

Report of two Moroccan siblings with trisomy 3q25 due to parental pericentric inversion of chromosome 3

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Abstract

3q2 duplication syndrome is a rare chromosomal disorder, in which the symptoms and evolution of patients vary widely depending on the length of the duplicated portion.

Here we report a case of two Moroccan siblings with 3q2 duplication syndrome. Both patients present with a dysmorphic syndrome, a polymalformative syndrome, growth delay and severe mental retardation. Abdominal ultrasonography of the second sibling described several gastrointestinal abnormalities.

We realized a karyotype for both patients and their parents, showing that the patients were carriers of an additional material on the short arm of chromosome 3, and the father had a balanced pericentric inversion of the chromosome 3. This result confirmed 3q25 trisomy in both patients.

The rarity of 3q2 duplication syndrome due to pure inversions of chromosome 3 makes this report relevant since it helps to further delineate the syndrome. Furthermore, we describe new clinical signs never reported in association with this disorder.

Keywords

trisomy 3q2; pericentric inversion; karyotype; polymalformative syndrome; gastrointestinal abnormalities

Introduction

Trisomy 3q2 is a rare chromosomal disease, clinically very similar to Cornelia de Lange syndrome [15], in which the totality or a portion of the region 2 of the long arm of chromosome 3 is repeated 3 times instead of 2.[4] In most cases (75%), the trisomy 3q2 is the product of unbalanced segregations of balanced inversions or translocations and/or insertion in the parents' gonads. [2,4,9,10].

The symptoms and evolution of patients with trisomy 3q2 vary depending on the length of the portion that is duplicated. However, many affected patients have mental retardation, psychomotor delay, hypotonia, peculiar craniofacial dysmorphism, hirsutism, neural tube defect, congenital heart defects, renal malformations and digestive abnormalities [2-8].

Here we report a case of two Moroccan siblings (male and female) with 3q2 duplication syndrome (3q25-qter), due to a balanced inversion in the father's cells, with clinical signs never reported in the

literature.

Case Presentation

1. Clinical Study

Patient 1

The patient I: 4 was seen at the age of 12 years old in our institution for a dysmorphic syndrome. He is the product of the fourth pregnancy, after 3 healthy children, from a non-consanguineous marriage (Figure 1). The antenatal and perinatal history was unremarkable. He presents a dysmorphic syndrome (figure 2), made of: Synophris, upper slanting palpebral fissure, long arched eyelashes, wide nasal bridge, short nose, and preauricular sinus, associated with widely spaced nipples, scoliotic attitude, hirsutism, coccygeal pit, type II thumb hypoplasia, and presents a severe mental retardation with growth delay.

Detailed X-Ray of the entire skeleton showed a hypoplasia of 2nd phalange of the thumb, a clinodactily of the 5th finger and bone age was estimated at 12 years according to Greulich and Pyle Atlas (figure 7).

The ophthalmic examination was normal. Abdominal ultrasound showed biliary stones (with up to fifteen, 5 mm stones), normal kidneys and liver. Cardiac sonogram was normal.

Patient 2

The patient II: 5 was also seen at the age of three and a half year old in our institution for a dysmorphic syndrome. She is the product of the fifth pregnancy with a low birth weight. Her sucking power was normal, but weight gain was negligible after birth. She presents hypotonia with dysmorphic syndrome, made of: low hairline on the forehead and the back of the neck, square-shaped face, synophyris, upper slanting palpebral fissures, long arched eyelashes, wide nasal bridge, short nose, anteverted nares, down-turned mouth corners, thin upper lip, ogival palate, and preauricular sinus, associated with short neck, generalized hirsutism, coccygeal pit, umbilical hernia, and overlapping toes (figure3).

An abdominal ultrasonography was performed, showing a median liver, biliary stones, right polysplenia, absent inferior vena cava (with a retro hepatic shunt through the azygos vein), stomach placed on the right and small pancreas, while the cranial ultrasonography was normal.

Ultrasonography examination of sacral region showed a small collection on the level of the sacral dermal sinus with anechoid content.

Detailed X-Ray of the entire skeleton showed a bilateral coxa-valga (figure 6).

The ophthalmic examination was normal. Cardiac sonogram was normal.

2. Cytogenetic analysis

A chromosomic analysis was performed on lymphocytes of both patients, cultivated in 37°C for 72h. The cells were blocked in metaphase stage using Colcemid. After a hypotonic shock using KCl, the mitotic cells were fixed using a mix of methanol and acetic acid. The obtained chromosomic preparations were spread on the microscope slide then denaturated into R-bands and colored with Giemsa. Photos of

the mitotic cells were then taken, and then a karyotype was established by semi-automatic classification of the chromosomes. The karyotype showed an additional chromosomal material on the short arm of one of the chromosomes 3 (Figure 4).

In order to investigate the origin of the additional chromosomal material, a karyotype was performed on both parents' lymphocytes using the same method. While the mother's karyotype was normal, the father's showed a balanced inversion of the chromosome 3, his karyotype was 46,XY,inv(3)(p26q25) (Figure 5).

We deduced from father's results, that the most likely origin of the additional material was the father's chromosomal inversion.

In order to confirm this hypothesis, we performed a fluorescent in situ hybridization on patient's chromosomes, using the probe poseidon st 3qter red ref pkbi-40206R that showed 3 spots of the 3q telomere, thus confirming that the karyotype of the patient II:4 was

46,XY,rec(3)dup(3q)inv(3)qter) → q25::p26 → qter) pat and that of the patient II:5 was

46,XX,rec(3)dup(3q)inv(3)qter) → q25::p26 → qter)pat.

Discussion

Trisomy 3q2 is a rare chromosomal abnormality characterized for the first time in 1966 by Falek et al. with a phenotype overlapping with Cornelia de Lange syndrome [15]. Since then, to our knowledge, this chromosomal abnormality has been reported over a 100 times in literature [14].

While the clinical presentation of the syndrome largely depends on the length of the portion of the arm of the chromosome 3 subject to the duplication, most patients have a mental retardation, psychomotor delay, hypotonia, craniofacial dysmorphism (hypertelorism, long arched eyelashes, anteverted nares, down turned corners of the mouth, and micrognathia), short/webbed neck, hirsutism, neural tube defect, short limbs, digital abnormalities (clinodactyly of 5th finger, camptodactyly, polydactyly), genital abnormalities (bifid vagina, uterus bicornus), congenital heart defects (septal defects), renal malformations (polycystic kidneys or dysplasia), ocular malformations (cataract, corneal opacities, and anophthalmia) and digestive abnormalities (Hernia, omphalocele) [2-8].

We reported the case of 2 siblings of pure duplication 3q25-qter, both due to a pericentric inversion of the chromosome 3 of the father. These 2 cases will help further delineate the 3q2 duplication syndrome.

In this study, we have compared our 2 cases with some 3q2 trisomy cases reported in literature (Table 1). We noted that there is an important heterogeneity of symptoms between the cases. But it is worth noting that hypertelorism was not found in the physical examination of our patients, while it is the most reported symptom among the pure 3q2 duplication syndrome cases that we found. While the second most frequent symptom (wide depressed nasal bridge) is found in both siblings.

We also noted that patient 2 has a more complete clinical presentation, with a more complete dysmorphic syndrome (10 abnormalities), having all 6 most frequently reported facial abnormalities (apart from hypertelorism). While patient 1 has only 6 facial abnormalities, among which are the 3 most frequently reported abnormalities (apart from hypertelorism). Considering that both patients have the

same chromosomal abnormality with the same portion of the long arm of the chromosome 3 duplicated, we did not find an explanation for this discrepancy in clinical features.

The phenotypic variability associated with certain chromosomal abnormalities such as trisomy 21 and 22q11 micro deletion has been explained by the intervention of complex mechanisms of regulation of gene expression, the effect of certain modifying genes, as well as epigenetic and environmental factors [22,28].

We also noted that developmental delay/mental retardation, present in both patients, is the 5th most frequently reported clinical sign.

It is worth noting then, that patient 2, in addition to her most complete clinical picture, has abnormalities never reported in the 3q2 duplication syndrome, namely: median liver, right stomach, small pancreas, biliary stones, polysplenia and absence of the inferior vena cava (with systemic venous circulation shunted through the Azygos vein and the portal circulation shunted directly to the right atrium through the hepatic vein). But with the absence of other evident cause of these signs, it is hard to explain this association by anything but the 3q2 duplication.

Also, many papers report cases of trisomy 3q2 as Cornelia de-Lange syndrome, showing a similarity between the 2 syndromes [16,17], to the point where some stipulated that the gene causing the Cornelia de-Lange syndrome is probably present on the chromosome 3 [18], although research has not yet found evidence for this relationship [19].

Lastly, the case reported here is due to a balanced pericentric inversion of the chromosome 3 of the father.

Inversions are chromosomal abnormalities that occur when 2 breaks occur in one chromosome, followed by a 180° rotation of the fragment between the break-points before rejoining with the end fragments [40].

In most cases, inversions do not change the overall amount of the genetic material, meaning that the individuals with this abnormality are viable and show no phenotypic abnormalities [1]. In our case, the duplication of the 3q2 fragment in the patients is explained by the fact that the father is heterozygous for a pericentric inversion in the chromosome 3. In this case, because of the presence of the centromere in the inverted segment, the chromosomes 3 that have crossed over disjoin without the creation of a bridge. However, the crossover produces chromatids that contain both a duplication and a deficiency for different parts of the chromosome 3 [1].

Following this model, we can thus hypothesize that there is probably a deletion of a distal segment of the short arm of the chromosome 3 where the duplicated segment is found. While we did not investigate to confirm this hypothesis, the clinical findings do not permit to rule out the deletion, since the 3p26.3 deletion can concern only the CHL1 gene [11], a deletion that can be in some cases asymptomatic [12] or associated with a mild isolated mental deficit [13] that can overlap with the delay seen in the 3q2 duplication syndrome. But in the absence of definitive proof of the deletion, this case is considered a pure duplication.

It would be interesting to complete this study by carrying out a CGH-array in order to demonstrate a possible deletion of the short arm of chromosome 3, to better characterize the duplication of the long

arm, the break points and the gene content of unbalanced regions [36].

Conclusion

In the era of high-throughput sequencing, this report shows that classical cytogenetic study keep its place in the diagnosis of the cause of a mental retardation associated with a dysmorphic syndrome. So we have been able to diagnose 3q2 duplication due to a balanced parental inversion, which allowed us to offer the adequate genetic counseling and eventually propose a prenatal diagnosis in case of pregnancy.

This report also enriches the clinical spectrum of trisomy 3q2 syndrome by reporting gastrointestinal abnormalities never described in literature.

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Figures

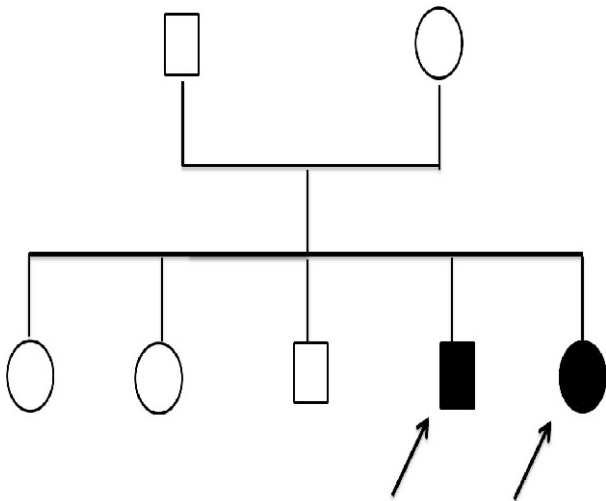


Figure 1: Pedigree of the family with Trisomy 3q2. Affected individuals are shaded. Asterisk indicate individuals in whom cytogenetic analysis was undertaken.



Figure 2: Photograph of the patient II:4 showing dysmorphic face



Figure 3 : Photographs of the patient II:5 showing facial dysmorphism (A) preauricular sinus (B) umbilical hernia (C) hirsutism and coccygeal pit (D).

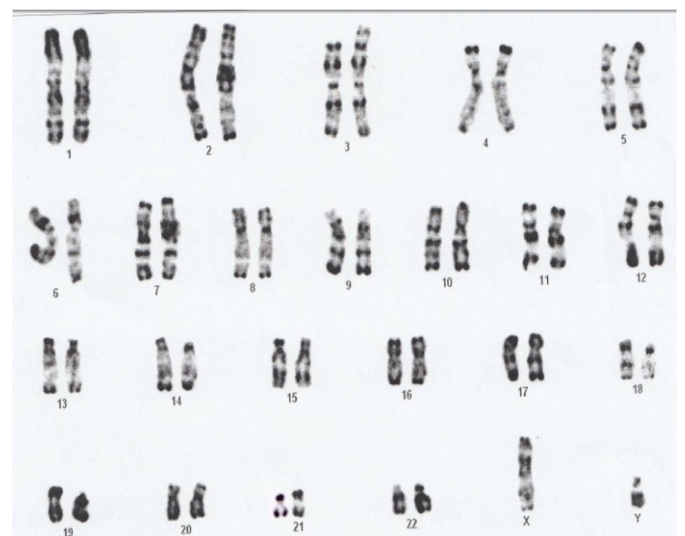


Figure 4 : Karyotype of patient II:4 in R bands showing an additional chromosomal material on the short arm of one of the chromosomes 3



Figure 5: Father's partial karyotype showing balanced pericentric inversion of the chromosome 3



Figure 6 : X-ray of patient 2 showing coxa valga



Figure 7: Left hand X-ray of patient 1 showing hypoplasia of 2nd phalanx of thumb, clinodactyly of 5th finger, and an estimated bone age of 12 years old according to Greulich and Pyle Atlas

Tables

Table 1: clinical data of patients with Trisomy 3q2 and comparison with literature

Reported clinical features	Case 1	Case 2	Reported cases in literature	References
Hypertelorism	no	no	17	(17; 22; 23; 11; 25; 26; 27; 28; 30; 6; 8; 33; 5; 34; 35; 29;)
Wide depressed nasal bridge	yes	yes	16	(8; 31; 17; 22; 32; 11; 25; 26; 28; 29; 6; 32; 5; 34; 35; 36;)
Anteverted nostrils	no	yes	14	(31; 32; 17; 22; 23; 11; 25; 26; 28; 30; 6; 33; 5; 36)
Down-turned mouth corners	no	yes	14	(17; 22; 32; 11; 25; 26; 28; 30; 33; 5; 34; 35; 29; 6;)
Developmental delay/Mental retardation	yes	yes	11	(17; 22; 32; 11; 25; 26; 27; 28; 29; 30; 6;)
Growth retardation	yes	yes	9	(17; 22; 32; 11; 27; 28; 37; 30; 6;)
Short neck	no	yes	8	(8; 31; 40; 33; 5; 41; 36; 6;)
Microcephaly	no	no	8	(17; 22; 32; 32; 26; 28; 37; 30)
Micrognathia	no	no	7	(8; 40; 33; 5; 34; 10; 39;)
Hypertrichosis	yes	yes	7	(17; 22; 32; 25; 5; 37; 6;)

Malformed ears	no	no	7	(8; 31; 33; 5; 41; 34;)
Clinodactyly 5th finger	yes	no	6	(8; 31; 32; 34; 36; 6;)
Ogival/Cleft palate	no	yes	6	(8; 32; 11; 25; 30;)
Congenital heart disease	no	no	6	(8; 31; 19; 34; 10; 39;)
Synophris	yes	yes	6	(15; 20; 30; 23; 35; 4;)
Long arched eyelashes	yes	yes	6	(15; 20; 30; 23; 25; 35;)
Low hairline	no	yes	5	(15; 20; 30; 9; 25;)
Renal abnormalities	no	no	4	(6; 29; 31; 39;)
Prominent philtrum	no	no	4	(3; 32; 33; 27;)
Short limbs	no	no	3	(30; 3; 34;)
Bilateral semian creases	no	no	3	(30; 3; 37;)
Epicanthic folds	no	no	3	(3; 32; 27)
low-set ears	no	no	2	(29; 3;)
Widely spaced nipples	yes	no	2	6; 3;)
Bicornuate uterus	-	no	2	(6; 30;)
square-shaped face	no	yes	2	(6; 29;)
Microphthalmia	no	no	2	(17; 39;)
Syndactyly	no	no	2	(38; 32;)
Short broad nose	yes	yes	2	(3; 4;)
Omphalocele	no	no	2	(3; 8;)
Long philtrum	no	no	1	(3;)
Small ears	no	no	1	(30;)
Duplication of vagina and cervix	-	no	1	(30;)
Streak ovaries	-	no	1	(30;)
Camptodactyly	no	no	1	(6;)
Hypoplastic dermal ridge	no	no	1	(6;)
Hypoplastic nails	no	no	1	(6;)
Prominent eyebrows	yes	no	1	(17;)
Upward slanting palpebral fissures	yes	yes	1	(4;)
Preauricular pits	yes	yes	1	(4;)
Trigonocephaly	no	no	1	(2;)
Right Polysplenia	no	yes	0	
Absent inferior vena cava	no	yes	0	
Biliary stones	yes	yes	0	
Median Liver	no	yes	0	
Right Stomach	no	yes	0	
Short Pancreas	no	yes	0	

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