RESEARCH ARTICLE

Schinzel–Giedion Syndrome: A Novel Case, Review and Revised Diagnostic Criteria

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ABSTRACT

Schinzel-Giedion syndrome (SGS) is a very rare autosomal dominant inheritance disorder. Heterozygous de novo mutations in the *SETBP1* gene have been identified as the genetic cause of SGS. We report a novel case with the syndrome with a novel insertion mutation in *SETBP1*. We also present a review of SGS cases, and first revise diagnostic criteria of SGS based on clinical findings and/or *SETBP1* mutation worldwide. A revised diagnostic criteria and typing of SGS can be determined. Type I (complex, classic type) SGS patients present a development delay and typical facial features (prominent forehead, midface retraction, and short, upturned nose) associated with hydronephrosis or two of the characteristic skeletal anomalies (a sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, and broad ribs). Type II (middle type) patients show development delay and the distinctive facial phenotype (midface retraction, short and upturned nose), lacking both hydronephrosis and typical skeletal abnormalities, with existence of *SETBP1* mutation. Type III (simple type) patients with *SETBP1* alteration show their major symptom is development delay, in which expressive language delay is the most striking feature. Central nervous system involvement with development delay in which expressive language delay is much more obviously affected is the most prominent feature of SGS. There is another indication that severity of phenotype of SGS may be inversely correlated with degree of *SETBP1* alteration, besides gain-of-function or dominant negative effects in *SETBP1* alteration causing SGS.
Keywords Schinzel-Giedion syndrome; *SETBP1*; Mutation; Diagnostic criteria

1. INTRODUCTION

Schinzel-Giedion syndrome (SGS, MIM #269150) was first described in 1978 in two siblings who presented severe midface retraction, multiple skull anomalies, clubfeet, and cardiac and renal malformations [Schinzel and Giedion, 1978]. A lot of other features have been reported subsequently. The diagnosis of this syndrome was previously based on characteristic clinical manifestations only. In 2008, Lehman and colleagues proposed clinical diagnostic criteria, based on the presence of a development delay and typical facial features (prominent forehead, midface retraction, and short, upturned nose) associated with hydronephrosis or two of the characteristic skeletal malformations (a sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, and broad ribs) [Lehman et al., 2008]. Heterozygous de novo mutations in the SET binding protein 1 (*SETBP1*) gene have recently been shown to cause SGS [Hoischen et al., 2010]. The diagnosis of SGS should be based on clinical features and/or *SETBP1* mutation，thus enlarging the phenotype spectrum of SGS. To date, about 80 cases have been reported, 58 individuals with a clinical diagnosis of SGS have been described [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; Silengo et al., 1997; 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; Beschorner et al., 2007; Radhakrishnan et al., 2006; Al-Mudaffer et al., 2008; Lehman et al., 2008; Sharma and Gonzales, 2009; Hoischen et al., 2010; Watanabe et al., 2012; Lach and Arredondo, 2013; Kishimoto et al., 2015], 25 patients with point mutations in *SETBP1* [Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Ko et al., 2013; Carvalho et al., 2015; Herenger et al., 2015; Landim et al., 2015; Lopez-Gonzalez et al., 2015; Miyake et al., 2015; Takeuchi et al., 2015; Volk et al., 2015] and 2 patients with proximal interstitial 18q deletions containing exclusively *SETBP1* [Filges et al., 2011] have been identifed. In the present study, we report a novel case with the syndrome with a novel insertion mutation in *SETBP1*. Herein, we present a review of these cases, and first revise diagnostic criteria of SGS for precise genotype-phenotype correlation research in future.

2. MATERIAL AND METHODS

2.1. A novel case

The proband is a 5.9-year-old Chinese girl，the second born of twins conceived. Her mother became pregnant through invitro fertilization and intracytoplasmic sperm injection due to male factor infertility. The parents are healthy, aside from paternal unilateral cryptorchidism and another unilateral congenital obstruction of the vas deferens, and non-consanguineous with an otherwise unremarkable family history. The patient and her twin brother were born at 37 weeks by caesarean section due to breech presentation. The patient was small for gestational age with a weight of 2100g compared to her healthy, normally developed brother who weighed 2500g. Her Apgar scores were normal. At birth, she was noted to have a markedly depressed nasal bridge, upturned nose, orbital hypertelorism. The fontanelles were normal. In the first 6 months, she had eczema on her face and experienced feeding difficulty with vomiting. She had psychomotor delay with sitting at 1 year, crawling at 2 years, walking at 2.5 years and drawing a circle at 4.5 years. Speech was markedly delayed with first words at 2.5 years, and only 4 words (mama, papa, gege and bye-bye) at 5.8 years. At 2.5 years she presented with 2 febrile seizures in a day (complex febrile seizure), each lasting about 5 minutes, but subsequently she has been seizure free without anticonvulsant medication. She presented drowsiness, poor sense of pain, and less crying before the age of 5. She tears normally and has not experienced recurrent infection since birth.

The patient was referred to our hospital at the age of 5.8 years because of development delay. Clinical examination revealed normal growth parameters, midface retraction, hypertelorism, small upturned nose, markedly low nasal bridge, thick eyebrows, severe epicanthus, dorsal hypertrichosis and a wide mouth, high palatal bow, bilateral hyperhidrosis and simian creases of palms and soles, without a coarse face, frontal bossing, exophthalmos, infraorbital grooves, micrognathia, retrognathia, macroglossia, bitemporal narrowing, and protruding abdomen, no significant abnormality including philtrum, teeth, ears, neck, and four extremities including fingernails and toenails. The child had hypohidrosis over the skin except the palms and soles. The patient still shows coordination deficits in fine motor skills. She has only the behavioral problem of attention deficit, but not aggression, hyperactivity and autistic like features. She can not distinguish between colors. Neurological evaluation showed no hypotonia. No cardiac murmur was auscultated. No abnormal findings were observed on genital examination. Hearing and vision were normal. Urinary tract ultrasound and brain magnetic resonance imaging were normal.

Skeletal radiology showed slightly steep anterior cranial fossa base, hook-like sella turcica, short and spacious middle phalanx of little finger, a bone age about 7 and 8 years in hand radiograph, and anterior process of the fifth lumbar vertebral body(Figure 1a-c). However, typical abnormalities such as sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, and broad ribs were not found. Neuropsychological development examination table for children aged 0-6years was used to test her developmental quotient and the result was 44 (large movements 86, free movements 41, adaptation ability 39, language 26, social behavior 26), which showed moderate developmental delay. The patient presented remarkable expressive language development delay, but language's comprehension skills are better than expression. Electroencephalogram (EEG) showed δ,θ slowings (2.70-7.69 Hz, 30-380 uV) rhythm of a high-amplitude paroxysmal

activity in the every lead, particularly in the parietal-occipital area(obviously on the left), and occasional sharp slow waves in P3, P4, O1, O2, T3, T4, T5, T6, FP1, FP2, F4, C4, and F8 leads (Figure 1d).

2.2. Genetic analysis and review

We investigated a novel case with SGS in this study. Blood samples were collected from the patient and parents and genomic DNA was isolated from peripheral blood lymphocytes using standard procedures. Conventional chromosomal analysis was performed from peripheral blood lymphocytes of the patient. Direct sequencing analysis of the *SETBP1* gene was performed. The study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University. Informed consent was obtained from the patient's parents. We present a literature review of all cases with SGS, summarize causative Gene of SGS and related genes, and revise diagnostic criteria of SGS.

3. RESULTS

G-banded karyotype of the patient was 46 XX. SGS was suspected based on distinctive facial phenotype and developmental delay. A novel *de novo* heterozygous mutation (c. 1181_1184insA; E394EfsX3) was identified in exon 4 of *SETBP1* (Figure 2), which resulted in a translational frameshift leading to a termination at codon 396. This mutation was not found in her parents and brother.

3.1. Clinical features of SGS

As classic cases, the syndrome is characterized by severe development delay, seizures, midface retraction, multiple anomalies including skeletal malformations, urogenital abnormalities, hypertrichosis, and heart defects, as well as a higher prevalence of tumors. Table 1 shows major clinical features in reported SGS patients by a clinical diagnosis.

3.1.1. Neurological features

Central nervous system involvement is observed in almost all of patients with SGS. Severe developmental delay is a hallmark of SGS. Common features including neonatal asphyxia, feeding difficulty, and recurrent apneic spells are found since birth [Carvalho et al., 2015]. There is a wide spectrum of abnormalities observed in the central nervous system in SGS, ranging from structural abnormalities to altered gyration pattern/migration defects [Maclennan et al., 1991; Robin et al., 1993; Rodriguez et al., 1994; Beschorner et al., 2007; Lestner et al., 2012; Watanabe et al., 2012; Lach et al., 2013; Carvalho et al., 2015]. Ventriculomegaly, agenesis or hypoplasia of the corpus callosum, cortical atrophy, and choroid plexus cysts are frequently reported findings in brain MRI/CT or autopsy [Shah et al., 1999; Kondoh et al., 2001; Lestner et al., 2012; Watanabe et al., 2012; Ko et al., 2013]. Some other CNS structural anomalies including white matter and brainstem atrophy, dysmyelination[Shah et al., 1999; Minn et al., 2002; Kishimoto et al., 2015], vacuolating myelinopathy [Watanabe et al., 2012], abnormal cortical gyration [Schinzel and Giedion, 1978], lissencephalic cortical dysplasia [Lach and Arredondo, 2013], polymicrogyria[Beschorner et al., 2007], small basal ganglia [Robin et al., 1993], and Chiari I malformation [Santos et al.,1994; Silengo et al., 1997; Rittinger et al., 1999]. There is marked evidence of progressive and diffuse neurodegeneration of deficient white matter myelination and cortical gray matter on serial studies of brain imaging [Shah et al., 1999; Watanabe et al., 2012; Ko et al., 2013]. Seizures are very common in patients with SGS. Seizure pattern is heterogeneous and includes tonic, tonic–clonic, myoclonic, or partial motor seizure and infantile spasms[Ko et al., 2013]. EEG findings associated with SGS include multifocal spikes, hypsarrhythmia, or burst suppression. West syndrome has been reported in 25% of epileptic patients with SGS [Kondoh et al., 2001; Grosso et al., 2003]. In general, seizures in SGS are extremely intractable to treatment with adrenocorticotropic hormone (ACTH), various antiepileptic drugs, and a ketogenic diet [Shah et al., 1999; Miyake et al., 2015]. Antiepileptic drug therapy was elementary effective in only 4 patients with seizures. The first patient with neonatal tonic seizures was reported to be responsive to phenobarbital, but the long-term effect was unavailable in this case [McPherson et al., 1998]. The second patient with partial seizures starting at the age of 2 months was controlled by combined therapy with phenobarbital and levetiracetam [Ko et al., 2013]. The third patient affected by West syndrome with SGS had a good response to ACTH therapy temporarily [Miyake et al., 2015]. The fourth patient with started tonic-clonic seizures to muscle spasms took topiramate and cannabidiol, with significant improvement in refractory epileptic seizures [Landim et al.,

2015]. Severe visual impairment, possibly secondary to abnormal optic nerves, is common, as is hearing impairment [Lehman et al., 2008]. Alacrima and corneal hypoesthesia are present in a few of patients, these phenomena of probably central or peripheral origin can be associated with SGS [Alembik et al., 1999; Minn et al., 2002; Manouvrier-Hanu et al., 2003; Carvalho et al., 2015]. Central diabetes insipidus and hypothyroidism were reported only in a minority of patients [Santos et al., 1994; Suphapeetiporn et al., 2011], the features might arise from brain anomalies.

3.1.2. Craniofacial features

The distinctive craniofacial features are essential for classic SGS. After birth, almost cardinal dysmorphic features are noted, including midface retraction, a large anterior fontanelle, a prominent forehead, ocular hypertelorism, low-set dysplastic ears, and a short and upturned nose [Minn et al., 2002; Hoischen et al., 2010]. Other distinctive facial features include significant prominent eyes or shallow orbits, infraorbotal grooves, coarse face, a wide mouth with macroglossia, ear malforations with protruding lobes and a short neck in a majority of patients. Affected children have remarkable midface retraction with protruding eyes, a short nose and a low nasal bridge, showing ‘‘figure of eight’’ appearance. Hypertrichosis is common and often disappears in infancy.

3.1.3. Urogenital features

Hydronephrosis with or without vesicoureteral reflux have been frequently reported (~90%) in SGS patients and more rarely megacalycosis [Rittinger et al., 1999; Touge et al., 2001; Minn et al., 2002; Herenger et al., 2015]. Abnormal kidneys are considered an important clue in the diagnosis of SGS. Most patients have genital abnormalities including hypoplasia of the genitals, hypospadias, and short perineum with an anteriorly placed anus. Affected boys may have hypospadias, micropenis, undescended testes, hypoplastic scrotum and ambiguous genitalia, affected girls may have bifid uterus and vagina, hypoplastic uterus, labial hypoplasia.

3.1.4. Radiographic features

Skeletal anomalies are highly prevalent. A sclerotic skull base, steep base, wide occipital synchondrosis, broad ribs, broad cortex and increased density of long bones, hypoplastic distal phalanges and hypoplastic pubic bones are usually associated skeletal malformations [Al-Mudaffer et al., 2008]. In addition, affected patients in a significant minority may have polydactyly, talipes, short first metacarpal, abnormal (long or irregular) clavicles, hypoplastic first rib(s), widening of distal femora or proximal humeri, bowing of tibiae, mesomelic brachymelia and abnormal vertebrae.

Typical skeletal abnormalities (sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, and broad ribs) are another important clue for the diagnosis of SGS.

3.1.5. Other features

On antenatal ultrasonography, prenatal abnormalities in clinical diagnostic SGS cases were observed including hydronephrosis (20/48), polyhydramnios (11/48), macrosomia(1/48), bilateral talipes (1/48) and cerebral ventriculomegaly (1/48) in 48 reported cases.

An increased prevalence of malignant tumors has been reported in cases with SGS，to date, malignant tumors (3 malignant sacrococcygeal teratoma, 2 lumbosacral primitive neuroectodermal tumor, 3 hepatoblastoma, 1 malignant kidney tumor, 1 anaplastic extradural ependymal tumor, and 1 malignant germ cell tumor) have been reported in 11 SGS patients [Burck , 1982; Robin et al., 1993; Rodríguez et al., 1994; Antich et al., 1995; Culic et al., 1996; McPherson, et al., 1998; Kondoh et al., 2001; Sandri et al., 2003; Matsumoto et al., 2005; Beschorner, et al., 2007; Watanabe et al., 2012; Kishimoto et al., 2015]. The sacrococcygeal region is the most frequent primary tumor site in SGS [Kishimoto et al., 2015]. Watanabe et al. reported a 4-year-old SGS boy with hepatoblastoma developed at 1 year old, and chemotherapy successfully brought complete remission within 6 months[Watanabe et al., 2012], but the prognosis of malignant neoplasms in most affected individuals is very severe. A surveillance system for malignant neoplasms in SGS patients should, therefore, be formulated.

Cardiac defects are present in nearly 1/3 of the patients, the affected individuals may have valve of dysplasia or stenoses , hypoplasia of the ventricles and chambers, septal defects, patent ductus arteriosus, pulmonary stenosis and atresia. In some cases, choanal stenosis was found [Hoischen et al., 2010]. Some patients have dermatologic anomalies such as hyperconvex nails, unusual palmar creases, hypoplastic dermal ridges, and hypoplastic nipples [Albano et al., 2004; Al-Mudaffer et al., 2008; Lehman et al., 2008; Sharma et al., 2009]. Visceral abnormalities（pulmonary hypoplasia, splenopancreatic fusion, annular

pancreas, umbilical/epigastric hernia, hirschsprung disease and streak ovaries）, neurocraniofacial abnormalities (neural tube defect, tuning-fork shaped stapes, abnormal cochlea, leukomalacia, deep frontal furrows, retrognathia, high arched palate, broad alveolar ridges), and orodental anomalies（delayed teeth eruption，hypodontia, macrodontia, and thickened gingiva）were reported only in a minority of cases [Santos et al., 1994; Silengo et al., 1997; Rittinger et al., 1999; Cooke et al., 2002; Minn et al., 2002; Radhakrishnan et al., 2006; Lehman et al., 2008; Carvalho et al., 2015; Herenger et al., 2015].

Almost half of all previously reported patients with SGS died within the first 2 years of life due to various causes such as epilepsy, respiratory failure, and infection [Jones et al., 2013]. Only few patients with long-term survival have been reported. Kondoh et al. [Kondoh et al., 2001] reported on a long-lived patient with SGS whose condition was complicated with severe gingival hyperplasia and progressive brain atrophy over 9 years of follow up. Sharma et al. [Sharma et al., 2009] presented the first case with SGS with scoliosis. The patient presented with scoliosis at the age of 8 years which rapidly progressed to severe thoraco-lumbar scoliosis at 10 years. Herenger et al. [Herenger et al., 2015] followed 2 children during 15 and 6 years respectively. Primary facial features were still present at age of 15 in patient 1. Neurological features progressively worsened with age. Hydronephrosis worsened progressively and patient 1 developed coraliform nephrolithiasis. Patient 1 presents an abnormal teeth phenotype including shape and structural anomalies, delayed teeth eruption and thickened gingival. They developed complications of severe condition, remarkable scoliosis, luxation of hip, articular retractions and severe constipation.

3.2. Molecular Genetics

3.2.1. Causative Gene of SGS

In 2010, Hoischen et al. reported that heterozygous de novo mutations in *SETBP1* gene cause SGS. Only nine kinds of missense mutations described to date are clustered in the exon 4 of *SETBP1*, in the *SKI* homologous region, outside of the SET interacting domain and they do not affect the DNA binding domains of the SETBP1[Hoischen et al., 2010; Suphapeetiporn et al., 2011; Lestner et al., 2012; Ko et al., 2013; Carvalho et al., 2015; Herenger et al., 2015; Landim et al., 2015; Lopez-Gonzalez et al., 2015; Miyake et al., 2015; Takeuchi et al., 2015; Volk et al., 2015]. Known and predicted protein domains of SETBP1 include DNA binding domains, SKI homologous region, SET binding domain and Repeat domain [Hoischen et al., 2010]. Although *SETBP1* was identifed as the SGS disease-determining gene, relatively little is known about the function of SETBP1 except that it encodes an oncogene binding protein and binds to SET domains [Minakuchi et al., 2001; Hoischen et al., 2010]. SETBP1 may regulate chromatin structure and/or transcription[Taubert, 2010]. The function of SETBP1 might be involved in the regulation of Ski-Ski homodimer and/or Ski-SnoN heterodimer formation, which both cause cellular transformation [Minakuchi et al., 2001; Hoischen et al., 2010]. It is thought to do so in connection with Ski/Sno, and thus could modulate Smad/transforming growth factor-β (TGF-β) signalling, a pathway of great significance in tumour development [Taubert, 2010]. There are ubiquitous expression and functions for SETBP1, which is consistent with the diverse abnormalities in individuals with SGS. Gain-of-function or dominant negative effects in *SETBP1* alteration causing the disease may be a causative mechanism in SGS [Hoischen et al., 2010].

3.2.2. *SETBP1* Gene and Related Gene (SGRG)

SGRG encompasses classic missense mutations in *SETBP1* as described above as well as conditions with other molecular genetic features such as part *SETBP1*deletion, complete *SETBP1*deletion and contiguous gene deletion.

Filges et al. identified de novo heterozygous microdeletions containing exclusively *SETBP1* in two patients with moderate developmental, expressive language delay and distinctive facial features (prominent forehead, sparse eyebrows, mild ptosis with periorbital fullness, and epicanthus). The complete and exclusive loss of one copy of *SETBP1* in their patients suggests an essential role for *SETBP1* in expressive speech development [Filges et al., 2011].

Marseglia et al. described an additional patient with the smallest 18q12.3 microdeletion including *SETBP1* and *SLC14A2* and a microRNA (MIR4319). The patient showed mild mental retardation and expressive speech impairment, inattention, peculiar facial features (long face, high forehead, synophris, small palpebral fissures with ptosis, periorbital fullness, epicanthus, small nostrils, high nasal bridge, broad nasal tip, thin upper lip, fleshy lower tip, high-arched palate and small chin) [Marseglia et al., 2012]. *SLC14A2* gene codifies for a renal tubular urea transporter and could be eliminated like

candidate gene due to his function nonspecific to neural and motor planning domains necessary for speech [Marseglia et al., 2012]. The significant phenotypic overlap between this patient and the cases previously reported by Filges et al. [Filges et al., 2011] enforced the hypothesis that *SETBP1* haploinsufficiency may have a role in expressive language development [Marseglia et al., 2012]. Moreover, a putative role of MIR4319 in the deleted region and/or a position effect due to the separation of regulatory sequences from coding sequences cannot be excluded [Buysse et al., 2008; Marseglia et al., 2012].

Del (18) (q12.2q21.1) syndrome including *SETBP1* as a contiguous gene deletion syndrome is much less common. These patients of del (18) (q12.2q21.1) typically have minor dysmorphic features including relative macrocephaly, abnormally shaped skulls, ears with prominent antihelices and large lobules, prominent foreheads, epicanthus, deep-set eyes, flat/wide nasal bridge, small nose, hypoplastic midface, wide/hypoplastic philtrum, abnormal mouth, high arched palate, an increased number of fingertip whorls, ptosis of the upper eyelids, full periorbital tissue, and strabismus [Tinkle et al., 2003]. They have a tendency toward short stature and obesity [Tinkle et al., 2003]. All of affected individuals had moderate to severe mental retardation [Tinkle et al., 2003]. Many had hypotonia and seizures or abnormal EEG tracings [Tinkle et al., 2003]. They displayed behavioral abnormalities (aggression, inattention, and hyperactivity, as well as autistic-like features including social withdraw and self-stimulation), expressive language delay, and the lack of serious malformations [Schinzel et al., 1991; Schinzel, 2001; Tinkle et al., 2003; Buysse et al., 2008]. Heterozygous deletion of *SETBP1* may primarily contribute to the phenotype of this contiguous gene syndrome [Filges et al., 2011].

The contiguous gene deletion syndromes including *SETBP1* as described above should be defined Related Disorders of Schinzel-Giedion syndrome.

3.3. Revised diagnostic criteria of SGS

Among 25 previously reported SGS patients with point mutations in *SETBP1*, clinical features were the following: typical craniofacial features, development delay, genital anomaly, seizure, hydronephrosis or vesicoureteral reflux, characteristic skeletal anomalies, hearing impairment, vision impairment, cardiac defect. Prenatal abnormalities were observed on ultrasonography including hydronephrosis (6/25), reduced fetal movements(1/25), cystic fluid collections in the brain(1/25), single umbilical artery(1/25), polydactyly at hand(1/25), bilateral talipes(1/25), nuchal translucency(1/25), rocker-bottom feet(1/25) and polyhydramnios(1/25). Malignant tumors have not been reported in cases with SGS with point mutations in *SETBP1*. Table 2 shows clinical and molecular features in SGS patients with point mutations in *SETBP1*.

Unlike previous reports, our milder patient with insertion mutation in *SETBP1* present with distinctive facial features, development delay and complex febrile seizure, without the typical skeletal anomalies, structural malformations, and audiovisual impairment. A previously described case with pS867R in *SETBP1* and our patient presented neither hydronephrosis nor typical skeletal anomalies, not fulfilling the previous diagnostic criteria [Lehman et al., 2008]. In 2011, Filges et al. identified de novo heterozygous microdeletions containing exclusively *SETBP1* in two patients with developmental delay, expressive language delay and minor facial anomalies [Filges et al., 2011].

Here we summarize data of above-mentioned patients and revise diagnostic criteria of SGS. SGS is subdivided into three types based on clinical findings and/or *SETBP1* mutation. Type I (complex, classic type) SGS patients have the typical clinical features. The patients present a development delay and typical facial phenotype (prominent forehead, midface retraction, and short, upturned nose) associated with hydronephrosis or two of the characteristic skeletal anomalies (a sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, and broad ribs), which is in accordance with previously proposed diagnostic criteria [Lehman et al., 2008]. Type II (middle type) patients show development delay and the distinctive facial features (midface retraction, short and upturned nose), lacking both hydronephrosis and typical skeletal abnormalities, with existence of *SETBP1* mutation. Type III (simple type) patients with *SETBP1* alteration show their major symptom is development delay, in which expressive language delay is the most striking feature.

4. DISCUSSION

SGS is a very rare autosomal dominant inheritance disorder. The precise prevalence of SGS is unknown. The classic clinical features of SGS are multiple developmental anomalies including psychomotor retardation with progressive

neurodegeneration, seizures, craniofacial, skeletal, and urogenital malformations, as well as a higher prevalence of malignant neoplasms. Most reported patients with SGS died before age 2. Our patient might have a long life span because she has no clinical evidence of life-threatening or progressive abnormalities. In 2010, heterozygous de novo mutations in the *SETBP1* gene were identified as the genetic cause of SGS. With the introduction of molecular genetics in the diagnosis of SGS, it is possible that atypical patients could be diagnosed. Some prenatal abnormalities can be identified on ultrasonography in SGS patients, and the early molecular diagnosis of SGS could also be confirmed by amniocentesis. In this study, our patient show distinctive facial features, moderate developmental delay, expressive language delay, and complex febrile seizure, but neither hydronephrosis nor typical skeletal abnormalities, the definitive diagnosis of the possible patient having SGS was identified by testing for *SETBP1* mutations. Our case and the previously reported patient with pS867R by Carvalho et al. [Carvalho et al., 2015] are consistent with our revised diagnostic criteria of Type II (middle type) SGS. Joss and Dean [Joss and Dean, 2002] followed two 12-year-old monozygotic twins from birth in 2002. Their features included midface hypoplasia, short nose and anteverted nostrils, a prominent forehead, coarse features, sensorineural deafness, short stature with thoracic kyphosis and lumbar lordosis, intellectual and language delay. Hydronephrosis and typical skeletal abnormalities were not found in two patients. We propose that two monozygous twins might fulfill the diagnostic criteria of Type II SGS, but *SETBP1* mutations first should be verified in two previously reported patients. Filges et al. [Filges et al., 2011] reported that two patients with de novo heterozygous microdeletions containing exclusively *SETBP1* presented developmental delay, expressive language delay and minor facial anomalies. Thus we consider the clinical type of the two patients' phenotype as Type III (simple type) SGS. Frequency of SGS patients in type I, II and III were 95.4(82/86), 2.3(2/86) and 2.3%(2/86), respectively. Since disease-determining gene of SGS has been identified, our revised diagnostic criteria of SGS which is based on clinical findings and/or molecular analysis may yield a higher diagnosis rate. The study may enlarge the phenotypic spectrum of SGS.

SGS is characterized by multiple developmental anomalies, which is consistent with ubiquitous expression of SETBP1. All detected point mutations of *SETBP1* in previous patients with SGS were missense mutation, all changes are clustered exclusively in exon 4, in the SKI homologous region. Although the exact function of the *SETBP1* gene and the effects of the mutations identified in SGS are currently unclear, a gain-of-function or dominant-negative effect is a likely result of these mutations [Hoischen et al., 2010]. In the present milder case with SGS, a novel insertion mutation (c. 1181_1184insA; E394EfsX3) was identified in exon 4 of the *SETBP1* gene. Study of the family constellation indicated that the mutation arose *de novo*. The insertion mutation would result in a complete loss of almost all functional domains including DNA binding domains, SKI homologous region, SET binding domain and Repeat domain, leading to severe impairment of SETBP1 function. Particularly, we presume that insertion mutation in our patient could be classified as more severer than missense mutation previously reported. The milder patient described here has the distinctive facial features and development delay of SGS. Interestingly, some features including epicanthus, developmental and expressive language delay, and behavioural problem in our case appear to overlap extensively with the patients' phenotype of chromosomal microdeletion including exclusive *SETBP1*, patient' features with the smallest 18q12.3 microdeletion including *SETBP1* and *SLC14A2* and a microRNA, and characteristics of del(18)(q12.2q21.1) syndrome including *SETBP1* as a contiguous gene deletion syndrome. Taken together, central nervous system involvement with development delay in which expressive language delay is much more obviously affected is the most prominent feature of SGS. There is another indication that severity of phenotype of SGS may be inversely correlated with degree of *SETBP1* alteration, besides gain-of-function or dominant negative effects in *SETBP1* alteration causing SGS. SKI homologous region of SETBP1 might play a possibly critical precise modulator of transcriptional correlation by SKI -mediated transcription factor regulatory networks. The pS867R mutation in a previously reported milder SGS case by Carvalho et al. [Carvalho et al., 2015] in the SKI homologous region might be more severer than other reported missense mutation. The findings also suggest that *SETBP1* is the major candidate gene for expressive language delay, in particular, part or complete heterozygous alteration of *SETBP1* including SKI homologous region is more important.

In conclusion, we report a novel milder case with SGS with a novel insertion mutation in *SETBP1*. We first revise diagnostic criteria of SGS based on clinical findings and/or *SETBP1* mutation worldwide. It is also highly likely that severity

of phenotype of SGS may be inversely correlated with degree of *SETBP1* alteration. The study may have important future implications for precise genotype-phenotype correlation research.

Information about *SETBP1*(https://www.ncbi.nlm.nih.gov/**):** transcript, NM_015559; ORF, ORF18; number of exons, 8; protein size, 242 aa; GenBank Accession no. of transcript, AAH62338.1.

5. ACKNOWLEDGEMENTS

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6. DECLARATION OF INTEREST

The authors report no conflict of interest.

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Clinical features	Reported cases	% (n=58)
Neurological features		
Developmental delay	46/46	79%
Seizures	43/46	74%
Vision impairment	12/14	21%
Hearing impairment	12/15	21%
Brain MRI/CT		
Ventriculomegaly	18/24	31%
Hypoplasia corpus callosum	18/26	31%
Cortical atrophy	14/21	24%
Choroid plexus cysts	10/17	17%
Craniofacial features		
Midface hypoplasia	53/53	91%
Prominent forehead	49/49	85%
Short, upturned nose	46/48	79%
Wide fontanelles	41/41	71%
Orbital hypertelorism	36/37	62%
Infraorbital grooves	35/35	60%
Low-set ears	43/46	74%
Radiographic features		
Skull		
Sclerotic base	24/36	41%
Wide occipital synchondrosis	27/36	47%
Steep base	24/34	41%

Wormian bones	10/23	17%
Extremities		
Cortices: dense, thickened, undertubulated	24/35	41%
Hypoplastic distal phalanges	20/26	35%
Short first metacarpal	8/19	14%
Mesomelicbrachymelia	17/24	29%
Chest and basin		
Broad ribs	41/47	71%
Abnormal (long or irreg) clavicles	10/20	17%
Hypoplastic/underossified pubic bones	17/29	29%
Structural anomalies		
Hydronephrosis or vesicoureteralrefux	51/55	88%
Genital abnormalities	44/47	76%
Cardiac defect	20/42	35%
Choanal stenosis	13/32	22%
Malignant tumors	11/11	19%

Table1. Major clinical features in reported SGS patients by a clinical diagnosis.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Our case	Cases	%（n=26）
Phenotype / Genotype	S867R	D868N	D868N	D868N	D868N	D868N	D868N	D868A	S869C	G870S	G870S	G870S	G870S	G870S	G870S	G870D	G870C	I871T	I871T	I871T	I871T	I871T	I871T	I871T	I871S	E394EfsX3		
Typical craniofacial features																												
Midface hypoplasia	+	+	+	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25/25	96%	
Prominent forehead	NA	+	+	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	+	—	+	+	NA	+	+	—	21/23	81%
Short, upturned nose	+	+	+	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25/25	96%	
Wide fontanelles	NA	+	NA	+	+	+	NA	—	NA	+	+	+	+	+	+	+	NA	—	+	+	+	+	+	NA	NA	—	16/19	62%
Hypertelorism	NA	+	+	+	+	+	NA	+	NA	+	NA	NA	+	+	+	+	NA	+	+	+	—	+	+	NA	NA	+	17/18	65%
Infraorbital grooves	NA	NA	NA	NA	NA	+	NA	NA	+	NA	+	+	NA	+	+	NA	+	NA	NA	NA	NA	NA	+	+	NA	—	9/10	35%
Low-set ears	NA	+	+	+	+	—	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	+	+	+	NA	—	21/23	81%
Development delay	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NA	+	+	+	+	+	25/25	96%
Seizure	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	+	+	+	25/26	96%
Hearing impairment	—	+	+	NA	+	NA	+	—	+	+	+	NA	+	+	+	NA	NA	+	+	NA	+	+	NA	NA	+	—	15/18	58%
Vision impairment	+	+	+	NA	+	NA	+	+	+	+	—	NA	+	+	+	NA	NA	+	+	NA	+	—	NA	NA	+	—	15/18	58%
Brain MRI/CT																												
Ventriculomegaly	—	NA	NA	NA	NA	+	NA	NA	NA	NA	+	+	+	+	+	NA	+	NA	NA	NA	NA	NA	+	+	+	—	10/12	38%
HCC	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	+	+	NA	+	NA	NA	NA	NA	NA	+	—	NA	—	4/7	15%
Cortical atrophy	—	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	+	+	NA	+	NA	NA	NA	NA	NA	+	—	+	—	6/9	23%
Choroid plexus cysts	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	—	NA	—	2/5	8%
Others	a	NA	NA	NA	NA	—	—	NA	b	NA	NA	NA	c	d	e	NA	NA	NA	NA	NA	NA	NA	f	g	h	—		
Hydronephrosis or VUR	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	24/26	92%
CSM	—	NA	+	+	+	+	NA	+	NA	+	+	+	+	+	+	+	+	NA	+	+	+	+	+	NA	+	—	19/21	73%
Genital anomaly	+	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	NA	+	+	+	+	+	NA	+	+	—	22/23	85%
Cardiac defect	—	+	+	—	+	—	NA	+	NA	+	NA	—	—	—	—	—	—	—	+	—	+	—	+	NA	—	—	8/22	31%
Prenatal abnormalities	—	NA	NA	NA	NA	+	+	NA	+	NA	NA	NA	+	+	+	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	—	7/9	27%
References	Carv-alho	Hoi-schen	Hoi-schen	Hoi-schen	Hoi-schen	Carv-alho	Volk	Hoi-schen	Lan-dim	Hoi-schen	Suphap-eetiporn	Suphap-eetiporn	Ko	Here-nger	Here-nger	Hoi-schen	López-González	Hoi-schen	Hoi-schen	Hoi-schen	Hoi-schen	Hoi-schen	Miy-ake	Les-tner	Take-uchi	This study		

Table2. Clinical and molecular features in SGS patients with point mutations in *SETBP1*

NA, not available; HCC, Hypoplasia corpus callosum; VUR, vesicoureteral reflux; CSM, Characteristic skeletal malformations. a.Reduction of the white matter volume and delayed myelination for age(MRI). b. Linear calcifications to the straight sinus level and confluence of the venous sinuses (CT). c. Delayed myelination(MRI). d. progressive cerebral atrophy affecting the white matter, the gray nuclei, and the brainstem, and sparing the cerebellum; calcification of the choroid cysts(MRI and CT). e. Brain and brainstem atrophy(MRI). f. Partial colpocephaly extraventricular enlargement, and delay of myelination(MRI). g.Extensive polymicrogyria involving the frontal, temporal and perisylvian regions(MRI). h. progressive brain atrophy involving the white matter, basal ganglia, thalamus, brainstem, and cerebellum; periventricular heterotopia at right anterior horn(MRI).

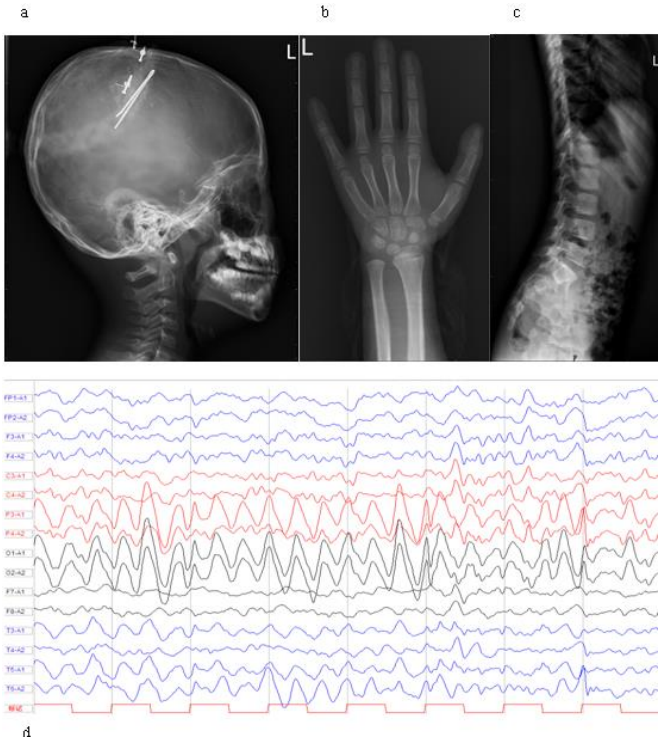

Figure 1. Skeletal radiographs and EEG of the present case at 5.8 y. (a) Lateral skull radiograph. (b) Left hand radiograph. (c) Lateral vertebrae radiograph. (d) EEG.

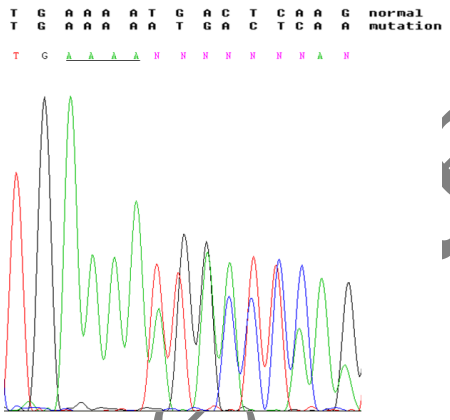

Figure 2. Mutation analysis of *SETBP1* of the SGS patient showing heterozygous c. 1181_1184insA; E394EfsX3 mutation, c. 1181_1184 are shown as bases underlined.