

Supplementary Table 1. Cephalometric landmarks and measurements used in the cephalometric analysis and their definition.

Symbol	Name	Definition	Measurement	Definition
S	Sella	Center of the pituitary fossa of the sphenoid bone	SN	Anterior cranial base (length in mm)
N	Nasion	Intersection of the internasal suture with the nasofrontal suture in the midsagittal plane	SAr	Posterior cranial base (length in mm)
Ar	Articulare	The point of intersection of the dorsal contours of the articular process of the mandible and the temporal bone	SNAr	Cranial base angle (angle in °)
A	A-point	Deepest point of the curve of the maxilla, between anterior nasal spine and the dental alveolus	SN-FH	SN plane to Frankfort Horizontal plane (angle in °)
Co	Condylion	Most posterior and superior point of the mandibular condyle	SNA	Sella-Nasion-A point (angle in °)
B	B-point	Most posterior point in the concavity along the anterior border of the symphysis	Co-A	Midface length in mm
Po	Porion	Most superior point of the external auditory meatus	ANB	A point - Nasion- B point (angle in °)
Or	Orbitale	Most inferior point of the external border of the orbital cavity	SNB	Sella-Nasion-B point (angle in °)
Pg	Pogonion	The most anterior point in the contour of the mandibular symphysis in the sagittal plane	N-Pg (perp)	Distance of Pg to N perpendicular (length in mm)
Gn	Gnathion	The midpoint between the most anterior and inferior point of the mandibular symphysis	Co-Gn	Mandibular unit length (in mm)
Go	Gonion	The most inferior, posterior, and lateral point on the angle of the mandible	N-Me	Anterior Face Height (length in mm)
Me	Menton	Most inferior point of the mandibular symphysis	SGo	Posterior Face Height (length in mm)
			SGo/NMe %	Posterior (Sella-Gonion) to anterior (Nasion-Menton) face height % ratio

Supplementary Table 2. Analytical table including the genetic variants encountered in this cohort, as well as the related known pathogenic assessments according to the information provided by searching the following databases: ClinVar, dbGap, dbSNP, dbVar, GTR, MedGen, Varsome and OMIM.

Study ID	Pedigree ID	LDS Type	Gene	Genetic Variant	Protein Description	Pathogenic Assessment
I	Proband	LDS1	TGFBR1	c.733G>A	p.(Glu245Lys)	Likely pathogenic
IIA	Proband	LDS1	TGFBR1	c.1199A>G	p.(Asp400Gly)	Pathogenic
IIB	Offspring	LDS1	TGFBR1	c.1199A>G	p.(Asp400Gly)	Pathogenic
IIIA	Proband	LDS1	TGFBR1	c.683_685delAAG	p.(Glu228del)	Pathogenic
IIIB	Mother	LDS1	TGFBR1	c.683_685delAAG	p.(Glu228del)	Pathogenic
IV	Proband	LDS1	TGFBR1	c.1279C>G	p.(Pro427Ala)	Likely pathogenic
V	Proband	LDS1	TGFBR1	c.1061T>G	p.(Leu354Arg)	Likely pathogenic
VI	Proband	LDS1	TGFBR1	c.722C>T	p.(Ser241Leu)	Pathogenic
VIIA	Proband	LDS1	TGFBR1	c.1459C>T	p.(Arg487Trp)	Pathogenic
VIIB	Offspring	LDS1	TGFBR1	c.1459C>T	p.(Arg487Trp)	Pathogenic
VIII	Proband	LDS1	TGFBR1	c.997G>C	p.(Asp333His)	Likely pathogenic
IX	Proband	LDS1	TGFBR1	c.1199A>T	p.(Asp400Val)	Likely pathogenic
X	Proband	LDS1	TGFBR1	c.1061T>G	p.(Leu354Arg)	Likely pathogenic
XI	Proband	LDS1	TGFBR1	c.722C>T	p.(Ser241Leu)	Pathogenic
XII	Proband	LDS1	TGFBR1	c.1067T>G	p.(Val356Gly)	Likely pathogenic
XIIIA	Proband	LDS2	TGFBR2	c.1256T>A	p.(Val419Glu)	Likely pathogenic
XIIIB	Offspring	LDS2	TGFBR2	c.1256T>A	p.(Val419Glu)	Likely pathogenic
XIV	Proband	LDS2	TGFBR2	c.1370T>A	p.(Met457Lys)	Likely pathogenic

XV	Proband	LDS2	TGFBR2	c.1277C>A	p.(Ala426Asp)	Pathogenic
XVI	Proband	LDS2	TGFBR2	c.1301T>C	p.(Met434Thr)	Uncertain significance
XVII	Proband	LDS2	TGFBR2	c.1583G>A	p.(Arg528His)	Pathogenic
XVIII	Proband	LDS2	TGFBR2	c.1583G>A	p.(Arg528His)	Pathogenic
XIX	Proband	LDS2	TGFBR2	c.1583G>A	p.(Arg528His)	Pathogenic
XX	Proband	LDS2	TGFBR2	c.985G>A	p.(Ala329Thr)	Pathogenic
XXI	Proband	LDS2	TGFBR2	c.1583G>A	p.(Arg528His)	Pathogenic
XXII	Proband	LDS2	TGFBR2	c.1190A>G	p.(Asp397Gly)	Uncertain significance
XXIII	Proband	LDS2	TGFBR2	c.1336G>A	p.(Asp446Asn)	Pathogenic
XXIV	Proband	LDS2	TGFBR2	c.1483C>G	p.(Arg495Gly)	Likely pathogenic
XXV	Proband	LDS2	TGFBR2	c.1583G>A	p.(Arg528His)	Pathogenic
XXVIA	Proband	LDS3	SMAD3	c.483del	p.(Glu162Lysfs*24)	Pathogenic
XXVIB	Mother	LDS3	SMAD3	c.483del	p.(Glu162Lysfs*24)	Pathogenic
XXVIC	Sibling	LDS3	SMAD3	c.483del	p.(Glu162Lysfs*24)	Pathogenic
XXVII	Proband	LDS4	TGFB2	c.989G>A	p.(Arg330His)	Likely pathogenic
XXVIII A	Proband	LDS4	TGFB2	c.1103G>A	p.(Gly368Glu)	Pathogenic
XXVIII B	Offspring	LDS4	TGFB2	c.1103G>A	p.(Gly368Glu)	Pathogenic
XXVIII C	Offspring	LDS4	TGFB2	c.1103G>A	p.(Gly368Glu)	Pathogenic
XXIX A	Father	LDS4	TGFB2	c.988C>T	p.(Arg330Cys)	Uncertain significance
XXIX B	Sibling	LDS4	TGFB2	c.988C>T	p.(Arg330Cys)	Uncertain significance

XXIXC	Offspring	LDS4	TGFB2	c.988C>T	p.(Arg330Cys)	Uncertain significance
XXX	Proband	LDS5	TGFB3	c.106A>T	p.(Lys36*)	Pathogenic
XXXI	Proband	SGS	SKI	c.349G>C	p.(Gly117Arg)	Pathogenic
XXXII	Proband	SGS	SKI	c.100G>T	p.(Gly34Cys)	Pathogenic
XXXIII	Proband	SGS	SKI	c.100G>T	p.(Gly34Cys)	Pathogenic
XXXIV	Proband	SGS	SKI	c.104C>A	p.(Pro35Gln)	Likely pathogenic

Supplementary Table 3. Types of craniofacial surgical procedures conducted in the different LDS subgroups, SGS an in total.

Craniofacial Surgery Type	TOTAL (n=44)		LDS1 (n=15)		LDS2 (n=14)		LDS3 (n=3)		LDS4 (n=7)		LDS5 (n=1)		SGS (n=4)	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Myringotomy tube placement	10	22.73	4	26.67	3	21.43	1	33.33	0	0.00	0	0.00	2	50.00
Adenoidectomy	9	20.45	3	20.00	2	14.29	2	66.67	0	0.00	0	0.00	2	50.00
Tonsilectomy	7	15.91	2	13.33	1	7.14	3	100.00	0	0.00	0	0.00	1	25.00
Craniosynostosis	6	13.64	1	6.67	2	14.29	0	0.00	0	0.00	0	0.00	3	75.00
Strabismus correction	6	13.64	1	6.67	3	21.43	0	0.00	2	28.57	0	0.00	0	0.00
Cleft deformity repair	4	9.09	2	13.33	2	14.29	0	0.00	0	0.00	0	0.00	0	0.00
Mandibular distraction osteogenesis	1	2.27	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	25.00
Tympanografts	1	2.27	0	0.00	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00
Removal of lip hemangioma	1	2.27	0	0.00	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00
Blepharoptosis	1	2.27	1	6.67	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lingual frenulectomy	1	2.27	1	6.67	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Supplementary Table 4. Analytical 3D facial measurements expressed in average z-scores for each LDS subtype and SGS with the use of the FaceBase normative database.

	MEASUREMENTS	LDS1	LDS2	LDS3	LDS4	LDS5	SGS	COHORT
Cranial Base	CranBaseWidth	-1.04	-1.52	-1.98	-1.35	0.11	-1.04	-1.14
Face	UpFaceDepth_R	-1.51	-1.16	-0.93	-1.38	-0.90	-0.41	-1.05
	UpFaceDepth_L	-1.17	-1.07	-0.82	-1.21	-0.64	-0.73	-0.94
	MidfaceDepth_R	-1.99	-2.14	-1.69	-1.41	-0.68	-2.12	-1.67
	MidfaceDepth_L	-1.31	-1.46	-1.53	-1.31	0.57	-1.18	-1.04
	LowFaceDepth_R	-2.28	-2.16	-1.94	-1.23	0.28	-2.71	-1.67
	LowFaceDepth_L	-1.66	-1.73	-1.61	-1.32	1.19	-2.86	-1.33
	MorphFaceHeight	-0.98	-1.40	-2.14	-1.84	0.26	-3.14	-1.54
	UpFaceHeight	-0.51	-0.47	-0.91	-0.95	0.60	-4.30	-1.09
	LowFaceHeight	-0.52	-1.33	-1.21	-1.33	0.31	-1.37	-0.91
Eyes	InCanthWidth	0.80	1.15	1.55	0.69	-0.35	3.13	1.16
	OutCanthWidth	1.02	1.20	0.67	0.87	-0.15	1.81	0.91
	PalpFisLength_R	1.51	0.86	0.08	0.72	0.27	0.48	0.66
	PalpFisLength_L	1.11	0.84	-0.04	0.91	-0.11	0.56	0.54
Nose	NasalWidth	0.06	0.70	1.45	0.10	0.21	0.53	0.51
	SubNasalWidth	0.48	1.94	1.95	0.77	0.73	1.31	1.20
	NasalPro	-0.62	-0.45	-0.15	-1.47	-1.58	-1.82	-1.01
	NasalAlaLength_R	-1.84	-1.47	0.00	-2.27	-0.97	-2.10	-1.44
	NasalAlaLength_L	-0.79	-1.73	-0.38	-2.41	-0.53	-1.93	-1.30
	NasalHeight	-1.14	-0.35	-1.21	-1.27	0.08	-1.78	-0.95
	NasalBridgeLength	-1.09	-0.13	-0.42	-0.83	0.24	-1.65	-0.65
Lips	LabFisWidth	-0.61	-0.80	0.02	-0.64	-0.36	-0.54	-0.49
	PhilWidth	0.76	0.55	0.97	0.49	0.10	1.57	0.74
	PhilLength	0.43	-0.68	0.27	-0.07	0.78	-0.19	0.09
	UpLipHeight	0.31	-0.58	0.36	0.19	0.83	-0.79	0.06
	LowLipHeight	-0.55	-0.33	0.48	-0.48	0.01	-1.80	-0.44
	UpVermHeight	-0.50	0.03	-0.05	0.31	-0.08	-1.54	-0.31
	LowVermHeight	-0.52	-0.56	-0.34	-0.68	-0.52	-0.98	-0.60
	CutLowLipHeight	-0.17	0.39	1.18	0.20	0.61	-1.04	0.20

Supplementary Table 5. Analytical table with the z-scores for the measurements included in the cephalometric analysis.

Cephalometric measurements		LDS type					Overall (n=20)
		LDS1 (n=6)	LDS2 (n=9)	LDS3 (n=2)	LDS4 (n=2)	LDS5 (n=1)	
SNA	(S-N-A) °	-0.9	-3.31	-1.51	0.86	-0.25	-1.84
SNB	(S-N-B) °	-1.88	-3.28	-1.77	-0.18	-1.39	-2.31
ANB	(A-N-B) °	1.85	1.72	0.89	2.08	2.23	1.74
Cranial Base Angle	(N-S-Ar) °	2.69	4.2	1.42	0.43	2.42	3
Anterior Cranial Base	(N-S) (mm)	-2.97	-2.21	-1.8	-2.21	-1.29	-2.35
Posterior Cranial Base	(S-Ar) (mm)	-1.55	-1.58	-1.87	-1.05	-1.94	-1.56
Midface Length	(Co-A) (mm)	-3.05	-3.37	-3.13	-2.3	-1.02	-3.02
Maxillary Unit Length	(Co-ANS) (mm)	-1.73	-1.34	-1.28	-0.53	0.58	-1.27
Mandibular Unit Length	(Co-Pog) (mm)	-1.26	-1.28	-0.61	-0.4	2.19	-0.94
Mandibular Body Length	(Go-Pog) (mm)	-3.21	-3.49	-1.67	-2.77	2.78	-2.83
Gonial Angle	(Ar-Go-Pog) °	1.18	0.15	0.56	0.05	1.12	0.54
Ramus Height	(Ar-Go) (mm)	0.02	0.81	-0.53	1.37	1.81	0.55
Posterior Face Height	(Se-Go) (mm)	-2.39	-1.94	-2.52	-0.45	-1.28	-1.95
Anterior Face Height	(N-Me) (mm)	-2.56	-1.98	-3.29	-4.06	-0.13	-2.45
Lower Face Height	(ANS-Me) (mm)	0.35	-0.22	0.99	0.08	4.23	0.39

Supplementary Figure 1. a. Quantitative airway space assessment with Invivo5.4 (Anatomage, San Jose, CA), depicting the airway analysis of an individual with LDS1. The volume of the pharyngeal airway space (PAS) and the minimum cross-sectional area (CSA) are calculated automatically and a heatmap is used to illustrate the pharynx by area. The distance of the hyoid bone from the mandibular plane (H-MP) is measured separately. **b.** Box plot depicting the minimum CSA per LDS subtype. LDS1 has the narrowest pharyngeal airway area. **c.** Box plot depicting the total PAS per LDS subtype. LDS1 has the smallest volume. **d.** Box plot depicting the average distance of the hyoid bone from the mandibular plane for the different subtypes. LDS5 and LDS1 have the greatest distance, which correlates with increased risk for sleep apnea. The red lines represent the average values for the unaffected population.



