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Case Report

20q13.2-q13.33 deletion syndrome: A case report

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Abstract. We report a 32-month-old female of Peruvian ethnicity identified with a rare 20q13.2-q13.33 deletion using microarray analysis. She presented with intellectual disability, absent speech, hypotonia, pre- and post-natal growth retardation and an abnormal face with a unilateral cleft lip. Clinical features and genetic findings with the loss of 30 genes, including *GNAS*, *MC3R*, *CDH4* and *TFAP2C*, are described in relationship to the very few cases of 20q13 deletion reported in the literature. Deletion of this region may play an important role in neurodevelopment and function and in causing specific craniofacial features.

Keywords: Microarray analysis, 20q13 deletion, intellectual disability, atypical development, dysmorphic features, cleft lip

1. Introduction

Deletions of the long arm of chromosome 20 are rare with the ring chromosome 20 being the most commonly reported anomaly with over 100 cases in the literature. Ring chromosome 20 is associated with seizures, developmental delay and microcephaly but no characteristic growth or dysmorphic anomalies [1–5]. Small deletions of the distal long arm of chromosome 20 have been reported in six cases without ring chromosome or unbalanced translocation involvement and with intellectual disability, decreased speech, hypotonia, growth retardation and abnormal facial features (high forehead, broad nasal bridge, thin upper lip, small chin, hypertelorism and malformed ears) [6–10].

Herein, we report another individual with the rare 20q13.2-q13.33 interstitial deletion (7.3 Mb in size) and the first detected using chromosomal microarray analysis. This patient was ascertained in a study to enroll infants and children with atypical development and autism from an underdeveloped country, Peru [11].

2. Case report

The proband is a female with a unilateral cleft lip, dysmorphic features, psychomotor developmental delay, hypotonia, speech delay, self-injury and failure to thrive. The pregnancy and delivery history included prematurity with delivery at 7 mo gestation by C-section secondary to oligohydramnios. Birth weight was 1.47 kg (<3%).

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There were no other pregnancy or family history issues. She was the first baby born to the mother at age 37 yr and father at age 39 yr. She remained in an incubator for one month after delivery. Due to multiple congenital anomalies, a chromosome study (at 400 band level) was obtained and a normal female karyotype was found. She had a history of bronchitis, ear infections and diarrhea during infancy. Hearing evaluation at 9 mo showed decreased hearing which improved after placement of ear tubes. Surgical correction of the left sided cleft lip was also successful.

At 11 mo of age, she was small (weight at 4.9 kg, < 3%; length at 59 cm, < 3%) and had sparse hair, large appearing simple ears, a triangular face with an asymmetric appearing nose secondary to cleft lip repair, mild right hemi-hypertrophy and chronic malnutrition. No other major illnesses, operations or hospitalizations were noted. Ultrasound studies of the abdomen and kidneys were normal. Microcytic anemia was reported by history. No endocrine, skeletal, laboratory or clinical findings of Albright hereditary osteodystrophy (AHO) were observed as noted in other individuals reported with mutations or disturbances of the GNAS gene located in the 20q13 band [12–15]. Prior to the microarray testing, Russell-Silver syndrome was considered as a possible diagnosis in the patient in view of her small size, mild hemi-hypertrophy, triangular face and small chin, all features commonly seen in this syndrome [12].

At 32 mo of age, her height was 72 cm (< 3%), weight was 8.1 kg (< 3%) and head circumference was 44 cm (< 3%) (Fig. 1). She was noted to have growth retardation, a flaccid hypotonic, triangular face with an open mouth and small pointed chin, protruding poorly formed, low-set ears, a flattened nasal bridge with hypertelorism, broad appearing eyebrows with synophrys, hirsutism, mild ptosis, anteverted nares with a flattened nasal tip, strabismus and a scar on left side of upper lip (secondary to surgical repair of cleft lip). She preferred to be alone, played little with family members and did not imitate others. The patient slept 8 h per night, did not speak and only signed when hungry. No seizure activity was reported by the family. Visual function was considered normal but mild myopia and astigmatism were noted. Dental caries were present. A bone age X-ray study showed delay and head magnetic resonance imaging showed no vascular malformations or other abnormalities. She received physical, language and sensory integration therapies.

As part of a research study to identify infants and children with atypical development in Peru, and after signed consent of approved forms by the Human Subjects Committee, buccal cells were collected using cotton swabs for deoxyribonucleic acid (DNA) isolation as described by Rethmeyer et al. [16] for chromosomal microarray analysis. The Affymetrix Genome-Wide Human SNP Array 6.0 version was used which consists

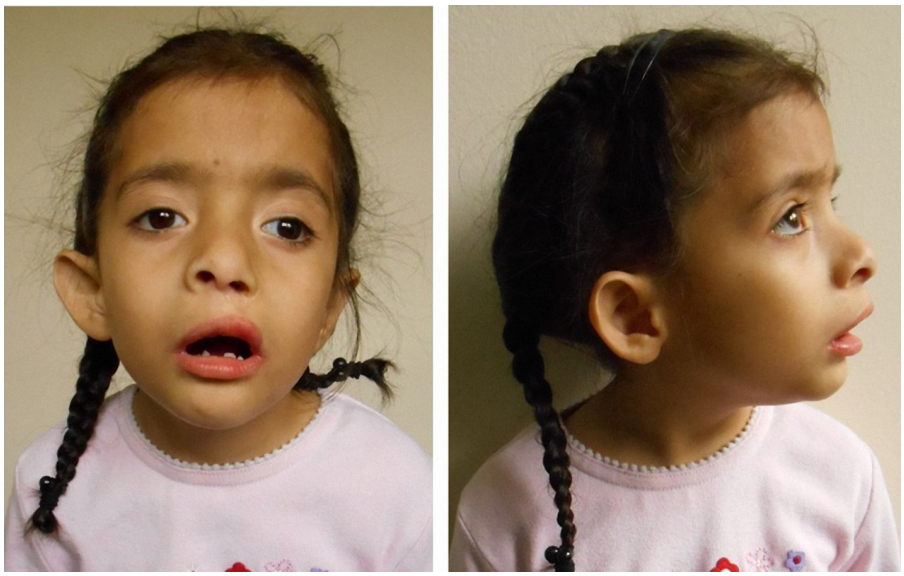

Fig. 1. Frontal and profile views of our patient at 71 mo of age with the 20q13.2-q13.33 deletion identified by microarray analysis.

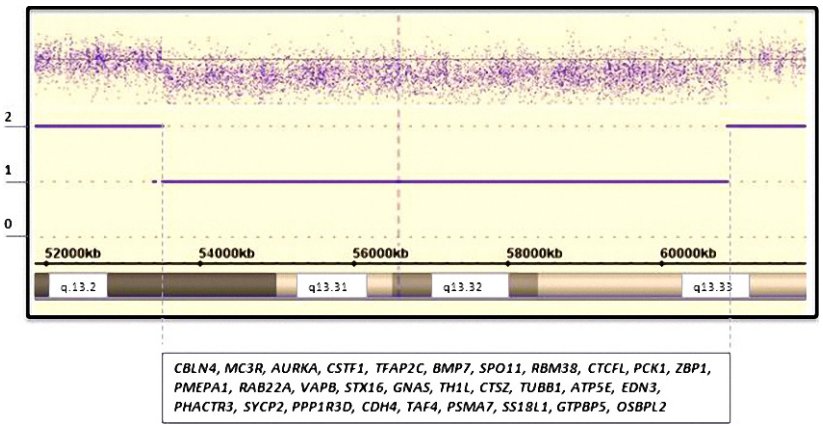

Fig. 2. Chromosomal microarray analysis using the Affymetrix Genome-Wide Human SNP Array 6.0 showing the location of the deletion on chromosome 20 involving bands q13.2 and q13.3 (53,512,484-60,850,110 bp from p terminus). Y axis shows the chromosome copy number (2 = normal or nondeletion; 1 = deletion from a single chromosome; 0 = deletion from both chromosomes). Genes in the deleted region are shown.

of 1.8 million DNA probes to determine deletions or duplications in the genome. A 7.3 Mb size deletion was found involving the 20q13.2-q13.33 region [53,512,484-60,850,110 bp based on the University of California, Santa Clara (UCSC) hg 19 human genome, National Center for Biotechnology Information (NCBI) build 37, February 2009)] (Fig. 2). The Affymetrix Chromosome Analysis Suite 1.2.2 software version was used for determination of the location and size of the chromosome anomaly and number of involved DNA markers.

3. Discussion

Chromosomal microarray analysis is now commonly used in the clinical setting in developed countries for evaluation of birth defects and intellectual disabilities in order to identify deletions or duplications in the genome. There are over 400 described syndromes in which cleft lip and/or palate are noted [17–20]. One of the more common deletion syndromes associated with a dysmorphic face including a cleft lip and/or palate, developmental delay and neuropsychiatric problems is 22q11.2 deletion also referred to as DiGeorge, velocardiofacial or Shprintzen syndrome [21,22]. Other deletion syndromes identified using chromosome analysis in which cleft lip and/or palate occurs include: partial monosomy of 1q, 4p, 4q, 5p, 6p, 7q, 9q, 11q, 12p, 12q, 18p, 18q and 21q [2,12].

To date, seven subjects (including our subject) have been reported with a distal chromosome 20q deletion including bands q13.1 and q13.3 without involvement of a ring chromosome, unbalanced chromosome translocations or subtelomeric 20q13.33 deletions detectable by fluorescence in situ hybridization analysis. Our subject did not present with AHO which is characterized by short stature, moderate obesity, a particular facial appearance, shortening of the fourth and fifth digits and metatarsals, hormone resistance and variable learning problems [9,12]. AHO is reported in some individuals with a 20q13 deletion including the GNAS gene. The GNAS gene is a complex, tissue-specific imprinting locus producing a G subunit-regulatory protein which functions as a guanine nucleotide-binding signal protein by stimulating the secondary messenger, cyclic adenosine monophosphate [15,23]. The GNAS gene produces multiple transcripts through alternative promoters and alternative splicing [24–27]. Why disturbances of GNAS function cause only some individuals to have AHO with the same or similar chromosome deletion is unknown.

Herein, we present our subject without features of AHO but with severe growth retardation, cognitive impairment, hypotonia, and dysmorphic features. Our subject had similar features seen in previous cases with a distal 20q deletion but had a larger deletion (7.3 Mb in size consisting of 30 genes and 6 sno/miRNAs) compared with the approximate 6.0 Mb deletion seen in two previously reported cases by Geneviève et al. [6] determined by microsatellite DNA marker analysis. Parental studies were not available for our subject.

The previous six distal 20q13 deletion cases were found to have severe growth retardation, intellectual disability, decreased speech, intractable feeding difficulties, hypotonia and similar facial dysmorphism with

Table 1
Clinical features of subjects with a 20q13.2- q13.3 deletion

Clinical features	Subject 1 Geneviève et al. [6] 20q13.2-q13.3	Subject 2 Geneviève et al. [6] 20q13.2-q13.3	Current subject 20q13.2-q13.33
Oligohydramnios	+	−	+
Growth retardation	+	+	+
Intellectual disability	+	+	+
Hypotonia	+	+	+
Feeding difficulties	+	+	+
Microcephaly	+	+	+
High forehead	+	+	+
Hypertelorism	+	+	+
Broad nasal bridge	+	+	+
Bulbous tip of the nose	+	+	−
Long philtrum	+	+	+
Thin upper lip	+	+	+
Small chin	+	+	+
Cleft lip	−	−	+
Malformed ears	+	+	+
Origin of the deletion	Paternal	Paternal	?

two patients presenting with features of AHO. Common physical anomalies seen in at least 50% of the reported subjects with the 20q13 deletion included intellectual disability, speech problems, pre- and postnatal growth retardation, microcephaly, hypotonia, a high forehead and broad nasal bridge, a thin upper lip and a small chin, malformed ears, hypertelorism, a bulbous nasal tip and malformed hands and feet. Of the previously reported cases only two (subjects 1 and 2 reported by Geneviève et al. [6]) were found with the same or similar interstitial deletion involving chromosome 20q13.2 and q13.3 bands and clinical findings seen in our subject (Table 1). Our subject had a unilateral cleft lip which was not previously observed in this contiguous deletion syndrome. The cleft lip could be considered a novel finding in this syndrome and possibly due to one of the deleted genes (i.e., *TFAP2C*) in the 20q region. This *TFAP2C* gene modulates the transcriptional activity of vitamin A target genes via the retinoic acid receptors and expressed in migrating neural crest cells found in the frontonasal and maxillary areas in the developing embryo [6,28]. Disturbances of this gene activity in our patient may account for cleft lip development. Other genes in the 20q13.2-q13.33 region including GNAS and a member of the cadherin gene family (i.e., *CDH4*) are reported to cause autism and developmental delay [6,29–31].

New genetic testing methods using microarray and next generation sequencing will provide more specific and detailed genetic information at the DNA level to further characterize the type and size of the genetic defect and more precisely determine the location in the genome. Therefore, the variability seen in clinical presentation of individuals with the same reported chromosome deletion by routine cytogenetic analysis may be further explained by comparing the size and position of the deletion using microarray analysis. The authors encourage the report of additional individuals with these chromosome findings with more precise localization of the deletion breakpoints and genes involved using microarray analysis. Better genotype/phenotype correlation will improve medical management and genetic counseling.

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