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A novel Xq22.1 deletion in a male with multiple congenital abnormalities and respiratory failure

Yang Cao, Umut Aypar*

Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Here we report the first male case of a novel Xq22.1 deletion. An 8-week-old boy with multiple congenital abnormalities and respiratory failure was referred to the Mayo Clinic Cytogenetics laboratory for testing. Chromosomal microarray analysis identified a novel 1.1 Mb deletion at Xq22.1. A similar deletion has only been described once in the literature in a female patient and her mother; both have intellectual disability and dysmorphic facial features. In addition, the mother had a son who died at 15 days due to breathing failure. Recently, a mouse model revealed that a 0.35 Mb sub-region, containing 4 genes, is sufficient to cause majority of the Xq22.1 deletion phenotypes. The deleted intervals in our male patient and the female patients contain 15 common genes, including the four described in the 0.35 Mb sub-region. Male mice with deletion of the 0.35 Mb sub-region died perinatally from respiratory failure due to pulmonary hypoplasia, consistent with the breathing problem and potential neonatal fatality in male patients. The phenotypes of the mouse models and the patients are strikingly similar; therefore, the deletion of these five genes (*ARMCX5*, *ARMCX5-GPRASP2*, *GPRASP1*, *GPRASP2*, and *BHLHB9*) is likely responsible for the novel Xq22.1 deletion syndrome.

1. Introduction

In 2010, a female patient and her mother both with a 1.1 Mb Xq22.1 deletion (100,934,364–102,047,069, genome build hg 19) were reported for the first time in the literature (Grillo et al., 2010). The 7-year-old female patient had severe intellectual disability, autism, micro-brachycephaly, generalized hypotonia with distal hypotrophy of lower limbs, scoliosis, dysmorphic facial features, asphyxia, cleft palate, and an unspecific periventricular white matter alteration on cerebral MRI. The 42-year-old mother had a relatively milder phenotype due to skewed X-inactivation; however, she had mild intellectual disability, short stature, brachycephaly, coarse face, and epilepsy. In addition, the mother had a son who died at 15 days of age due to breathing failure. There were no additional phenotypic information or test results available for the son. Here we report the first male patient and third patient ever with a 1.1 Mb Xq22.1 deletion.

2. Clinical report

An 8-week-old male infant has failure to thrive, hypoglycemia, subtle dysmorphic features, umbilical hernia, hypotonia with spasticity in the lower extremities, focal enlargement of frontal temporal lobe on cerebral MRI, and respiratory failure with thoracic insufficiency syndrome, tracheomalacia, and laryngomalacia. At 9 weeks of age, he had a supraglottoplasty performed to release his breathing and he was discharged at 14 weeks of age. He was re-admitted to the hospital at 20 weeks of age for tracheostomy placement. The 25-week-old continued to be on the ventilator and was doing well at the time. Mother of our patient has intellectual disability; however, no other information is available since the patient is currently in foster care.

This 8-week-old male infant with multiple congenital abnormalities was referred to the Mayo Clinic Cytogenetics laboratory for testing. Chromosomal microarray analysis (CMA) identified a 1.1 Mb deletion at Xq22.1 (100,857,290–101,991,488, genome build hg 19) (Fig. 1). This interstitial deletion was subsequently confirmed by fluorescence *in-situ* hybridization (FISH) analysis (Fig. 2 A, B). The deleted interval contains 18 known genes: *ARMCX6*, *ARMCX3*, *ARMCX2*, *NXF5*, *ZMAT1*, *TCEAL2*, *TCEAL6*, *BEX5*, *NXF2*, *NXF2B*, *TCP11X2*, *TMSB15A*, *NXF4*, *ARMCX5*, *ARMCX5-GPRASP2*, *GPRASP1*,

* Corresponding author. Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail address: Aypar.Umut@mayo.edu (U. Aypar).

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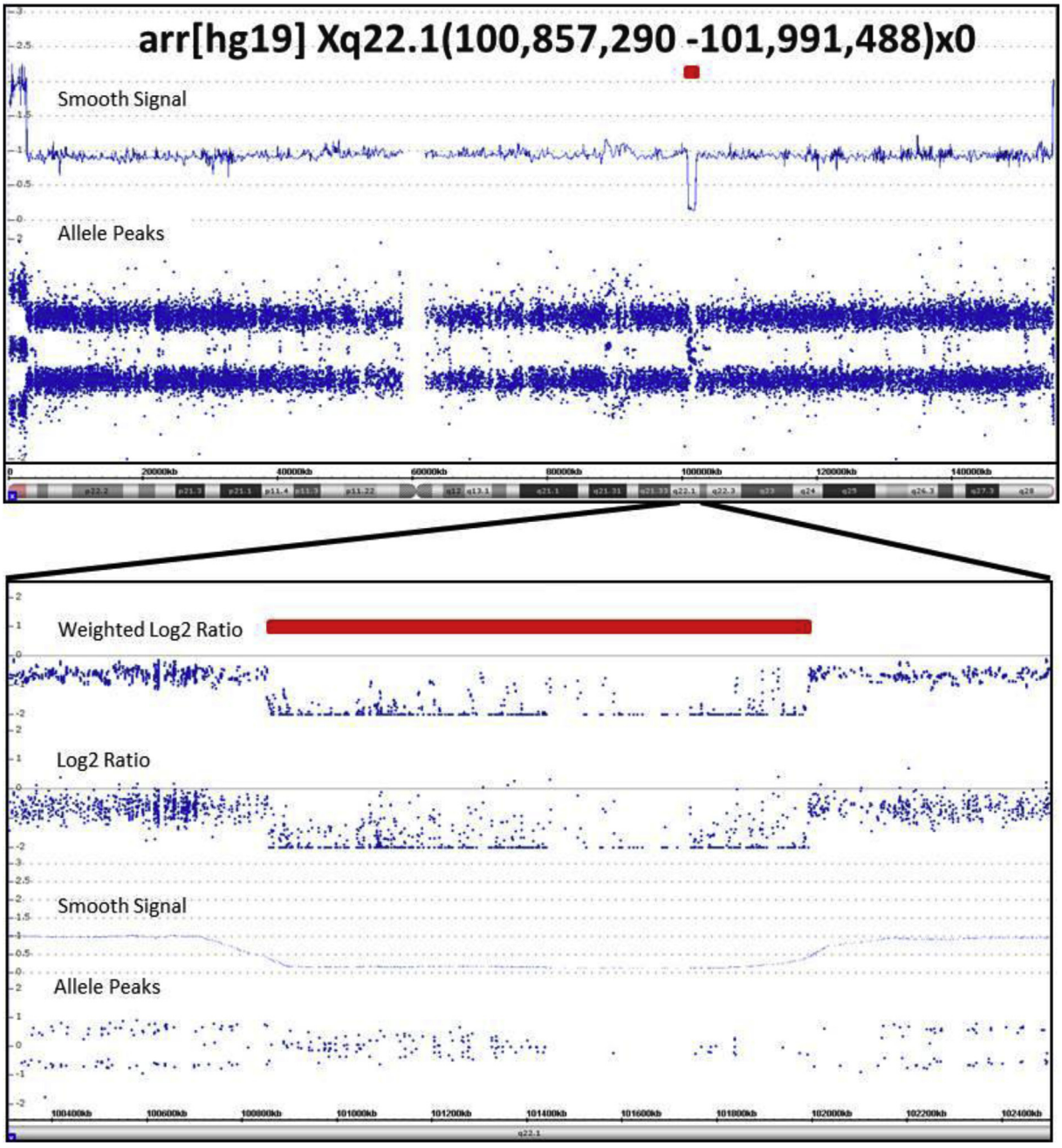

Fig. 1. A novel 1.1 Mb Xq22.1 deletion detected by CMA. Affymetrix CytoScan chromosomal microarray analysis of chromosome X detects a 1.1 Mb deletion at Xq22.1 (100,857,290–101,991,488, genome build hg 19) in our male patient. The nullisomic region (represented by a red bar) is indicated by weighted log2 ratio, log2 ratio, copy number state and allele peaks.

GPRASP2, and *BHLHB9* (Fig. 3). Parental testing was not possible since the patient is currently in foster care; however, based on the mother's phenotype, the mother is likely a carrier of this heterozygous deletion.

3. Method

3.1. DNA extraction and chromosomal microarray analysis (CMA)

Genomic DNA extraction was performed using Autopure LS (Qiagen, Valencia, CA) on peripheral blood lymphocytes. DNA samples are quantified using NanoDrop ND-2000 Spectrophotometer (Thermo Scientific, Waltham, MA) and diluted to a final concentration of 50 ng/μl. NspI enzyme (Affymetrix, Santa Clara, CA) digestion of patient genomic DNA was proceeded at 37 °C for 2 h followed by 65 °C for 20 min for enzyme inactivation. NspI adaptors (Affymetrix) were applied and ligated to NspI restriction sites by T4 DNA ligase (Affymetrix) at 16 °C for 3 h followed by 70 °C for 20 min for enzyme inactivation. PCR amplification of ligated DNA was performed using TITANIUM DNA Amplification Kit (Clontech, Mountain View, CA). PCR products were purified by purification beads (Affymetrix). The purified PCR products are fragmented into smaller pieces by using GeneChip Fragmentation Reagent (Affymetrix). The fragmented PCR products were then labeled with TdT (terminal Deoxynucleotidyl Transferase) (Promega, Madison, WI) at the 3′ end. TdT labeled samples then