

Case Report

Prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial duplication of 11q (11q22.3 → q23.3) associated with abnormal maternal serum biochemistry

Chih-Ping Chen^{a,b,c,d,e,f,g,*}, Yi-Ning Su^h, Shuan-Pei Lin^{b,c,i,j}, Schu-Rern Chern^b, Jun-Wei Su^{a,k},
Yu-Ting Chen^b, Meng-Shan Lee^a, Wayseen Wang^{b,l}

^a Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan

^b Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan

^c Department of Medicine, Mackay Medical College, New Taipei City, Taiwan

^d Department of Biotechnology, Asia University, Taichung, Taiwan

^e School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan

^f Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan

^g Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan

^h Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

ⁱ Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan

^j Mackay Medicine, Nursing and Management College, Taipei, Taiwan

^k Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan

^l Department of Bioengineering, Tatung University, Taipei, Taiwan

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Abstract

Objective: To present prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial duplication of 11q (11q22.3 → q23.3) in a pregnancy associated with abnormal maternal serum biochemistry.

Case Report: A 33-year-old woman underwent amniocentesis in the second trimester because of abnormal maternal serum biochemistry. Her husband was 33 years old. At 17 weeks of gestation, the levels of α -fetoprotein (AFP), unconjugated estriol (uE3), total β -human chorionic gonadotropin (β -hCG), and inhibin A were 0.65 multiples of median (MoM), 0.61 MoM, 0.32 MoM, and 0.55 MoM, respectively, consistent with a positive trisomy 18 risk of 1/128. Results of amniocentesis revealed a small *de novo* interstitial duplication of 11q encompassing 11q23. An array comparative genomic hybridization analysis detected a 9.04-Mb duplication at chromosome 11q22.3–q23.3. A polymorphic DNA marker analysis was carried out, which determined a paternal origin of the duplication. Results of fluorescence *in situ* hybridization analysis showed a direct duplication of interstitial 11q. The karyotype was 46,XX,dup(11)(q22.3q23.3). Level II ultrasound was unremarkable. The parents opted to continue the pregnancy. A 2792-g female baby was delivered at 38 weeks of gestation. When examined at 10 months of age, the neonate was small for age and was abnormal in psychomotor development with apparent facial dysmorphisms, and small hands and feet.

Conclusion: Low levels of AFP, uE3, β -hCG, and inhibin A in the second trimester maternal serum biochemistry may be a distinctive prenatal feature in pregnancy with fetal chromosome 11q duplication.

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Keywords: 11q22.3 → q23.3; duplication 11q; interstitial duplication; maternal serum biochemistry; prenatal diagnosis

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

Introduction

Partial trisomy 11q with a duplication of 11q (11q21 to q23→qter) has been associated with a recognizable pattern of abnormalities such as mental retardation, intrauterine growth restriction, postnatal growth retardation, microcephaly, hypotonia, distinct facial dysmorphisms, atrial septal defect, ventricular septal defect, limb malformations, cryptorchidism, micropenis, inguinal hernia, scoliosis, and psychomotor retardation [1–3]. Other rare findings include multiple hemivertebrae, spina bifida with tethered spinal cord, renal agenesis, congenital hip dislocation, diaphragmatic hernia, pulmonary valve stenosis, and sensorineural hearing loss [3]. Most reported cases with partial trisomy 11q had a familial translocation of t(11;22)(q23.3;q11.2) with a 3:1 meiotic segregation and 47 chromosomes, as well as manifestations of clinical findings of partial trisomy 11q and partial trisomy 22q and are therefore considered impure.

Cases of pure partial trisomy 11q with an interstitial duplication of distal 11q are rare and can be caused by an intrachromosomal duplication event or an intrachromosomal insertion event. To date, only 10 cases with distal interstitial 11q duplication have been reported [2,4–12]. Herein, we report prenatal diagnosis and molecular cytogenetic characterization of a *de novo* interstitial duplication of 11q (11q22.3→q23.3) in a pregnancy associated with abnormal maternal serum biochemistry.

Case report

A 33-year-old, primigravid woman underwent second-trimester screening for chromosome abnormalities using maternal serum biochemistry at 17 weeks of gestation. Her husband was 33 years old. The levels of α -fetoprotein (AFP), unconjugated estriol (uE3), total β -human chorionic gonadotropin (β -hCG), and inhibin A were 0.65 multiples of median (MoM), 0.61 MoM, 0.32 MoM, and 0.55 MoM, respectively. The woman was screened positive for a trisomy 18 risk of 1/128. At 18 weeks of gestation, she underwent amniocentesis, which revealed a small interstitial duplication of 11q encompassing 11q23. An array comparative genomic hybridization (aCGH) on cultured amniocytes revealed a 9-Mb duplication of 11q22.3–q23.3. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. At 24 weeks of gestation, she consulted our hospital and requested for repeated amniocentesis. Oligonucleotide-based aCGH using CytoChip Oligo Array (BlueGnome, Cambridge, UK) on uncultured amniocytes detected a 9.04-Mb duplication at chromosome 11q22.3–q23.3, or arr cgh 11q22.3q23.3 (109,596,777–118,636,760) \times 3 (UCSC hg18, NCBI build 36, March 2006) (Fig. 1). Quantitative fluorescent polymerase chain reaction assays on uncultured amniocytes using polymorphic DNA marker specific for chromosome 11q revealed a paternal origin of the duplication (Fig. 2, Table 1). For fluorescence *in situ* hybridization (FISH) determination of the orientation of the duplication of the chromosome 11 [dup(11)], the bacterial artificial chromosome (BAC) clone probes mapping the genomic region of 11q22.3–

q23.3 were used. The BAC clone probes RP11-262J9 (111,212,061–111,368,866 bp) (green spectrum) at 11q23.1 and RP11-2020 (116,250,688–116,416,874 bp) (red spectrum) at 11q23.3 were used to determine the orientation of the duplication. FISH analysis showed an orientation of green–red–green–red (Fig. 3), consistent with the direct duplication of interstitial 11q. The karyotype was 46,XX,dup(11)(q22.3q23.3) (Fig. 4). Level II ultrasound was unremarkable. The parents opted to continue the pregnancy. At 38 weeks of gestation, a healthy female baby was delivered with a body weight of 2792 g (15th centile), a body length of 48 cm (15–50th centile), a head circumference of 34 cm (50th centile), and a chest circumference of 32 cm (15–50th centile). At 4 months of age, her body weight was 6.2 kg (15–50th centile) and body length was 58.7 cm (15th centile). When examined at 10 months of age, her body weight was 7.6 kg (<5th centile) and body length was 68 cm (<5th centile). She was small for age and was abnormal in psychomotor development with apparent dysmorphisms of frontal bossing, bilateral palpebral fissures, sunken eyes, depressed nasal bridge, dysplastic ears, right ear tag, and small hands and feet.

Discussion

An abnormal maternal serum biochemistry result may incidentally detect rare chromosome aberration in early pregnancy. We have previously reported prenatal diagnosis of partial trisomy 16p and partial monosomy 22q associated with abnormal maternal serum biochemistry in the first trimester [13], and prenatal diagnosis of der(18;18)(q10;q10) del(18)(q11.1q12.1) del(18)(q22.1q22.3) associated with abnormal maternal serum biochemistry in the second trimester [14]. The present case underwent prenatal genetic testing because of a positive screen risk of 1/128 for trisomy 18 calculated by abnormally low levels of AFP, uE3, β -hCG, and inhibin A. The present case provides evidence that fetuses with an interstitial duplication of 11q may present low levels of AFP, uE3, β -hCG, and inhibin A in the second trimester. We suggest that low levels of AFP, uE3, β -hCG, and inhibin A in the second-trimester maternal serum biochemistry may be a distinctive prenatal feature in pregnancy with fetal chromosome 11q duplication.

Previous reports of isolated interstitial 11q duplications that overlapped with the present case have been associated with a wide variability of phenotypic findings [7,10–12,15]. de Die-Smulders and Engelen [15] reported a duplication of 11q22→q23 in a 50-year-old woman with mental retardation, prominent eyes, hypertelorism, tip of the nose overriding the upper lip and everted lower lip, microcephaly, kyphoscoliosis, and prognathism. Delobel et al [7] reported a duplication of 11q23.3 in a 19-year-old girl with atypical Rett syndrome, facial dysmorphism, hypertrichosis, scoliosis, and bilateral clinodactyly. Partida-Pérez et al [10] reported a constitutional duplication of 11q23 involving the *MLL* gene in an 18-month-old boy with mental retardation, trigonocephaly, bitemporal narrowing, relative hypotelorism, short and beaked nose, shotgun nostrils, cupid's bow mouth, thickened and everted

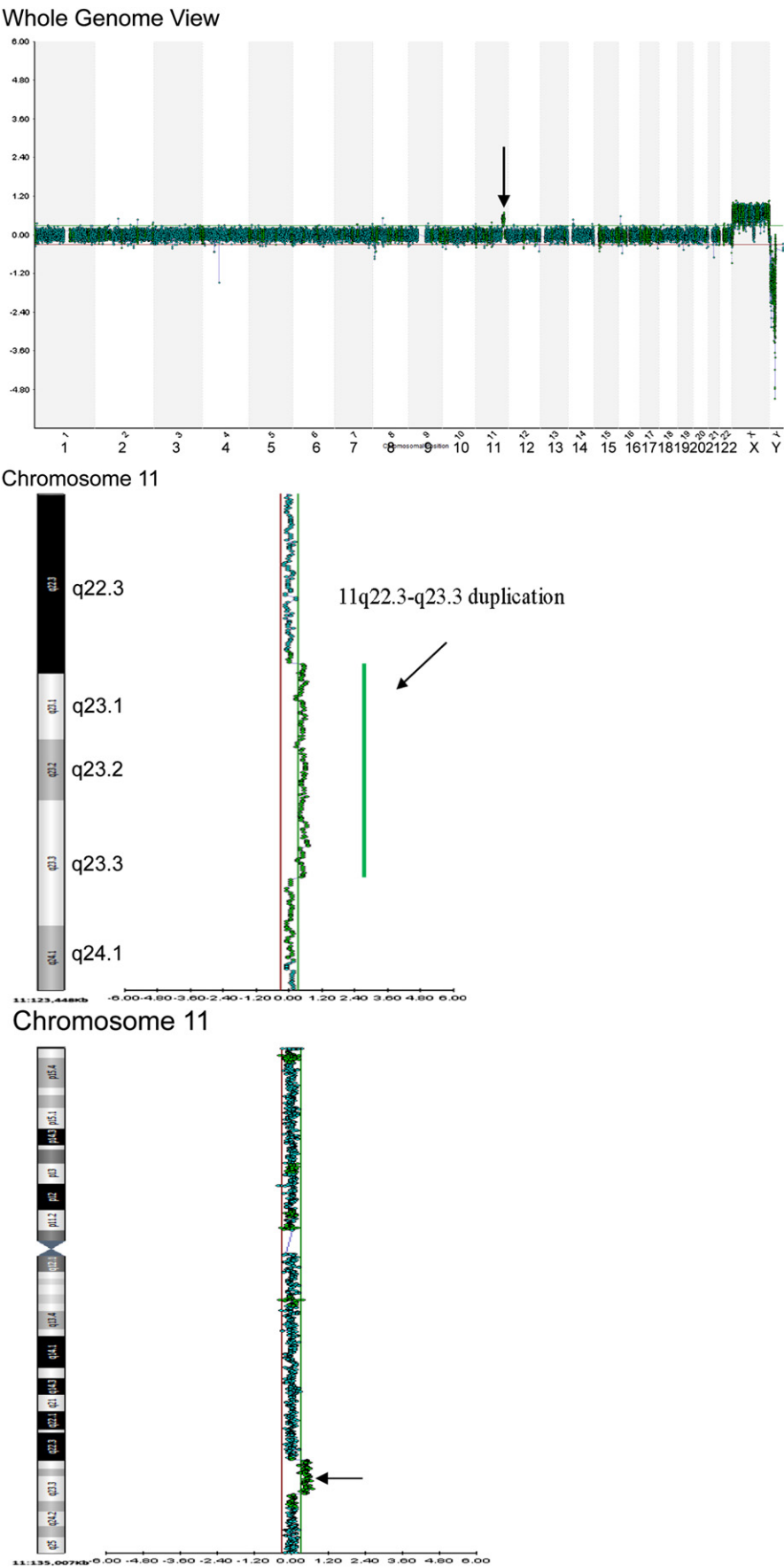


Fig. 1. Oligonucleotide-based array comparative genomic hybridization on uncultured amniocytes shows a 9.04-Mb duplication at 11q22.3-q23.3 (arrow).

Table 1
Molecular results using polymorphic DNA markers specific for chromosome 11q^a.

Markers	Father	Mother	Fetus	Location ^b
D11S2180	121, 121	117, 117	117, 121	11q22.3: 108,177,922–108,178,029
D11S1990	166, 172	172, 172	166, 166, 172	11q23.1: 110,364,473–110,364,638
D11S1986	164, 172	172, 172	164, 164, 172	11q23.1: 110,728,815–110,729,050
D11S1998	148, 152	144, 148	148, 152, 152	11q23.3: 117,202,970–117,203,126
D11S4460	208, 214	211, 220	208, 220	11q23.3: 120,096,868–120,097,073

^a Alleles (base pair sizes) are listed below each individual; ^b Location according to NCBI build 36 (hg18).

lower lip, micrognathia, short neck, corpus callosum hypoplasia, and patent ductus arteriosus. Burnside et al [12] later identified a triplication within 11q23.3 involving the *MLL* gene in a boy aged 5 years and 4 months who was originally

reported by Partida-Pérez et al [10] and was associated with mental retardation, brain anomalies, congenital heart defects, scoliosis, and facial dysmorphism. The duplicated region of

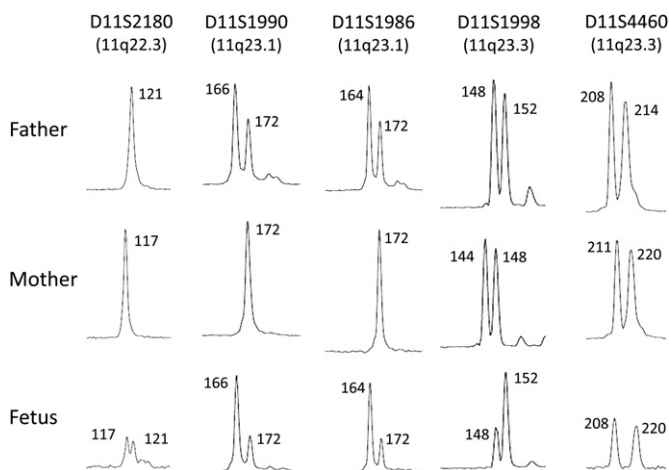


Fig. 2. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem repeat markers specific for chromosome 11q using uncultured amniocytes and parental DNAs. The markers D11S1990 (11q23.1), D11S1986 (11q23.1), and D11S1998 (11q23.3) show two different parental alleles of unequal fluorescent activity with a paternal:maternal dosage ratio of 2:1, indicating a paternal origin of the interstitial duplication.

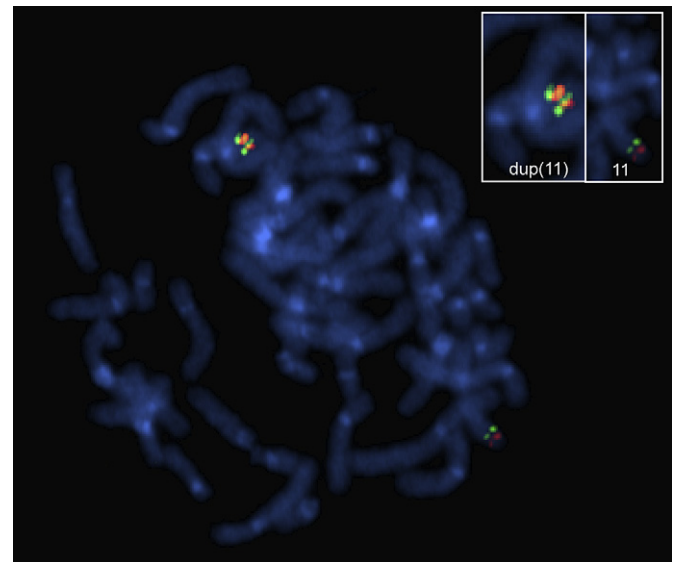


Fig. 3. Fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-262J9 (111,212,061–111,368,866 bp) (spectrum green) at 11q23.1 and RP11-2020 (116,250,688–116,416,874 bp) (spectrum red) at 11q23.3. A direct duplication of 11q in the orientation of green–red–green–red is evident in the dup(11). The inset shows the amplified dup(11) and chromosome 11. dup(11) = the chromosome 11 with a duplication.



Fig. 4. Karyotype of 46,XX,dup(11)(q22.3q23.3). The arrows indicate the breakpoints.

11q22.3→q23.3 in the present case also contains the *MLL* gene. The *MLL* gene (OMIM 159555) is located at 11q23.3 and regulates the *HOX* gene expression by directly binding to the promoter sequences. Translocations involving the *MLL* gene have been found in acute myeloid leukemia (AML), acute lymphoblastic leukemia, or mixed lineage leukemia (MLL). *MLL* amplification has been observed in myeloid malignancies [16]. However, Schnittger et al [17] reported that *MLL* tandem duplications are less common than previously reported. Schnittger et al [18] found partial tandem duplications of the *MLL* gene are detectable in peripheral blood and bone marrow of nearly all healthy donors and suggested that *MLL* duplications are not implicated in the malignant transformation in AML. Zarate et al [11] first reported a *de novo* interstitial 11q duplication (11q21→q23.1) in a 4-year-old boy with normal development and intelligence. Our case is an additional case with abnormal development having a *de novo* interstitial 11q duplication (11q22.3→q23.3), which requires long-term observation.

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