

Case Report

Partial monosomy 13q (13q21.32 → qter) and partial trisomy 8p (8p12 → pter) presenting with anencephaly and increased nuchal translucency: array comparative genomic hybridization characterization

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Abstract

Objective: To present array comparative genomic hybridization (aCGH) characterization of partial monosomy 13q (13q21.32 → qter) and partial trisomy 8p (8p12 → pter) presenting with anencephaly and increased nuchal translucency (NT).

Case Report: A 34-year-old primigravid woman was referred to the hospital at 12 weeks of gestation for termination of the pregnancy because of major structural abnormalities of the fetus. Prenatal ultrasound revealed a malformed fetus with anencephaly and an increased NT thickness of 5 mm at 12 weeks of gestation. Cytogenetic analysis of the fetus revealed a derivative chromosome 13. The mother was subsequently found to carry a balanced reciprocal translocation between 8p12 and 13q21. Bacterial artificial chromosome-based aCGH using fetal DNA demonstrated partial trisomy 8p and partial monosomy 13q [arr cgh 8p23.3p12 (RP11-1150M5 → RP11-1145H12)×3, 13q21.32q34 (RP11-326B4 → RP11-450H16)×1]. Oligonucleotide-based aCGH showed a 36.7-Mb duplication of distal 8p and a 48.4-Mb deletion of distal 13q. The fetal karyotype was 46,XY,der(13) t(8;13)(p12;q21.32)mat. The maternal karyotype was 46,XX,t(8;13)(p12;q21.32).

Conclusion: The 13q deletion syndrome can be associated with neural tube defects and increased NT in the first trimester. Prenatal sonographic detection of neural tube defects should alert chromosomal abnormalities and prompt cytogenetic investigation, which may lead to the identification of an unexpected parental translocation involving chromosomal segments associated with neural tube development.

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Keywords: Chromosome 8; Chromosome 13; Monosomy 13q; Neural tube defects; Nuchal translucency; Trisomy 8p

Introduction

The 13q deletion syndrome, or 13q- syndrome, is a rare condition that presents with widely varying phenotypes, including moderate-to-severe mental retardation; developmental delay; and growth retardation; central nervous system anomalies, such as meningocele, encephalocele, anencephaly,

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Dandy-Walker malformation (DWM), corpus callosum agenesis, and holoprosencephaly (HPE); craniofacial abnormalities, such as microcephaly, brachycephaly, trigonocephaly, hypertelorism, microphthalmia, a broad nasal bridge, micrognathia, and facial cleft; hand and foot anomalies, such as thumb aplasia or hypoplasia, digital anomalies, and talipes; and other disorders, such as lung hypoplasia, intestinal malrotation, bowel atresia, and ambiguous genitalia [1–9]. We previously described the application of array comparative genomic hybridization (aCGH) in the prenatal diagnosis of aneuploidy [10,11]. Here, we report aCGH characterization of partial monosomy 13q (13q21.32→qter) and partial trisomy 8p (8p12→pter) presenting with anencephaly and increased nuchal translucency (NT) in the first trimester.

Case report

A 34-year-old primigravid woman was referred to the hospital at 12 weeks of gestation for termination of pregnancy because of major structural abnormalities of the fetus. The parents were nonconsanguineous and healthy. The father was aged 34 years. The mother reported no illness or recent infections. She neither had any history of prenatal exposure to teratogenic agents nor any family history of congenital malformations. Prenatal ultrasound at 12 weeks of gestation revealed a malformed fetus with anencephaly and an increased NT thickness of 5 mm. The pregnancy was subsequently terminated and a 6-g anencephalic fetus was delivered (Fig. 1). The external genitalia were ambiguous. Cytogenetic analysis of the fetal umbilical cord fibroblasts revealed a derivative chromosome 13 or der(13) (Fig. 2).

Subsequent parental karyotyping revealed that the mother carried a balanced reciprocal translocation between 8p12 and 13q21 (Fig. 3). The paternal karyotype was normal. Bacterial artificial chromosome-based aCGH using fetal DNA demonstrated partial trisomy 8p and partial monosomy 13q [arr cgh 8p23.3p12 (RP11-1150M5→RP11-1145H12)×3, 13q21.32q34 (RP11-326B4→RP11-450H16)×1] (Fig. 4). Oligonucleotide-based aCGH showed a 36.7-Mb duplication of distal 8p and a 48.4-Mb deletion of distal 13q (Fig. 5). The maternal karyotype was 46,XX,t(8;13) (p12;q21.32). The fetal karyotype was 46,XY,der(13)t(8;13) (p12;q21.32)mat.

Discussion

The present case was associated with increased NT in the first trimester. The 13q deletion syndrome has been associated with increased NT [7], nuchal edema [12], and cystic hygroma [13]. Proposed mechanisms for the increase in NT thickness include altered composition of the extracellular matrix, abnormalities of the heart and great arteries, and disturbed or delayed lymphatic development [14]. The present case had haploinsufficiency of *COL4A1* and *COL4A2*, which are located on chromosome 13q34 and encode collagen type IV α -1 chain and α -2 chain, respectively. Collagen type IV is associated with laminin, entactin, and heparan sulfate proteoglycans to form the sheet-like basement membranes that separate epithelium from connective tissue. Increased NT is well known to be a first-trimester sonographic marker of trisomy 13 [15]. von Kaisenberg et al [16] suggested that increased NT in trisomy 13 fetuses is because of alteration in the composition of collagen type IV.

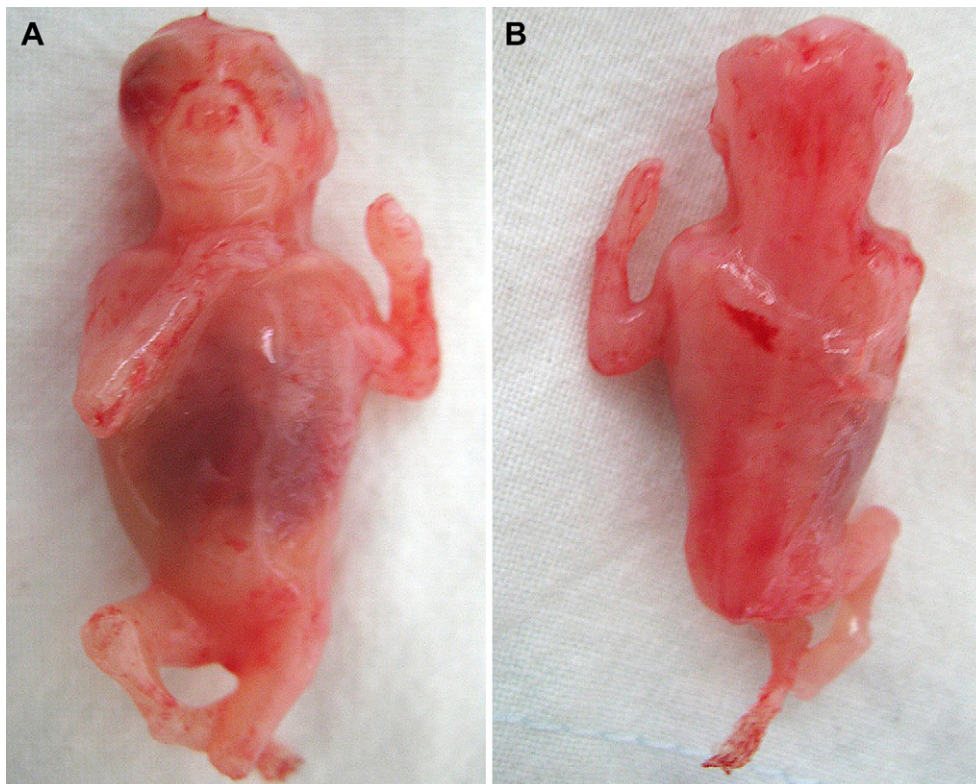


Fig. 1. (A) Anterior view and (B) posterior view of the fetus.

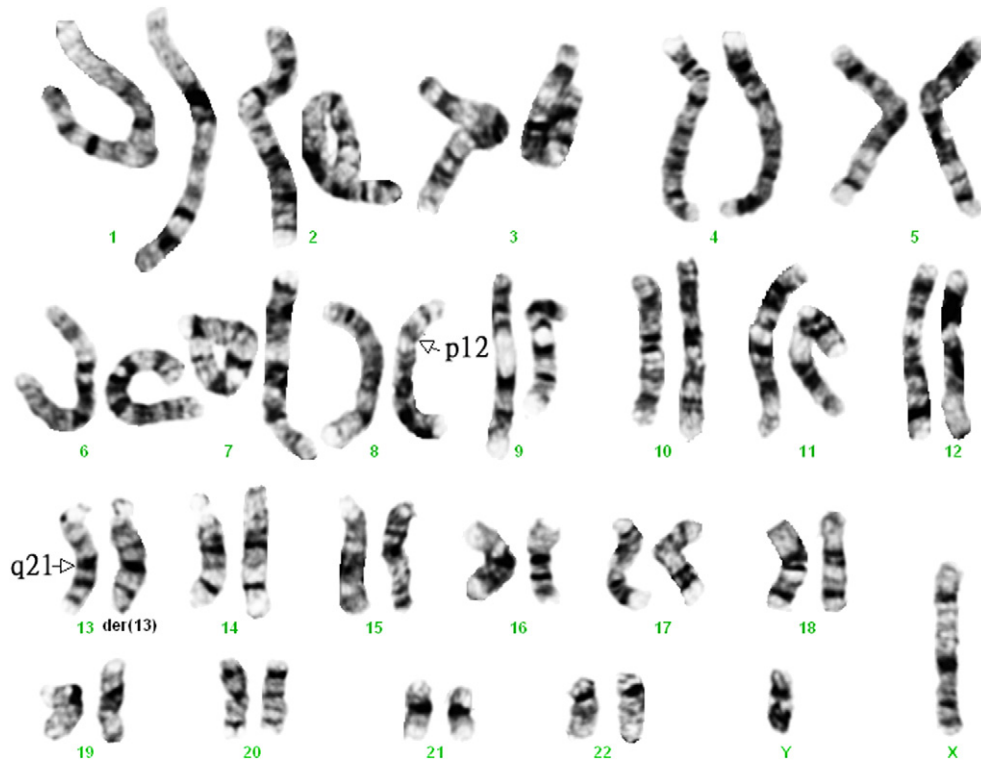


Fig. 2. G-banded karyotype of the fetus shows a derivative chromosome 13 or der(13). The karyotype is 46,XY,der(13)t(8;13)(p12;q21.32)mat. The arrows indicate the breakpoints on normal chromosomes.

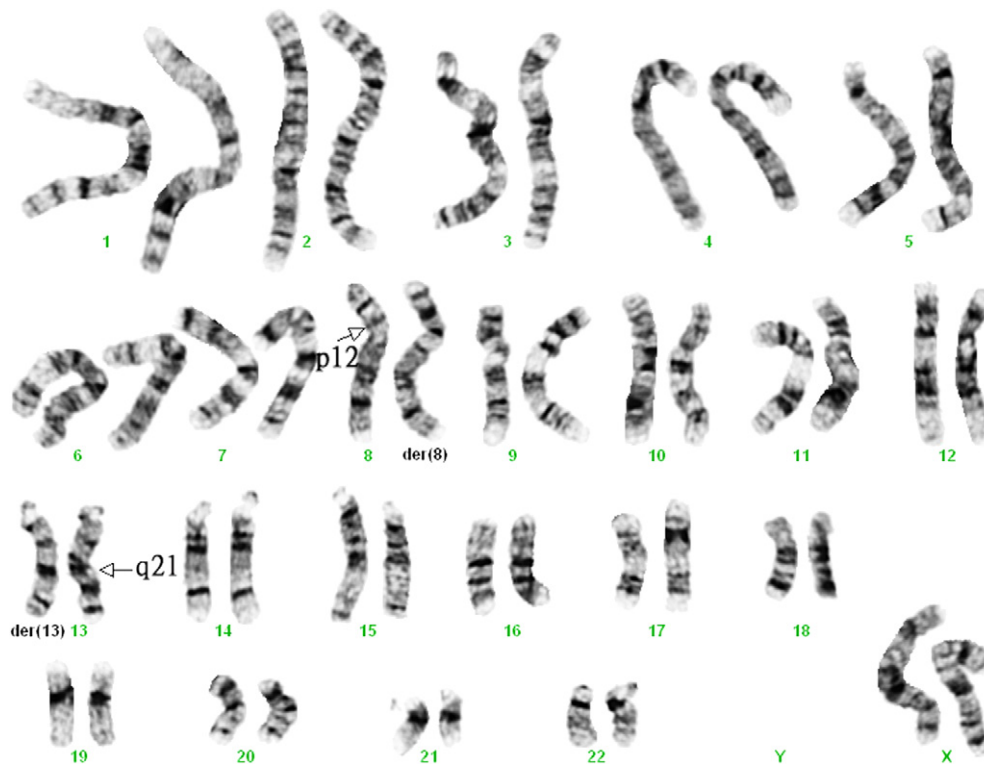


Fig. 3. G-banded karyotype of the mother shows a der(13) and a der(8). The karyotype is 46,XX,t(8;13)(p12;q21.32). The arrows indicate the breakpoints on normal chromosomes.

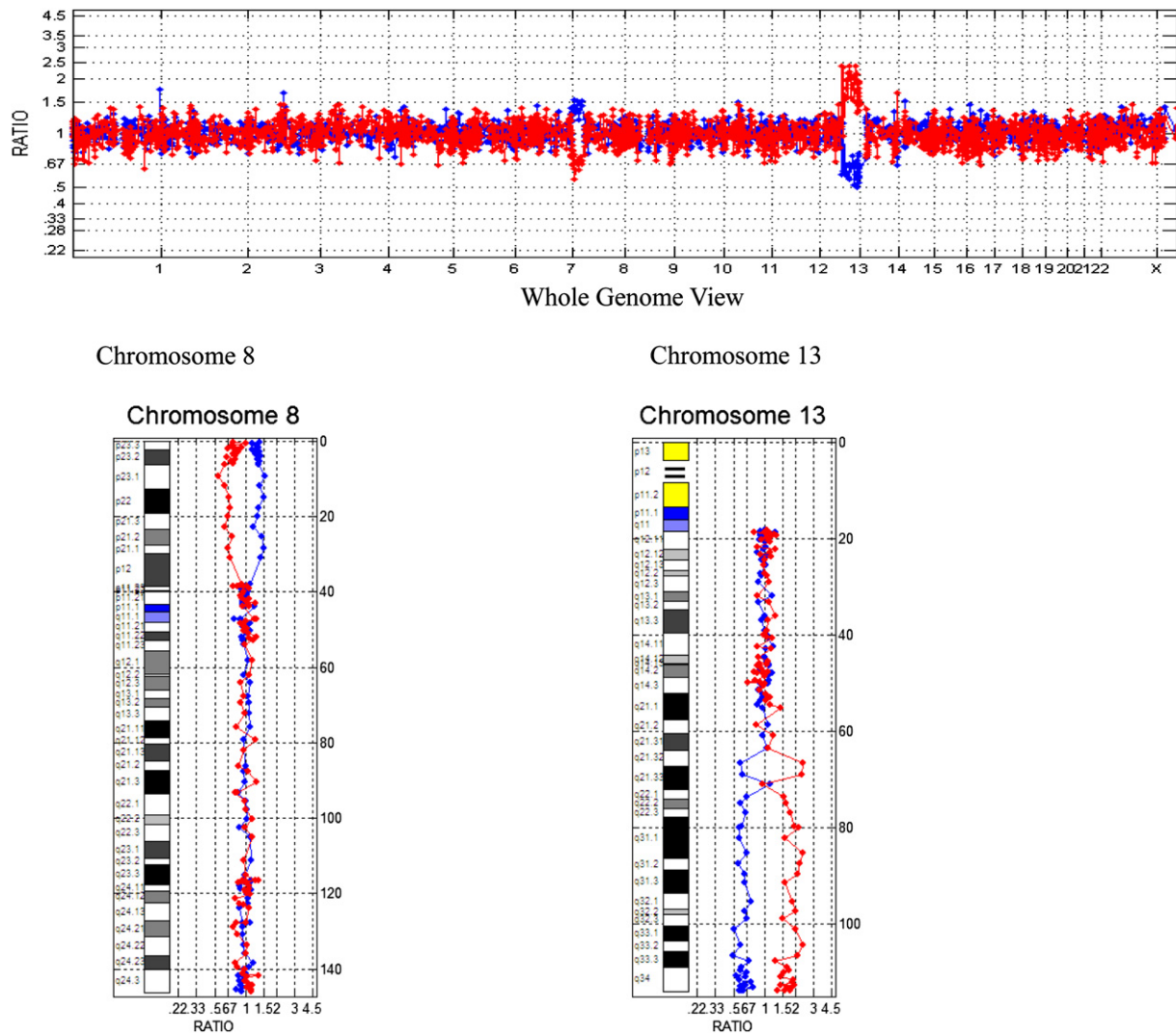


Fig. 4. BAC-based aCGH using CMDX BAC-based aCGH CA2500 chips (CMDX, Irvine, CA, USA) shows partial trisomy 8p [arr cgh 8p23.3p12 (RP11-1150M5→RP11-1145H12)×3] and partial monosomy 13q [arr cgh 13q21.32q34 (RP11-326B4→RP11-450H16)×1]. BAC = bacterial artificial chromosome; aCGH = array comparative genomic hybridization.

Overexpression of *COL4A1* and *COL4A2* can cause altered composition of the extracellular matrix. The present case additionally provides evidence that a decreased gene dosage effect of *COL4A1* and *COL4A2* in the 13q deletion syndrome can also be associated with increased NT.

The reported neural tube defects (NTDs) associated with del(13q) and r(13) include spina bifida, encephalocele, anencephaly, atelencephaly, exencephaly, and aprosencephaly [17]. The present case was associated with anencephaly and a deletion of 13q21.32→qter encompassing the critical region of 13q31.3→q33.1 for NTDs. Ballarati et al [6] suggested that dosage-sensitive genes proximal to 13q33.2 may be involved in NTDs. Kirchhoff et al [9] refined the smallest deletion region linked to meningocele/encephalocele as 13q31.3-qter and the smallest deletion region linked to DWM, corpus callosum, and NTDs taken together as 13q32.3-q33.1. Brown et al [3] had previously defined 13q32 as the critical deletion region associated with the 13q deletion syndrome, including brain malformations. Within this 13q32 critical region, two *ZIC* genes,

ZIC2 and *ZIC5*, are located. *ZIC5* maps 16-kb proximally to *ZIC2*. The *ZIC* is a zinc finger protein that is involved in the mechanism for the development of the cerebellum and human malformations, such as DWM, HPE, NTDs and heterotaxy [18]. *ZIC* gene family members are the vertebrate homologs of the *Drosophila* odd-paired gene. The *ZIC2* gene is well known to be responsible for human HPE type 5 [19]. In a study of screening 192 NTD patients for mutations in *ZIC2*, Brown et al [20] did not find *ZIC2* mutations but did find a possible association of NTDs with a polyhistidine tract polymorphism in the *ZIC2* gene. However, several studies found no supportive evidence for an association between *ZIC2* and NTDs [21,22]. On the other hand, an association between NTDs and *ZIC5* has been noted. Nakata et al [23] found that *Zic5* mediated neural crest development in *Xenopus*. Inoue et al [24] found that *Zic5*-deficient mice exhibited NTDs and malformed neural-crest-derived facial bones. In addition, the *zic2* and *zic5* gene pair has been shown to play an important role in regulating midbrain growth and developing neural tube in zebrafish [25,26].

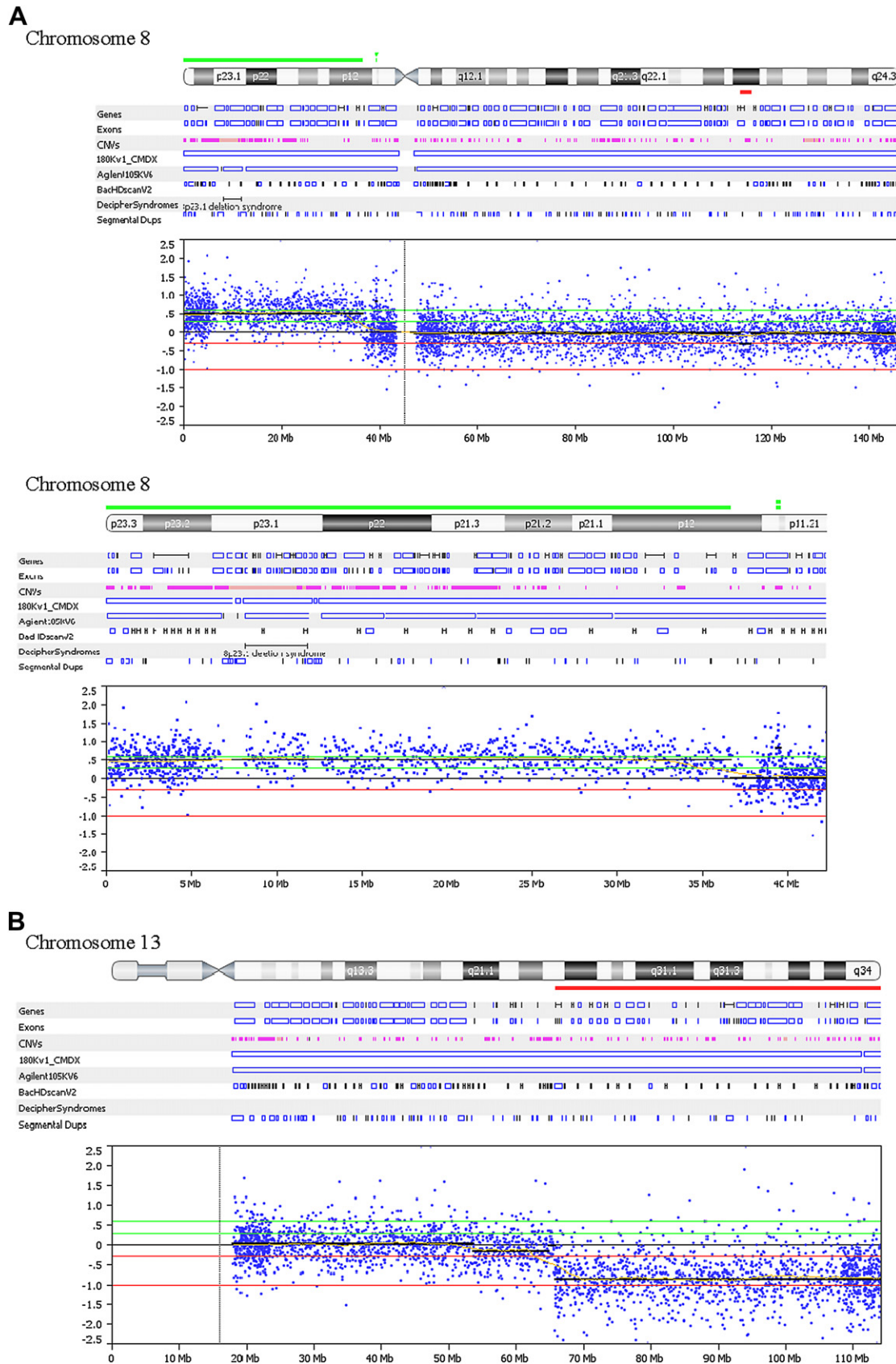


Fig. 5. Oligonucleotide-based aCGH using Oligo HD Scan (CMDX, Irvine, CA, USA) shows (A) a 36.7-Mb duplication in 8p23.3→8p12 [arr cgh 8p23.3p12 (0–36,666,008)×3] and (B) a 48.4-Mb deletion of 13q21.32→13q34 [arr cgh 13q21.32q34 (65,740,620–114,142,980)×1]. aCGH = array comparative genomic hybridization

Chromosome 13

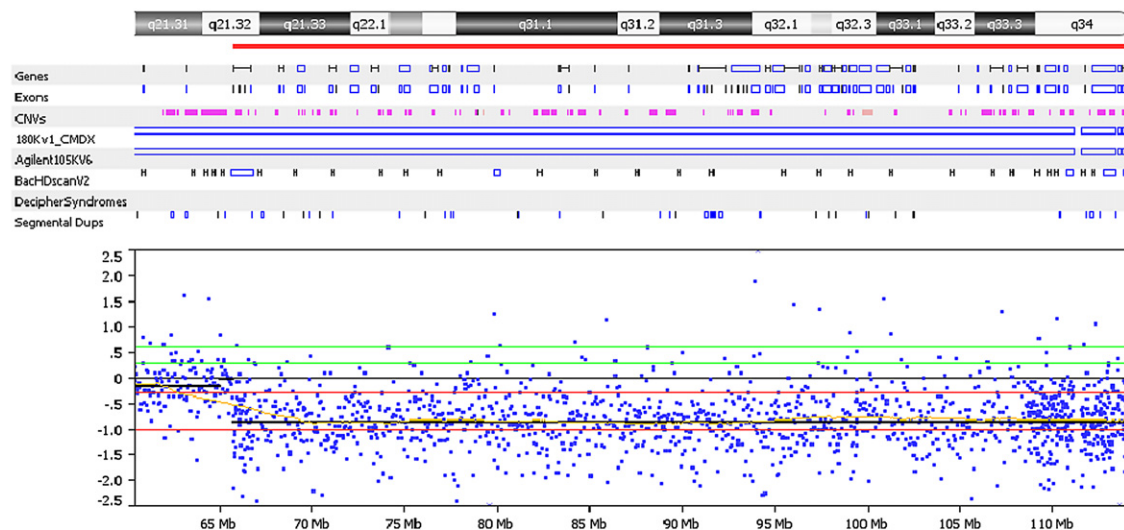


Fig. 5. (Continued)

The present case was also associated with partial trisomy 8p (8p12→pter). Patients with trisomy 8p and multiple congenital anomaly syndrome have been reported sporadically. The reported major brain malformations associated with trisomy 8p include DWM, dilation of the third ventricle, and corpus callosum agenesis [27–30]. However, NTDs have not previously been described in association with dup(8p) [17]. Partial trisomy 8p may be associated with nuchal cystic hygroma. Frants et al [31] reported a fetus with partial monosomy 7q (7q34→qter) and partial trisomy 8p (8p12→pter) with marked growth retardation, facial cleft, and posterior nuchal cystic hygroma.

In conclusion, prenatal sonographic detection of NTDs should alert chromosomal abnormalities and prompt cytogenetic investigation, which may lead to the identification of an unexpected parental translocation involving chromosomal segments associated with neural tube development. The information acquired through perinatal studies is helpful for both genetic counseling and investigation in the following pregnancies.

Acknowledgments

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