Short Report

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8p11 Microduplication Is Associated with Neonatal Stridor

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Chromosomal microduplication · Congenital anomaly · Developmental delay · Neonatal stridor · 8p11.21 microduplication

Abstract
We report a term male infant with congenital stridor secondary to tracheomalacia and a mild coarctation of the aorta. Developmental delay was noted upon follow-up. Whole genome SNP microarray analysis showed an ~846-kb interstitial duplication of the short arm of chromosome 8 (8p11.21p11.1). We report novel clinical findings of this rare genetic condition.

Duplication of the short arm of chromosome 8 is a rare chromosomal anomaly. To date, more than 75 cases of 8p duplication have been published [Engelen et al., 1995; Tsai et al., 2002]. Although duplication of the short arm of chromosome 8 from 8p11.1 to 8p23 is known to be associated with characteristic clinical manifestations [Engelen et al., 1995], the phenotype of microduplication 8p, region 8p11.21p11.1 has not been previously described. Here, we report a novel case of 8p11.21p11.1 duplication and a review of the literature.

Case Report

A male infant was delivered at 39 weeks of gestation to a 32-year-old G3P2 mother by vacuum-assisted vaginal delivery. Apgar scores were 8 and 9 at 1 and 5 min, respectively. Pregnancy was complicated by gestational diabetes mellitus, which required a diet control. Family history was negative for congenital anomalies. There was no history of in-utero exposure to any known teratogens. Physical examination revealed: weight 3,040 g (25th centile), length 50 cm (40th centile), and head circumference 34 cm (40th centile).

No visible anomalies were identified. The infant was noted to have cyanotic episodes at about 17 h of life and was transferred to the neonatal intensive care unit (NICU) for further evaluation and management. During 12 days in the NICU, an inspiratory stridor occurred. Initial supraglottic laryngoscopy was unremarkable. Echocardiography showed a mild coarctation of the aorta. Cyanotic episodes associated with crying/agitation were reported in the NICU; a sleep study was performed which revealed desaturation episodes in REM sleep. He was discharged home with apnea and pulse oximeter monitors. Due to persistent inspiratory stridor, a direct laryngoscopy and bronchoscopy at 8 weeks of age revealed mild posterior tracheal wall collapse consistent with a tracheomalacia. Delayed developmental milestones and speech were observed upon follow-up; a genetic test was done at 10 months of age.

The father subsequently revealed a history of a cleft soft palate, velopharyngeal insufficiency with speech disorder and learning difficulties during childhood. The infant's sister also was found to have tracheomalacia, feeding difficulties, and speech and developmental delay; she has entered a preschool disabled program (Ta-

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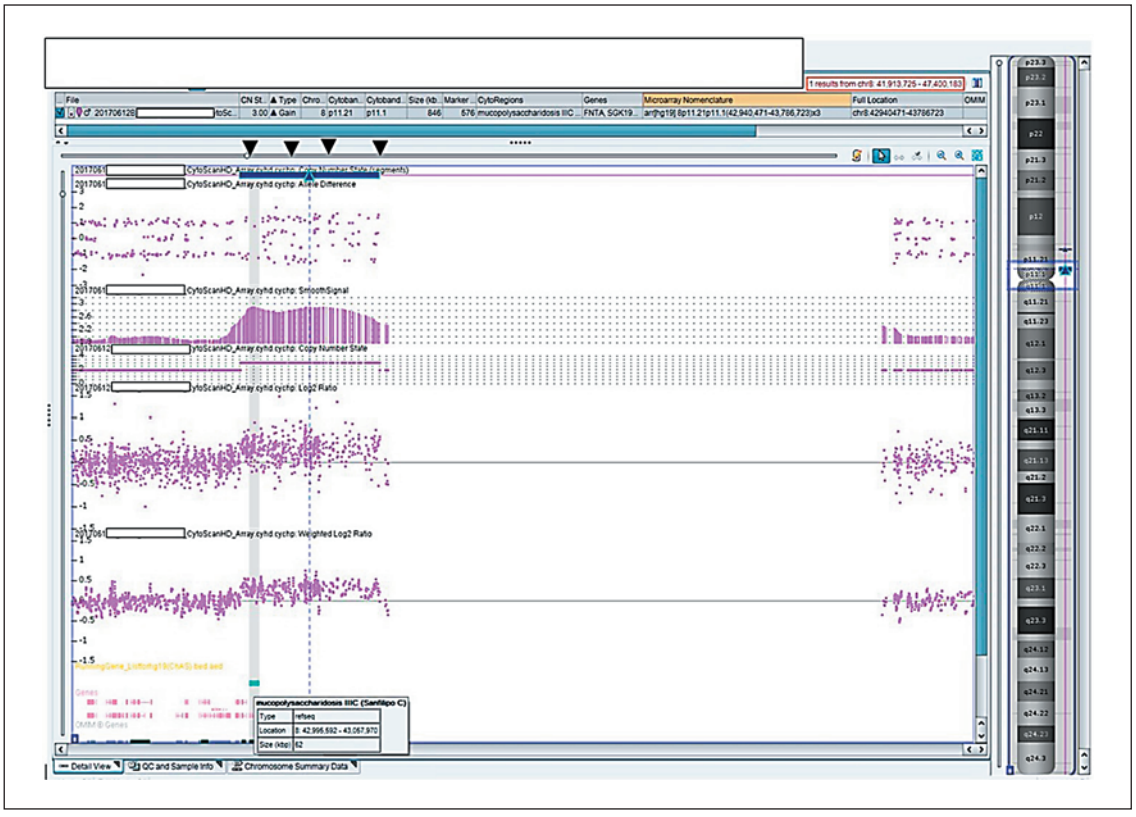

Fig. 1. Microarray showing 8p11.21p11.1 duplication (arrowheads).

ble 1). Upon follow-up at 19 months of age, the boy's weight was 10 kg (5th centile), height 80 cm (25th centile), and his head circumference was 46 cm (5th centile). He had both speech and developmental delay.

Methods and Results

Whole genome SNP microarray analysis was performed using the Affymetrix CytoScan HD platform, which uses over 743,000 SNP probes and 1,953,000 NPCN probes with a median spacing of 0.88 kb. 250 ng of total genomic DNA extracted from lymphocytes was digested with NspI and then ligated to NspI adaptors, respectively, and amplified using Titanium Taq with a GeneAmp PCR system 9700. There was an 846-kb microduplication between 8p11.21 and p11.1 – arr[hg19] 8p11.2 1p11.1(42,940,471–43,786,723)×3 (Fig. 1). The duplicated region includes 4 OMIM genes: *FNTA* (OMIM 134635), *POMK* (OMIM 615247), *HGSNA* (OMIM 610453), and *POTEA* (OMIM 608915).

Table 1. Summary of clinical features of the family with 8p11.21p11.1 microduplication

	Proband	Sister	Father
Age	19 months	4 years	39 years
Psychomotor/learning disabilities	Yes	Yes	Yes
Speech/feeding disorders	Yes	Yes	Yes
Respiratory disorders[a]	Yes	Yes	NA
Cleft palate	No	No	Yes
Cardiac anomaly	Yes	NA	NA

NA, not available or unknown. [a] Stridor, tracheomalacia, noisy breathing.

Array-CGH of the father and the infant's 3-year-old sister revealed the same microduplication.

Discussion

Trisomy 8p, partial duplication of the short arm of chromosome 8, is a rare chromosomal anomaly. The phenotypes are highly variable ranging from no dysmorphic

features and only mild intellectual disability to patients with severe developmental delay, neonatal hypotonia, short stature, profound intellectual disability, dysmorphic features (e.g., high forehead, frontal or parietal bossing, mild ptosis, hypertelorism, downslanting palpebral fissures, broad nasal bridge, short prominent philtrum, carp mouth, abnormal dentition, full cheeks, and a round face), congenital heart defects (e.g., coarctation of the aorta), musculoskeletal anomalies, and CNS malformations (e.g., agenesis of corpus callosum, Dandy-Walker malformation). Autism, epilepsy, and spastic paraplegia have also been reported (Orphanet, www.orphadata.org) [Gibbons et al., 1999; Mahjoubi et al., 2005].

The short arm of chromosome 8 contains about 484 annotated genes (NCBI Build 36.3) of the human genome [Nusbaum et al., 2006; Yu et al., 2010]. More than 50 genes in 8p are associated with various genetic disorders and diseases. Patients with chromosome 8p duplication may present with developmental delay, intellectual disability, behavioral problems, and distinctive facial features. A 3-year-old girl presenting with language, gross/fine motor, and cognitive delay was found to have a de novo 8p11.21→q11.21 duplication [Vander Pluym et al., 2015]. A 1-month-old male infant with a multicystic kidney and ventriculomegaly was reported to have a duplication of 8p11.21→q11.1 [Chen et al., 2010]. Rearrangement of the 8p11.21→q11 region has been reported in association with developmental and intellectual delays, seizures, attention deficit disorders, mental retardation, autism, and behavior problems [de Die-Smulders et al., 1995; Batanian et al., 2000; Anderlid et al., 2001; Brecevic et al., 2006]. We cannot find any case reports or recognizable phenotypes with "pure" duplication of the 8p11 region.

A close examination of the duplication interval in our case (8p11.21p11.1) revealed 4 OMIM genes – *FNTA*, *POMK*, *HGSNA*, and *POTEA*. The *POMK* (protein O-mannose kinase) gene has been linked to congenital muscular dystrophy, Walker-Warburg syndrome, eye anomalies, and intellectual disabilities [von Renesse et al., 2014]. The *HGSNAT* (heparan-alpha-glucosaminide N-acetyltransferase) gene encodes a lysosomal acetyltransferase, which is one of several enzymes involved in the lysosomal degradation of heparin sulfate. Mutations in this gene are associated with Sanfilippo syndrome type C (mucopolysaccharidosis) and retinitis pigmentosa [Canals et al., 2011; Haer-Wigman et al., 2015]. *FNTA* (farnesyltransferase) is a protein-encoding gene related to apoptotic cleavage of cellular protein. The tissue expressions of the *FNTA* gene include the eye and nervous system [Wang et al., 1996]. *POTEA* (POTE ankyrin domain family member A) is a protein-encoding gene. The POTE protein contains 7 ankyrin repeats between the amino acids 140 and 380. The *POTE* gene family is tightly related to prostate, ovary, testis, and placental cancers. There are no established disorders reported with the *POTEA* gene.

The patient presented herein, along with the father and sister, exhibit similar clinical manifestations: feeding difficulty/speech delay, breathing problems/stridor, and psychomotor/learning disabilities. We propose that these are important clinical manifestations of the duplication of 8p11.21p11.1.

In summary, we report a novel case with microduplication of 8p11. This is the first report of a family with this rare genetic entity. The findings that we have described may help identify more cases with duplications in this region.

Statement of Ethics

Written informed consent was obtained from the parents of the patient for publication of this case report and any accompanying images. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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