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Research Article

Cytogenetic Evaluation of Cleft Lip and/or Palate

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Abstract

Possible causes of congenital defects such as the common cleft palate and/or libidinal (CLP) are multifactorial. It is known that they occur as a result of both genetic and environmental risk factors. Although it seems that these defects are due to a genetic cause, the cause of most cases is still unknown. In this study, the relationship of CLP with possible cytogenetic causes was evaluated. It includes 10 children (mean 1.2 years) who were sent for cytogenetic analysis with the complaint of CLP. In this study, conventional karyotyping was performed in 10 patients who were referred to our genetics laboratory with complaints of cleft lip and/or palate. Structural and numerical CAs were found in four of the 10 patients with CLP, and a normal karyotype was found in 6 of them. Two male patients had XXY karyotype, one had 22q12 trisomy and one had pericentric inversion on chromosome 9. Our findings support that an excess of an X chromosome can affect the development of cleft palate and lip, and that the dosage of some genes in the 22q12 region contributes to CLP. It has also created new opportunities for both the advancement of our understanding of orofacial cleft (OFC) biology and clinical research. However, molecular genetic analyzes in patients with CLP will help to fully reveal the genetic etiology of the disease.

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INTRODUCTION

CLP is one of the most common and well-known congenital orofacial anomalies. CLP are the most common craniofacial birth defects in humans. Orofacial clefts may or may not be associated with a syndrome (syndromic, non-syndromic). These combined factors complicate the genetic analysis of non-syndromic forms of CLP. Clefts affect approximately 1 in 700 individuals [1]. The average incidence for CL/P is reported to be around 1 in 700 newborns [2,3]. Cleft palate is seen in 1 in 1500 newborn babies. Data on the incidence of PLC in our country are not sufficient. The incidence of cleft lip and palate in Turkey has been reported as 1.1 per thousand, and the incidence of isolated cleft palate as 0.77 per thousand [4]. The possible causes of CLP are multifactorial and include both genetic and environmental risk factors. Although these defects seem more likely due to a genetic cause, the cause of most cases is still unknown. These defects may occur alone or as part of a wide variety of chromosomal, gene, or teratogenic syndromes. Although significant progress has been made in identifying genetic and environmental triggers for syndromic ones, the etiology of non-syndromic forms has not yet been fully defined. Recently, several different genetic and environmental risk factors have been identified and validated for non-syndromic CLP through careful phenotyping, genome-wide association studies, and analyzes of animal models. In a large series of patients, some appear to result from single mutant genes, some from chromosomal abnormalities, some from specific environmental agents, and some from the interaction of many genetic and environmental differences, each with a relatively minor effect. Because of the heterogeneous etiology of CLP, it is necessary to know the biology of facial development and how environmental risks interact with genetic factors. Genome-wide linkage and association studies have identified new loci with significant relevance. As a result, it shows a multifactorial inheritance pattern in which small individual genetic risk factors can interact with environmental covariates [5]. There is significant phenotypic variation in individuals and family members with birth defects with orofacial clefts. The incidence of structural and numerical chromosomal changes in patients with orofacial clefts (OFC) has been reported as 3.6% [6]. This study may provide information to better interrogate cytogenetic analysis for loci other than CLP-related coding regions. Our knowledge on this topic is largely biased, so more extensive research is needed to understand the mechanisms underlying these defects. This study may provide information to better interrogate cytogenetic analysis for loci other than CLP-related coding regions.

METHODS

Ten children from the pediatric clinic with complaints of cleft palate and lip were sent to our laboratory for genetic analysis. The male/female ratio of the cases was 4/6 (0.7), the mean

gestational week was 37.7, and the mean maternal age was 26.0. These children ranged from 17 days to 3 years (mean 1.2 years). There was only cleft palate in one of the cases, and both cleft palate and lip in the others. A seventeen-day-old boy with cleft lip and cleft palate was admitted to the neonatal service because he could not be fed. The patient's parents were the first children of a 25-year-old mother and a 27-year-old father, who were second-degree relatives. There was no similar disease in her family history, and her physical examination revealed low ear, hypertelorism, bilateral cleft lip and complete cleft palate deforming the nasal root, low hairline, and pes equinovarus (Figure 1). A three-year-old boy was sent for genetic analysis for unilateral cryptoorchidism. The patient had previously been operated for cleft palate and lip, and there were surgical scars on the upper lip and philtrum (Picture 3,4). The patient's parents were related, he was the first child of a 23-year-old healthy mother and 29-year-old healthy father, and there was a diagnosis of CLP in his family history. Other children were those with only cleft palate or cleft lip and palate defect without any other congenital defect. There was consanguineous marriage between the parents of four cases. Conventional karyotyping was performed using 4 ml of peripheral blood for sowing, harvesting, banding and analysis. All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee (Scientific Research Ethics Committee Directive) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

Numerical and structural damage were found in 4 of 10 patients analyzed. Two of these 4 patients had 47,XXY, one 47,XX,del(22q12 > qter) or partial trisomy 22q12, and one had inv(9)(p11;q13). The other 6 cases had normal chromosome establishment.

DISCUSSION

The identification of many genes and loci involved in the etiology of OFCs has emerged as the result of decades of research. Nevertheless, Although many studies have also been conducted on the genetics of cleft lip and palate, no consensus has been reached on the inheritance patterns. Understanding the etiology of OFCs is also important for developmental biology. There has recently been evidence to support a multifactorial inheritance pattern. Many genetic and environmental factors play a role in most clefts, as well as polygenic factors. Genetic factors cause clefts in about 20% to 50% of cases, while the rest can be attributed to environmental factors or gene-environment interactions. In a large series of patients, some appear to result from single mutant genes, some from chromosomal abnormalities, some from specific environmental agents, and some from the interaction of many genetic and environmental differences, each with a relatively minor effect. In the present study, it was observed that only one patient had a cleft palate, and it was not accompanied by a lip. To date, there have been a large number of recognized syndromes, each of which is rare, that includes cleft lip and/or palate as a single feature. Of these, about 60% are manifestations of mutant genes and 40% do not appear to be familial. Some mutant genes can cause isolated cleft palate in some cases and cleft lip in others, with or without cleft palate. In other cases, isolated cleft palate is visible but not cleft lip. It has been estimated that less than 3% of all cases of cleft lip and/or palate represent a syndrome of some kind and that those with a genetic basis are more likely to have isolated cleft palate than cleft lip with or without cleft palate. There is strong evidence that secondary cleft palate is generally different from primary cleft palate and lip both developmentally and genetically during the embryonic period. Genetic findings in family studies showed that the incidence of isolated cleft palate increased in siblings of patients with isolated cleft palate, but the incidence of cleft lip did not increase. Genetic aberrations are known predisposing factors for syndromic and nonsyndromic CLPs. Structural and/or numerical CAs are associated with the OFCs. Changes in the structure or number of chromosomes disrupt the genetic balance. Such genetic changes lead to malformations of the genes responsible for lip and palate development, such as CL, CP, or both. Many studies have shown that orofacial clefts are associated with structural and numerical CAs or that they occur incidentally in Down, Patau, Edward and Klinfelter syndromes. In the present study, the sex ratio was 3/7 (male:female). It appears more in female cases than in males. This contradictory situation may be due to the small number of cases. Worldwide, it has been reported that CL/P is more common in men, while CP is more common in women. The sex ratio of CLP in the Caucasian population is 2:1 (male:female) [7].

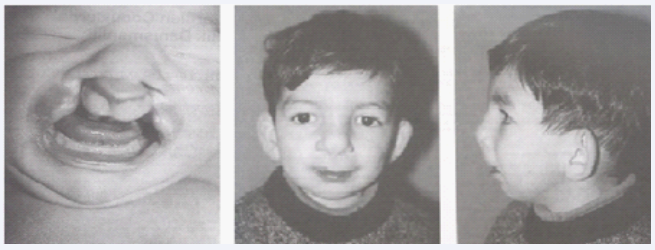

Figure 1 The facial appearance of two cases with 47,XXY karyotype.

A change in chromosome number can lead to abnormal genetic material that disrupts the embryonic development process. There are some autosomal and sex chromosome aberrations, albeit in small numbers, associated with oral abnormalities. In the present study, we reported 47,XXY karyotype (Klinefelter syndrome=KS) in two boys. The seventeen-day case had phenotypic abnormalities such as CLP, droopy ears, hypertelorism, and unilateral cryptoorchidism. The other three-year-old case had unilateral cryptorchidism and mild mental retardation. The parents of both cases were under the age of thirty. Most newborns with KS have small, stiff testicles and varying symptoms of androgen deficiency, including gynecomastia, hypogonadism and infertility, short stature microcephaly, hypertelorism, flat nasal bridge, fifth finger clinodactyly, bifid uvula, heart defect, radioulnar synostosis, genu valgum, and similar clinical abnormalities [8,9]. However, oral anomalies are not among the phenotypic findings of XXY syndrome. Nevertheless, it has been suggested that the

loss or addition of an X chromosome may affect the shape of the skull base and thus the measurement of facial prognathism [10,11]. Thus, in a very recent study, it was reported that XXY karyotype in one patient with OFC [12]. Similarly, one study reported a newborn baby with a 48, XXXY/46, XY karyotype with a cleft palate [13-17]. Mental retardation, cryptorchidism, radioguinal synostosis, clinodactyly, chest deformity and other bone anomalies, strabismus and cleft palate abnormalities have been reported in patients with XXXXY syndrome [18,19] addition, congenital cleft palate anomaly was reported in two cases of 48, XXXY/46,XY mosaic in the past 13,20]. Although the relevance of such a difference is unknown due to the rarity of these cases, it is possible that an unusual phenotype of our case, cleft palate may be related to its karyotype.

The structural or numerical chromosomal changes may disrupt the functioning of the gene and cause malformations in the development of the lip and palate [21,22]. Similarly, several autosomal injuries are known to cause oriofacial abnormalities. In the present study, we also found deletion and inversion type structural CA. The patient with only cleft palate had two normal complete chromosome 22 in addition to del [22] (q12 > qter) or an extra 22q12 region, and the other patient with both cleft palate and lip had inv [9]. Microdeletions or microduplications occur very frequently in the region of chromosome 22q11.2 located in the proximal region. In addition to 22q11.2 deletions and duplications, other chromosomal abnormalities are also associated with CLP, often occurring in complex syndromes such as the chromosome 4p16.3 deletion in Wolf-Hirschhorn syndrome [23]. Similarly, genetic heterogeneity of chromosome regions 6p23, 2q13 and 19q13.2 and loci 4q25-4q31.3 and 17q21 has been reported in patients with cleft palate. CLP-associated microdeletions have also been reported in chromosome regions 20p12.3, 5q35.2-q35.3, 14q22.1-22.2, 4q21, 6p25.3 and 16p13.3 [24-30]. Also, it has been reported that bilateral cleft lip and bilateral thumb polydactyly develop as a result of deletion of some genes in chromosome regions 7p14.1, 4q32 and 4q34 [31,32]. Although there are still a few candidate genes and molecular pathways, we do not have a definitive mutation to explain the genetic background of most cases. Recent findings suggest that mutations or cytogenetic disruptions affecting specific cis-acting regulatory regions may play a decisive role. It has been reported that the inheritance pattern of CLP is compatible with the recessive single gene model [33]. Many genes contribute to the incidence of isolated syndromic cleft lip/palate cases. Although CLP formation is known to be associated with a number of genes such as transmembrane protein 1 and GAD1, it has also been found to be associated with mutations in the HYAL2 gene [34,35]. Especially sequence variants in IRF6, PVRL1 and MSX1 genes, and BMP4, SHH, SHOX2, FGF10 and MSX1 genes involved in midface morphogenesis have been widely reported [36].

Chromosome 22 is the second smallest chromosome in the human genome. The long arm of this acrocentric chromosome contains protein-coding genes. These disorders are common, with a prevalence of 1:2000, such as velocardiofacial syndrome (22q11 deletion syndrome, DiGeorge syndrome). Extra copies of the proximal region of chromosome 22q are known to cause cat eye syndrome, 22q11.2 duplication. Der(22) syndrome and cat eye syndrome are rare conditions characterized by increased copy number of the 22q11 region. The clinical findings of patients with this deletion show a wide spectrum. The reason for the wide phenotypic variation is unknown. It has also been suggested that patients with 22q11.2 deletion are susceptible to other syndromes. The reason for the wide phenotypic variation is unknown. Syndromes associated with recurrence of the 22q11.2 region show phenotypic variability ranging from severe abnormality to mild features or even a completely normal phenotype [37,38]. The most frequently reported symptoms in this duplication syndrome are mental retardation/learning difficulties, delayed psychomotor development, growth retardation, and muscle hypotonia. Other most common dysmorphic features are hypertelorism, broad flat nose, micrognathia, velopharyngeal insufficiency, dysplastic ears, epicanthal folds, and downward sloping palpebral fissures. Less common symptoms are congenital heart malformation, visual and hearing impairment, seizures, microcephaly, ptosis, and urogenital abnormalities.14 It has been reported that the prenatal phenotypes of the repeat sequences in the 22q11.2 region are different and this may be related to gene function [39]. In the literature, haploinsufficiency or triplosensitivity score would further support pathogenicity assessment of chromosomal repeat sequences to evaluate whether the phenotypic differences occurring in patients with 22q11.2 variants are evidence that these genes/regions are dose sensitive. Although most of the dozens of genes in the 22q11.2 region are well characterized, most of the expression mechanism of 22q11 is not yet known. Data on the penetration of this number of repetitive sequences are quite lacking. Some patients appear phenotypically normal, while others with the same genotype have mild to severe abnormalities. Therefore, more evidence needs to be gathered regarding the genotype-phenotype contributions of different 22q11.2 duplicated regions. It has been reported that proximal region-associated variants of abnormal 22q11.2 repeat sequences show more severe clinical phenotypes, while those associated with central and distal regions show milder or even normal features [40]. Considering all the phenotypic differences, we think that anomalies such as cleft palate and lip can be considered as an indicator for 22q aberrations.

Chromosome inversions are a relatively common structural alteration. We found 46,XY,inv(9)(p11q13) chromosomal aberration in one patient. Inv(9) is one of the most common (1-3%) balanced structural chromosomal abnormalities and is considered a normal familial variant. However, it has been reported in individuals with recurrent miscarriages, mild growth retardation, craniofacial malformations, undescended testicles, skeletal malformations, mental retardation, and hermaphroditism [41-43]. It seems difficult to decide whether this inversion is a chromosomal abnormality or a polymorphic variant of the chromosome. Geneticists have sought the answer to this question for years. A different dysmorphic symptom was described in many cases with del(9)(pter-p22 or 21). While malformations of facial features are more common in these patients, other

congenital malformations are relatively rare and mild. Rarely, cleft palate, diaphragmatic hernia, hydronephrosis, radiological anomalies of the ribs and vertebrae are also seen [44]. Similarly, pericentric inversion of chromosome 9 was reported in two patients with oriofascial cleft in a very recent study [12]. More research is needed to definitively state the relationship of inv(9) to cleft palate.

CONCLUSION

Although oral anomalies are not among the phenotypic findings of XXY syndrome, our findings suggest that an excess of one X chromosome may affect the development of cleft palate and lip. At the same time, our findings support that the dosage of some genes in the 22q12 region contributes to CLP, suggesting that it may be effective in better characterizing the complex genotype-phenotype relationship of the disease. Therefore, the 22q12 region may help us better understand the complex pathogenesis of CLP. Nevertheless, more evidence needs to be collected for the evaluation of the pathogenicity (genotype-phenotype) of the 22q12 region repeat/trisomy. It is still unknown whether trisomy 22q12 is associated with other serious congenital anomalies such as cleft palate. Cytogenetic studies contribute to finding genes involved in the unknown genetic etiology of CLP. Furthermore, our findings both advance our understanding of CLP developmental biology and open up new opportunities for clinical research.

Ethics Statement

Informed consents were obtained from the patients› parent who participated and managed in this report for publication and any accompanying images. The report conformed to the guidelines of the institutional review board of our Institution, which approved its ethical aspects.

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Author Contribution Statement

OD designed the study, obtained the date, wrote and revised the article.

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