La Prensa Medica Argentina

Case Report

Familial Y Micro deletion with Cleft Lip

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Rec date: Feb 26, 2016 **Acc date**: April 05, 2016 **Pub date**: April 10, 2016

Abstract

Cleft lip and cleft palate are frequent congenital malformations that occur as isolated presentations or as a constellation of symptoms with other genetic complications or as part of a specific genetic syndrome. However, there have only been few reports of cleft lip or palate with Y chromosome abnormalities. We report a rare case of familial Yq11.22-Yq11.23 micro deletion with cleft lip and palate.

Keywords: Chromosome Y deletion; Cleft lip; Cleft palate

Introduction

The most common craniofacial malformation identified in the newborn is the orofacial cleft, which consists of cleft lip with or without cleft palate (CL/P) or isolated cleft palate (CP). They can occur as part of a syndrome involving multiple other organs or as an isolated malformation, although most studies suggest that about 70 percent of cases of CL/P and 50 percent of CP are non-syndrome. Although both congenital anomalies result in malformation of the mid face, CL/P and CP differ with respect to embryology, etiology, candidate genes, associated abnormalities, and recurrence risk [1].

In the United States, the estimated prevalence of orofacial clefts is 16.9/10,000 live births. CL/P occurred in 10.5/10,000 live births and isolated CP occurred in 6.4/10,000live births. The prevalence of CL/P varies by race/ethnicity with the lowest in African American, highest in Native Americans and Asians, and at an intermediate level in Caucasians. The sex ratio among affected infants varies by type of defect with CL/P occurring more often in males while CP is more common in females [2]. There are many factors implicated in the cause of CL/CP including genetic defects, environmental agents, and medications including antiepileptic agents, cigarette smoke, alcohol, and possibly foliate deficiency [2,3,4,5].

Case Report

Our patient is a 7 year old male who was brought in by his parents for evaluation of abnormal behavior; attention deficit and hyperactivity disorder (ADHD), and generalized delays. He had been receiving speech therapy and was previously enrolled in Early Childhood Intervention (ECI) to help with delays and had been improving very slowly, particularly with speech. On physical exam he was hyperactive but with pleasant demeanor. He was around the 50th percentile for both height (124.5cm 55%) and weight (22.2 kg 47%). He was dimorphic with a scar on his upper lip from repair of cleft lip and palate and a depressed nose. He also had a grade II/VI pan-systolic murmur heard over entire precordium [6].

He was born at term after an uncomplicated pregnancy. Cleft lip and palate were discovered at birth and subsequently repaired. Both Father and Mother have similar cognitive delays. Father, Grandfather, and paternal uncle also had cleft lip and palate (Figure 1).

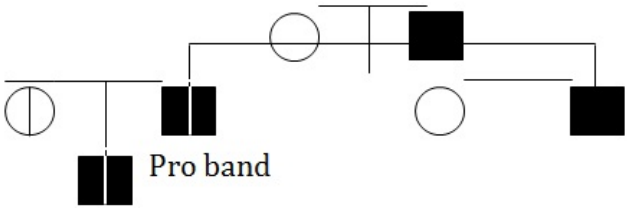

Figure 1: Family Pedigree.

Methods

Microarray analysis

Comparative Genomic Hybridization analysis was performed on this patient's peripheral blood DNA. A deletion was found on chromosome Y within banding region q11.223-q11.23 with the molecular size of 1.75Mb (Figure 2). The genomic sequence covered by this deletion spans from 23,683,071 to 25,438,059 base pairs. This deletion contains different gene families such as RBMY and DAZ. DAZ gene clusters are present in a non-overlapping manner on the Y-chromosome described as AZFa, AZFb, and AZFc (azoospermia factors a, b, and c) [7]. After comparison with the genomic sequence database (Decipher syndrome database) deletion in this patient partially involving AZFb and AZFc regions as these regions sequence span from 19,964,826 to 27,793,830 base pairs [8].

Discussion

The process of mid face development involves genes which control cell patterning, cell proliferation, extracellular communication, and differentiation. Gene defects in each of these developmental processes crucial to mid face development are associated with cleft malformations. While at least one major gene may be operative in one-half of patients with CP or CL/P, in most cases, 2 to 20 genes are thought to interact to result in facial clefting. There are some genes which have been implicated in animal models as responsible for orofacial clefting including sonic hedgehog gene, TGF-alpha variant causing extracellular matrix defects, TGF-beta gene causing differentiation defects, and IRF-6 which is involved with interferon regulatory factors. Similar findings in humans have been more limited [3]. However, in our patient there were no mutations affecting the genes known or thought to cause facial clefting, and there were no other deletions other than on the Y chromosome seen on the microarray. According to the Decipher syndrome database, there has been no report of cleft lip or palate in patients with similar deletions, only azospermia, making this the first report of a familial cleft lip and palate with a familial deletion in the AZFb and AZFc regions of chromosome Y [8].

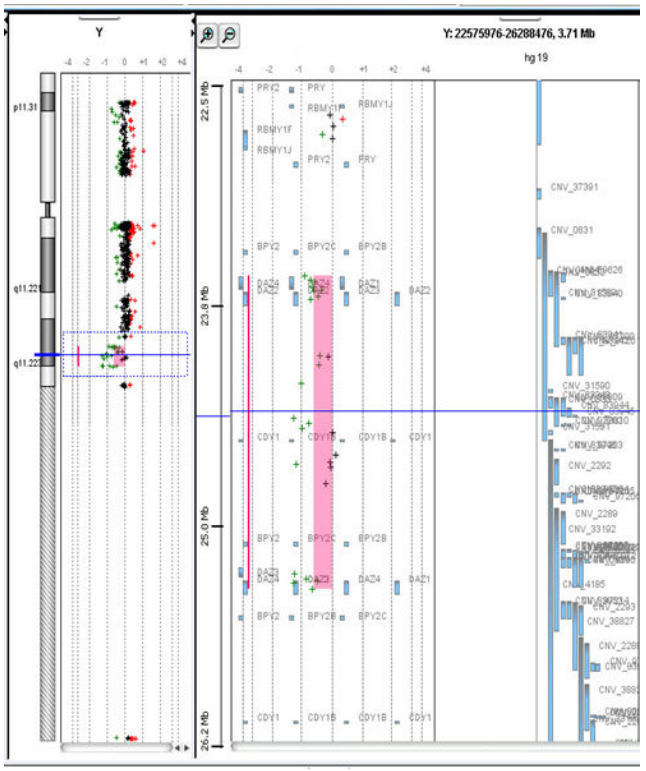

Figure 2: Banding region and genes involved in deletion on chromosome Y.

A follow up microarray analysis was performed on the father who had the same exact deletion making this a familial deletion and not a de novo event.

Due to the relative frequency of isolated cleft lip and cleft palate without chromosomal abnormalities, and with the lack of current knowledge of genes causing cleft lip or cleft palate on the Y chromosome, and without the full comprehension of all the genes and gene functions found in the deleted region, it is difficult to determine whether this is an isolated finding or if it is due to genetic abnormalities in the specified gene region. This could be a case of familial facial clefting not directly caused by the familial deletion. Although it is unclear whether there is a direct link between the CL/P and the chromosomal deletion, it is clear that there is a familial inheritance of CL/P with cognitive delays and an inherited chromosomal deletion. This deletion is most likely a familial variant with incomplete penetrance leading to possible fertility, and possibly a new variant phenotype leading to cleft lip and palate and developmental delays, with a possible epigenetic factor. With this section being the only deletion found on chromosomal analysis, and with the father having the same deletion and cleft lip/palate phenotype, it cannot be ruled out that this deletion in the Y chromosome is the cause for the cleft lip and palate. This should lead to further investigation of this region as the molecular characterization of these regions at gene level can unveil the functions of these gene clusters.

Acknowledgments

This study makes use of data generated by the DECIPHER Consortium. Funding for the project was provided by the Welcome Trust.

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