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Trisomy 15 with Loss of the Paternal 15 as a Cause of Prader-Willi Syndrome Due to Maternal Disomy

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Summary

Uniparental disomy has recently been recognized to cause human disorders, including Prader-Willi syndrome (PWS). We describe a particularly instructive case which raises important issues concerning the mechanisms producing uniparental disomy and whose evaluation provides evidence that trisomy may precede uniparental disomy in a fetus. Chorionic villus sampling performed for advanced maternal age revealed trisomy 15 in all direct and cultured cells, though the fetus appeared normal. Chromosome analysis of amniocytes obtained at 15 wk was normal in over 100 cells studied. The child was hypotonic at birth, and high-resolution banding failed to reveal the deletion of 15q11-13, a deletion which is found in 50%–70% of patients with PWS. Over time, typical features of PWS developed. Molecular genetic analysis using probes for chromosome 15 revealed maternal disomy. Maternal nondisjunction with fertilization of a disomic egg by a normal sperm, followed by loss of the paternal 15, is a likely cause of confined placental mosaicism and uniparental disomy in this case of PWS, and advanced maternal age may be a predisposing factor.

Introduction

In 1981, Ledbetter et al. (1981) found, on high-resolution chromosome analysis, that Prader-Willi syndrome (PWS) was associated with a deletion at 15q11-13. Since then, a number of studies on series of patients have shown that only about 50%–70% have this deletion (reviewed by Butler 1990). The deletion was first noted by Butler and Palmer (1983) to invariably occur in the paternally derived chromosome 15. Among the clinically typical patients who appear to lack a cytogenetic deletion, a small percentage have some other rearrangement involving proximal chromosome 15, and the remainder are cytogenetically normal (reviewed by Ledbetter and Cassidy 1988). In 1989, Nicholls et al. (1989*a*) noted that some patients with apparently normal chromosomes 15 had maternal disomy, a state in which both normal chromosomes 15 were maternal and in which there was no paternal chromosome 15. This finding supported a concept first proposed by Engel (1980)—i.e., that uniparental disomy could result in human disorders. Genetic imprinting has been implicated in the cause of PWS because the 15q deletions associated with it are always paternal, while the uniparental disomy is always maternal (Nicholls et al. 1989*a;* Hall 1990). The existence of an imprinting effect is further supported by the presence of both the same or a very similar deletion of 15q11-13 in the maternal chromosome and occasional paternal disomy in a clinically distinct disorder, Angelman syndrome (Knoll et al. 1989; Magenis et al. 1990; Williams et al. 1990; Malcolm et al. 1991).

Speculation as to the mechanisms which might lead to maternal disomy suggests the following four likely processes by which this could occur: (1) disomic egg + monosomic sperm producing a trisomic zygote, followed by subsequent loss of the paternal 15; (2) disomic egg + nullisomic sperm; (3) monosomic egg +

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nullisomic sperm producing monosomic zygote, followed by duplication of maternal 15; and (4) postfertilization nondisjunction producing trisomic and monosomic cell lines, with subsequent duplication in the monosomic line. Documentation of any of these mechanisms as a cause of PWS has not yet occurred. However, recently it has been found that many cases of PWS with maternal disomy show advanced maternal age, while those with deletion usually do not (Robinson et al. 1991; Nicholls et al. 1992). Since advanced maternal age predisposes to nondisjunction, as is well known for autosomal trisomies, this finding suggests that mechanisms for producing maternal disomy which begin with a disomic egg are likely to cause PWS.

We have studied a child with PWS who was born to a mother with advanced maternal age who had prenatal diagnosis by chorionic villus sampling (CVS), which showed trisomy 15. The child was found postnatally to have maternal disomy for chromosome 15. This case confirms that maternal nondisjunction for chromosome 15 is a mechanism which can lead to PWS resulting from maternal disomy.

Material and Methods

Cytogenetic Analysis

Chromosome studies on lymphocytes and amniocytes employed the usual techniques, based on modified procedures developed by Moorhead et al. (1960). Chorionic villus tissue was prepared and analyzed using modified procedures developed by Simoni et al. (1983), involving analysis both from direct preparation and of cultured cells. For the cultured chorionic villus tissue and the amniocytes, at least two independently grown cultures were used. Lymphocyte karyotyping involved phytohemagglutinin stimulation and Giemsa banding.

DNA Probes

The DNA probes pML34 (D15S9), p3-21 (D15S10), pIR4-3R (D15S11), pIR10-1 (D15S12), p189-1 (D15S13), and pCMW-1 (D15S24) were obtained from the American Type Culture Collection (Rockville, MD) and have been described elsewhere (Donlon et al. 1986; Rich et al. 1988; Nicholls et al. 1989*b*). The probe pMS620 (D15S86), which detects a highly variable region in terminal 15q, was provided by Drs. J. A. Armour and A. J. Jeffreys (Armour et al. 1990). We used a chromosome 1 dinucleotide repeat, D1S104 (Weber et al. 1990), an HLA-DRβ probe (Cox et al. 1988), a COL6A1 probe from chromosome 21 (Francomano et al. 1991), and a VNTR probe from chromosome 2 (D2S44; Nakamura et al. 1987) to study paternity in this family.

RFLP Analysis

Isolation of high-molecular-weight DNA from peripheral blood, restriction-enzyme digestion of DNA, electrophoresis of the restriction fragments, Southern transfer, and blot hybridization were performed using standard technology (Maniatis et al. 1982).

Case Report

A 43-year-old gravida 3 woman was referred for prenatal diagnosis because of advanced maternal age. She was healthy except for hypothyroidism adequately treated with Synthroid. Her family history was unremarkable; she had two healthy teenage children, a boy and a girl, and her father had an identical twin brother with five normal children. After ultrasound dating at 10 wk, a CVS was performed at week 11 of gestation, without complications. Direct preparation of chorionic villus tissue and analysis of six Giemsa-banded karyotypes at 320-band resolution showed no structural chromosome abnormalities, but all 6 cells, as well as each of the next 35 cells counted, showed trisomy 15: 47,XX + 15 (fig. 1). Cultured cells from the same sample also showed trisomy 15 in all 40 cells counted, and again there were no structural chromosome abnormalities, at 450-band resolution. Detailed follow-up ultrasound examinations of the fetus at

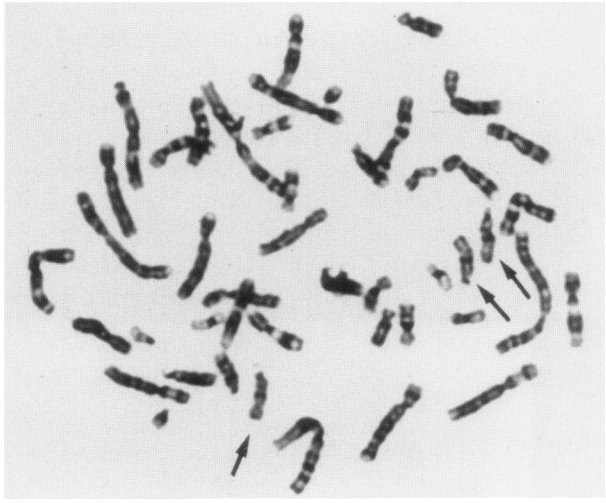

Figure 1 Cytogenetic analysis from CVS, showing trisomy 15 (arrows)

weeks 12, 15, and 21 of gestation were normal. Amniocentesis at week 15 of gestation revealed a normal female karyotype, 46,XX, in two independently grown cultures from which over 150 cells were counted, and 12 cells were specifically analyzed for a chromosome 15 deletion and other structural abnormalities (band resolution ≥600) (fig. 2, *left*). Amniotic fluid alpha-fetoprotein level was normal. The pregnancy was monitored closely and proceeded well until the mother developed premature labor and preeclampsia. When the fetal movements decreased and the biophysical profile fell from 8–10 to 4, she was delivered by cesarean section at week 35 of gestation.

The birth weight was 2,197 g, length was 43 cm, and head circumference was 31 cm. Apgars were 3 and 8 at 1 and 5 min, respectively. The baby was significantly hypotonic, with a weak cry but no seizures or focal neurologic signs. She developed mild persistent respiratory distress, episodes of apnea, and poor suck leading to marked feeding problems. She had decreased deep-tendon reflexes, a normal skull shape, small palpebral fissures, a relatively narrow face, mild micrognathia, single transverse palmar creases, decreased flexion creases, and decreased muscle mass. She was hospitalized for 8 wk during which the hypotonia and feeding problems gradually improved. The diagnosis of PWS was considered, but findings were too nonspecific for diagnostic certainty. Results of numerous studies to document an infection or metabolic disorder were normal, as were a cranial computed-tomography scan, cranial magnetic-resonance-imaging scan, and electroencephalogram. Lymphocyte karyotyping with Giemsa banding at >600-band resolution showed a normal female karyotype, 46,XX, in 105 cells, without evidence of trisomy 15 mosaicism or structural abnormalities; the two chromosomes 15 showed different polymorphisms, one with short satellite stalk and the other without a satellite stalk (fig. 2, *right*).

For the first 6 mo of life the patient required gavage feeding to supplement regular bottle feeding. She was generally healthy, but she had several fever episodes which appeared to represent an exaggerated fever response to relatively mild infections. She continued to be hypotonic. At 14 mo of age, her length was at the 20th percentile, weight at the 5th–10th percentile, and head circumference at the 40th percentile. She had a relatively narrow face with a narrow bifrontal diameter, epicanthal folds, thin lips, and small hands and feet. Her developmental milestones corresponded to those of an 11-mo-old, except that gross motor development was at the 8-mo level. She required physical, occupational, and speech therapies.

A summary of the cytogenetic studies is presented in table 1. Molecular genetic studies were performed on the patient, her mother, and her father when the patient was 20 mo of age. These revealed maternal disomy for distal chromosome 15, with complete ab-

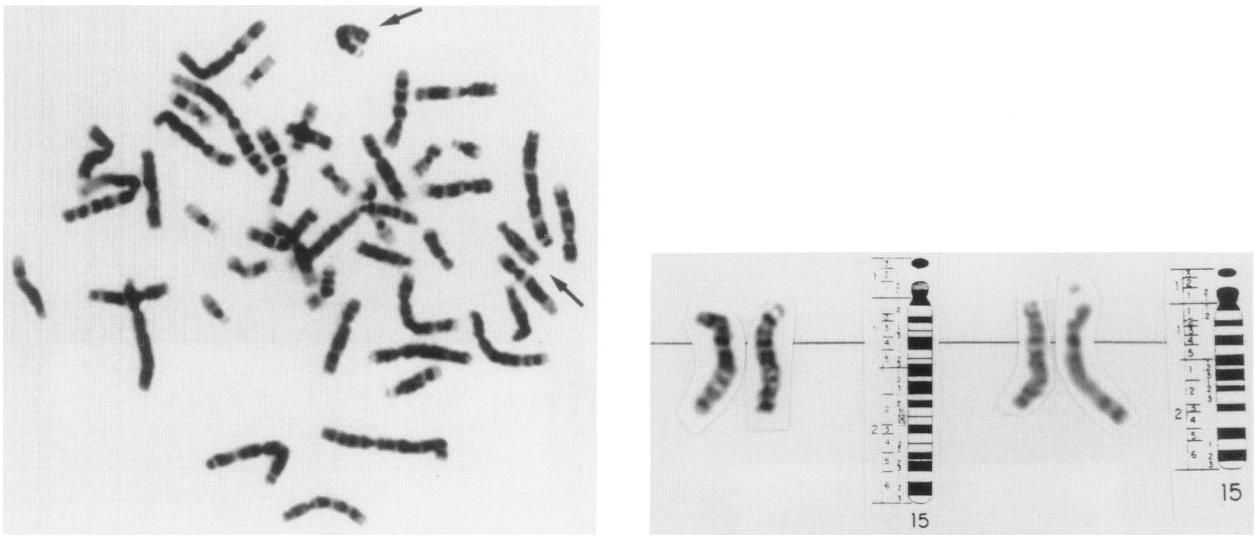

Figure 2 Cytogenetic analysis on the basis of amniocytes (*left*) and peripheral blood (*right*). Note euploidy and absence of apparent 15q deletion. Note also that the two chromosomes 15 differ in appearance, one having a short satellite stalk and the other having no stalk (indicated by arrows in left panel).

Table 1

Cytogenetic Studies in the Proband

Study	Age of Patient	Results	No. of Cells
CVS	11 wk gestation	Direct: 47,XX + 15	41
		Cultured: 47,XX + 15	40
Amniocytes	15 wk gestation	46,XX (550 bands)	>150
Peripheral blood	Newborn	46,XX (600 bands)	105

sence of paternal chromosome 15 material when tested with probe pMS620 (fig. 3). However, the probes in the PWS chromosome region were not informative for disomy or deletion, since both parents had the same alleles and since both the mother and the child were homozygous for all of the probes (table 2). No faint alleles were detected in the mother or child, despite overexposure of the Southern blot.

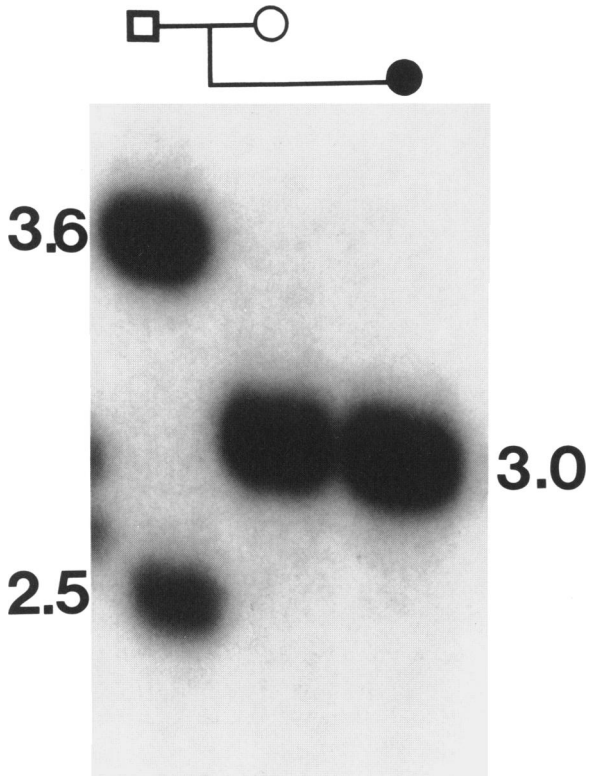

Figure 3 RFLP analysis of DNA from the patient and her parents. DNAs (3 μg) were digested with *Mbo*I, and the restriction fragments were separated by 0.7% agarose gel electrophoresis, transferred to a nylon filter, and hybridized with ^{32}P-labeled probe pMS620. The autoradiogram was performed after 7 d exposure at −70°C. The molecular weights of the alleles are shown in kilobase pairs (kb).

Testing for paternity indicated that the father and child shared the 162-bp allele at D1S104 (population frequency .45), DR3 or DRw6 at HLA-DR$^{\beta}$ (the two are not distinguishable with *Taq*I; population frequency .37), and the 9.2-kb *Bam*HI allele at COL6A1 (Caucasian population frequency .46). We also used the VNTR probe D2S44, with the frequency utilized for the most abundant *Taq*I allele being .075, which is that in the Caucasian population (S. Odelberg, personal communication), since slight variation in conditions precludes accurate assignment of the allele. Using all the above frequencies, we calculated a paternity index of 10.8, making nonpaternity unlikely.

Discussion

Trisomy 15 is one of the more common autosomal trisomies found in series of karyotyped abortuses, comprising about 8% (Warburton et al. 1991). In some cases, these abortions occurred in the fetal, rather than the embryonic, stage of the gestation. The maternal age of abortuses trisomic for chromosome 15 is statistically significantly advanced compared with maternal age of chromosomally normal abortuses, being about 4 years older on average (Hassold et al. 1984). Although surviving infants with trisomy 15 have not been described, it is apparent that conceptuses with trisomy 15 are not rare and may be significantly increased in women with advanced maternal age. With the recent increase in utilization of CVS as a prenatal diagnostic tool in early gestation, it should not be surprising, therefore, to find an occasional sample with trisomy 15. Should one of the chromosomes 15 in the fetus be lost sufficiently early in life, it seems possible that the fetus might survive to term, either with somatic mosaicism or with complete loss of trisomic cells due to selective disadvantage. Confined placental mosaicism for trisomy 15 may also reflect a previously trisomic embryo which has lost the third chromosome 15 and thus survived but whose placenta and thus CVS would remain trisomic. Recent molecu-

Table 2

Alleles of Family Members at the PWS Region

Locus	Probe	Enzyme	Size (kb)	Father	Mother	Patient
D15S9	pML34	*Sca*I	6.5	+	+	+
			6.3			
D15S10	p3-21	*Taq*I	9.0	+	+	+
			8.2			
D15S11	pIR4-3R	*Rsa*I	1.2	+		
			1.0	+	+	+
D15S12	pIR10	*Sca*I	17.5			
			16.1	+	+	+
			12.5			
D15S13	p189-1	*Taq*I	3.8	+	+	+
			2.0			
D15S24	pCMW-1	*Taq*I	VNTR	2.2 kb		
				2.0 kb	2.0 kb	2.0 kb
D15S86	pMS620	*Mbo*I	VNTR	3.6 kb		
					3.0 kb	3.0 kb
				2.5 kb		

lar analysis in patients with PWS without visible 15q deletion, using probes within and outside of 15q11-13, have suggested that, in most cases studied, maternal disomy extends over the entire chromosome (Nicholls et al. 1992). The finding of heterozygosity or homozygosity for maternal loci near the centromere, and the finding of the reverse pattern distally, also suggests the occurrence of nondisjunction during meiosis I or meiosis II, respectively (Rogan et al. 1991).

An alternative possible explanation for cases such as the one we present would be mitotic nondisjunction leading to a trisomic line (paternal/paternal/maternal) and a monosomic cell line (maternal) with subsequent duplication of the monosomic line, as suggested by Spence et al. (1988). This would lead to homozygosity at all loci, whereas the mechanism discussed above (meiotic maternal nondisjunction leading to a paternal/maternal/maternal constitution with subsequent loss of the paternal chromosome in the fetus) is likely to result in heterozygosity at some loci. Although the studies in our case failed to show molecular heterozygosity, there was cytogenetic heterozygosity (fig. 2), making postfertilization nondisjunction unlikely.

In the family with PWS presented here, maternal disomy was detected in distal 15q by probe pMS620. Both the patient and her mother are homozygous for the same alleles detected by the probes within 15q11-13 (D15S11, D15S13, D15S9, D15S10, D15S12, and D15S24, as well as D15S86; table 2). This situation is likely to be coincidental and related to (*a*) the fact that the mother and child are both homozygous for the most common allele at each locus and (*b*) the fact that linkage disequilibrium is likely to be present for proximal 15q. Cytogenetically it was thought that there were two different chromosomes 15 in the patient, on the basis of 15p variation. Unfortunately, blood for maternal grandparental cytogenetic and molecular studies is currently unavailable.

Whether liveborns who are euploid but who were trisomic as early embryos would be normal is unknown. In the case we present, the resultant maternal disomy for a presumably imprinted area of the genome resulted in an abnormality, PWS. It is not known what the outcome would be if one of the two maternal chromosomes 15, rather than the paternal 15, had been eliminated from the trisomic embryo, nor what the outcome would be if this event occurred on a different chromosome in a nonimprinted region of the genome. These processes will be far more difficult to demonstrate. Other questions are also raised by this case. Is it possible for the fetus, not just the placenta, to survive having trisomy 15 for several gestational weeks? What if there is mosaicism? What tissues are most susceptible to the effects of trisomy or uniparental disomy? Is uniparental disomy the cause of some of the dysmorphic syndromes of unknown etiology or of unrecognized patterns of malformation? This case also raises questions about the management of the patient whose CVS demonstrates a trisomy of any chromosome but

whose amniocentesis is "normal." Can one no longer be merely reassuring? When the trisomic chromosome is 15, it is appropriate to do molecular studies seeking uniparental disomy, the presence of which would suggest PWS or Angelman syndrome, depending on whether it is maternal or paternal disomy. In the future, as probes to test for heterozygosity are developed for other chromosomes, it may be appropriate to seek potentially harmful uniparental disomy in all such cases.

The issue of recurrence risk for PWS must also be readdressed in light of this case. A recent review of published and in-press reports of patients studied by molecular genetic techniques demonstrates that virtually all individuals with clinically typical PWS have paternal deletion 15q11-13 or maternal disomy for 15q (Cassidy 1992). Indeed, even patients with PWS who had inherited familial apparently balanced chromosome rearrangements (primarily translocations) involving chromosome 15 were found, by molecular techniques, to have associated deletion or disomy of 15q, presumably predisposed to by the rearrangement (Nicholls et al. 1989*a*; Hultén et al. 1991; Smeets et al. 1992). Thus, all typical PWS appears to be caused by absence of the paternal contribution to 15q11-13. Although recurrence of typical PWS under any circumstances is rare, recurrence of PWS in a family in which one member has a cytogenetic deletion or maternal disomy has not been demonstrated. The few families with recurrence in siblings showed normal chromosomes and have either not yet been studied with molecular techniques (Lubinsky et al. 1987) or have shown absence of deletion and of uniparental disomy (Anvret et al. 1992). In the past, prior to the discovery of uniparental disomy in this disorder, the empiric recurrence risk for PWS was suggested to be as little as <0.1% (Cassidy 1987) to as much as 1.6% (Clarren and Smith 1977). Since deletions likely represent a de novo mutational event, it now seems reasonable to propose a very low recurrence risk when a deletion is present: certainly <1%. When maternal disomy is present, it may be more appropriate to propose a maximum recurrence risk similar to that for Down syndrome due to nondisjunction—namely, 1%–2%—though the need for an additional event (loss of the paternal chromosome 15) would be expected to reduce this risk. The magnitude of recurrence in cases of familial balanced translocation involving chromosome 15 is unknown but presumably is increased above background risk and is probably >1%–2%, on theoretical grounds. Confirmation or refutation of these suggested recurrence risk figures will await larger-scale studies of patients with PWS by using molecular genetic techniques.

The mechanisms and consequences of uniparental disomy and genetic imprinting in humans are just beginning to be unraveled. Publications which address these issues have been incisive but primarily theoretical (e.g., see Hall 1990; Engel and DeLozier-Blanchet 1991). The case we present here demonstrates that at least one of the mechanisms does occur—namely, embryonic trisomy 15 with subsequent loss of the paternal 15 resulting in PWS due to maternal disomy. This process is presumed to be due to maternal nondisjunction, a presumption strengthened by the presence of advanced maternal age in this case and in many cases of PWS with uniparental disomy. The higher incidence of maternal versus paternal nondisjunction is a likely explanation of the fact that paternal disomy of chromosome 15 as a cause of Angelman syndrome is far less frequent than maternal disomy of chromosome 15 as a cause of PWS (Knoll et al. 1991). It is apparent that there is still much to learn about both the genetics of PWS and the mechanisms by which this multisystem complex disorder can occur. In the meantime, it will be important to give recurrence risk counseling with caution and to be on the alert for potentially instructive cases such as the one presented.

Note added in proof.—After submission of this manuscript, the *Journal* published a letter which describes a case similar to that reported in the present paper. That patient, a male, had trisomy 15 on CVS followed by a finding of normal amniocyte chromosomes, and, after his birth, he was shown to have PWS with maternal disomy for chromosome 15 (Purvis-Smith et al. 1992). The authors of that letter note that confined placental mosaicism is common and that this type of "correction" of fetal trisomy by loss of a parental chromosome may be a frequent cause of human abnormality based on uniparental disomy. Since the consequences of uniparental disomy for most chromosomes remains unknown, we concur with these authors that patients in whom trisomy is detected on CVS and not confirmed on amniocentesis deserve close clinical follow-up not only for the remainder of the pregnancy but also for months or years thereafter.

References

Anvret M, Martony A, Örstavik KH, Brŭndum-Nielsen K (1992) DNA studies in sibs with PWS. Am J Med Genet 42:256

Armour JA, Povey S, Jeremiah S, Jeffreys AJ (1990) Systematic cloning of human minisatellites from ordered array chromid libraries. Genomics 8:501–512

Butler MG (1990) Prader-Willi syndrome: current understanding of cause and diagnosis. Am J Med Genet 35: 319–332

Butler MG, Palmer CG (1983) Parental origin of chromosome 15 deletion in Prader-Willi syndrome. Lancet 1: 1285–1286

Cassidy SB (1987) Recurrence risk in Prader-Willi syndrome. Am J Med Genet 28:59–60

——— (1992) Conference report: First International Scientific Workshop on Prader-Willi Syndrome and Other Chromosome 15q Deletion Disorders. Am J Med Genet 42:220–230

Clarren SK, Smith DW (1977) Prader-Willi syndrome. Am J Dis Child 131:798–801

Cox NJ, Mela AP, Zmijewski CM, Spielman RS (1988) HLA-DR typing "at the DNA level": RFLPs and subtypes detected with a DRβ cDNA probe. Am J Hum Genet 43: 954–963

Donlon TA, Lalande M, Wyman A, Bruns G, Latt SA (1986) Isolation of molecular probes associated with the chromosome 15 instability in the Prader-Willi syndrome. Proc Natl Acad Sci USA 83:4408–4412 (correction in Proc Natl Acad Sci USA 83:6964)

Engel E (1980) A new genetic concept: uniparental disomy and its potential effect, isodisomy. Am J Med Genet 6: 137–143

Engel E, DeLozier-Blanchet CD (1991) Uniparental disomy, isodisomy, and imprinting: probable effects in man and strategies for their detection. Am J Med Genet 40:432–439

Francomano CA, Cutting GR, McCormick MK, Li Chu M, Timple R, Hong HK, Antonarakis SE (1991) The COL6A1 and COL6A2 genes exist as a gene cluster and detect highly informative DNA polymorphisms in the telomeric region of human chromosome 21q. Hum Genet 87:162–166

Hall JG (1990) Genomic imprinting: review and relevance to human diseases. Am J Hum Genet 46:857–873

Hassold T, Warburton D, Kline J, Stein Z (1984) The relationship of maternal age and trisomy among trisomic spontaneous abortions. Am J Hum Genet 36:1349–1356

Hultén M, Armstrong S, Challinor P, Gould C, Hardy G, Leedham P, Lee T, et al (1991) Genomic imprinting in an Angelman and Prader-Willi translocation family. Lancet 338:638–639

Knoll JHM, Glatt KA, Nicholls RD, Malcolm S, Lalande M (1991) Chromosome 15 uniparental disomy is not frequent in Angelman syndrome. Am J Hum Genet 48:16–21

Knoll JHM, Nicholls RD, Magenis RE, Graham JM Jr, Lalande M, Latt SA (1989) Angelman and Prader-Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion. Am J Med Genet 32:285–290

Ledbetter DH, Cassidy SB (1988) Etiology of Prader-Willi syndrome. In: Caldwell ML, Taylor RL (eds) Prader-Willi syndrome: selected research and management issues. Springer, New York, pp 13–28

Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan SB, Crawford JD (1981) Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. N Engl J Med 304:325–329

Lubinsky M, Zellweger H, Greenswag L, Larson G, Hansmann I, Ledbetter D (1987) Familial Prader-Willi syndrome with normal chromosomes. Am J Med Genet 28: 37–43

Magenis RE, Toth-Fejel S, Allen LJ, Black M, Brown MG, Budden S, Cohen R, et al (1990) Comparisons of the 15q deletions in Prader-Willi and Angelman syndromes: specific regions, extent of deletions, parental origin, and clinical consequences. Am J Med Genet 35:333–349

Malcolm S, Clayton-Smith J, Nichols M, Robb S, Webb T, Armour JAL, Jefferys AJ, et al (1991) Uniparental paternal disomy in Angelman's syndrome. Lancet 337:694–697

Maniatis T, Fritsch EF, Sambrook J (1982) Molecular cloning: a laboratory manual. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Moorhead PS, Nowell PC, Mellman WJ, Battips DM, Hungerford DA (1960) Chromosome preparations of leukocytes cultured from human peripheral blood. Exp Cell Res 20:613–616

Nakamura Y, Gillilan S, O'Connell P, Leppert M, Lathrop GM, Lalouel J-M, White R (1987) Isolation and mapping of a polymorphic DNA sequence pYNH24 on chromosome 2 (D2S44). Nucleic Acid Res 15:10073

Nicholls RD, Gottlieb W, Mascari MJ, Rinchik EM, Pai GS, Driscoll DJ, Butler MG, et al (1992) Molecular analysis in Angelman syndrome, Prader-Willi syndrome and potential mouse models. In: Cassidy SB (ed) Prader-Willi syndrome and other chromosome 15q deletion disorders. NATO ASI Series, vol 61. Springer, Heidelberg, pp 41–51

Nicholls RD, Knoll JHM, Butler MG, Karam S, Lalande M (1989*a*) Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. Nature 342:281–285

Nicholls RD, Knoll JHM, Glatt K, Hersh JH, Brewster TD, Graham JM, Wurster-Hill D, et al (1989*b*) Restriction fragment length polymorphisms within proximal 15q and their use in molecular cytogenetics and the Prader-Willi syndrome. Am J Med Genet 33:66–77

Purvis-Smith SG, Saville T, Manass S, Yip M-Y, Lam-Po-Tang PRL, Duffy B, Johnston H, et al (1992) Uniparental disomy 15 resulting from "correction" of an initial trisomy 15. Am J Hum Genet 50:1348–1350

Rich DC, Witkowski CM, Summers KM, van Tuinen P,

Ledbetter DH (1988) Highly polymorphic locus D15S24 (CMW-1) maps to 15pter-q13. Nucleic Acids Res 16: 8740

Robinson WP, Bottani A, Yagang X, Balakrishnan J, Binkert F, Mächler M, Prader A, Schinzel A (1991) Molecular, cytogenetic and clinical investigations of Prader-Willi syndrome patients. Am J Hum Genet 49:1219–1234

Rogan PK, Mascari MJ, Ladda RL, Gottlieb W, Nicholls RD (1991) The origin of maternal disomy in Prader-Willi syndrome. Am J Hum Genet 49 [Suppl]: A287

Simoni G, Brambati B, Danesino C, Rossella F, Terzoli GL, Ferrari M, Fraccaro M (1983) Efficient direct chromosome analyses and enzyme determinations from chorionic villi samples in the first trimester of pregnancy. Hum Genet 63:349–357

Smeets DFCM, Nelen MR, Hamel BCJ, Smits APT, Smeets HJM, Bollen JHM, van Oost BA (1992) Prader-Willi syndrome and Angelman syndrome in two female cousins as a result of a familial translocation. In: Cassidy SB (ed) Prader-Willi syndrome and other chromosome 15q deletion disorders. NATO ASI Series, vol 61. Springer, Heidelberg, pp 95–100

Spence JE, Perciaccante RG, Greig GM, Willard HF, Ledbetter DH, Heijtmancik JF, Pollack MS, et al (1988) Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 42:217–226

Warburton D, Byrne J, Canki N (eds) (1991) Trisomy. In: Chromosome anomalies and prenatal development: an atlas. Oxford University Press, New York, pp 57–62

Weber JL, Kwitek AE, May PE (1990) Dinucleotide repeat polymorphism at the D1S104 locus. Nucleic Acids Res 18:2835

Williams CA, Zori RT, Stone JW, Gray BA, Cantu ES, Ostrer H (1990) Maternal origin of 15q11-13 deletions in Angelman syndrome suggests a role for genomic imprinting. Am J Med Genet 35:350–353