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A rare case of partial trisomy 9q with dysmorphic clinical features and Hirschsprung's disease

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Abstract

Background: Partial trisomy 9q is a rare condition and the newborns have a chance to survive. Depending on the size and location of the duplicated segment, clinical signs and symptoms are varied. We report a novel chromosomal rearrangement in a 3-day-old female with some general facial abnormalities.

Method: High resolution karyotyping in peripheral blood with the G-banding method was performed.

Results: The method revealed 46,XX,der(5)t(5;9)(p15.3;q34.1),dup(9)(q33q12). This suggested a complete duplication of the long arm of chromosome 9. There was an inverted duplication of the q arm of chromosome 9 with a translocation between the long arm of chromosome 9 and the short arm of chromosome 5. The newborn had a diagnosis of Hirschsprung's disease.

Conclusion: The karyotyping revealed a novel chromosomal rearrangement. The partial trisomy 9q in conjunction with Hirschsprung's disease has not been reported. This condition may be due to a complete duplication of chromosome 9q or a translocation with chromosome 5p. The facial abnormalities may be diagnosed in the clinic and genetic counseling. A patient with hirschsprung's disease and craniofacial abnormalities should be evaluated for partial trisomy 9q.

Key Words: Duplication 9q, Facial abnormality, Hirschsprung's disease, Partial Trisomy 9q.

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1- INTRODUCTION

Complete trisomy 9 pregnancies result in spontaneous abortion or death shortly after birth. However, those who suffer from mosaicism and partial trisomy have more chances to survive. Depending on the size and location of the duplicated segment, signs and symptoms vary. Sometimes an unbalanced condition can be inherited from one carrier parent with the balanced translocation, but it can also be a de novo condition (1-9).

1-1. General Clinical Features

A 3-day-old female case was referred to Hope Generation Genetic & Feto Maternal Clinic for genetic investigation. She had a diagnosis of Hirschsprung's disease. The patient was the second child of the family. Her parents were non-consanguineous and the first child was a healthy 2-year-old. Her mother had no history of any specific illness or drug use during pregnancy. According to the physical examination, her craniofacial features included hypertelorism and micrognathism (**Fig. 1**). She also had a short, webbed neck with normal genitalia and anus. The patient had atrial septal defect. The abdominal ultrasonography and pathological reports confirmed that she had Hirschsprung's disease.

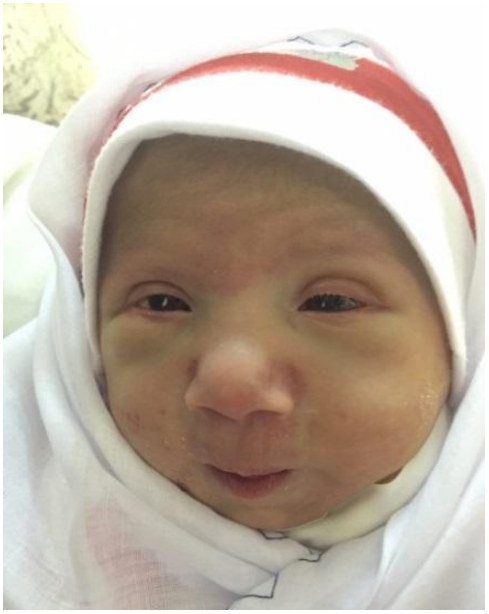


Fig. 1. The dysmorphic clinical features in the patient with partial trisomy 9q.

1-2. Facial Clinical Features

In **Fig. 1**, there are several other facial characteristics including small face, hypertelorism (broad nasal bridge), bulbous nasal tip, short nasal bridge (saddle nose), thin upper lip, and a long, protruding philtrum on the upper lip. The image also shows a broad and long forehead, facial asymmetry, small mouth, and mandibular hypoplasia (micrognathia).

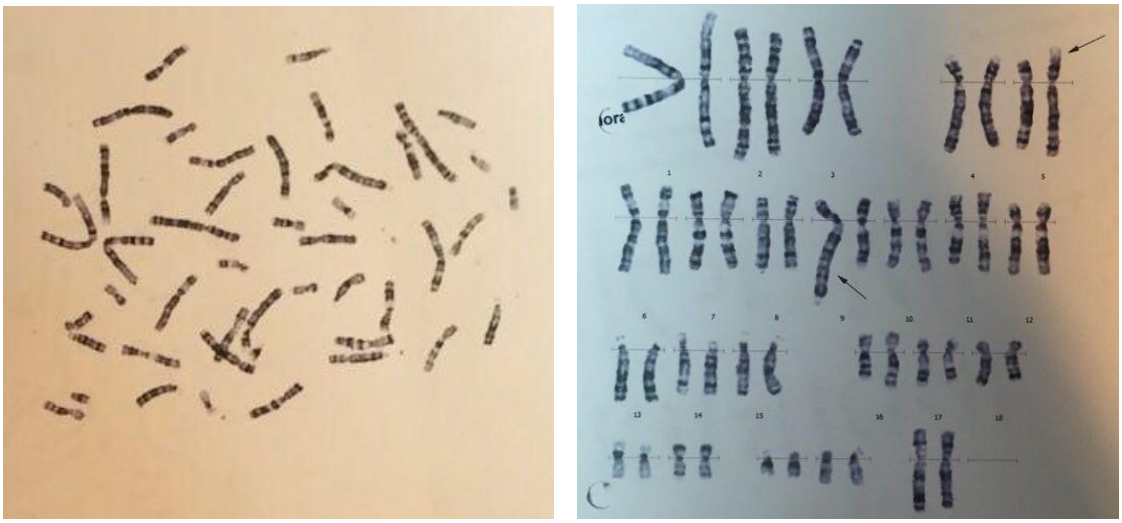
2- MATERIALS AND METHODS

Peripheral venous blood samples were aseptically transferred into sterile culture tubes with 4 ml of RPMI Medium 1640 each (Gibco), supplemented with L-glutamine, 20% fetal bovine serum (Gibco), penicillin–streptomycin solution and phytohaemagglutinin (Gibco). Two cultures were set and the culture tubes were marked and incubated. Forty-eight hours after culture initiation, blood

cultures were synchronized with 100 microliters of excess thymidine and returned to the incubator. After 16 hours, the thymidine is removed by rinsing. Cultured cells were harvested 4 hours later by adding Colcemid (Gibco) for 10 minutes. The cell suspensions were centrifuged for 10 min at 1700 rpm and the pellet was treated with a hypotonic solution (0.075 M KCl, Merck, Germany) for 15 minutes at 37°C. The treated cells were then fixed using Carnoy's fixative (3:1 methanol-glacial acetic acid; Merck, Germany). The tubes were again centrifuged carefully at 1700 rpm for 10 min and finally the pellet was washed with Conroy's fixative repeatedly 3–4 times. The slides were prepared by air-drop method. GTG banding was performed and the slides were stained with 10% Giemsa stain. Fifteen metaphase spreads were analyzed with Video Test-Karyo software version 3.1. The Karyotype report was based on the International System for Human Cytogenetic Nomenclature (ISCN) recommendations, 2016.

3- RESULTS

High resolution karyotyping in peripheral blood with G-banding method revealed an inverted duplication of the q arm of chromosome 9, and a derivative chromosome 5 resulted from a translocation of chromosome 9 to the short arm of chromosome 5 in all of the cells. The results show 46,XX,der(5)t(5;9)(p15.3;q34.1),dup(9)(q33q12) (**Fig. 2**).



(A) **(B)**

Fig. 2. A) Metaphase spread and GTG banded chromosomes. **B**) Karyotype of the patient with 46,XX,der(5)t(5;9)(p15.3;q34.1),dup(9)(q33q12) pattern. The derivative chromosomes are indicated by the arrows.

4- DISCUSSION

Trisomy 9 is a rare and often fatal chromosomal abnormality. A wide variety of clinical symptoms have been reported for this disorder. According to the previous reports, trisomy 9 can be seen in three forms: complete, mosaicism and partial. Complete trisomy 9 has severe general morphological abnormalities such as skeletal abnormalities and vital organ malformations. It is associated with spontaneous abortion or death shortly after birth (1-5). There are only three reports where patients had non-mosaic trisomy 9 but could live more than one year.

Unrecognized mosaicism is a possible explanation (6). Trisomy 9 mosaicism may have several malformations similar to the complete trisomy but usually milder, so the patient has a chance to survive (7-9). Partial trisomy 9 has two types; partial trisomy 9q and partial trisomy 9p. The patient with partial trisomy 9q has more chances to survive (5, 10); but according to a review by Lopez-Felix et al., partial trisomy 9p usually has pregnancy termination (3).

Partial trisomy 9q is a very rare chromosomal syndrome which was first described by Turleau et al., in 1975. This syndrome is associated with various general abnormalities including facial malformations (3-11). No stable pattern of general dysmorphisms is associated with partial trisomy 9q, but congenital heart defects are common in all of them (5, 7, 8, 9, 12). Some of the previously reported abnormalities in trisomy 9q, such as pyloric stenosis, were absent in our case. However, some others including cardiac abnormalities were present.

All types of trisomy 9 had similar dysmorphia of facial appearance. Hypertelorism and micrognathia were two common facial features (4-7). However, most of them including hypertelorism, micrognathism, and bulbous nasal tip can be observed in our case (**Fig. 1**).

The present case had Hirschsprung's disease with partial trisomy 9q, which has not been previously reported. Hirschsprung's disease is an intestinal disorder in which there is a lack of neurons in some parts of the intestine. Therefore, the fecal matter cannot be pushed through, causing severe constipation or complete blockage of the intestine. Other symptoms in this condition are vomiting, abdominal pain, diarrhea, poor feeding, malnutrition, and slow growth. Hirschsprung's disease can be due to mutations in several genes, including the RET, EDNRB and EDN3 genes (13). However, none of these genes are present in 9q or 5p. The presence of partial trisomy 9q with Hirschsprung's disease seems to be a new syndrome which may occur due to two causes. One is gene disruption in the translocated region and another one is the presence of some genes in the duplicated segment which have not been identified in the past.

5- CONCLUSION

Cases such as the current case that described in this report can help us identify the genotype-phenotype correlations. We may also use the information about facial dysmorphia for first the clinical visit of newborns, children or adults and/or in genetic counseling. We can use the CGH-array method to confirm the amount of areas removed or added. The partial trisomy 9q should be considered in the list of causes of craniofacial syndromes. The possible growth retardation may have an effect on the future maxillary/ mandibular growth, and tooth occlusion. Finally, the patient with hirschsprung's disease and craniofacial abnormalities should be evaluated for partial trisomy 9q.

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