overview to inventory the specific loci subject to the imprinting

Table 7 Frequencies of UPD in the aetiology of major imprinted syndromes

Syndromes	*UPD type*	*Frequency (%)*
Transient neonatal DM	6 pat	±20
Silver–Russell	7 mat	6–10
Wiedemann–Beckwith	11 pat	20–30
Prader–Willi	15 mat	±20
Angelman	15 pat	2

Table 8 Approximate population frequencies of uniparental pairs

Pair	*Disorder*	*Frequency of disorder*	*Pair frequency of disorder (%)*	*Population frequency*
15 mat	PWS	1/20 000	25	1/80 000
15 pat	AS	1/20 000	2	$1/10^6$
11 pat	BWS	1/15 000	20	1/75 000
6 pat	TNDM	1/500 000	40	1/1 250 000
7 mat	SRS	?	6	?

of paternal or maternal chromosomes of major clinical interest, but Figure 2 is an attempt at showing some of the main ones involved. The interested reader may refer to some attuned reviews available on the Internet.

I have not so far written about some cytogenetic suggestive oddities met in the laboratory search to unmask UPD, namely translocations, isochromosomes or markers, such as, to quote but a few isolated examples:

(a) one paternal 13/14 balanced translocation which as a back-up brings about a 14/14 maternal isochromosome in the offspring, as a substitute for the paternal nullisomy segregating from this rearrangement[98];
(b) a monosomy rescue which resorts to a paternal isochromosome of one arm – i(7p) pat – and a maternal one for the other – i(7q) mat – to restore euploidy, thereby setting up a mixed (paternal and maternal) segmental UPD in a same genome[99];
(c) a tiny centromeric marker which represents either a minimal leftover of the rescued nearly nullisomic culprit or a remnant of the not quite vanished member of a trisomy![6] The result is a flag for either trisomy or monosomy rescue!

Rescue

The word rescue comes back quite often in any discussion of the mitotic twists involved in the return to a cytogenetically balanced development imposing a uniparental pair! Poor salvage, indeed, when it relies on biological outlaws or imposters that too often disseminate recessive traits or ontogenic derailments. Indeed, on the path to euploid rescue, four things may happen:

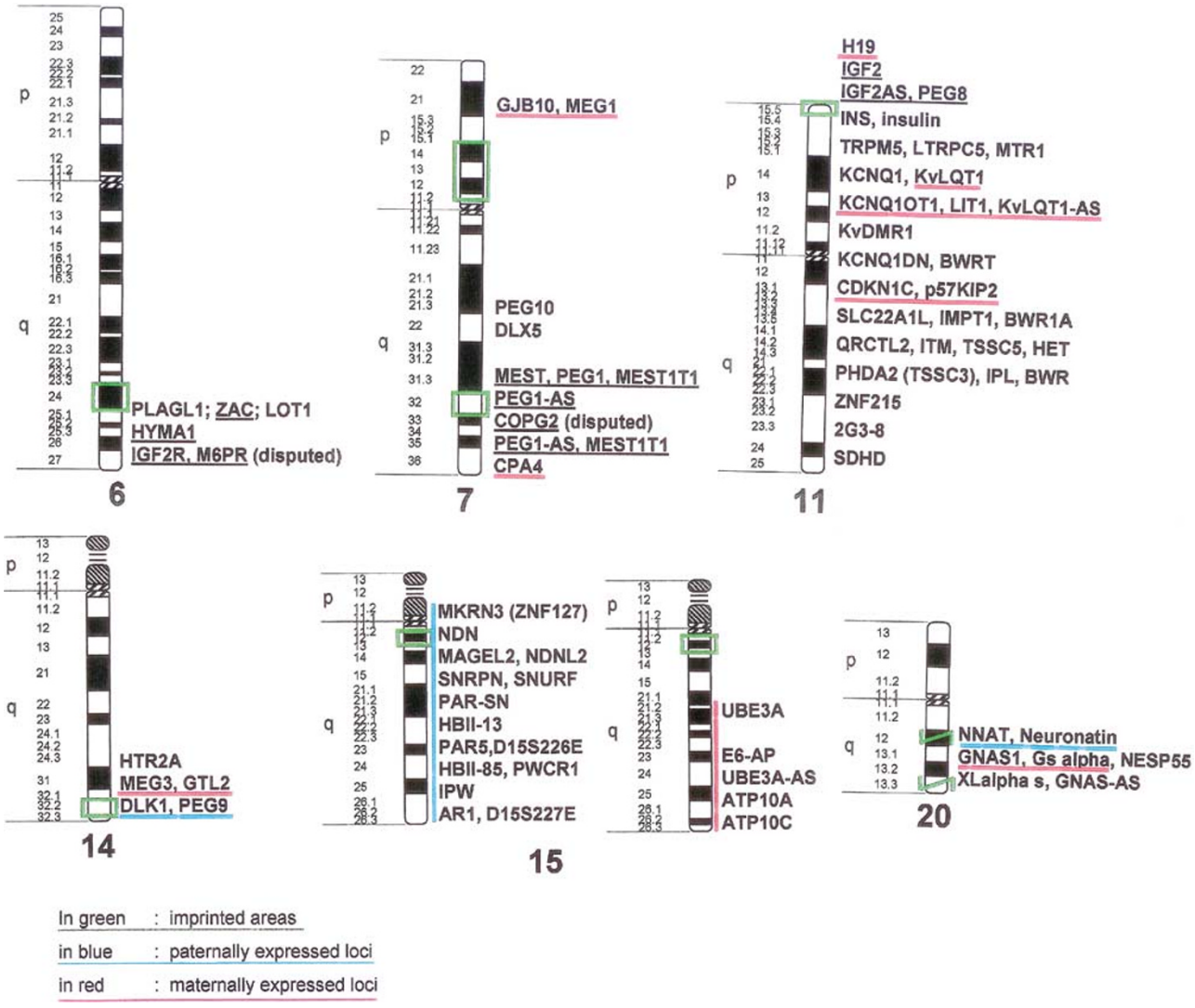

Figure 2 Major imprinted areas involved in clinical disorders (NB: GRB10 and MEG1 are localized on 7p).

(a) rescue at the cost of a recessive trait,
(b) rescue at the cost of an imprinting disorder,
(c) rescue at the cost of both (rarely!),
(d) true, healthy rescue.

Leo, with my wholehearted best wishes to a distinguished retiree, the following quotes hopefully constitute two fascinating offerings for your appreciation. In one, a pattern of homologous centric fusion for chromosome 22 is found in a woman who aborts 10 times in a row before producing a normal female offspring who will in turn miscarriage several times,[100] Figure 3.

In another example, a homologous 13/13 centric fusion (or an isochromosome 13q) is found in a balanced woman without an inherited maternal 13,[24] Figure 4.

In this figure, the habitual aborter exemplifies a case of paternal UPD13. In the end, she produces a balanced male offspring, born after five spontaneous abortions. Her balanced offspring, with the inherited 13/13 fusion of the mother and no paternal 13 is an example of maternal UPD13,[29] the second case over two generations of this family! A true miracle.

I shall now close with some nagging (and fascinating) questions to be resolved in the areas of UPD and genomic imprinting[6]: What is the spectrum of all possible UPD types? What is the frequency of UPD? What is the extent and role of segmental UPD? How can the cytologic mechanisms involved in UPD be elucidated? What is the level of implication of UPD in recessive disorders? How can we improve the diagnostic tests for fast detection of UPD? What is the evolutionary significance of genomic imprinting?

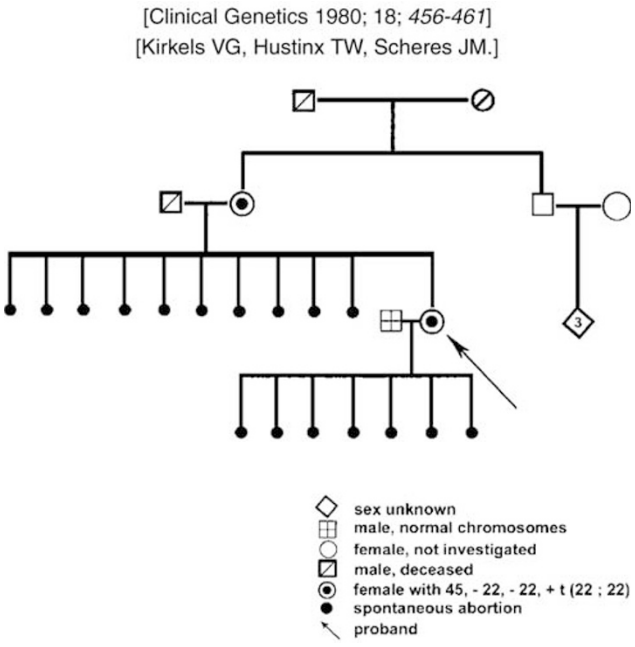

Figure 3 Habitual abortion and translocation (22q;22q): unexpected transmission from a mother to her phenotypically normal daughter (published with permission of the Authors).

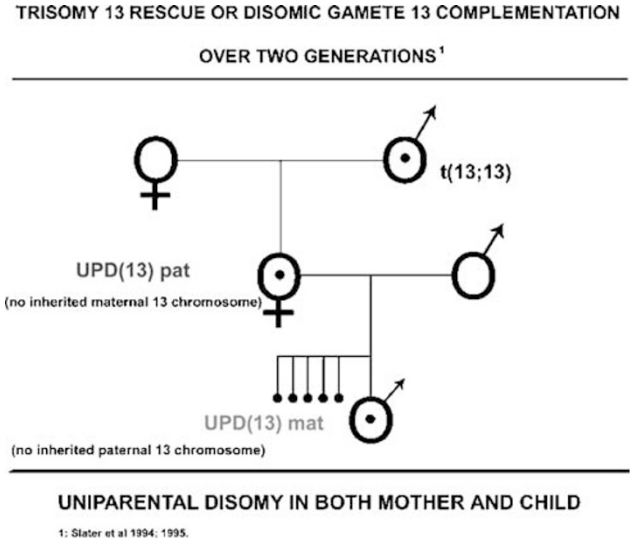

Figure 4 Trisomy 13 rescue or disomic gamete 13 complementation over two generations.

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