

*Full Length Research Paper*

# Five opitz G/B.B.B syndrome cases report with two chromosomal abnormalities; x chromosome duplication (47, XXY) and translocation 46XX t(3q;4q)

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**Opitz G/BBB syndrome is a genetic condition that affects several structures along the midline of the body. The most common features of this condition are wide-spaced eyes (hypertelorism) with structural defects of the larynx, trachea, and/or esophagus causing breathing problems and difficulty swallowing (dysphagia). Some times in males, the urethra opening on the underside of the penis (hypospadias) is observed. Mild intellectual disability occurs in 30% approximately of patients with Opitz G/BBB syndrome (GBBBS), most likely caused by structural defects in the brain. About half of affected individuals also have cleft lip with or without a cleft palate as in this study. Some have cleft palate alone. Heart defects, imperforate anus, and brain defects such as absence of the corpus callosum. Facial abnormalities that may be seen in this disorder include a flat nasal bridge, thin upper lip, and low set ears. There are two forms of Opitz G/BBB syndrome, which are distinguished by their genetic causes and patterns of inheritance. The X-linked form of Opitz G/BBB syndrome is caused by a mutation in a specific gene, MID1, on the X chromosome. Autosomal dominant Opitz G/BBB syndrome is caused by a mutation in an as-yet unidentified gene on chromosome 22. Two chromosomal aberrations in this study were observed in two patients; chromosome duplication 47,XXY and translocation 46,XX t(3;4). However one patient with oral encephalocele presented normal karyotype 46,XY.**

**Key words:** Hypertelorism, cleft lip with or without cleft palate, chromosomes, klinefelter syndrome, chromosomal translocation.

## INTRODUCTION

The Opitz GBBB syndrome (GBBBS) was first reported by Opitz et al. (1969) as two separate entities, BBB syndrome and G syndrome; subsequent reports of

families in which the BBB and G syndromes represented a single entity.

In 1995 and 1996 two genes in GBBBS were reported, a syndrome which is genetically heterogeneous, with different inheritance patterns, X-linked chromosome (Xp22) (McDonald-Mc Ginn et al., 1995; Fryburg and Golden, 1996; Verloes et al., 1995; Cho et al., 2006),

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chromosome 22 (22q) (Robin et al., 1995, 1996), and autosomal dominant form.

Verloes et al. (1995) reported a large pedigree in which GBBBS had a pericentric inversion of the X chromosome: inv(X) (p22.3q26). This suggested the existence of a true X-linked form of GBBBS that does not appear phenotypically different from its autosomal dominant inheritance pattern.

Robin (1995) demonstrated that the GBBBS is a heterogeneous disorder, with X-linked and autosomal, 22q-linked; forms named as type I and type II, respectively. In a study of multiple families, they found 3 patients associated to Xp22 McDonald-McGinn et al., 1995; Fryburg and Golden, 1996; Verloes et al., 1995; Cho et al., 2006 and 5 patients associated to chromosome 22q11.2 (Robin et al., 1995, 1996), where no phenotypic differences between the 2 types were observed. In both there are craniofacial anomalies, hypospadias, swallowing difficulties, and developmental delay (Quaderi et al., 1997; So et al., 2005; Mnayer et al., 2006; Scheweiger and Schhneider, 2003; Jacobson et al., 1998; Brooks et al., 1998). The original G family (Opitz et al., 1969) was shown by linkage to have the X-linked form. Robin (1995) pictured an affected brother and sister from a family which also showed X linkage; both had widely spaced eyes and the boy had repaired cleft lip and tracheotomy. Although the Opitz syndrome maps to Xp22 (De Falco et al., 2003; Cox et al., 2000), Muenke (1996) concluded that they represent separate loci.

This genetic disorder is a congenital midline malformation syndrome (Quaderi et al., 1997), characterized by the following clinical features; hypertelorism, hypospadias, cleft lip/palate, laryngotracheoesophageal anomalies, imperforate anus, developmental retardation, and cardiovascular defects among others clinical manifestations (So et al., 2005; Mnayer et al., 2006; Scheweiger and Schhneider, 2003; Jacobson et al., 1998; Brooks et al., 1998).

By comparing the phenotypic features of the X-linked and autosomal forms of the Opitz syndrome, Robin (1996) observed more frequently that anteverted nares and posterior pharyngeal cleft can be seen only in the X-linked form. However, hypertelorism, swallowing difficulties, hypospadias, and developmental delay, were observed in both inheritance patterns.

In relation to twin patients, unusually severe cases with early lethality occurs (Opitz et al., 1996). Two pair of non twinning brothers and sisters with this syndrome was studied and different chromosomal results as clinical features were observed. Congenital heart disease and genitourinary anomalies have been observed in (GBBBS) (Jacobson et al., 1998) as double outlet right ventricle with pulmonary atresia, malalignment ventriculoseptal defect, right-sided aortic arch with left ductus arteriosus and bladder exstrophy. A male patient in this study Figure 1, with normal 46,XY karyotype had an oral encephalocele

compared to pituitary macroadenoma and cranial osteoma observed by Brooks (1998) in a 43 year-old woman, a heterozygote mother with some clinical features (telecanthus, anteverted nares, and a history of frequent respiratory and urinary tract infections) with her GBBBS son. These patient's clinical manifestations were hypertelorism, bilaterally cleft lip and palate, hypospadias, and dysphagia with multiple episodes of aspiration pneumonia. The Linkage analysis demonstrated X-linked inheritance in this family (Robin et al., 1995; Brooks et al., 1998) concluded that cranial osteomas are not associated with growth hormone hypersecretion and that therefore cranial osteomas and perhaps pituitary tumors should be investigated.

## MATERIALS AND METHODS

Five patients from three different families with GBBBS were presented in this study:

(1) A 9 months old male patient Figure 1 with hypertelorism, bilateral cleft lip with cleft palate and normal intellectual coefficient. This patient was evaluated by neurosurgery due to oral encephalocele, were titanium shell was used for surgical palate restructuration. Tissue biopsy and 3rd dimension CAT (computerized axial tomography) (Figures 10 a, b and c) and chromosomal studies (karyotype) were also performed for this particular patient.

(2) Two 6 and 8 years old females patients (sisters) (Figures 2 and 5). The first female patient had craniofacial malformation, hypertelorism, wide bridge nose with unilateral cleft lip with cleft palate and psychomotor retardation. Thorax X-rays and chromosomal studies were done, where chromosomes 3 and 4 had a translocation event, 46,XX t(3q;4q) (Figures 4 and 5). The second female patient with less severe craniofacial malformation in comparison with her sister with hypertelorism, wide bridge nose without cleft lip with cleft palate with a normal karyotype 46, XX.

(3) Two 3 and 5 years old male patients. The first patient (Figures 6 and 9) with hypertelorism, wide bridge nose with unilateral cleft lip with cleft palate. Echocardiography, Thyroid and chromosomal studies were performed. Hypothyroidism and abnormal karyotype was reported (Figure 7), 47,XXY (Klinefelter syndrome). The second male patient (Figures 8 and 9) with hypertelorism, wide bridge nose with bilateral cleft lip with cleft palate. Intestinal biopsy was also performed in this patient due to chronic constipation. The chromosomal study was reported as normal 46,XY.

## DISCUSSION

Five patients from three different families with GBBBS were diagnosed in this study. This syndrome is a genetic disease characterized by hypertelorism (McDonald-McGinn et al., 1995; Fryburg and Golden, 1996; Verloes et al., 1995; Cho et al., 2006; Robin et al., 1995, 1996), bilateral cleft lip with cleft palate Quaderi et al., 1997). The first 9 months old male patient Figure 1 with hypertelorism, bilateral cleft lip and cleft palate, normal intellectual coefficient, was evaluated by neurosurgery due to oral encephalocele, were titanium shell was used for surgical palate restructuration. To confirm the



**Figure 1.** A 9 months old male patient with hypertelorism, bilateral cleft lip with cleft palate and normal intellectual coefficient. This patient was evaluated by neurosurgery due to an oral encephalocele, were titanium shell was used for surgical palate restructuration. Chromosomal study was reported normal 46,XY.

diagnosis, tissue biopsy was performed and 3rd dimension CAT (computerized axial tomography) Figures 10 a, b, c. It was reported; (A) Craniofacial bone structures disjunction along the midline, wide-spaced eye orbits (hypertelorism) and bilateral cleft lip and palate. (B) Wide midline cranial base disjunction and (C) Duramadre defect can be observed, where primary reconstruction with titanium shell was used for surgical palate restructuration by neurosurgery due to oral encephalocele. The chromosomal studies for this patient (karyotype) were normal 46,XY.

Although the second and third 6 and 8 years old female patients (sisters) (Figures 2, 4 and 5) had unilateral and

bilateral cleft lip with cleft palate. The first female patient Figure 2 had more severe clinical manifestations as craniofacial malformation, hypertelorism, wide bridge nose with and psychomotor retardation in comparison with her sister. Similarly, the chromosomal studies showed that the second patient (Figures 4, 5) was normal with 46,XX in comparison to her sister who was observed with chromosomes 3 and 4 translocation 46,XX t(3q;4q) (Figure 3, 4 and 5).

In relation to the last two 3 and 5 years old male patients, the first male patient (Figures 6 and 9) with hypertelorism, wide bridge nose, unilateral cleft lip with cleft palate, and cardiopathy (arterial conduct persistence)



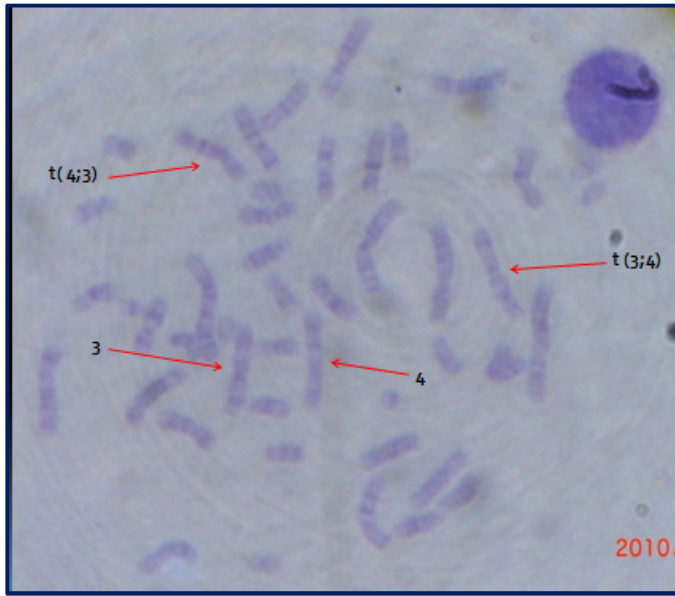
**Figure 2.** A 6 years old female patient with craniofacial malformation, hypertelorism, wide bridge nose with unilateral cleft lip with cleft palate and psychomotor retardation.

was confirmed by transthoracic echocardiogram. Similar findings as hypothyroidism confirmed in this patient by thyroid studies and treated with thyroid hormone. Chromosomal aberration was reported (Figure 7) 47,XXY (Klinefelter syndrome) which is considered to be the most frequent cause of male hypogonadism. Whereas his brother (Figures 8 and 9) intestinal biopsy (reported as normal) was performed in this patient due to chronic intestinal constipation with a normal karyotype and less severe clinical findings.

In relation to the main clinical manifestation reported for GBBBS, De Falco et al. (2003) confirmed that hypertelorism, and hypospadias are the most frequent manifestations, being present in almost all individuals, same as craniofacial anomalies, swallowing difficulties,

and developmental delay, as in the five patients from this study. Laryngotracheoesophageal defects were also common and they were manifested (So et al., 2005; Mnayer et al., 2006; Schweiger and Schanneider, 2003; Jacobson et al., 1998; Brooks et al., 1998) by GBBBS patients as congenital heart and anal abnormalities were less frequent than reported. De Falco (2003) included limb defects as syndactyly.

Vermis hypoplasia or agenesis in patients with no developmental delay was also suggested by Pinson (2004) as an important clinical feature that should be routinely sought even in patients without mental retardation. Funke (2006) and Younge et al. (2004) reported a patient with congenital chylothorax, a collection of lymph in the pleural space. The patient's mother



**Figure 3.** The 6 years old female patient chromosomal studies were performed, where chromosomes 3 and 4 had a long arms translocation 46,XX t(3q;4q).



**Figure 4.** The second 8 years old female patient with less severe craniofacial malformation in comparison with her sister. Her clinical features were hypertelorism, wide bridge nose without cleft lip with cleft palate. A normal karyotype 46,XX was reported.

was marked with hypertelorism. The boy also had bilateral cleft lip and palate, hypertelorism, hypospadias, right cryptorchidism, left hydrocele, widow's peak, prominent forehead, low-set and posteriorly angulated ears, and flat, broad nasal bridge.



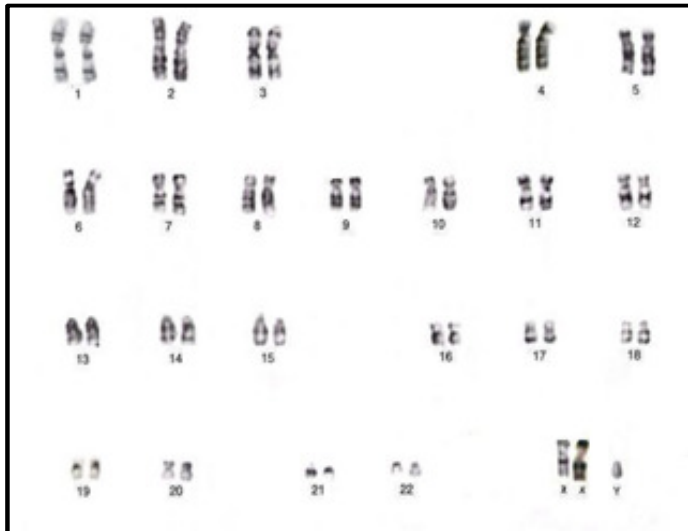
**Figure 5.** Two 6 and 8 years old female patients were sisters and different craniofacial alterations were observed.



**Figure 6.** A 3 years old male patient with hypertelorism, wide bridge nose and unilateral cleft lip with cleft palate.

Strehl (2003) reported Intestinal alteration as lymphangiectasia in Noonan syndrome patient. In this study one patient (Figures 8 and 9) with normal karyotype and with less severe clinical findings if compared to his brother (46,XXY) (Figures 6 and 9) with Klinefelter syndrome (Figure 7), Intestinal biopsy was performed in this patient due to chronic intestinal constipation. However, biopsy results were reported as normal.

In 1995 and 1996 two genes in GBBBS associated to this syndrome, which is genetically heterogeneous, by different inheritance patterns, X-linked chromosome (Xp22) (McDonald-McGinn et al., 1995; Fryburg and Golden, 1996; Verloes et al., 1995; Cho et al., 2006). One male patient in this study with a sexual X chromosome duplication, (Figure 6) diagnosed cytogenetically as Klinefelter syndrome (Figure 7), was thought that gen



**Figure 7.** The 3 years old male patient had an X chromosome duplication, with 47,XXY karyotype and diagnosed genetically as klinefelter syndrome associated to Opitz GBBB syndrome (GBBBS).



**Figure 9.** Two male 3 and 5 years old patients from the same family (brothers) had different craniofacial alterations.



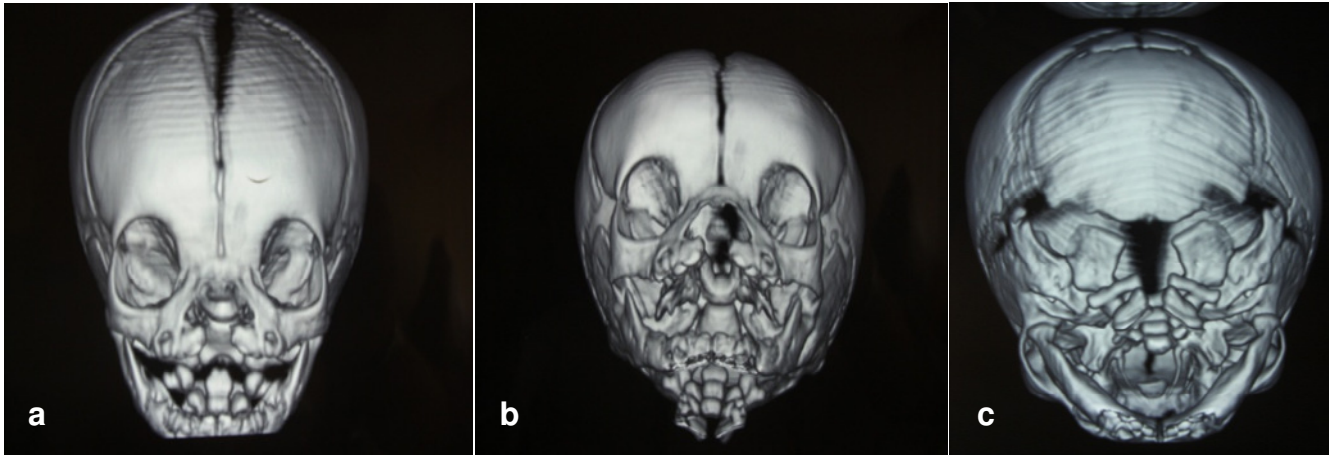
**Figure 8.** The 5 years old male patient with hypertelorism, wide bridge nose with bilateral cleft lip with cleft palate, the chromosomal study was reported as normal 46,XY.

activation, located at Xp22 (De Falco et al., 2003 and Cox et al., 2000) might be occurred. The GBBBS is also associated to chromosome 22 (22q) Robin et al., 1995, 1996 and autosomal dominant forms, so the syndrome can be observed in both males and females, as in this

study.

Verloes in 1995 reported a large pedigree in which GBBBS with a pericentric inversion of the X chromosome:  $inv(X)(p22.3q26)$ . This suggested the existence of a true X-linked form of GBBBS that does not appear phenotypically different from its autosomal dominant inheritance pattern. Robin (1995) demonstrated that the GBBBS is a heterogeneous disorder, with X-linked and autosomal, 22q-linked; forms named as type I and type II, respectively. In a study of multiple families, they found 3 in which there was associated to Xp22 (McDonald-McGinn et al., 1995; Fryburg and Golden, 1996; Verloes et al., 1995; Cho et al., 2006); and 5 in which there was associated to chromosome 22q11.2 (Robin et al., 1995, 1996), where no phenotypic differences between the 2 types were observed. In both types there are craniofacial anomalies, hypospadias, swallowing difficulties, and developmental delay (So et al., 2005; Mnayer et al., 2006; Scheweiger and Schhnneider, 2003; Jacobson et al., 1998 and Brooks et al., 1998). The original G family, Opitz et al. (1969) was shown by linkage to have the X-linked form. Robin (1995) pictured an affected brother and sister from family 5 which also showed X linkage; both had widely spaced eyes and the boy had repaired cleft lip and tracheotomy necessitated by a laryngotracheal cleft. Although the Opitz syndrome maps to Xp22 in approximately the same area as craniofrontonasal dysplasia, Muenke (1996) concluded that they represent separate loci.

Prenatal diagnosis might be important (Hogdall et al., 1989). The GBBBS is considered a genetic syndrome where clinical manifestations are similar among patients despite the inheritance pattern. However, some minor differences have been reported and confirmed within this study. The incidence of this disease is considered to be rare and there might be a late or misdiagnosis. Therefore,



**Figures 10.** Nine months old male patient 3<sup>rd</sup> dimension CAT (computerized axial tomography). (A) Craneofacial bone structures disjunction along the midline, wide-spaced eye orbits (hypertelorism) and bilateral cleft lip and palate. (B) Wide midline cranial base disjunction. (C) Duramadre defect can be observed, where primary reconstruction with titanium shell was used for surgical palate reconstruction by neurosurgery due to oral encephalocele.

an early diagnosis might be important for a better quality of life.

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