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Research Letter

Prenatal diagnosis of an interstitial deletion of 10q (10q11.21 → q21.1): Array comparative genomic hybridization characterization and literature review

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A 36-year-old, gravida 2, para 1 woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Cytogenetic analysis revealed a small proximal deletion of chromosome 10q. Array comparative genomic hybridization (aCGH) using CytoChip Oligo array (BlueGnome, Cambridge, UK) on cultured amniocytes revealed a 12.4-Mb deletion at chromosome 10q11.21−10q21.1 or arr 10q11.21q21.1 (45,525,726−57,919,309)×1 (NCBI, build 36, March 2006) (Fig. 1). The prenatal ultrasound findings were unremarkable. The parental karyotypes were normal. aCGH analysis of the parental blood did not reveal any deletion at chromosome 10q.

The woman underwent a second amniocentesis at 21 weeks of gestation for confirmation. aCGH using Human CGH 3×720K Whole-Genome Tiling v3.0 Array (Roche NimbleGen, Madison, WI, USA) on uncultured amniocytes revealed a 12.4-Mb deletion at chromosome 10q11.21−10q21.1 or arr 10q11.21q21.1 (45,487,499−57,962,499)×1 (NCBI, build 36, March 2006). Conventional cytogenetic analysis revealed a karyotype of 46,XY,del(10)(q11.21q21.1) (Fig. 2). The parents elected to terminate the pregnancy, and a 942-g male fetus was delivered at 24 weeks of gestation with no apparent phenotypic abnormalities.

The present case had a 12.4-Mb deletion at chromosome 10q11.21 → q21.1 encompassing at least 86 genes, including *CHAT*, *SLC18A3*, *ERCC6*, *MSMB*, *PCDH15*, and *MBL2*, which are known to contribute to human disorders. *CHAT* (OMIM 118490) encodes choline acetyltransferase, and compound heterozygous or homozygous mutations in *CHAT* can cause congenital myasthenic syndrome associated with episodic apnea (OMIM 254210) [1,2].

SLC18A3 (OMIM 600336) encodes vesicular acetylcholine transferase (VACHT). In a study of *Vacht* knockdown homozygous mice, Lara et al [3] found that the $Vacht^{-/-}$ mice displayed dysautonomia due to reduced cholinergic neurotransmission.

ERCC6 (OMIM 609413) is involved in the nucleotide excision repair pathway and is associated with autosomal recessive type B Cockayne syndrome (OMIM 133540) [4], autosomal recessive cerebro-oculo-facio-skeletal syndrome (OMIM 214150) [5], susceptibility to age-related macular degeneration 5 due to polymorphism of c.-6530C>G (rs3793784:C>G) SNP in *ERCC6* [6], and autosomal recessive UV-sensitive syndrome 1 (OMIM 600630) [7]. *ERCC6* is located at 10q11.23.

Fryns et al [8] first reported a 24-year-old man with late-onset Cockayne syndrome and an interstitial deletion del(10)(q11.23q21.2). Ghai et al [9] recently reported a 4.5-year-old girl with Cockayne syndrome, a paternally inherited 5-Mb deletion at 10q11.22−q11.23 causing a complete deletion of *ERCC6* along with 49 additional genes, and a maternally inherited frameshift

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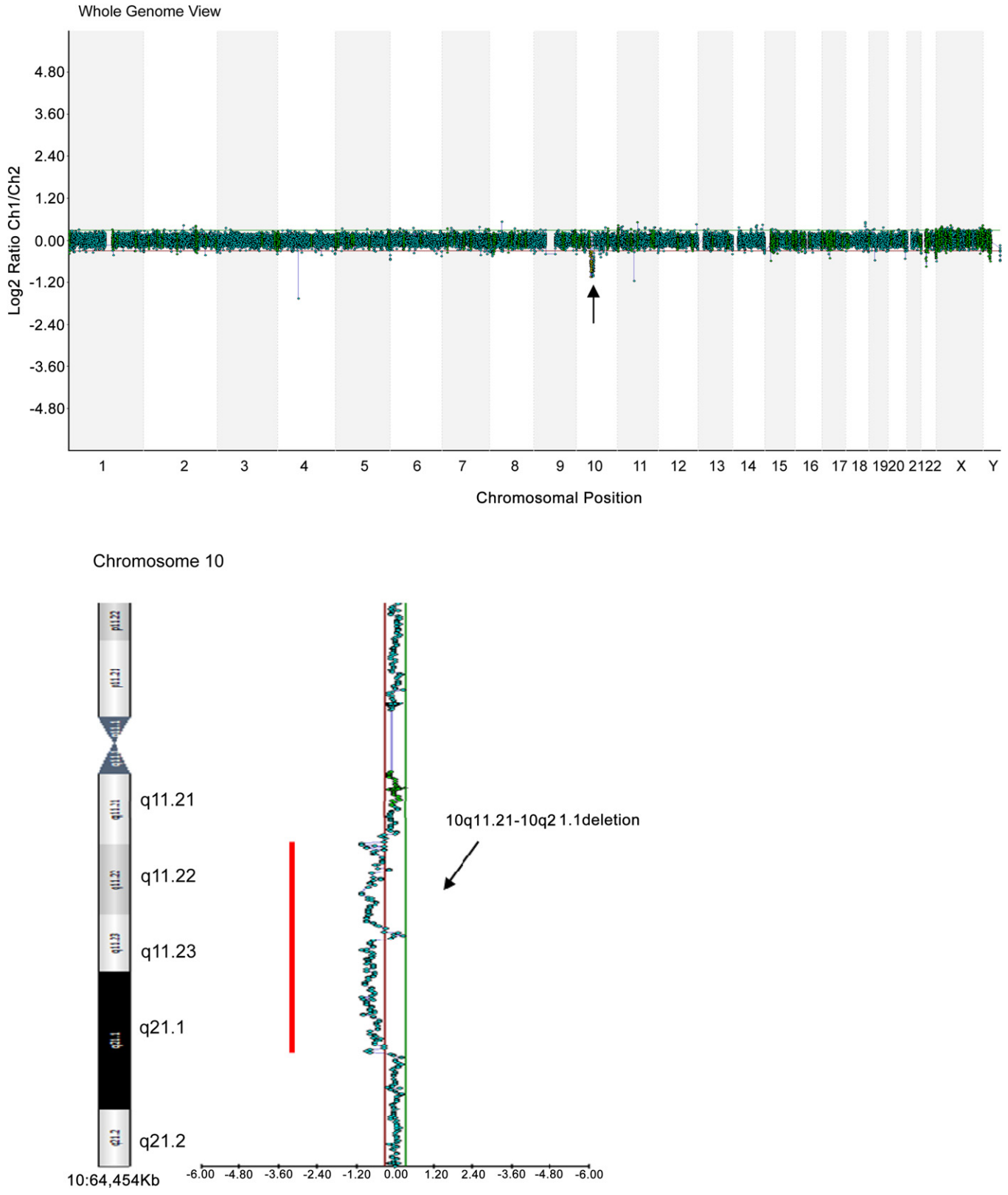

Fig. 1. A deletion at region 10q11.21–q21.1 involving a 12.4-Mb segment (arrows) from position 45,525,726 to position 57,919,309 bp is identified by oligonucleotide-based array comparative genomic hybridization.

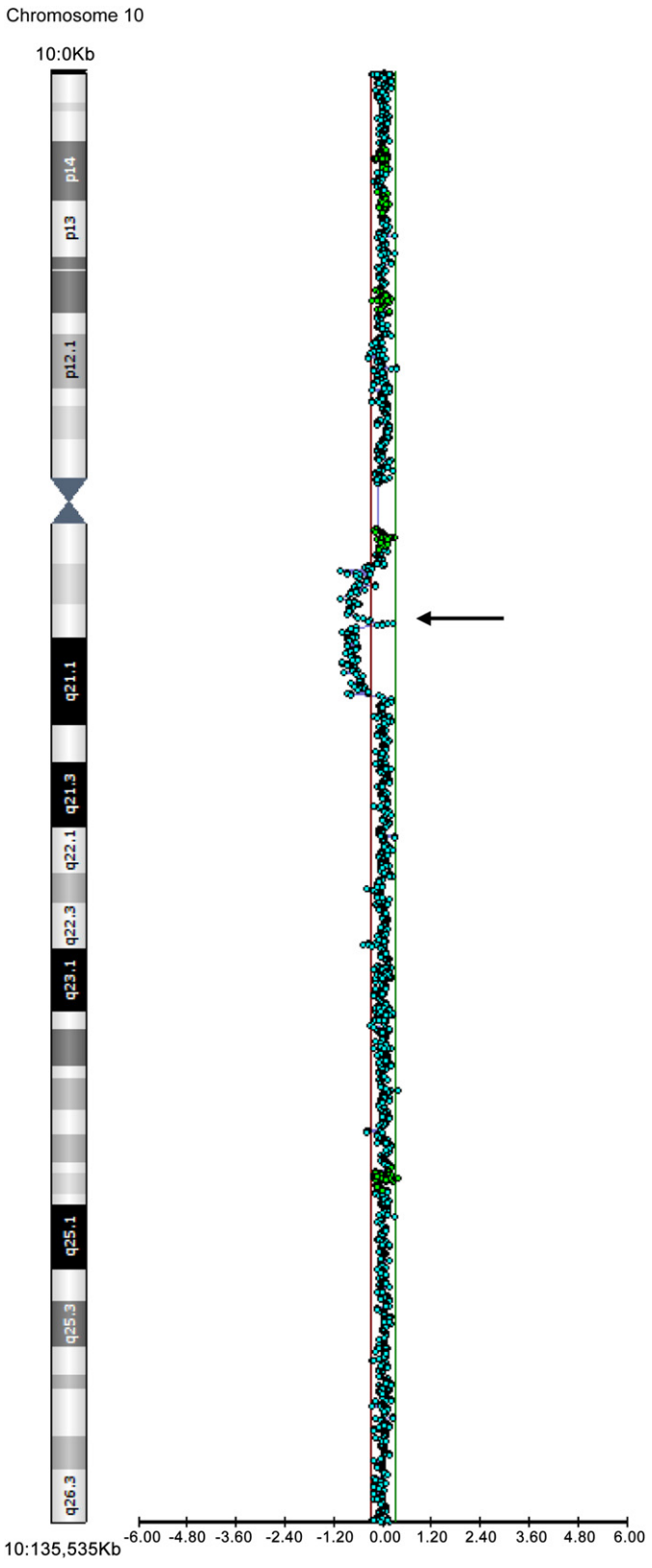

Fig. 1. (*Continued*)

mutation of *ERCC6*. The parents were clinically normal. *ERCC6* is also associated with susceptibility to lung cancer (OMIM 211980). Lin et al [10] found that c.-6530CC carriers had a 1.7-fold excess risk of developing lung cancer compared with the CG or GG genotypes.

MSMB (OMIM 157145) encodes beta-microseminoprotein, which is a prostatic secretory protein. Thomas et al [11] and Eeles et al [12] identified single nucleotide polymorphism rs10993994 in the proximal promoter of the *MSMB* gene, which had a significant association with prostate cancer (hereditary prostate cancer 13; OMIM 611928).

PCDH15 (OMIM 605514) encodes protocadherin 15, which is expressed in both retina and cochlea. Mutations in *PCDH15* cause Usher syndrome type 1F (OMIM 602083) [13,14], Usher syndrome type 1D/F (OMIM 601067) [15], and autosomal recessive deafness 23 (OMIM 609533) [16].

MBL2 (OMIM 154545) encodes mannose-binding protein or lectin. Mannose-binding protein deficiency is associated with susceptibility to and recovery from infection, cystic fibrosis mortality and morbidity, vascular disease, gestational diabetes mellitus, and preterm delivery [17–21].

Cases with interstitial 10q deletions involving 10q11.2 and clinical findings have been well reported [8,9,22–33]. Stankiewicz et al [33] suggested that recurrent deletions and reciprocal duplications of 10q11.21q11.23 including *CHAT* and *SLC18A3* are likely mediated by complex low-copy repeats of locus control region (LCR) 10q11.2A to LCR 10q11.2F. In a study of 24 unrelated individuals with deletions at 10q11.21q11.23, Stankiewicz et al [33] concluded that the subjects carrying 10q11.21q11.23 deletions may exhibit variable phenotype expressivity, incomplete penetrance, common clinical features of developmental delay, and/or intellectual disability, and variable features of hypotonia, sleep apnea, chronic constipation, gastroesophageal and vesicoureteral refluxes, epilepsy, ataxia, dysphagia, nystagmus, and ptosis, which may result from deletion of *CHAT* and *SLC18A3*.

Ray et al [22] reported a 1-year-old boy with a karyotype of 46,XY,del(10)(q11q21), mental retardation, significant developmental delay, facial dysmorphism, limitation of joint movement, and mild hypotonia. Holden and MacDonald [23] described the case of a 9-year-old girl with a karyotype of 46,XX,del(10)(q11.2q21), cleft palate, ptosis, developmental delay, mild hypotonia, deficit in language function, mental retardation, and seizures. Similarly, Shapiro et al [24] a 5-year-old girl with an interstitial deletion of 10q11.2 → q22.1 due to a t(10;13). The girl manifested facial dysmorphism, gross developmental delay, strabismus, hypoplasia of the right optic nerve, hypotonia, ventricular septal defect, and flexion deformity of the fingers.

Fryns et al [8] and Ghai et al [9] described patients with interstitial 10q deletions and Cockayne syndrome. Lobo et al.'s [25] 12-month-old female patient had a karyotype of 46,XX,del(10)(q11.1q22.1), facial dysmorphism, strabismus, psychomotor retardation, hypotonia, and ventricular septal defect. Martucciello et al [26] and Puliti et al [27] reported a 21-month-old girl with a karyotype of 46,XX,del(10)(q11.21q21.2) and Hirschsprung disease. Zenger-Hain et al

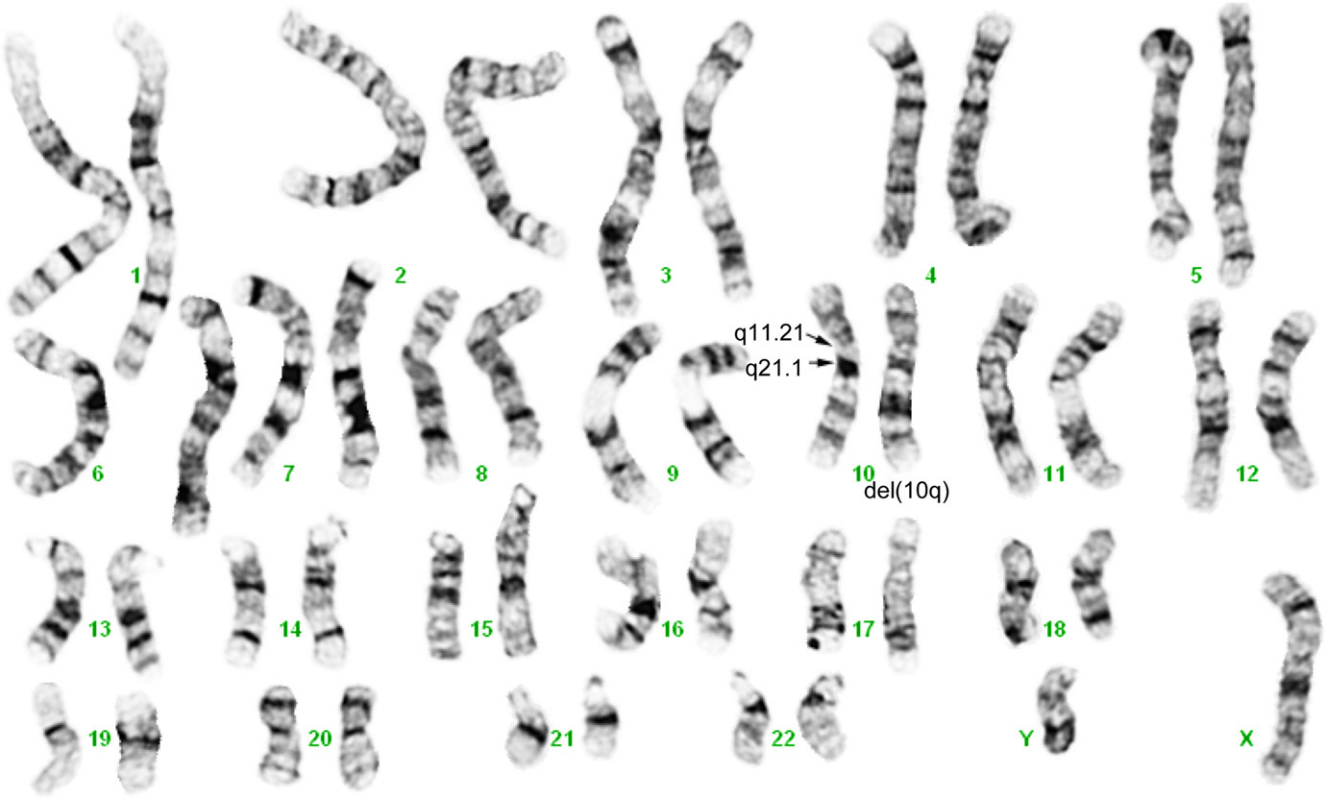

Fig. 2. Karyotype 46,XY,del(10)(q11.2q21.1). The arrows indicate the breakpoints. The del(10q) chromosome is on the right of the chromosome 10 pair.

[28] discussed a 4-year-old boy with a karyotype of 46,XY,del(10)(q11.2q22.1), facial dysmorphism, hypotonia, postnatal-onset slow growth, short stature, mental retardation, and subaortic stenosis. Fewtrell et al [29] reported an 8-month-old girl with a karyotype of 46,XX,del(10)(q11.2q21.2), meconium ileus, and Hirschsprung disease. Kirchhoff et al [30] and Bisgaard et al [31] described an aCGH diagnosis of del(10) (q11.1q21.1) in a 3-month-old girl with mental retardation, facial dysmorphism, and Bohring-Opitz syndrome. The mother and two siblings had the same deletion but were unaffected. Chen et al [32] described the prenatal diagnosis of a *de novo* 4.9-Mb deletion of 10q11.21 → q11.23 by aCGH in a fetus with facial dysmorphism.

Cases with no recognizable phenotype have been reported with interstitial deletions of 10q [33–35]. Derksen et al [34] reported the prenatal diagnosis of 46,XY,del(10)(q11.2q21.1) by amniocentesis because of advanced maternal age. The mother and maternal grandmother carried the same chromosome aberration. The parents elected to continue the pregnancy, and the baby was normal at age 12 weeks. The deletion of 10q11.2 → q21.1 presented no phenotypic consequences in this family. Davis et al [35] described a 29-year-old phenotypically normal male with a karyotype of 46,XY, del(10)(q11.2q21.2)dn. Stankiewicz et al [33] observed apparently normal carrier parents in 10 of 13 inherited cases with a 10q11.21q11.23 deletion, and affected carrier parents with affected carrier siblings in two cases. The variable expressivity and clinical heterogeneity have been suggested to be caused by additional genetic and nongenetic modifiers such as atypical or variable-sized copy number changes and a "two-hit" model [33].

In summary, we report prenatal diagnosis and molecular cytogenetic characterization of *de novo* del(10) (q11.21 → q21.1) in a fetus with no apparently phenotypic abnormalities. Genetic counseling for prenatally detected interstitial deletions involving 10q11.2 remains difficult because no ultrasound abnormalities can be expected, and the reported cases show phenotypic diversity.

Acknowledgments

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