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Case Report

Fetoplacental cytogenetic discrepancy in a pregnancy with fetal mosaic tetrasomy 12p and Pallister–Killian syndrome detected by amniocentesis

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ABSTRACT

Objective: We present fetoplacental cytogenetic discrepancy in a pregnancy with prenatally detected mosaic tetrasomy 12p by amniocentesis.

Case report: A 34-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+i(12)(p10)[7]/46,XX[16]. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from cultured amniocytes revealed arr (12p)×3, (X)×2. Prenatal ultrasound findings were unremarkable. The pregnancy was subsequently terminated, and a fetus was delivered with facial dysmorphism consistent with the clinical features of Pallister–Killian syndrome (PKS). Postnatal cytogenetic analysis of the cultured cells from umbilical cord, skin, cord blood and placenta revealed 47,XX,+i(12)(p10)[6]/46,XX[34] in umbilical cord, 47,XX,+i(12)(p10)[11]/46,XX[29] in skin, 47,XX,+i(12)(p10)[3]/46,XX[47] in cord blood and 46,XX[40] in placenta. The mosaic tetrasomy 12p levels of the umbilical cord, skin, cord blood and placenta were 15%, 27.5%, 6% and 0%, respectively. aCGH analysis of the DNA extracted from uncultured cord blood and placenta revealed arr 12p13.33p11.1 (230,421-34,756,209)×3.0 in cord blood but no genomic imbalance in placenta. Polymorphic DNA marker analysis showed a maternal origin of the supernumerary isochromosome 12p in cord blood but biparental inheritance with equal fluorescent activity in placenta.

Conclusion: Pregnancy with fetal PKS and mosaic tetrasomy 12p may present fetoplacental cytogenetic discrepancy. Therefore, genetic analysis on placenta alone may fail to detect fetal mosaic tetrasomy 12p associated with PKS.

Introduction

Pallister–Killian syndrome (PKS) [Online Mendelian Inheritance in Man (OMIM) 601803] is a dysmorphic syndrome with an incidence of 5.1 per one million live births, and is characterized by facial dysmorphism of prominent forehead, sparse anterior scalp hair, hypertelorism, short nose and flat nasal bridge, short neck, flat occiput, intellectual disability, seizures and pigmentary skin lesions, and occasional congenital malformations of diaphragmatic hernia, cleft, omphalocele, congenital cardiac defects, anal atresia, sacral appendages, polydactyly, and autonomic system abnormalities of anhidrosis/hypohidrosis and episodic hyperventilation [1,2].

Fetuses with PKS may prenatally manifest sonographic abnormalities of flat facial profile, short limbs, diaphragmatic hernia, thickened nuchal fold, increased nuchal thickness, cystic hygroma,

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polydactyly, polyhydramnios, fetal hydrops, fetal overweight, intrauterine growth restriction, absent visualization of the stomach, ambiguous genitalia, echogenic bowel and single umbilical artery [3–8].

Pallister–Killian syndrome is characterized by tissue-limited mosaicism for tetrasomy 12p due to a supernumerary isochromosome for the short arm of chromosome 12 or i(12)(p10), and the population of abnormal cells with a supernumerary i(12)(p10) or tetrasomy 12p in lymphocytes and fibroblasts does not correlate with the severity of clinical phenotype [9]. Here, we present feto-placental cytogenetic discrepancy in a pregnancy with prenatally detected mosaic tetrasomy 12p by amniocentesis.

Case report

A 34-year-old, gravida 2, para 0, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 35 years old, and there was no family

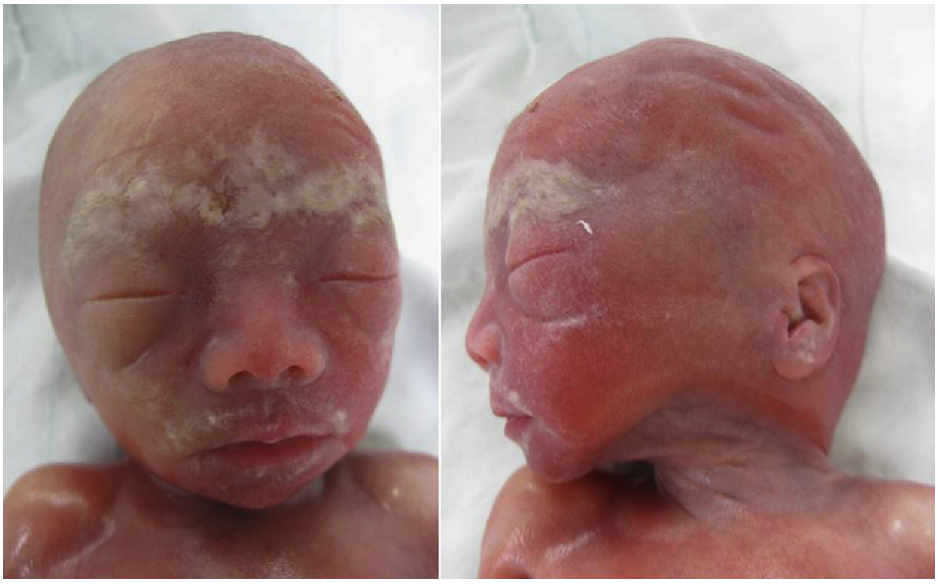


Fig. 1. The craniofacial appearance of the fetus at birth.

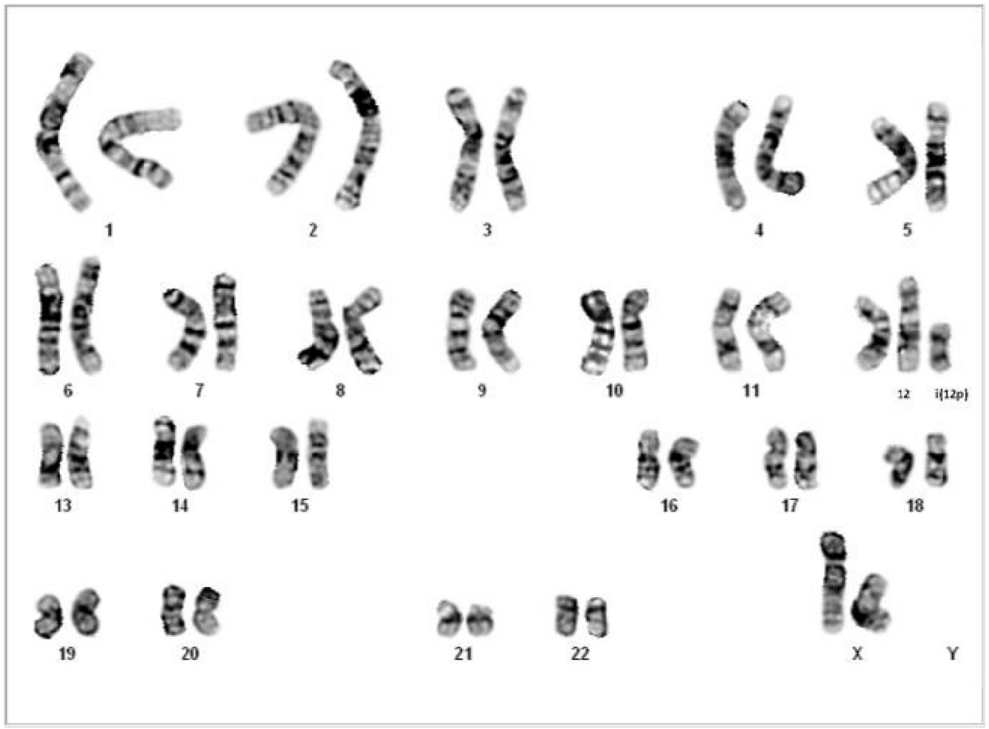
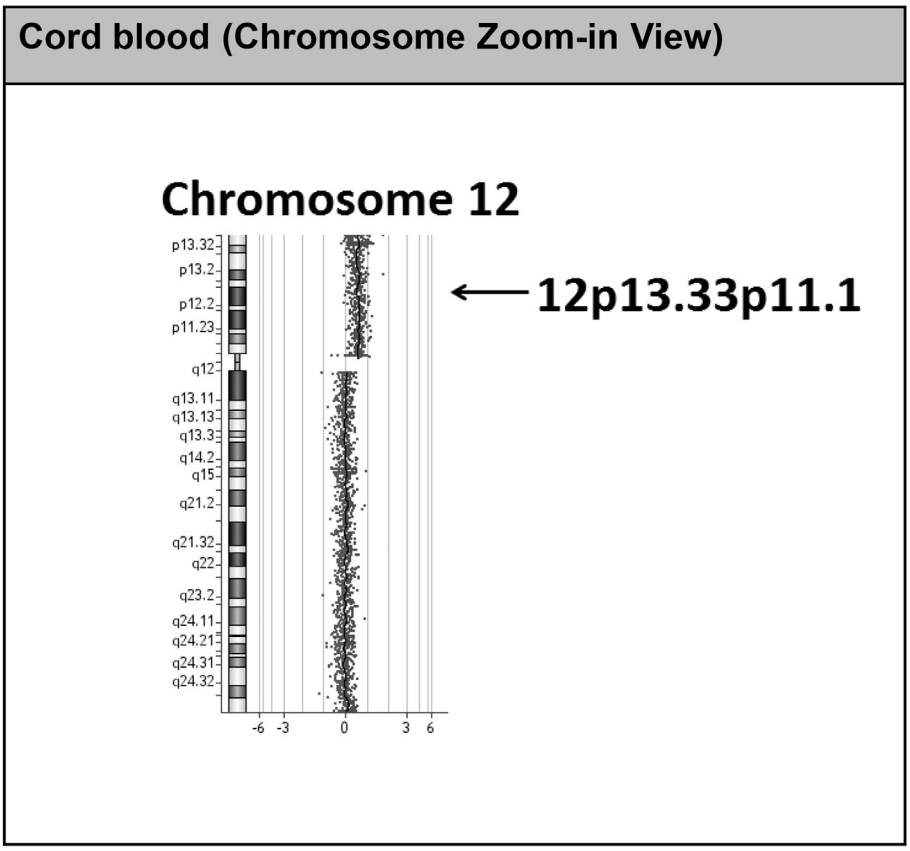


Fig. 2. A karyotype of 47,XX,+i(12)(p10).

(A)



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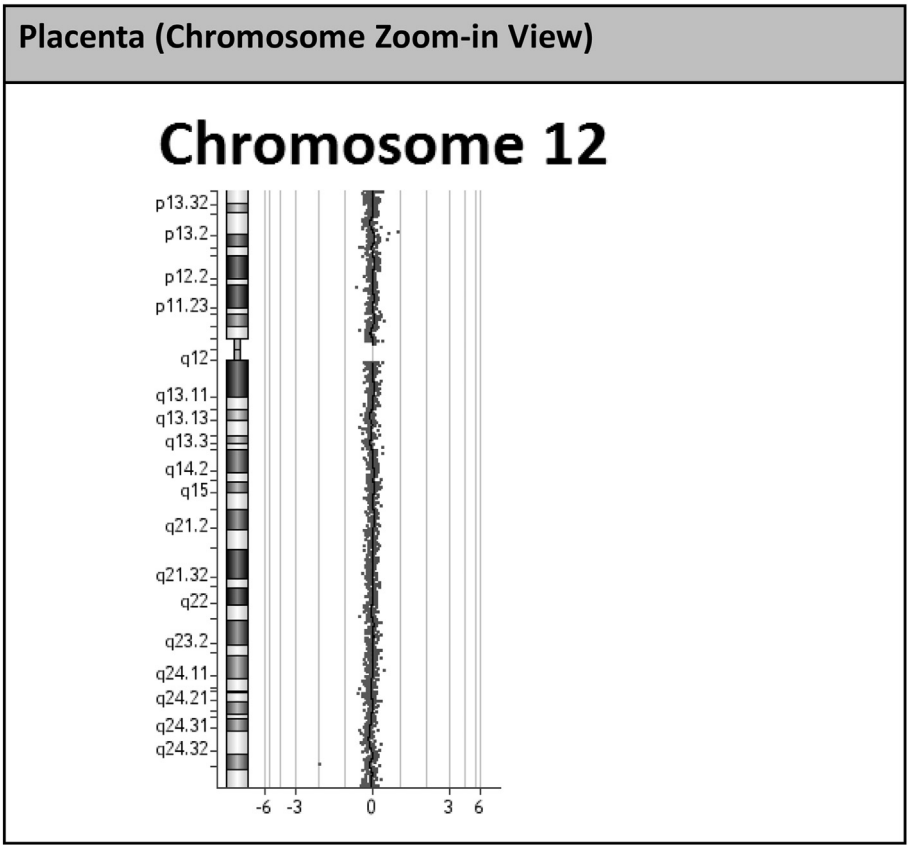

Fig. 3. Array comparative genomic hybridization analysis of the DNAs extracted from uncultured cord blood and placenta shows (A) 12p13.33p11.1 (230,421-34,756,209)×3.0 in cord blood and (B) no genomic imbalance in placenta.

history of congenital malformations. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XX,+i(12)(p10)[7]/46,XX[16]. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from cultured amniocytes revealed a result of arr (12p)×3, (X)×2. Prenatal ultrasound examination revealed no structural abnormalities in the fetus. The pregnancy was subsequently terminated at 21 weeks of gestation, and a 426-g fetus was delivered with facial dysmorphism of hypertelorism, prominent forehead, low-set ears, and a short nose with a flat nasal bridge and anteverted nostrils consistent with the clinical features of PKS (Fig. 1). Postnatal cytogenetic analysis on the cultured cells of umbilical cord, skin, cord blood and placenta revealed the results of 47,XX,+i(12)(p10)[6]/46,XX[34] in umbilical cord, 47,XX,+i(12)(p10)[11]/46,XX[29] in skin, 47,XX,+i(12)(p10)[3]/46,XX[47] in cord blood and 46,XX[40] in placenta (Fig. 2). The mosaic tetrasomy 12p levels of the umbilical cord, skin, cord blood and placenta were 15%, 27.5%, 6% and 0%, respectively. aCGH analysis of the DNAs extracted from uncultured cord blood and placenta, respectively using SurePrint G3 Unrestricted CGH ISCA v2, 8×60 K Array (Agilent Technologies, Santa Clara, CA, USA) revealed a result of arr 12p13.33p11.1 (230,421-34,756,209)×3.0 with a $\log_2$ ratio of 0.585 in cord blood (Fig. 3A) but no genomic imbalance in placenta (Fig. 3B). Polymorphic DNA marker analysis of the DNAs extracted from cord blood and placenta, respectively using the informative markers of D12S374 (12p12.31) and D12S290 (12p11.22) showed a maternal origin of the supernumerary isochromosome 12p derived from a maternal meiosis II non-disjunction error followed by post-zygotic rearrangements in cord blood but biparental inheritance with equal fluorescent activity in placenta (Fig. 4).

Discussion

The present case had a maternal origin of the supernumerary i(12)(p10). Dutly et al. [10] suggested that the origin of the supernumerary i(12)(p10) is predominantly maternal and is caused by the maternal meiosis II non-disjunction error followed by post-zygotic rearrangements. However, the supernumerary i(12)(p10) can be of paternal origin and occur post-zygotically [11,12], and can be of maternal origin caused by meiosis I non-disjunction followed by a post-zygotic mitotic event [13]. In the present case, the supernumerary i(12)(p10) is likely caused by a maternal meiosis II non-disjunction error followed by post-zygotic rearrangements as described by Dutly et al. [10].

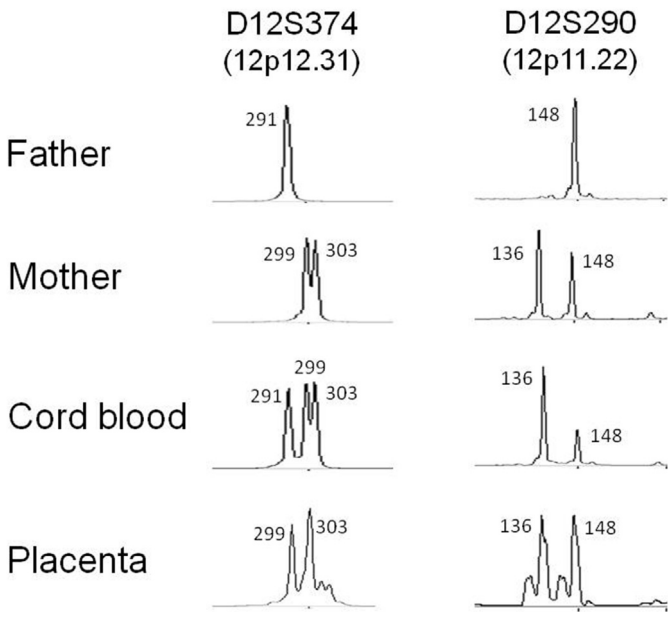

Fig. 4. Polymorphic markers analysis of the DNAs extracted from cord blood and placenta, respectively using the informative markers of D12S374 (12p12.31) and D12S290 (12p11.22) shows a maternal origin of the supernumerary isochromosome 12p derived from a maternal meiosis II non-disjunction error followed by post-zygotic rearrangements in cord blood but biparental inheritance with equal fluorescent activity in placenta.

Prenatal diagnosis of PKS by means of chorionic villus sampling (CVS), amniocentesis or cord blood sampling may result in a false-negative result because of tissue-limited mosaicism. Priest et al. [14] observed that cells with tetrasomy 12p in blood and amniocytes were less stable than skin fibroblasts, and the young cultures had more cells with tetrasomy 12p than the old cultures. Polityko et al. [15] observed a rapid decrease of cells with tetrasomy 12p during amniocyte subcultures. Tang and Wenger [16] suggested that the cell death of abnormal clones with tetrasomy 12p is responsible for tissue-limited mosaicism in PKS. In a review of 28 cases with cytogenetic discrepancy among various tissue samplings in pre- or postnatally detected PKS, Chen et al. [12] observed that a false-negative result occurred in 55% (12/22) from blood lymphocyte cultures, 43% (3/7) from short-term cultures/direct preparations of CVS, 50% (1/2) from long-term cultures of CVS, and 12% (3/25) from amniocyte cultures. Chen et al. [13] found that cord blood sampling and placental sampling were prone to have a false-negative result comparing with amniocentesis in the diagnosis of PKS by conventional culture cytogenetics. Chen et al. [17] additionally found that aCGH on uncultured cord blood or interphase fluorescence *in situ* hybridization analysis on cultured cord blood lymphocytes can detect more abnormal cells with tetrasomy 12p than conventional cytogenetic analysis of cultured lymphocytes. In the present case, the cultured cord blood lymphocytes had only 6% (3/50) mosaic level of tetrasomy 12p, but aCGH detected a higher level of (12p)×3 with a $\log_2$ ratio of 0.585 in uncultured cord blood. The present case also had normal results in the postnatal placental sampling analyzed by conventional cytogenetic analysis, polymorphic DNA marker analysis and aCGH analysis.

Fetoplacental cytogenetic discrepancy has previously been reported in cases of pre- or postnatally detected PKS. Horn et al. [18] reported the karyotype of 46,XY in both prenatal CVS and cord blood, but the skin had 85% mosaicism for tetrasomy 12p. Turleau et al. [19] reported 0% mosaicism for tetrasomy 12p in postnatal placental sampling, but the mosaic levels of tetrasomy 12p for amniocytes, blood and skin were 70%, 8% and >90%, respectively. Chiurazzi et al. [20] reported the karyotype of 46,XY in both prenatal CVS and cord blood, but the skin had 48% mosaicism for tetrasomy 12p. Our case adds to the literature of fetoplacental cytogenetic discrepancy in cases of pre- or postnatally detected PKS. Our presentation implicates the limitation of using CVS and non-invasive prenatal testing (NIPT) in prenatal diagnosis of mosaic tetrasomy 12p and PKS.

In conclusion, pregnancy with fetal PKS and mosaic tetrasomy 12p may present fetoplacental cytogenetic discrepancy. Therefore, genetic analysis on placenta alone such as CVS, non-invasive prenatal testing or postnatal placental sampling may fail to detect fetal mosaic tetrasomy 12p associated with PKS.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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References

[1] Wilkens A, Liu H, Park K, Campbell LB, Jackson M, Kostanecka A, et al. Novel clinical manifestations in Pallister-Killian syndrome: comprehensive evaluation of 59 affected individuals and review of previously reported cases. Am J Med Genet 2012;158A:3002–17.

[2] Blyth M, Maloney V, Beal S, Collinson M, Huang S, Crolla J, et al. Pallister-Killian syndrome: a study of 22 British patients. J Med Genet 2015;52:454–64.

[3] Chen C-P, Chien S-C. Prenatal sonographic features of Pallister-Killian syndrome. J Med Ultrasound 2010;18:43–53.

[4] Chen C-P, Su Y-N, Hsu C-Y, Tsai F-J, Chien S-C, Chern S-R, 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.

[5] Özlü T, Ocak Z, Ozyurt O. Prenatal diagnosis of Pallister Killian Syndrome in a fetus with congenital diaphragmatic hernia, short limbs, and increased nuchal translucency. Taiwan J Obstet Gynecol 2014;53:404–5.

[6] Desseauve D, Legendre M, Dugué-Maréchaud M, Vequeau-Goua V, Pierre F. Prenatal and clinicopathological study of 6 cases of Pallister-Killian syndrome and review. Gynécol Obstét Fertil 2016;44:200–6 [French].

[7] Libotte F, Bizzoco D, Gabrielli I, Mesoraca A, Cignini P, Vitale SG, et al. Pallister-Killian syndrome: cytogenetics and molecular investigations of mosaic tetrasomy 12p in prenatal chorionic villus and in amniocytes. Strategy of prenatal diagnosis. Taiwan J Obstet Gynecol 2016;55:863–6.

[8] Kucińska-Chahwan A, Bijok J, Dąbkowska S, Jóźwiak A, Ilnicka A, Nowakowska B, et al. Targeted prenatal diagnosis of Pallister-Killian syndrome. Prenat Diagn 2017;37:446–52.

[9] Schinzel A. Tetrasomy 12p (Pallister-Killian syndrome). J Med Genet 1991;28:122–5.

[10] Dutly F, Balmer D, Baumer A, Binkert F, Schinzel A. Isochromosomes 12p and 9p: parental origin and possible mechanisms of formation. Eur J Hum Genet 1998;6:140–4.

[11] de Ravel TJ, Keymolen K, van Assche E, Wittevronghel I, Moerman P, Salden I, et al. Post-zygotic origin of isochromosome 12p. Prenat Diagn 2004;24:984–8.

[12] Chen C-P, Tsai F-J, Chern S-R, Lee C-C, Town D-D, 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.

[13] Chen C-P, Su Y-N, Chern S-R, Tsai F-J, Wu P-C, Chen H-E, et al. Mosaic tetrasomy 12p with discrepancy between fetal tissues and extraembryonic tissues: molecular analysis and possible mechanism of formation. Taiwan J Obstet Gynecol 2010;49:235–8.

[14] Priest JH, Rust JM, Fernhoff PM. Tissue specificity and stability of mosaicism in Pallister–Killian +i(12p) syndrome: relevance for prenatal diagnosis. Am J Med Genet 1992;42:820–4.

[15] Polityko AD, Goncharova E, Shamgina L, Drozdovskaja N, Podleschuk L, Abramchik E, et al. Pallister-Killian syndrome: rapid decrease of isochromosome 12p frequency during amniocyte subculturing. Conclusion for strategy of prenatal cytogenetic diagnostics. J Histochem Cytochem 2005;53:361–4.

[16] Tang W, Wenger SL. Cell death as a possible mechanism for tissue limited mosaicism in Pallister-Killian syndrome. J Assoc Genet Technol 2005;31:168–9.

[17] Chen C-P, Peng C-R, Chern S-R, Kuo Y-L, Wu P-S, Town D-D, et al. Interphase fluorescence *in situ* hybridization characterization of mosaicism using uncultured amniocytes and cultured stimulated cord blood lymphocytes in prenatally detected Pallister-Killian syndrome. Taiwan J Obstet Gynecol 2014;53:566–71.

[18] Horn D, Majewski F, Hildebrandt B, Körner H. Pallister-Killian syndrome: normal karyotype in prenatal chorionic villi, in postnatal lymphocytes, and in slowly growing epidermal cells, but mosaic tetrasomy 12p in skin fibroblasts. J Med Genet 1995;32:68–71.

[19] Turleau C, Simon-Bouy B, Austruy E, Grisard M-C, Lemaire F, Molina-Gomes D, et al. Parental origin and mechanisms of formation of three cases of 12p tetrasomy. Clin Genet 1996;50:41–6.

[20] Chiurazzi P, Bajer J, Tabolacci E, Pomponi MG, Lecce R, Zollino M, et al. Assisted reproductive technology and congenital overgrowth: some speculations on a case of Pallister-Killian syndrome. Am J Med Genet 2004;130A:315–6.