



Case Report

Prenatal diagnosis of partial monosomy 5p (5p15.1 → pter) and partial trisomy 7p (7p15.2 → pter) associated with cystic hygroma, abnormal skull development, and ventriculomegaly

Chih-Ping Chen^{a, b, c, d, e, f, *}, Liang-Kai Wang^a, Schu-Rern Chern^b, Peih-Shan Wu^g, Kevin Ko^b, Yen-Ni Chen^a, Shin-Wen Chen^a, Meng-Shan Lee^a, Wayseen Wang^{b, h}^a Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan^b Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan^c Department of Biotechnology, Asia University, Taichung, Taiwan^d School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan^e Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan^f Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan^g Gene Biodesign Co. Ltd, Taipei, Taiwan^h Department of Bioengineering, Tatung University, Taipei, Taiwan

ARTICLE INFO

Article history:

Accepted 13 June 2016

Keywords:

cystic hygroma
5p deletion
7p duplication
prenatal diagnosis
ventriculomegaly

ABSTRACT

Objective: Prenatal diagnosis of concomitant chromosome 5p deletion syndrome and chromosome 7p duplication syndrome in a fetus with abnormal prenatal ultrasound is presented.**Case Report:** A 34-year-old woman was referred for amniocentesis at 22 weeks of gestation because of an irregular-shaped skull, bilateral ventriculomegaly, and nuchal cystic hygroma. Amniocentesis revealed a derivative chromosome 5 with a distal 5p deletion and an addendum of an extra unknown chromosomal segment at the breakpoint of 5p. Cytogenetic analysis of parental bloods revealed a karyotype of 46, XX, t(5;7)(p15.1;p15.2) in the mother and a karyotype of 46, XY in the father. The karyotype of the fetus was 46, XX, der(5) t(5;7)(p15.1;p15.2)mat consistent with partial monosomy 5p (5p15.1 → pter) and partial trisomy 7p (7p15.2 → pter). A malformed fetus was subsequently delivered with an irregular-shaped skull, a large anterior fontanelle, brachycephaly, hypertelorism, a high and prominent forehead, a large nuchal cystic hygroma, large low-set ears, a short and flattened nose, and micrognathia. Array comparative genomic hybridization analysis of the placenta revealed the result of arr 5p15.33p15.1 (22,179–18,133,327)×1.0, 7p22.3p15.2 (54,215–25,551,540)×3.0, indicating an 18.11-Mb deletion of 5p (5p15.33–p15.1) and a 22.5-Mb duplication of 7p (7p22.3–p15.2). Cord blood sampling revealed a karyotype of 46, XX, der(5)t(5;7) (p15.1;p15.2)mat.**Conclusion:** Fetuses with 5p deletion syndrome and 7p duplication syndrome may present ventriculomegaly, abnormal skull development, and cystic hygroma on prenatal ultrasound.Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The chromosome 7p duplication syndrome is characterized by dolichocephaly or brachycephaly, large fontanelles, large low-set malformed ears, hypertelorism, down-slanting palpebral fissures,

a high or prominent forehead, a broad or prominent nasal bridge, and micrognathia [1–10]. The critical region for the 7p duplication syndrome has been suggested to be in the segment of 7p21–7p22 [11,12].

The chromosome 5p deletion syndrome, or the cri-du-chat syndrome (OMIM 123450), is characterized by the common features of a high-pitched, monotonous cat cry, microcephaly, broad nasal bridge, epicanthic folds, micrognathia, abnormal dermatoglyphics, growth delay, and psychomotor and mental retardation [13–18]. In the chromosome 5p deletion syndrome, the critical

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

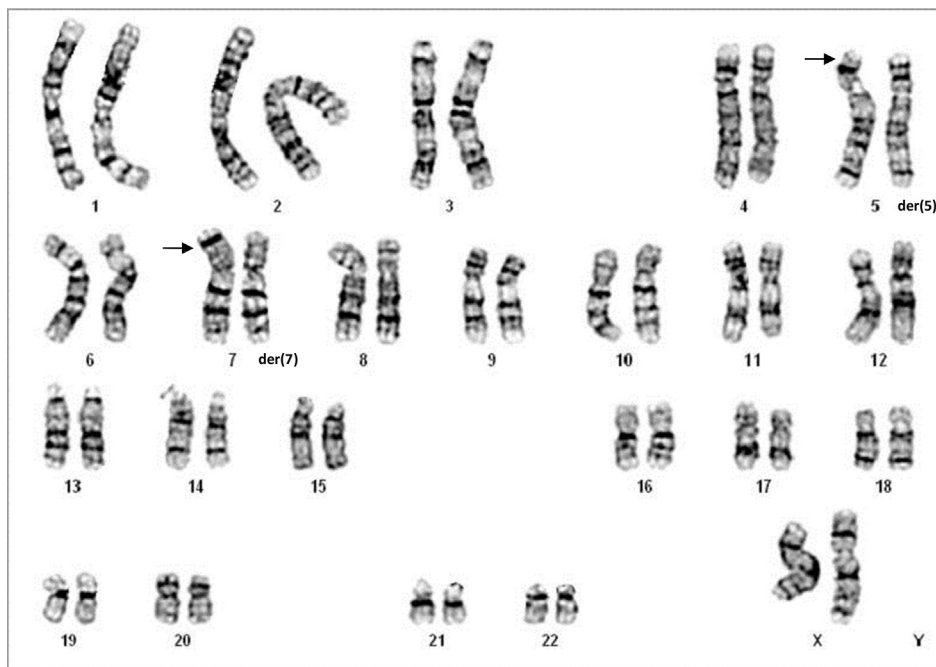


Figure 1. A karyotype of 46,XX,t(5;7)(p15.1;p15.2) in the mother. The arrows indicate the breakpoints. der = derivative.

region for microcephaly has been assigned to be located more proximally to 5p15.31, for dysmorphism and psychomotor retardation in 5p15.2, for cat cry in 5p15.3, and for speech delay in a separate region in 5p15.3 [13,19].

Prenatal diagnosis of concomitant occurrence of chromosome 5p deletion syndrome and chromosome 7p duplication syndrome simply by abnormal fetal ultrasound is very rare. Here, we present such a case with array comparative genomic hybridization (aCGH) characterization.

Case report

A 34-year-old, gravida 2, para 0, woman was referred for amniocentesis at 22 weeks of gestation because of abnormal prenatal ultrasound. The woman had experienced one spontaneous abortion. Her husband was 34 years of age, and there was no family history of congenital malformations. Bilateral ventriculomegaly, an irregular-shaped skull, a nuchal cystic hygroma, and oligohydramnios were noted on fetal ultrasound at 21 weeks of gestation.

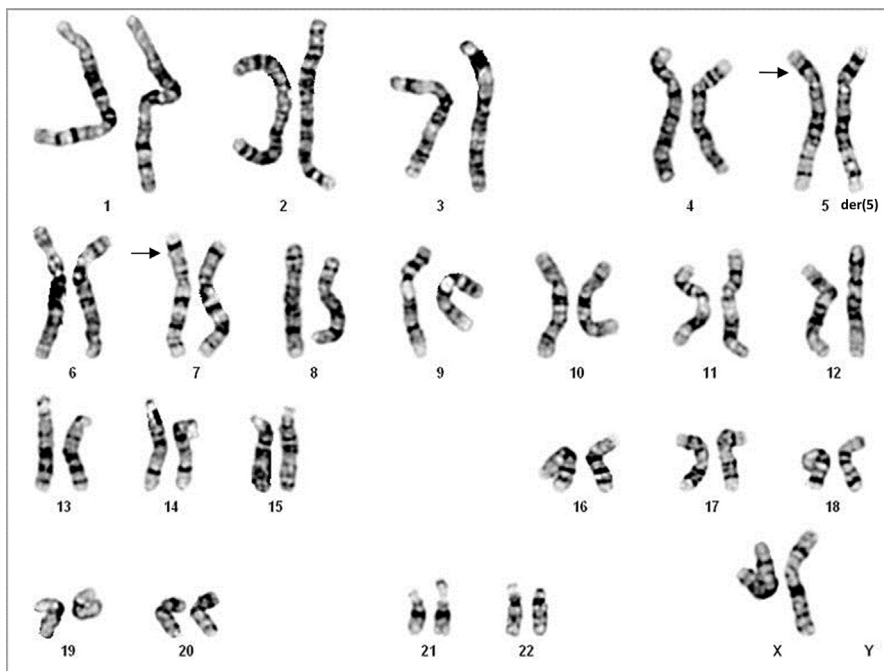


Figure 2. A karyotype of 46,XX,der(5)t(5;7)(p15.1;p15.2) in the fetus. The arrows indicate the breakpoints. der = derivative.

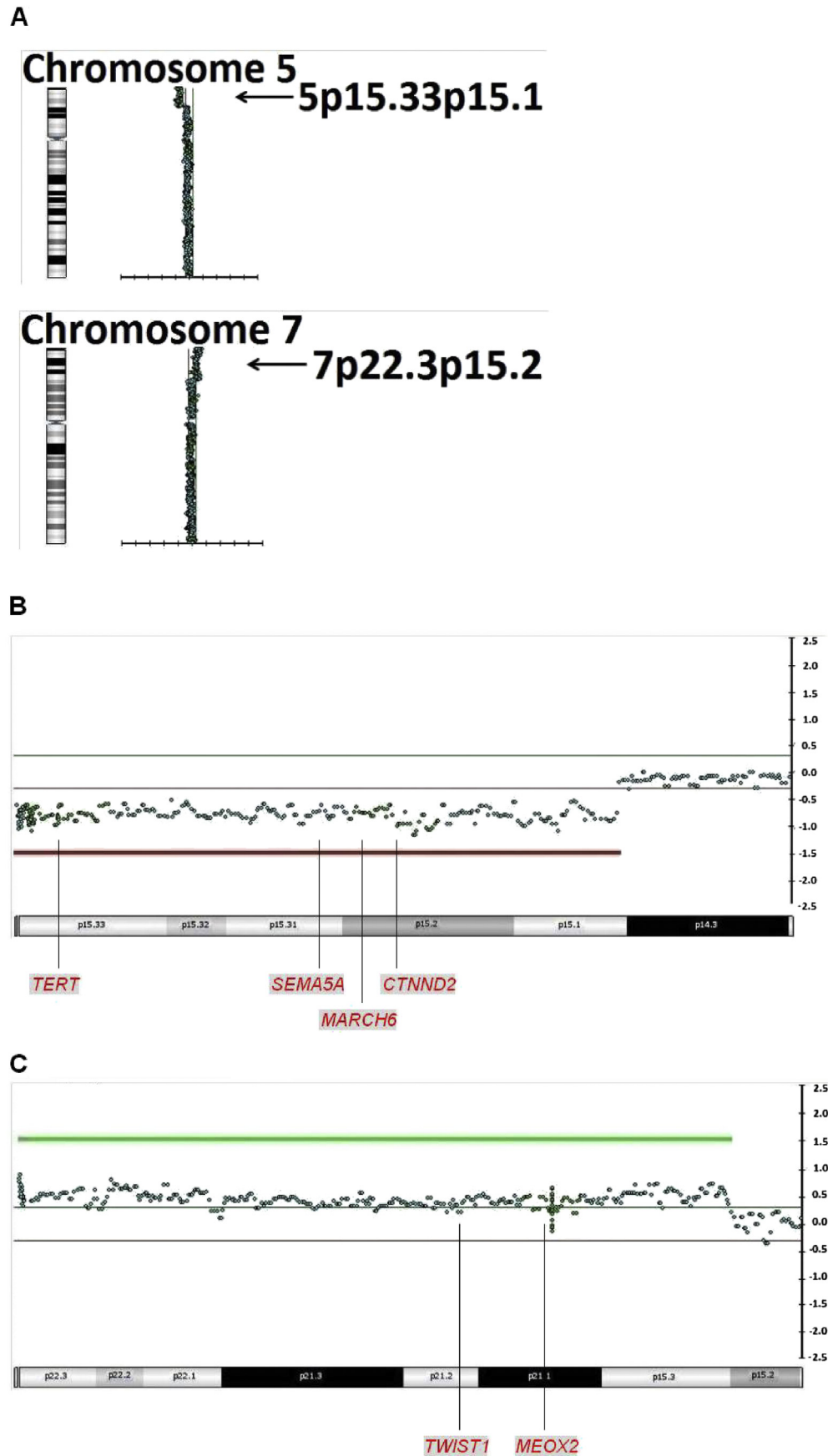


Figure 3. Array comparative genomic hybridization shows an 18.11-Mb deletion of 5p (5p15.33-p15.1) encompassing the genes of *TERT*, *SEMA5A*, *MARCH6*, and *CTNND2*, and a 22.5-Mb duplication of 7p (7p22.3-p15.2) encompassing the genes of *TWIST1* and *MEOX2*. (A) Chromosome zoom-in view; (B) chromosome 5; (C) chromosome 7.

Amniocentesis revealed a derivative chromosome 5 [der(5)] with a distal 5p deletion and an addendum of an extra unknown chromosomal segment at the breakpoint of 5p. Cytogenetic analysis of parental bloods revealed a karyotype of 46,XX,t(5;7)(p15.1;p15.2) (Figure 1) in the mother and a karyotype of 46,XY in the father. The karyotype of the fetus was 46,XX,der(5)t(5;7)(p15.1;p15.2)mat (Figure 2) consistent with partial monosomy 5p (5p15.1→pter) and partial trisomy 7p (7p15.2→pter). A malformed fetus was subsequently delivered with an irregular-shaped skull, a large anterior fontanelle, brachycephaly, hypertelorism, a high and prominent forehead, a large nuchal cystic hygroma, large low-set ears, a short and flattened nose, and micrognathia. aCGH analysis of the placenta revealed the result of arr 5p15.33p15.1 (22,179–18,133,327) ×1.0, 7p22.3p15.2 (54,215–25,551,540) ×3.0, indicating an 18.11-Mb deletion of 5p (5p15.33–p15.1) and a 22.5-Mb duplication of 7p (7p22.3–p15.2) (Figure 3). Cord blood sampling revealed a karyotype of 46,XX,der(5)t(5;7) (p15.1;p15.2)mat.

Discussion

The peculiar aspect of the present case is the association of chromosome 5p deletion syndrome and chromosome 7p duplication syndrome with bilateral ventriculomegaly, irregular-shaped skull, and nuchal cystic hygroma on prenatal ultrasound. We previously reported partial monosomy 5p (5p14.1→pter) and partial monosomy 14q (14q32.31→qter) associated with fetal nuchal edema, microcephaly, intrauterine growth restriction, and single umbilical artery [16]. Chromosome 5p deletion syndrome has been reported to be associated with central nervous system (CNS) abnormalities such as arachnoid cyst, encephalocele, agenesis of the corpus callosum, Dandy–Walker malformation, hydrocephalus, cerebellar hypoplasia, and vermian hypoplasia [15]. In addition to severe psychomotor retardation, hypotonia, skull anomalies with dolichocephaly or microbrachycephaly, large anterior fontanelle and facial dysmorphism, chromosome 7p duplication syndrome may occasionally manifest choanal atresia/stenosis, cardiovascular anomalies, and skeletal, gastrointestinal, and genital defects [20]. We previously reported partial trisomy 7p (7p15.3→pter) and partial monosomy 13q (13q33.3→qter) associated with Dandy–Walker malformation, abnormal skull development, and microcephaly [10]. The present case additionally adds ventriculomegaly and cystic hygroma to the prenatal ultrasound findings of concomitant distal 5p deletion and distal 7p duplication.

The present case had a 22.5-Mb duplication of 7p (7p22.3–p15.2) encompassing the genes of *TWIST1* and *MEOX2*. The present case had an irregular-shaped skull, a large fontanelle and brachycephaly, which are characteristic features of partial trisomy 7p syndrome. In the 7p duplication syndrome, the skeletal abnormalities including abnormal skull development, a large fontanelle and prominent sutures are related to the involvement of duplication of the genes of *TWIST1* and *MEOX2* [5,6,8,9,11,21]. The *TWIST1* gene encodes a transcription factor containing a basic helix–loop–helix domain. The increased gene dosage effect of the *TWIST1* gene may cause delayed closure of the large fontanelles and abnormal skull development, whereas mutations or haploinsufficiency of the *TWIST1* gene will cause craniosynostosis [8,11]. The present case also had ventriculomegaly and cystic hygroma. In a review of 37 cases with partial trisomy 7p, Kozma et al [21] found that 19% (7/37) had hydrocephalus and 35% (13/37) had other CNS anomalies. Witters et al [22] reported prenatal diagnosis of partial trisomy 7p (7p22.1→pter) and partial monosomy 18p (18p11.22→pter) in a fetus with nuchal edema. Chen et al [23] reported Dandy–Walker variant in a boy with partial trisomy 7p (7p21.2→pter) and partial monosomy 12q (12q24.33→qter).

The present case had an 18.11-Mb deletion of 5p (5p15.33–p15.1) encompassing the genes of *TERT*, *SEMA5A*, *MARCH6*, and *CTNND2*. *TERT* and *SEMA5A* may be responsible for some of the features of cri-du-chat syndrome, *CTNND2* is responsible for mental retardation in cri-du-chat syndrome, and *MARCH6* may play a role in the high-pitched cry of individuals with cri-du-chat syndrome [15,18].

In summary, prenatal diagnosis and molecular cytogenetic characterization of concomitant 5p deletion syndrome and 7p duplication syndrome associated with abnormal ultrasound findings is presented. It is suggested that prenatal diagnosis of multiple anomalies of skull, brain, and neck should alert the occurrence of fetal chromosomal abnormalities.

Conflicts of interest

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

Acknowledgments

This work was supported by research grants MOST-103-2314-B-195-010 and MOST-104-2314-B-195-009 from the Ministry of Science and Technology and MMH-E-105-04 from Mackay Memorial Hospital, Taipei, Taiwan.

References

- [1] Milunsky JM, Wyandt HE, Milunsky A. Emerging phenotype of duplication (7p): a report of three cases and review of the literature. *Am J Med Genet* 1989;33:364–8.
- [2] Kleczkowska A, Decock P, van den Berghe H, Fryns JP. Borderline intelligence and discrete craniofacial dysmorphism in an adolescent female with partial trisomy 7p due to a *de novo* tandem duplication 7 (p15.1→p21.3). *Genet Couns* 1994;5:393–7.
- [3] Lurie IW, Schwartz MF, Schwartz S, Cohen MM. Trisomy 7p resulting from isochromosome formation and whole-arm translocation. *Am J Med Genet* 1995;55:62–6.
- [4] Pallotta R, Dalprà L, Fusilli P, Zuffardi O. Further delineation of 7p trisomy. Case report and review of literature. *Ann Génét* 1996;39:152–8.
- [5] Reish O, Berry SA, Dewald G, King RA. Duplication of 7p: further delineation of the phenotype and restriction of the critical region to the distal part of the short arm. *Am J Med Genet* 1996;61:21–5.
- [6] Cai T, Yu P, Tagle DA, Xia J. Duplication of 7p21.2→pter due to maternal 7p;21q translocation: implications for critical segment assignment in the 7p duplication syndrome. *Am J Med Genet* 1999;86:305–11.
- [7] Arens YHJM, Toutain A, Engelen JJM, Offermans JPM, Hamers AJH, Schrandt JJP, et al. Trisomy 7p: report of two patients and literature review. *Genet Couns* 2000;11:347–54.
- [8] Stankiewicz P, Thiele H, Baldermann C, Kruger A, Giannakidis I, Dörr S, et al. Phenotypic findings due to trisomy 7p15.3-pter including the *TWIST* locus. *Am J Med Genet* 2001;103:56–62.
- [9] Papadopoulou E, Sifakis S, Sarri C, Gyftodimou J, Liehr T, Mrasek K, et al. A report of pure 7p duplication syndrome and review of the literature. *Am J Med Genet* 2006;140A:2802–6.
- [10] Chen C-P, Chen M, Su Y-N, Tsai F-J, Chern S-R, Hsu C-Y, et al. Prenatal diagnosis and molecular cytogenetic characterization of *de novo* partial trisomy 7p (7p15.3→pter) and partial monosomy 13q (13q33.3→qter) associated with Dandy–Walker malformation, abnormal skull development and microcephaly. *Taiwan J Obstet Gynecol* 2010;49:320–6.
- [11] Mégarbané A, Le Lorc HM, Elghezal H, Joly G, Gosset P, Souraty N, et al. Pure partial 7p trisomy including the *TWIST*, *HOXA*, and *GLI3* genes. *J Med Genet* 2001;38:178–82.
- [12] Cox H, Stewart H, Hall L, Donnai D. Phenotypic spectrum of interstitial 7p duplication in mosaic and nonmosaic forms. *Am J Med Genet* 2002;109:306–10.
- [13] Cerruti Mainardi P, Perfumo C, Calì A, Coucourde G, Pastore G, Cavani S, et al. Clinical and molecular characterization of 80 patients with 5p deletion: Genotype–phenotype correlation. *J Med Genet* 2001;38:151–8.
- [14] Chen C-P, Lee C-C, Chang T-Y, Town D-D, Wang W. Prenatal diagnosis of mosaic distal 5p deletion and review of the literature. *Prenat Diagn* 2004;24:50–7.
- [15] Chen C-P, Huang M-C, Chen Y-Y, Chern S-R, Wu P-S, Su J-W, et al. Cri-du-chat (5p-) syndrome presenting with cerebellar hypoplasia and hypospadias: prenatal diagnosis and aCGH characterization using uncultured amniocytes. *Gene* 2013;524:407–11.
- [16] Chen C-P, Fu C-H, Chern S-R, Wu P-S, Su J-W, Su Y-N, et al. *De novo* unbalanced translocation resulting in monosomy for distal 5p (5p14.1→pter) and 14q (14q32.31→qter) associated with fetal nuchal edema, microcephaly, intrauterine

- growth restriction and single umbilical artery: Prenatal diagnosis and molecular cytogenetic characterization. *Taiwan J Obstet Gynecol* 2013;52:401–6.
- [17] Cerruti Mainardi P. Cri du Chat syndrome. *Orphanet J Rare Dis* 2006;1:33.
 - [18] Nguyen JM, Qualmann KJ, Okashah R, Reilly A, Alexeyev MF, Campbell DJ. 5p deletions: Current knowledge and future directions. *Am J Med Genet C Semin Med Genet* 2015;169:224–38.
 - [19] Van Buggenhout GJCM, Pijkels E, Holvoet M, Schaap C, Hamel BCJ, Fryns JP. Cri du chat syndrome: changing phenotype in older patients. *Am J Med Genet* 2000;90:203–15.
 - [20] Alfardan J, Brown K, Gessner J, Lunt B, Schärer G. Small duplication of chromosome (7)(p22.1p22.2) and consideration of a dup 7p syndrome critical region. *Clin Dysmorphol* 2011;20:217–21.
 - [21] Kozma C, Haddad BR, Meck JM. Trisomy 7p resulting from 7p15;9p24 translocation: report of a new case and review of associated medical complications. *Am J Med Genet* 2000;91:286–90.
 - [22] Witters I, Moerman P, Fryns JP. Maternal serum positive triple test screening in a fetus with partial distal trisomy 7p associated with maternal 7p;18p translocation. *Genet Couns* 2002;13:65–8.
 - [23] Chen C-P, Lin S-P, Lin C-C, Li Y-C, Hsieh L-J, Huang J-K, et al. Spectral karyotyping and fluorescence *in situ* hybridization of *de novo* partial trisomy of 7p (7p21.2→pter) and partial monosomy 12q (12q24.33→qter). *Genet Couns* 2006;17:57–63.