21

Euploid Chromosome Aberrations, Uniparental Disomy, and Genomic Imprinting

Uniparental Disomy

In some individuals, both copies of a particular chromosome come from one parent and none from the other; this is called *uniparental disomy* (UPD) (Engel, 1980). It is not yet clear how common each type of uniparental disomy is, but many deviations from Mendelian inheritance could be explained by it, as described below. Most UPD has a meiotic origin that leads to a trisomic zygote, with loss of one copy of the chromosome in a subsequent mitosis. One-third of the time, the single copy from one parent will be lost, producing UPD. Trisomy of meiotic origin is usually the result of maternal meiosis I nondisjunction, so most UPD of meiotic origin is maternal UPD (Robinson et al., 1997). Paternal UPD is more likely to have a postzygotic origin from a normal zygote by mitotic nondisjunction. A much smaller proportion of maternal UPD arises in this way.

O. J. Miller et al., *Human Chromosomes*

Trisomic cells produced by *mitotic* nondisjunction have two identical copies of the chromosome from one parent. In trisomies due to meiotic nondisjunction, restoration of disomy by loss of a chromosome will produce uniparental *isodisomy* one-third of the time. The two identical chromosomes are, naturally, homozygous at all their gene loci, including any that are mutated. UPD of a maternally derived chromosome has been observed for chromosomes 1, 2, 4, 6, 7, 9, 10, 13–16, 21, 22, and X. Paternal UPD has been observed for chromosomes 1, 5–8, 11, 13–16, 20–22, X, and XY (Engel, 1998). For years, the most commonly observed UPDs were those of chromosomes 7, 11, 14, and 15, perhaps because these are associated with characteristic phenotypes that bring them to medical attention and cytogenetic study. However, many more cases have been discovered since the introduction of earlier prenatal diagnostic studies, based on first-trimester placental biopsies (chorionic villus sampling).

Confined Placental Mosaicism and the Origin of UPD

Usually the embryo and the trophoblast have the same chromosome constitution, but sometimes a karyotypically abnormal cell line is limited to the placenta. The widespread use of chorionic villus sampling early in pregnancy has led to the discovery that a surprisingly high proportion (1–2%) of first-trimester conceptuses are mosaics with a trisomic and a disomic cell line. Fortunately, it is rare to find any evidence of residual mosaicism in the fetuses or newborns resulting from these pregnancies, so this condition has been called *confined placental mosaicism* (CPM). However, about one-third of these fetuses or newborns show UPD for the chromosome in question, as expected if restoration of disomy involves random loss of one of the three copies of the chromosome. These findings have important implications for genetic counseling.

The trisomic cell line in CPM can arise during meiosis or in postfertilization mitoses. Most CPM involving chromosomes 9, 16, and 22 is meiotic in origin, while CPM involving chromosomes 2, 7, 8, 10, and 12 is predominantly somatic in origin. A poor pregnancy outcome is restricted to CPM of meiotic origin, which is also associated with a higher proportion of trisomic cells in the placenta, and fetal UPD. The embryo proper arises from only 3–5 of the 64 cells of the early blastocyst and is clearly more likely to receive trisomic cells if these make up a higher percentage of cells in the blastocyst (Robinson et al., 1997). The most important question for the family seeking counseling is the pregnancy

outcome expected with CPM and resultant UPD of a particular chromosome. Just how important are these as causes of disease? It is too early to give more than a rough estimate. Consider chromosome 16, which is inordinately over-represented among human trisomies (Chapter 11). Its frequency is 15 per 1000 recognized pregnancies, and 80–95% arise in maternal meiosis I. Most 16-trisomics are aborted by the twelfth week of pregnancy, but about 10% reduce to disomy, and 3% show no trisomic cells in the fetus (CPM). One-third of these (10 cases observed) have UPD16 associated with fetal loss late in pregnancy or severe intrauterine growth retardation, and a high percentage of trisomic cells in the placenta at delivery. There have even been cases of 16-trisomy/disomy mosaicism in liveborns (Wolstenholme, 1995).

UPD Can Lead to Homozygosity of a Recessive Disease Gene

The occurrence of the autosomal recessive disease cystic fibrosis in a child whose mother carried the mutant gene but whose father did not, led to the discovery of uniparental isodisomy. The child received identical copies of a chromosome 7 from the carrier mother and none from the father (Spence et al., 1988). Autosomal recessive disorders caused by isodisomy of 11 different chromosomes have been reported, including Bloom syndrome in isodisomy 15, spinal muscular atrophy in isodisomy 5, and the skeletal disorder pycnodysostosis in isodisomy 1. The two chromosomes from one parent do not have to be completely identical, or *isodisomic;* only the disease locus needs to be homozygous. In one case, the skin disease epidermolysis bullosa was caused by heterodisomy 1 in which only a 35-cM (35% recombination) region was homozygous on the two maternally derived chromosomes 1, as a result of crossing over (reviewed by Engel, 1998). As many as 1–2% of cases of recessive disease may be due to UPD, with only one parent a heterozygote.

UPD Can Lead to Disease Due to a Novel Mechanism: Genomic Imprinting

The increasing availability of genetic markers has made the identification of UPD much easier, and this has led to the discovery that a series of disorders are

Table 21.1. Imprinted Autosomal Genes and Their Locations

Gene	Location	Imprinted allele
IGF2	11p15.5*	Maternal†
H19	11p15.5	Paternal
KIP2	11p15.5	Paternal
IMPT1	11p15.5	Paternal
KVLQ1	11p15.5	Paternal
SNRNP	15q11–q13‡	Maternal
IPW	15q11–q13	Maternal
ZNF27	15q11–q13	Maternal
ZNF27AS	15q11–q13	Maternal
NDN	15q11–q13	Maternal
UBE3A	15q11–q13	Maternal
HIC-1	17p13.3	?
GNAS	20q13.3	Paternal

*Imprinted gene cluster about 1.5 Mb in size

†Tissue-specific pattern of imprinting

‡Imprinted cluster about 1 Mb in size

due to the absence of a maternal (or paternal) copy of a particular chromosome, chromosome region, or gene. This indicates that in one sex an imprint is placed on the gene or genes during gametogenesis. This process, called *genomic imprinting*, permanently inactivates (or more rarely, activates) the gene. The children described earlier whose cystic fibrosis was due to UPD7mat had an additional trait, short stature, which is not usually seen in cystic fibrosis but has been seen in many other UPD7mat cases without cystic fibrosis, and even in association with UPD7qmat (Eggerding et al., 1994). UPD7mat accounts for about 10% of the cases of the Russell-Silver syndrome, in which short stature is a prominent feature. For extensive reviews of genomic imprinting, see Reik and Surani (1997) or Bartolomei and Tilghman (1997).

At least 12 autosomal genes have been shown to be imprinted (Table 21.1). An imprinting map has been developed as a guide in evaluating the potential danger of confined placental mosaicism (Ledbetter and Engel, 1995). The most striking feature of imprinted genes is their presence in clusters. One could regard the very large regions on the X chromosome that are subject to inactivation as

even larger clusters of imprinted genes, since they too show monoallelic expression. The known autosomal clusters occur on chromosome 11 at p15.5 and on chromosome 15 at q11–q12. Clustering may have evolved so that a single regulatory element could mediate the coordinated imprinting of an entire cluster. This is the case for the X chromosome, whose inactivation is mediated by the untranslated RNA product of the *XIST* gene (Chapter 18). It is also true for the cluster at 11p15.5, with the untranslated RNA product of the *H19* gene playing the regulatory role. All these regulatory RNAs bind to chromatin regions containing diverse DNA sequences that are clearly not homologous in sequence to the RNA. The binding must involve as yet unknown proteins and lead to heterochromatinization. Imprinted autosomal alleles therefore replicate asynchronously, in contrast to nonimprinted alleles, which replicate synchronously (Knoll et al., 1994). Small deletions first pinpointed the location of imprinted regions and of the syndromes associated with these segmental aneusomies.

Three Imprinting Disorders: Beckwith–Wiedemann, Prader–Willi, and Angelman Syndromes

The Beckwith–Wiedemann syndrome (BWS) is marked by overgrowth of muscles, tongue, heart, kidney, and liver. Large adrenal cells (cytomegaly) and renal dysplasia are also seen. In about one-fifth of the cases, the cause is paternal UPD11, and specifically the presence of two paternal copies of the 11p15.5 region instead of the usual one paternal and one maternal. One gene in this region that is partially responsible for the phenotypic effects is *IGF2* (insulin-like growth factor 2). This gene is expressed only from the paternal, not the maternal, copy, so the presence of two paternal copies doubles the dose of *IGF2*, stimulating growth (Sun et al., 1997). In many of the cases in which UPD11pat is not present, there may be a breakdown in imprinting, so that the maternal copy of the gene is also active (Weksberg et al., 1993).

The BWS critical region contains not only a gene that is imprinted in male gametogenesis but also one that is imprinted in female gametogenesis. This second imprinted gene is *KIP2*, which is expressed only from the maternal chromosome (Hatada et al., 1996). Therefore, paternal UPD11 leaves no functioning *KIP2* gene. Since the *KIP2* gene product, p57, is an inhibitor of

cyclin- dependent kinases (Chapter 2), absence of the gene product can lead to the kind of unregulated cell proliferation and predisposition to childhood tumors seen in Beckwith–Wiedemann syndrome. Loss of *KIP2* function can also be the result of mutation, and such mutations may account for nearly 10% of BWS patients (O'Keefe et al., 1997).

Prader–Willi syndrome (PWS) is marked by hypotonia, obesity, hypogonadism, and sometimes mild mental retardation. Nearly 30% of cases of PWS are due to the absence of the paternal chromosome 15 as a result of UPD15mat. However, almost 70% are due to a deletion of the paternal 15q11–q13 region. This can be the result of either inter- or intrachromosomal rearrangements (Carrozzo et al., 1997). Analysis of many such cases has established a minimal region of overlap of the various deletions, defining a critical region within which the relevant gene or genes must lie. The first expressed gene identified in this region was *SNRPN* (small nuclear ribonucleoprotein polypeptide N). Only the paternal allele of this gene is expressed in fetal brain and heart. Thus, absence of the paternal copy of *SNRPN* may be responsible for PWS (Reed and Leff, 1994; Glenn, 1996). This is strongly supported by the finding of Prader-Willi syndrome in a patient with a de novo balanced translocation, t(4;15)(q27;q11.2)pat with breakpoint between exons 2 and 3 of the *SNRPN* gene (Fig. 21.1; see also Kuslich et al., 1999). Six additional imprinted genes that are expressed exclusively from the paternal allele have been identified in the Angelman/Prader-Willi critical region. The maternal alleles of all six are late replicating, highly methylated, and transcriptionally silent. Five of these apparently have nothing to do with the PWS phenotype. A sixth, *NDN* (*necdin*), is expressed in brain neurons and may also be involved in generating the PWS phenotype (Jay et al., 1997).

Angelman syndrome (AS), marked by severe mental retardation, seizures, absence of speech, and inappropriate laughter, occurs about once in 15,000 live births. Although most of the more than 300 cases reported have been children, almost 5% of institutionalized adults with profound mental retardation have this disorder (Buckley et al., 1998). Angelman syndrome is most often (70% of cases) caused by a deletion of the maternally derived chromosome 15q11–q13, but it is sometimes due instead to paternal UPD15, to defective imprinting, or, in about 20% of cases, to a mutation of the *UBE3A* gene in the Angelman/Prader-Willi critical region. In one study, 17 of 56 subjects with Angelman syndrome had a mutation of this gene (Fang et al., 1999). *UBE3A* is a ligase that covalently links a protein to ubiquitin, targeting the protein for degradation. Initially, *UBE3A* was considered an unlikely candidate gene for either syndrome, because it was not

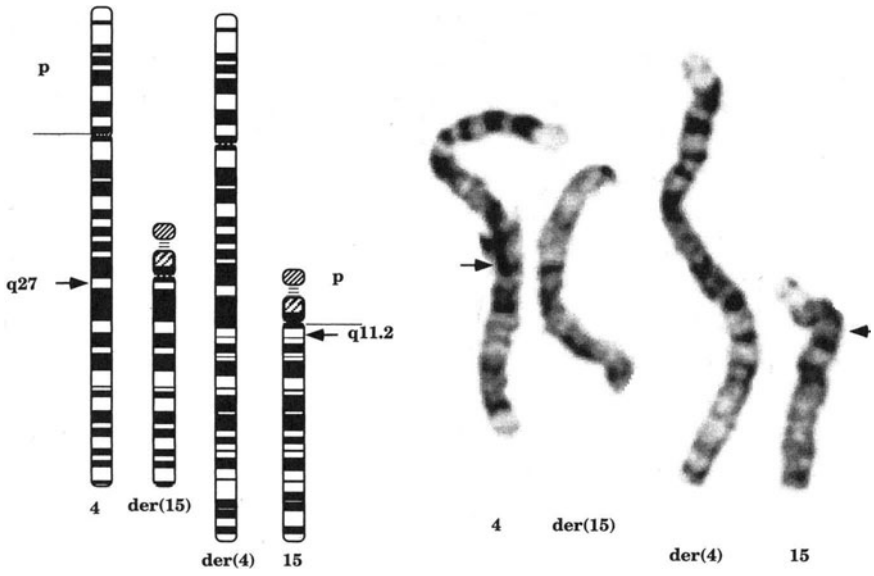

Figure 21.1. A translocation, t(4;15)(q27;q11.2), whose breakpoint disrupts the *SNRPN* gene at 15q11.2 in an individual with Prader–Willi syndrome (reproduced from Kuslich et al., Am J Hum Genet 64:70–76, copyright 1999, American Society of Human Genetics, with permission of the University of Chicago Press).

imprinted in lymphocytes. In fact, imprinting of *UBE3A*, with expression only from the maternal allele, is restricted to the brain. This may explain why the phenotypic effects in Angelman syndrome are similarly restricted (Vu and Hoffman, 1997).

Chimeras, Triploidy, and Tetraploidy

Fusion of two different zygotes into a single embryo produces a *chimera*. When one of the zygotes is XX and the other XY, the chimeric individual may develop as a true hermaphrodite and thus come to medical attention. Most chimeras probably escape detection, although the increasing use of genetic markers should detect more of them. The use of molecular markers has also shed light on the mechanisms leading to the production of chimeras. In one XX/XY true hermaphrodite, microsatellite markers showed that there was a single haploid maternal contribution, a single haploid paternal genome, and both X

chromosomes in the XX cells were maternal. The explanation in this case (Fig. 21.2A) involves mitotic division of a haploid oocyte, followed by fertilization of one product by a Y-bearing sperm and diploidization of the other maternal product (Strain et al., 1995). In this case, chimerism was the result of a single fertilization, combined with parthenogenetic diploidization. In a similar case, two different sperm had contributed to the proband's genome, while the presence of a single maternal allele at each of 40 marker loci indicated a single haploid maternal contribution. This could be accounted for if the haploid oocyte divided mitotically and each product were then fertilized by a different sperm, as illustrated in Fig. 21.2B (Giltay et al., 1998).

A triploid zygote may occur as the result of various processes. The egg or the sperm may have an unreduced chromosome number as a result of restitution in either the first or the second meiotic division; the second polar body may reunite with the egg nucleus; or two sperms may penetrate and fertilize the same egg.

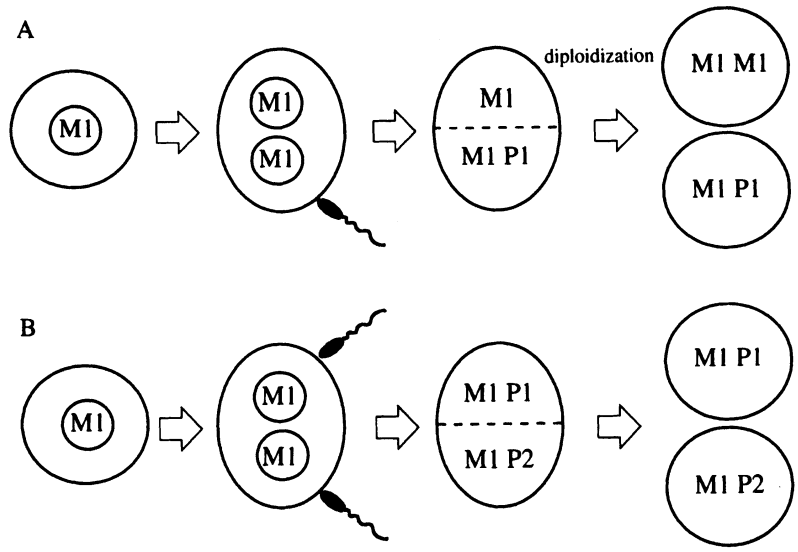

Figure 21.2. How chimeras can arise. In both (A) and (B), an ovum (M1) is parthenogenetically activated. (A) One of the two haploid maternal cells is fertilized by a normal sperm (P1), and the other is diploidized. (B) Each of the two haploid maternal cells is fertilized by a normal sperm (P1 and P2) (reproduced from Giltay et al., Am J Hum Genet 62:937–940, copyright 1998, American Society of Human Genetics, with permission of the University of Chicago Press).

Triploids constitute about 17% of spontaneous abortuses with an abnormal chromosome number (Chapter 11). Only about 1 in 10,000 triploid zygotes results in a liveborn infant, and most of these die within a day. A few triploid infants have survived for a few months. In such rare cases, hidden mosaicism must be considered; indeed, most polyploid infants have been mixoploid, with a diploid cell line too. It is unclear why triploidy and tetraploidy are so deleterious. Altered dosage compensation between the X chromosome and autosomes or between imprinted maternal and paternal autosomal genes may contribute to the phenotypic effects of triploidy. Tripolar mitoses have been described in some dispermic fertilized eggs and could lead to aneuploidy and lethality in this type of triploid, although no trace of it is seen in aborted triploid embryos.

A small number of infants and a 22-month-old girl with apparently nonmosaic tetraploidy have been reported, but the few other liveborn children have been diploid/tetraploid mosaics. Tetraploid embryos are rarer than triploids, probably because there are fewer mechanisms for producing them. The most probable of these is duplication of the diploid complement in a somatic cell at a very early stage of development. Other possible origins, such as the chance fertilization of a rare diploid ovum by an equally rare diploid sperm, are unlikely. The fertilization of one egg by three sperm does occur but leads to the development of a hydatidiform mole, as described below.

Ovarian Teratomas: Both Genomes Maternal in Origin

Ovarian teratomas are very distinctive benign tumors of the ovary. They are quite heterogeneous in their makeup, but all contain disorganized bits and pieces of various tissues, including thyroid, teeth, and hair. In fact, each looks like an ovarian pregnancy that originated by aberrant triggering of embryonic development in a nonovulated, unfertilized egg (*gynogenesis*, or *parthenogenesis*). This is consistent with the 46,XX karyotype of all ovarian teratomas and has been confirmed by analysis of genetic markers: All were maternally derived (Linder et al., 1975). The distance of particular loci from the centromere can be determined by the segregation of markers in teratomas that originated from oocytes that retained the second polar body rather than diploidizing a haploid complement, but this method has been largely supplanted by other mapping methods (Chapter 29).

The absence of any placental tissue in ovarian teratomas suggests that imprinted genes expressed only from the paternal genome are essential for the development of placental tissue. This is consistent with the presence of placental tissue only in *androgenetic* conceptuses, those with paternal genomes only. One imprinted gene, *H19*, which maps to 11p15, is always hypomethylated on both alleles in ovarian teratomas, whereas in normal fetal and adult organs one allele is hypermethylated and transcriptionally silent (Zhang et al., 1993). This supports the idea that the maternal allele is the expressed one and suggests its overexpression, and perhaps that of other paternally imprinted genes, leads to the abnormal phenotype. Obviously, any imprinted gene that is transcriptionally silent on maternal chromosomes would not be expressed at all in these gynogenetic ovarian teratomas, and that might have an even more deleterious effect.

Hydatidiform Moles: Both Genomes Usually Paternal in Origin

Hydatidiform moles are abnormal trophoblastic growths that are seen mainly in association with abnormal chromosome complements or uniparental disomy and imprinting. In Western countries, 1 in 1500–2000 pregnancies results in the development of a mole, whereas in the Orient, Taiwan for instance, the frequency can be as high as 1 in 200. Moles can resemble malignant tumors because of the presence of giant nuclei that have arisen by endomitosis and endoreduplication (Sarto et al., 1984). In fact, more than 50% of choriocarcinomas arise from moles. Hydatidiform moles are *partial* or *complete*. Partial moles are usually associated with a triploid embryo produced by fertilization of an egg by two sperm (Jacobs et al., 1982). Complete moles have no associated embryo. Although 2.1% of partial and 10% of complete moles become malignant, fortunately, some 80% of these highly malignant tumors respond very favorably to chemotherapy.

Nearly 80% of complete moles arise by fertilization of an "empty" egg (without a nucleus) by an X-bearing sperm and a subsequent doubling of the paternal chromosome set (diploidization) to produce an androgenetic zygote. The origin of the empty egg is not known. The chromosome complement of complete moles is almost always 46,XX, with two identical paternal chromosome sets. Rarely, they are XY, arising by fertilization of an empty egg by two sperm or by a diploid sperm. The androgenetic origin of complete moles was first

shown using chromosome polymorphisms as markers (Kajii and Ohama, 1977) and confirmed with genetic markers (Jacobs et al., 1980). These findings indicate that one or more maternally derived chromosomes are essential for normal embryonic development but that the paternal genome contains at least some of the expressed genes important for placental development. A few tetraploid moles have been produced by fertilization of a haploid oocyte by three sperm (Surti et al., 1986). This indicates that the relative dosage of competing maternal and paternal genes is important for normal development.

The association between the absence of a maternal set of chromosomes and the occurrence of a hydatidiform mole suggests that some genes are imprinted (inactivated) on the paternal chromosomes but remain active on the maternal set. If so, then the 20% of moles in which both maternal and paternal sets are present could be explained by a mutant maternal allele for one of these genes, leaving the embryo with no functional copy. A woman who inherited such a mutation from her father might have *only* molar pregnancies, and such families have been described. An alternative explanation is necessary for couples who have recurrent hydatidiform moles but also some normal pregnancies: homozygosity for a mutant, nonimprinted gene. In two families (one consanguineous), a genome-wide scan of molecular markers (Chapter 29) revealed the presence of a region of homozygosity for markers in a 15.2-cM region of 19q13.3–q13.4 in all six women who had repeated molar and nonmolar pregnancies (Moglabey et al., 1999).

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