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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial duplication of 14q (14q31.3→q32.12) associated with abnormal maternal serum biochemistry

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Abstract

Objective: To present prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial duplication of 14q (14q31.3→q32.12) in a pregnancy associated with abnormal maternal serum biochemistry.

Case Report: A 19-year-old woman underwent amniocentesis in the second trimester because of abnormal maternal serum biochemistry. Her husband was 33 years old. At 16 weeks of gestation, the levels of α-fetoprotein, unconjugated estriol, total β-human chorionic gonadotropin, and inhibin A were 0.8 multiples of median (MoM), 0.84 MoM, 3.06 MoM, and 1.14 MoM, respectively, consistent with a positive trisomy 21 risk of 1/269. Results of an amniocentesis revealed a small *de novo* interstitial duplication of 14q encompassing 14q31-q32.1. An array comparative genomic hybridization analysis detected a 6.6-Mb duplication at chromosome 14q31.3-q32.12. Results of a fluorescence *in situ* hybridization analysis showed a direct duplication of interstitial 14q. The karyotype was 46,XY,dup(14) (q31.3q32.12). Level II ultrasound was unremarkable. The parents decided to continue the pregnancy. A 3805-g healthy male baby was delivered at 39 weeks of gestation. When examined at 6 months of age, the neonate was normal in growth and psychomotor development with no apparent phenotypic abnormalities, although long-term follow-ups are required.

Conclusion: Abnormal maternal serum biochemistry in the second trimester may be a distinctive prenatal feature in pregnancy associated with fetal chromosome 14q duplication.

Keywords: 14q31.3→q32.12; duplication 14q; interstitial duplication; maternal serum biochemistry; prenatal diagnosis

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Introduction

Partial trisomy 14q with a duplication of 14q (14q22 → q32) has been associated with a distinct 14q duplication syndrome characterized by craciofacial dysmorphisms of high forehead, wide sutures and fontanels, sparse hair and eyebrows, broad nasal bridge, hypertelorism, thin upper lip, abnormal ears, broad mouth and micrognathia, developmental delay, mild mental retardation, spasticity, hyperreflexia, premature puberty, and primordial short stature [1−5].

Cases of partial trisomy 14q with a duplication of 14q31 → qter are rare and present only minor anomalies of an asymmetric face, frontal bossing, low-set and dysplastic ears, hypertelorism, sparse eyebrows and lashes, prominent nasal bridge, small mandible, growth retardation, and moderate mental retardation [6−13]. Herein, we present prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial duplication of 14q (14q31.3 → q32.12) in a pregnancy associated with abnormal maternal serum biochemistry but without apparent phenotypic abnormalities. To our knowledge, such a case has not previously been described.

Case report

A 19-year-old, gravida 2, para 1, woman underwent second-trimester screening for chromosome abnormalities using maternal serum biochemistry at 16 weeks of gestation. Her husband was 33 years old. The levels of α-fetoprotein (AFP), unconjugated estriol (uE3), total β-human chorionic gonadotrophin (β-hCG), and inhibin-A were 0.8 multiples of median (MoM), 0.84 MoM, 3.06 MoM, and 1.14 MoM, respectively, consistent with a positive trisomy 21 risk of 1/269. At 18 weeks of gestation, she underwent amniocentesis, which revealed a small interstitial duplication of 14q encompassing 14q31-q32.1 (Fig. 1). Prenatal ultrasound findings were unremarkable. A repeated amniocentesis was performed at 20 weeks of gestation. Oligonucleotide-based array comparative genomic hybridization using CytoChip Oligo Array (BlueGnome, Cambridge, UK) on uncultured amniocytes detected a 6.6-Mb duplication at chromosome 14q31.3-q32.12, or arr cgh 14q31.3q32.12 (84,238,307−90,839,109) × 3 (UCSC hg18, NCBI build 36, March 2006) (Fig. 2). The parental karyotypes were normal. For fluorescence *in situ* hybridization (FISH) determination of the orientation of the duplication of the chromosome 14 [dup(14)], the bacterial artificial chromosome (BAC) clone probes mapping the genomic region of 14q31.3-q32.1 were used. The BAC clone probes RP11-35P13 (85,596,133−85,731,472) (UCSC hg18, NCBI build 36) (green spectrum) at 14q31.3 and RP11-99C24 (89,927,464−90,094,722) (red spectrum) at 14q32.11 were used to determine the orientation of the duplication. A FISH analysis showed an orientation of green−red−green−red (Fig. 3), consistent with a direct duplication of interstitial 14q. Conventional cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XY,dup(14)(q31.3q32.12) (Fig. 1). Level II ultrasound was unremarkable. The parents opted to continue the pregnancy. At 39 weeks of gestation, a healthy male baby was delivered with a body weight of 3805 g (85th centile), a body length of 51 cm (85th centile), and a head circumference of 36 cm (85th centile). There was no dysmorphism. Ultrasound examinations of internal organs showed normal findings. When examined at 6 months of age, he was normal in growth and psychomotor development with no apparent phenotypic abnormalities, although long-term follow-ups are required.

Discussion

Abnormal maternal serum biochemistry tests in the first or second trimester may result in incidental detection of rare fetal chromosomal abnormalities [14−16]. The present pregnant woman was 19 years old. She underwent amniocentesis because of a positive screen risk of 1/269 for trisomy 21 calculated by relatively low levels of AFP and uE3, and an

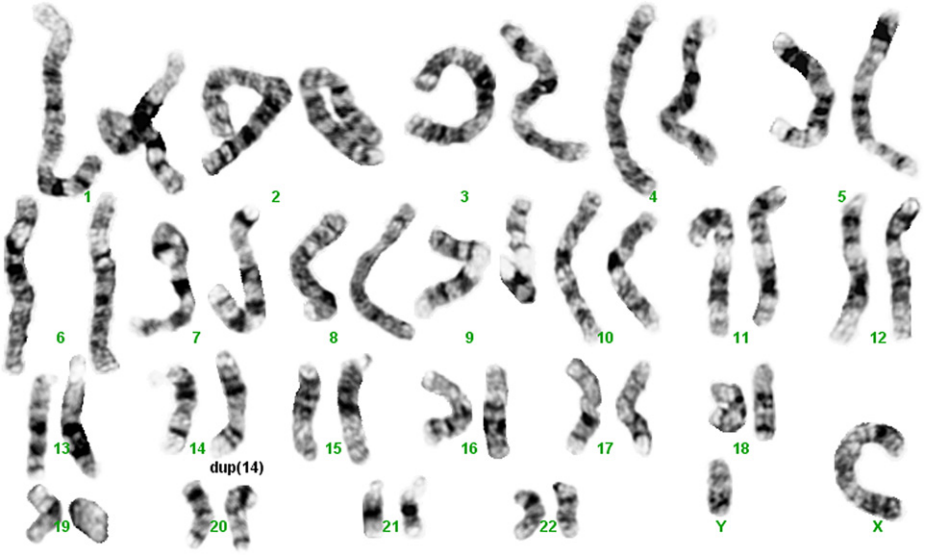

Fig. 1. A karyotype of 46,XY,dup(14)(q31.3q32.12).

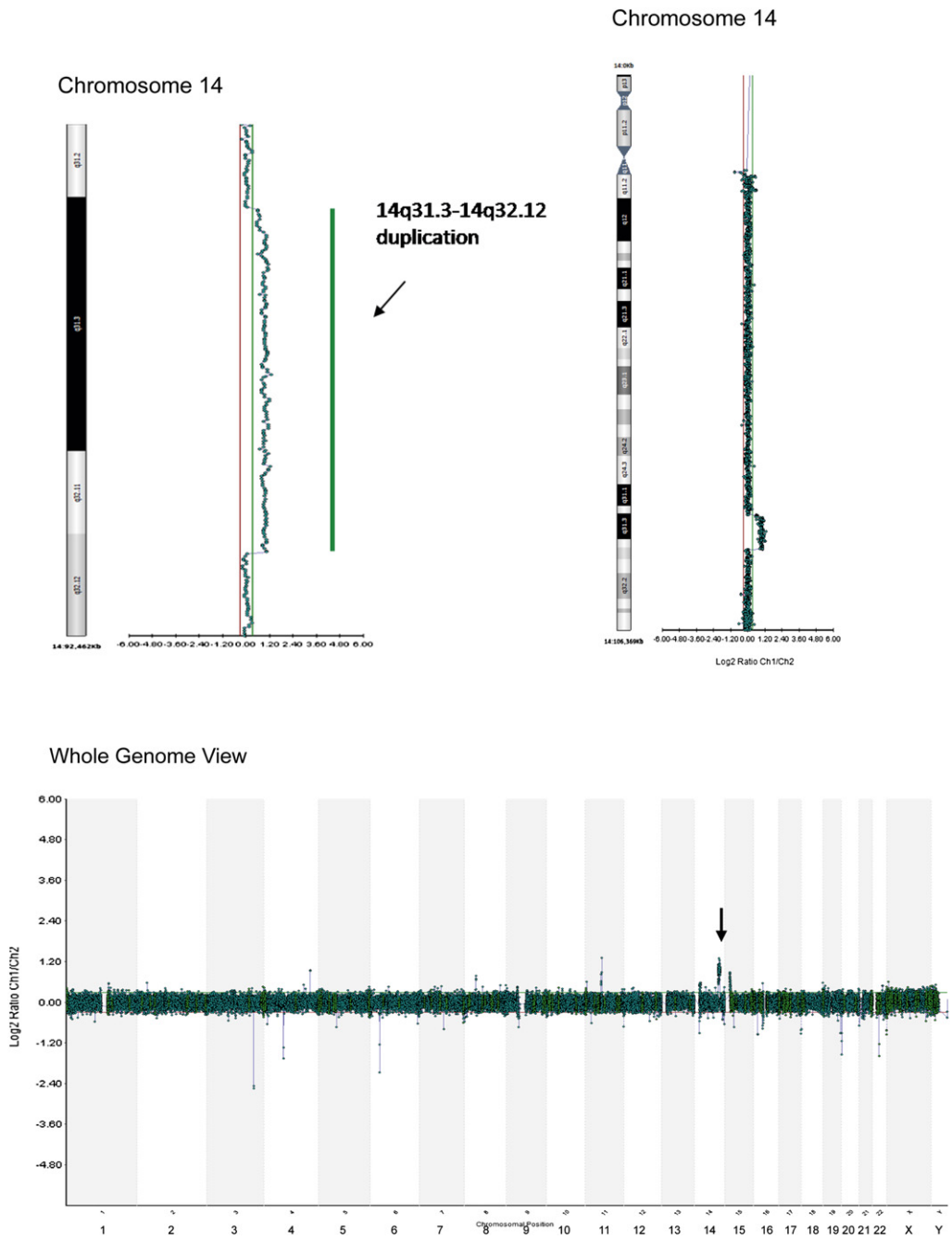

Fig. 2. Oligonucleotide-based array comparative genomic hybridization on uncultured amniocytes shows a 6.6-Mb duplication at 14q31.3-q32.12 (arrow).

abnormally high level of β-hCG. The present case shows that fetuses with an interstitial duplication of 14q may present abnormal maternal serum biochemistry in the second trimester, and suggests that abnormal maternal serum biochemistry may be a distinctive prenatal feature in pregnancy associated with fetal chromosome 14q duplication.

Our case is the first report of a *de novo* tandem duplication encompassing the chromosomal bands from 14q31.3 to 14q32.12 without involving 14q32.2. The present case did not have the phenotype of uniparental disomy (UPD) 14 and 14q duplication syndrome. Maternal UPD 14 manifests a phenotype of short stature, growth retardation, muscular hypotonia, joint laxity, truncal obesity, small hands, hyperextensible joints, scoliosis, and mild dysmorphic features of the face, whereas paternal UPD 14 manifests intrauterine growth restriction, polyhydramnios, severe psychomotor retardation, mild contractures of the fingers, cardiomyopathy, and the "coat-hanger sign" of the thoracic ribs [17,18]. Genomic imprinting effects have been observed in chromosome 14 because the 14q32.2 region in human chromosome harbors paternally expressed genes such as *DLK1* and *RTL1*, maternally expressed genes such as *MEG3* (also known as *GTL2*), *RTL1as* (*RTL1* antisense), and *MEG8*, and the differentially methylated region (DMR) of intergenic DMR and

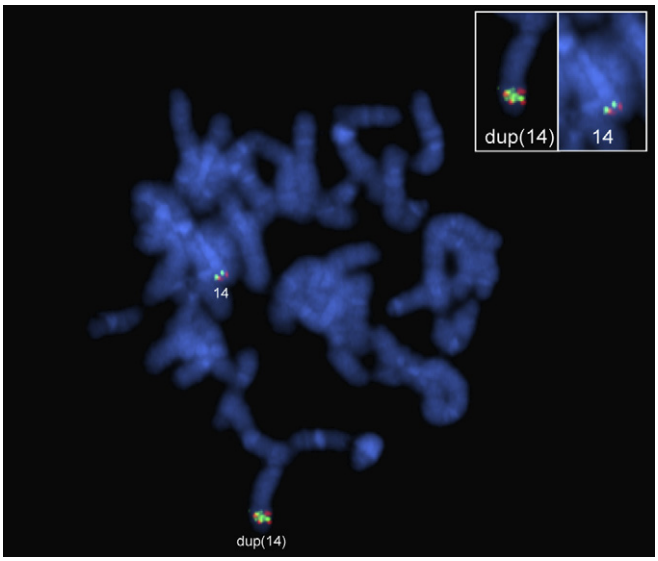

Fig. 3. Fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-35P13 (85,596,133−85,731,472) (green spectrum) at 14q31.3 and RP11-99C24 (89,927,464−90,094,722) (red spectrum) at 14q32.11. A direct duplication of 14q in the orientation of green−red−green−red is evident in the dup(14). The inset shows the amplified dup(14) and chromosome 14. dup(14) = the chromosome 14 with a duplication.

MEG3-DMR [19−22]. Our case did not involve duplication of the imprinting genes. However, our case did involve the duplication of other genes such as *FLRT2*, *GALC*, *GPR65*, *KCNK10*, *SPATA7*, *PTPN21*, *ZC3H14*, *EML5*, *TTC8*, *FOXN3*, *C14orf143*, *TDP1*, *KCNK13*, *PSMC1*, *C14orf102*, *CALM1*, *TTC7B*, *RPS6KA5*, *C14orf159*, *SNORA11B*, *GPR68,* and *CCDC88C*. The gene dosage increase effect of those genes is unknown at the present time. Although this reported neonate was normal in growth and psychomotor development with no apparent phenotypic abnormalities, long-term follow-ups are required for delineating the genotype−phenotype correlation of dup(14)(q31.3→q32.12).

Acknowledgments

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