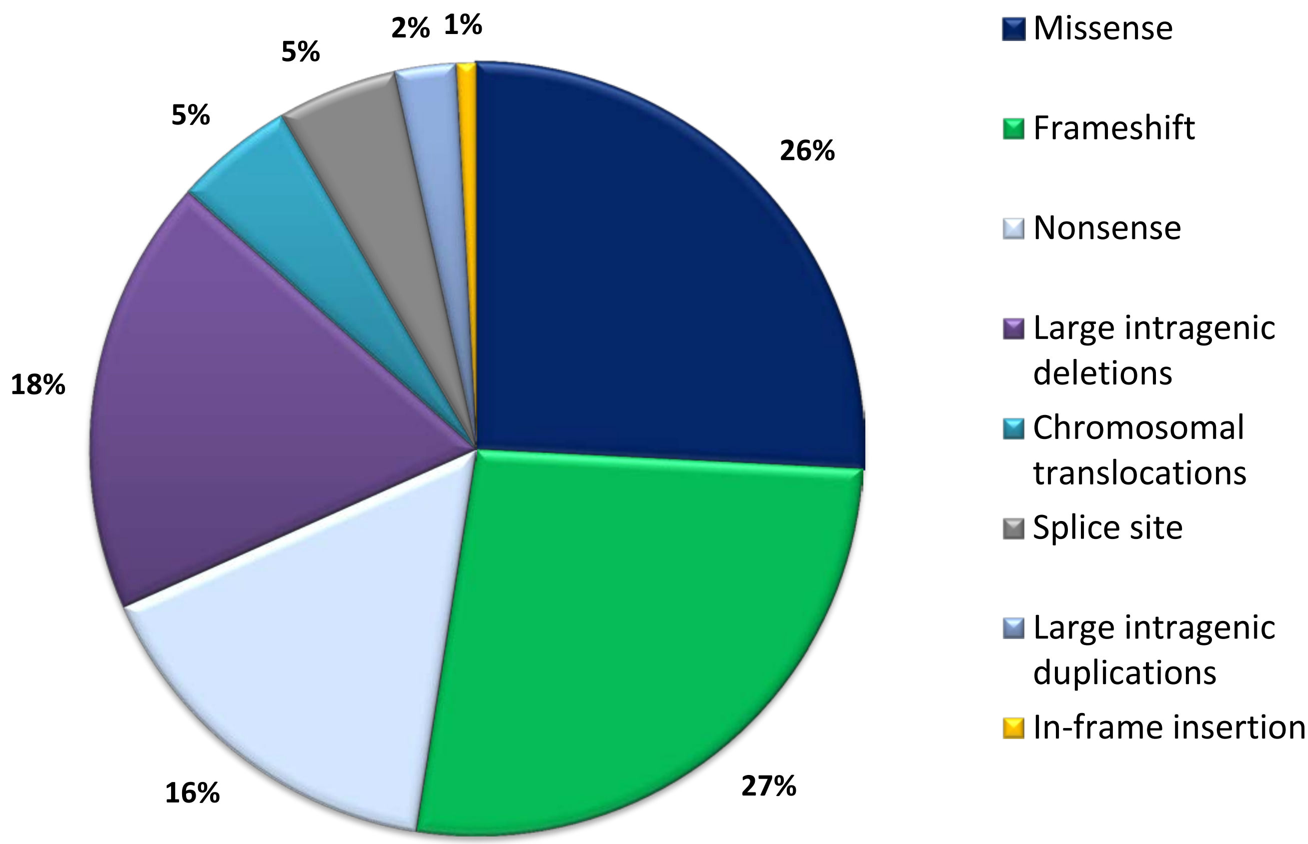
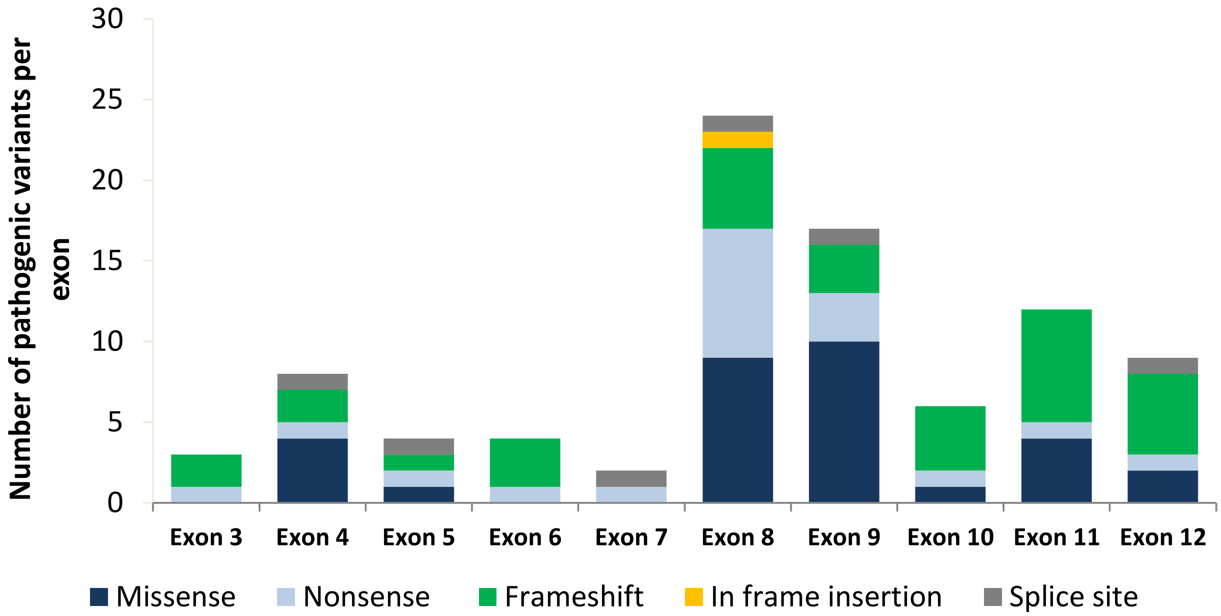
Supplementary Figure S1. Distribution of the 118 unique *SATB2* pathogenic variants

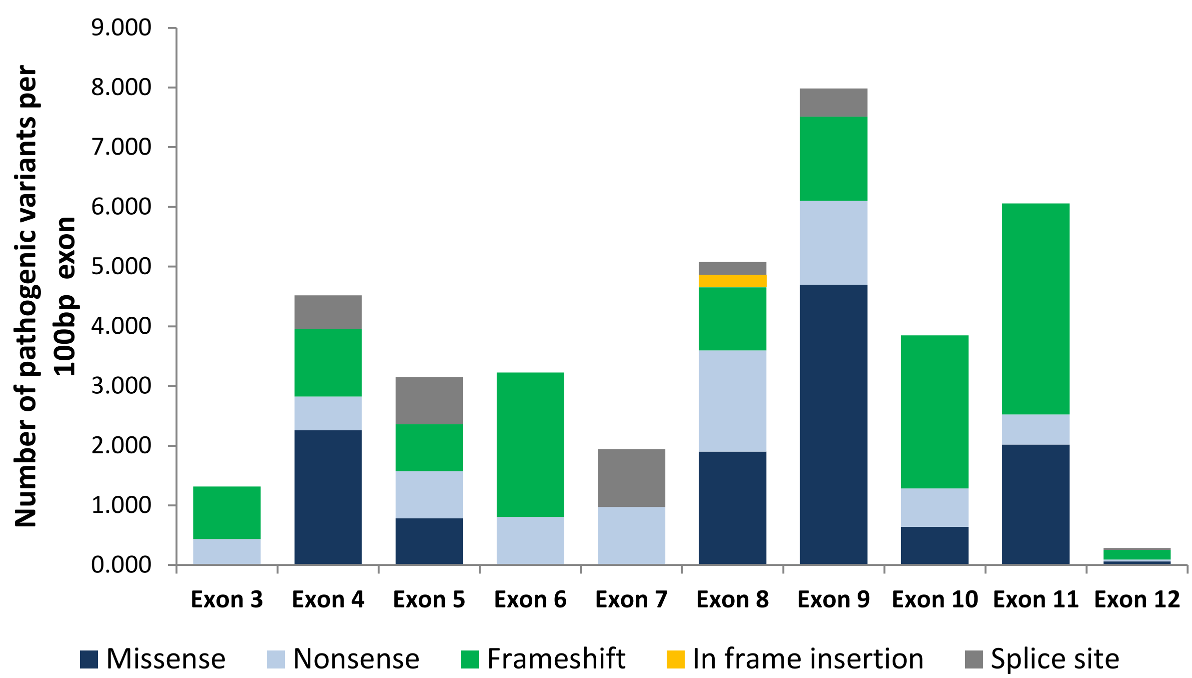


Supplementary Figure S2. A) Frequency distribution of 89 *SATB2* point pathogenic variants per exon. B) Frequency of *SATB2* point pathogenic variants normalized to the length of each exon per 100bp

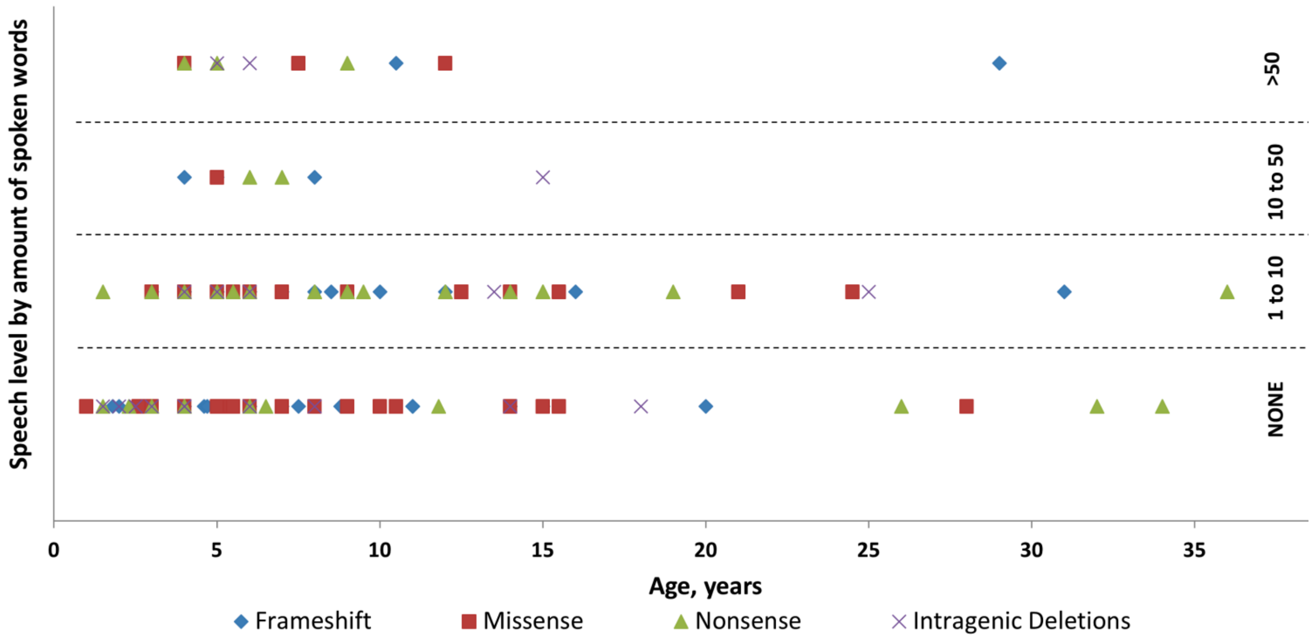
A.



B.



Supplementary Figure S3. Severity of speech delay as determined by current number of spoken words according to molecular mechanisms and age at assessment.



Supplementary Table S1. *In silico* predictions supporting evidence of pathogenicity for 11 novel missense variants reported in 12 individuals included in this manuscript. Variants were determined to be *de novo* in all 12 cases. Numbering is according to the cDNA (NM_015265.3).

Record ID	coding	protein	Number of individuals with missense variants at position	Genomic	Frequency (gnomAD)	SIFT (score)	Polyphen 2 (score)	PROVEAN (score)	CADD score	Mutation taster (p-value)	GERP	Variant interpretation
SATB2-136	c.257T>G	p.Leu86Arg	1	chr2:200298150A>C	0	Deleterious (0.011)	Probably damaging (0.983)	Deleterious (-4.96)	29.6	Disease causing (1)	Conserved	Likely pathogenic
SATB2-68	c.760C>T	p.His254Tyr	1	chr2:200213837G>A	0	Deleterious (0.001)	Probably damaging (1)	Deleterious (-2.63)	23.1	Disease causing (1)	Conserved	Likely pathogenic
SATB2-133	c.1102G>T	p.Val368Phe	1	chr2:200213495C>A	0	Deleterious (0)	Probably damaging (1)	Deleterious (-2.69)	29.2	Disease causing (1)	Conserved	Likely pathogenic
SATB2-131	c.1136A>C	p.Gln379Pro	1	chr2:200213461T>G	0	Deleterious (0.002)	Probably damaging (1)	Deleterious (-2.74)	26.3	Disease causing (1)	Conserved	Likely pathogenic
SATB2-112	c.1175G>A	p.Gly392Glu	2	chr2:200193632C>T	0	Deleterious (0.003)	Probably damaging (1)	Deleterious (-4.64)	28.5	Disease causing (1)	Conserved	Likely pathogenic
SATB2-129	c.1196G>T	p.Arg399Leu	7	chr2:200193611C>A	0	Deleterious (0)	Probably damaging (1)	Deleterious (-3.21)	34.0	Disease causing (1)	Conserved	Likely pathogenic
SATB2-96	c.1253T>G	p.Met418Arg	1	chr2:200193554A>C	0	Deleterious (0)	Probably damaging (0.998)	Deleterious (-3.14)	27.0	Disease causing (1)	Conserved	Likely pathogenic
SATB2-111	c.1541A>G	p.Gln514Arg	1	chr2:200188527T>C	0	Deleterious (0)	Probably damaging (0.998)	Tolerable (-2.02)	25.0	Disease causing (1)	Conserved	Likely pathogenic
SATB2-109	c.1554T>G	p.Cys518Trp	1	chr2:200173669A>C	0	Deleterious (0)	Probably damaging (1)	Deleterious (-5.98)	24.7	Disease causing (1)	Non Conserved	Likely pathogenic
SATB2-101	c.1564C>T	p.Arg522Cys	1	chr2:200173659G>A	0	Deleterious (0)	Probably damaging (1)	Deleterious (-4.19)	35.0	Disease causing (1)	Conserved	Likely pathogenic
SATB2-116	c.1903G>T	p.Asp635Tyr	1	chr2:200137233C>A	0	Deleterious (0)	Probably damaging (1)	Deleterious (-5.03)	29.3	Disease causing (1)	Conserved	Likely pathogenic

gnomAD browser (v2.1.1): https://gnomad.broadinstitute.org/gene/ENSG00000119042
SIFT (v6.2.1): https://sift.bii.a-star.edu.sg/. SIFT score ranges from 0.0 (deleterious) to 1.0 (tolerated) with scores from 0.0 to 0.05 considered deleterious.
Polyphen2 (v2.2): http://genetics.bwh.harvard.edu/pph2/. A prediction of probably damaging means that the query substitution is predicted to be damaging with high confidence
PROVEAN (v1.1.3): http://provean.jcvi.org/index.php. Score threshold is set at -2.5 for binary classification (i.e. deleterious vs neutral)
CADD: https://cadd.gs.washington.edu/. A scaled CADD score of 20 means that a variant is amongst the top 1% of deleterious variants in the human genome and of 30 means that the variant is in the top 0.1%
Mutation taster: http://www.mutationtaster.org/. The probability value is the probability of the prediction, a value close to 1 indicates a high 'security' of the prediction
GERP: http://mendel.stanford.edu/SidowLab/downloads/gerp/index.html. GERP++ is a position-specific estimate of evolutionary constraint using maximum likelihood evolutionary rate estimation compared to 35 other mammalian species

Supplementary Table S2. Detailed clinical information from 158 individuals with *SATB2*-associated syndrome previously reported and from this report

	Record ID	Age (years)	Gender	coding/exonic abnormality	Origin	Developmental delay/Intellectual disability	Cleft palate	Low Bone mineral density	Abnormal Neuroimaging	Age at walking (months)	Age at first word (months)	Current speech (# of words)	Dental issues	Clinical seizures	Growth Retardation past or present	Feeding difficulties during infancy	Reference
Frameshift	SATB2-130	4	Female	c.9_16delGCGGAGCG	de novo	Yes	Yes	N/A	No	20	9	10 to 50	Yes	No	No	Yes	This study
	SATB2-88	29	Female	c.19dupA	de novo	Yes	Yes	N/A	No	12	N/A	Greater than 50	Yes	No	No	Yes	This study
	SATB2-142	8	Female	c.245_263del	de novo	Yes	No	N/A	Yes	15	36	10 to 50	Yes	No	No	Yes	This study
	SATB2-90	5	Male	c.334delG	de novo	Yes	Yes	N/A	No	25	20	1 to 10	Yes	No	Yes	Yes	This study
	SATB2-05	5	Female	c.400delG	de novo	Yes	No	N/A	No	22	42	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-28	11	Male	c.482delA	de novo	Yes	Yes	N/A	Yes	20	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-16	6	Male	c.583dupT	de novo	Yes	Yes	Yes	N/A	35	N/A	None	Yes	No	Yes	Yes	Zarate et al., 2018a; Bengani et al.
	SATB2-73	4.6	Male	c.594_595delCC	de novo	Yes	Yes	N/A	N/A	21	N/A	None	Yes	No	No	N/A	Bengani et al.
	SATB2-65	12	Female	c.808_809delCA	de novo	Yes	Yes	No	N/A	15	36	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a; Scott et al.
	SATB2-10	14	Male	c.816delT	de novo	Yes	No	Yes	Yes	22	13	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-123	3	Male	c.832delC	unknown	Yes	Yes	N/A	N/A	19	24	1 to 10	Yes	No	No	Yes	This study
	SATB2-46	10	Female	c.1131_1132delGT	unknown	Yes	No	Yes	No	16	24	1 to 10	Yes	Yes	No	No	Zarate et al., 2018a
	SATB2-119	4	Female	c.1132_1133insAC	de novo	Yes	No	N/A	N/A	18	36	1 to 10	Yes	No	No	Yes	This study
	SATB2-98	8.5	Female	c.1196delG	de novo	Yes	No	N/A	N/A	24	48	1 to 10	Yes	Yes	No	Yes	This study
	279803	7	Male	c.1203dupA	de novo	Yes	No	N/A	No	24	N/A	1 to 10	Yes	Yes	No	N/A	Bengani et al.
	SATB2-48	2	Male	c.1311_1314dupGGAG	unknown	Yes	No	N/A	No	30	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a
	Patient 3	16	Male	c.1478_1479delAG	de novo	Yes	Yes	N/A	N/A	N/A	N/A	1 to 10	Yes	N/A	N/A	N/A	Kikuiri et al.
	SATB2-135	5	Male	c.1498delG Mosaic	de novo	Yes	No	N/A	N/A	17	16	10 to 50	Yes	No	No	Yes	This Study

	SATB2-103	10.5	Female	c.1511_1512insCAAGCCT	de novo	Yes	Yes	N/A	Yes	17	24	Greater than 50	Yes	No	No	Yes	This study
	SATB2-79	20	Male	c.1515delT	de novo	Yes	No	No	Yes	30	N/A	None	Yes	No	Yes	Yes	Zarate et al., 2018a; Scott et al.
	262560	8.8	Female	c.1574delA	de novo	Yes	No	N/A	N/A	17	N/A	None	Yes	No	No	N/A	Bengani et al.
	SATB2-75	6	Female	c.1592dupA	unknown	Yes	Yes	Yes	No	27	28	1 to 10	Yes	Yes	No	Yes	Zarate et al., 2018a
	#28	9	Male	c.1627delC	de novo	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Cherot et al.
	SATB2-120	11	Male	c.1639_1642delinsTTT	de novo	Yes	Yes	Yes	Yes	24	N/A	None	Yes	No	No	Yes	This study
	265038	4.7	Male	c.1645delC	de novo	Yes	Yes	N/A	N/A	30	N/A	None	No	No	No	N/A	Bengani et al.
	SATB2-81	7.5	Male	c.1657delG	unknown	Yes	Yes	N/A	Yes	28	N/A	None	Yes	No	No	Yes	This study
	SATB2-07	7	Male	c.1728delT	unknown	Yes	No	N/A	Yes	26	14	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-03	8	Male	c.1945dupT	de novo	Yes	Yes	N/A	Yes	48	N/A	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-43	1.8	Male	c.1972_1973delAC	de novo	Yes	Yes	N/A	No	N/A	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-67	31	Male	c.2005dupC	de novo	Yes	Yes	Yes	N/A	36	42	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a
	N/A	15	Male	c.2018dupA	de novo	Yes	Yes	Yes	Yes	18	N/A	None	N/A	No	Yes	Yes	Boone et al.
	SATB2-26	4	Male	c.2028delG	de novo	Yes	No	N/A	Yes	30	19	None	Yes	No	Yes	Yes	Zarate et al., 2018a
Missense	SATB2-57	3	Female	c.185T>A	de novo	Yes	No	N/A	N/A	19	24	1 to 10	Yes	No	No	No	Zarate et al., 2018a
	SATB2-136	4	Male	c.257T>G	unknown	Yes	No	N/A	No	13	10	Greater than 50	Yes	No	No	Yes	This Study
	SATB2-51	12	Female	c.287T>G	de novo	Yes	No	N/A	No	19	14	Greater than 50	Yes	No	No	No	Zarate et al., 2018a
	SATB2-01	3	Female	c.346G>C	de novo	Yes	No	N/A	Yes	21	16	1 to 10	Yes	No	Yes	Yes	Zarate et al., 2018a
	SATB2-54	5	Male	c.392T>A	de novo	Yes	Yes	N/A	No	26	22	1 to 10	Yes	No	Yes	Yes	Zarate et al., 2018a
	SATB2-68	9	Male	c.760C>T	de novo	Yes	No	No	Yes	60	N/A	None	Yes	Yes	Yes	Yes	This study
	N/A	12	N/A	c.983C>A	de novo	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Farwell et al.
	SATB2-133	15.5	Male	c.1102G>T	de novo	Yes	No	N/A	N/A	14	N/A	1 to 10	Yes	No	No	No	This study
	SATB2-131	15.5	Male	c.1136A>C	de novo	Yes	No	Yes	Yes	15	N/A	None	Yes	Yes	No	Yes	This study
	ER52725	2.7	Female	c.1142T>G	de novo	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Rauch et al.
	SATB2-31	14	Male	c.1157C>T	de novo	Yes	No	N/A	N/A	31	30	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a; Bengani et al.
	SATB2-41	4	Female	c.1165C>T	de novo	Yes	No	N/A	Yes	19	24	1 to 10	Yes	No	No	No	Zarate et al., 2018a
	SATB2-42	7	Male	c.1165C>T	de novo	Yes	Yes	N/A	Yes	15	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2	4	Fem	c.1165C>T	de novo	Yes	No	N/A	No	24	N/A	None	Yes	No	No	No	Zarate et al., 2018a

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SATB2-84	10.5	Female	c.1165C>T	de novo	Yes	Yes	N/A	Yes	19	N/A	None	Yes	No	Yes	Yes	This study
SATB2-122	10	Female	c.1165C>T	de novo	Yes	No	N/A	No	29	N/A	None	Yes	Yes	Yes	No	This study
SATB2-100	28	Female	c.1165C>T	de novo	Yes	No	Yes	No	24	N/A	None	Yes	Yes	No	No	This study
SATB2-132	4	Male	c.1165C>T	de novo	Yes	No	N/A	No	24	N/A	None	Yes	No	No	Yes	This study
SATB2-138	5.5	Female	c.1165C>T	de novo	Yes	Yes	N/A	No	23	48	1 to 10	Yes	No	Yes	Yes	This Study
N/A	3	Male	c.1165C>T	de novo	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Trakadis et al.
271044	2.6	Female	c.1165C>T	de novo	Yes	Yes	N/A	No	24	N/A	None	N/A	No	No	N/A	Bengani et al.
SATB2-104	21	Male	c.1166G>T	de novo	Yes	No	N/A	Yes	27	45	1 to 10	Yes	No	Yes	Yes	This study
261355	10.5	Male	c.1166G>T	de novo	Yes	Yes	N/A	N/A	30	N/A	None	Yes	No	No	N/A	Bengani et al.
SATB2-58	24.5	Male	c.1169C>T	de novo	Yes	No	Yes	N/A	30	10	1 to 10	Yes	No	No	No	Zarate et al., 2018a
SATB2-110	7	Male	c.1169C>T	de novo	Yes	No	N/A	Yes	30	N/A	None	Yes	No	Yes	Yes	This study
SATB2-35	9	Female	c.1174G>C	unknown	Yes	No	Yes	Yes	N/A	144	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a
SATB2-112	6	Male	c.1175G>A	de novo	Yes	No	Yes	No	46	N/A	None	Yes	Yes	Yes	Yes	This study
263440	5.3	Female	c.1181T>C	de novo	Yes	Yes	N/A	N/A	22	N/A	None	N/A	No	No	N/A	Bengani et al.
Case 1	3	Female	c.1186G>C	de novo	Yes	No	Yes	Yes	N/A	N/A	None	Yes	No	No	No	Lee et al.
SATB2-36	14	Female	c.1196G>C	unknown	Yes	Yes	Yes	No	36	N/A	None	Yes	No	No	No	Zarate et al., 2018a
SATB2-53	7.5	Male	c.1196G>A	de novo	Yes	No	N/A	Yes	22	5	Greater than 50	Yes	Yes	Yes	No	Zarate et al., 2018a; Scott et al.
SATB2-94	12.5	Male	c.1196G>A	de novo	Yes	No	N/A	No	16	36	1 to 10	Yes	Yes	Yes	Yes	This study
SATB2-134	4	Female	c.1196G>A	unknown	Yes	No	N/A	No	24	24	1 to 10	Yes	Yes	No	Yes	This study
259950	5.5	Male	c.1196G>A	de novo	Yes	No	N/A	N/A	18	N/A	None	N/A	No	No	N/A	Bengani et al.
SATB2-125	6	Male	c.1196G>T	de novo	Yes	No	N/A	No	28	N/A	None	Yes	No	Yes	Yes	This study
SATB2-129	5.5	Female	c.1196G>T	de novo	Yes	No	N/A	Yes	24	N/A	None	Yes	No	No	Yes	This study
SATB2-47	7	Male	c.1204G>A	de novo	Yes	No	N/A	Yes	N/A	48	1 to 10	No	No	Yes	Yes	Zarate et al., 2018a; Bengani et al.
SATB2-96	12.5	Male	c.1253T>G	de novo	Yes	No	Yes	No	30	60	1 to 10	yes	No	No	No	This study
SATB2-14	15	Male	c.1286 G>A	de novo	Yes	No	N/A	No	22	N/A	None	Yes	Yes	Yes	Yes	Zarate et al., 2018a
SATB2-23	3	Male	c.1286 G>A	de novo	Yes	No	N/A	Yes	20	N/A	None	Yes	Yes	No	No	Zarate et al., 2018a
SATB2	5	Fem	c.1286G>A	de novo	Yes	No	Yes	No	24	16	None	Yes	No	No	Yes	Zarate et al., 2018a

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	SATB2-105	12.5	Female	c.1286G>A	unknown	Yes	No	No	Yes	21	N/A	1 to 10	Yes	Yes	No	No	This study
	SATB2-111	1	Female	c.1541A>G	de novo	Yes	No	N/A	Yes	N/A	N/A	None	N/A	No	Yes	Yes	This study
	262240	5.5	Male	c.1543G>A	de novo	Yes	No	N/A	No	48	N/A	None	N/A	Yes	Yes	N/A	Bengani et al.
	SATB2-109	5	Male	c.1554T>G	de novo	Yes	No	N/A	No	30	30	10 to 50	Yes	Yes	Yes	No	This study
	SATB2-101	4	Female	c.1564C>T	de novo	Yes	No	N/A	No	15	N/A	Greater than 50	Yes	No	No	Yes	This study
	264840	1.5	Female	c.1696G>A	de novo	Yes	No	N/A	N/A	N/A	N/A	N/A	N/A	No	No	N/A	Bengani et al.
	SATB2-116	6	Male	c.1903G>T	de novo	Yes	No	No	Yes	20	14	1 to 10	Yes	Yes	No	No	This study
	SATB2-18	8	Female	c.1964C>T	de novo	Yes	No	N/A	No	18	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a
Nonsense	SATB2-24	7	Female	c.124G>T	de novo	Yes	No	Yes	Yes	14	N/A	10 to 50	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-39	9	Male	c.346G>T	de novo	Yes	Yes	Yes	Yes	15	N/A	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a; Scott et al.
	SATB2-27	9	Female	c.390T>A	unknown	Yes	No	N/A	No	60	96	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a; Bengani et al.
	SATB2-55	34	Male	c.505C>T	de novo	Yes	No	N/A	N/A	42	48	None	Yes	No	Yes	Yes	Zarate et al., 2018a
	#62	N/A	N/A	c.688A>T	de novo	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Vissers et al.
	SATB2-33	6.5	Female	c.715C>T	unknown	Yes	Yes	Yes	No	22	18	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-76	3	Male	c.715C>T	unknown	Yes	Yes	No	N/A	19	18	1 to 10	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-114	5	Male	c.715C>T	de novo	Yes	No	N/A	Yes	N/A	N/A	1 to 10	Yes	No	No	Yes	This study
	SATB2-139	3	Male	c.715C>T	unknown	Yes	Yes	N/A	N/A	32	N/A	None	Yes	No	No	Yes	This Study
	SATB2-121	9.5	Male	c.715C>T	unknown	Yes	Yes	No	No	28	48	1 to 10	Yes	Yes	No	Yes	This Study
	N/A	36	Male	c.715C>T	de novo	Yes	Yes	Yes	No	N/A	N/A	1 to 10	Yes	Yes	Yes	No	Leoykland e tal.
	Patient 3	32	Male	c.748C>T	de novo	Yes	Yes	Yes	No	N/A	N/A	None	Yes	Yes	No	No	Zarate et al., 2015
	SATB2-117	12	Male	c.847C>T	de novo	Yes	No	Yes	Yes	38	48	1 to 10	Yes	No	Yes	Yes	This study
	SATB2-04	4	Male	c.847C>T	de novo	Yes	No	N/A	N/A	11	14	Greater than 50	Yes	No	No	Yes	Zarate et al., 2018a; Scott et al.
	SATB2-89	1.5	Female	c.847C>T	de novo	Yes	No	N/A	Yes	N/A	20	1 to 10	Yes	No	Yes	No	This study
	Patient 5	4	Male	c.847C>T	de novo	Yes	No	N/A	Yes	21	N/A	None	Yes	No	No	No	Zarate et al., 2018a
	N/A	N/A	N/A	c.847C>T	unknown	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Farwell et al.
	Patient 2	19	Female	c.847C>T	de novo	Yes	Yes	N/A	N/A	N/A	N/A	1 to 10	yes	N/A	N/A	N/A	Kikuiri et al.
	SATB2-83	6	Female	c.868C>T	de novo	Yes	Yes	No	Yes	N/A	N/A	1 to 10	Yes	No	No	Yes	This study

	SATB2-91	26	Male	c.868C>T	unknown	Yes	Yes	N/A	Yes	30	N/A	None	Yes	No	Yes	Yes	This study
	SATB2-127	8	Female	c.988C>T	de novo	Yes	No	N/A	No	22	60	1 to 10	Yes	No	Yes	Yes	This study
	SATB2-97	5.5	Female	c.997C>T	de novo	Yes	No	N/A	Yes	18	13	1 to 10	Yes	No	No	No	This study
	SATB2-106	4	Male	c.1135C>T	de novo	Yes	Yes	N/A	No	27	N/A	1 to 10	Yes	No	No	Yes	This study
	SATB2-20	6	Male	c.1171C>T	de novo	Yes	Yes	N/A	No	24	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a; Scott et al.
	SATB2-06	8	Male	c.1255C>T	de novo	Yes	Yes	Yes	Yes	20	N/A	1 to 10	Yes	No	Yes	Yes	Zarate et al., 2018a; Scott et al.
	SATB2-108	14	Male	c.1285C>T	de novo	Yes	No	N/A	No	18	N/A	1 to 10	Yes	No	Yes	Yes	This study
	SATB2-29	1.5	Male	c.1285C>T	de novo	Yes	No	N/A	No	N/A	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a; Scott et al.
	Case 8 AN	N/A	Female	c.1285C>T	de novo	Yes	Yes	N/A	No	20	N/A	1 to 10	Yes	No	No	N/A	Bengani et al.
	N/A	2.3	Male	c.1285C>T	de novo	Yes	Yes	N/A	Yes	N/A	N/A	None	Yes	No	No	No	Lv et al.
	259030	11.8	Male	c.1375C>T	de novo	Yes	Yes	N/A	N/A	30	N/A	None	Yes	No	No	N/A	Bengani et al.
	SATB2-59	15	Male	c.1375C>T	de novo	Yes	Yes	N/A	No	22	22	1 to 10	Yes	No	No	No	Zarate et al., 2018a
	SATB2-60	15	Male	c.1375C>T	de novo	Yes	Yes	N/A	No	22	21	1 to 10	Yes	No	No	No	Zarate et al., 2018a
	SATB2-124	12	Female	c.1375C>T	de novo	Yes	Yes	N/A	No	30	36	1 to 10	Yes	No	No	No	This study
	SATB2-69	6	Male	c.1375C>T	unknown	Yes	No	Yes	N/A	11	19	10 to 50	Yes	No	Yes	Yes	Zarate et al., 2018a; Scott et al.
	Case 2	4	Female	c.1375C>T	de novo	Yes	Yes	N/A	No	N/A	N/A	None	Yes	No	No	No	Lee et al.
	SATB2-38	5	Female	c.1495A>T	de novo	Yes	No	No	Yes	16	32	Greater than 50	Yes	No	No	No	Zarate et al., 2018a; Scott et al.
	SATB2-137	9	Male	c.1756C>T	unknown	Yes	No	No	No	36	48	Greater than 50	Yes	No	Yes	Yes	This Study
	Case 14	N/A	N/A	c.2074G>T	de novo	Yes	No	N/A	No	60	N/A	None	Yes	No	No	N/A	Bengani et al.
In frame insertion	25	N/A	N/A	c.929_930insTTGTAAGGCAAC	de novo	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Gilissen et al.
splice site	Patient 1	7	Male	c.346+2T>G	de novo	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes	Yes	Yes	No	Zarate et al., 2015
	SATB2-95	4	Male	c.473+1delG	unknown	Yes	No	N/A	No	24	N/A	None	Yes	No	No	No	This study
	SATB2-86	21	Male	c.598-2A>G	germline	Yes	No	N/A	N/A	36	N/A	None	Yes	No	Yes	Yes	Bengani, This study
	SATB2-87	17.5	Male	c.598-2A>G	germline	Yes	No	N/A	Yes	12	50	Greater than 50	Yes	No	No	No	Bengani, This study
	260175	4.3	Male	c.1173+2T>C	de novo	Yes	Yes	N/A	No	16	N/A	None	Yes	No	No	N/A	Bengani et al.
	SATB2-34	12	Female	c.1174-2A>G	de novo	Yes	No	N/A	No	23	60	1 to 10	Yes	Yes	Yes	Yes	Zarate et al., 2018a; Scott et al.
	Patient 1	19	Female	c.1741-1G>A	de novo	Yes	Yes	N/A	N/A	N/A	N/A	1 to 10	Yes	N/A	N/A	N/A	Kikuiri et al.

Intragenic Deletions	SATB2-02	6	Female	Exons 1-8	presumed germline	Yes	No	Yes	No	21	27	Greater than 50	Yes	Yes	No	Yes	Zarate et al., 2018a; Scott et al.
	SATB2-08	2	Female	Exons 9-10	unknown	Yes	Yes	N/A	N/A	N/A	N/A	None	Yes	No	No	Yes	Zarate et al., 2018a
	SATB2-22	14	Female	Exons 1-11	unknown	Yes	No	Yes	No	22	N/A	None	Yes	No	Yes	Yes	Zarate et al., 2018a
	SATB2-25	4	Female	Exons 5-12	de novo	Yes	Yes	N/A	N/A	23	N/A	None	Yes	No	Yes	No	Zarate et al., 2018a
	SATB2-49	18	Male	Exon 9	unknown	Yes	Yes	N/A	Yes	144	N/A	None	Yes	Yes	Yes	Yes	Zarate et al., 2018a
	SATB2-52	8	Male	Exons 2-4	de novo	Yes	No	N/A	No	18	N/A	None	Yes	No	No	No	Zarate et al., 2018a
	SATB2-64	25	Male	Exons 5-8	unknown	Yes	Yes	Yes	No	12	N/A	1 to 10	Yes	No	Yes	Yes	Zarate et al., 2018a
	SATB2-78	5	Female	Exon 4	unknown	Yes	No	N/A	No	15	12	Greater than 50	Yes	No	No	No	Zarate et al., 2018a
	SATB2-80	1.5	Female	Exons 4-8	unknown	Yes	No	N/A	N/A	N/A	N/A	None	Yes	No	No	No	This study
	SATB2-82	4	Male	Exons 8-9	unknown	Yes	Yes	Yes	N/A	15	36	1 to 10	Yes	No	Yes	Yes	This study
	SATB2-92	6	Male	Exon 7	unknown	Yes	No	N/A	Yes	20	36	1 to 10	Yes	Yes	No	Yes	This study
	SATB2-126	15	Male	Exons 1-12	de novo	Yes	No	No	N/A	24	N/A	10 to 50 words	Yes	No	No	No	This study
	SATB2-115	2.5	Female	Exons 7-8	de novo	Yes	Yes	N/A	Yes	N/A	N/A	None	Yes	No	Yes	Yes	This study
	SATB2-102	4	Male	Exons 7-8	de novo	Yes	Yes	N/A	Yes	N/A	N/A	None	Yes	No	Yes	Yes	This study
	SATB2-128	0.5	Female	Exons 4-8	presumed germline	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	No	No	No	This study
	SATB2-107	5	Female	Exon 5	de novo	Yes	Yes	No	N/A	18	N/A	1 to 10	Yes	No	No	No	This study
	SATB2-113	2.5	Male	Exons 1-4	unknown	Yes	No	N/A	N/A	20	N/A	None	N/A	No	No	No	This study
	SATB2-140	13.5	Male	Exon 9	de novo	Yes	Yes	N/A	No	23	N/A	1 to 10	Yes	Yes	No	Yes	This study
	Patient 5	3	Male	Exons 9-11	unknown	Yes	Yes	N/A	N/A	24	N/A	None	N/A	No	No	Yes	Balasubramanian et al.
	Subject 1	9.5	Female	Exons 4-12	unknown	Yes	No	N/A	No	N/A	N/A	N/A	Yes	No	No	No	Rosenfeld et al.
	Subject 2	21	Male	Exons 3-11	unknown	Yes	Yes	N/A	N/A	30	N/A	N/A	Yes	No	No	Yes	Rosenfeld et al.
	Subject 3	6	Female	Exons 1-11	unknown	Yes	No	N/A	N/A	N/A	N/A	None	N/A	No	No	No	Rosenfeld et al.
Intragenic Duplications	70886	4	Male	Exon 4	de novo	Yes	Yes	N/A	N/A	18	N/A	1 to 10	Yes	N/A	N/A	Yes	Asadollahi et al.
	N/A	10	Female	Exon 4	de novo	Yes	No	N/A	Yes	N/A	N/A	1 to 10	Yes	No	No	Yes	Kaiser et al.
	N/A	20	Male	Exons 5-7	de novo	Yes	Yes	Yes	No	N/A	N/A	1 to 10	Yes	N/A	N/A	N/A	Lieden et al.
Translocation	Case 1	24	Female	c.?	de novo	Yes	Yes	No	Yes	24	N/A	N/A	Yes	No	No	Yes	Rainger et al.
	Case 2	33	Male	c.?	de novo	Yes	Yes	Yes	N/A	60	N/A	None	Yes	N/A	N/A	Yes	Rainger et al.

Case 1	13	Female	c.?	de novo	Yes	Yes	N/a	N/A	24	N/A	N/A	N/A	N/A	No	N/A	Brewer et al.
N/A	0.1	Male	c.?	de novo	Yes	No	Yes	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	Tegay et al.
Case 49	21	N/A	c.?	de novo	Yes	Yes	N/A	N/A	N/A	N/A	None	N/A	N/A	N/A	N/A	Baptista et al.
DGAP211	N/A	Male	c.?	de novo	Yes	N/A	Yes	N/A	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Talkowski et al.

†Individual SATB2-111 was found to have multiple fractures (femur and ribs) and leg bowing at 5 months of age. DXA scan at that age revealed a low bone mineral density (BMD) of -2SD. Given the lack of normal control data available for this age group, the presence of low BMD is marked as N/A

Supplementary Table S3. Genotype-phenotype correlations according to underlying molecular mechanism of disease.†

CLINICAL FEATURE	Missense	Nonsense	Frameshift	Intragenic deletions	Splicing	Translocations
Cleft palate	11/49 (22.4%)**	21/37 (56.8%)	18/31 (58.1%)	11/22 (50.0%)	3/7 (42.9%)	4/5 (80.0%)
Abnormal Brain Neuroimaging	18/39 (46.2%)	12/29 (41.4%)	11/20 (55.0%)	4/11 (36.4%)	2/5 (40.0%)	2/2 (100%)
Low bone mineral density	9/12 (75.0%)	8/13 (61.5%)	7/9 (77.8%)	4/6 (66.7%)	1/1 (100%)	3/4 (75.0%)
Feeding difficulties	24/40 (60.0%)	21/32 (65.6%)	25/26 (96.2%)**	12/22 (54.5%)	2/5 (40.0%)	3/3 (100%)
Growth retardation	17/46 (37.0%)	10/35 (28.6%)	5/30 (16.7%)	7/22 (31.8%)	3/6 (50.0%)	2/4 (50.0%)
Seizures	14/46 (30.4%)*	3/35 (8.6%)*	4/30 (13.3%)	4/22 (18.2)	2/6 (33.3%)	2/3 (66.7%)
NEURODEVELOPEMENTAL						
Average age at walking in months [range] (n with data)	24.9 [13-60] (41)	26.2 [11-60] (27)	23.7[12-48] (29)	28.6 [12-144] (15)	22.2 [12-36] (5)	36 [24-60] (3)
Average age at 1st word in months [range] (n with data)	32.6 [5-144] (20)	35.1[[13-96] (16)	26.9[[9-48] (16)	27.8 [12-36] (4)	55 [50-60] (2)	N/A
Individuals older than 4 years with absent verbal words	20/39 (51.3%)*	8/29 (27.6%)	12/28 (42.9%)	6/14 (42.9%)	3/6 (50.0%)	2/2 (100%)

†Each molecular mechanism group was compared to all other mechanisms using either Chi-square or Fisher's exact tests (when at least one cell had an expected count of less than 5) for categorical variables, and t-tests for continuous variables.

*p<0.05

**p<0.001