SUPPLEMENTARY DATA

Isolated NIBPL missense mutations that cause Cornelia de Lange syndrome alter MAU2 interaction.

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Table S1: MAU2 polymorphisms identified

Gene	Nucleotide Change	Amino Acid Change	Location	refSNP ID	Alleles Identified	Allele Frequency
MAU2	c.9_23del	p.Gln4_Ala8del	Exon 1		2/368	0.005
MAU2	c.301+19G>T		Intron 1	rs12460764	40/368	0.109
MAU2	c.339G>A		Exon 3	rs769267	241/368	0.655
MAU2	c. 1200G>C	synonymous	Exon 4		1/368	0.003
MAU2	c.528G>T		Exon 5	rs2074090	158/368	0.428
MAU2	c.774+33G>A		Intron 7	rs2301668	13/368	0.035

Table S2. Clinical Features of Patients with Mutations and Rare Variants in the NIBPL and MAU2 interaction regions

Patient info	Patient ID	CDLLU1	CDLAD6	CDL252P	CDLP737	CDL225P	CDL424P	CDLP52	CDL181P	CDL046P	CDL383P
	Sex	M	M	F	M	M	M	F	M	F	F
	Gene	NIPBL	NIPBL	NIPBL	NIPBL	NIPBL	NIPBL	NIPBL	NIPBL	MAU2	MAU2
	Variant Type	missense	missense	missense	missense	missense	missense	missense	missense	in-frame deletion	in-frame deletion
	cDNA mutation	c.43G>A	c.86C>A	c.332G>C	c.535G>T	c.535G>A	c.535G>A	c.737A>G	c.760C>G	c.9_23del	c.9_23del
	Protein effect	p.Gly15Arg	p.Pro29Gln	p.Ser111Thr	p.Ala179Ser	p.Ala179Thr	p.Ala179Thr	p.Asp246Gly	p.Leu254Val	p.del5	p.del5
Mutation notes										in unaffected mother	also with 5.1MB deletion on 2q23
HEAD	Brachycephaly	microbrachy		1	microcbrachycephaly	+	-	microcephaly	-	+	-
	Low anterior hairline		+	1	+	+	-	+	+	+	+
FACE		typical	mild	classic	typical	typical	classic	classic	mild	classic	atypical
Eyes	Arched eyebrows	+		+	+	+	+	+	+	+	full
	Synophrys		+	+	+	+	+	+	+	+	+
	Long eyelashes	+	+	+	+	+	+	+	+	+	-
	Ptosis			-	-	+	+	-	+		-
Nose	depressed nasal bridge	+	-	-	+	+	+	+	+	+	+
	Anteverted nostrils	+	+	+	+	+	+	-	+	+	+
	Long/featureless philtrum	+	+	+	+	+	+	-	+	+	-
Mouth	Thin upper lip	+	+	+	+	+	+	+	+	+	+
	Downturned corners of mouth	-	+	+	+	+	+	+	+	+	-
	Palate - high arch	-	-	+	+	-		+	+		+
	Palate - cleft	-		-	-	+		-	-		-
	Teeth (small, widely spaced)	+	+	widely spaced	+	hypertrophied gums	-	+	+	+	-
	Micrognathia	+	-	-	+	+	-	+	+	+	-
Skin	Cutis marmorata	-	+	+	-	-	+	-	+	+	-
	Hirsutism	-	+	+	-	+	-	-	+	+	+
Hands	Small hands	+	+	+		-	-		+	+	+
	Proximally set thumbs	+		+	-	+	+	-	+	+	+
	Clinodactyly 5th finger	+	+	+	+	-	+	+	+	+	-
	Single Palmar crease	-	+	+	-			+	+ L	-	
Feet	Small feet		+	+	+	+, Rocker bottom		+	+	+	+
	2,3 Syndactyly of toes	-	-	+	-	+	-	-	+	-	+
Arms	Restriction of elbow movements	-	+	+	+			+	-	+	+
CARDIAC	Cardiac defects	-	-	aortic coarctation	-	PS, ASD, mitral regurg	Tetralogy of Fallot	PDA	-	ASD closed spontaneously	-
GENITOURINARY	Genitourinary defects	cryptorchidism,	-	-	-	-	-	-	+ testes descended	-	spina bifida

		hypospadias							once walked		
GASTROENTEROLOGY	GER		-	+	+	+	+	+	+	+	-
	Feeding problems in infancy	+		-	+	+	+, plyloric stenosis	+	+	+	malrotation
OTOLARYNGOLOGY	Hearing loss	choanal atresia +	-	-	-			-	- loss; tubes 3x	+	hyperacusis
OPHTHALMOLOGY	Eye problems	Hyperopia	+	-	-			-	+	ptosis	astigmatism
	Myopia	-	+	-	+			+	+ lacrimal duct obst @birth	+	
CNS	CNS anomalies	-	-	-	-			-	-	-	-
	Seizures	-	-		-	infantile		-	moderate	febrile	+
COGNITIVE	Mental Retardation	severe	mild	very mild	mild		moderate	severe	energetic and curious about surroundings; quiet on exam	moderate	moderate-severe MR
	Behavior			normal	hyperactivity		self-injurious	hyperactivity, autistic-like,		temper tantrums	mild SIB, aggression, high pain tolerance, anxiety
DEVELOPMENT	Verbal development	few words		near normal	mild, sentences		marked delay	minimal speech uses some syllables nonspecific	minimal speech at 17 mo; uses "mama" - nonspecific	few words at 9 y	
	Motor development	Walked at 7 mo		near normal	mild		walked at 4.5 y	moderate	walked at 2 y	walked at 40 mo	walked at 5.5 y
MEASUREMENTS	Gestational age (wks)	36	41	40	38	31	40	39	40	38	40
Birth	BW (gm)	1760	3100	2784	1700	1984	2840	1700	3543	2700	2600
	%ile weight (reg chart)	<10%	40%	15%	<5%	90%	25%	<<10%	75%	75%	10%
	Length at birth	42 cm	48 cm	45.7 cm	46 cm	44 cm	45.72cm	46 cm	19.25 in	45.7 cm	48cm
	%ile length (reg chart)	<10%	40%	10%	20%	75-90%	10%	10%	50%	75%	25%
	Head circumference at birth				29 cm	30.7 cm		31 cm	13.25 in	31 cm	30.5 cm
	%ile HC (reg chart)				<10%	75-90%		<<10%	25-50%	50%	<<10%
	APGAR score (1min/5min)	?		9/9	10	5/7		10/10	6/9		
Later evaluations	Age at evaluation	7.5 y	14 y	9 y	14 y	5 mo	9 y	28 y	3 y	9 y	23 y
	Weight (kg)	12		20.8	42	4.6	19.8	36.4	10.45		68.6
	%ile weight (reg chart)	<5%		<5%	10%	<5%, 50%	<5%	<5; 50% for	<5%, 50%		80%

						for 1 mo		11 y	for 12 mo		
	%ile weight (CdLS chart)			95%	95%	50-95%	60%	60%	~ 95%		>95%
	Height (cm)	98	150.1	119	146		116.4	142	82.5		144.5
	%ile height (reg chart)	<5%		<5%	<5%		<5%	<5; 50% for 10 y	<5%, 50% for 18 mo		<5%, 50% for 11 y
	%ile height (CdLS chart)	40%	90%	80%	95%		70%	5%	70%		75%
	Head circumference	43.5	50.8	48.25	49			51	46.75		48.5
	%ile HC (reg chart)	< 3%		<5%	<3%			<3; 50% for 4 y	<5%, 50% for 13 mo		<2%
	%ile HC (CdLS chart)		60%	98%	60%			90%	75%		

No notation indicates that information is unavailable. Numbering is based on *NIPBL* and *MAU2* cDNA sequences from the first nucleotide of the open reading frame (RefSeq accession numbers NM_015384 and NM_015329, respectively). Nomenclature is per den Dunnen (2000). Abbreviations included: PS, pulmonic stenosis; ASD, atrial septal defect; MR, mental retardation; SIB, self-injurious behavior;

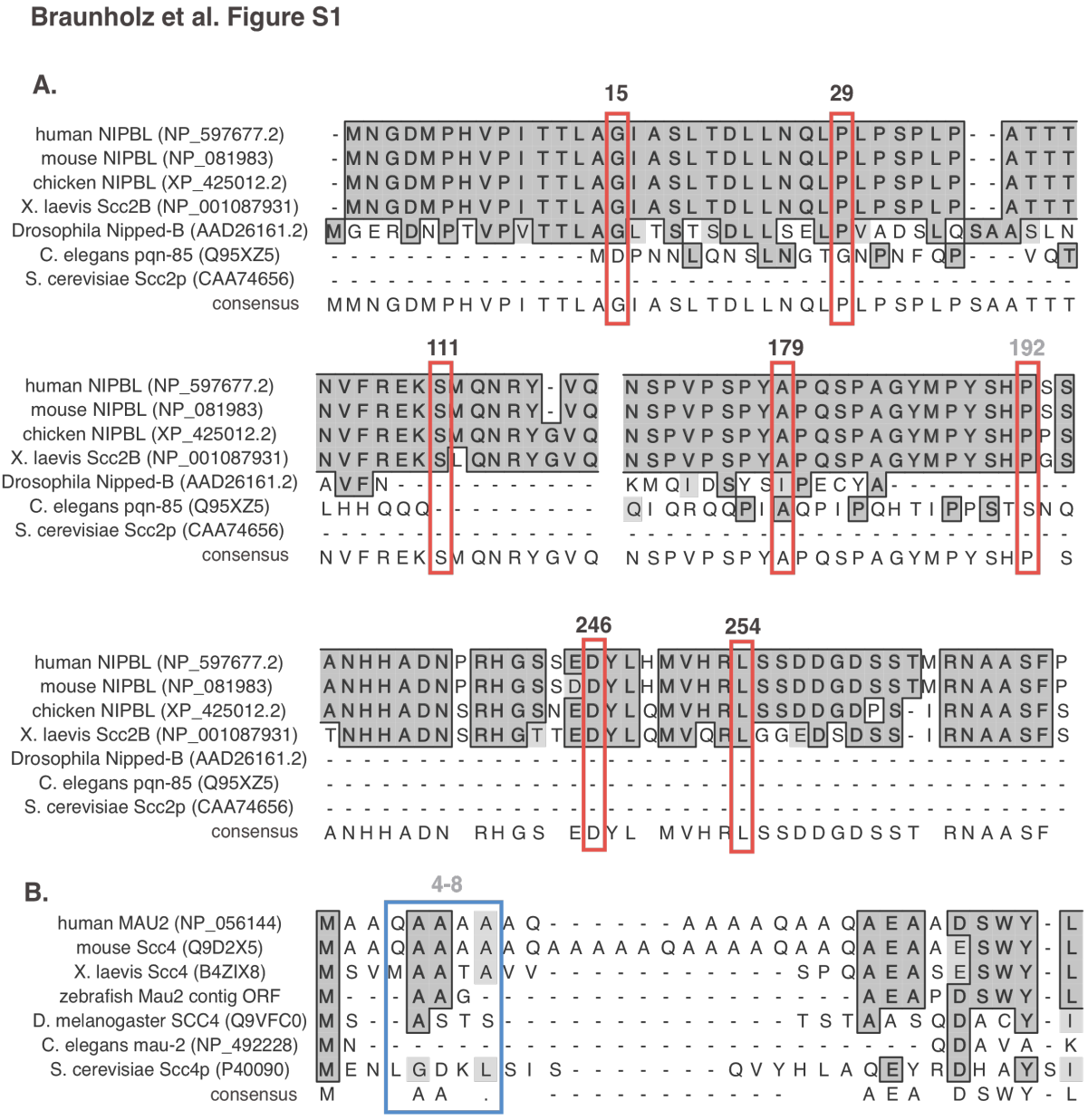

Figure S1. Location and Conservation of Mutations

ClustalW alignments of NIPBL and MAU2 homologs are labelled with species, corresponding protein name and accession number at the left. Dark grey boxes represent identical residues when compared to the human protein. Light grey shaded boxes indicate similar residues. Mutation residue positions are numbered above and indicated by red and blue boxes in NIPBL and MAU2, respectively. Presumed non-pathogenic residues are indicated by a grey number above the residue(s).