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NOTCH3-related lateral meningocele syndrome presenting as radiological Copenhagen syndrome

Short title: Lateral Meningocele Syndrome and differential diagnoses

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Abstract

Background: Lateral meningocele syndrome is a rare skeletal syndrome caused by truncating variants in the final exon of the *NOTCH3* gene. It is characterised by multiple lateral meningoceles that may result in neurological sequalae. A wider systemic phenotype has been demonstrated including musculoskeletal abnormalities, feeding difficulties, structural cardiac and renal anomalies, and facial dysmorphism.

Method: We describe the clinical details of a child who was initially diagnosed with Copenhagen syndrome (progressive non-infectious anterior vertebral body fusion), based on radiological findings, in the context of kyphosis and back pain. Later, a novel *de novo* c.6723_6736del p.(Glu2241AspfsTer8) *NOTCH3* variant was identified from the 100,000 Genomes Project, in keeping with a genetic diagnosis of lateral meningocele syndrome.

Discussion: Without the context of additional features that may point towards an underlying syndrome, radiological findings - when reviewed in isolation - may be suggestive of alternate diagnoses. In this case, the radiological finding of anterior vertebral fusion suggested Copenhagen syndrome, whereas the identification of dural ectasia prompted further investigation into Ehlers-Danlos syndrome subtypes. Recognition of dysmorphology prompted wider investigation by Whole Genome Sequencing.

Conclusion: Features of lateral meningocele syndrome significantly overlap with those of connective tissue disorders including EDS, Marfan syndrome, and Loeys-Dietz syndrome. We describe the clinical features of the here reported proband with a novel *NOTCH3* variant, and compare the phenotypes of these differential diagnoses.

Background

Lateral meningocele syndrome (LMS) is a rare skeletal syndrome caused by heterozygous pathogenic variants in exon 33 of the NOTCH3 gene, located on chromosome 19p13 (OMIM #130720). The condition is characterised by lateral meningoceles - protrusions of the spinal meninges through the vertebrae - which can result in neurological sequelae.

NOTCH3 encodes the NOTCH3 transmembrane protein, belonging to the evolutionarily conserved family of NOTCH receptors (Penton et al., 2012). After protein-ligand binding, the NOTCH3

intracellular domain translocates to the nucleus to activate transcription factors that drive cell growth and proliferation (Monet-Leprêtre et al., 2009). Pathogenic variants in exon 33—the final exon—result in protein truncation with an mRNA product that escapes nonsense mediated decay, resulting in decreased clearance of the active intracellular product. A dominant gain-of-function mechanism has been speculated as a result of likely prolonged signalling effects, although the specific pathophysiology of disease is not well understood (Gripp et al., 2015).

Neurological manifestations depend on the location and size of lateral meningoceles, but can include paraparesis, paraesthesia, and neurogenic bladder. Additional features variably comprise feeding difficulties, musculoskeletal abnormalities, features of connective tissue disorders, facial dysmorphism, hearing problems, developmental delay, and structural cardiac and renal anomalies (Brown et al., 2017; Cappuccio et al., 2020; Ejaz et al., 2016; Gripp et al., 2015; Han et al., 2022; Pasa et al., 2024; Rubadeux et al., 2024; Yamada et al., 2022).

Thus far, there are a limited number of individuals in the medical literature with genetically confirmed *NOTCH3*-related LMS. A radiological diagnosis of LMS may not be considered without appreciation for the potential additional syndromic manifestations. A clinical diagnosis may be difficult to establish in the absence of genetic testing due to overlapping features with other disorders, in particular, connective tissue conditions. Here we compare LMS and its differential diagnoses.

Individual description

This female proband was born at term by normal vaginal delivery weighing 3.66kg (72nd centile), following an uneventful pregnancy. At age four months, she was diagnosed with failure to thrive because of feeding issues and recurrent upper respiratory tract infections. Investigations into an abnormal head shape revealed benign hydrocephalus.

Early development was within normal limits, and she has since academically progressed as expected. Throughout childhood, her weight remained in the lower centiles for age (recent growth parameters at 15 years of age were: weight 18th centile, height 32nd centile, and head circumference 98th centile).

As an infant, she was diagnosed with right conductive hearing loss because of stenosis of the inner ear for which she required bone amplified hearing aids. She had chronic constipation but no autonomic bladder or bowel dysfunction.

At age three years, she had initial genetic investigations due to dysmorphic features pertaining to shallow orbits, up-slanting palpebral fissures, thin and tented upper lip, slight micrognathia, and high arched palate (Figure 1). She subsequently developed overcrowding of teeth with discolouration and caries, requiring multiple extractions.

At age five years, she suffered a traumatic elbow dislocation. At age six years, she was referred for orthopaedic assessment due to back pain and concerns regarding spinal alignment. MRI imaging at six years and seven months showed reversal of lumbar lordosis with loss of intervertebral disc spaces in the thoracic (T) and lumbar (L) spine and irregularity of the end plates of T6–T10. There was also evidence of dural ectasia with prominent dural sacs extending into the intervertebral foramina (Figure 2A).

Following identification of dural ectasia, and in view of hypermobility (Beighton score 7/9), she was assessed in the Ehlers-Danlos Syndrome (EDS) National Diagnostic Service. However, a rare EDS subtype was deemed unlikely due to the absence of additional positive findings. At that time, she was enrolled into the 100,000 Genomes Project to investigate a possible underlying explanation.

Over time, she developed worsening pain in her knees, hands, and back, aggravated by activity, and causing night wakening. She was easily fatigued with physical exertion. Examination at eight years revealed loss of spinal lordosis with poor spinal extension. A rigid extension brace was provided to attempt to improve the lumbar lordosis before spontaneous fusion. Radiographs identified irregularity of the lateral spine with early fusion of the vertebral end plates and reduced disc spaces, particularly in the lumbar and lower thoracic spine (Figure 2B). These features were reported as consistent with Copenhagen syndrome, a progressive non-infective childhood-onset spinal disorder of unknown aetiology.

At age 12 years, there was progression of the upper lumbar kyphosis, with fully fused vertebrae (Figure 2C). She could only stand with her hips and knees flexed. To maintain sagittal balance, retroversion of her pelvis became a compensatory mechanism. She later developed paraesthesia in her legs and was most comfortable in the sitting-position.

Following the genetic diagnosis at 14 years, a baseline echocardiogram revealed a structurally and functionally normal heart, whilst an ECG recorded predominant sinus rhythm. There was evidence of very mild aortic incompetence, not considered clinically significant. A renal ultrasound scan identified a larger right than left kidney (12.1cm compared to 9.6cm respectively), with a posteriorly located spleen.

Recent magnetic resonance imaging of the spine showed deterioration, with fusion of the L1 to L4 vertebrae, a 40-degree kyphosis, but a normal cervico-cranial junction, no spinal stenosis, and no syrinx (Figure 2D,2E). Recent clinical examination revealed no neurological deficit, except for unexplained poor sharp-blunt discrimination. Current management includes input from the Specialist Pain Clinic (currently on Paracetamol, Ibuprofen, Amitriptyline, Gabapentin), Physiotherapy, and follow-up in the joint Neurology-Spinal Clinic.

Methods

Initial genetic testing requested by her Paediatrician at age three years comprised a karyotype and FRAX analysis. Unsurprisingly, this identified a 46,XX profile with no detectable FRAX expansion.

At age eight years she was referred for assessment by Clinical Genetics, and enrolled in the 100,000 Genomes Project (Genomics England) (Turnbull et al., 2018). Consent was taken locally in Sheffield Clinical Genetics service. Blood samples were sent to the local Laboratory for the proband and parents, where DNA was extracted and sent to Illumina for trio whole genome sequencing analysis.

DNA extraction was performed using TruSeq DNA PCR-Free Library Preparation and sequenced using the high-throughput HiSeq X platform. Data were passed through Genomic England's bioinformatics pipeline. No variants were tiered on primary analysis of Skeletal Dysplasia and Thoracic Aortic Aneurysm or Dissection panel[1]. The *NOTCH3* gene was not included on these panels at the time of primary analysis. A negative reported was issued in 2019.

Subsequently in 2023, a *de novo* c.6723_6736del p.(Glu2241AspfsTer8) frameshift variant in *NOTCH3* was identified (NM_000435.2) via the 100,000 Genomes Diagnostic Discovery project (Genomics England) (Turnbull et al., 2018). Reanalysis of whole genome sequencing data was carried out by application of up-to-date panels, as well as looking beyond the scope of the initial panels applied. In house Sanger sequencing provided confirmation of this variant. The variant was classified as ‘likely pathogenic’ as per ACMG criteria (Richards et al., 2015). This *de novo* variant was absent from population databases (gnomAD) and the variant location in the terminal exon was located in a mutational hotspot of truncating variants without benign variation.

Discussion

The first individual with multiple lateral meningoceles and additional syndromic features was described by Lehman et al. in 1977. Several individuals with similar clinical presentations have been described since then (Amuthabarathi et al., 2020; Avela et al., 2011; Castori et al., 2014; Chen et al., 2005; Gripp et al., 1997; Philip et al., 1995). Some of these historical cases were conducive to Gripp et al. (2015) identifying the underlying genetic aetiology. Since then, 13 individuals have been published in the medical literature with confirmed disease-causing *NOTCH3* variants (Brown et al., 2017; Cappuccio et al., 2020; Ejaz et al., 2016; Gripp et al., 2015; Han et al., 2022; Pasa et al., 2024; Rubadeux et al., 2024; Yamada et al., 2022).

Additional systemic features of LMS can be variable. Signs or symptoms may include brain or spinal abnormalities (Chiari 1 malformation, ventriculomegaly, white matter changes, encephaloceles, hydrocephalus, syringomyelia, arachnoid cysts, dural ectasia, tethered cord), musculoskeletal features (scoliosis, vertebral scalloping, vertebral fusion, pectus excavatum, Wormian bones), connective tissue features (hypotonia, hypermobility of joints, skin hyperextensibility, aortic dilatation), congenital cardiac abnormalities (PDA, PFO, ASD, VSD, bicuspid aortic valve, coarctation), renal-uro-genital abnormalities (renal cysts, microlithiasis, cryptorchidism), feeding and growth abnormalities, developmental delay or intellectual disability, and vision and hearing problems (Brown et al., 2017; Cappuccio et al., 2020; Ejaz et al., 2016; Gripp et al., 2015; Han et al., 2022; Pasa et al., 2024; Rubadeux et al., 2024; Yamada et al., 2022). A biliary phenotype has been described in one individual by Pasa et al. (2024).

The presence of lateral meningoceles in childhood was thought to be cardinal feature of LMS. Paradoxically, lateral meningoceles were not identified in an eight-year-old child with a pathogenic *NOTCH3* variant, who had additional systemic features otherwise in keeping with LMS (Rubadeux et al., 2024). This may represent phenotypic variability, or variability in rate of spinal disease progression. Lateral meningoceles, or dural ectasia, can also be seen in individuals with EDS subtypes, Marfan syndrome, Loeys-Dietz syndrome and *NOTCH2*-related Hadju-Cheney syndrome (Brady et al., 2017; Cortés-Martín et al., 2020; Giunta et al., 1993; Meester et al., 2017.; Rohrbach and Giunta, 1993).

Also integral to the NOTCH signalling pathway, *NOTCH2*-related Hadju-Cheney syndrome shares many overlapping multisystemic features with *NOTCH3* lateral meningocele syndrome, including musculoskeletal abnormalities, cardiac and renal phenotype and facial dysmorphology (Cortés-Martín et al., 2020). However, the condition is distinguished by severe and progressive bone loss, which was not in accordance with the here reported proband's presentation.

Rare EDS subtypes were also considered as a potential underlying diagnosis following identification of dural ectasia and evidence of hypermobility. There are currently 13 subtypes of EDS that together form a group of connective tissue disorders characterised by variable skin, joint, vessel, and organ abnormalities. Although hypermobility may be indicative of an underlying connective tissue disorder such as EDS, hypermobility is also a feature of LMS.

Neurofibromatosis type 1 can also commonly present with dural ectasia (Polster et al., 2020). However, visual stigmata of Neurofibromatosis type 1 typically present throughout childhood, and hence this was never a considered differential in this individual. Vertebral fusion and dural ectasia (or its related sign, posterior vertebral scalloping) have been described in other individuals with LMS (Gripp et al., 2015).

Feeding and growth problems in LMS may be the result of muscle or structural differences causing difficulty with mastication. Kyphoscoliotic EDS may result in feeding issues as a result of significant congenital hypotonia (Brady et al., 2017), whereas individuals with *NOTCH3*-related LMS have been described to have more non-specific difficulties (as in the described proband, resulting in failure-to-

thrive). This may contribute to the small stature described in some, which is discordant to the observed tall stature often seen in Marfan syndrome or Loeys-Dietz syndrome.

There is a described facial phenotype shared by individuals with LMS, including the here reported proband. Dysmorphic features may include hypertelorism, up- or down-slanting palpebral fissures, ptosis, micrognathia, malar hypoplasia, long or smooth philtrum, thin upper lip, low set ears and high arched palate (Brown et al., 2017; Cappuccio et al., 2020; Ejaz et al., 2016; Gripp et al., 2015; Han et al., 2022; Pasa et al., 2024; Rubadeux et al., 2024; Yamada et al., 2022). Dysmorphic features are not pathognomonic of the condition, but may somewhat overlap with features present in other connective tissue disorders.

The initial working diagnosis in this individual was progressive anterior vertebral fusion, or Copenhagen syndrome, based on radiological vertebral end plate fusion. Copenhagen syndrome is a very rare spinal disorder defined by evolving thoracic and lumbar vertebral fusion that first occurs in childhood, develops over months to years, and can result in ankylosis and kyphosis (Cebulski et al., 2012). It can cause pain and stiffness, and is typically managed with bracing. Neurological sequalae are rare but may require surgical correction (Safaei et al., 2023). Kyphosis can be a congenital or early feature of an underlying connective tissue disorder such as congenital Marfan syndrome, Loeys-Dietz syndrome or Kyphoscoliotic-type EDS, but unlike these conditions, Copenhagen syndrome does not have multi-system manifestations. However, with its unknown aetiology, a diagnosis of Copenhagen syndrome was somewhat supported initially in this individual by the absence of relevant genetic findings on primary whole genome analysis.

Conclusion

LMS is a rare multisystem skeletal disorder caused by pathogenic variants in the final exon of *NOTCH3.* Limited numbers of individuals have been described in the medical literature thus far. Here we describe and compare the 14th individual with a pathogenic *NOTCH3* variant associated with LMS. The diagnostic evolution in this case illustrates that imaging is not pathognomonic. In the absence of a genetic diagnosis, specific specialist assessment for overlapping syndromes, including connective tissue conditions, should be considered. This case highlights the need for careful consideration of differential diagnoses for lateral meningoceles, especially in the context of additional systemic features.

1. N.B. Skeletal Dysplasia panel at the time comprised: *ABCC9 ACAN ACP5 ACVR1 ADAMTSL2 AGA AGPS ALG12 ALG3 ALG9 ALPL ALX3 ALX4 AMER1 ANKH ANKRD11 ANO5 ANTXR2 ARHGAP31 ARSB ARSE ASXL1 ASXL2 ATP6V0A2 ATP7A B3GALT6 B3GAT3 B4GALT7 B9D1 BHLHA9 BMP1 BMP2 BMPER BMPR1B C21orf2 C2CD3 CA2 CANT1 CASR CC2D2A CCDC8 CDC45 CDH3 CDKN1C CDT1 CEP120 CEP290 CHST14 CHST3 CHSY1 CLCN5 CLCN7 COL10A1 COL11A1 COL11A2 COL1A1 COL1A2 COL2A1 COL9A1 COL9A2 COL9A3 COLEC11 COMP CREBBP CRTAP CSPP1 CTSA CTSC CTSK CUL7 CYP27B1 DDR2 DHCR24 DHODH DIS3L2 DLL3 DLL4 DLX3 DLX5 DMP1 DNMT3A DOCK6 DPM1 DVL1 DVL3 DYM DYNC2H1 DYNC2LI1 EBP EED EFNB1 EFTUD2 EIF2AK3 ENPP1 EOGT ERF ESCO2 EVC EVC2 EXT1 EXT2 EXTL3 EZH2 FAM111A FAM20C FAM58A FBN1 FBN2 FERMT3 FGF10 FGF16 FGF23 FGFR1 FGFR2 FGFR3 FIG4 FKBP10 FLNA FLNB FUCA1 GALNS GALNT3 GDF5 GDF6 GHR GJA1 GLB1 GLI3 GNAS GNPAT GNPTAB GNPTG GNS GORAB GPC6 GPX4 GSC GUSB GZF1 HDAC4 HDAC8 HES7 HGSNAT HOXA13 HOXD13 HPGD HSPG2 ICK IDH1 IDS IDUA IFITM5 IFT122 IFT140 IFT172 IFT43 IFT52 IFT80 IFT81 IHH IKBKG IL11RA IL1RN IMPAD1 INPPL1 KIF22 KIF7 LBR LEMD3 LIFR LMBR1 LMNA LMX1B LONP1 LPIN2 LRP4 LRP5 LTBP3 MAFB MAN2B1 MAP3K7 MATN3 MEGF8 MEOX1 MESP2 MGP MKS1 MMP13 MMP2 MNX1 MPDU1 MSX2 MYCN NAGLU NANS NEK1 NEU1 NF1 NFIX NIN NIPBL NKX3-2 NLRP3 NOG NOTCH1 NOTCH2 NPR2 NSD1 NSDHL OBSL1 OFD1 ORC1 ORC4 ORC6 OSTM1 P3H1 PAPSS2 PCNT PCYT1A PDE3A PDE4D PEX5 PEX7 PGM3 PHEX PHGDH PIGT PIGV PIK3R1 PITX1 PLOD2 PLS3 POC1A POLR1A POLR1C POLR1D POP1 POR PPIB PRKAR1A PRMT7 PSAT1 PSPH PTDSS1 PTH1R PTHLH PTPN11 PUF60 PYCR1 RAB23 RASGRP2 RBM8A RBPJ RECQL4 RFT1 ROR2 RPGRIP1L RUNX2 SALL1 SALL4 SBDS SCARF2 SEC24D SERPINF1 SERPINH1 SETD2 SF3B4 SFRP4 SGSH SH3BP2 SH3PXD2B SHOX SKI SLC17A5 SLC26A2 SLC29A3 SLC34A3 SLC35D1 SLC39A13 SLCO2A1 SMAD3 SMAD4 SMARCAL1 SMC1A SMC3 SMOC1 SNRPB SNX10 SOST SOX9 SUMF1 TALDO1 TBCE TBX15 TBX3 TBX4 TBX5 TBX6 TBXAS1 TCF12 TCIRG1 TCOF1 TCTEX1D2 TCTN2 TCTN3 TERT TGFB1 TGFB2 TGFBR1 TGFBR2 THPO TMCO1 TMEM165 TMEM216 TMEM231 TMEM38B TMEM67 TNFRSF11A TNFRSF11B TNFSF11 TP63 TRAPPC2 TREM2 TRIP11 TRPS1 TRPV4 TTC21B TWIST1 TWIST2 TYROBP WDR19 WDR34 WDR35 WDR60 WISP3 WNT1 WNT10B WNT5A WNT7A XRCC4 XYLT1 XYLT2 YY1 ZIC1 ZMPSTE24.* Thoracic Aortic Aneurysm or Dissection panel at the time comprised: *ABL1 ACTA2 BGN COL1A1 COL1A2 COL3A1 COL5A1 COL5A2 EFEMP2 ELN FBN1 FBN2 FLCN FLNA LOX MED12 MYH11 MYLK NOTCH1 PLOD1 PRKG1 SKI SLC2A10 SMAD2 SMAD3 SMAD4 TGFB2 TGFB3 TGFBR1 TGFBR2.*

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Contributions

EW wrote the manuscript, CJ helped with the literature review and liaising with the family, AO provided radiological expertise and accuracy and provided radiographs and MRI images, AC and JF ensured spinal/ orthopaedic accuracy, JJ ensured scientific accuracy of genomic variants and methodology, DJ coordinated investigation and diagnosis of the patient and supervised the project.

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Figure 1.

Proband at 14 years of age demonstrating facial dysmorphism of shallow orbits, slightly up-slanting palpebral fissures, and thin upper lip.

Figure 2.

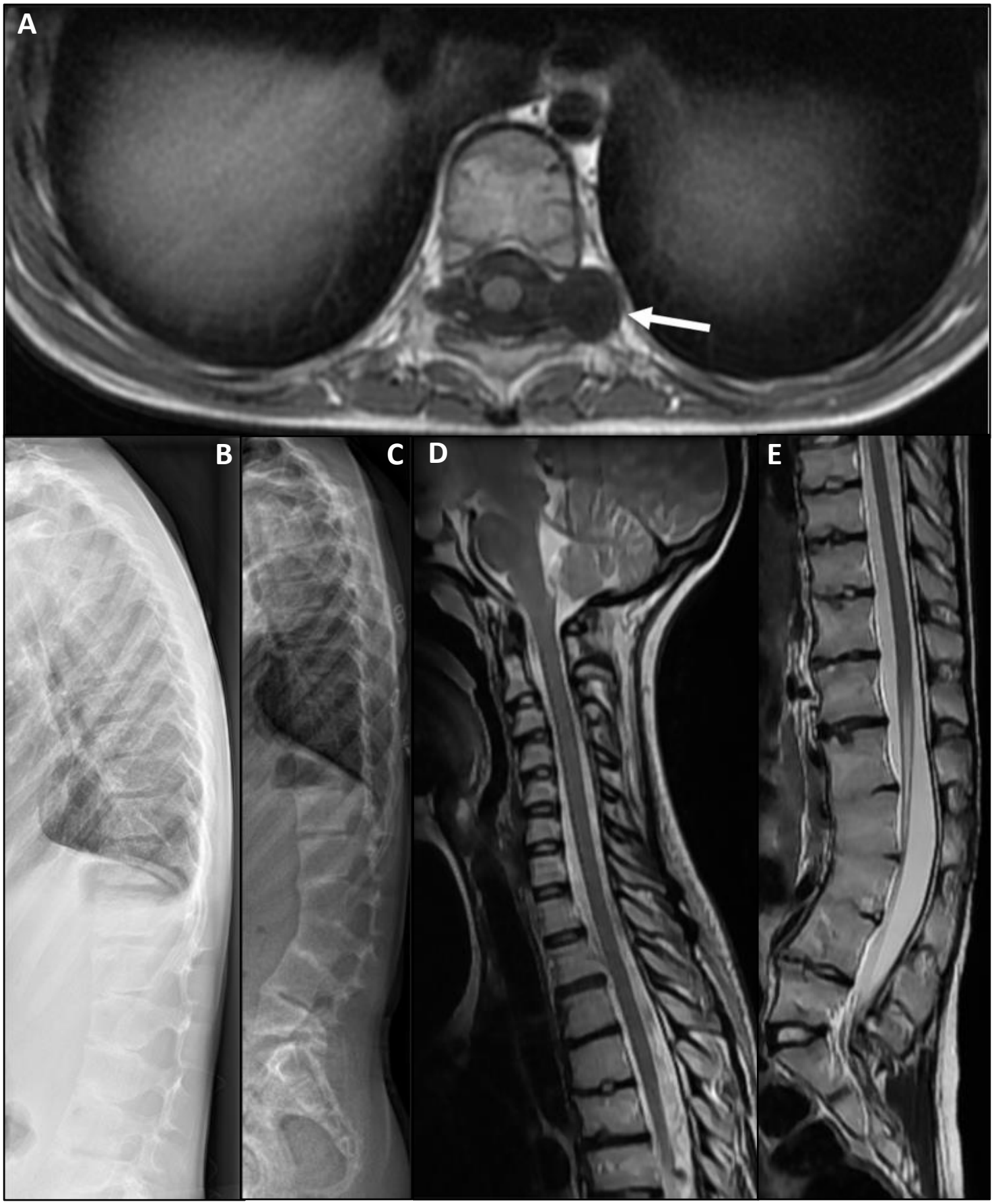

Figure 2 – Radiological Imaging.

A = Axial T1 MRI aged six years seven months shows dural ectasia with 1.5cm diameter dural pouch extending through the left T10/T11 intervertebral foramen (*arrow*).

B = Lateral thoracolumbar spine radiograph aged eight years five months shows irregular end plates and narrowing of the intervertebral disc spaces of the lower thoracic and lumbar spine, with a mild thoracic kyphosis.

C = Lateral thoracolumbar spine EOS image aged 12 years six months shows almost complete fusion of the L2 to L4 vertebral bodies and anterior fusion at L4/L5.

D = Sagittal T2 MRI cervical spine aged 13 years 11 months.

E = Sagittal T2 MRI lower thoracic and lumbar spine aged 13 years 11 months.

Individual	1	2	3	4	5	6	7	8	9	10	11	12	13	Presenting individual
Publication	Gripp et al. 2015 (Gripp et al. 1997)	Gripp et al. 2015 (Avela et al. 2011)	Gripp et al. 2015 (Gripp et al. 1997)	Gripp et al. 2015 (Chen et al. 2005)	Gripp et al. 2015 (Correia-Sa et al. 2013)	Gripp et al. 2015	Ejaz et al. 2016	Brown et al. 2017	Cappucio et al. 2020	Han et al. 2022	Yamada et al. 2022	Pasa et al. 2024	Rubadeux et al. 2024	
NOTCH3 variant	c.6461_6486del, p.(Gly2154fsTer78)	c.6692_93dup, p.(Pro2231fsTer11)	c.6692_93dup, p.(Pro2231fsTer11)	c.6732C>A, p.(Tyr2244Ter)	c.6663C>G, p.(Tyr2221Ter)	c.6247A>T, p.(Lys2083Ter)	c.6498_6577del, p.(Ala2167ProfsTer48)	c.6659_6660del, p.(Glu2220ValfsTer21)	c.6409_6410del, p.(Lys2137GlyfsTer104)	c.6603del, p.(Val2202SerfsTer44)	c.6732C>G, p.(Try2244Ter)	c.6602_6603del p.(Pro2201ArgfsTer40)	c.6663C>G p.(Tyr2221Ter)	c.6723_6736del, p.(Glu2241AspfsTer8)
Inheritance	De novo	De novo	Unknown	De novo	De novo	De novo	De novo	Unknown	De novo	De novo	De novo	Unknown	Unknown	De novo
Gender	Male	Male	Male	Male	Male	Male	Male	Female	Female	Male	Female	Female	Male	Female
Feeding problems	NC	Nasogastric-tube fed	NC	Feeding disinterest and avoidance Gastroesophageal reflux	NC	NC	Dysphagia Gastric-tube fed	Refractory dysphagia Gastrostomy	Gastroesophageal reflux Gastrostomy	-	Poor feeding	Feeding difficulties	Feeding difficulties Hiatus hernia Previously nasogastric-, now gastric-tube fed	Non-specific feeding problems in infancy
Growth problems	Disproportionately long extremities compared to torso	Disproportionately long extremities compared to torso	-	Short stature Extremely short trunk	-	Short stature	-	Failure to thrive	Failure to thrive Short stature	-	-	-	Short stature	Failure to thrive in infancy
Developmental delay (DD)/ Intellectual disability (ID)	+/+	+/-	+/ N/A	+/-	+/-	+/-	+/ N/A	+/NC	+/ N/A	NC	+/-	+/N/A	+/+	-
Vision problems	NC	NC	NC	Moderate visual impairment (20/70 vision)	NC	NC	Amblyopia	NC	NC	NC	-	NC	Nystagmus Exotropia Astigmatism	-
Hearing and ear issues	NC	NC	NC	Mixed hearing loss	Bilateral conductive hearing loss	NC	Conductive hearing loss	Middle ear effusions Narrow external ear canals	Sensorineural hearing loss Hypoplasia of the apical turn of the cochlear and modiolus Dysmorphic vestibule	NC	-	NC	Conductive hearing loss	Stenosis of inner ear Conductive hearing loss
Structural brain abnormality	Mild ventricular dilatation	NC	Chiari I malformation Hydrocephalus Chronic cerebellar herniation Sclerotic cerebellum and leptomeninges (autopsy)	-	-	N/A	Chiari I malformation Middle cranial fossa encephaloceles	Chiari I malformation with low-lying cerebellar tonsils Ventriculomegaly Dura mater 3-4 times thicker than normal	Bilateral temporal encephaloceles	Chiari 1 malformation	Chiari I malformation	Chiari I malformation Ventriculomegaly	Arachnoid cyst Chiari I malformation Periventricular leukomalacia Ventriculomegaly Moderate volume loss	Benign hydrocephalus

													white matter Thinning of corpus callosum	
Spine/ spinal cord abnormality	Syringomyelia Thoracic kyphosis Lumbar spina bifida occulta Dural ectasia Small nerve roots	Syringomyelia Kyphoscoliosis	Syringomyelia Scoliosis Malformed C1 vertebrae	Scoliosis Spinal fusion	Scoliosis	Tethered cord	Dural ectasia	Hemivertebra at L2 on prenatal ultrasonography Cervical spinal cord anteriorly displaced Kyphoscoliosis	Kyphosis Scoliosis Tethering of filum terminale Intra and extradural arachnoid spinal cysts Multiple abnormal vertebrae (odontoid process retroflexion, cleft anterior arch C1, cuneal deformation, posterior scallopping of multiple vertebrae)	Syringomyelia	Intradural spinal arachnoid cysts Wide spinal canal	Scalloped vertebrae	Scalloped vertebrae Ventral sacral extradural arachnoid cyst	Kyphosis Vertebral fusion
Lateral meningoceles	+	+	+	+	+	+	+	+	+	+	+	+	-	+
Neurological abnormalities	Hypotonia	Hypotonia Leg weakness	Hypotonia Reduced muscle bulk Neurogenic bladder	Hypotonia	Hypotonia	Hypotonia Incontinence Neuropathic pain	Hypotonia Hypotonic face	Facial and corporeal hypotonia	-	-	-	Hypotonia	Hypotonia Wide-based gait	Hypotonia Paraesthesia
Musculoskeletal features	Hypermobility Wormian bones Thickened calvaria Mild pectus carinatum Ossified sphenoid wings	Hypermobility Acro-osteolysis of the distal phalanges Single palmar crease Slender long bones with reduced mineral density	Hypermobility Wormian bones Mild pectus excavatum	Hypermobility Pectus excavatum	Hypermobility Pectus excavatum Thickened calvaria Mandibular distraction osteogenesis	Hypermobility Pectus excavatum	Hypermobility	Hyperextensible joints Round feet	Hypermobility	NC	Hypermobility Skin hyperextensibility Pectus excavatum	Hypermobility Pectus excavatum	Mild pectus excavatum	Hypermobility
Cardiovascular	Aortic dilatation	NC	PDA VSD Structural vascular anomalies (retro-oesophageal right subclavian artery, interrupted inferior vena cava)	PDA VSD Aortic dilatation	Bicuspid aortic valve	NC	Tubular hypoplasia of the aortic arch Coarctation VSD ASD Bicuspid aortic valve Bilateral SVC	NC	PDA ASD	NC	PDA PFO	ASD Aberneth y type 2 shunt PFO	Abnormal coronary artery Asymmetric hypertrophy of ventricular septum	-
Genitourinary	Inguinal hernia with hydrocele Unilateral	Inguinal hernia Secondary hydronephrosis	Cryptorchidism	Cryptorchidism Bilateral Inguinal hernia	Cryptorchidism	Cryptorchidism Incontinence	NC	Bilateral vesicoureteral reflux	Bilateral renal cysts Hypoplasia left kidney Microlithiasis	NC	-	-	-	Right anteriorly located asymmetric kidney

	cryptorchidism													
Facial dysmorphism	Down-slanting palpebral fissures Ptosis Low set ears Malar hypoplasia High palate Micrognathia Coarse hair Dolichocephaly Low posterior hairline Long and smooth philtrum Thin upper lip Dental crowding Prominent metopic sutures Narrow nasal root	Hypertelorism Ptosis Low set, posteriorly angulated ears with railroad tracks in helices and attached lobules Malar hypoplasia High narrow palate Dental crowding and defective tooth enamel Central incisors canonical in shape Micrognathia Coarse hair Dolichocephaly Epicanthic folds Thick and arched eyebrows Underdeveloped orbits Flame-like shape of palpebral fissures	Hypertelorism Down-slanting palpebral fissures Ptosis Low set ears Malar hypoplasia High narrow palate Micrognathia Coarse hair Trigonocephaly (prominence of metopic sutures) Flat suborbital ridges Low nuchal hairline Tented upper lip Short, webbed neck	Hypertelorism Down-slanting palpebral fissures Ptosis Low set ears Malar hypoplasia Micrognathia Coarse hair Dolichocephaly Shallow orbits Telecanthus	Telecanthus Down-slanting palpebral fissures Ptosis Low set ears Malar hypoplasia Long philtrum Tented upper lip High narrow palate Dental crowding Micrognathia Coarse hair Glossoptosis Hypertelorism	Down-slanting palpebral fissures Epicanthic folds Hypotonic face Ptosis Low set ears Thin upper lip Malar hypoplasia Dental crowding Micrognathia Coarse hair	Plagiocephaly Tall cranial vault Sparse hair Hypoplastic supraorbital ridges Epicanthus Hypertelorism Ptosis Down-slanting palpebral fissures Midface hypoplasia Small nares Long philtrum Thin upper vermillion High arched palate Bifid uvula Short upper lingual frenulum Asymmetric low set ears with short canals Microretrognathia	Dolichocephaly, bitemporal narrowing, flattened facial profile, hypertelorism with telecanthus, unilateral left eye ptosis, narrow external ear canals, posteriorly rotated low-set ears, micrognathia, thin vermillion border, smooth philtrum Hypotonic face	Prominence of the occipital bone Low posterior hairline Arched eyebrows Synophyrs Bilateral ptosis Down-slanting palpebral fissures Low set ears Anteverted nares Protruding columella Smooth philtrum Thin lips Micrognathia High and narrow palate	Hypertelorism Telecanthus Ptosis High arched eyebrows Low set ears Low posterior hairline	Proptosis Ptosis Up-slanting palpebral fissures Hypertelorism Arched eyebrows Sagging cheeks Long philtrum Micrognathia	Low hairline Arched eyebrows Down-slanting palpebral fissures Hypertelorism Ptosis Epicanthic folds Malar hypoplasia Long philtrum Thin upper vermillion Micrognathia Low-set ears Posteriorly rotated ears Webbed neck	Metopic ridging Broad forehead Arched eyebrows Down-slanting palpebral fissures Hypertelorism Ptosis Epicanthic folds Malar hypoplasia Long philtrum Thin upper vermilion Micrognathia Posteriorly rotated ears High arched palate	Shallow orbits Slightly up-slanting palpebral fissures Malar hypoplasia Thin upper lip Overcrowding of teeth
Cleft palate	-	-	-	+	-	-	-	+	-	-	+	-	-	-
Additional features	Keloid scaring High nasal voice Pseudo-clubbing	Obstructive sleep apnoea High nasal voice	Keloid scaring Tracheostomy Obstructive sleep apnoea Hypertrichosis Umbilical hernia	High pitched voice	Keloid scaring High nasal voice Umbilical hernia	Omphalocele Keloid scaring High nasal voice Macrocytic anaemia Open anterior fontanelle	Hoarse voice Weak cry Bilateral single palmar crease	Severe obstructive sleep apnoea	Transient hypothyroidism	-	-	Bile duct dilation Hypoplastic, irregular and intrahepatic gallbladder	Epilepsy Self-injurious behaviour Autism spectrum disorder	-
Surgical management	Surgical repair of bilateral ptosis, right inguinal hernia with hydrocele, and cryptorchidism Spinal fusion	Vertical expandable prosthetic titanium rib	Mitrofanoff procedure Hydrocephalus shunting repair Lateral meningocele surgical repair	Atenolol for aortic dilatation Growing rod spinal construct Multiple lengthening procedure	Bilateral mandibular expansion	Repeat surgical release of tethered cord	Surgical repair of cardiac abnormalities	Decompression of Chiari malformation Ventriculostomy Ladd procedure for malrotation of the intestine Furlow palatoplasty	Fundoplication	-	-	Tracheostomy	-	Pain clinic Physiotherapy

	surgery from T1 to L3			Shilla construct Tympanostomy tubes Orchidopexy Herniorrhaphy Palate repair										

Summary of individuals with *NOTCH3* variants in the medical literature, in comparison to our described individual. N/A – Unable to determine (for intellectual disability, this applies either due to age of child or death of child). NC – Not commented on in publication. – Persistent ductus arteriosus. PFO – Patent foramen ovale.VSD – Ventricular septal defect.

Feature	Presenting individual	*NOTCH3*-related lateral meningocele syndrome	*NOTCH2*-related Hadju-Cheney syndrome (Cortés-Martín et al., 2020)	Copenhagen syndrome	Kyphoscoliotic subtype of Ehlers-Danlos syndrome (Brady et al., 2017; Giunta et al., 1993; Rohrbach and Giunta, 1993)	Congenital Marfan syndrome (Dietz, 1993)
Prevalence	Very rare (<1/1,000,000)	Very rare (<1/1,000,000)	Very rare (<1/1,000,000)	Very rare (<1/1,000,000)	Kyphoscoliotic subtype very rare (<1 in 1,000,000) All subtypes 2000 per million	Rare 1/5,000-1/10,000
Gene	*NOTCH3*	*NOTCH3*	*NOTCH2*	-	*PLOD1* *FKBP14*	*FBN1*
Inheritance type	Autosomal dominant	Autosomal dominant	Autosomal dominant	Unknown aetiology	Autosomal recessive	Autosomal dominant
Feeding problems	+	Non-specific feeding issues Gastroesophageal reflux Dysphagia Feeding support	-	-	Feeding issues associated with hypotonia/ weakness	-
Growth problems	+	Short stature Growth problems	Short stature	-	-	Bone overgrowth Tall stature
Developmental delay	-	May have developmental delay/ intellectual disability	Delayed motor development	-	Gross motor delay Intelligence usually normal	Congenital forms of Marfan Syndrome
Vision/ eye problems	-	Visual acuity problems Structural eye abnormality	-	-	Blue-tinge to sclera Microcornea Myopia Rupture of eye globe	Ectopia lentis Myopia Retinal detachment Early onset cataracts Glaucoma
Hearing issues	+	Hearing loss	Hearing loss	-	Hearing loss	-
Structural brain abnormality	+	Hydrocephalus Chiari I malformation	Hydrocephalus	-	-	-
Spine abnormality	+	Scoliosis Kyphosis Vertebral scalloping Vertebral fusion Syringomyelia	Biconcave vertebrae Kyphoscoliosis Cervical instability Vertebral collapse	Ankylosis Kyphosis Progressive anterior vertebral fusion	Kyphoscoliosis, (often congenital)	Scoliosis
Lateral meningoceles	+	Present	Present	-	May be present in EDS (not specific to Kyphoscoliotic subtype)	May be present
Neurological abnormalities	+	Weakness Paraesthesia Neurogenic bladder	Complications of meningoceles or hydrocephalus	-	-	-
Musculoskeletal features	+	Ligamentous laxity Hypotonia Hypermobility Hyperextensibility of skin Wormian bones	Severe progressive bone loss Acroosteolysis Generalised osteoporosis Generalised osteopenia Cranial abnormalities (e.g. delayed suture closure, Wormian bones, thickened dome of skull) Fractures of long bones Joint laxity Genu valgum Serpentine fibula Short fingers Thoracic deformities	-	Hypermobility Hypotonia Joint subluxations/ dislocations Hand deformities Arachnodactyly Pectus deformity Soft, doughy skin Skin fragility Atrophic scarring	Joint laxity Pes planus Chest wall deformity Bone overgrowth Hindfoot deformity Dural ectasia Protrusio acetabulae Skin striae
Cardiovascular	-	Aortic abnormalities Septal defects Valve abnormalities Persistent foetal circulation	Congenital heart disease PDA Septal defects	-	Medium vessel rupture Aneurysms Dissection Aortic root dilatation	Dilatation of the aorta Mitral valve prolapse
Genitourinary	+	Cryptorchidism (males) Renal abnormality	Hypospadias Cryptorchidism Renal cysts Kidney failure	-	-	-
Facial dysmorphism	+	Hypertelorism High arched eyebrows Down-slanted palpebral fissures Ptosis Malar flattening Long philtrum Thin upper lip	Premature loss of teeth Coarse features Elongated philtrum Micrognathia Low set eats Telecanthus Hypertelorism Synophyrs	-	Epicanthic folds Down-slanting palpebral fissures Synophyrs Low set ears High palate	Enophthalmos Down-slanting palpebral fissures Malar hypoplasia Micrognathia High arched palate

		High palate Micrognathia	Long eyelashes Wide nose High arched palate Jaw malocclusion Hirsutism			
Cleft palate	-	+	-	-	+	-
Management	Pain clinic Physiotherapy	Pain clinic Physiotherapy Treatment of neurological sequelae Surgery	Management of complications	Bracing Surgical correction of deformity	Cardiac screening Blood pressure control with antihypertensive Treatment of complications	Cardiac screening Blood pressure control with antihypertensive Treatment of complications

Summary of features present in this individual compared to those that may present in differential diagnoses