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Trisomy First, Translocation Second, Uniparental Disomy and Partial Trisomy Third: A New Mechanism for Complex Chromosomal Aneuploidy

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Abstract

A 2-year-old, short, microcephalic and developmentally retarded boy revealed a pattern of multiple minor anomalies, hypospadias and a dysplastic right kidney. Maternal age at delivery was 41 years. His karyotype showed two cell lines, one apparently normal, the other with a 1p+ chromosome. FISH examinations showed that the segment attached to 1p was from chromosome 16, and molecular investigations disclosed maternal heterodisomy 16, except for the segment (16)(pter→p13.1) for which there was mosaicism between trisomy and uniparental disomy (UPD). Most likely, the zygote was trisomic for chromosome 16 due to a maternal meiosis I nondisjunction; a somatic rearrangement would have then occurred at an early postzygotic stage whereby a segment of the paternal chromosome 16 was translocated onto 1p. Subsequently, the paternal chromosomes 16 and 16p- had been lost in the normal and the translocation cell line, respectively. The chromosome aberration was detected secondary to the disclosure of maternal UPD 16 because of the demonstration of a paternal band at several loci on distal 16p. This case shows that chromosome aberrations may be formed in a more complicated manner than primarily assumed. Hence, the phenotype might also be due to underlying factors such as UPD or undetected mosaicism in addition to the more obvious implications of the chromosome rearrangement itself (e.g. partial trisomy).

Key Words

Mosaicism
Trisomy 16p
Uniparental disomy

Introduction

Uniparental disomy (UPD), maternal and/or paternal, has so far been reported for about half of the chromosomes [1] and has, due to imprinting, an impact on the phenotype for chromosomes 6 (paternal), 7 (maternal), 14 (probably maternal and paternal), 15 (maternal and paternal), 16 (possibly maternal) and 11p15 (paternal). For

chromosome 16, maternal UPD was always detected following the prenatal determination of trisomy or mosaic trisomy in the placenta at chorionic villus examination. Most patients are small for dates; however, intrauterine growth retardation is also a feature of diploid fetuses with normal biparental inheritance of chromosome 16 with trisomic placenta and thus probably is, at least partly, due to placental dysfunction [2]. Further findings in a propor-

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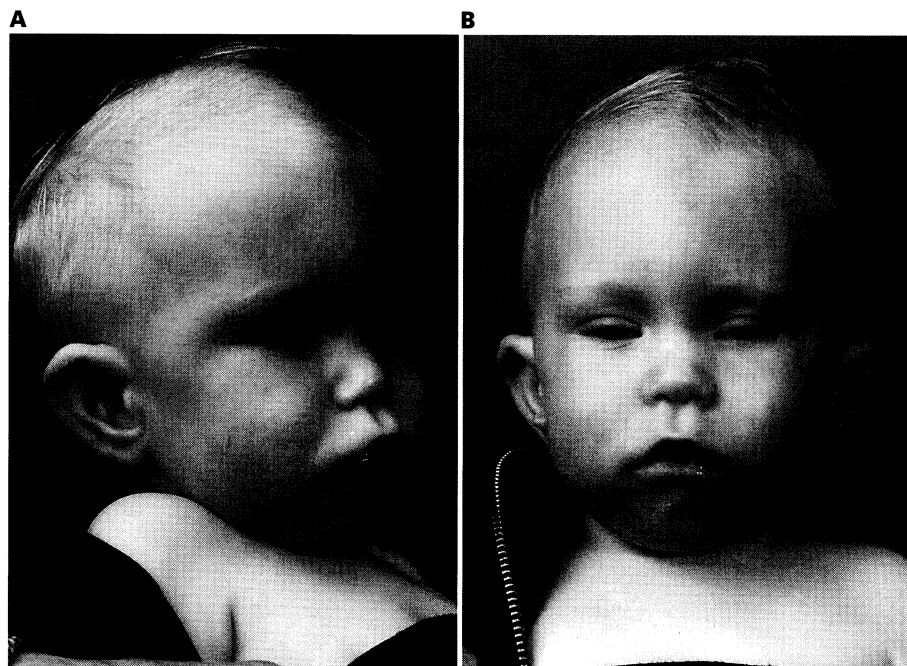


Fig. 1. A, B Head of the propositus at the age of 2 years. Note the narrow forehead with metopic ridge, upslanting and narrow palpebral fissures, ptosis of upper eyelids, prominent upper lip with distinct philtrum, small mandible, posteriorly rotated ears with prominent upper helix and absent lobules.

tion of patients with maternal UPD 16 include prenatal demise, anal atresia, inguinal hernias, microcephaly of prenatal onset and others [3, 4]. However, fetuses with UPD16 and completely normal phenotype have also been observed, and it has therefore been suggested that the phenotype in the cases with congenital developmental defects is due to hidden mosaicism for trisomy 16 rather than to UPD [5].

We report a patient with maternal UPD 16 and mosaicism for partial trisomy 16p due to a postzygotic translocation between chromosomes 1 and 16. The zygote most likely had maternal trisomy 16, and subsequently, the paternal chromosome 16 was lost except for the segment which, in one cell line, was translocated to 1p.

Case Report, Materials and Methods and Results

The propositus, a male, date of birth 25.7.1992, is the fourth of a sibship, born almost 20 years after the third child. At his birth, his mother was 41 and his father 46 years old. The pedigree is unremarkable with respect to congenital developmental defects and mental retardation. The father is a manager of a grocery, and the mother worked part time in the shop during the pregnancy. The pregnancy was normal, with early and relatively vivid fetal activity. Amniotic fluid cell chromosome examination, performed for advanced maternal age, disclosed a 46,XY karyotype. At 26 weeks of pregnancy, hydrops with hydrothorax and ascites and bilateral hydronephrosis were diagnosed on ultrasound. Hydrops spontaneously dissolved after a few weeks. Following premature rupture of the membranes,

spontaneous vertex delivery occurred during the 35th week. Birthweight was 1,960 g, length was 40 cm and OFC was 29.5 cm (all below the 3rd percentile). Multiple minor anomalies were noticed. The newborn stayed at the neonatology unit for the first 8 weeks for low birthweight and respiratory and feeding problems. Myoclonic seizures set in at 3 weeks, and an EEG disclosed epileptic activity. At 4 months of age, an umbilical hernia and bilateral inguinal hernias were operated. Motor and mental development were distinctly delayed from the beginning.

The propositus was first referred to us with the tentative diagnosis of Smith-Lemli-Opitz syndrome at the age of 15 months. A second examination was performed when he was 2 years old. At 15 months of age, length was 64.5 cm, weight was 6.6 kg and occipito-frontal head circumference (OFC) was 42.5 cm (all below the 3rd percentile). At 2 years of age, length (77 cm) was about -3 SD, weight (8 kg) was around -3.5 SD and OFC (44.5 cm) was more than 4 SD below the average for age. At this examination, the following further measurements were obtained: inner canthal distance 2.7 cm (approximately 50th percentile), lid length 2.8 cm, ear length 5.0 cm (50th percentile), left hand length 9.0 cm (<3 rd percentile), left middle finger length 2.5 cm (<3 rd percentile), and left foot length 11.8 cm (3rd percentile).

The following abnormalities were found at both examinations (fig. 1): microcephaly, a narrow forehead with metopic prominence, a broad nasal bridge, upturned nares, upslanting and narrow palpebral fissures, bilateral ptosis of upper lids, no squint, no epicanthic folds, long philtrum, prominent upper lip and retracted lower lip, downturned corners of the mouth, prominent lateral palatine ridges, small mandible, normal teeth which had erupted at normal time, prominent upper helix and absent lobules of ears; mild pectus excavatum, hypopigmented nipples, scars from bilateral inguinal hernia operations, nonpalpable testes (despite of operation at the occasion of herniorrhaphy), short incurved penis with 2° penile hypospadias,

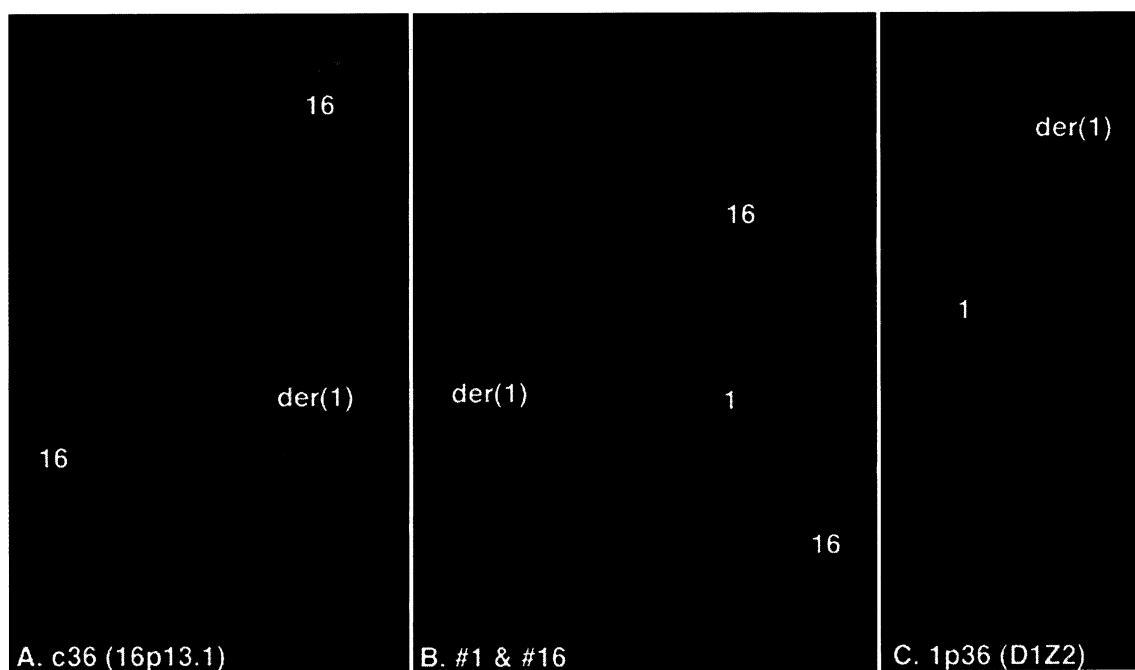


Fig. 2. Results of FISH examinations on metaphases with the 1p+ cell line from a fibroblast culture of the proband. **A** Hybridization with the cosmid c36 (biotin-labeled/detected via avidin-FITC) mapping to proximal 16p13.1. Note the signals on the short arms of both chromosomes 16 and on the der(1). **B** Dual-color painting with a library 1 (digoxigenin-labeled/detected via anti-digoxigenin-rhodamine, Fab fragments) and a chromosome 16 library (biotin-labeled/detected via avidin-FITC). Note a chromosome 16 segment on the der(1) chromosome. **C** The hybridization signal with the D1Z2 midisatellite probe mapping to 1p36 (Oncor®, biotin-labeled and detected via avidin-FITC) marks the distal ends of both the normal chromosome 1 and the der(1). Analysis was performed on a Zeiss Axioplan epifluorescence microscope, and images were recorded with a Photometrics CCD KAF camera (Tucson, Ariz., USA) controlled with Smart Capture imaging software (Vysis, Framingham, Mass., USA).

normal position of the anus, a sacral dimple, no signs of a heart defect, flexion contractures of and dorsal dimples on elbows and knees, short and broad hands with short, flexed and tapering fingers 2–5 and distally tapering nails, excess of whorls on fingertips; clinodactyly of the halluces, partial cutaneous syndactyly between second and third toes, toenail hypoplasia. There was cutis marmorata. He learned to sit, to stand up and to walk with assistance at about 2 years of age, but so far has not developed any speech.

Renal ultrasonography revealed a 2° vesicoureteral reflux with dilated calices on the left side and a multicystic dysplastic right kidney with a blindly ending right ureter. Ophthalmologic examination revealed normal findings except for prominent and poorly defined papillae.

The first chromosome examination performed at another laboratory from an amniotic fluid cell culture (indication: maternal age of 41 years) revealed a normal male karyotype. A second postnatal chromosome examination from a lymphocyte culture, again at another laboratory, also showed a normal result. A further normal result was obtained from our laboratory at the first examination of the patient. At this occasion, only 7 cells were examined for structural aberrations in view of the normal results from the two previous examinations. After having obtained the molecular results (see below), a FISH study

was conducted. Painting with a chromosome 16 library disclosed two cell lines in the patient; one in which, apart from two chromosomes 16, no other genomic material was painted, the other in which, in addition to both homologues 16, the terminal portion of the short arm of one of the homologues 1 was painted as well. By combined painting with libraries 1 and 16 (fig. 2B) and independently with cosmid c40 (data not shown) which maps to the very distal 16p13.3, the ratio between the two cell lines was estimated; in lymphocytes, only 10% of metaphases revealed a partial trisomy 16p, while in fibroblasts, 80% of cells displayed the segmental trisomy 16p. In each case, 200 cells were analyzed. In order to determine more precisely the breakpoints on both 1p and 16p and the size of the segments involved in the rearrangement, we performed FISH with the cosmid c36 which maps to proximal 16p13.1 (fig. 2A) and with the midisatellite probe D1Z2 (fig. 2C) which maps to 1p36 close to the telomere. It could be shown that the breakpoint on 1p is very terminal as the hybridization with D1Z2 revealed a bright and distinct signal on the der(1) chromosome, probably implying 'minimal' loss of the chromosome 1 material (fig. 2C). Hybridization with the cosmid c36 revealed that the breakpoint on 16p is most likely at the borderline between the bands 16p13.1 and 16p12. Therefore, the karyotype can be written as 46,XY,der(1)t(1;16)(p36.3;p13.1)/46,XY.

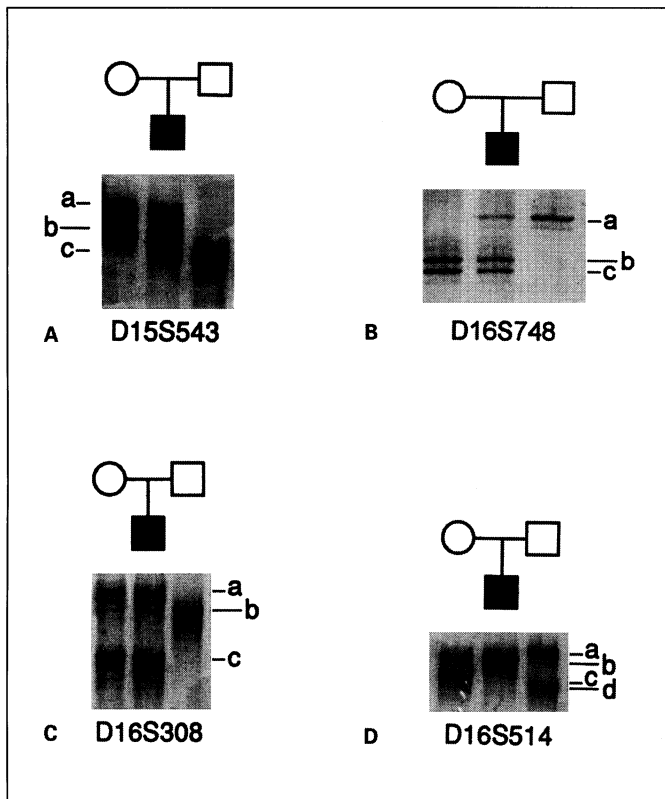


Fig. 3. Results of microsatellite marker analysis for D15S543 (**A**), D16S748 (**B**), D16S308 (**C**) and D16S514 (**D**) in the propositus and his parents. **A, B** Three alleles including two maternal ones and one paternal in the propositus. **C, D** Absence of a paternal allele with (**D**) and without (**C**) reduction of maternal heterozygosity to homozygosity in the propositus. a–d = Alleles (arbitrary designation).

Reexamination of the karyotypes of the three chromosome examinations revealed that the 1p+ chromosome was present in amniotic cells, but had been overlooked. Due to a low percentage of 1p+ in the lymphocytes (10%) and similarities in the banding patterns of distal 1p and 16p, one metaphase with 1p+ (out of 7) analyzed in our laboratory was interpreted as a difference in the contraction stage between two chromosomes 1. Parental chromosomes were normal.

Molecular Investigations

The results of microsatellite marker analyses of loci on chromosome 16 are presented in table 1 and figure 3. Except for the segment 16p13, all allele constellations were compatible with maternal UPD 16, and four informative markers demonstrated the absence of a paternal allele; D16S308 revealed maintenance of maternal heterozygosity in the infant, D16S514 and D16S265 showed reduction of maternal heterozygosity to homozygosity in the propositus, and D16S305 was uninformative for hetero- versus homozygosity.

Several loci mapping to 16p13 showed evidence of a paternal allele: D16S748 revealed three alleles (bands) including one fainter paternal band; D16S291 and D16S423 showed one faint paternal band and one strong maternal band suggestive of double dosage; D16S521, D16S509 and D16S418 showed evidence for double dos-

Table 1. Results of microsatellite examination for chromosome 16 in the propositus and his parents

Marker	Locus	Distance cM	Alleles	Maternal alleles
D16S521	16p13.3	(1)	acc,ac,ab	R
D16S525	16p13.3	(2)	ab,ab,bc	?
D16S291	16p13.3	(4)	<u>abb,bc,ac</u>	R
D16S423	16p13.3	9	<u>abb,bc,ab</u>	R
D16S509	16p13.3	12	abb,ab,aa	R
D16S418	16p13.3	14	bcc,bc,ab	R
D16S406	16p13.3	16	ab,ab,bc	?
D16S407	16	18	<u>bcc,ac,bc</u>	R
D16S748 ¹	16(p13.1)	(25–29)	<u>abc,bc,aa</u>	N
D15S543 ²	16p	no data	<u>abc,ab,cc</u>	N
D16S292	16	(30)	<u>abb,bb,ab</u>	?
D16S287	16p13.1	34–36	ab,ab,ab	N
D16S410	16p13.11	37	ab,ab,bc	N
D16S2691	16p12.2–p12.1	no data	ab,ab,aa	N
D16S299	16p12.1–p11.2	no data	bc,bc,ac	N
D16S401	16p12	49	ac,ac,bb	N
D16S308	16q12.1	no data	ac,ac,bb	N
D16S409	16	59	aa,aa,ab	?
D16S416	16q12.1	67	ab,ab,bc	N
D16S531	16q13	no data	ab,ab,aa	N
D16S514	16q21	87	bb,bc,ad	R
D16S265	16q21	(104)	bb,ab,cd	R
D16S347	16q22.1	no data	aa,ac,ab	R
D16S186	16q22	(106)	bc,bc,ab	N
D16S289	16q24.1	113	bc,bc,ab	N
D16S431	16q24.3	no data	aa,ab,ab	R
D16S422	16q24	119	bb,bc,ab	R
D16S305	16q24.3	(139)	bb,bb,ac	?

Distances are based on the current CEPH map; distances in parentheses are inferred from other maps listed in the genome database. The alleles are given in the order patient, mother, father. The markers showing absence of a paternal allele are given in bold. Markers showing evidence of a paternal allele either by a third band or by one band not present in the mother are underlined. Allele designations (a–d) are arbitrary. Switch between heterozygosity (non-reduced, N) and homozygosity (reduced, R) of maternal alleles is indicated in the right column.

¹ D16S748 is located 23.1 cM from D16S521, between D16S404 (16p13.13) and D16S292 (16p13.1).

² D15S543 amplifies microsatellite repeats both on chromosome 15 and chromosome 16.

age of one (the maternal for D16S509 and D16S418) band. D15S543, a marker mapping to both chromosomes 15 and 16 [in the latter chromosome to the short arm: Christian S. and Ledbetter D.H., pers commun. 1996], also revealed three alleles at the chromosome 16 locus including two maternal ones of similar intensity and a fainter paternal band, thus giving evidence of localization at 16p13. The combined results with marker D16S748 and cosmid c36 confirm the localization of both markers at 16p13.1.

Several loci, both at 16p13 and outside 16p13, were informative for maternal hetero- versus homozygosity. As there were no obvious intensity differences for the alleles of D16S406, it cannot be distinguished whether the propositus had the alleles a and b from the mother and a faint b from the father or two copies of a from the mother and b from the father, although the former seems more likely. The results show that there were at least four crossover events, three of which had occurred in the long arm of the maternal chromosome 16 (table 1). Heterozygosity of markers flanking the centromere indicate maternal first meiotic nondisjunction.

Microsatellite marker analysis of loci on chromosome 1 (D1S318, D1S180, D1S1609, D1S438 and D1S2141) from DNA of the patient's blood cells and fibroblasts and the parents did not show any difference in the alleles between the DNA from the two tissues of the patient, nor did it reveal any faint second paternal band. Marker analysis of at least one informative locus each on chromosomes 2-15 and 17-22 did not show evidence of nonpaternity or UPD for another chromosome.

Discussion

Full trisomy 16, being one of the most frequent chromosome aberrations in spontaneous abortions, is nonviable in humans. Mosaic trisomy has been reported in a few patients; however, their broad spectrum of clinical findings does not allow a characteristic pattern of congenital anomalies to be defined [3]. UPD 16 (always maternal) has so far been detected secondary to the discovery of placental trisomy or mosaic trisomy through prenatal chorionic villus sampling which was, at later examination, not found in the fetus. Maternal trisomy or mosaic trisomy 16 is probably the most frequent type of detected confined placental mosaicism. Most of these newborns do not exhibit congenital anomalies apart from severe intrauterine growth retardation, and not all catch up later. In addition, a proportion of gestations with 16-trisomic placentas with or without fetal UPD terminate through fetal demise [4]. Only in a minority of newborns with maternal UPD 16 are congenital anomalies present, most often anal atresia [2, 6] and cardiac defects [7, 8], followed by inguinal hernia [9] and, in single patients, hypospadias [7], dislocation of elbows [7], hypothyroidism [9], clubfeet [7] and lung hypoplasia [6]. The patient with most congenital anomalies [7] was the only one with complete isodisomy. Thus, his congenital malformations could also be due to the homozygous state of a mutated recessive gene and not predominantly, as possibly in the other patients who showed segmental hetero- and segmental isodisomy, to imprinting or hidden mosaicism.

While full trisomy 16 is not viable in humans, trisomy of the entire or of part of the short arm is associated with a distinct pattern of anomalies [3, 10], the most important

of which are growth retardation, microcephaly, narrow upslanting palpebral fissures, small mandible, cleft palate, low-set and dysplastic ears, flexion position of fingers, seizures and severe mental retardation [3]. The pattern is not very different in patients trisomic for the entire short arm or the distal one half or one third of 16p. Two patients with full trisomy of (16)(pter→p13) due to familial translocation were reported in the literature; one was born underweight (birthweight at term 2,280 g [11] while the other had a birthweight within the normal range (3,300 g at term) [12].

Our propositus has both maternal UPD and mosaic trisomy for (16)(pter→p13). His pattern of congenital anomalies resembles patients with full or partial trisomy 16p. Despite mosaicism, however, his birthweight is lower than in any other full-term patient with partial trisomy 16p. Thus, it is likely that either fetal UPD 16 or placental (mosaic) trisomy 16 contributed largely to the severe intrauterine growth retardation in our propositus.

Strictly speaking, the propositus shows maternal UPD for (16)(p13.1→qter) (hence, almost the whole chromosome 16) and mosaic disomy/trisomy for (16)(pter→p13.1). A similar situation has not been reported previously. There are, however, a few other instances of fetal mosaicism between UPD and trisomy. Willatt et al. [13] reported a patient with mosaicism for trisomy 9. The trisomic cell line contained two maternal and one paternal chromosome 9, while the diploid cell line contained only the two maternal chromosomes 9. Thus, the patient was a mosaic between maternal UPD 9 and trisomy 9. The phenotype of this patient resembled mild trisomy 9 mosaicism syndrome, without further striking anomalies; this is in agreement with the normal phenotype in maternal UPD 9 (apart from the homozygous state of mutated recessive genes) [1]. An analogous patient was reported with multiple congenital anomalies and mosaicism for trisomy 20: two paternal chromosomes 20 were fused with each other, and in a minority of cells, a normal maternal chromosome 20 was also present [14]. Furthermore, Temple et al. [15] reported a 15-month-old girl with mosaicism for an extra ring 6. This girl had paternal UPD 6, except for the segment of the ring which was maternally inherited. The patient thus had full paternal UPD for (6)(pter→p21) and (6)(q11→qter) and mosaicism between trisomy and maternal UPD for (6)(p21→q11). She had neonatal diabetes and low birthweight, but no other anomalies and, up to the age at report, developed normally. Dawson et al. [16] reported a patient with partial trisomy 11q and 22 due to a de novo extra 11;22 translocation chromosome. This is the first

documented case in which the aneuploidy did not arise from a familial t(11;22) translocation. Molecular marker analysis revealed that the additional marker chromosome was of paternal origin, while the two normal homologous chromosomes 22 were both maternal, with heterodisomy.

In all these patients, the mosaic trisomy or partial trisomy was first detected cytogenetically, and the UPD was found secondarily through molecular marker analysis.

In contrast to these patients, our propositus did not have mosaicism for an extra chromosome, but for a structural chromosome aberration which is more difficult to detect and was overlooked at three chromosome examinations. Screening for UPD was performed because of his unrecognized phenotype with similarities to Smith-Lemli-Opitz syndrome and the advanced maternal age. A screening for all 22 chromosomes was initiated, and only after detection of maternal UPD 16 and the demonstration of a faint paternal allele at one locus was the chromosome examination repeated and chromosome painting performed. Chromosome painting easily detected the mosaic 1p+ chromosome, and at examination of a larger number of metaphases, the 1p+ cell line was detected. It may have been detected earlier if a second cell line, e.g. fibroblasts, had been examined since, in contrast to lymphocytes, the abnormal cell line prevailed in fibroblasts. However, in this case, one would have assumed that an early postnatal structural rearrangement would have occurred from a diploid precursor zygote, and UPD 16 would almost certainly not have been investigated and hence not detected.

Once again, the cytogenetic findings in this patient show evidence for a high degree of nondisjunction and fetal selection in embryogenesis. The chromosome constitution probably is the only one possible with which the fetus could survive. The somatic rearrangement between the paternal chromosome 16 and a chromosome 1 had obviously occurred in early embryogenesis, but could not have taken place at the zygote and probably not immediately after the zygote state. Subsequently, and independently from each other, most probably a paternal 16 (full chromosome) has been lost in the progenitor cell line, and the 16p- translocation chromosome (also paternal) has been lost in the translocation cell line (fig. 4). The tiny piece of (16)(pter→p13.1) could not be lost as it was attached to 1p. Theoretically, there is the possibility that a 1;16 translocation occurred premeiotically during spermiogenesis and that, due to adjacent segregation, the fertilizing sperm contained the normal and translocation chromosome 1, but no chromosome 16. If this was the

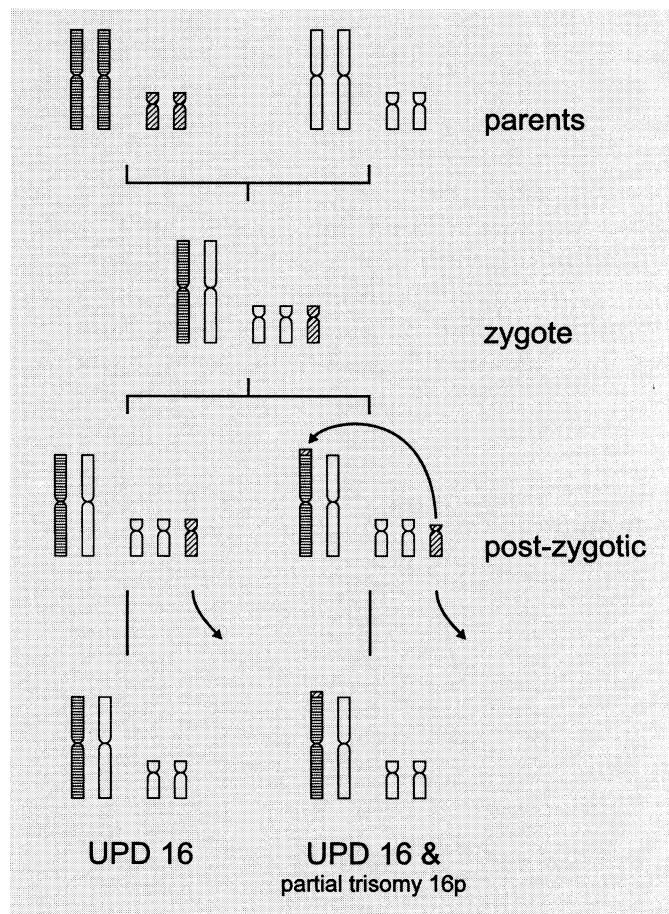


Fig. 4. Proposed mechanism of the formation of the two cell lines in the patient; only chromosomes 1 and 16 are depicted. The zygote shows maternal trisomy 16. Postzygotically, a segment of the short arm of the paternal chromosome 16 is translocated to 1p in one cell line (right); subsequently, the paternal chromosomes 16 are lost in both the normal (trisomic) and the translocation (also trisomic) cell line, leading to full maternal UPD16 in the former and UPD for 16p13.1→qter combined with trisomy for 16pter→p13.1 in the latter cell line. □ = Maternal chromosomes; ▨ = paternal chromosome 1; ▩ = paternal chromosome 16.

case, either the normal or the translocation chromosome 1 from the father must have been lost in different postzygotic divisions. Apart from the extremely remote probability of independent nondisjunction in the mother and alternative loss of one of the father's chromosomes 1 in addition to a somatic 1;16 rearrangement, one would have expected differences in allele distributions and/or intensities between DNA from blood, with a predominantly 46,XY karyotype, and from fibroblasts, where the 46,XY,1p+ cell line prevailed distinctly. However, microsatellite analysis revealed the same allele distributions and intensi-

ties in both samples, thus indicating that the translocation most likely did not occur premeiotically.

In summary, this case shows that UPD is more frequent than generally assumed. As the majority of UPD is probably secondary to trisomy, the question could be raised whether a general UPD search could be considered for the diagnostic work-up of patients with unrecognized patterns of congenital anomalies born to 'old' mothers. Thus, this case shows that it might not always be correct to anticipate that, if a chromosome aberration is found in a malformed patient, this aberration is exclusively respon-

sible for the phenotype. It might be that the aberration had occurred secondarily to a more complex aberration, e.g. UPD or (hidden) trisomy, and that the phenotype is due or partly due to either UPD or undetected trisomy.

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References

- 1 Schinzel A, McKusick VA, Francomano C: Report of the Committee for Clinical Disorders and Chromosome Aberrations. pp 1017-1071; in Cuticchia AJ (ed): Human Genet Mapping 1995. A Compendium. Baltimore, John Hopkins University Press, 1996.
- 2 Kalousek DK, Langlois S, Barrett I, Yam I, Wilson DR, Howard-Peebles PN, Johnson MP, Giorgiutti E: Uniparental disomy for chromosome 16 in humans. *Am J Hum Genet* 1993; 52:8-16.
- 3 Schinzel A: Human Cytogenetics Database. Oxford Medical Databases Series. Oxford, Oxford University Press, Electronic Publishing, 1994.
- 4 Wolstenholme J: An audit of trisomy 16 in man. *Prenat Diagn* 1995;15:109-121.
- 5 Robinson WP, Barrett IJ, Bernard L, Telenius A, Bernasconi F, Wilson RD, Best R, Howard-Peebles PN, Langlois S, Kalousek DK: Meiotic origin of trisomy in confined placental mosaicism is correlated with presence of fetal uniparental disomy, high levels of trisomy in trophoblast and increased risk for fetal IUD. *Am J Hum Genet* 1997;60:917-927.
- 6 Vaughan J, Ali Z, Bower S, Bennett P, Chard T, Moore G: Human maternal uniparental disomy for chromosome 16 and fetal development. *Prenat Diagn* 1994;14:751-756.
- 7 Whiteford ML, Coutts J, Al-Roomi L, Mather A, Lowther G, Cooke A, Vaughan JI, Moore GE, Tolmie JL: Uniparental isodisomy for chromosome 16 in a growth-retarded infant with congenital heart disease. *Prenat Diagn* 1995;15:579-584.
- 8 O'Riordan S, Greenough A, Moore GE, Bennett P, Nicolaides KH: Uniparental disomy 16 in association with congenital heart disease. *Prenat Diagn* 1996;16:963-965.
- 9 Dworniczak B, Koppers B, Kurlemann G, Holzgreve W, Horst J, Miny P: Maternal origin of both chromosomes 16 in a phenotypically normal newborn. *Am J Hum Genet* 1992;52: A11.
- 10 Schinzel A: A catalogue of unbalanced chromosome aberrations in man. Berlin, de Gruyter, 1984.
- 11 Hunter AGW, Rimoin DL, Koch UM, MacDonald GJ, Cox DM, Lachmann RS, Adomian G: Chondrodysplasia punctata in an infant with duplication 16p due to a 7;16 translocation. *Am J Med Genet* 1985;21:581-589.
- 12 O'Connor TA, Higgins RR: Trisomy 16p in a liveborn infant and review of trisomy 16p. *Am J Med Genet* 1992;42:316-319.
- 13 Willatt LR, Davison BCC, Goudie D, Alexander J, Dyson HM, Jenks PE, Ferguson-Smith ME: A male with trisomy 9 mosaicism and maternal uniparental disomy for chromosome 9 in the euploid cell line. *J Med Genet* 1992;29: 742-744.
- 14 Spinner NB, Rand E, Bucan M, Jirik F, Gogolin-Ewens C, Riethman HC, McDonald-McGinn DM, Zackai EH: Paternal uniparental isodisomy for human chromosome 20 and absence of external ears. *Am J Hum Genet* 1994; 55:A118.
- 15 Temple IK, James RS, Crolla JA, Sitch FL, Jacobs PA, Howell WM, Betts P, Baum JD, Shield JPH: An imprinted gene(s) for diabetes? *Nat Genet* 1995;9:110-112.
- 16 Dawson AJ, Mears AJ, Chudley AE, Bech-Hansen T, McDermid H: Der(22)t(11;22) resulting from a paternal de novo translocation, adjacent 1 segregation, and maternal heterodisomy of chromosome 22. *J Med Genet* 1996; 33:952-956.