RESEARCH REVIEW

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SATB2-Associated Syndrome: Mechanisms, Phenotype, and Practical Recommendations

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The *SATB2*-associated syndrome is a recently described syndrome characterized by developmental delay/intellectual disability with absent or limited speech development, craniofacial abnormalities, behavioral problems, dysmorphic features, and palatal and dental abnormalities. Alterations of the *SATB2* gene can result from a variety of different mechanisms that include contiguous deletions, intragenic deletions and duplications, translocations with secondary gene disruption, and point mutations. The multisystemic nature of this syndrome demands a multisystemic approach and we propose evaluation and management guidelines. The *SATB2*-associated syndrome registry has now been started and that will allow gathering further clinical information and refining the provided surveillance recommendations.

Key words: *SATB2*; *SATB2*-associated syndrome; Glass syndrome; 2q33.1 microdeletion syndrome; 2q32 deletion syndrome

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INTRODUCTION

The SATB2-associated syndrome (SAS) is a recently described syndrome characterized by developmental delay (DD)/intellectual disability (ID) with absent or limited speech development, craniofacial abnormalities including palatal and dental abnormalities, behavioral problems, and dysmorphic features [Docker et al., 2014; Zarate et al., 2015]. Skeletal anomalies and osteopenia were recently added to the list of distinctive features in SAS [Zarate et al., 2015]. Abnormalities of the *SATB2* gene have also been described under the term Glass syndrome (OMIM 612313).

Alterations to the *SATB2* Locus can result from a variety of different mechanisms that include contiguous deletions, intragenic deletions and duplications, translocations with secondary gene disruption, and point mutations. In this review, we will discuss the clinical features of SAS caused by the different mechanisms. It begins with a review of the function of the gene and how animal models have helped to elucidate its role in human disease, followed by a discussion on the current theories behind the molecular mechanisms that result from alterations in *SATB2*. Finally, after a brief discussion of the role of SATB2 in cancer, all the clinical information from reported cases with cytogenetic imbalances (including contiguous deletions, intragenic deletions and duplications, and translocations with gene disruption) and *SATB2* point mutations is presented. Through reviewing all this information, we attempt to delineate the SAS phenotype, analyze for potential differences according to molecular mechanism, and comment on the current terminology being used when referring to alterations in the *SATB2* gene. Recommendations for diagnosis and evaluation of these patients are also provided.

SATB2 STRUCTURE AND FUNCTION

SATB2 was originally identified as the causative gene on 2q32-q33 associated with cleft palate, one of very few genomic regions where haploinsufficiency is significantly associated with isolated cleft palate [Brewer et al., 1999; FitzPatrick et al., 2003]. The *SATB2* gene encodes a protein of 733 amino acids with two CUT domains and a homeodomain [FitzPatrick et al., 2003]. These functional domains are highly conserved across vertebrate taxa, where the human protein shares 100% identity with mouse, 98–100% identity with chicken, and up to 96% identity with zebrafish [FitzPatrick et al., 2003; Sheehan-Rooney et al., 2010].

SATB2 functions as a transcription factor that binds to nuclear matrix-attachment regions (MARs), where it activates transcription of multiple genes simultaneously [Dobreva et al., 2003; Gyorgy et al.,

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2008]. As such, SATB2 is a high-level regulator of several gene regulatory networks (GRNs), and has critical roles in multiple developmental processes [Britanova et al., 2006; Dobreva et al., 2006].

SATB2 in Development

Studies in animal model systems have revealed diverse yet conserved roles for *Satb2* during development. Satb2 is involved in jaw growth and patterning, upper layer neuron specification, and osteoblast differentiation [Britanova et al., 2006; Dobreva et al., 2006; Savarese et al., 2009]. *Satb2* expression in the developing jaw, brain, and skeleton is conserved across a broad range of vertebrates, including zebrafish, *Xenopus*, chicken, and mouse [Sheehan-Rooney et al., 2010; Fish et al., 2011]. These expression domains correspond to tissues that are affected by mutations in human patients with SAS [Zarate et al., 2015].

In mice, studies have found a critical role for *Satb2* in brain development, particularly in the specification of cortical upper layer neurons [Alcamo et al., 2008; Britanova et al., 2008]. *Satb2* is expressed in cortico-cortical projection neurons that occupy the superficial layers of the cortex where they extend axons across the midline to form the corpus callosum [Alcamo et al., 2008; Britanova et al., 2008]. In the absence of *Satb2*, cortico-cortical neurons are not properly specified and fail to extend axons laterally across the corpus callosum, and instead make subcortical projections [Britanova et al., 2006; Alcamo et al., 2008]. Thus, cognitive defects seen in SAS patients are likely associated with defects in the migration and axonal projections of cortical neurons.

The SAS phenotype also includes craniofacial anomalies that include micrognathia and cleft palate. Similarly, *Satb2* knock-out mice display hypoplasia of the distal jaw skeleton. At birth, mice lacking *Satb2* have severely reduced jaw length and die from cleft palate [Britanova et al., 2006; Dobreva et al., 2006]. Interestingly, one quarter of mice heterozygous for *Satb2* also die of cleft palate, while surviving heterozygotes exhibit a variable reduction in dentary length and facial asymmetry [Britanova et al., 2006; Fish et al., 2011]. These data mirror the variation in disease severity of patients affected by SAS, and suggest that *Satb2* may be especially susceptible to perturbation during development [Fish, 2015].

Recently, the SAS phenotype was expanded to include skeletal anomalies and osteopenia [Zarate et al., 2015]. Similarly, in mice, loss of *Satb2* leads to reduced levels of bone mineralization, resulting in short and brittle limb bones [Dobreva et al., 2006]. Studies have shown that *Satb2* regulates osteogenesis by promoting the expression and function of osteoblast-specific genes, including *Runx2* and *Atf4* [Dobreva et al., 2006; Gong et al., 2014].

MOLECULAR MECHANISMS BEHIND *SATB2* ALTERATIONS

In both mice and humans, mutations in *Satb2* are associated with variation in the severity of developmental defects. In mice, *Satb2* acts in a dosage-dependent manner. This is particularly evident in jaw size, where $Satb2^{+/-}$ heterozygote mice exhibit significant variation in micrognathia and cleft palate. In humans, gene dosage effects (haploinsufficiency) with a resulting deficiency of functional SATB2 protein have been postulated to be the primary mechanism responsible for the clinical features seen in the SAS for those patients with SAS deriving from small interstitial deletions/duplications and those with chromosomal aberrations such as large deletions and translocations that directly disrupt *SATB2* [Rosenfeld et al., 2009; Leoyklang et al., 2013; Lieden et al., 2014; Kaiser et al., 2015]. In addition, translocations with breakpoints that lie in the gene desert 3′ of *SATB2* can also result in its functional haploinsufficiency and with clinical consequences that resemble those with heterozygous loss of function variants [Rainger et al., 2014].

While the exact pathomechanism of point mutations in *SATB2* remains unknown, the possibility of a dominant negative effect has been suggested [Leoyklang et al., 2007]. This theory was later explored further and the truncated SATB2 was, indeed, documented to interfere with the repressive function of the wild-type SATB2 [Rosenfeld et al., 2009; Leoyklang et al., 2013]. These data suggest that variation in phenotypic penetrance in human patients may result from both differences in genetic background as well as differences in SATB2 function related to the specific genetic mechanism disrupting the *SATB2* Locus. These differences are discussed in more detail below.

CLINICAL DATA

To obtain the clinical information presented here, an online literature search was conducted in PUBMED using the keywords: "SATB2," "SATB2-associated syndrome," "Glass syndrome," "2q32-q33 deletion syndrome," and "2q33.1 microdeletion syndrome."

SATB2 and Isolated Clefting

The 2q32-q35 area had been shown to be a cleft susceptibility locus in the past [Marazita et al., 2004]. However, studies looking at point mutations of *SATB2* in patients with isolated orofacial clefts have failed to reveal alterations. An initial screen of 70 unrelated isolated cleft palate patients (including 23 patients with Pierre Robin sequence) found no pathogenic *SATB2* mutations [FitzPatrick et al., 2003]. Similarly, targeted testing or full sequencing of *SATB2* failed to reveal mutations in a combined population of over 350 patients with nonsyndromic cleft lip with or without cleft palate [Vieira et al., 2005; Gurramkonda et al., 2015]. The presence of other phenotypic features in addition to orofacial clefts is likely to increase the detection yield when looking for *SATB2* alterations.

Cytogenetic Abnormalities Encompassing *SATB2*

Reports of individuals with large deletions, intragenic deletions and duplications, and rearrangements involving the *SATB2* locus at chromosome 2q33.1 were reviewed. Only papers in which the alteration of *SATB2* was well documented with supplemental molecular techniques (e.g., microarrays, fine mapping, FISH, PCR) were included. Similarly, several other cases of deletions that encompass *SATB2* have been briefly mentioned in large studies although with no full phenotypic description and therefore, were excluded from this review [Talkowski et al., 2012; Conte et al., 2016]. The included cases are shown in Figure 1, while the phenotypic features are presented in Table I.

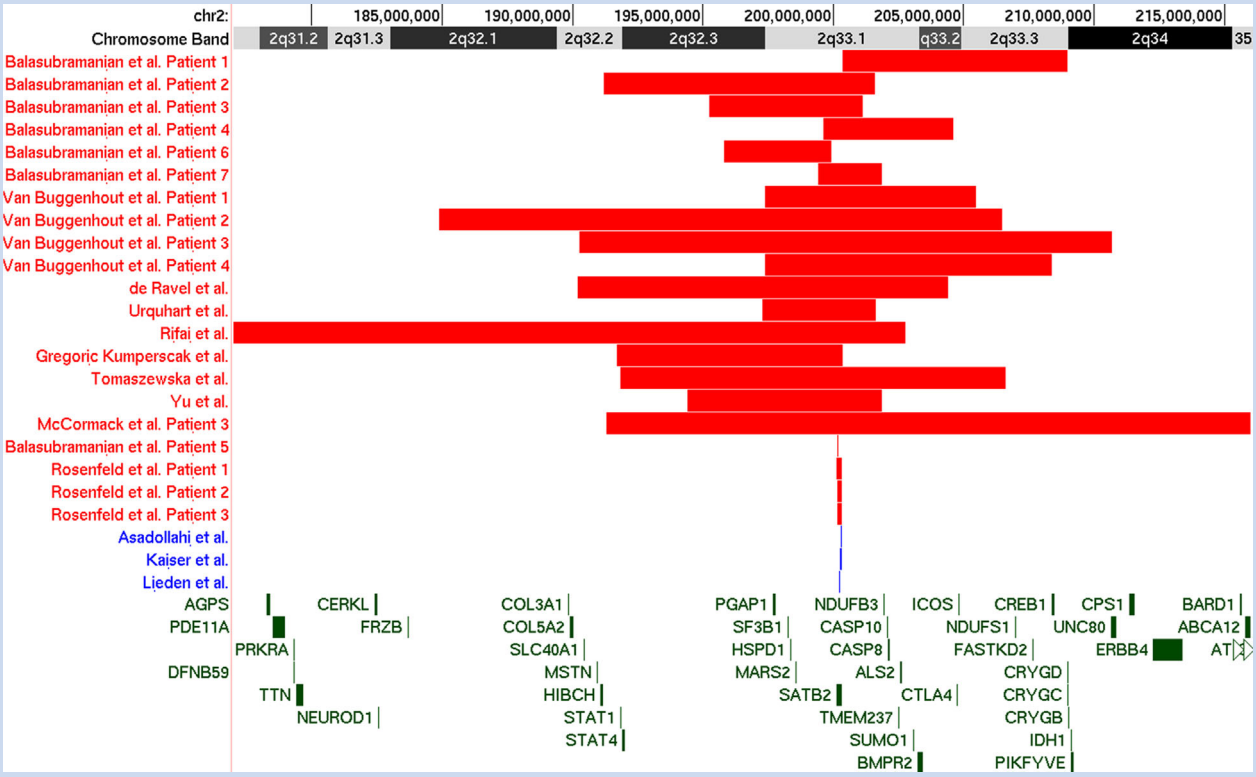


FIG. 1. UCSC Genome Browser (GRCh37/hg19) assembly depiction of published deletions encompassing *SATB2* included in this review. Deletions are represented in red while duplications are represented in blue. [Color figure can be viewed at wileyonlinelibrary.com].

Large deletions. In 1989, a 16-year-old male with severe intellectual disability, epilepsy, microcephaly, cleft palate, short stature, and craniofacial dysmorphism was first described [Glass et al., 1989]. In this individual, a G banded karyotype of peripheral lymphocytes showed an interstitial deletion of the long arm of chromosome 2: del(2)(q32.2q33.1) [Glass et al., 1989]. Since this report, several other cases of 2q deletions have been reported but only 17 with sufficient molecular characterization to determine that the *SATB2* gene was part of the deleted region [Van Buggenhout et al., 2005; de Ravel et al., 2009; Urquhart et al., 2009; Rifai et al., 2010; Balasubramanian et al., 2011; Mc Cormack et al., 2013; Tomaszewska et al., 2013; Yu et al., 2015; Gregoric Kumperscak et al., 2016]. The deletions range in size from 2.4 to 26.3 Mb.

The first report of patients with deletions at 2q33 with further molecular cytogenetic characterization was published in 2005 [Van Buggenhout et al., 2005]. In this report, four males with large deletions that included the *SATB2* gene were described as having a consistent phenotype that included severe neurodevelopmental delay with significant speech impairment, craniofacial dysmorphism, dental and palatal anomalies, growth retardation, and behavioral issues. Most of these features were subsequently replicated in several case reports and a case series.

Overall, DD/ID is the most consistently reported finding in patients with large deletions (Table I). All cases described today with deletions that encompass the *SATB2* gene have this feature independently of the deletion size in patients that were old enough to be assessed. When quantified, the degree of DD/ID has been reported as severe in over half the patients (55%). Verbal communication is the most affected area of development with speech delay in all patients that have been old enough to develop such expected skills and with absent speech in 38% of cases. Developmental regression and/or cognitive decline, on the other hand, had not been described until recently. Gregoric Kumperscak et al. [2016] described the case of an adult female with a history of a cleft palate and craniofacial dysmorphism with an 8.6 Mb deletion of 2q32.2q33.1 with 22 known OMIM genes including *SATB2*. The patient was documented to have cognitive decline between ages of 6 and 12 years of age and from mild ID (IQ 50–55) to severe ID (IQ of 25–30) and from poor to absent speech during the same timeframe. From the neurodevelopmental perspective, behavioral abnormalities are commonly described as well with a spectrum that goes from autistic behaviors and hyperactivity to aggression and difficult to control patterns of behavior. Other common features described in patients with large deletions include feeding difficulties (76%), pre- or postnatal growth retardation (71%), hypotonia (53%), thin skin or reduced subcutaneous fat (53%), cleft palate (47%), brain MRI abnormalities (45%), and dental crowding (44%).

Intragenic deletions and duplications. Intragenic deletions have only been reported in four patients thus far (Fig. 1). Rosenfeld et al. [2009] reported three patients (two females) with microdeletions of 2q33.1 that ranged from 173 to 185 kb in size and with only *SATB2* included in the region. All three patients had severe

TABLE I. Frequencies of the Features Reported in More Than a Single Patient With Alterations of *SATB2* According to Molecular Mechanism

	Large deletions	%	Intragenic duplication	%	Intragenic deletion	%	Gene disruptions	%	Point mutations	%	Total	%
Number of patients (with feature/with data)	17		3		4		6		11		41	
Males	10	59	2	67	2	50	3	50	6	60	23	56
Females	7	41	1	33	2	50	2	33	4	40	16	39
Age ranges in years (Median)	0.5–37 (8.5)		4–20 (10)		3-21 (7.75)		0.1–33 (17.5)		2.7–36 (4)		0.1–37 (8)	
DD/ID	16/16	100	3/3	100	4/4	100	6/6	100	11/11	100	40/40	100
Severe	10	63	2	67	3	75	1	17	6	55	22	55
Mild/Moderate	3	19	0	0	1	25	2	33	4	36	10	25
Speech delay	16/16	100	3/3	100	4/4	50	5/6	83	10/11	91	38/40	95
Absent	6	38	0	0	2	50	2	33	9	82	19	48
Limited	8	50	3	100	2	50	2	33	1	9	16	40
Dental	15/16	94	3/3	100	3/4	75	2/2	100	7/9	78	30/34	88
Abnormal shape/size of teeth	7	44	1	33	0	0	1	50	7	78	16	47
Crowding	7	44	1	33	1	25	0	0	5	56	14	41
Missing teeth	5	31	1	33	0	0	2	100	0	0	8	24
Delayed Primary dentition	0	0	1	33	1	25	0	0	0	0	2	6
Diastema	2	13	0	0	0	0	0	0	0	0	2	6
Behavior	12/14	86	2/3	67	2/3	67	3/5	60	5/10	50	24/35	69
Hyperactivity/distractibility	6	43	1	33	0	0	0	0	1	10	8	23
Autistic/repetitive behaviors	2	14	1	33	1	33	1	20	2	20	7	20
Agitation/Aggressive outbursts	5	36	0	0	0	0	2	40	0	0	7	20
Sleeping difficulties	0	0	1	33	1	33	0	0	4	40	6	17
Happy demeanor/inappropriate laughter/friendly	2	14	2	67	1	33	0	0	1	10	6	17
Difficult behavior	3	21	0	0	0	0	0	0	1	10	4	11
Sensory issues	2	14	0	0	1	33	0	0	0	0	3	9
Cleft palate	8/17	47	2/3	67	2/4	50	4/6	67	8/11	73	24/41	59
Brain MRI/CT performed	11	65	2	67	1	25	2	33	10	91	26	63
Normal	6	55	1	50	1	100	0	0	5	50	13	50
Abnormal	5	45	1	50	0	0	2	100	5	50	13	50
Enlarged ventricles	2	12	0	0	0	0	2	33	1	9	5	19
Abnormal myelination	0	0	1	33	0	0	0	0	2	18	3	12
Agenesis of corpus callosum	1	6	0	0	0	0	1	17	0	0	2	8
Prominent perivascular spaces	2	12	0	0	0	0	0	0	0	0	2	8
Skeletal	5/12	42	2/3	67	0/2	0	4/4	100	4/7	57	15/28	61
Pectus excavatum	2	17	1	33	0	0	0	0	1	14	4	14
Kyphosis/lordosis	1	8	0	0	0	0	0	0	1	14	2	7
Tibiae bowing	0	0	1	33	0	0	0	0	1	14	2	7
Osteopenia/osteoporosis	0	0	1	33	0	0	3	75	4	57	8	29
Neurological (with data)	17		3		4		3		9		36	
Feeding difficulties	13	76	2	67	2	50	2	67	1	11	20	56
Hypotonia	9	53	1	33	0	0	0	0	5	56	15	42
Clinical seizures	3	18	0	0	0	0	2	67	3	33	8	22

TABLE I. (*Continued*)

	Large deletions	%	Intragenic duplication	%	Intragenic deletion	%	Gene disruptions	%	Point mutations	%	Total	%
Abnormal gait	5	29	0	0	0	0	0	0	1	11	6	17
Hypertonicity/spasticity	1	6	1	33	1	25	0	0	0	0	3	8
Hyperreflexia	0	0	1	33	1	25	0	0	0	0	2	6
Dysmorphic features (with data)	17		3		4		6		10		40	
High/prominent forehead/frontal bossing	9	53	1	33	1	25	1	17	2	20	14	35
Long face	4	24	1	33	2	50	3	50	0	0	10	25
Low-set ears	5	29	0	0	1	25	1	17	2	20	9	23
Long philtrum	4	24	1	33	0	0	0	0	3	30	8	20
Down-slanted palpebral fissures	4	24	1	33	0	0	0	0	2	20	7	18
High/broad nasal bridge	3	18	1	33	1	25	2	33	0	0	7	18
Smooth philtrum	3	18	1	33	1	25	0	0	2	20	7	18
Thin upper lip	6	35	0	0	0	0	0	0	1	10	7	18
Hypertelorism/telecanthus	2	12	1	33	0	0	1	17	2	20	6	15
Long nose	0	0	0	0	1	25	5	83	0	0	6	15
Small mouth	1	6	0	0	1	25	3	50	1	10	6	15
Upturned nose	3	18	0	0	0	0	0	0	1	10	4	10
Prominent nose	2	12	1	33	0	0	0	0	0	0	3	8
Short palpebral fissures	1	6	1	33	0	0	0	0	1	10	3	8
Short philtrum	2	12	0	0	1	25	0	0	0	0	3	8
Broad nose	0	0	1	33	0	0	0	0	2	20	3	8
Deeply set eyes	2	12	0	0	0	0	0	0	1	10	3	8
Anteverted nares	0	0	1	33	0	0	0	0	1	10	2	5
Flat face	1	6	1	33	0	0	0	0	0	0	2	5
Large ears	0	0	1	33	1	25	0	0	0	0	2	5
Low nasal bridge	0	0	1	33	0	0	0	0	1	10	2	5
Prominent ears	1	6	0	0	0	0	0	0	1	10	2	5
Thin/small nose	1	6	0	0	0	0	1	17	0	0	2	5
Triangular face	1	6	0	0	0	0	0	0	1	10	2	5
Craniofacial (with data)	17		3		4		5		11		40	
Micrognathia	6	35	1	33	3	75	3	60	7	64	20	50
High (arched) palate	8	47	1	33	0	0	0	0	0	0	9	23
Flat occiput	2	12	0	0	0	0	0	0	0	0	2	5
Abnormal sinuses	0	0	0	0	0	0	0	0	2	18	2	5
Extremities (with data)	14		3		2		5		6		30	
Broad thumbs/halluces	2	14	2	67	1	50	0	0	1	17	6	20
Arachnodactyly	1	7	0	0	0	0	4	80	0	0	5	17
Clinodactyly	2	14	0	0	0	0	1	20	1	17	4	13
Small hands/feet	2	14	1	33	0	0	0	0	1	17	4	13
Contractures/camptodactyly	2	14	1	33	0	0	0	0	0	0	3	10
Club feet	2	14	0	0	0	0	0	0	0	0	2	7
Ophthalmologic (with data)	14		0		4		4		6		28	
Strabismus	1	7	0	0	1	25	1	25	3	50	6	21
Refractive errors	0	0	0	0	0	0	0	0	3	50	3	11
Tegumentary (with data)	14		0		4		2		5		21	
Joint hypermobility/ligamentous laxity	4	29	0	0	0	0	0	0	1	20	5	24

TABLE I. (*Continued*)

	Large deletions	%	Intragenic duplication	%	Intragenic deletion	%	Gene disruptions	%	Point mutations	%	Total	%
Genitourinary (with data)	11		1		4		0		0		16	
Small/undescended testicles	4	36	0	0	1	25	0	0	0	0	5	31
Inguinal hernia	4	36	0	0	0	0	0	0	0	0	4	25
Hypospadias	2	18	0	0	0	0	0	0	0	0	2	13
Cardiovascular (with data)	9		1		3		0		0		13	
Atrial/ventricular septal defects	2	22	0	0	0	0	0	0	0	0	2	15
Pre- or postnatal growth retardation (with feature/with data)	12/17	71	0/3	0	0/4	0	2/4	50	0/10	0	14/38	37
Microcephaly (with feature/with data)	6/17	35	1/3	33	1/4	25	1/2	50	1/8	9	10/34	29
Ectodermal changes (with data)	15		0		4		0		1		20	
Thin skin/reduced subcutaneous fat	8	53	0	0	0	0	0	0	0	0	8	40
Thin/fine/sparse hair	6	40	0	0	0	0	0	0	0	0	6	30

Shaded rows represent the most common/proposed main clinical findings in this syndrome. All percentages have been adjusted to those with data.

developmental delay with little to no speech and dentofacial abnormalities, while two of the subjects also had unusual behavior [Rosenfeld et al., 2009]. In another case series, the smallest reported intragenic deletion thus far of only 35 kb was found in a 3-year-old male with a history of cleft palate, feeding difficulties, developmental delay with absent speech, facial dysmorphism, and minor skeletal anomalies [Balasubramanian et al., 2011].

Intragenic duplications seem to be equally rare with only three reported cases (Fig. 1). A 32 kb intragenic duplication that affects exon 4 was reported in a 4-year-old patient with a history of hypotonia, feeding difficulties, and a cleft palate. The patient also had DD with profoundly delayed speech, a double row of upper incisors, craniofacial dysmorphism, and behavior anomalies [Asadollahi et al., 2014]. In another case, a 10-year-old female with moderate to severe ID, nearly absent speech, sleeping problems, feeding difficulties, facial dysmorphic features, and dental anomalies was found to have a de novo 84-kb duplication within chromosomal region 2q33.1 and encompassing exon 3 of the *SATB2* gene [Kaiser et al., 2015]. Lastly, a 20-year-old male patient with moderate to severe ID, severe language impairment, cleft palate, dental anomalies, and facial dysmorphism was found to have a duplication of exons 5, 6, and 7 of *SATB2* [Lieden et al., 2014].

Translocations with SATB2 disruption. Two children with de novo apparently balanced chromosomal rearrangements involving distal 2q32 were described with a combination of cleft palate, minor craniofacial and digital dysmorphisms, and delayed development, particularly of language skills [Brewer et al., 1999]. Through high-resolution mapping of the 2q breakpoints in this pair of patients, disruption of the coding region of the *SATB2* gene between exons 2 and 3 in one case (de novo 46,XY,t(2;3)(q33.1;q26.33)) and of the long-range *cis* regulatory elements located in the centromeric gene desert 3′ area near *SATB2* in the other (de novo 46,XX,t(2;11)(q32;p14)), were later documented [FitzPatrick et al., 2003; Rainger et al., 2014]. Four additional cases of *SATB2* disruption secondary to chromosomal translocations were subsequently described [Baptista et al., 2008; Tegay et al., 2009; Talkowski et al., 2012; Rainger et al., 2014]. Developmental delay with significantly compromised speech development, facial dysmorphism, and craniofacial anomalies were described in all cases while bone mineralization abnormalities were present in three patients and seizures in two more (Table I).

Point Mutations

Population data from the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/) and the Exome Aggregation Consortium (ExAC) database (http://exac.broadinstitute.org/, accessed August, 2016), does not show any loss of function type variants present in the general population. The first report of an intragenic *SATB2* point mutation came from a cohort of 59 unrelated patients with craniofacial dysmorphism, with or without intellectual disability that were screened for alterations in this gene. The only alteration in *SATB2* was documented in a 36-year-old man with a history of cleft palate, generalized osteoporosis, profound intellectual disability, epilepsy, and a jovial personality [Leoyklang et al., 2013]. The same de novo nonsense variant (c.715C>T, p.R239*) in *SATB2* identified in this patient was again

found through trio-exome sequencing in an unrelated 3-year-old girl with cleft palate, severely delayed speech development, mild hypotonia, facial dysmorphic features, and dental anomalies [Docker et al., 2014].

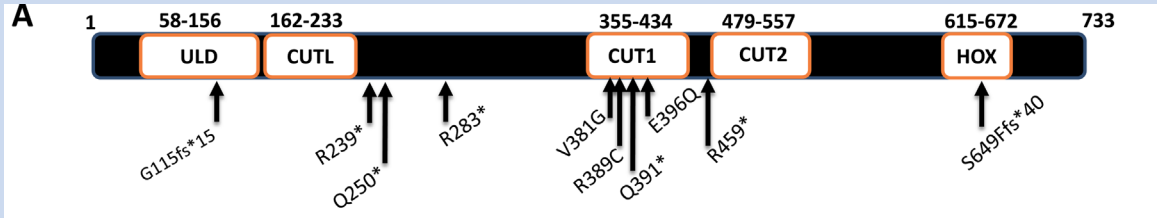
Nine additional patients with point mutations (eight de novo) in *SATB2* have been described (four nonsense, three missense, one splice site, and one frameshift) (Fig. 2). In all cases, developmental delay/ID was present, while severe compromise of verbal communication was documented in the majority (Fig. 2, Table I). Of interest, two patients (one with a de novo missense variant and the other with a de novo nonsense variant) with Rett-like phenotypes were recently described [Lee et al., 2016]. In addition to the history of developmental delay, dental anomalies, and craniofacial dysmorphism, both female patients were described to have limited purposeful hand movements with stereotyped repetitive movements, poor sleep at night, and bruxism.

SATB2 in Cancer

SATB2 is selectively expressed in glandular cells of the lower gastrointestinal tract with retained expression in the majority of primary and metastatic colorectal adenocarcinomas. This pattern of expression has contributed to the argument that SATB2 is a marker for colorectal adenocarcinomas and other hindgut well-differentiated neuroendocrine tumors [Li et al., 2015; Kim et al., 2016]. SATB2 has been shown to be highly expressed in osteosarcoma cells and has been used as a sensitive marker for this type of bone malignancy [Seong et al., 2015; Davis and Horvai, 2016]. In contrast, some reports suggest that SATB2 acts as a tumor suppressor, however no patients with documented SATB2 haploinsufficiency have been reported to have malignancies thus far [Brocato and Costa, 2015; Guo et al., 2015; Mansour et al., 2016; Wu et al., 2016]. Thus, the precise role of SATB2 in cancer remains to be fully elucidated.

CORE FEATURES OF SAS

Regardless of the underlying genetic mechanism that results in alteration of the *SATB2* gene, some clinical features have been consistently described. Developmental delay/ID is almost universally reported and frequently in the severe range. Language development is the main area of development affected and often with very limited or absent speech. Behavioral abnormalities, facial dysmorphism, cleft palate, micrognathia, dental anomalies, and musculoskeletal changes have also been reported consistently in all etiological subgroups (Table I).



B

Mutation (reference)	G115fs*15 (Zarate et al.)[a]	R239* (Ieoyklang et al.)[b]	R239* (Docker et al.)[a]	Q250* (Zarate et al.)[a]	R283* (Zarate et al.)[a]	V381G (Rauch et al.)[c]	R389C (Trakadis et al.)	Q391* (Zarate et al.)[a]	E396Q (Lee et al.)[b]	R459* (Lee et al.)[b]	S649Ffs*40 (Zarate et al.)[a]
Severe speech delay	+	+	+	+	+	+	+	+	+	+	+
Abnormalities of the palate	+	+	+	+	−	+	+	+	−	+	+
Teeth (dental) anomalies	+	+	+	+	+			+	+	+	+
Behavioral issues	+	+	+	+	−			−	+	+	+
Brain MRI Anomalies	+	−	−	−	+	+		−	+	−	+
Bone Anomalies	+	+	−	+	−			−	+	+	−

FIG. 2. A. Schematic diagram of the SATB2 protein according to Uniprot and Pfam with location of point mutations depicted with arrows. In addition to the two CUT domains (CUT1 and CUT2) and a homeodomain (HOX), the SATB, ubiquitin-like oligomerization domain (ULD) and the SATB, CUT1-like DNA-binding domain (CUTL) are depicted. B. Presence (+) or absence (−) of the main clinical features for those point mutations represented in A. Blank spaces represent no information provided for the given feature. [a]NM_001172517, accessed June 2016; [b]NM_15265, accessed June 2016; [c]NM_001172509, accessed June 2016. [Color figure can be viewed at wileyonlinelibrary.com].

DIFFERENCES AMONG PATIENTS ACCORDING TO UNDERLYING *SATB2* MECHANISM OF ALTERATION

Genitourinary anomalies such as hypospadias and inguinal hernias and cardiac defects such as atrial or ventricular septal defects have only been reported in patients with large deletions (Table I). Similarly, ectodermal changes (other than dental) seem to be particular prevalent in patients with large deletions but not with other mechanisms. In the report by Rifai et al. [2010] a 16-year-old female with a very large 2q31.2q33 deletion was described as having thin, atrophic skin and sparse, brittle, and slowly growing hair. Similar descriptions of hair sparseness and thin skin with reduced subcutaneous fat were present in a few additional cases [Van Buggenhout et al., 2005; de Ravel et al., 2009; Balasubramanian et al., 2011; Tomaszewska et al., 2013; Gregoric Kumperscak et al., 2016]. The issue of whether these ectodermal manifestations are the result of other deleted genes different than *SATB2* remains to be elucidated.

CURRENT NOMENCLATURE: SAS, GLASS SYNDROME, OR 2q32-q33/2q33.1 MICRODELETION SYNDROME?

Such as is the case for many genetic syndromes, alterations in *SATB2* have been lumped together regardless of the mechanism in the Online Mendelian Inheritance in Man (OMIM) under the eponym "Glass syndrome" (OMIM 612313). This designation was made after the 1989 report by Glass et al. [1989] of a patient with a cytogenetically visible deletion in chromosome 2q32.2q33.1. As molecular cytogenetic techniques improved and better characterization of patients with deletions in this area became possible, other terms have been used based on the cytogenetic breakpoints with descriptions such as 2q33.1 microdeletion syndrome or 2q32 deletion syndrome [de Ravel et al., 2009; Rosenfeld et al., 2009; Rifai et al., 2010]. The designation of *SATB2*-associated syndrome (SAS) was recently proposed by Docker et al. [2014] as a new clinically recognizable syndrome that should be considered in patients with ID and absent or severely impaired speech, cleft or highly arched palate, dental abnormalities, and skeletal anomalies.

Having different mechanisms that result in alterations of a given gene and a recognizable phenotype is of common occurrence in genetics (*EHMT1* and Kleefstra syndrome or *ARID1B* and Coffin–Siris syndrome, to name just a couple of examples). For *SATB2* alterations, however, the multiple designations for a fairly consistent phenotype depending on the underlying pathomechanism has created some degree of confusion particularly for families of affected patients (personal communication) so that there are even separate social media support groups, one for deletions and another for point mutations. In this review, we have documented a consistent phenotype without major differences among the different *SATB2* genetic alterations. The phenotypic differences among individuals appear to relate to differences in severity, rather than differences in the affected system, with few exceptions as mentioned above. Therefore, in an attempt to unify the nomenclature, we suggest the use of *SATB2*-associated syndrome as the preferred term.

DIAGNOSTIC EVALUATION AND HEALTH SURVEILLANCE

The use of the following acronym of major features to help recognize this syndrome is proposed: *S*, *S*evere speech anomalies; *A*, *A*bnormalities of the palate; *T*, *T*eeth anomalies; *B*, *B*ehavioral issues with or without *B*one or *B*rain MRI anomalies, and age of onset before 2 years of age (S.A.T.B.2). In agreement with the proposal by Docker et al. [2014], SAS should be considered in patients that display early neurodevelopmental delay with severely compromised or absent speech and who also have palatal and dental abnormalities. The multisystemic nature of SAS requires ongoing multisystem evaluation. While the literature on SAS continues to expand, given the spectrum of documented abnormalities thus far, we outline a proposal for initial evaluation and subsequent surveillance in Table II.

TABLE II. Suggested Evaluations and Health Surveillance/Treatment for *SATB2*-Associated Syndrome

System	Initial evaluation	Surveillance/treatment
Genetic	SATB2 sequencing with deletion/duplication analysis/ array CGH	Provide genetic counseling
Neurological	Consider brain MRI and EEG at baseline	Treat seizures if present, Neurosurgery referral if enlarged ventricles present
	Physical therapy evaluation	Physical and occupational therapies if needed
	Occupational therapy evaluation	Orthotics or mechanical aids
	Consider referral to habilitation	
Psychological/ psychiatric	Developmental evaluation	Treat behavioral issues if needed
	Neuropsychological evaluation	
Language	Speech evaluation	Aggressive speech/language therapy (3×/week)
		Augmentative and alternative communication devices
Craniofacial	Evaluate for cleft palate/submucous cleft palate	Cleft palate/submucous cleft palate repair
Gastrointestinal	Assess feeding	Special nipples/bottle for cleft palate, feeding education
Musculoskeletal	Consider osteopenia evaluation (bone density)	Optimize bone mineralization as needed
	Consider referral to orthopedics	
Dental	Dental evaluation	Dental/orthodontic management

Besides whole exome sequencing, point mutations of *SATB2* will also be detected through the currently offered next generation sequencing panels that include this gene for the evaluation of neurodevelopmental phenotypes and/or intellectual disability. The addition of *SATB2* to panels targeting craniofacial phenotypes including cleft palate could potentially help identify patients suspected to have a syndromic cause at an earlier age prior to the development of the more distinctive neurodevelopmental phenotype. Lastly, the addition of deletion and duplication analysis to the analysis of *SATB2* is recommended because of the recently reported cases with these types of alterations. From the genetics perspective, there are no reports of parental transmission for point mutations or intragenic imbalances, suggesting a highly predominant de novo nature of the SAS.

Given that the greatest impact of SAS is on the neurological system with different structural and functional abnormalities of the central nervous system, a comprehensive neurodevelopmental evaluation at diagnosis seems warranted. With the high frequency of brain neuroimaging abnormalities documented in reported cases, brain MRI should be considered as part of the evaluation process. Enlarged ventricles have been documented before in a few cases and further neurosurgical care might be needed. While clinical seizures and gait abnormalities have been documented in a relatively small proportion of cases, neurological medical management could also be required. Of interest, subclinical seizures with EEG abnormalities have been reported in some patients [Leoyklang et al., 2007; Lee et al., 2016]. Physical and occupational therapies assessment is equally indicated, with therapy provided as necessary. From the neurodevelopmental perspective, medical management of behavioral issues could be required with further psychological mental health support. Lastly, with the almost universal presence of severely affected speech, an early evaluation for speech therapy is indicated. The authors are aware of at least one patient that started Prompts for Restructuring Oral Muscular Phonetic Targets (PROMPT) and aggressive speech therapy (3×/week) at 2 years with great speech improvement over time. Equally, augmentative and alternative communication devices such as Picture Exchange Communication System (PECS) may provide additional help in the affected patients.

With the majority of patients diagnosed later in life, it is very likely that craniofacial care would have already been established to repair potential cleft palate defects. For those without an obvious palatal defect, an otolaryngology evaluation could also be necessary to diagnose a submucous-type cleft palate. Similarly, early feeding education is likely to be required with a high frequency of feeding difficulties (apparently larger than anticipated compared to patients with non-syndromic cleft palate). The high frequency and the broad spectrum of dental anomalies that start with primary dentition are also likely to need early assessment and management.

Finally, while the overall frequency of musculoskeletal abnormalities does not appear to be very high, we call special attention to the relatively higher incidence of documented osteopenia and/or osteoporosis. While numbers are still very limited, this type of bone health abnormality appears to be particularly common in patients with point mutations. Based on the current information available evaluation for such problems especially in late childhood should be considered.

In summary, SAS is a relatively recently described syndrome caused by alterations in the *SATB2* gene. Animal models have documented the role of this gene in craniofacial, bone, and brain development, organs that have been noticed to be affected in humans with alterations in this gene. The use of the acronym S.A.T.B.2 (*S*, *S*evere speech anomalies; *A*, *A*bnormalities of the palate; *T*, *T*eeth anomalies; *B*, *B*ehavioral issues with or without *B*one or *B*rain MRI anomalies, and age of onset before 2 years of age) should help identify patients affected with SAS that do not get diagnosed through expanded next generation sequencing panels and/or whole exome sequencing. Because there are still relatively few patients that have received this diagnosis and with many questions that remain unanswered, we have started a SAS patient database. Any clinician or laboratory specialist with knowledge of a patient with a *SATB2* mutation is encouraged to visit a dedicated website for this syndrome www.SATB2gene.com. Similarly, parents and caregivers will be able to visit the website for further information and resources.

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