Case Report

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Expanding the Phenotype of Treacher Collins Syndrome?

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Abstract

Treacher Collins Syndrome (TCS) is a congenital disorder of craniofacial development with variable phenotypic expression. Multiple genes have been implicated in TCS presentation, however most reported cases are caused by mutations in the TCOF1 gene. Here, we provide a description of a male infant with a familial mutation (c.4218dupG) in TCOF1 and concomitant holoprosencephaly (HPE), dysgenesis of the corpus callosum and cutis aplasia. Genetic analysis of common genes associated with HPE revealed a previously unreported variant of uncertain significance in the SIX3 gene but no definitive causal mutation. This is the first known case report of a CNS migrational malformation in TCS.

Keywords: Treacher Collins Syndrome (TCS), TCOF1, SIX3, Holoprosencephaly (HPE).

Introduction

Treacher Collins Syndrome (TCS), also known as mandibulofacial dysostosis, is a congenital disorder of craniofacial development with variable phenotypic expression. Down-slanting palpebral fissures, malar hypoplasia, mandibular hypoplasia, malformation of auricular pinna, coloboma of the lower eyelids, conductive deafness, and cleft palate are among the most frequent clinical presentations. Most cases are caused by mutations in the TCOF1 gene, although multiple causative genes have been identified [1-4].

Case Report

We report a 5-month old male infant born with TCOF1-related Treacher Collins Syndrome (TCS) in conjunction with holoprosencephaly, Dysgenesis of the corpus callosum and cutis aplasia. Fetal MRI showed middle interhemispheric holoprosencephaly (HPE), which was re-demonstrated on postnatal CT studies. In addition to typical craniofacial features of TCS, the infant has an approximately 1cm region of cutis aplasia of the posterior scalp. The child's mother is known to be affected with TCS, but has had normal brain imaging. Maternal and paternal family histories are reportedly negative for any known microforms of holoprosencephaly.

Targeted TCOF1 analysis on amniocytes was positive for familial c.4218dupG mutation with negative maternal cell contamination studies. Prenatal 500-band karyotype and postnatal aCGH/SNP chromosome microarray both show normal 46, XY male.

The infant had an attempted mandibular distraction procedure at 8 months of age, which was aborted due to adverse reactions to anesthesia including hyperthermia, hypercarbia and tachycardia. This event raised concern for malignant hyperthermia. Sequencing of RYR1, CACNA1S and STAC3 genes did not reveal any pathogenic mutations.

Molecular assessment of eleven genes related to HPE revealed one variant of uncertain significance in the SIX3 gene, specifically c.851C>G (p.Ala284Gly) which has not been reported in the medical literature.

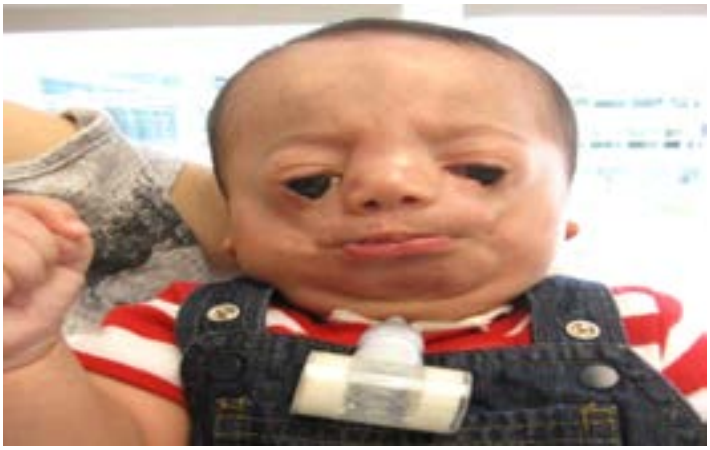
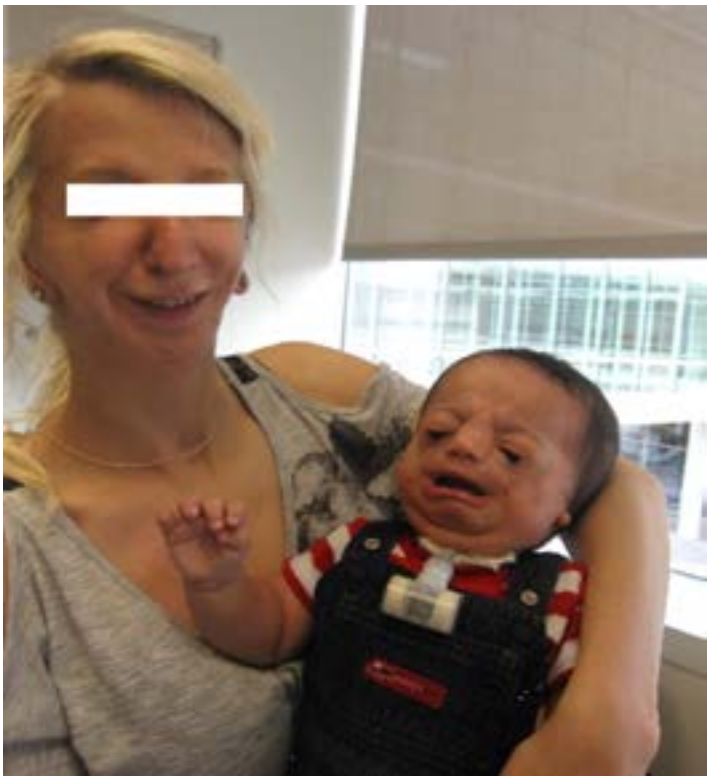


Figure 1: Clinical features of infant. Hypoplasia of the zygomatic bones and mandible, lower eyelid colobomas with sparse eyelashes, micrognathia, severe microtia and conductive deafness.



Figures 2 and 3: Clinical features of infant's mother. Mother has craniofacial features of TCS and has undergone greater than forty facial reconstruction surgeries. The patient's mother is known to be affected with TCS but has had normal brain imaging.

Discussion

The particular c.4218dupG mutation in TCOF1 that was detected in our patient is predicted to result in a frameshift, which is consistent with a majority of TCS-related mutations. It has been reported in association with classical TCS. To date, there have been no individuals described with a TCOF1 mutation in association with brain malformations, and thus, we believe this is the first reported pediatric patient with this scope of findings. The etiology of his adverse reaction to anesthesia is unknown but may be related to Autonomic dysregulation secondary to his brain anomalies. The identified c.851C>G variant of uncertain significance in the SIX3 gene has not been reported in the medical literature. An alteration at this same codon was described by the reporting laboratory in another patient with holoprosencephaly who had an alternate pathogenic mutation in another HPE gene, potentially negating the significance of this particular finding.

This is the first known case report of a CNS migrational malformation in TCS. Additional experience is needed to determine the extent to which CNS malformations may be related to the TCS spectrum. In order to evaluate for other genetic etiologies of holoprosencephaly in this patient, more comprehensive analysis including whole exome sequencing or whole genome sequencing is warranted.

Acknowledgment

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