Case Report

An insight into genetics of non-syndromic cleft palate

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Abstract

Our proband is a 29-year-old man, who is affected with soft cleft palate and hypernasality. A study of about six generations of this family pedigree shows that cleft palate has repeatedly occurred in males, with probably a X-linked recessive pattern of inheritance. Interestingly, the sister of the proband is affected with hypernasality and she has an affected son. This is the first report of X-linked inheritance pattern of cleft palate in Iran.

Key Words: Cleft palate, inheritance pattern, X-linked

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INTRODUCTION

Cleft palate (CP) is birth defect which occurs during 7–12 weeks of embryonic development.[1] The development of secondary palate is an important step in the evolution of head and face, with significant roles in breathing and eating. It is clear that a variety of transcription factors and signaling molecules contribute to growth, elevation, and fusion of the palatal shelves. CP happens when the roof of the baby's mouth (palate) does not develop normally during pregnancy, leaving an opening (cleft) in the palate that may go through to the nasal cavity. A cleft can form on any part of the palate, including the front part of the roof of the mouth (hard palate), the soft tissue constituting the back of the roof of the mouth (soft palate also known as velum or muscular palate), and the small flap of tissue that hangs down from the soft palate (uvula).[2,3] The soft palate is moved around by a complex series of muscles that can lift it up, pull it down, contract it, or stretch it wide. The purpose of the soft palate is to serve as a mobile flap preventing food and water from entering the nasal passages during swallowing.

Speech problems including hypernasality are the most common deficits of CP patients. In normal speech, the soft palate lifts and moves toward the back of the throat, separating the nasal cavity from the mouth so that air and sound can be directed out of the mouth. In patients with CP, the muscles of the palate work less effectively and the palate is too short to reach the back of the throat and achieve closure between the mouth and nose, so hypernasality occurs. In hypernasality, air leaks from the nose during speech and some may say that hypernasal speakers sound as if they talk through their nose.[4-6]

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Cleft palate can be divided into two groups syndromic that is associated with deficits or structural abnormalities occurring outside the region of cleft and non-syndromic form which is an isolated condition unassociated with any recognizable anomalies. Although the exact cause of non-syndromic CP is unknown, however, most researchers believe they are caused by a combination of environmental and genetic factors.[3,7-9] Most of the efforts are concentrated on the finding relevant loci, because the identification of responsible genes will make clear the molecular pathways involved in this complex disorder and provide a better understanding of pathophysiology of CP.[10] The suggested inheritance patterns for CP are autosomal dominant and X-linked recessive. Approximately half of all babies are born with cleft anomalies are affected by only CP, a quarter have a cleft lip, and a quarter have a cleft lip and palate. Prevalence varies by ethnic group, geographic region, and sex. The frequency of isolated CP is higher among females than males,[1,7,11] but there are some studies reporting that the frequency of isolated CP in males is proportionally higher than females. So, it seems that in these studies the inheritance pattern of CP is X-linked. [10,12-14] In X-linked form of CP, defect in some genes such as *TBX22*, *CPXCR1*, and *KLHL4* are mentioned to cause related problems. *TBX22* is a recently described member of the T-box containing transcription factor gene family that is conserved throughout evolution and is responsible for X-linked CP in some cases.[15-21] These family members are implicated in early development and in particular mesoderm specification. This gene is located on Xq21.1 [10]Although no gene deletion has been described yet, various mutations including nonsense, splice site, frame shift, and missense mutations have been identified in *TBX22* gene, which are related to non-syndromic CP.[2] Another gene that has been suggested for X-linked CP is *CPXCR1* (CPX chromosomal region candidate gene 1 protein). This gene was assigned to the Xq21.3-q22 region between DXYS12 and DXS17 and is associated with X-linked CP. The protein of this gene contains a motif similar to the motif of zinc-finger proteins.[22,23] *KLHL4* [kelch-like 4 (*Drosophila*)] is another gene located on Xq21.3 and involved in CPX. This gene encodes a member of the kelch family of proteins, which are characterized by kelch repeat motifs at the C-terminus and a POZ/BTB protein-binding domain toward the N-terminus. It is thought that repeats are actin-binding domains. This gene consists of 11 exons spanning a genomic interval of approximately 150 kb and alternative splicing of it results in two transcript variants encoding different isoforms. The mRNAs of *KLHL4* and *CPXCR1* are widely expressed in fetal tissues, including the tongue, mandible, and palate. However, the specific function of this protein has not been determined.[20]

In this study, we report a family with X-linked CP for the first time in Iran.

CASE REPORT

Proband is a 29-year-old man who is affected with CP and was under treatment at Cleft Lip and Palate Clinic of Isfahan Medical University. Based on the medical interview, physical exams, echocardiogram, ophthalmologic evaluations, eudiometry test, and a routine blood examination, especially for checking if thyroid and parathyroid hormones were normal, the patient was diagnosed to have non-syndromic soft CP with hypernasality. He was born in a third-degree consanguineous marriage and was originally from Charmahal-Bakhtiyari province of Iran. He had a third-degree consanguineous marriage and has a 3-year-old healthy daughter, but his uncle IV-8 and nephew (VI-4) were affected by soft CP. Study of about six generations of this family pedigree showed that CP repeatedly occurred in males [Figure 1]. Another considerable point in this pedigree is that the sister of the proband (V-3) who has been affected with hypernasality disorder has an affected son. Regarding the occurrence of the disorder only in males who were born in consanguineous and non-consanguineous marriages in several successive generations, It seems that CP is a genetic disease in this family and its inheritance pattern is X-linked recessive.It seems that the sister of proband (V-3) is carrier of soft CP, leading to an affected son. Howevere, regarding the X-linked recessive inheritance pattern of the disorder, V-3 should not be affected phenotypically, like the other carrier females of the pedigree who have affected sons. But V-3 showed the mild form of

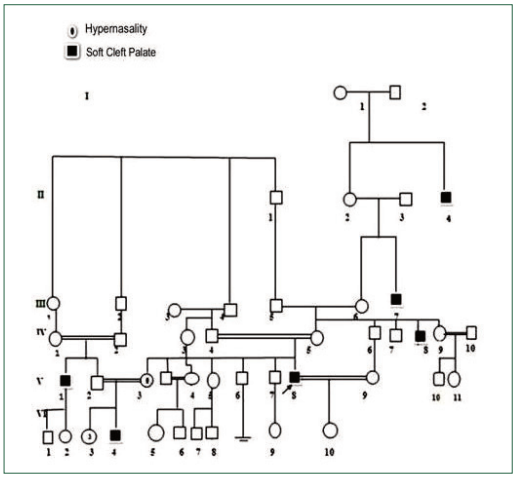

Figure 1: Six generations of pedigree with X-linked soft cleft palate

disorder by just having hypernasality that is probably due to unusual inactivation of the X-chromosome, so that mutated copy of the gene is located on the X chromosome which is active in most of the cells.

DISCUSSION

CP is one of the most common congenital malformations worldwide. Non-syndromic form of CP can be caused by various genetic and environmental factors, so it seems to be a multifactorial disorder.[24] Usually geneticists consider CP as a multifactorial disorder in determining risk in a family tree that has several occurrences of the CP; however, according to recent progress in determining the genes involved in this disorder, autosomal dominant and X-linked recessive inheritance patterns have been suggested in patients with familial history of the disorder, and it is necessary to draw the pedigree of the family to determine the exact inheritance pattern of it and estimate the recurrent risks in the family. In X-linked non-syndromic CP, *TBX22* is the most important gene that has been identified till now.[10,11] Although it has been reported that the frequency of cleft lip or combined cleft lip and palate is more common in boys and CP on its own is more common in girls, there have been some researches that imply the frequency of CP is much higher among males than females,[12] especially when the inheritance pattern of CP is X-linked. Therefore, it is completely logical to have majority of patients among males than females. In this study, investigation of proband and his family in six generations indicated six males with soft palate and one female with hypernasality. X-linked inheritance pattern of CP has been found in this family. It seems that the female showed milder form of the disease by just having hypernasality because of possessing two X chromosomes. But males with one X chromosome show severe form of soft CP. X-linked recessive diseases usually occur in males because males have only one X chromosome, whereas female carriers are generally normal in phenotype due to the random inactivation of one of the two X chromosomes in all somatic cells. Normal females are thus a mosaic of two cell populations, each expressing the alleles from one X chromosome or the other. Thus, in female carriers of an X-linked mutation, approximately 50% of cells on average have the normal allele on the active X chromosome (with the mutant allele being on the inactive X chromosome), and these functionally normal cells are generally sufficient to spare females from the clinical effects of an X-linked disease. The noticeable fact is that occasionally, females do have clinical manifestations of an X-linked disorder. In some cases, it is caused by either mutations in autosomal genes (genocopies) that have the same clinical effect as a mutation in an X chromosome gene in males or a mutated copy of the gene on an X chromosome that is active in most of cells;[25] the latter one probably occurred in our proband's sister (V-3) so that mutated copy of the gene had been located on one of her X chromosomes which is active in most of her cells, leading to milder form of the disorder.

For further help to this family, linkage analysis can be used to prove the hypothesis of X-linked recessive inheritance pattern in this family, and then sequencing analysis on the *TBX22*, *CPXCR1*, and *KLHL4* is suggested to be performed on the proband.

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