Novel nonsense mutation of *GPC3* gene in a patient with Simpson-Golabi-Behmel syndrome

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Simpson-Golabi-Behmel Syndrome (SGBS) is a rare recessive X-linked disorder characterized by pre- and postnatal overgrowth, distinctive dysmorphic facies and variable congenital malformations. Most cases have been attributed to mutations in the *Glypican-3 (GPC3)* gene located at Xq26. *Glypican-3* plays essential roles in development by modulating cellular responses to growth factors and morphogens. We report here a novel nonsense mutation of the *GPC3* gene in a five-year-old Moroccan patient of consanguineous parents who had SGBS phenotype associated with congenital hypothyroidism.

Key words: GPC3 gene, congenital hypothyroidism, supernumerary nipple, overgrowth, Simpson-Golabi-Behmel syndrome.

Simpson-Golabi-Behmel syndrome (SGBS) (MIM# 312870) is a recessive X-linked disorder characterized by pre- and postnatal overgrowth[1]. The common clinical manifestations of SGBS include a distinctive dysmorphic facies, mild to severe mental retardation, supernumerary nipples, and congenital heart disease, associated with skeletal, genitourinary and hand abnormalities[2,3]. In addition, there is an increased risk of embryonic cancers, mostly Wilms tumor and neuroblastoma[4]. The incidence of SGBS is unclear. More than one hundred cases have been reported[4]. SGBS is due to loss-of-function mutations of the Glypican-3 (*GPC3*) gene at Xq26, which encodes a heparan sulfate proteoglycan that is linked to the cell membrane by a glycosylphosphatidylinositol anchor[5]. It plays essential roles in development by modulating cellular responses to growth factors and morphogens[6].

We report here a novel nonsense mutation of the *GPC3* gene in a five-year-old Moroccan child of consanguineous parents who had SGBS phenotype associated with congenital hypothyroidism.

Case Report

The patient was the second child of healthy consanguineous parents (second-degree), born of a 38-year-old mother and 45-year-old father. The pregnancy was reported as without complications or history of drug ingestion. There was no family history of congenital anomalies. On evaluation, both the parents and the other sibling were found to be normal.

The patient presented a neonatal hypotonia with psychomotor and developmental delay. He had a mental retardation. A congenital hypothyroidism was diagnosed late at four years of age. His thyroid hormone levels were 8.35 mIU/L for thyroid-stimulating hormone (TSH) (normal: 0.49-4.67 mIU/L) and 2.85 ng/L for free thyroxine (FT4) (normal: 7.1-18.5 ng/L). He was under thyroid hormone substitution.

On general examination at five years, his body weight was 23 kg (95th percentile), head circumference 53 cm (95th percentile), and height 1.14 m (97th percentile). He was dysmorphic with a coarse face, hypertelorism, short nose with anteverted nares, macrostomia, thin upper vermilion border with downturned

lower lip, macroglossia, and multiple dental caries. He had supernumerary nipples, a postaxial polydactyly on the left hand and cryptorchidism (Fig. 1).

Skeletal X-ray investigations revealed ribs synostosis. Brain scan, cardiac and abdomino-genito-urinary ultrasonographies were normal.

A SGBS was suspected because of the association of the overgrowth, typical dysmorphic features, supernumerary nipples, and genital abnormality. The molecular analysis of the *GPC3* gene detected a non-reported nonsense mutation c.271C>T (p.GLn91Stop) in exon 2. This mutation is *de novo* because it was not revealed in the molecular analysis of the mother. However, a gonadic mosaicism could not be excluded.

Discussion

The description of the clinical spectrum of SGBS was gradual over decades. It was first described in 1975 by Simpson et al.[7] in two male cousins with coarse face. Then, Behmel[8] reported an X-linked dysplasia gigantism syndrome in 11 male infants, similar to that initially described, by expanding the facial features and reporting anomalies of the extremities. In the same year, Golabi and Rosen[9] described a similar syndrome in four related males with other facial features and musculoskeletal features. Thereafter, the syndrome was named Simpson-Golabi-Behmel-Rosen syndrome. SGBS is a rare recessive X-linked overgrowth disorder with a large clinical spectrum, varying from very mild forms in carrier females to infantile lethal forms in some males[1]. It is classically characterized by pre- and postnatal macrosomia, distinctive dysmorphic facies including macrocephaly, coarse face, downslanting palpebral fissures, ocular hypertelorism, epicanthal folds, broad flat nasal bridge with short nose, macrostomia, macroglossia, midline groove of lower lip, and low-set and posteriorly rotated ears. Other clinical features are described, including supernumerary nipples, genitourinary and skeletal anomalies, and cardiac defects, and neonatal hypotonia may be reported by the parents[10]. Hypoglycemia may be present during the neonatal period[11]. SGBS is also associated with an increased risk of embryonic tumors, mostly Wilms tumor and neuroblastoma [4,12]. In our patient, the phenotype of SGBS was quite mild, including essentially some dysmorphic features, associated with supernumerary

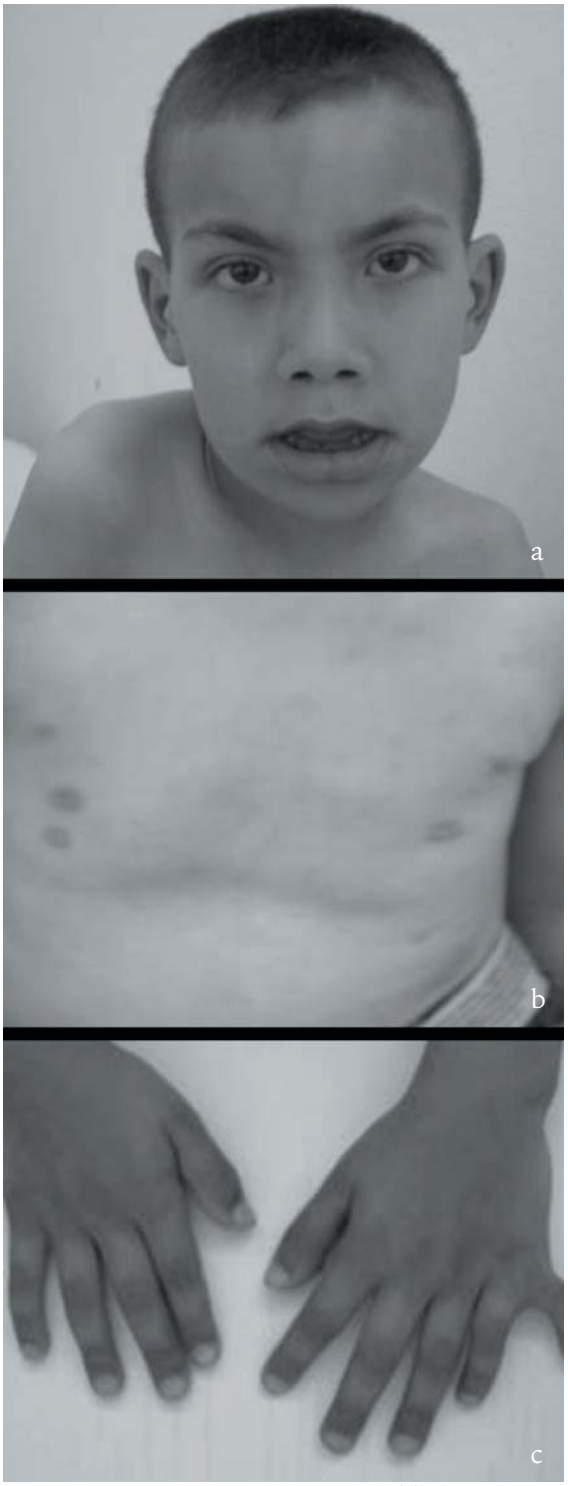

Fig. 1: Patient photographs showing **(a)** dysmorphic facies, **(b)** supernumerary nipples and **(c)** post-axial polydactyly of the left hand.

nipples, rib synostosis, polydactyly, and cryptorchidism, with no other skeletal, cardiac or renal malformations. He also had a congenital hypothyroidism with low FT4 and high TSH levels that to our knowledge has never been reported in SGBS. He is under thyroid hormone substitution. In our patient, the mental retardation may have been due to the late diagnosis of congenital hypothyroidism since there is no national neonatal screening program for this pathology in Morocco. The reports of developmental delay and abnormal intelligence quotient (IQ) in SGBS have been inconsistent [10]. We wonder if the congenital hypothyroidism was coincidental in this case of SGBS or if it may correspond to the characterization of an unreported symptom of this syndrome.

Simpson-Golabi-Behmel syndrome results from mutations in the *GPC3* gene localized at Xq26[5]. *GPC3* encodes for a membrane-associated heparin sulphate proteoglycan of 580 amino acids, a member of the glypican-related integral membrane proteoglycans (GRIPS), which are linked to the cell surface via glycosylphosp hatidylinositol and modulate the interaction between growth factors and receptors[5].

Most of the *GPC3* gene mutations identified to date are loss-of-function point mutations (nonsense and missense) or microdeletions encompassing a varying number of exons, with no relevant hotspot[13-16].

In our case, the patient had an unreported nonsense mutation (c.271C>T; p.GLn91Stop), which to the best of our knowledge had never been documented before. This premature termination leads to the loss of 489 amino acids of the 580 amino acids of the normal protein, which causes a truncated protein.

Simpson-Golabi-Behmel syndrome has clinical overlap with other overgrowth syndromes, in particular with Beckwith-Wiedemann syndrome (BWS), but also Perlman syndrome and Weaver syndrome (Table I)[17]. BWS demonstrates the most clinical similarities with SGBS, including macrosomia, macroglossia, ear anomalies, genitourinary malformations, and an increased incidence of embryonic tumors. However, the facies in these two syndromes are appreciably different. The skeletal abnormalities seen in SGBS are not present in BWS, and omphalocele seen in BWS is rare in SGBS. Additionally, the X-linked inheritance of SGBS may help to differentiate these two overgrowth syndromes[18].

In conclusion, the management of SGBS includes treatment of neonatal hypoglycemia and multidisciplinary support of a pediatric orthopedist, cardiologist and urologist as needed. A speech therapy can be proposed. A surveillance of renal function in the presence of renal anomalies and for Wilms tumor, gonadoblastoma, hepatocellular carcinoma, and neuroblastoma is required. The prognosis of SGBS is conditioned by the severity of malformations and the risk of embryonic tumors.

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Table I. Other Overgrowth Syndromes

Overgrowth syndromes	Gene abnormalities
Beckwith-Wiedemann	Imprinted genes within the chromosome 11p15.5 region
Sotos	*NSD1* (5q35)
Bannayan-Riley-Ruvalcaba	*PTEN* (10q23)
Proteus	Unknown
Perlman	Unknown
Weaver	Unknown

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