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ARTICLE

# Phenotypic Spectrum of Simpson–Golabi–Behmel Syndrome in a Series of 42 Cases With a Mutation in *GPC3* and Review of the Literature

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Simpson–Golabi–Behmel syndrome (SGBS) is a rare X-linked multiple congenital abnormality/intellectual disability syndrome characterized by pre- and post-natal overgrowth, distinctive craniofacial features, macrocephaly, variable congenital malformations, organomegaly, increased risk of tumor and mild/moderate intellectual deficiency. In 1996, Glypican 3 (*GPC3*) was identified as the major gene causing SGBS but the mutation detection rate was only 28–70%, suggesting either genetic heterogeneity or that some patients could have alternative diagnoses. This was particularly suggested by some reports of atypical cases with more severe prognoses. In the family reported by Golabi and Rosen, a duplication of *GPC4* was recently identified, suggesting that *GPC4* could be the second gene for SGBS but no point mutations within *GPC4* have yet been reported. In the genetics laboratory in Tours Hospital, *GPC3* molecular testing over more than a decade has detected pathogenic mutations in only 8.7% of individuals with SGBS. In addition, *GPC4* mutations have not been identified thus raising the question of frequent misdiagnosis. In order to better delineate the phenotypic spectrum of SGBS caused by *GPC3* mutations, and to try to define specific clinical criteria for *GPC3* molecular testing, we reviewed the clinical features of all male cases with a *GPC3* mutation identified in the two molecular laboratories providing this test in France (Tours and Paris). We present here the results of the analysis of 42 patients belonging to 31 families and including five fetuses and three deceased neonates. 

**KEY WORDS:** Simpson–Golabi–Behmel syndrome; SGBS; overgrowth; XLID; *GPC3*

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## INTRODUCTION

Simpson–Golabi–Behmel syndrome (SGBS) is a rare X-linked multiple congenital abnormality (MCA)/intellectual disability (ID) syndrome first reported by Simpson et al. [1975]. Subsequent to additional cases reported by Golabi and Rosen and Behmel et al. [1984], the syndrome became known as Simpson–Golabi–Behmel syndrome [Neri et al., 1988]. SGBS is characterized by pre- and post-natal overgrowth, distinctive craniofacial features with macrocephaly, variable congenital malformations, organomegaly, an increased tumor risk and mild/moderate intellectual deficiency (ID). Since its first descriptions, many other cases have been reported with a wide range of clinical symptoms and severity. Among them, a few cases were significantly different with an atypical clinical presentation associated with a more severe prognosis [Opitz, 1984; Opitz et al., 1988; Le Merrer et al., 1989], but these descriptions occurred before *GPC3* molecular analysis was available. In addition, an MCA syndrome postulated to be a severe form of SGBS or so-called infantile lethal variant [Terespolsky et al., 1995], raised the question of genetic heterogeneity of SGBS, and was designated SGBS2 as the locus for this condition was further mapped to Xp22 [Brzustowicz et al., 1999].

***SGBS is characterized by pre- and post-natal overgrowth, distinctive craniofacial features with macrocephaly, variable congenital malformations, organomegaly, an increased tumor risk and mild/moderate intellectual deficiency (ID).***

In 1996, pathogenic mutations within Glypican 3 (*GPC3*), which maps to Xq26 and encodes a heparan sulphate proteoglycan belonging to the glypican family, were identified in patients with the typical form of SGBS, also designated as SGBS1 [Pilia et al., 1996]. Further studies have confirmed that *GPC3* is the major gene of SGBS. A few publications have reported molecular analyses of *GPC3* on relatively small series of patients with a mutation detection rate ranging from 28% for deletion screening only [Lindsay et al., 1997] to around 70% with additional sequencing [Veugelers et al., 1998; Lin et al., 1999]. This low detection rate could further support genetic heterogeneity in SBGS, but there have been no recent reports on larger series of patients where *GPC3* analyses have been undertaken using current, more efficient technologies. In 2011, in the family reported by Golabi and Rosen, a duplication of *GPC4*, mapping close to the 3-prime end of *GPC3* and coding for another member of the glypican family, was identified, suggesting that *GPC4* could be the second gene for SGBS [Waterson et al., 2010]. However no point mutations within *GPC4* have since been described in SGBS. This could also be explicable by alternative mechanisms, such as *GPC3* intronic mutations or mutations within regulatory sequence in *GPC3* not detectable by the routine methods used. Alternatively, misdiagnosis in a number of patients is possible as is exemplified by SGBS2 which is now considered a distinct disorder with overlapping features [Golabi et al., 2011].

In the genetics laboratory of Tours University Hospital, molecular analysis of *GPC3*, by MLPA and sequencing, was undertaken on 183 index patients with somatic overgrowth, macrocephaly and/or an intellectual disability, and has identified a mutation in only 8.7%. In addition, *GPC4* testing in 40 cases did not identify a pathogenic mutation. We therefore hypothesized that these results most likely reflect an unfamiliarity with the phenotype of SGBS amongst clinicians requesting *GPC3* analysis. In order to better delineate the phenotypic spectrum of SGBS caused by *GPC3* mutations, and to try to define specific clinical criteria for *GPC3* molecular testing, we reviewed the clinical features of all male cases with a *GPC3* mutation identified in the two molecular laboratories providing this test in France (Tours and Paris).

## PATIENTS AND METHODS

Over more than a decade, 33 *GPC3* variants have been identified in the two laboratories including two missense variants predicted to be benign. In one of these two cases with missense variants, the phenotype was not suggestive of SGBS and not enough clinical data were available for the other. These cases were therefore not included in our study. Similarly, two unrelated cases with the same sequence variation of unknown significance in the 5' region of the gene, one with a typical SGBS clinical picture whereas the other had isolated tall stature, were also excluded. A clinical questionnaire based on literature data was sent to the referring physicians in order to collect pre- and post-natal data, that is, amniotic fluid amount; fetal malformations and growth parameters during pregnancy and, postnatally, growth; organomegaly; tumors; congenital malformations; dysmorphic features, and psychomotor development. We could not obtain information for only one patient with a deletion of exons 6–8 of *GPC3*. Two patients already published [Pénisson-Besnier et al., 2008; Ratbi et al., 2010] were part of this study as additional information could be obtained. Finally 42 cases (22 sporadic and 20 familial) belonging to 31 families were analyzed. The *GPC3* mutations identified in these 31 families were mostly large rearrangements: 11 deletions of one or several exons, including one case of deletion of all eight exons, and one duplication of exon 2. Apart from a partial deletion of exon 8 extending to the 3' region of the gene, which was first detected by array-CGH, deletions were identified only by MLPA. Therefore, the 5' boundary of the four deletions involving exon 1, the 3' boundary of three deletions involving exon 8, and the two boundaries of the deletion involving all eight exons were not precisely delineated. The point

mutations included seven frameshift, five nonsense, and five missense mutations and were distributed throughout the gene. No mutational hot-spots were detected but it is worth noting that the missense mutation, Gly556Arg, previously reported was observed in two other unrelated families [Pénisson-Besnier et al., 2008]. The same amino-acid was also involved in another substitution, Gly556Val, in one family.

The genetic status of the mother was known in only 13 of the sporadic cases, eight of whom carried the *GPC3* mutation identified in their son.

Apart from five fetuses examined after termination of pregnancy (TOP), three deceased neonates and one child who died at 8 years, all the patients were alive at the time of the study. The oldest patient was 64 years old at the last examination. Most cases had been seen by French physicians, but two were from Australia, one from Portugal, one from Morocco, and three from Belgium.

## RESULTS

### Prenatal Findings

Pregnancy related data were collected in 36 cases (Table IA). Macrosomia was observed in nearly all cases where growth parameters were available (19/20). The second most common association in pregnancy was polyhydramnios (24/33) which was noted from the second trimester in 6 out of 11 cases for which the information was available and was identified as early as 15 weeks gestation (WG) in one pregnancy. Organomegaly was detected prenatally in 62% cases and consisted of either hypertrophy of one organ (eight cases with nephromegaly, two with macroglossia, and one with hepatomegaly), or combined organomegaly (nephromegaly and macroglossia in one fetus, nephromegaly and hepatomegaly in three, and nephromegaly, hepatomegaly and splenomegaly in one). Diaphragmatic hernia and heart defects were the most common malformations detected, in 24% and 10% of cases, respectively, and hyperechogenicity was the most frequent renal anomaly (16%).

**TABLE I. Summary of the Clinical Findings**

| | Total | |
|---|---|---|
| A: Prenatal period, growth and development | | |
| Prenatal findings | | |
| Macrosomia | 19/20 | 95 |
| Polyhydramnios | 24/33 | 73 |
| Organomegaly | 18/29 | 62 |
| Diaphragmatic hernia | 8/33 | 24 |
| Cardiac malformations | 3/30 | 10 |
| Hyperechogenic kidneys | 5/31 | 16 |
| Birth parameters | | |
| Term of delivery <37 weeks | 13/31 | 42 |
| Birth weight ≥90th percentile | 26/35 | 74 |
| Birth length ≥90th percentile | 26/30 | 87 |
| Head circumference ≥90th percentile | 16/25 | 64 |
| Growth | | |
| Height ≥ +2SD | 16/30 | 53 |
| Head circumference ≥ +2 SD | 13/27 | 48 |
| Body mass index ≥97th percentile | 5/29 | 17 |
| Advanced bone age | 2/9 | |
| Organomegaly | 30/37 | 81 |
| Macroglossia | 28/37 | 76 |
| Nephromegaly | 17/30 | 57 |
| Hepatomegaly | 15/33 | 45 |
| Neonatal hyperinsulinism/hygoglycemia/hyperplasia of | 3/26 | 12 |
| Langerhans islets | | |
| Neoplasias | | |
| Wilms tumor | 1/34 | |
| Other (leukemia) | 1/34 | |
| Psychomotor development | | |
| Neonatal hypotonia | 16/22 | 73 |
| Childhood hypotonia | 11/18 | 61 |
| Speech disorder | 17/22 | 77 |
| Intellectual disability | 15/32 | 47 |
| B: Dysmorphic features and malformations | | |
| Facial features | | |
| Coarse/square face | 37/41 | 90 |
| Macrocephaly | 27/36 | 75 |
| Hypertelorism | 19/36 | 53 |
| Short nose/broad nasal bridge | 28/35 | 80 |
| Prominent nose | 8/27 | 30 |
| Anteverted nares | 23/37 | 62 |
| Macrostomia | 32/37 | 86 |
| Midline groove of the lower lipdeep median furrow | 17/34 | 50 |
| of the tongue | | |
| Downturned lower lip/swelling under lower lip | 24/34 | 71 |
| Macrognathia | 23/37 | 62 |
| Posterior helical pits/ear lobe creases | 5/30 | 17 |
| Extremities | 31/40 | 78 |
| Broad and/or short hands | 23/28 | 82 |
| Broad fingertips | 8/15 | 53 |
| Brachydactyly | 13/27 | 48 |
| Cutaneous syndactyly | 7/33 | 21 |

**TABLE I.** (*Continued*)

| | Total | |
|---|---|---|
| Hypoplasia of proximal phalanx of index finger | 1/22 | |
| Nail dysplasia | 8/30 | 27 |
| Postaxial polydactyly | 8/40 | 20 |
| Maformations/visceral problems | | |
| Supernumerary nipples | 18/34 | 53 |
| Genito-urinary | 28/38 | 74 |
| Urinary tract malformations | 15/31 | 48 |
| Renal dysplasia/cysts | 10/30 | 33 |
| Cryptorchidism | 10/36 | 28 |
| Hydrocele | 4/31 | 13 |
| Gastro-intestinal | 28/40 | 70 |
| Diaphragmatic hernia | 12/36 | 33 |
| Inguinal hernia | 10/34 | 29 |
| Diastasis recti/umbilical hernia | 9/30 | 30 |
| Cleft lip/cleft palate/bifid uvula | 10/38 | 26 |
| Heart | 14/37 | 38 |
| Heart defects | 13/36 | 36 |
| Rhythm abnormalities/conduction defects | 4/27 | 15 |
| Cardiomyopathy | 1/31 | |
| Skeletal anomalies | 18/35 | 51 |
| Pectus excavatum/chest deformity | 12/32 | 38 |
| Scoliosis | 4/32 | 13 |
| Abnormal number of ribs | 2/21 | 10 |
| Rib shape anomalies | 3/16 | 19 |
| Abnormal number of vertebrae | 3/20 | 15 |
| Vertebral shape anomalies | 6/21 | 29 |

Additional reported malformations included four cases with urinary tract anomalies (one with pyelectasis and three with hydronephrosis), one case with ventriculomegaly, and bilateral hand polydactyly with talipes equinovarus in one case. Increased nuchal translucency at the first trimester or cystic hygroma were reported in five fetuses. Alpha-fetoprotein was increased in three of the five documented pregnancies.

Four pregnancies had been interrupted during the second trimester (at $23^1/_2$, $24^1/_2$, 25, and 28 WG). In a dizygotic twin pregnancy both fetuses had macrosomia, hepatomegaly, major polyhydramnios and one of them had a diaphragmatic hernia whereas the other had nephromegaly. In another pregnancy, which followed the neonatal death of a male child with MCA (macrosomia, diaphragmatic hernia, multicystic kidneys), a recurrence was diagnosed on ultrasound scan (USS) showing macrosomia, diaphragmatic hernia, and hyperechogenic kidneys. In these two families, the diagnosis of SGBS was suggested on post-mortem examination and subsequently confirmed by molecular analysis. For the two other pregnancies, SGBS had been previously recognized in an index case and the mutation was known in the family. In both cases, USS had shown macrosomia associated with other fetal anomalies (diaphragmatic hernia with severe pulmonary hypoplasia, nephromegaly, and macroglossia in one; polyhydramnios in the other).

### Birth and Neonatal Period

A significant proportion of patients were born prematurely, but most (9/13) were moderately premature (between 35 and 36 WG), and it is worth noting that in nearly all cases (11/12) the pregnancy had been complicated by polyhydramnios (Table IA).

Three patients died during the neonatal period, one at 2 hr of life from respiratory compromise secondary to a diaphragmatic hernia, another at 2 days due to prematurity (29 WG) and severe refractory hypoxemia secondary to diaphragmatic hernia, and the third, who also had diaphragmatic hernia, at 13 days from sepsis.

Birth length and weight were at or above the 90th centile (≥90th) in 87% and 74% of cases, respectively (Fig. 1), and 19 of 28 (68%) patients, for whom both birth length and weight measurements were available, had both growth parameters above the 95th centile (>95th). Only four patients had a birth length <90th, but they all were in the upper range (≥50th; Fig. 1A). Similarly, only one of the nine cases with a birth weight <90th, was below the 50th (Fig. 1B). When macrosomia had been detected prenatally, it was confirmed by birth measurements in all of the 18 documented cases (both length and weight >95th percentile in 14). Head circumference at birth was ≥90th in 64% cases (40% being ≥95th) and eight were in the upper range (≥50th; Fig. 1C).

### Post-natal Growth

At their last examination, only 53% of patients had a height ≥ +2SD but, with

***At their last examination, only 53% of patients had a height ≥ +2SD but, with the exception of one individual, all had a height in the upper range. As illustrated in Figure 2A, a specific age-related growth profile was not evident amongst our series.***

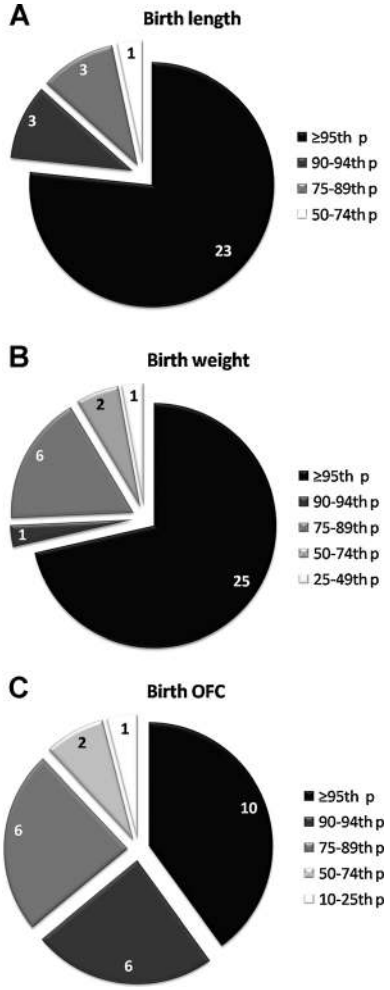


**Figure 1.** Birth parameters. Proportion of patients for different sections of percentiles. (**A**) Length, (**B**) Weight, and (**C**) OFC.

the exception of one individual, all had a height in the upper range. As illustrated in Figure 2A, a specific age-related growth profile was not evident amongst our series. Similarly, only 48% of cases had an OFC $\geq +2$DS, but 12 of the 14 remaining cases were in the upper range (Table IA and Fig. 2B).

Figure 2C shows the body mass index (BMI) at their last examination for 24 patients in childhood or adolescence, showing that only three were mildly overweight. Of the five adults within our series, but not represented on the chart, three had a BMI between 20 and 25 and two had a BMI of 25.1 and 26.8, respectively.

The bone age was evaluated only for nine patients; it was advanced in one neonate and at 24 months for a child aged 14 months.

## Psychomotor Development and Intellectual Disability

Although numerous patients had neonatal and/or childhood hypotonia, the acquisition of motor skills was not significantly delayed in most patients. The average age to sit independently was $8^{1}/_{2}$ months (range: 6–12 months) in the 11 patients for whom information was available, and the average age to walk independently was 16 months in 21 patients (range: 11–27 months). Language delay was reported in seven patients whilst four affected individuals had normal language development (Table IA).

Many patients had speech problems which may be partly explained by mechanical factors as 12 of them had macroglossia and three had a cleft palate. However three cases with macroglossia and one with macroglossia and cleft had no speech disorder, suggesting other or additional mechanisms.

Intellectual disability was reported in less than half of the patients. It was most often said to be mild (9/12) and was not always correlated with walking or language delay. However, very few patients had precise neuropsychological evaluation and IQ was available for only three cases. In addition, five patients, reported not to have ID, had other specific cognitive or behavioral problems: learning difficulties in two, two individuals had attention disorder with hyperactivity; two had difficulties with concentration; two struggled with handwriting and one patient had behavioral problems with temper tantrums.

## Dysmorphic Features

Facial photographs were available for 35 cases, including four fetuses, and a clinical description of facial appearance could be obtained for all patients. Only one patient was reported with no dysmorphic features but he died in intensive care unit at 13 days. Analysis of photographs showed that all but two individuals had a suggestive or even typical facial appearance of SGBS. Photographs at different ages also showed that the main dysmorphic features evolved with time (Table IB and Fig. 3).

At any age, the most frequently reported features were coarse or square face and macrostomia. We also noted that the wide mouth was frequently associated with an everted lower lip and/or a thickening under the lower lip (Fig. 3). In addition, half of the patients had a midline furrow of the tongue or the lower lip. This characteristic of the mouth was even present in young fetuses (Fig. 3). In contrast, macrognathia was not observed in fetuses, neonates, or infants but became evident in childhood and was prominent in all adults. Similarly, in young patients the nose was most often described as short with a broad nasal bridge whereas a prominent nose was more frequently reported in older patients. Ear abnormalities were infrequent and only five cases had creases on the lobules or posterior helical pits.

## Extremities

In our series, 78% of patients had at least one anomaly of the extremities, the most frequent being broad and/or short hands, and 48% had brachydactyly. Although the number of patients for whom the information was available is low, more than a half had broad fingertips. Nail dysplasia, particularly of the index finger, and partial cutaneous syndactyly of the hands, mainly between the second and third fingers, were also reported in a significant proportion of cases (Table IB). Postaxial polydactyly of the hands was present in only eight cases and hypoplasia of the proximal phalanx of the index in a single patient (Fig. 4).

## Skeletal Problems

In addition to polydactyly, we identified 51% of patients with at least one skeletal anomaly. Chest deformity, mainly pectus excavatum, was present in 38% and

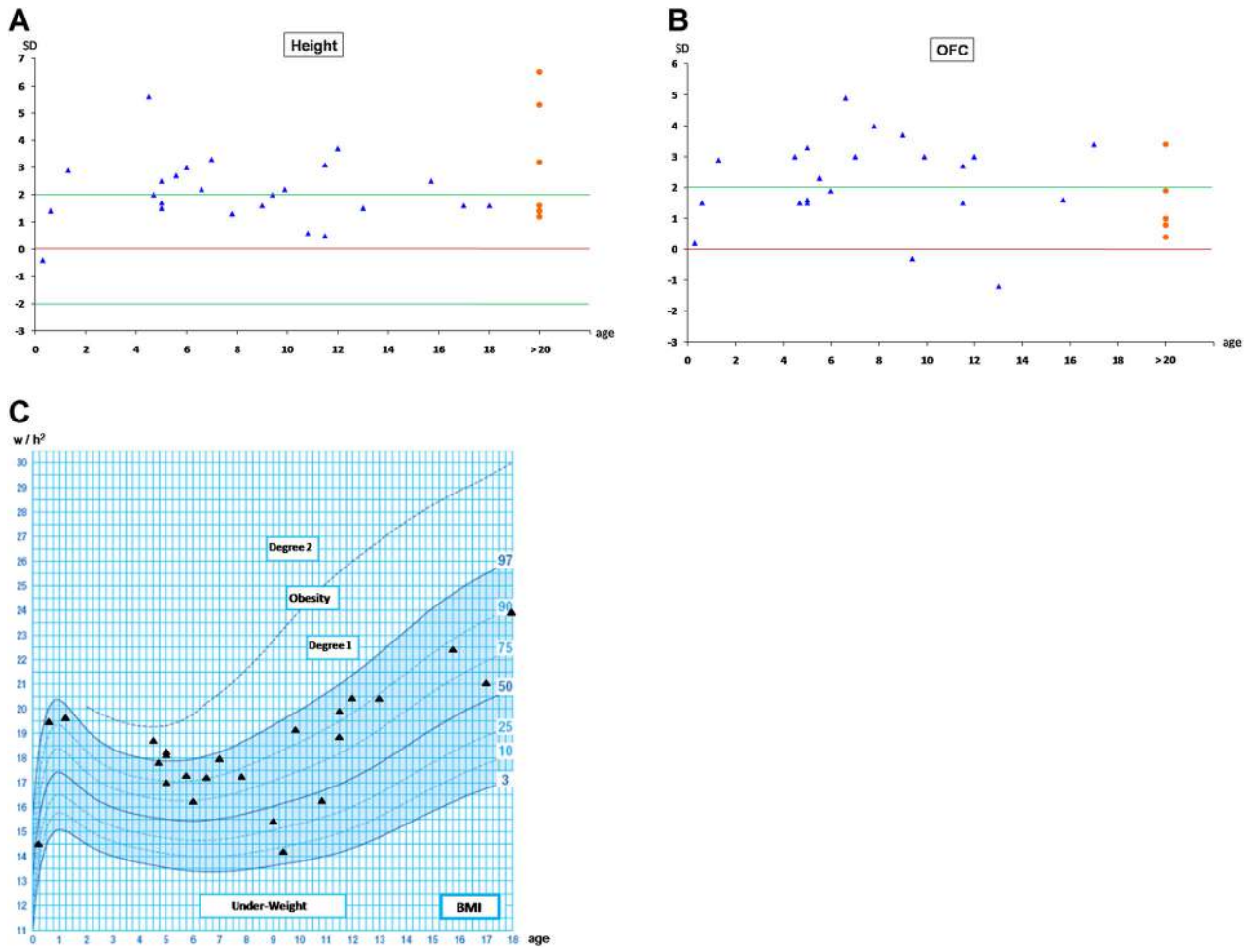


**Figure 2.** Post-natal growth parameters. (**A**) Height represented as standard deviation from the mean for 30 patients. Values for adults above 18 years are plotted on the same line. (**B**) OFC represented as standard deviation from the mean for 27 patients. Values for adults above 20 are plotted on the same line. (**C**) Body mass index for 24 patients (values of five patients older than 18 years are not showed).

scoliosis in 13%. Some patients also had a lateral narrowing of the thorax (Fig. 5). Rib and vertebral anomalies were not well documented as very few patients had X-rays. Besides number anomalies, abnormal shape consisted of rib synostosis (two cases) and bifid ribs (one case), and six patients had one or more vertebral anomalies, including one case with a conical ondotoid, one case with dysplasia of the first lumbar vertebra, one spina bifida occulta, and one case of cervicothoracic segmentation defects. Finally, one patient had talipes equinovarus (Table IB).

## Organomegaly

A large majority of patients had organomegaly (81%), most frequently macroglossia, followed by nephromegaly and hepatomegaly, although the percentage of nephromegaly is probably overestimated due to the presence of renal cysts in six of these patients. Two patients had splenomegaly: one a fetus and the other a patient who was additionally noted to have polysplenia at postmortem examination. Neonatal hyperinsulinism was reported only in two patients and hyperplasia of the islets of Langerhans was discovered on microscopic examination in one fetus (Table IA).

## Tumors

Microscopic examination diagnosed a small Wilms tumor associated with bilateral nephroblastomatosis in a fetus. No other cases of embryonal tumor have been reported in our series but one patient died at 8 years of leukemia.

## Additional Malformations

Supernumerary nipples were observed in more than half of the patients and one of them had several areolar skin tags (Table IB).

In 74% of patients at least one genito-urinary anomaly was reported. A malformation of the urinary tract was diagnosed in nearly half of cases and consisted of a duplicated collecting system in six cases, a megaureter in two cases, one case with vesicoureteral reflux, one case with ureteropelvic junction stenosis, one case with pyelectasis and seven cases with undocumented

**Figure 3.** Facial features of 19 patients, from fetuses and newborns at the top line to adolescent and adult patients at the bottom line. Photographs joined inside squares represent a same patient at different ages.

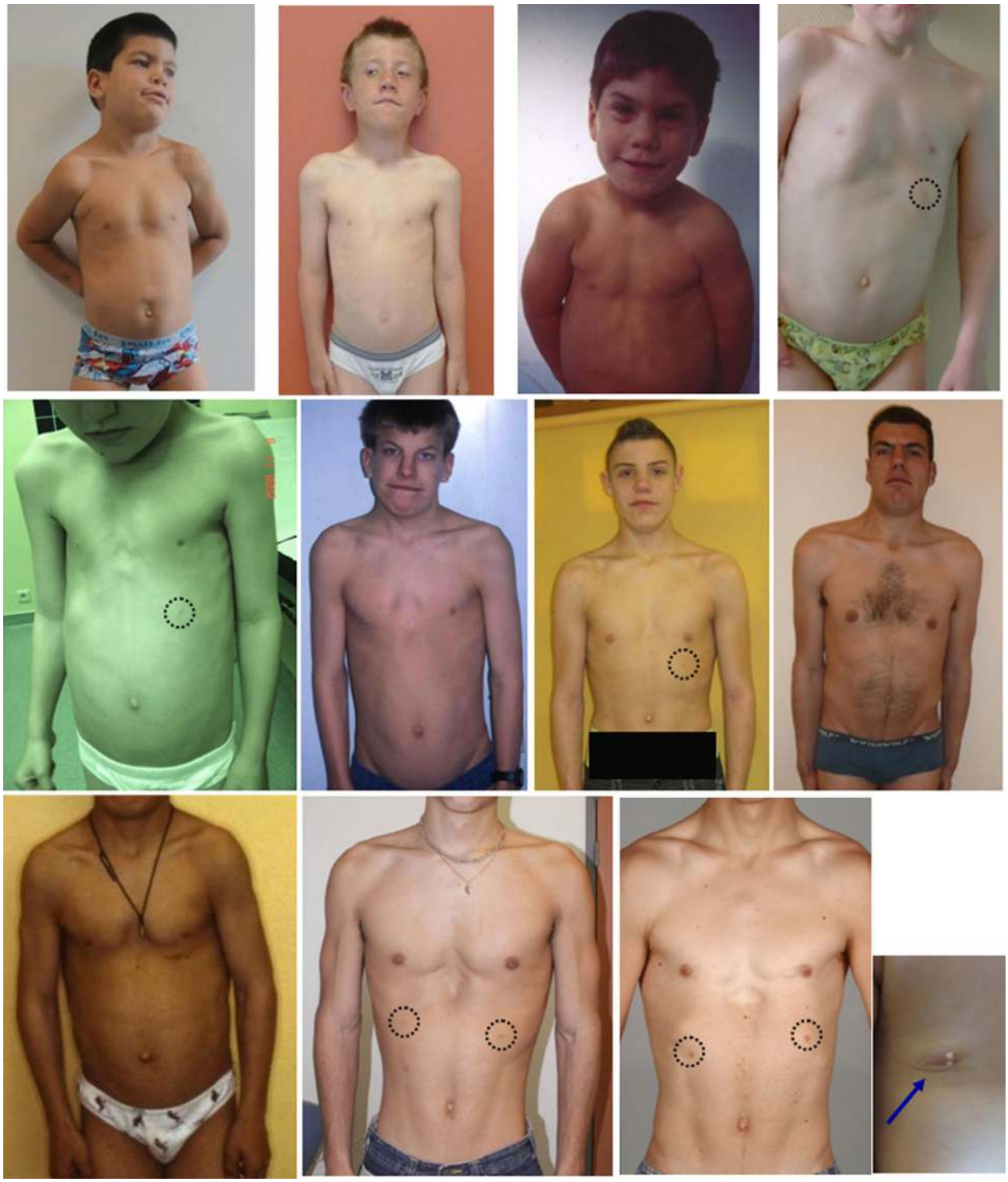

**Figure 4.** General appearance and trunk. Note the abnormal chest shape with pectus excavatum and narrowing of the thorax in some patients. Dotted circles indicate supernumerary nipples. The arrow shows areolar skin tags.

dilatation of the upper urinary tract. Renal dysplasia was found in 33% of patients, with nine cases of cystic disease of the kidney described as "macrocysts," "medullary renal cysts," "multiple renal cysts," "polycystic kidneys," "multicystic dysplasia," and one case of renal hypoplasia probably secondary to repeated urinary infections. In addition, one patient developed nephrocalcinosis. Abnormalities of the external genitalia consisted mainly of cryptorchidism (28%) and hydrocele (13%). Three cases had a micropenis and one had a hypoplastic prepuce.

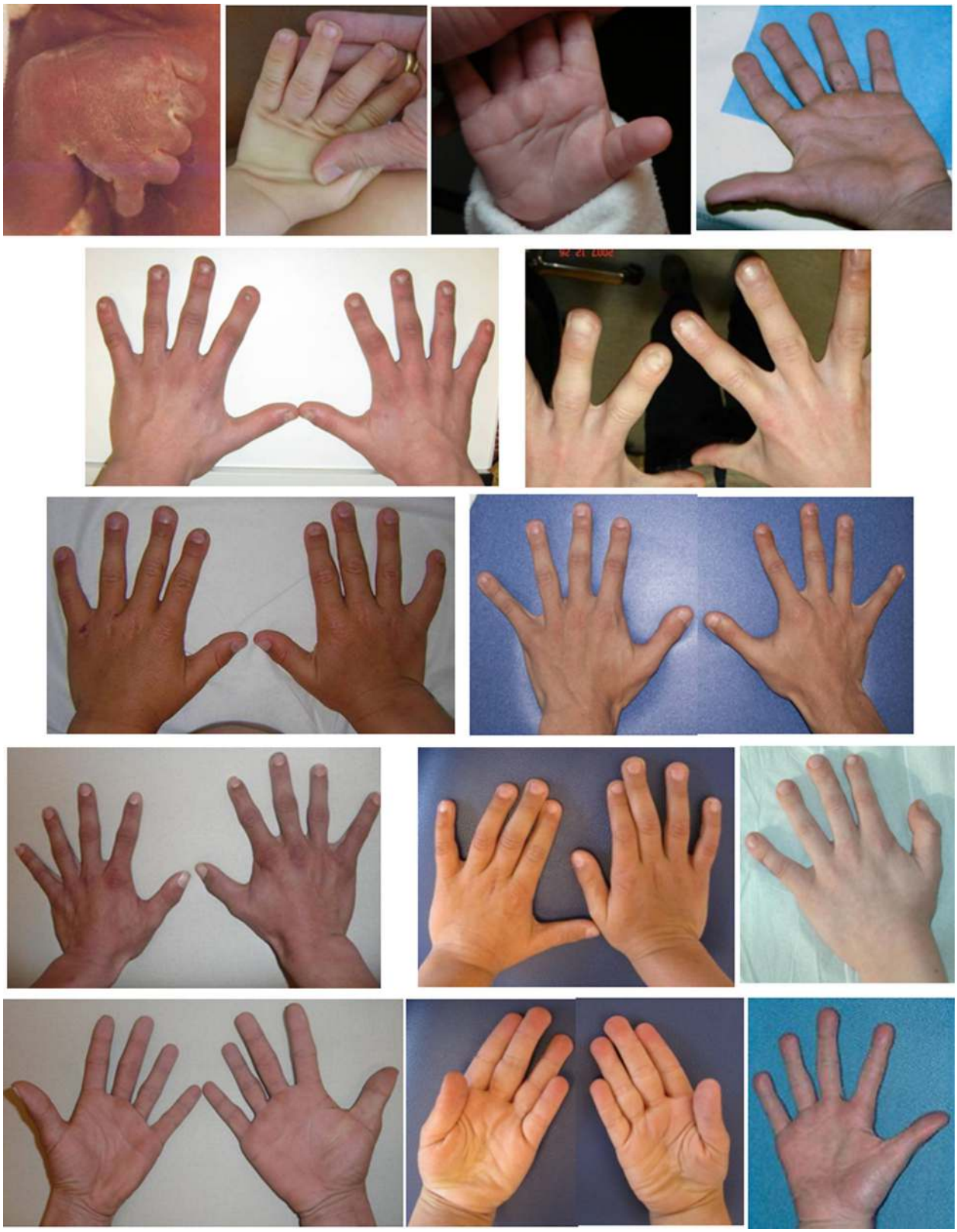

**Figure 5.** Extremities. Note the broad and short hands, broad fingertips, brachydactyly, nail dysplasia of the index, and mild cutaneous syndactylies.

At least one gastrointestinal or abdominal wall malformation was seen in 70% of patients. The most common was diaphragmatic hernia (34%), which was the cause of neonatal death in three cases and justified three of the four terminations of pregnancy. Therefore only two of the cases for whom diaphragmatic hernia was diagnosed in utero were alive. Inguinal hernia and diastasis recti or umbilical hernia were each observed in 30%. Cleft lip/palate or equivalent was seen in 26% of cases (four cleft palate, two labio-alveolar clefts, one cleft lip, one cleft soft palate, and two bifid uvula). In addition, were reported: intestinal malrotation in three patients, persistant omphalomesenteric duct in two, one umbilical cord cyst, duodenal stenosis in one patient and cholelithiasis at 13 years in the patient who also had nephrocalcinosis. One case had a Meckel's diverticulum detected at autopsy. Finally, esophageal hypotonia was described in one case, and one patient had liver fibrosis. No choledochal cyst has been reported in our series.

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A heart defect was reported in 13 patients and described in 12 (nine had a VSD, two had a bicuspid aortic valve, two had an ASD, and two pulmonary stenosis). Arrhythmia occurred in four patients but in one case supraventricular tachycardia happened after surgical treatment of VSD. The three others had pre- and neonatal supraventricular tachycardia, infrahisian block with atrial fibrillation, and right bundle branch block with left anterior hemiblock, respectively. One patient had at birth a transient biventricular cardiomyopathy without neonatal hyperinsulinism. No case of sudden death was observed in our series.

### Central Nervous System (CNS) Malformations

CNS malformations were described in five patients. Partial agenesis of the corpus callosum with agenesis of the septum pellucidum and bilateral ventriculomegaly were already reported [Pénisson-Besnier et al., 2008]. Arrhinencephaly and sacral dimple were seen in one patient. Thin corpus callosum, lipoma of the floor of the third ventricle, and "external hydrocephalus" were seen each in one patient.

### Miscellaneous Problems

Various additional problems, of which the relationship with SGBS is unclear, were mentioned such as fusion of two lower incisors, thyroglossal cyst, laryngomalacia, congenital hypothyroidism, and a retrovesical urothelial cyst. Similarly various visual problems, congenital nystagmus with myopia, strabismus, unexplained decreased visual acuity, and Duane anomaly, were observed each in one patient.

## DISCUSSION

We describe here the phenotypic spectrum of a series of 42 individuals with a molecularly confirmed diagnosis of Simpson–Golabi–Behmel syndrome. This is the largest series of SGBS cases ever published.

Although we could not collect information for all clinical features in all cases and were thus unable to evaluate the precise frequency of rare associations, our study improves significantly the knowledge on SGBS. Our data may be compared with those of the 63 cases carrying a mutation in *GPC3* for whom clinical details are available in the literature [Hughes-Benzie et al., 1996; Lindsay et al., 1997; Veugelers et al., 1998, 2000; Okamoto et al., 1999; Li et al., 2001; Mariani et al., 2003; Day and Fryer, 2005; Rodríguez-Criado et al., 2005; Young et al., 2006; Romanelli et al., 2007; Sakazume et al., 2007; Glamuzina et al., 2009; Gertsch et al., 2010; Gurrieri et al., 2011; Yano et al., 2011; Garavelli et al., 2012; Thomas et al., 2012; Li and McDonald, 2009].

### Prenatal Findings

There have been few publications, mostly case reports, describing prenatal findings in SBGS [Chen et al., 1993; Hughes-Benzie et al., 1996; Li and McDonald, 2009; Weichert et al., 2011; Garavelli et al., 2012]. Weichert et al. [2011] and Chen [2012] have reviewed the main published data. However they included cases with no mutation in *GPC3* such as the family reported by Golabi and Rosen [1984] who has a *GPC4* duplication, one family with no known molecular defect [Yamashita et al., 1995] and the family described by Terespolsky et al. [1995] as a type 2 SGBS. Moreover, in the case reported by Weichert et al., who had early detectable signs during the pregnancy with early and marked macrosomia, both *GPC3* and *GPC4* were deleted. In the three remaining cases, the prenatal findings reported were comparable to those of our series and consisted of polyhydramnios (3/3), macrosomia (2/3), increased maternal serum alpha fetoprotein (2/2), visceromegaly (1/3), increased nuchal translucency (1/3), pyelectasis (1/3), ventriculomegaly (1/3), and craniofacial anomalies (1/3).

### Neonatal Data

Information about the term of delivery was rarely available for the 63 cases from the literature. We nevertheless noticed that very few babies were born at full term although, as in our series, they were only slightly premature. One of the reason seems to be macrosomia that may require caesarean section, although polyhydramnios could also be an explanation.

Neonatal death has been recorded as high as 50% in SGBS [Neri et al., 1988] but this was based on the first 26 cases published in the eighties,

including the severely affected Michigan family [Opitz, 1984; Opitz et al., 1988] for whom the diagnosis remains debatable, and no recent evaluation, since the development of USS prenatal diagnosis, has been made. One stillbirth and six neonatal deaths were reported for the 63 published cases with a *GPC3* mutation (11%). In our series the three neonatal deaths (8%) were all attributable to diaphragmatic hernia.

The percentage of macrosomia at birth in the 63 cases from the literature is grossly similar to our results as 83% of cases had one parameter (weight or length) ≥90th percentile or ≥+2 SD or reported as "increased." In three cases the weight was normal but in the upper range (75th–90th percentile, +1.5 SD and +0.8 SD, respectively) [Romanelli et al., 2007; Sakazume et al., 2007]. OFC at birth was rarely mentioned; it was ≥90th percentile in six cases and three others were in the upper range (2 at 75th–90th percentile and 1 at 50th percentile).

### Post-natal Growth

Among the 63 reviewed cases, 27 were described with an overgrowth but precise figures were not always given, and there was no mention for the others except one case who had a height at +1SD [Sakazume et al., 2007]. OFC was reported for five cases, all ≥97th centile or ≥+2SD. It is therefore not possible to evaluate the exact frequency of these symptoms which are however key features. It is noticeable that in our series no more than 53% had a tall stature and only 48% had macrocephaly. A height or an OFC in the normal range therefore does not exclude the diagnosis of SGBS. Our study also shows that SGBS patients generally have a weight in keeping with their stature and that increased weight is not a hallmark of the condition. This observation is particularly pertinent given a recent study that showed that a human SGB pre-adipocyte cell strain expressed higher levels of adipocyte-specific transcripts and suggested that it is a relevant in vitro model for obesity in humans [Allott et al., 2012].

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### Psychomotor Development and Intellectual Disability

Although SGBS remains classified as a syndromic form of X-linked ID (XLID) [Lubs et al., 2012], there has been no review on this topic since the paper of Neri et al. [1998] reporting that most patients are not mentally deficient. Only five patients were reported with ID in the group of 63 cases from the literature which is strikingly different from our results. However, we strongly suspect that the percentage of ID has been overestimated in our series as very few patients had precise neuropsychological evaluation. Our feeling is that patients with SGBS are slow in their development, as illustrated by the frequent report of neonatal or childhood hypotonia and of motor and/or language delay (26/63), but finally reach normal milestones. In addition they are handicapped by speech problems, sometimes caused by macroglossia and/or cleft palate [Van Borsel et al., 2008]. SGBS patients have therefore many similarities with Beckwith–Wiedemann syndrome. Further and more accurate studies will be necessary to evaluate precisely the cognitive functions in SGBS.

### Dysmorphic Features

The literature also reflects that the facial gestalt is a good clue for the diagnosis of SGBS. Among the 63 reviewed cases, 57 were said to have a specific or suggestive facial dysmorphia. Only one case was reported as not dysmorphic [Li et al., 2001]. Our study shows that the most typical is the lower part of the face. The particular aspect of the mouth, which is wide with an everted lower lip and/or a thickening below the lower lip and a midline groove, may be present in fetal life whereas the large mandible becomes obvious with age, giving a massive appearance and a square face.

### Extremities

Our study confirms the descriptions made in the previous publications concerning the hand anomalies which are broad and/or short, frequently with broad fingertips, in keeping with the general appearance of most patients, but statistical estimation from the literature data was impossible. More specific, but less frequently associated features, are nail dysplasia predominating on the index finger and mild cutaneous syndactyly. Hypoplasia of the proximal phalanx of the index is a very rare sign, which was observed in two cases from the literature [Day and Fryer, 2005; Gertsch et al., 2010], and in one case in our series.

Polydactyly is considered as a good clue for the diagnosis of SGBS. However it is not such a frequent finding. It was reported in only seven of the 63 patients from the literature and we found eight cases among 40 in our series, leading to an overall frequency at around 14.5%. Polydactyly was post-axial in all cases, always involved only the hands, but was unilateral in some cases [Gertsch et al., 2010].

### Skeletal Anomalies

In the series of 63 reviewed cases we found 78% (28/36) of skeletal problems consisting, as in our patients, of pectus excavatum or chest deformity (16), scoliosis (2) abnormal ribs (9), and abnormal vertebrae (8).

### Organomegaly

It is also not possible to evaluate the exact percentage of organomegaly in the 63 cases from the literature, but macroglossia was the most frequently reported (31 cases), followed by nephromegaly (17 cases) and hepatomegaly (five cases). Neonatal hyperinsulinism was reported in two cases.

### Tumors

The risk of developing an embryonal tumor was evaluated by Lapunzina [2005] at 10% in view of the previous reports but including cases with no *GPC3* mutation [Lapunzina et al., 1998]. Among the 63 reviewed cases, three had developed Wilms tumor, three hepatoblastomas and one medulloblastoma [Hughes-Benzie et al., 1996; Lindsay et al., 1997; Li et al., 2001; Rodríguez-Criado et al., 2005; Thomas et al., 2012], whereas we had only one case of Wilms tumor in our series. This leads to an overall frequency of 8%, but the small size of the sample hampers evaluation of a precise frequency. The occurrence of leukemia in one of our patients may be coincidental as theoretically it would be expected that SGBS would not increase the risk for hematologic malignancies given the absence of expression of *GPC3* is white blood cells [Thomas et al., 2012].

### Additional Malformations

Extra-nipples were reported in 29/44 of the 63 cases in the literature, giving with our data an overall proportion of 60%. Areolar skin tags as seen in one of our patients have already been described in one patient by Hughes-Benzie et al. [1996].

It is difficult or even impossible to evaluate the percentage of kidney, urinary tract, intestinal tract, abdominal wall, or genital anomalies in the cases from the literature as there were not always clear information in the reports. In the series of 63 reviewed cases, renal dysplasia was reported in 9/11 patients and urinary tract malformations in 16/25; 19/29 cases had cleft lip/palate, 16/28 had inguinal hernias, 7/21 diaphragmatic hernias, 16/16 cases diastasis recti or umbilical hernia, and 11 patients had cryptorchidism.

Heart defects in SGBS have been reviewed by several authors [König et al., 1991; Lin et al., 1999] but these reviews included cases with no mutation identified. Lin et al. reported 46% of heart problems in the subgroup of patients with *GPC3* mutations. In the group of 63 reviewed cases we could find 17 patients with cardiac malformations but clear information on heart problems was reported in only 35 cases. Cardiac malformations were very similar to those observed in our cases (six cases with a ventricular septal defect, three with a atrial septal defect, two with a patent foramen ovale, four with pulmonary stenosis, one with aortic stenosis, one with patent ductus arteriosus, two with abnormal tricuspid valves, one with transposition of great arteries and a subaortic membrane). Arrythmias were reported in three patients but no case of sudden death was reported in the 63 cases.

### Genotype/Phenotype Correlation

Mutations in our group of patients consist of 38% exonic deletions, 24% frameshift, 17% nonsense, 17% missense mutations, and one exonic duplication (3%). Whatever the type or the location of the mutation in the *GPC3* gene, no genotype/phenotype correlation was observed in our series.

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### Differential Diagnosis

Several conditions with overgrowth may be differentiated from SGBS and are well discussed in Golabi's review [Golabi et al., 2011], but the main differential diagnosis is certainly Beckwith–Wiedemann syndrome (BWS) which is often suggested at first in SGBS patients, and which has many features in common, particularly in delayed motor development. However, several findings may help to distinguish both conditions. Supernumerary nipples, hand anomalies, skeletal problems, and diaphragmatic hernia are usually not found in BWS whereas omphalocele is not part of SGBS. In addition, although SGBS has some facial resemblances with BWS at a young age particularly in infancy, and there may be ear creases or pits in both conditions (but less frequently in SGBS), we agree with Golabi et al. [2011] that the facial appearance *in fine* is appreciably different.

In conclusion, our data confirm that SGBS has a recognizable clinical picture and should be diagnosed clinically in the majority of cases. Macrosomia with visceromegaly at birth are the most frequent findings whereas post-natal overgrowth is far from being constant. In patients with overgrowth, the diagnosis of SGBS relies on typical facial features, hand anomalies, supernumerary nipples, and a constellation of congenital malformations among which diaphragmatic hernia, duplicated urinary tract, dysplastic kidneys, and skeletal anomalies with chest deformity are the most suggestive. Better knowledge of the SGBS phenotype should render molecular testing more efficient.

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