Schinzel–Giedion Syndrome in Two Brazilian Patients: Report of a Novel Mutation in SETBP1 and Literature Review of the Clinical Features

Ellaine Carvalho,1* Rachel Honjo,1 Monize Magalhães,2 Guilherme Yamamoto,1,2 Katia Rocha,2 Michel Naslavsky,2 Mayana Zatz,2 Maria Rita Passos-Bueno,2 Chong Kim,1 and Debora Bertola1,2

1Genetics Unit, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil
2Centro de Estudos do Genoma Humano, Departamento de Biologia, Instituto de Biociências, Universidade de São Paulo, Sao Paulo, Brazil

Manuscript Received: 12 January 2014; Manuscript Accepted: 29 August 2014

Schinzel–Giedion syndrome is a rare autosomal dominant disorder comprising postnatal growth failure, profound developmental delay, seizures, facial dysmorphisms, genitourinary, skeletal, neurological, and cardiac defects. It was recently revealed that Schinzel–Giedion syndrome is caused by de novo mutations in SETBP1, but there are few reports of this syndrome with molecular confirmation. We describe two unrelated Brazilian patients with Schinzel–Giedion syndrome, one of them carrying a novel mutation. We also present a review of clinical manifestations of the syndrome, comparing our cases to patients reported in literature emphasizing the importance of the facial gestalt associated with neurological involvement for diagnostic suspicion of this syndrome. © 2015 Wiley Periodicals, Inc.

Key words: Schinzel–Giedion syndrome; clinical features; facial gestalt; SETBP1

INTRODUCTION

Schinzel–Giedion syndrome (SGS) was first described in 1978 in two siblings who presented facial dysmorphisms, renal, and cardiac defects [Schinzel and Giedion, 1978]. This syndrome is recognized by typical craniofacial features (wide fontanels, coarse facies with high protruding forehead, orbital hypertelorism, infraorbital grooves, midface retraction, short upturned nose, and low-set ears) and multiple congenital malformations (genitourinary, skeletal, neurological, and cardiac defects), associated with growth failure, seizures, profound developmental delay, and a propensity to develop neuroectodermal tumors. Recurrent infections and refractory seizures are the major difficulties in the clinical management of these patients. Most affected individuals die before the age of two from respiratory failure or infections [Schinzel and Giedion, 1978; Al-Gazali et al., 1990; Hoischen et al., 2010]. To date, more than 70 cases have been reported in the literature [Schinzel and Giedion, 1978; Donnai and Harris, 1979; Kelley et al., 1982; Al-Gazali et al., 1990; Pul et al., 1990; MacLennan et al., 1991; Herman et al., 1993; Robin et al., 1993; Verloes et al., 1993; Alavi et al., 1994; Labrun et al., 1994; Rodriguez et al., 1994; Santos et al., 1994; Antich et al., 1995; Okamoto et al., 1995; Culic et al., 1996; Elliott et al., 1996; Ozkinay et al., 1996; McPherson et al., 1998; Alembik et al., 1999; Rittinger et al., 1999; Shah et al., 1999; Kondoh et al., 2001; Cooke et al., 2002; Minn et al., 2002; Grosso et al., 2003; Manouvrier-Hanu, 2003; Sandri et al., 2003; Albano et al., 2004; Matsumoto et al., 2005; Beschorner et al., 2007; Al-Mudaffer et al., 2008; Lehman et al., 2008; Sharma and Gonzales, 2009; Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Watanabe et al., 2012; Ko et al., 2013; Lach and Arredondo, 2013].

Prior to the determination of SGS pathogenesis, the diagnosis of the disease was based on clinical features only. Lehman et al. [2008] have proposed clinical diagnostic criteria that yielded

How to Cite this Article:

Conflict of interest: none
*Correspondence to: Ellaine Doris Fernandes Carvalho, MD, Genetics Unit, Instituto da Criança, Hospital das Clínicas, FMUSP, Avenida Doutor Enéas de Carvalho Aguiar, 647–7° andar, Cerqueira César, São Paulo, Brasil. E-mail: ellainecarvalho@hotmail.com
Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2015
DOI 10.1002/ajmg.a.36789
100% sensitivity for the previously reported cases, based on the presence of developmental delay and facial phenotype (prominent forehead, midface retraction, short and upturned nose) plus either hydronephrosis or two of the typical skeletal abnormalities (sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, and broad ribs) [Lehman et al., 2008].

It was recently revealed that SGS is caused by de novo heterozygous mutations in **SETBP1**, although the first description suggested an autosomal recessive mode of inheritance [Schinzel and Giedion, 1978; Donnai and Harris, 1979; Pul et al., 1990; Alavi et al., 1994 Antich et al., 1995]. This gene, located on chromosome 18q21.1, is ubiquitously expressed and its function is not yet fully elucidated. It encodes an oncogene-binding protein and binds to SET domains that are involved in methylation of lysine residues on histone tails [Hoischen et al., 2010]. All mutations described to date are located exclusively in the exon 4 of **SETBP1**, outside of the SET interacting domain and they do not affect the DNA binding domains of the SET-binding protein (Fig. 1) [Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Ko et al., 2013]. Although the precise mechanism of how these mutations cause the phenotype is currently unknown, Hoischen et al. [2010] suggested that these mutations could exert a gain of function or a dominant-negative effect, since the patients presenting a partial chromosome 18q deletions, including **SETBP1**, do not present an SGS phenotype.

The reported recurrence of SGS in siblings [Schinzel and Giedion, 1978; Antich et al., 1995] could be attributed to gonadal mosaicism [Hoischen et al., 2010]. Since the description of the mutations responsible for SGS in 2010, only 17 patients had been tested for mutations in **SETBP1** and confirmation of the diagnosis was possible in 16 of them [Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Ko et al., 2013].

In this study, we report on two unrelated Brazilian patients with SGS confirmed by molecular analysis, one of them with a mutation not previously described. We also present a review of clinical manifestations of SGS and compare our patients with those reported in literature.

**CLINICAL REPORTS**

**Patient 1**

Patient 1 is an 8-month-old male infant who is the first child of a nonconsanguineous and healthy couple. There was no family history of congenital abnormalities. Two prenatal ultrasound exams showed bilateral hydronephrosis. Except for the fetal abnormality, the pregnancy was uneventful. The patient was born at term by elective cesarean because of breech presentation. His BW was 2920 g (25th–50th centile) and BL 43 cm (<3rd centile); OFC was not available. Apgar scores were 7 and 9 at 1 and 5 min, respectively. At birth, craniofacial and genital anomalies were noted. At 1 month of age, the physical examination disclosed: failure to thrive, microcephaly with large anterior fontanels, protruding forehead with midface retraction, orbital hypertelorism, upslanting palpebral fissures, infraorbital grooves, small upturned nose, retrognathia, anteriorly folded earlobes with normal ear implantation, dorsal hypertrichosis, protruding abdomen, bilateral clinodactyly of the fifth fingers, transitional palmar creases, talipes equinovarus, small testes, and perineal hypospadias. The patient developed respiratory distress and poor feeding during the first days of life. He presented seizures since the first month and severe developmental delay was identified in the follow-up at 8 months of age. This was the last time that the patient was evaluated at our service and no further information was obtained. Figure 2 shows the patient at ages 1 month and 8 months, respectively.

An abdominal ultrasound confirmed bilateral hydronephrosis and radiologic studies showed wormian bones, occipital synchondrosis, sclerotic skull base (Fig. 2), bell-shaped chest with broad ribs, hypoplasia of iliac bones, widening of the pubic symphysis, and widening of distal femoral metaphyses. Brain CT scan revealed bilateral ventriculomegaly. Echocardiogram and G-banded karyotype were normal.

**Patient 2**

Patient 2 is a 3-year-old female infant, the first and only child of nonconsanguineous parents with no family history of congenital abnormalities. The mother has been previously diagnosed with hypothyroidism and used levothyroxine during pregnancy. Prenatal...
ultrasounds were normal. She was born at term, by cesarean, with a BW of 3185 g (25th–50th centile), BL of 49 cm (50–75th centile), and OFC of 34 cm (50th–75th centile). Apgar scores were 9 and 10 at 1 and 5 min, respectively. At birth, the patient had transient hypothyroidism, poor feeding, and congenital dislocation of the left hip was confirmed by ultrasound. She evolved with severe neuropsychomotor delay and seizures beginning at five months of age, which were initially successfully controlled with anticonvulsant medication. Physical examination at 23 months of age disclosed normal growth parameters, midface retraction, upslanting palpebral fissures, synophrys, thick eyebrows, high nasal bridge, bulbous nose with antverted nares, retrognathia, simplified and prominent ears, hirsutism, elongated fingers with proximally implanted thumbs, hypoplastic toenails, and clitoral hypertrophy. In the follow-up at 3 years old, her milestones continued severely delayed, despite of physiotherapy and the seizures were refractory to the medications. Additionally, reduced visual acuity with optic nerve pallor, alacrimia, and delayed eruption of the deciduous teeth were also disclosed. Urinary tract ultrasound, echocardiogram, and brain evoked response audiometry were normal. X-rays showed diffuse osteopenia, gracile long bones, left femur with valgus deformity, and vertical acetabulum. Brain MRI revealed reduction of the white matter volume and delayed myelination for age. G-banded karyotype and array-CGH were normal.

The two patients presented here shared the facial gestalt of SGS, the first one with the complementary typical features described in the syndrome and the second one, lacking the frequent genital and skeletal abnormalities. Consequently, molecular analysis of SETBP1 was performed in both individuals.

**MATERIALS AND METHODS**

The patients here presented were enrolled in this study, after parental informed consent was obtained. Genomic DNA from peripheral blood was subjected to molecular analysis using specific primers (5'-AGCCGTGCCTTCCAACTTTCAG-3'; 5'-CGGTGGGAGATTCTGAACACTTGG-3') for SETBP1 exon 4) analysis (RefSeq NM_015559.2). PCR amplification was made using Taq DNA polymerase (GE Healthcare) and comprising 35 cycles of 45 sec at 94 °C, 57 sec at 58 °C, and 60 sec at 72 °C followed by an extension of 6 min. Sequencing was performed using BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems) on ABI 3730 DNA Analyzer (Applied Biosystems) Sequencer.

**FIG. 2.** Patient 1: typical facial features (at 1 and 8 months of age in the left and right, respectively), short neck, protruding abdomen, ambiguous genitalia and talipes. Lateral skull radiograph showing: large anterior fontanels, wormian bones, occipital synchondrosis, and sclerotic and steep base of the skull.
We also performed a detailed review of all patients with SGS reported in literature from January, 1978 to September, 2013 using PubMed database with the keywords “Schinzel–Giedion syndrome”. Only articles in English were included. We evaluated a total of 41 articles [Schinzel and Giedion, 1978; Donnai and Harris, 1979; Kelley et al., 1982; Al-Gazali et al., 1990; Pul et al., 1990; MacLennan et al., 1991; Herman et al., 1993; Robin et al., 1993; Verloes et al., 1993; Alavi et al., 1994; Labrune et al., 1994; Rodriguez et al., 1994; Santos et al., 1994; Antich et al., 1995; Okamoto et al., 1995; Culic et al., 1996; Elliott et al., 1996; Ozkinay et al., 1996; McPherson et al., 1998; Alembik et al., 1999; Rittinger et al., 1999; Shah et al., 1999; Kondoh et al., 2001; Touge et al., 2001; Cooke et al., 2002; Minn et al., 2002; Grosso et al., 2003; Manouvrier-Hanu, 2003; Sandri et al., 2003; Albano et al., 2004; Matsumoto et al., 2005; Beschoner et al., 2007; Al-Mudaffer et al., 2008; Lehman et al., 2008; Sharma and Gonzales, 2009; Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Watanabe et al., 2012; Ko et al., 2013; Lach and Arredondo, 2013]. The features were considered positive only if they were specifically reported by the authors or seen in photographs.

RESULTS

In the first patient, DNA sequence analysis of SETBP1 detected the previously described heterozygous mutation: c.2602G>A (NM_015559.2: p.Asp868Asn) (Fig. 3A). In the second patient, a novel heterozygous mutation c.2601C>A (p.Ser867Arg) (Fig. 3B) was found and assumed as pathogenic based on the facts that the mutation was de novo, in silico analysis by PolyPhen2, Sift, and Mutation Taster predicted it as probably damaging, the residue is conserved among different species, and this mutation was not present in 609 controls from the Brazilian population that were exome sequenced.

The clinical findings (including those observed in our patients) are shown in Tables I and II according to its prevalence: present in ≥50% and 30–50%, respectively.

DISCUSSION

Prior to the identification of the genetic background responsible for a specific genetic disorder, clinical criteria are the sole and important tools to define its diagnosis and are largely applied by clinical geneticists. Once mutations in a gene are unmasked, the importance of these criteria remains as a first step to define which patient should undergo molecular investigation. We described here two patients with SGS, the first one has fulfilled the diagnostic criteria proposed by Lehman et al. [2008]: developmental delay, typical face, skeletal malformations, and hydronephrosis. On the other hand, Patient 2 presented the classic facial phenotype, developmental delay, but neither hydronephrosis nor typical skeletal abnormalities, not fulfilling the diagnostic criteria. In this sense, the facial gestalt was the driving force that led us to perform the molecular analysis in this case. Therefore, caution should be taken not to rely on very restrictive criteria, once the less typical

FIG. 3. Chromatograms demonstrating nucleotides changes in mutations analysis of Patients 1 [c.2602G>A] (A) and 2 [c.2601C>A] (B).
cases may be undiagnosed. Interestingly, two monozygous twins with a clinical picture resembling SGS, especially in their facial features, but showing relatively good neurodevelopment and long survival were described by Joss and Dean [2002]. The authors proposed that SGS diagnosis was unlikely, but hypothesized that the mild phenotype could be explained by a mutation in the gene responsible for SGS, unknown at that time, resulting in less severe disruption of the protein product or by a mutation in another gene belonging to the same pathway [Joss and Dean, 2002].

SGS is a very rare autosomal dominant disorder, which precise incidence is unknown. Detailed literature review associated with the data from our two patients showed that the sex ratio (male/female) is 1.6:1. Prenatal abnormalities were seen in some patients: polyhydramnios (13/18), urogenital findings (bilateral hydronephrosis, pyeloectasia, and multicystic dysplastic kidney) (26/32) and increased nuchal translucency (2/32). The majority of them were born at term with an appropriate BL (19/20) and BW (42/43) for gestational age.

Neurological compromise (68/68) is observed since birth, characterized by neonatal asphyxia (8/10), feeding problems (21/21), and recurrent apneic spells (18/18). Severe developmental delay is the rule for these patients. Seizures are very common and in most of patients are intractable. There is a wide spectrum of abnormalities observed in the central nervous system in these individuals, ranging from structural abnormalities [Maclennan et al., 1991; Robin et al., 1993; Rodriguez et al., 1994; Watanabe et al., 2012] to altered gyration pattern/migration defects [Beschorner et al., 2007; Lestner et al., 2012; Lach and Arredondo, 2013] (Tables I and II). Nonetheless, a neurodegenerative process caused by deficient white matter myelination has been described in some patients more recently [Watanabe et al., 2012; Ko et al., 2013]. Patient 2 here described also showed an abnormal pattern of myelination. Thus, white matter abnormalities emerge as an important CNS finding. It is possible that its presence and, especially its progressive course are under reported, hampered by the severity of the disorder, since these individuals rarely survive beyond the age of two [Al-Mudaffar et al., 2008].

The other two hallmarks of SGS, congenital hydronephrosis, and specific skeletal abnormalities (Tables I and II) are important clues for the diagnosis, but, as shown in Patient 2 here presented, its absence do not rule out its diagnosis. Along with the severe neurological involvement, neuroepithelial tumors have been reported in eight SGS patients – hepatoblastoma (1), sacroccygeal teratoma (3), lumbosacral teratoma (1),

### Table I. Clinical Manifestations That Are Present in ≥ 50% of Patients

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>No. SETBP1 analysis (n = 53)</th>
<th>SETBP1 mutation (n = 16)</th>
<th>No. SETBP1 mutation (n = 1)</th>
<th>Total of patients (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial</td>
<td>+</td>
<td>+</td>
<td>53/53</td>
<td>16/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Wide fontanelles</td>
<td>+</td>
<td>+</td>
<td>41/41</td>
<td>12/14</td>
<td>1/1</td>
</tr>
<tr>
<td>High/protruding forehead</td>
<td>+</td>
<td>+</td>
<td>44/44</td>
<td>15/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Orbital hypertelorism</td>
<td>+</td>
<td>+</td>
<td>37/37</td>
<td>12/13</td>
<td>1/1</td>
</tr>
<tr>
<td>Midface hypoplasia</td>
<td>+</td>
<td>+</td>
<td>41/41</td>
<td>15/15</td>
<td>1/1</td>
</tr>
<tr>
<td>Upturned nose</td>
<td>+</td>
<td>+</td>
<td>39/41</td>
<td>16/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Saddle nose with short bridge</td>
<td>+</td>
<td>+</td>
<td>42/44</td>
<td>13/13</td>
<td>1/1</td>
</tr>
<tr>
<td>Low-set ears</td>
<td>–</td>
<td>–</td>
<td>41/43</td>
<td>14/14</td>
<td>0/1</td>
</tr>
<tr>
<td>Neurological</td>
<td>+</td>
<td>+</td>
<td>49/49</td>
<td>16/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Neuroradiological findings</td>
<td>+</td>
<td>+</td>
<td>29/31</td>
<td>16/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Seizures and/or abnormal EEG</td>
<td>+</td>
<td>+</td>
<td>39/40</td>
<td>15/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Development delay/severe mental retardation/hypotonia</td>
<td>+</td>
<td>+</td>
<td>42/42</td>
<td>14/14</td>
<td>1/1</td>
</tr>
<tr>
<td>Characteristic skeletal findings</td>
<td>+</td>
<td>–</td>
<td>46/46</td>
<td>14/14</td>
<td>1/1</td>
</tr>
<tr>
<td>Broad ribs</td>
<td>+</td>
<td>–</td>
<td>35/41</td>
<td>11/11</td>
<td>1/1</td>
</tr>
<tr>
<td>Wide occipital ‘synchondroses’</td>
<td>+</td>
<td>–</td>
<td>25/33</td>
<td>11/11</td>
<td>1/1</td>
</tr>
<tr>
<td>Sclerotic base of skull</td>
<td>+</td>
<td>–</td>
<td>25/37</td>
<td>11/11</td>
<td>1/1</td>
</tr>
<tr>
<td>Urological findings</td>
<td>+</td>
<td>–</td>
<td>51/51</td>
<td>16/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Congenital hydronephrosis</td>
<td>+</td>
<td>–</td>
<td>40/44</td>
<td>16/16</td>
<td>1/1</td>
</tr>
<tr>
<td>Vesicoureteric reflux</td>
<td>+</td>
<td>–</td>
<td>29/30</td>
<td>13/13</td>
<td>1/1</td>
</tr>
<tr>
<td>Genital findings</td>
<td>+</td>
<td>+</td>
<td>38/38</td>
<td>8/8</td>
<td>NA</td>
</tr>
</tbody>
</table>

Present (+); absent (–); NA (not available); No. (number of patients presenting the finding); No. known (number of patients assessed for the specific finding).
lumbosacral primitive neuroectodermal tumor (1), Wilms tumor (1), and extradural ependymomas (1). Most tumors described so far in SGS were congenital (4/8), but there were also tumors discovered after the first year of life (3/8). One reported patient with a Wilms tumor, detected at the age of 8 years, died of systemic metastatic disease one year after tumor detection [Robin et al., 1993; Rodriguez et al., 1994; Antich et al., 1995; McPherson et al., 1998; Sandri et al., 2003; Matsumoto et al., 2005; Beschorner et al., 2007; Watanabe et al., 2012]. Sacrococcygeal teratoma is the most frequent congenital germ cell tumor, with an incidence of 1/35,000 to 1/40,000 live births [Shue et al., 2013] and is the most frequently found tumor in SGS. The frequency of all tumors in SGS is estimated at 11%, a higher percentage than ones found in other disorders, notably overgrowth syndromes such as Beckwith–Wiedemann and Simpson–Golabi–Behmel, for which screening protocols are well established [Koufos et al., 1989; Li et al., 2001]. Although in most cases, patients with SGS have a very severe disease with a low life expectancy, we suggest that families should be notified of the increased incidence of embryonic tumors and a periodic tumor screening protocol for tumor surveillance (with periodic renal ultrasound and measurement of serum alpha-fetoprotein) could be counterbalanced with the severity of patient’s clinical framework. Since we do not know the extent of the phenotype very well, it is possible that milder cases could benefit from this approach.

Among the rarer clinical findings, alacrimia is present in our Patient 2 and it was described previously in four out of five individuals evaluated for this feature [Alembik et al., 1999; Minn et al., 2002; Manouvrier-Hanu, 2003]. Congenital alacrimia could be identified as an isolated finding (OMIM 231550) or be part of a small number of monogenic disorders, such as triple A syndrome – achalasia–addisonianism–alacrimia syndrome (OMIM#231550), anhidrotic ectodermal dysplasia (305100), and dysautonomia (223900). As a very restricted sign, this ophthalmologic finding raises the possibility of SGS, especially when associated with developmental delay.

The gene responsible for SGS (SETBP1) was recently identified and yielded a high positive rate (18/19) between individuals that fulfill the diagnostic criteria proposed by Lehman et al. [2008]. The only patient who was negative for SETBP1 gene mutations had also shown a typical phenotype, comprising epilepsy, typical facial features, hydronephrosis, and skeletal findings. As the cohort of tested patients is still small, it remains to be determined if SGS is genetically heterogeneous. The five different mutations found so far are clustered in exon 4, in the SKI homologous region, between the DNA bindings domains. Their prevalence, including our cases, is the following: p.Ile871Thr (6/18–33%), p.Asp868Asn (5/18–28%), p.Glu870Ser (4/18–22%), p.Asp868Ala (1/18–5%), p.Glu870Asp (1/18–5%), and p.Ser867Arg (1/18–5%) (Fig. 1) [Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Ko et al., 2013].
Since the molecular background of this syndrome is now recognized, it is possible that atypical patients or patients with a milder presentation could have mutations in the same gene, broadening the phenotypic spectrum within SETBP1 gene. In this scenario, the diagnostic criteria of SGS would need to be revised in the future. In the meantime, as we described a patient not fulfilling the clinical criteria and showing mutation in SETBP1, we suggest that the facial gestalt associated with neurological involvement would be sufficient to indicate molecular analysis of this particular gene.

**REFERENCES**


