Case Report

Study of a Family Presenting Novel Mutation of the TCOF1 Gene Associated with Treacher Collins Syndrome

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Abstract

Treacher Collins syndrome (TCS), due to a mutation in the treacle gene (5q31-32), is the most common type of Mandibulofacial Dysostosis (MDF). The most important features of the considered diseases are hypoplasia, micrognathia, microtia, conductive hearing loss, and cleft palate. In this paper molecular and clinical analysis in a family with several members affected by MDF are reported. Clinical signs as well as inheriting pattern have been considered to reach a correct diagnosis.

As genealogic tree showed Autosom Dominant pattern (AD), Autosom recessive diseases were not considered in different diagnosis. Furthermore, pathognomonic signs drew us to focus the attention on the possibility that Treacher Collins Syndrome occurred. The molecular research of gene TCOF1 confirmed the presence of a mutation that have never been described in literature before now (c.599delG.). MDF occurs in clinical and genetic different typologies of diseases, and in most cases a certain diagnosis can be reached by means of molecular genetics analysis.

Keywords: Mandibulofacial Dysostosis (MFD); Treacher Collins Syndrome (TCS); Orofacial features

Introduction

Mandibulofacial Dysostosis (MDF) concerns a genetically heterogeneous group of disorders characterized by abnormal craniofacial development that is not associated with any limb anomalies [1].

Treacher-Collins syndrome (TCS; OMIM#154500) or Franceschetti-Klein Syndrome is the most common form of MDF [2]. The incidence of TCS is about 1 in 50,000 newborns [3], it has autosomal dominant inheritance and high penetrance (90%).

TCOF1 are a de novo event in about 50-60% of cases, while in 40-50% of cases are maternally or paternally inherited [4]. Clinical and molecular analysis developed on a family where three members have been affected by TCOF1 are reported. Clinical examination on members of the above mentioned family suggested TCS. TCOF1 molecular analysis highlighted a mutation never described in literature, confirming clinical diagnosis.

Materials and Methods

After a gynaecologic request, a 22 years old pregnant woman (V.S. at 11 week), has been investigated for the prenatal screening of the first trimester (Down and Edwards syndromes, through bitest).

Clinical examination and personal as well as family Y anamnesis highlighted some specific signs, suggesting clinical diagnosis of MDF (Figure 1).

Mister V.F. (Figure1, I1), Mister V.D. (Figure 1, II2) and Mrs V.S. (Figure 1, II3) showed the following dysmorphic signs: zygomatic bones hypoplasia, mandibular hypoplasia, inferior eyelids coloboma and partial cilia absence, downslanting palpebral fissures, microtia and partial Artesia of external ear duct (Figure 2). They did not show mental retardation or any intellectual disability.

V.S. was hospitalised at the age of 9 for urgent surgery for a left
PCR products were purified either by digestion with Antarctic Phosphatase and Exonuclease I (New England BioLabs Inc.) and were sequenced in both directions using the Applied Biosystem Big Dye Terminator v3.1 Cycle sequencing kit. The new mutation was confirmed on more than 100 controls chromosomes by sequencing.

The mutation was named according to the genomic reference (NT_029289) and the cDNA that corresponds to the major treacle isoform (NM_001135243.1) [6]. Mutation nomenclature is based on Human Genome Variation Society (H.G.V.S.) nomenclature guidelines (http://www.hgvs.org/mutnomen) [7].

Results

Molecular analysis of TCOF1 gene confirmed clinical diagnosis of V.F., V.D. and V.S., highlighting the mutation c.599delG (Figure 3).

It was located in exon 6 and it produces a stop codon 19 codons later. Such mutation has not been previously described, and results in TCS clinical phenotype.

Mrs V.S. asked for genetic counselling: she was informed about the 50% risk of conceiving a child carrying her TCOF1 mutation and about the changeable clinical expression of the disease. After reflection, she refused to undergo genetic prenatal diagnosis. At twenty weeks ultrasound screening did not evidence any sign of TCS. A healthy male was born after uneventful physiological pregnancy.

Discussion

Mandibular facial Dysostosis (MDF) are to be considered as variable clinical phenotypes. In several cases molecular genetics analysis can be helpful to define the correct diagnosis. In the investigated family, clinical suspicion was confirmed by TCOF1 analysis.

Accurate etiological definition and molecular mechanisms insights allow defining prenatal diagnosis strategies or, in postnatal diagnosis. Early diagnosis in TCS patients allows planning early and accurate interventions from clinical as well as psychological point of view. A multidisciplinary approach, including maxillofacial surgery and orthodontist, allows treating anesthetic and functional disabilities and improving quality of life.

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References