Mosaic Tetrasomy 12p With Discrepancy Between Fetal Tissues and Extraembryonic Tissues: Molecular Analysis and Possible Mechanism of Formation

Chih-Ping Chen[1,2,3,4,5,6]*, Yi-Ning Su[7], Schu-Rern Chern[2], Fuu-Jen Tsai[4,8,9], Pei-Chen Wu[1], Hsiao-En Cindy Chen[10], Shu-Shien Chiang[2], Wayseen Wang[2,11]

Departments of [1]Obstetrics and Gynecology and [2]Medical Research, Mackay Memorial Hospital, Taipei, [3]Department of Biotechnology, Asia University, [4]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, [5]Institute of Clinical and Community Health Nursing, National Yang-Ming University, [6]Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, [7]Department of Medical Genetics, National Taiwan University Hospital, Taipei, Departments of [8]Medical Genetics and [9]Medical Research, China Medical University Hospital, Taichung, Taiwan, [10]School of Medicine, University of Wollongong, New South Wales, Australia, and [11]Department of Bioengineering, Tatung University, Taipei, Taiwan.

A healthy 40-year-old, gravida 2, para 1, woman underwent amniocentesis at 16 weeks of gestation because of her advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed mosaicism for tetrasomy 12p, or 47,XX,+i(12p)/46,XX (64%/36%; 16 colonies/9 colonies). The parental karyotypes were normal and the pregnancy was subsequently terminated. A 399 g fetus was delivered with a craniofacial appearance characteristic of Pallister-Killian syndrome (PKS). The clinical findings for this case were described previously [1]. Postnatal cytogenetic analysis revealed a 47,XX,+i(12p) karyotype in 100% (30 of 30) of cultured umbilical cord cells and a 47,XX,+i(12p)/46,XX karyotype in the cultured cells of fetal skin and liver. The level of cells with tetrasomy 12p was 53% (16 of 30) and 60% (18 of 30) in skin and liver, respectively. Genomic DNAs were isolated from parental blood, umbilical cord blood and the uncultured tissues of umbilical cord, placental chorionic villi, amniotic membrane, liver, and skin. Quantitative fluorescent polymerase chain reaction and polymorphic short tandem repeat markers specific for chromosome 12p and chromosome 12q were used for determination of aneuploidy, possible mechanism of formation and parental origin of the isochromosome 12p (Table, Figure 1). The placental tissue exhibited a biparental inheritance, and the amnion showed maternal uniparental heterodisomy. Dosage increase of an extra maternal heterozygous allele was noted in the tissues of cord blood, umbilical cord, liver, and skin. Molecular analysis showed that this case was most likely the result of trisomic zygote rescue of a meiosis I nondisjunction error of maternal origin and a postzygotic mitotic error (Figure 2).

PKS (OMIM 601803) is a dysmorphic syndrome characterized by mosaicism for the supernumerary isochromosome 12p. Chen et al [2] observed cytogenetic variability in the proportion of abnormal cells between various tissues in prenatally detected mosaic tetrasomy 12p. In a meta-analysis of the cases of prenatally detected or postnatally confirmed PKS, Chen et al [2] reported that a false-negative result was found in 55% (12 of 22) of cases from blood lymphocyte cultures, 43% (3 of 7) of cases from chorionic villus sampling (CVS) short-term cultures/direct preparations, 50% (1 of 2) of cases from CVS long-term cultures, and in 12% (3 of 25) of cases from amniocyte cultures. In the present case, placental chorionic villi had a biparental inheritance, the amnion had maternal uniparental heterodisomy, and umbilical cord, cord blood and fetal skin and liver had a gene dosage increase of an extra maternal heterozygous allele. The fetoplacental and fetoamniotic discrepancies observed in this case implies a limitation of using placenta and amnion as confirmatory tools for mosaic tetrasomy 12p as detected by amniocentesis. The present case indicates that amniocentesis can provide a better genotype–phenotype correlation compared with CVS in the diagnosis of PKS.

*Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: cpc_mmh@yahoo.com
Accepted: January 19, 2010

Table. Molecular results using polymorphic microsatellite markers specific for chromosome 12*

Marker	D12S1062	D12S372	D12S378
Locus	12p13	12p13	12q24.2–q24.3
Father			
Blood	184, 184	188, 188	168, 168
Mother			
Blood	176, 192	180, 196	160, 160
Proband			
Cord blood	176, 184, 192†	180, 188, 196†	160, 168
Umbilical cord	176, 184, 192†	180, 188, 196†	160, 168
Placenta	176, 184	180, 188	160, 168
Amnion	176, 192	180, 196	160, 160
Liver	176, 184, 192†	180, 188, 196†	160, 168
Skin	176, 184, 192†	180, 188, 196†	160, 168

**Alleles (in base pairs) are listed below each individual; †gene dosage increase.*

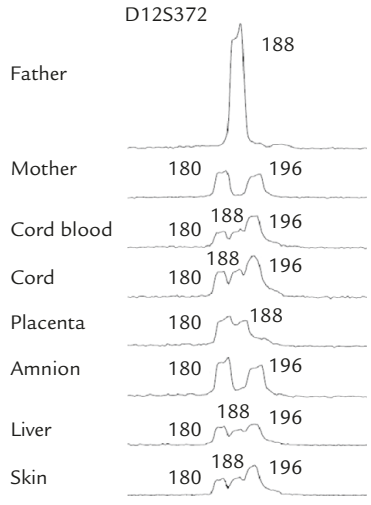

Figure 1. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem repeat markers specific for chromosome 12p. With the marker D12S372 (12p13), two peaks (maternal, 180 bp; paternal, 188 bp) of equal fluorescent activity from two different parental alleles with a ratio of 1:1 in placenta indicating a biparental inheritance, and two peaks (maternal, 180 bp; maternal, 196 bp) with a ratio of 1:1 in amnion indicating maternal heterodisomy. The three peaks (maternal, 180 bp; paternal, 188 bp; maternal, 196 bp) of unequal fluorescent activity (1:1:>1) in cord blood, umbilical cord, liver and skin indicated a heterozygous maternal origin of isochromosome 12p.

Several mechanisms have been proposed to explain the origin of the i(12p) in PKS. Hunter et al [3] proposed *de novo* formation of the i(12p) from a trisomic zygote. Rivera et al [4] and Struthers et al [5] suggested premeiotic mitotic centromeric misdivision, nondisjunction at meiosis I or centromeric misdivision at either meiosis I or II. Van Dyke et al [6] suggested a meiotic origin of the i(12p) with nondisjunction at meiosis I resulting in a gamete with a normal chromosome 12 and an i(12p). Cormier-Daire et al [7] reported a case of PKS as the result of a prezygotic event with a nondisjunction event during maternal meiosis. Dutly et al [8] reported a maternal origin of the i(12p) and formation of the i(12p) because of meiosis II nondisjunction followed by meiotic or postmeiotic mitotic misdivision and subsequent loss of the long arms in two cases and a postzygotic nondisjunction event in one case. De Ravel et al [9] reported a paternal origin and postzygotic formation of the i(12p) in a single case.

The present case was most likely caused by both a maternal meiosis I nondisjunction event generating a disomic oocyte that resulted, upon conception, in a trisomic zygote, and a postzygotic event generating formation of i(12p) and mitotic nondisjunction (Figure 2). Maternal heterodisomy in amnion occurred through trisomic zygote rescue with loss of the chromosome from the father and subsequent disappearance of the trisomy 12 cell line because of the incompatibility of the life in trisomy 12. The trisomic zygote underwent mitotic cleavage with isochromosome formation and subsequent generation of a diploid biparental 46,XX cell line because of a mitotic nondisjunction. The occurrence of only a diploid biparental 46,XX cell line in the placental chorionic villi was due to the selection against the i(12p) cell line. The occurrence of only an i(12p) cell line in the umbilical cord was due to the disappearance of a normal 46,XX cell line.

Acknowledgments

This work was supported by research grants NSC-96-2314-B-195-008-MY3 and NSC-97-2314-B-195-006-MY3 from the National Science Council, and

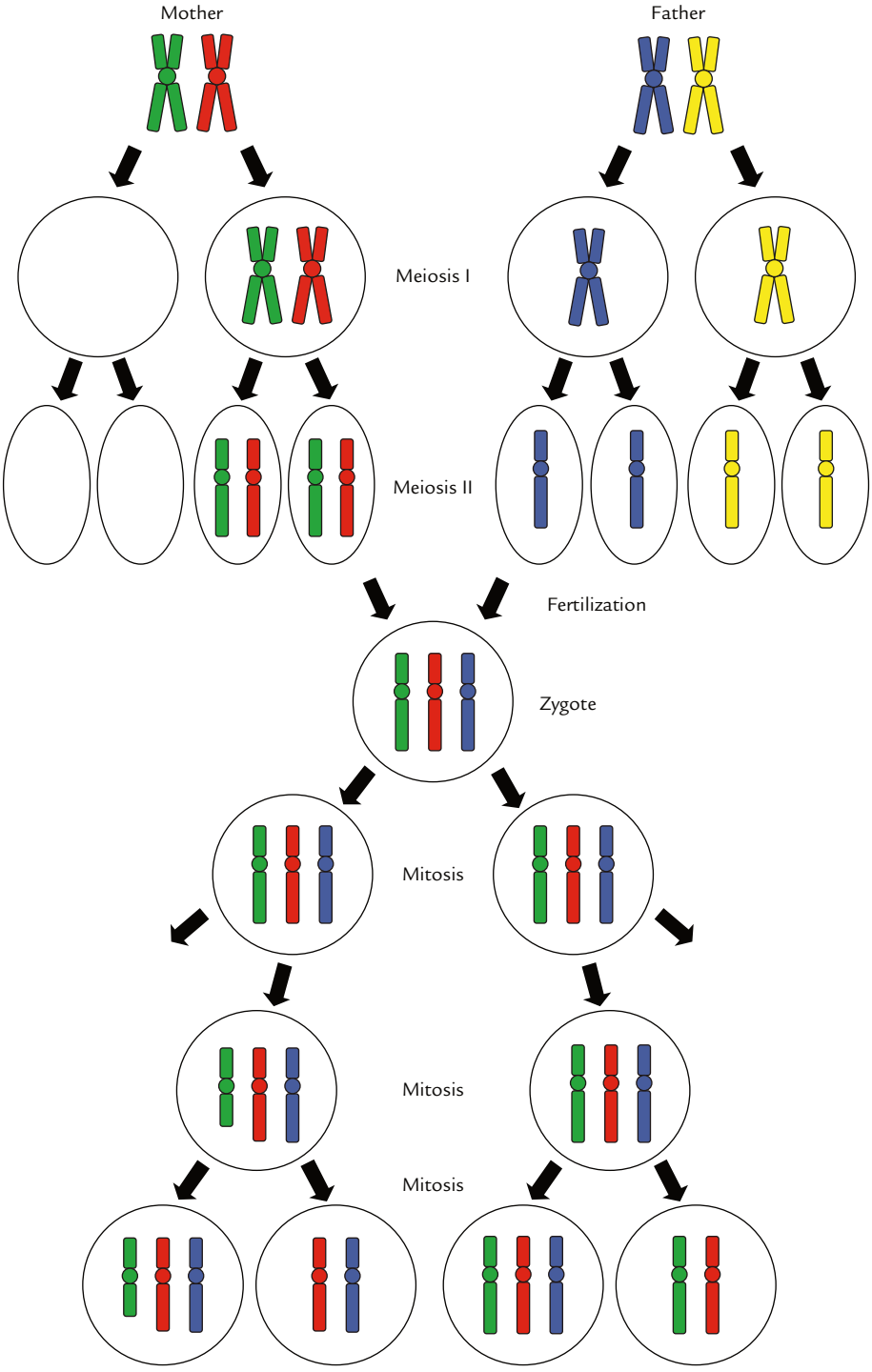

Figure 2. Schematic representation of the most probable mechanism of formation of an isochromosome 12p cell line, a maternal heterodisomy cell line and a diploid biparental cell line as found in the present case.

MMH-E-99004 from Mackay Memorial Hospital, Taipei, Taiwan.

References

1. Chen CP, Su YN, Hsu CY, et al. Abnormally flat facial profile on two- and three-dimensional ultrasound and array comparative genomic hybridization for the diagnosis of Pallister-Killian syndrome. *Taiwan J Obstet Gynecol* 2010;49:124–8.
2. Chen CP, Tsai FJ, Chern SR, Lee CC, Town DD, Wang W. Cytogenetic variability in the proportion of abnormal cells between the various tissues in prenatally detected mosaic tetrasomy 12p. *Prenat Diagn* 2007;27:1170–3.
3. Hunter AGW, Clifford B, Cox DM. The characteristic physiognomy and tissue specific karyotype distribution in the Pallister-Killian syndrome. *Clin Genet* 1985;28:47–53.

4. Rivera H, Rivas F, Cantú JM. On the origin of extra isochromosome. *Clin Genet* 1986;29:540–1.
5. Struthers JL, Cuthbert CD, Khalifa MM. Parental origin of the isochromosome 12p in Pallister-Killian syndrome: Molecular analysis of one patient and review of the reported cases. *Am J Med Genet* 1999;84:111–5.
6. Van Dyke DL, Babu VR, Weiss L. Parental age, and how extra isochromosome (secondary trisomy) arise. *Clin Genet* 1987;32:75–80.
7. Cormier-Daire V, Le Merrer M, Gigarel N, et al. Prezygotic origin of the isochromosome 12p in Pallister-Killian syndrome. *Am J Med Genet* 1997;69:166–8.
8. Dutly F, Balmer D, Baumer A, Binkert F, Schizel A. Isochromosomes 12p and 9p: parental origin and possible mechanisms of formation. *Eur J Hum Genet* 1998;6: 140–4.
9. de Ravel TJ, Keymolen K, van Assche E, et al. Post-zygotic origin of isochromosome 12p. *Prenat Diagn* 2004;24:984–8.