THE FREQUENCY OF UNIPARENTAL DISOMY IN PRADER–WILLI SYNDROME

Implications for Molecular Diagnosis

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Abstract *Background.* Prader–Willi syndrome is a genetic disorder characterized by infantile hypotonia, obesity, hypogonadism, and mental retardation, but it is difficult to diagnose clinically in infants and young children. In about two thirds of patients, a cytogenetically visible deletion can be detected in the paternally derived chromosome 15 (15q11q13). Recently, patients with Prader–Willi syndrome have been described who do not have the cytogenetic deletion but instead have two copies of the 15q11q13 region that are inherited from the mother (with none inherited from the father). This unusual form of inheritance is known as maternal uniparental disomy. Using molecular genetic techniques, we sought to determine the frequency of uniparental disomy in Prader–Willi syndrome.

Methods. We performed molecular analyses using DNA markers within 15q11q13 and elsewhere on chromosome 15 in 30 patients with Prader–Willi syndrome who had no cytogenetically visible deletion. We also studied their parents. Three patients with Prader–Willi syndrome who had a cytogenetic deletion served as controls.

Results. In 18 of the 30 patients without a cytogenetic deletion (60 percent), we demonstrated the presence of maternal uniparental disomy for chromosome 15 and its association with advanced maternal age. In another eight patients (27 percent), we identified large molecular deletions. The remaining four patients (13 percent) had evidence of normal biparental inheritance for chromosome 15; three of these patients were the only ones in the study who had some atypical clinical features.

Conclusions. In about 20 percent of all cases, Prader–Willi syndrome results from the inheritance of both copies of chromosome 15 from the mother (maternal uniparental disomy). With the combined use of cytogenetic and molecular techniques, the genetic basis of Prader–Willi syndrome can be identified in up to 95 percent of patients. (N Engl J Med 1992;326:1599-607.)

PRADER–WILLI syndrome is a complex developmental and neurobehavioral genetic disorder affecting approximately 1 in 10,000 newborns.[1] It represents the most common dysmorphic form of obesity, with more than 700 cases reported.[2] Clinical diagnosis of Prader–Willi syndrome can be difficult because of the subtle nature of the dysmorphic features and the wide discrepancy between the clinical presentation in infancy and that seen in childhood, adolescence, and adulthood.[1,3,4] The first phase of the disorder is characterized by hypotonia, with a poor sucking reflex, hypogonadism, and subtle dysmorphic features. The second phase typically begins between two and four years of age, with the development of hyperphagia (leading to obesity) and extreme changes in temperament. Other features include short stature, small hands and feet, and various degrees of mental retardation or learning disability.[1,2] Early diagnosis of Prader–Willi syndrome is essential for medical and nutritional management as well as for appropriate genetic counseling.

Chromosome 15 was first implicated in the etiologic process of Prader–Willi syndrome by reports of a translocation, t(15;15), in several patients.[2,5] High-resolution cytogenetic studies subsequently showed

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Glossary

Aneusomic or aneuploid Describing a cell in which the chromosome number is not an exact multiple of the haploid number

Biparental inheritance Inheritance of one maternal and one paternal allele of a gene (apparently normal mendelian inheritance)

Genomic imprinting Differential modification and expression of alleles of a gene, dependent on the sex of the parent of origin

Heterodisomy Inheritance of two different copies of a gene or chromosome from one parent

Heteromorphism Differences in morphology between homologous chromosomes

Isodisomy Inheritance of two identical copies of a gene or chromosome from one parent

Nondisjunction Failure of homologous chromosomes or chromatids to separate during meiosis or mitosis

Nullisomic gamete A gamete lacking a specific chromosome, as contrasted with a disomic gamete, which contains an extra copy of a specific chromosome

Uniparental disomy Inheritance of two copies of a gene or chromosome from one parent (nonmendelian inheritance)

Variable number of tandem repeats (VNTR) A type of DNA polymorphism created by the tandem arrangement of multiple copies of short DNA sequences that results in a high degree of polymorphism

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that 55 to 70 percent of affected patients have a deletion of 15q11q13, a finding that has aided in the early diagnosis of the disorder.[2,6,7] Other rearrangements of 15q11q13 have been identified, although they occur in less than 4 percent of patients with Prader–Willi syndrome.[2,7] The remaining 25 to 40 percent of patients have no detectable alteration in chromosome 15.[2,7]

A similar chromosome 15 deletion has been found in Angelman syndrome, a clinically distinct neurobehavioral disorder characterized by severe mental retardation, lack of speech, inappropriate paroxysms of laughter, seizures, ataxic gait, and puppet-like movements of the limbs.[8-12] The critical deletion regions in both syndromes appear to overlap substantially in the majority of affected patients at the cytogenetic[11] and molecular[13-15] level. However, the parental origin of the deletion differs: only paternal deletions occur in Prader–Willi syndrome,[16-18] and only maternal deletions have been demonstrated in Angelman syndrome.[10,11,19] The dependence of the clinical outcome on parental origin is strongly supported by the molecular demonstration in Prader–Willi syndrome of maternal uniparental disomy (in which both copies of chromosome 15 are inherited from the mother and none are inherited from the father).[20] Paternal uniparental disomy has been shown in Angelman syndrome.[21,22] These observations imply that the phenotypic expression of both syndromes is determined by the parental origin of a gene or genes within chromosome 15q11q13. The differential modification and expression of alleles of a gene dependent on parental origin are known as genomic imprinting. Prader–Willi and Angelman syndromes are the clearest examples to date of genomic imprinting in humans.[20,23-25] This differential expression has subsequently been confirmed by two additional studies,[26,27] and a recent editorial in the *Journal* reviewed the clinical implications of genomic imprinting.[28]

Since molecular analysis has revealed large deletions of 15q11q13 in many patients with Prader–Willi syndrome,[10,13,18] and preliminary studies in patients without this deletion have shown uniparental disomy,[20] we designed a study to determine the frequency of uniparental disomy in patients who have Prader–Willi syndrome but not the classic chromosome 15q11q13 deletion.

Methods

Patients

To be eligible for the study, patients had to have features considered essential for the diagnosis of Prader–Willi syndrome, as documented by a clinical evaluation or a study of their medical records[1,2,29]; both biologic parents available for study; and no evidence of a chromosome 15q11q13 deletion on the basis of a cytogenetic evaluation. Thirty patients met the criteria and were included in the study. Three patients (one female and two male) with cytogenetic deletions of chromosome 15 were included in the study as controls. The study population included one set of monozygotic twins concordant for Prader–Willi syndrome (Patients 7a and 7b), one black patient (Patient 28), one patient (Patient 14) with a spontaneous balanced translocation (t(8;18)(p24.1;q23)), and one patient (Patient 26) mosaic for a marker chromosome of unknown origin. There were 15 male and 15 female patients, ranging from 2 to 41 years of age. Patients 2, 3, 4, 5, and 6 have been described in a previous report.[30] In addition, preliminary molecular findings in Patients 1 and 2 have been reported previously.[20]

Cytogenetic and Molecular Studies

Chromosomal studies were carried out in each patient at the 550-band level with the use of standard techniques.[17,31,32] For the molecular studies, genomic DNA was extracted from peripheral-blood lymphocytes,[33] and 3 μg of DNA was digested with the appropriate restriction enzyme. The DNA was then separated by agarose-gel electrophoresis, transferred to nylon membranes, and prehybridized and hybridized with DNA probes under standard conditions.[18] Membranes were washed at 56°C, or 49°C for probe IR4-3R, in 0.1× saline sodium citrate buffer (0.015 mol of sodium chloride per liter, 0.0015 mol of sodium citrate per liter, and 0.1 percent sodium dodecyl sulfate) for one hour.

DNA Probes

Seven DNA probes specific for chromosome 15q11q13 were used in the molecular studies (the loci defined are given in parentheses): 34 (D15S9), 3-21 (D15S10), IR4-3R (D15S11), IR10-1 (D15S12), 189-1 (D15S13), IR39d — a *Sac*I/*Hin*dIII subfragment of IR39 (D15S18) — and CMW-1 (D15S24).[18,34,35] The restriction-fragment–length polymorphisms (RFLPs) for these probes have been described previously.[18,20,35] In addition, a three-allele RFLP for IR4-3R with *Kpn*I-digested DNA was analyzed after separation by field-inversion gel electrophoresis (unpublished data). Several genomic probes distal to 15q11q13, MS1-14 (defining locus D15S81),[36] DP151 (defining locus D15S2),[37] and MS620 (defining locus D15S86), a variable-number tandem repeat (VNTR) probe that maps near the telomere of chromosome 15,[38] were also used. (MS620 has been deposited with the United Kingdom Human Genome Mapping Project Resource Center, CRC, Watford Rd., Harrow, Middlesex HA1 3UJ, United Kingdom, and can be obtained from Dr. Gabrielle Fisher.) The number of copies of each 15q11q13-specific sequence of DNA was determined by comparison with an internal standard, H2-26 (defining locus D13S28), a DNA probe specific for chromosome 13 with *Hin*dIII-digested DNA.[14,20,39] Each proband in this study inherited one maternal and one paternal allele for 3′HVR (defining locus D16S85), a VNTR probe specific for chromosome 16[40] — a pattern consistent with biologic parentage.

Statistical Analysis

Statistical analysis of parental ages was carried out with analysis of variance.

Results

Molecular Deletions in Prader–Willi Syndrome

We detected molecular deletions in 8 of 30 patients with Prader–Willi syndrome (27 percent) without a cytogenetic deletion on the basis of RFLP studies (Fig. 1A) and the determination of the number of copies per genome of each DNA probe (Fig. 1B). The deletions encompassed either five DNA probes specific for the 15q11q13 chromosomal region (IR4-3R, 189-1, 34, 3-21, and IR10-1) or these five probes plus a proximal probe, IR39d.[41] Since similar deletions of these markers in patients with Angelman syndrome can be detected cytogenetically,[14] the deletions reported here in Prader–Willi syndrome may be detectable cytogenetically at a higher level of resolution. One patient

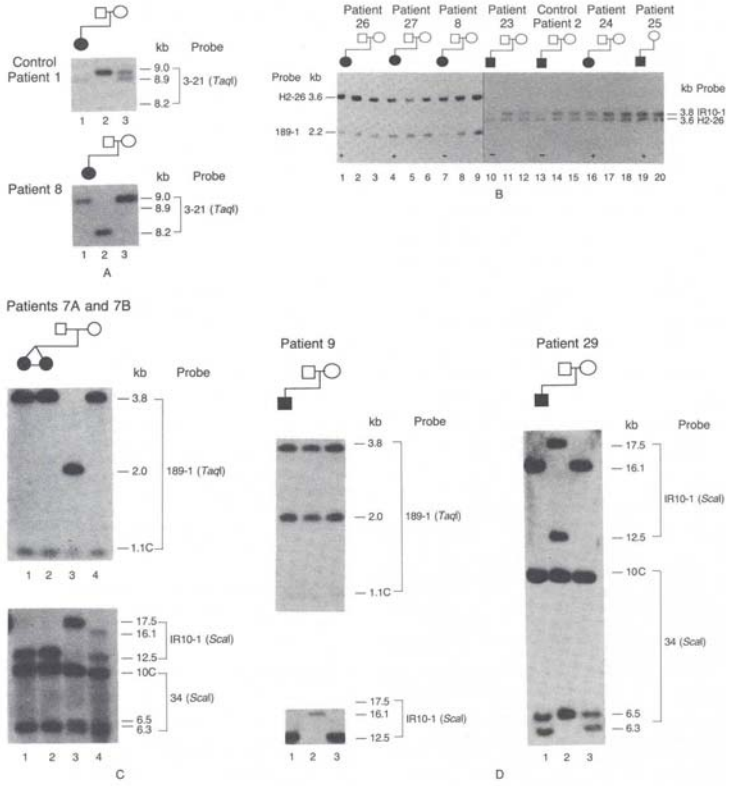

Figure 1. Representative Autoradiographs Obtained by Molecular Analysis of DNA Patients with Prader–Willi Syndrome with DNA Probes Specific for Chromosome 15q11q13.

With the exception of Panel B, the various enzymes used are given in parentheses; *Hin*dIII was used with all probes shown in Panel B. The sizes of the DNA fragments are listed in kilobases (kb). C represents a constant, nonpolymorphic fragment. Probands are denoted by solid symbols. Panel A shows paternal deletions by RFLPs in two families. Both probands (lane 1) receive a single copy of a maternal allele (lane 3), but no paternal alleles (lane 2). In Panel B, the number of copies per genome of chromosome 15q11q13–specific probes is compared with the number of copies per genome of a chromosome 13 control probe (H2-26). For each proband, a deletion is indicated by a minus sign, and a two-copy hybridization by a plus sign. Panel C shows uniparental disomy in the monozygotic twins, as detected by probe 189-1 (upper autoradiograph). Use of probe IR10-1 (lower autoradiograph) showed that the specific type of uniparental disomy present was isodisomy, whereas probe 34 was uninformative. Panel D shows uniparental disomy in two additional probands with Prader–Willi syndrome, as detected by probe IR10-1, and heterozygosity (parental origin undetermined), as detected by probes 189-1 and 34.

with Prader–Willi syndrome had a smaller molecular deletion than has previously been described in the literature[41] (and unpublished data), and one of the control patients with a cytogenetic deletion had a larger molecular deletion. Analysis of DNA from 9 of the 11 patients with Prader–Willi syndrome with a cytogenetic (the three controls) or a molecular deletion did identify the parental origin; all these deletions occurred on the paternally derived chromosome 15 (Fig. 1A), as found in previous studies.[16-18]

Uniparental Disomy in Prader–Willi Syndrome

Uniparental disomy refers to the inheritance of two copies of a genetic locus from only one parent[20,42] and can be detected when the mother's alleles differ from the father's alleles at a particular locus. The following three inheritance patterns detected by molecular analysis are indicative of uniparental disomy in Prader–Willi syndrome: maternal isodisomy,[42] the inheritance of two copies of an allele from a heterozygous mother and of none from the father; maternal heterodisomy,[20] the inheritance of one copy of each allele from a heterozygous mother and of none from the father (the detection of this pattern requires a marker system with a minimum of three alleles); and maternal disomy, the inheritance of two copies of a gene at a particular locus only from the mother, with apparent homozygosity of both mother and child. The third pattern does not distinguish between isodisomy and heterodisomy.

Twenty-two of the 30 cytogenetically normal study subjects inherited two copies of each of the chromosome 15 loci. For example, we determined the number of copies of each DNA locus in three patients with maternal uniparental disomy and found that they had two copies of DNA probes 189-1 (Patient 26) or IR10-1 (Patients 24 and 25) (Fig. 1B). Eighteen of these patients with an intact 15q11q13 region were subsequently found to have maternal uniparental disomy on RFLP analysis* (Fig. 2).

Uniparental disomy in Prader–Willi syndrome was also detected in a pair of monozygotic twins (Patients 7A and 7B). Probe 189-1 detected two copies of the maternally specific 3.8-kilobase (kb) band in *Taq*I-digested DNA, but no paternal 2-kb band (Fig. 1C, upper autoradiograph). This pattern is that of maternal disomy, but the probe used did not determine whether or not the chromosomes in the monozygotic twins were identical. Isodisomy was identified with probe IR10-1: the twins each inherited two copies of one allele (12.5 kb) from their heterozygous mother (Fig. 1C, lane 4), since their father (lane 3) was homozygous for a third, distinguishable allele of 17.5 kb (Fig. 1C, lower autoradiograph). Analyses of DNA from Patients 9 and 29 showed that both had maternal disomy at the IR10-1 locus (Fig. 1D). However, analysis with probes 189-1 and 34 of DNA from Patients 9 and 29, respectively, showed that two different alleles were inherited but did not identify the parental origin of the alleles (Fig. 1D). Uniparental disomy at IR10-1 flanked by closely linked markers that are heterozygous suggests the likelihood of maternal heterodisomy for much or all of 15q11q13, provided that recombination between these markers has not occurred.

Probes localized to the 15q11q13 region identified 12 of the 18 cases (67 percent) of uniparental disomy. Fourteen patients were heterozygous at several loci, but the probes did not identify the parental origin of the two alleles (Fig. 2). At each of these loci, the informative allele was consistently of maternal origin (no paternally informative alleles were detected), suggesting that maternal uniparental disomy might be demonstrated in a significant proportion of these patients with the use of more informative DNA probes. MS620 (defining locus D15S86), a highly informative probe near the telomere of chromosome 15, identified uniparental disomy in DNA from 11 of the 17 patients tested (65 percent), including 5 of the 6 patients in whom it was not detectable with 15q11q13 DNA markers (Fig. 2). For example, heterodisomy was found at the MS620 locus in Patients 12, 14, 18, and 25, whereas isodisomy was found in Patients 17 and 26 (Fig. 3). The remaining case of maternal uniparental disomy (in Patient 13), which was not detected with 15q11q13 or MS620 probes, was identified with probe MS1-14 (defining locus D15S1) (Fig. 2).

Biparental Inheritance in Prader–Willi Syndrome

Four patients (13 percent) without cytogenetic deletions had biparental inheritance of chromosome 15q11q13.* For example, Patient 27 inherited one paternal (2.3 kb) and one maternal (approximately 1.2 kb) allele with the MS620 probe (Fig. 3). Three patients with biparental inheritance (Patients 15, 27, and 28) did not have the classic features of Prader–Willi syndrome. One patient (Patient 27) had a bulbous, upturned nose, sparse hair, and large hands and feet and did not have compulsive eating behavior. She apparently does not have Prader–Willi syndrome, although a revised diagnosis has not yet been made. The fourth patient with biparental inheritance (Patient 19) had a typical clinical appearance that could not be distinguished from that of patients with Prader–Willi syndrome who have a deletion or uniparental disomy, all of whom have classic phenotypic features.

Effect of Maternal Age in Prader–Willi Syndrome

Both the mothers and the fathers of the patients with uniparental disomy were significantly older than the parents of the patients with cytogenetic or molecu-

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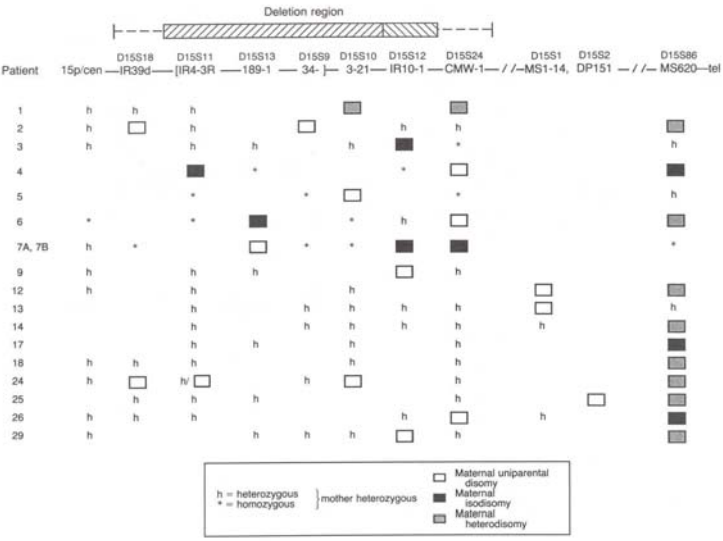

Figure 2. Patterns of Uniparental Disomy in 18 Patients with Prader–Willi Syndrome.

The order of seven DNA probes within chromosome 15q11q13 and three DNA probes distal to this region is shown from the centromere (cen) to the telomere (tel)[14,18,20,39] (and unpublished data). Brackets indicate that the order of probes is unknown. The loci defined are listed above the probes. Four alternative molecular classes of deletions in Prader–Willi syndrome, as discussed in the text, are shown (deletion region). DNA probes MS1-14 and DP151 map to 15q14–q22, whereas MS620 maps close to the telomere. Cytogenetic heteromorphisms (15p/cen) are noted.

Patient 1 was not studied with probe MS620, and locus IR39d was not evaluated in Patients 3, 4, 5, 6, and 29. In addition, not all families were evaluated with probes MS1-14 and DP151. Patient 24 demonstrated maternal uniparental disomy after digestion of DNA with *Kpn*I and was found to be heterozygous with the use of *Sty*I[42] at the IR4-3R locus, and Patient 3 was found to be heterozygous with the use of *Pvu*II at the IR4-3R locus (unpublished data).

lar deletions ($P = 0.018$ for mothers and $P = 0.0085$ for fathers) (Table 1). Because of the evidence of maternal nondisjunction, it is presumed that the paternal ages simply reflect the mothers' ages.

Discussion

Uniparental disomy was suggested by Engel as a likely mechanism of disease, given the high rate of germ-cell aneuploidy in humans.[42] However, this type of inheritance in which both chromosomes of a particular pair come from the same parent seemed to violate traditional genetic theory. The first conclusive evidence of its occurrence in humans[44] was obtained after the development of molecular techniques, although at the time it was thought "unlikely that uniparental disomy will turn out to be anything but an interesting rarity."[45] In the present study, we found that the selection of cytogenetically normal patients with Prader–Willi syndrome greatly increases the frequency of detection of uniparental disomy. Of 29 patients with Prader–Willi syndrome who did not have a cytogenetic deletion, 17 (59 percent) had maternal uniparental disomy for chromosome 15 (Fig. 2) (the monozygotic twins were counted as 1). Since two thirds of patients have a cytogenetic deletion of 15q11q13, we suggest that one fifth of all those with Prader-Willi syndrome have maternal uniparental disomy for chromosome 15 — a remarkably high frequency in a human disease. These conclusions are supported by the independent finding that 7 of 37 patients with Prader–Willi syndrome had uniparental disomy.[46] Uniparental disomy has now been found for

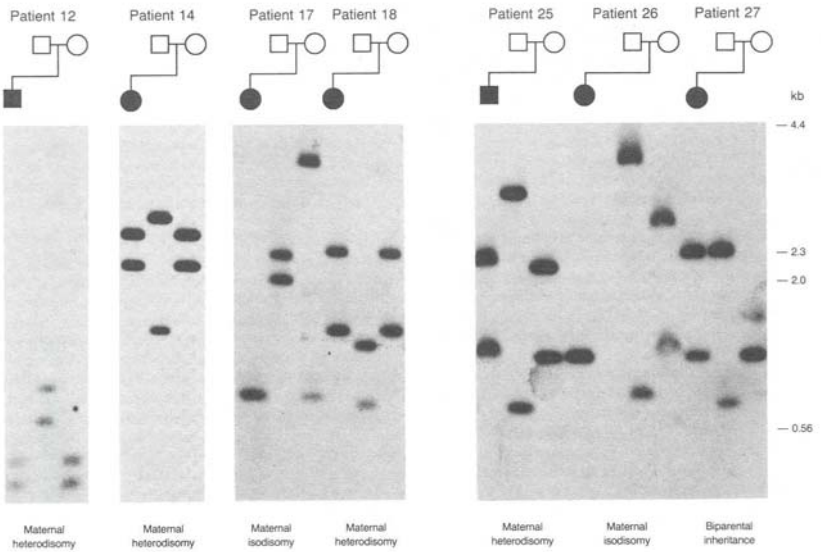

Figure 3. Detection of Maternal Uniparental Disomy in Prader–Willi Syndrome with a Highly Informative Chromosome 15 DNA Probe. Autoradiographs are shown for probe MS620, on *Alu*I-digested DNA from representative families with a proband with Prader–Willi syndrome. The sizes of DNA standards are listed on the right.

10 human chromosomes (unpublished data), suggesting that it may be more common than previously proposed.

Our data on cytogenetic and DNA markers spanning the length of chromosome 15 in 18 patients with Prader–Willi syndrome show that the entire chromosome is involved in uniparental disomy. Additional markers throughout 15q with a high degree of polymorphism[47] will substantially aid in the detection of uniparental disomy and help identify the type (iso or hetero) of disomy present (unpublished data). The different types of disomy reflect two events occurring during meiosis: nondisjunction and recombination. In each case, the disomic state near the centromere identifies the stage of meiosis at which nondisjunction occurred. Heterodisomy in the region of the centromere indicates the occurrence of a nondisjunctional error during the first meiotic division, whereas isodisomy close to the centromere identifies either an error occurring during the second meiotic division or a postzygotic event.[44] Accordingly, at least 60 percent of the 17 independent events analyzed in our study occurred during the first meiotic division, and this value might be closer to 82 to 94 percent, if markers proximal to loci IR4-3R and IR39d could be scored in the six patients in whom these analyses were uninformative (Fig. 2). These findings are similar to those in trisomy 21, in which the extra chromosome results from a maternal error during the first meiotic division in the majority of cases.[48] In addition, the regional patterns of heterodisomy and isodisomy that we detected (Fig. 2) are explained by the occurrence of recombination before nondisjunction. The localization of these recombination events allows polymorphic genes or markers to be mapped with respect to these sites (unpublished data).

The evidence that maternal nondisjunction represents the first step in the process of maternal uniparental disomy in Prader–Willi syndrome is supported by a maternal-age effect (Table 1), which has been corroborated independently in a smaller group of patients.[46] An increased frequency of nondisjunctional events has previously been associated with advanced maternal age in Down's syndrome and other aneuploid conditions.[49-52] The chromosome 15 system that we describe is a simpler model to analyze, since no additional chromosome is present from the second parent. Furthermore, paternal uniparental disomy for chromosome 15 has been observed in three patients with Angelman syndrome, occurring in about 2 to 4 percent of affected patients[21,22] in contrast to its high frequency (20 percent) in Prader–Willi syndrome. This suggests that paternal nondisjunction for chromosome 15 is not as common as maternal nondis-

Table 1. Ages of the Parents at Conception of Their Children with Prader–Willi Syndrome.*

Molecular Finding	No. of Families	Maternal Age	Paternal Age
		yr	
Deletion†	11	24.2±4.1	26.1±3.5
Uniparental disomy‡	17	30.5±7.7	32.9±7.3
Biparental inheritance§	3	27.7±2.5	29.7±0.6

*Plus–minus values are means ±SD. There was a significant difference in parental ages between the deletion and uniparental disomy groups ($P = 0.018$ for mothers and $P = 0.0085$ for fathers, by the t-test). The biparental group was not included because of the small sample. However, an F test of all three groups yielded P values of 0.049 for the mothers and 0.02 for the fathers.

†The families of eight patients and three controls were studied.

‡The parents of the monozygotic twin (Patients 7A and 7B) were counted only once.

§The ages of the parents of Patient 28 were not available.

junction. Alternatively, a fetus with paternal uniparental disomy for chromosome 15 may be less viable in utero.

A number of possible meiotic or postzygotic mechanisms for uniparental disomy have been proposed,[42,44] including gamete complementation by the union of a nullisomic and disomic gamete and a trisomic conception followed by random chromosome loss. These two mechanisms are most likely to occur in maternal uniparental disomy for the following three reasons. First, it is possible in most cases of maternal uniparental disomy to rule out postzygotic events, since most events result from nondisjunction occurring during the first meiotic division, a process that requires the transmission of two different maternal chromosomes to the zygote. Second, the association of uniparental disomy with advanced maternal age is consistent with maternal nondisjunction. Third, there is a high frequency of trisomy for chromosome 15.[49] Since trisomy 15 is lethal to the embryo, the loss of one chromosome 15 by mitotic nondisjunction could "rescue" a nonviable embryo. The random loss of a maternal chromosome in trisomy 15 would allow normal development, whereas the loss of the paternal chromosome would lead to Prader–Willi syndrome. The latter should occur in one third of the cases of uniparental disomy, and its occurrence has recently been supported by clinical and molecular data on a single patient.[33]

The role of genomic imprinting[20,23-25] in Prader–Willi and Angelman syndromes has recently been reviewed.[28,54,55] Since we have shown that uniparental disomy spans chromosome 15 and that patients with uniparental disomy do not differ clinically from patients with the 15q11q13 deletion (except for the occurrence of hypopigmentation, as discussed below), we conclude that no other gene on chromosome 15 whose phenotypic expression can be detected at this time is affected by genomic imprinting. Because of the influence of genomic imprinting in Prader–Willi and Angelman syndromes, the expression of one parental chromosome or the other in these disorders provides a biologic assay to identify candidate genes. To date, only one imprinted gene (locus detected by the complementary DNA DN34) has been identified in chromosome 15q11q13, although its function and role in either syndrome are as yet unknown.[54-56]

All the patients with deletions or uniparental disomy in the present study had classic phenotypic features of Prader–Willi syndrome. Those with uniparental disomy did not have hypopigmentation, as was commonly seen in those with a deletion (unpublished data). Therefore, hypopigmentation may result from a gene-dosage effect, and the gene does not appear to be imprinted. Hypopigmentation in Prader–Willi[17,30] and Angelman[57] syndromes has previously been associated with cytogenetic deletions, and more recently, a candidate gene and a mouse model of hypopigmentation have been identified.[58] It was interesting that three of the four patients with biparental inheritance had some atypical features that were not consistent with Prader–Willi syndrome. Each of these patients had been given a diagnosis at a different genetics center and thus might benefit from careful study in a single clinical setting. In contrast, there is a large group (20 percent) of patients with classic Angelman syndrome who do not have a detectable deletion or uniparental disomy[59] (and Zori R, Nicholls RD: unpublished data). These patients with Prader–Willi and Angelman syndromes may have a small molecular abnormality involving loci for which DNA probes are not yet available. A mutation in an unlinked gene, a mutation in the imprinting mechanism, and an incorrect diagnosis — as was the case in Patient 27 — are other possible explanations.

Our study indicates that in approximately 95 percent of all patients with Prader–Willi syndrome, at least those with the classic phenotype, the disease can be diagnosed with molecular techniques. This conclusion is based on our findings that maternal uniparental disomy occurs in 60 percent of patients who do not have a cytogenetic deletion, that molecular deletions occur in 29 percent, and that there is no detectable molecular abnormality in 11 percent (with the exclusion of the patient whose disease was incorrectly diagnosed). In addition, in all patients with cytogenetic deletions (approximately 66 percent of all those with Prader–Willi syndrome), whom we excluded from our study, the deletion can be detected by molecular techniques.[10,13,18,39,41,46] Additional DNA markers are needed for a more refined diagnosis of Prader–Willi syndrome. More recently, we have demonstrated that polymerase-chain-reaction analysis of DNA markers throughout chromosome 15q that have a high degree of polymorphism can detect a substantial number of cases of uniparental disomy (unpublished data). Similar types of DNA markers[47] within 15q11q13 are clearly needed for studies of the parental origin of Prader–Willi and Angelman syndromes. The accuracy of molecular diagnosis can also be increased by the use of probe DN34 in a DNA methylation test at the putative imprinted locus from chromosome 15q11q13,

a technique that to date has specifically identified all patients with Prader–Willi and Angelman syndromes who have a deletion or uniparental disomy.[56] Technically, prenatal screening could be offered to older women, who as we have shown are at increased risk of delivering a child with maternal uniparental disomy for chromosome 15. However, it remains to be demonstrated whether screening is feasible at an acceptable cost. In conclusion, our studies have demonstrated the feasibility of molecular techniques in the diagnosis of Prader–Willi syndrome. Molecular diagnosis should therefore be included in the comprehensive assessment of a child suspected of having Prader–Willi syndrome.

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