Asian Journal of Pediatric Research

5(1): 1-5, 2021; Article no.AJPR.62455
ISSN: 2582-2950

Case Study: Patient with 7p14–P21 Deletion Spanning the *TWIST* Gene and the *HOXA* Gene Cluster

Nadia Mebrouk[1*] and Amina Barkat[1]

[1]Medicine and Neonatal Resuscitation Service, Reference National Center for Neonatology and Nutrition of Rabat, Children's Hospital Rabat, Morocco.

Authors' contributions

This work was carried out in collaboration between both authors. Authors NM and AB designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript and managed the analyses of the study. Authors NM and AB managed the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJPR/2021/v5i130162
Editor(s):
(1) Dr. Emiliana Cristina Melo, Universidade Estadual do Norte do Paraná, Brazil.
Reviewers:
(1) S. Mustaq Ahammed, Bharathiar University, India.
(2) Taha Hassan, Beni Sueif University, Egypt.
Complete Peer review History: http://www.sdiarticle4.com/review-history/62455

Case Study

Received 28 October 2020
Accepted 03 January 2021
Published 28 January 2021

ABSTRACT

Introduction: While several literature reports have been published about patients with microdeletions within chromosome 7p, only a small fraction of those reports is specific to deletions that encompass the TWIST gene and HOXA gene cluster. The large-span deletions within this cluster result in haploinsufficiency of six genes known to have a role in different autosomal dominant genetic disorders: TWIST1, GSDME (DFNA5), CYCS, HOXA11, HOXA13, and GARS. Deletion of TWIST1 gene on 7p21 and deletion of HOXA cluster on 7pl5.2 lead to Saethre-Chotzen syndrome and to hand-foot-genital syndrome, respectively.

Objectives: Our patient presented with a phenotype combining Saethre-Chotzen syndrome (SCS) and hand-foot-genital syndrome (HFS), which is similar to previously reported cases with a deletion spanning 7p21– p14.3. The objective of our report is to correlate the clinical observations with the patient's genetic test result, namely 46,XY,del(7)(p14p21).

Patient and Methods: We describe a patient who had manifestations of SCS and HFU, caused by an interstitial deletion of chromosome 7p21–p14 detected by RHG band.

**Corresponding author: Email: nadia.mebrouk@hotmail.com;*

Results and Conclusion: We therefore confirm previous reports that microdeletions of 7p spanning the TWIST gene and HOXA gene cluster lead to a clinically recognizable 'haploinsufficiency syndrome'. All of the features of this patient could be accounted for by combined effect of the deletion of the TWIST and HOXA cluster.

Keywords: Contiguous gene syndrome; hand-foot-uterus syndrome; HOXA; Saethre-chotzen syndrome; TWIST.

1. INTRODUCTION

The short arm of chromosome 7 contains several developmental regulator genes, including the TWIST1 gene on 7p21 and the HOXA gene cluster on 7p15. Deletion or mutation of these genes leads to Saethre-Chotzen syndrome (SCS) and hand-foot-uterus syndrome (HFU), respectively [1]. SCS is a genetic condition characterized by craniosynostosis due to the premature fusion of certain skull bones which results in an abnormally shaped head [1,2]. Other dysmorphic features may manifest as ptosis (droopy eyelids), a high forehead, a low frontal hairline, a wide nasal bridge, or broadly spaced eyes. One side of the face may appear noticeably different from the other (facial asymmetry), and two or more digits may be fused together (cutaneous syndactyly). Some patients exhibit maxillary hypoplasia and prominent ear crura [1,2]. HFU (also known as hand-foot-genital syndrome) is characterized by small hands with hypoplastic proximally placed thumbs and feet with small halluces. Some patients also exhibit short or uni-phalangeal second toes with absent nails, or with postaxial polydactyly of the hands. Although both sexes may have ureteral malformations, males tend to have hypospadias and females have duplication of the uterus and sometimes the cervix in addition o a septate vagina. While HFU is caused by mutations of the HOXA13 gene on 7p15.2 [1], larger deletions of the HOXA gene cluster (HOXA1–HOXA13) result in HFU in combination with other malformations [3].

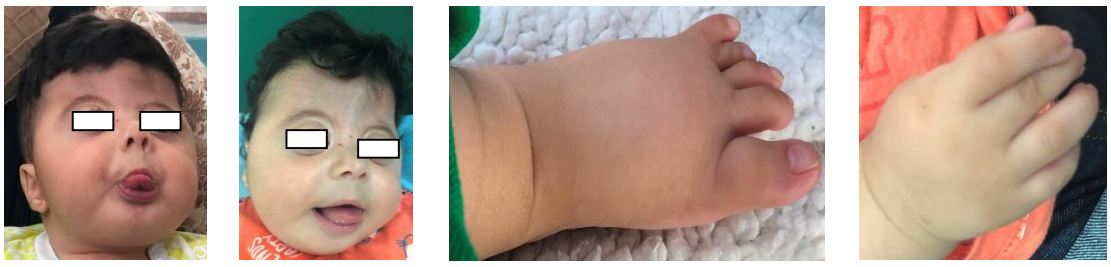
We report a patient with clinical features of both SCS and HFU due to a much larger deletion that spans the TWIST and HOXA gene clusters. The case of our patient confirms Fryssira et al.'s suggestion that deletions encompassing TWIST and HOXA genes represent a recognizable 'haploinsufficiency syndrome' [1].

2. PATIENT AND METHODS

2.1 Case Report

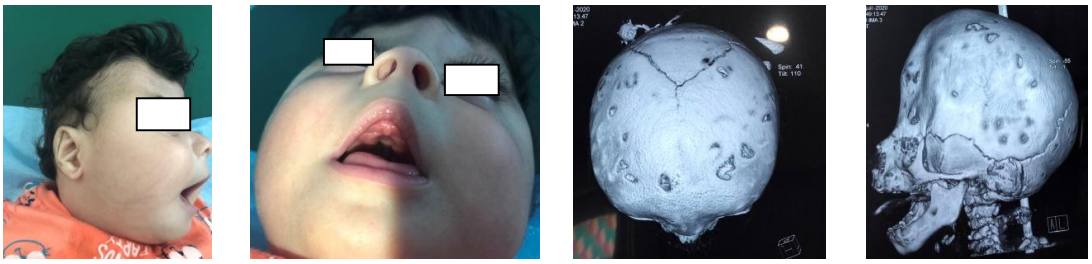
A Moroccan boy was born at 38 weeks' gestation by caesarian section. The patient was the third child of parents who are second-degree relatives, and there was no significant family history. There were no complications during pregnancy, and delivery was normal. Birth weight was 3,300 g, length 45 cm, and head circumference 34.5 cm, and APGAR scores were normal.

The patient had many malformations such as face asymmetry, hypertrichosis of the forehead, and a low nasal bridge with anteverted nostrils, and hypertelorism with epicanthic folds (Fig. 1). The ears were low-set with underdevelopment of the helix, hyperplastic anti-helix and anti-tragus, and a prominent intertragic notch (Fig. 2a). The philtrum was long and smooth (Fig. 1b). The patient had a high palate and clefting of the soft palate (Fig. 2b), a short neck and widely spaced nipples as well as several limb anomalies fingers with clinodactyly, digital webbing between the second, third, and



(a) **(b)** **(c)** **(d)**

Fig. 1. Morphology



(a) (b) (c) (d)

Fig. 2. Patient presents with craniosynostosis

fourth fingers, and abnormal hand creases). As shown in Fig. 1c, the patient's second and fourth toes were short, whereas the halluces were relatively long, medially deviated, and broad. There was no radioulnar synostosis. The scrotum was hypoplastic with left cryptorchidism. The hematological and biochemical tests were normal.

As shown in Fig. 2c and 2d, the patient presents with craniosynostosis due to the premature closure of the sagittal, coronal; and metopic sutures resulting in Turricephaly.

Although patients with a large genomic deletion are at an increased risk for intellectual challenges [4], our patient did not exhibit any signs of abnormal cognitive development at his age. A cerebral scan showed that surgery should be considered before the patient is one year old in order to relieve or reduce risk of intracranial hypertension due to calvarial deformity.

2.2 Molecular Analysis

Genetic analysis, based on RHG band, was performed by a private laboratory and revealed a microdeletion on the short arm of chromosome 7: (46,XY,del(7)(p21p14)dn,inv(10)(p11p21)pat. Genetic analysis performed for the parents indicated that the microdeletion was a de novo event in this patient, and the pericentric inversion of chromosome 10 was transmitted by the father. However, the inversion was a polymorphism with no consequence on the phenotype.

3. DISCUSSION

The deleted region as shown by genetic analysis includes a large number of genes, six of which are responsible for a range of autosomal dominant diseases: TWIST, GSDME (also known as DFNA5), CYCS, HOXA11, HOXA13, and GARS. Several cases of deletions of chromosome 7p have been reported in the literature [1], but only a single report has been about microdeletion encompassing both the *TWIST* and *HOXA* clusters. Kosaki et al. [5] described a patient with left coronal craniosynostosis, maxillary hypoplasia, prominent ear crura, rectoperineal fistula, anal atresia, patent ductus arteriosus, hypoplastic fifth finger, and psychomotor delay. The facial anomalies could be assigned to haploinsufficiency of the *TWIST* gene, whereas the other anomalies were more difficult to attribute to specific gene deletions. Chotai et al. [6] reported a panel of 6 7p deletion cases, 3 with craniosynostosis.

TWIST1, (7p21.1; ONIM 601622), is a protein encoding gene that encodes a basic helix-loop-helix (bHLH) transcription factor with an important role in embryonic development. The encoded protein regulates the transcription of genes involved in cranial suture patterning and fusion during skull development. This protein may also regulate neural tube closure, limb development and brown fat metabolism [2]. Mutations in this gene cause Saethre-Chotzen syndrome (SCS) in human patients, but the ability to detect pathogenic variants in TWIST1, the phenotypic spectrum of (SCS) is increasingly broad [4]. Both milder and more severe phenotypes are recognized. The diagnosis of SCS is established in a proband based on clinical observations as well as the presence of a heterozygous pathogenic variant in TWIST1 as identified by molecular genetic testing. Classic SCS is characterized by unilateral or bilateral coronal synostosis, facial asymmetry, strabismus, ptosis, and typical appearance of the ear (small pinna with a prominent superior and/or inferior crus). Syndactyly of digits two and three of the hand is variably present. Cognitive development is usually normal, although the risk for intellectual challenges increases with the extent of the genomic deletion. Less common manifestations of SCS include other skeletal findings (parietal foramina, vertebral segmentation

defects, radioulnar synostosis, maxillary hypoplasia, ocular hypertelorism, hallux valgus, duplicated or curved distal hallux), hypertelorism, palatal anomalies, obstructive sleep apnea, increased intracranial pressure, short stature, and congenital heart malformations [4].

Our patient had the typical observable characteristics of SCS, namely: craniostenosis, clefting of the soft palate, limb anomalies, and his ears resembled those common in SCS patients. He had an interrupted ear tragi and hyperplastic antihelices and antitragi, and prominent helical crura. He had no ptosis of the eyelids.

GSDME gene, a protein encoding gene (7p15.3; OMIM 608798). The protein encoded by this gene is expressed in fetal cochlea, however, its function is not known [7]. Diseases associated with GSDME include autosomal dominant 5 deafness and autosomal dominant non-syndromic sensorineural deafness type DFNA. This consists of a form of non-syndromic sensorineural hearing loss which is caused by damage to the neural receptors of the inner ear, the nerve pathways to the brain, or the area of the brain that receives sound information. Another gene in the deleted region (PDE1C; 7p14.3; OMIM 602987) is also associated with deafness. Duno et al. [8] described two patients who had deletions of the complete GSDME gene without hearing loss. Deafness is suspected for our patient, and an auditory evoked potential test is planned.

CYCS gene is a protein coding gene (7p15.3; OMIM 123970). The encoded protein associates with the inner membrane of the mitochondrion where it accepts electrons from cytochrome b and transfers them to the cytochrome oxidase complex. This protein is also involved in initiation of apoptosis. Mutations in this gene are associated with autosomal dominant non-syndromic thrombocytopenia 4 and autosomal thrombocytopenia with normal platelets [9]. However, hematology tests for our patient showed normal platelets.

GARS gene (7p14.3; OMIM 600287) is a protein coding gene. Diseases associated with GARS1 include neuronopathy, distal hereditary motor, type Va and Charcot-Marie-Tooth disease, and axonal, type 2D [7] and distal spinal muscular atrophy V [1]. Until now, only *GARS* missense mutations have been found, and it is unknown whether *GARS* haploinsufficiency leads to neurological deficits [1]. Our patient did not have any neurological signs of Charcot-Marie-Tooth neuropathy or distal spinal muscular atrophy.

There are 4 *HOX* gene clusters *(HOXA, HOXB, HOXC,* and *HOXD)* which are the basic developmental regulators that define positional information for the embryo along the anterior-posterior axis of the body [1]. *HOXA13* (OMIM 142959) mutations result in the dominantly inherited hand-foot-uterus and Guttmacher syndromes [1]. Our male proband had some limb defects that are typical in these disorders, namely, shortening of the carpals and tarsals and fifth finger clinodactyly. He also presented the typical genital anomalies seen in patients with a *HOXA13* mutation [1]. A single *HOXA11* truncating mutation has been reported to cause a specific syndrome with skeletal defects (radioulnar synostosis) and amegakaryocytic thrombocytopenia [1].

4. CONCLUSION

Deletion of 7p21 spanning the TWIST and the HOXA clusters results in a combined phenotype of Saethre-Chotzen syndrome and hand-foot-uterus syndrome. Our patient will need cranioplasty in the first year of life and midface surgery in childhood as needed for dental malocclusion, swallowing difficulties, and respiratory problems. This would be followed by surgical repair of the cleft palate. Other operations may be considered, if necessary, such as orthodontic treatment and/or orthognathic surgery at the completion of facial growth; developmental intervention; routine treatment of hearing loss, ophthalmologic evaluation. When there is evidence of increased intracranial pressure, further evaluation should be considered with brain imaging. Finally, and in addition to clinical examination for facial asymmetry as needed, periodic evaluations of the patients should be performed. This includes annual ophthalmologic examination for papilledema, speech evaluation every year starting at age 12 months, audiology evaluations once or twice a year, and annual clinical evaluation for sleep-disordered breathing and developmental delays.

CONSENT

Informed consent was taken from the parents of the patient.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fryssira H, et al. Severe developmental delay in a patient with 7p21. 1–p14. 3 microdeletion spanning the TWIST gene and the HOXA gene cluster. Molecular Syndromology. 2011;2(1):45-49.
2. Available:https://www.genecards.org/cgi-bin/carddisp.pl?gene=TWIST1
3. Devriendt K, Jaeken J, Matthijs G, Van Esch H, Debeer P, et al. Haploinsufficiency of the HOXA gene cluster, in a patient with hand-foot-genital syndrome, velopharyngeal in-sufficiency and persistent patent ductus botalli. Am J Hum Genet. 1999;65:249–251.
4. Gallagher ER, Ratisoontorn C, Cunningham ML. Saethre-Chotzen Syndrome. 2003 May 16 [Updated 2019 Jan 24]. In: Adam MP, Ardinger HH, Pagon RA, et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Available:https://www.ncbi.nlm.nih.gov/books/NBK1189
5. Kosaki R, Higuchi M, Mitsui N, Matsushima K, Ohashi H, Kosaki K. Deletion involving the TWIST locus and the HOXA cluster: A contiguous gene syndrome on 7p? Congenit Anom (Kyoto). 2005;45:35–38.
6. Chotai KA, Brueton LA, van Herwerden L, Garrett C, Hinkel GK, et al. Six cases of 7p deletion: Clinical, cytogenetic, and molecular studies. Am J Med Genet. 1994;51:270–276.
7. Available:https://www.genecards.org/cgi-bin/carddisp.pl?gene=GSDME
8. Duno M, Hove H, Kirchhoff M, Devriendt K, Schwartz M. Mapping genomic deletions down to the base: A quantitative copy number scanning approach used to characterize and clone the breakpoints of a recurrent 7p14.2p15.3 deletion. Hum Genet. 2004;115:459–467.
9. Available:https://www.genecards.org/cgi-bin/carddisp.pl?gene=GARS

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/62455