Case Report

A case report of 22q11 deletion syndrome confirmed by array-CGH method

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Velo-cardio-facial syndrome (VCFS) is caused by a submicroscopic deletion on the long arm of chromosome 22 and affects approximately 1 in 4000 persons, making it the second most prevalent genetic syndrome after Down syndrome and the most common genetic syndrome associated with cleft palate. Most of the 22q11.2 deletion cases are new occurrences or sporadic; however, in about 10 % of families, the deletion is inherited and other family members are affected or at risk for passing this deletion to their children. This report describes a 1.5 years-old male child with clinical signs of velo-cardio-facial syndrome (VCFS) presented with heart defect, soft cleft palate, developmental delay, acrocephaly, seizure, MRI abnormalities and descriptive facial feature, such as hypertelorism. Array-CGH test was done to confirm the diagnosis; the result revealed a 2.6 Mbp deletion in 22q11.2 chromosome that containing *TBX1* and *COMT* genes. Our data suggest that haploinsufficiency of *TBX1* gene is probably a major contributor to some of the syndrome characteristic signs, such as heart defect. Because of developmental delay and dysmorphic facial feature were observed in the index's mother and relatives, inherited autosomal dominant form of VCF is probable, and MLPA (multiplex ligation-dependent probe amplification) test should be performed for parents to estimate the recurrent risk in next pregnancy.

Key words: VCF, 22qdel, CGH Array, Cleft Palate

INTRODUCTION

22q11 deletion syndrome (22q11 DS) is one of the most common human genetic syndromes and being the most common human microdeletion syndromes with an estimated frequency of 1 of 4000 in live births.[1,2] This deletion is common in most cases of DeGoerge syndrome, velo-cardio-facial syndrome and conotruncal anomaly face syndrome, all of which are encompassed by the designation '22q11.21 microdeletion syndrome'.[3-6] It is caused by deletion in long arm of chromosome 22, which has a wide phenotype spectrum and more than 180 features associate with the deletion. Although expanding phenotypes exist among 22q11 DS patients, most clinical features associate the syndrome with congenital heart disease velopharyngal insufficiency, anatomic and/or neuromuscular abnormalities of the palate, dysmorphic faces, immunodeficiency and learning and psychiatric problems.[7,8]

In the large majority of cases with 22q11DS, about 3 Mb is missed in one copy of chromosome 22 and in less than 10% of the affected individuals, a smaller 1.5 Mb deletion has been reported.[9,10]

Although several genes are located in 22q11, contribution of some genes, such as *TBX1* gene to the features of

Because of low-copy repeat (LCR) sequences located in the 22q11.2 region, non-allelic homologous recombination (NAHR) occurs in this region; leading to high prevalence of de novo deletions. De novo mutations occur in most of 22q11DS cases, but about 10% of the cases show autosomal dominant (AD) inheritance pattern.[5,12]

The primary symptom that is usually recognized in VCF children are cleft palate and whether the other late onset or mild anomalies, such as congenital heart defects, developmental delay (that might be confused with low IQ), immunological defects, hypothyroidism and hyper severe calcemia because of parathyroid hormone abnormalities, which may cause seizure, not be recognized as a part of a syndrome very early and be followed up properly first years of age, would

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cause severe effects. However, it is necessary to confirm the recognition of this group of cleft palate patients by molecular diagnosis in early ages to predict their probable abnormalities and learning problems in future to prevent some of them. In addition, molecular analysis of the syndrome in family will characterize the inheritance pattern of the disease to calculate the recurrent risk for next pregnancies.

In this study, we described the clinical and molecular findings in a 1.5 years old boy with a 2.6 Mb submicroscopic deletion in 22q11.21 concordance with 22q11DS. An aim of this study is to correlate the molecular findings with the proband's clinical phenotype.

CASE REPORT

A family with 2 boys, 9 and 1.5 years old was referred to Tohid genetic counseling center, Iran, Isfahan in 2011 for next pregnancy. The affected individual was a 1.5 years-old male child, born of a first-cousin consanguineous marriage. The boy was born at term after a normal pregnancy with a birth weight of 2790 gm, length of 52 cm and head circumference of 34.5 cm, which at present are 10 kg, 70 cm and 44.5 cm, respectively. He was the second child of the family and his 9 years old brother was normal. He had several clinical features including suborbital congestion, narrow palpebral fissures, small low set ears, prominent nasal bridge, brachycephaly, soft cleft palate and uvula cleft, closed PFO, right inguinal hernia, mild developmental delay and febrile seizures. He had mild developmental delay but no hyperactivity was seen, however, regarding to his age, it is a little soon to judge about his IQ and hyperactivity.

Mild atrophic change in tempo frontal and narrowing of corpus callosum, mostly in anterior was seen in C.T scan. Hearing test, thyroid test and blood calcium was normal. PTH test was 60 ng/ml (normal range is 10-65 ng/ml), that was extreme limit of normal and is better to be followed up in future.

Combination of these phenotypes made chromosome 22q11DS syndrome as a possible diagnosis. For this reason, the genomic DNA was examined by human Genome Microarray kit 105A (Agilent). This is an array with more than 100000 probes covering the whole human genome with an average theoretical spacing of 15 Kb. After hybridization, the array was scanned with the Agilent Microarray Scanner (G2565BA), the results were analyzed using Feature Extraction Software v.9.5 and Genomic Workbench 5.0 Microarray CGH; result revealed a chromosomal imbalances in this patient including a 2.6 Mb submicroscopic deletion in 22q11.21 concordance with 22q11DS.

DISCUSSION

22q11DS is one of the most clinically variable syndromes, including several features associated with the deletion region.[13] Variable phenotypic expression may change over time; therefore, its early diagnosis requires much awareness. One of the clinical features of this syndrome is seizures, which can be related to hypocalcemia, stroke, cerebellar or cerebral cortical atrophy, or transient or chronic ischemia.[8,13-15] Although study of Ryan and his colleagues[15] showed that seizures in most cases of the 22q11DS are due to hypocalcemia, our case had an early onset of febrile seizures without hypocalcemia.

Patients with chromosome 22q11.2 deletion syndrome can have a variety of brain abnormalities when assessed by neuroimaging. Mild atrophic change in tempo frontal and narrowing of corpus callosum mostly in anterior was seen in C.T scan of the patient presented in this case report. Regarding to normal blood calcium in this boy, it seems that his seizures might be because of brain atrophic changes.

We used array- CGH to detect successfully identified gains and/or losses of DNA copies in our case examined. It is a powerful tool for the rapid and accurate detection of genetic disorders, associated with copy number abnormalities and can significantly improve clinical genetic diagnosis and care.[16] Array-CGH detected a microdeletion in the 22q11.2 region, which underlies velo-cardio-facial spectrum.

To our knowledge, this is the first report of velo-cardio-facial syndrome in an Iranian population, confirmed by molecular diagnosis. As developmental and speaking delay, dysmorphic facial feature and hearing loss were observed in the proband's relatives, and also the proband's facial features is similar to both his mother and grandfather, inherited autosomal dominant form of VCFS is probable and detection of VCFS by MLPA[17] for proband's parents to estimate the recurrent risk in the next pregnancy is suggested.

We suggest that any family, with an unusual history of apparently unconnected clinical problems (for example, congenital heart disease, developmental delay, immune deficiency, hearing loss and seizure), may well be segregating a 22q11 deletion and should be investigated by molecular techniques. It seems likely that the true incidence of velo-cardio-facial syndrome is considerably higher than previously suspected.

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