Supplementary

Table S1 Detailed clincial characteristics of 11 patients with ASXL2-related Shashi-Pena Syndrome

Characteristics	Summary	Individual 1 (this paper)	Individual 2 (5)[#]	Individual 3 (1)	Individual 4 (4)	Individual 5 (1)	Individual 6 (1)	Individual 7 (3)[&]	Individual 8 (2)	Individual 9 (1)	Individual 10 (1)	Individual 11 (1)
Demographic data												
Age at diagnosis	4.6 years (21 day-31 years)*	21 days	6 months	10 months	3 years	4 years 1 month	4 years 7 months	6 years	7 years	8 years	10 years	31 years
ASXL2 variants	8 had de novo truncating mutations	c.1792C>T, p.Gln598*	c.2485C>T, p.Gln829*	c.2081dupG, p.Gly696Argfs*11	c.1217dup, p.Glu407*	c.2472delC, p.Ser825Valfs*16	c.1225_1228delCCAA, p.Pro409Asnfs*13	t(2;11)(p23;q23)	c.4228T>G, p.Cys1410Gly	c.2424delC, p.Thr809Profs*32	c.2971_2974delGGAG, p.Gly991Argfs*3	c.1288G>T, p.Glu430*
Sex	Male 72.7% (8/11)**	Male	Male	Male	Male	Male	Female	Female	Male	Male	Male	Female
Gestational age	39 weeks (32 - 42)*	40^{+2} weeks	34 weeks	39 weeks	Term	33^{+6} weeks	40^{+2} weeks	39^{+5} weeks	32 weeks	35 weeks	37 weeks	42 weeks
Birth weight	3,000 g (2,071-4,860)*	3,030 g	2,100 g	4,860 g	N/A	2,071 g	3,300 g	2,715 g	N/A	3,900 g	2,140 g	3,000 g
Birth length	49.3 cm (42-59.5)*	48 cm	42 cm	59.5 cm	N/A	N/A	53 cm	49cm	N/A	52.1 cm	48 cm	49.6 cm
OFC	35.5 cm (34-37)*	36 cm	N/A	37 cm	N/A	N/A	35.5 cm	N/A	N/A	34 cm	N/A	34.5 cm
Macrocephaly at birth	18.2% (2/11)**	Yes	N/A	Yes	N/A	No	No	No	No	No	No	No
Clinical manifestations after birth												
Feeding difficulties	90.9% (10/11)**	Yes, transient	Yes, at 2 months of age	Yes, transient	Yes, transient	Yes, transient	Yes, transient	Yes, transient	Yes, persistent	Yes, transient	Yes, transient	N/A
Causes for feeding difficulties		GERD	N/A	N/A	Intestinal obstruction treated with Meckel's diverticulectomy	N/A	N/A	N/A	GERD	N/A	N/A	N/A
Hypoglycemia	54.5% (6/11)**	Yes, persistent	No	Yes, persistent	Yes, transient	N/A	Yes, transient neonatal hypoglycemia and episodic early morning hypoglycemia starting at 2.5 years	No	Yes, persistent between 12–24 months of age	N/A	N/A	Yes, transient
Potential cause hypoglycemia	2 inappropriate insulin level, 1 ketotic hypoglycemia and central adrenal insufficiency	Inappropriate insulin level	N/A	Unknown cause	Unknown cause	N/A	Inappropriate insulin level, low free fatty acids and ketones	N/A	Ketotic hypoglycemia, central adrenal insufficiency at 9 years of age	N/A	N/A	Unknown cause
Therapy for hypoglycemia	1 octreotide intracutaneously, 1 10% dextrose intravenously, 1 continuous feeding via gastric tube, 1 gastro-jejunal feeding with glucocorticoid replacement 1 regular feeding to avoid fasting periods	Octreotide	N/A	Continuous feedings via gastric tube	N/A	N/A	Eating regularly and avoiding long fasting periods.	N/A	Total TPN supplementation since 6 months and gastro-jejunal tube decompression as needed; Glucocorticoid replacement.	N/A	N/A	10% dextrose
Prognosis at follow-up												
Age at follow-up	4.1 years (4 months - 31 years)*	4 months	16 months	4 months	4 years	4 years 1 month	4 years	6 years	13 years	8.5 years	7 years 10 months	31 years
Developmental delay	90.9% (10/11)**	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Macrocephaly at follow-up	72.7% (8/11)**	No	N/A	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes
Hypotonia	72.7% (8/11)**	No	Yes	Yes	Yes	Yes	Yes, axial	No	Yes, axial	Yes	Yes	No
Seizure activities (SA) in infancy	54.5% (6/11)**, 2 male had febrile SA at 1.2 years and 8.5 years, 2 (male and female) had non-febrile SA at 13 years and 23 years, 1 female had both febrile and non-febrile SA at 4 years	No SA at 4 months	No	No SA at 4 months	Yes, treated with sodium valproate.	Yes, febrile SA at 14 months of age	Yes, febrile and non-febrile at 4 years, treated with sulthiame	No	Yes, non-febrile SA at 13 years, treated with lacosamide and phenobarbital	Yes, febrile seizure at 8.5 years	No, suspected SA not confirmed with EEGs at 7.5 years	Yes, epilepsy at 23 years
Hypertonia	18.2% (2/11)**	No	No	No	No	No	Yes, appendicular	No	Yes, appendicular	No	No	No
Growth retardation	18.2% (2/11)**	No	Yes	No	N/A	No	No	Yes	No	No	No	No
Clinical synopsis												
Facial features												
Hypertelorism	100.0% (11/11)**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Broad nasal tip	90.9% (10/11)**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Arched eyebrows	81.8% (9/11)**	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
V-shaped glabellar nevus flammeus	81.8% (9/11)**	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Low-set ears	72.7% (8/11)**	Yes	N/A	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Posteriorly rotated ears	63.6% (7/11)**	Yes	N/A	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes

Table S1 (*continued*)

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Table S1 (*continued*)

Characteristics	Summary	Individual 1 (this paper)	Individual 2 (5)[#]	Individual 3 (1)	Individual 4 (4)	Individual 5 (1)	Individual 6 (1)	Individual 7 (3)[&]	Individual 8 (2)	Individual 9 (1)	Individual 10 (1)	Individual 11 (1)
Proptosis	54.5% (6/11)**	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes	No
Deep palmar creases	54.5% (6/11)**	Yes	No	Yes	Yes	No	Yes	No	No	Yes	N/A	Yes
Broad forehead	45.5% (5/11)**	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No	No
Hirsutism	45.5% (5/11)**	Yes	Yes	No	Yes	No	Yes	No	No	No	No	Yes
Retrognathia	36.4% (4/11)**	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No
Ptosis	36.4% (4/11)**	No	No	No	Yes	No	Yes	No	No	Yes	No	Yes
Capillary malformations	27.3% (3/11)**	No	No	Yes	No	No	Yes	No	No	Yes	No	No
Long face	27.3% (3/11)**	No	No	No	No	Yes	No	No	Yes	Yes	No	No
Flat face	9.1% (1/11)**	No	No	No	No	No	Yes	No	No	No	No	No
Other abnormal eye findings	36.4% (4/11)**	Yes, paving stone like white lesions since birth	N/A	N/A	N/A	N/A	N/A	N/A	Yes, pigmentary retinal dystrophy, mild left optic atrophy at 7 years	ovoid shaped corneas	N/A	Bilateral presenile cataracts at 24 years old
Skeletal and/or extremity manifestations												
Overlapping toes	27.3% (3/11)**	Yes, toe 2 overlapping 3; toe 4 overlapping 5	No	No	No	Yes, toe 2 overlapping 4	No	No	Yes, toe 2 overlapping 3	No	N/A	No
Osteoporosis	27.3% (3/11)**	No	No	No	No	Yes	No	Yes	No	No	N/A	Yes
Kyphosis	18.2% (2/11)**	No	No	Yes	No	No	No	No	Yes	No	N/A	No
Advanced bone age	18.2% (2/11)**	No	No	No	No	No	No	No	No	Yes	N/A	Yes
Fractures	18.2% (2/11)**	No	No	No	No	Yes, at 39 months	No	No	Yes	No	N/A	No
Scoliosis	9.1% (1/11)**	No	No	No	No	No	Yes	No	No	No	N/A	No
Torticollis	9.1% (1/11)**	No	No	No	No	Yes	No	No	No	No	N/A	No
Cardiovascular findings												
Normal	9.1% (1/11)**	No	No	No	N/A	N/A	No	No	No	No	N/A	Yes
Atrial septal defect	36.4% (4/11)**	Yes	No	Yes	N/A	N/A	Yes	No	No	Yes	N/A	No
Patent Foramen Ovalle	27.3% (3/11)**	Yes	Yes	No	N/A	N/A	No	No	No	Yes	N/A	No
Other cardiovascular problems	27.3% (3/11)**	No	Yes, patent ductus arteriosus, mild tricuspid insufficiency, pulmonary hypertension, small pericaridal effusion	No	N/A	N/A	No	Yes, mild mitral and tricuspid regurgitation	Yes, bradycardia, ventricular ectopy	No	N/A	No
Brain MRI findings												
Normal	18.2% (2/11)**	No	N/A	No	N/A	No	N/A	No	Yes	No	No	Yes
Enlarged extra-axial spaces	18.2% (2/11)**	No	N/A	Yes	N/A	Yes	N/A	No	No	No	No	No
White matter volume loss	18.2% (2/11)**	No	N/A	No	N/A	No	N/A	No	No	Yes	Yes	No
Ventriculomegaly	18.2% (2/11)**	No	N/A	No	N/A	No	N/A	Yes	No	No	Yes	No
Small cerebellum	9.1% (1/11)**	Yes	N/A	No	N/A	No	N/A	No	No	No	No	No
Choroid plexus papilloma	9.1% (1/11)**	No	N/A	Yes	N/A	No	N/A	No	No	No	No	No

[#], This patient was reported to have minor ear abnormalities and congenital foot deformity but without details. He died of heart disease at 16 months of age. [&], Only the female proband of the family was included in the review. *, median (range). **, percentage (case/total number of patients). OFC, occipitofrontal circumference; N/A, not available; GERD, gastro-esophageal reflux disease.

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Table S2 Candidate variants of the neonate in this paper

Gene	Location	Mutation	Zygosity	Disease	Inheritance	ExAC (AC|Hom)	HGMD	Source
ACADSB	chr10:124810704	NM_001609:exon9:c.1128+3_1128+7del	Heterozygous	2-methylbutyrylglycinuria, [MIM:610006]	AR	0|0	DM?-related	De novo
ADGRV1	chr5:89989749	NM_032119:exon33:c.7176C>T(p.S2392S)	Heterozygous	Usher syndrome, type 2C, [MIM:605472]; Usher syndrome, type 2C, GPR98/PDZD7 digenic, [MIM:605472]	AD/AR/DD/Digenic	402|0	DM	Paternal
ASXL2	chr2:25972633	NM_018263:exon11:c.1792C>T(p.Q598X)	Heterozygous	Shashi-Pena syndrome, [MIM:617190]	AD	0|0		De novo
BRCA2	chr13:32971119	NM_000059:exon26:c.9586A>G(p.K3196E)	Heterozygous	Fanconi anemia, complementation group D1, [MIM:605724]	AD/AR	12|0	DM?	Maternal
COL4A3	chr2:228177642	NM_000091:exon52:c.*1057_*1058del	Heterozygous	Hematuria, benign familial, [MIM:141200]; Alport syndrome 3, autosomal dominant, [MIM:104200]; Alport syndrome 2, autosomal recessive, [MIM:203780]	AD/AR	0|0		De novo
KLHL10	chr17:39998122	NM_152467:exon2:c.242A>T(p.N81I)	Heterozygous	Spermatogenic failure 11, [MIM:615081]	AD	68|0	DM?	Maternal
LPIN2	chr18:2937867	NM_014646:exon7:c.991G>T(p.A331S)	Heterozygous	Majeed syndrome, [MIM:609628]	AR	138|0	DM?	Maternal
NKX2-5	chr5:172659738	NM_004387:exon2:c.809G>A(p.C270Y)	Heterozygous	Hypoplastic left heart syndrome 2, [MIM:614435]; Tetralogy of Fallot, [MIM:187500]; Hypothyroidism, congenital nongoitrous, 5, [MIM:225250]; Conotruncal heart malformations, variable, [MIM:217095]; Ventricular septal defect 3, [MIM:614432]; Atrial septal defect 7, with or without AV conduction defects, [MIM:108900]	AD	7|0	DM	Paternal
PROS1	chr3:93624903	NM_000313:exon5:c.431C>A(p.T144N)	Heterozygous	Thrombophilia due to protein S deficiency, autosomal dominant, [MIM:612336]; Thrombophilia due to protein S deficiency, autosomal recessive, [MIM:614514]	AD/AR	92|2	DM	Maternal
PSEN1	chr14:73602899	.	Heterozygous	Pick disease, [MIM:172700]; Alzheimer disease, type 3, with spastic paraparesis and apraxia, [MIM:607822]; Dementia, frontotemporal, [MIM:600274]; Cardiomyopathy, dilated, 1U, [MIM:613694]; Alzheimer disease, type 3, with spastic paraparesis and unusual plaques, [MIM:607822]; Alzheimer disease, type 3, [MIM:607822]	AD	0|0	DM?	Paternal
SCAPER	chr15:76866620	NM_020843:exon23:c.2717A>G(p.Q906R)	Heterozygous	Intellectual developmental disorder and retinitis pigmentosa, [MIM:618195]	AR	4|0	.	Paternal
SCAPER	chr15:76696901	NM_020843:exon27:c.3431A>G(p.H1144R)	Heterozygous	Intellectual developmental disorder and retinitis pigmentosa, [MIM:618195]	AR	19|0	.	Maternal
SYT1	chr12:79842893	NM_005639:exon11:c.1258G>A(p.V420I)	Heterozygous	Baker-Gordon syndrome, [MIM:618218]	AD	278|1	DM?	Maternal
TNFRSF13B	chr17:16852187	NM_012452:exon3:c.310T>C(p.C104R)	Heterozygous	Immunodeficiency, common variable, 2, [MIM:240500]; Immunoglobulin A deficiency 2, [MIM:609529]	AD/AR	390|1	DM	Maternal
TSPEAR	chr21:46086421	NM_144991:exon1:c.82+44927C>A	Heterozygous	Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis, [MIM:618180]	AR	1|0	.	Maternal
TSPEAR	chr21:46011414	NM_144991:exon2:c.83-23525G>A	Heterozygous	Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis, [MIM:618180]	AR	150|1	.	Paternal
TTN	chr2:179519476	NM_001267550:exon191:c.38198_38202delinsT (p.P12733Lfs*213)	Heterozygous	Muscular dystrophy, limb-girdle, autosomal recessive 10, [MIM:608807]; Cardiomyopathy, familial hypertrophic, 9, [MIM:613765]; Tibial muscular dystrophy, tardive, [MIM:600334]; Salih myopathy, [MIM:611705]; Cardiomyopathy, dilated, 1G, [MIM:604145]; Myopathy, myofibrillar, 9, with early respiratory failure, [MIM:603689]	AD/AR	0|0	DM?-related	De novo
TTN	chr2:179441038	NM_001267550:exon326:c.69821G>A(p.G23274D)	Heterozygous	Muscular dystrophy, limb-girdle, autosomal recessive 10, [MIM:608807]; Cardiomyopathy, familial hypertrophic, 9, [MIM:613765]; Tibial muscular dystrophy, tardive, [MIM:600334]; Salih myopathy, [MIM:611705]; Cardiomyopathy, dilated, 1G, [MIM:604145]; Myopathy, myofibrillar, 9, with early respiratory failure, [MIM:603689]	AD/AR	119|0	DM	Maternal
WNT10A	chr2:219757893	NM_025216:exon4:c.1154G>C(p.R385P)	Heterozygous	Schopf-Schulz-Passarge syndrome, [MIM:224750]; Tooth agenesis, selective, 4, [MIM:150400]; Odontoonychodermal dysplasia, [MIM:257980]	AD/AR	0|0	.	Maternal
WNT10A	chr2:219747116	NM_025216:exon2:c.347T>C(p.I116T)	Heterozygous	Schopf-Schulz-Passarge syndrome, [MIM:224750]; Tooth agenesis, selective, 4, [MIM:150400]; Odontoonychodermal dysplasia, [MIM:257980]	AD/AR	20|0	DM	Maternal
WNT10A	chr2:219746977	NM_025216:exon2:c.208C>T(p.R70W)	Heterozygous	Schopf-Schulz-Passarge syndrome, [MIM:224750]; Tooth agenesis, selective, 4, [MIM:150400]; Odontoonychodermal dysplasia, [MIM:257980]	AD/AR	240|2	DM	Paternal

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