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A novel mutation in the *SOX5* gene c.1627del; p.(Tyr543IlefsTer14) is associated to Lamb–Shaffer syndrome: a case report

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Abstract

Background Lamb–Shaffer syndrome (LAMSHF) is a rare neurodevelopmental disorder caused by heterozygous mutation or microdeletion involving the *SOX5* gene. LAMSHF is characterize by developmental delay, intellectual disability, poor expressive speech, mild dysmorphic facial features and skeletal abnormalities.

Case presentation We presented a case of a child with delayed psychomotor development in all areas, scoliosis, peculiar facies, and suspicion of intermittent endotropia, alteration in the alignment of one foot and difficulty in standing. These clinical features lead to genetics studies, in which a novel pathogenic variant in the *SOX5* gene was detected in association with LAMSHF.

Conclusions LAMSHF should be suspected in patients with developmental delay, speech delay, intellectual disability, behavioural disturbances, ophthalmological alterations and skeletal abnormalities. A novel pathogenic mutation in the *SOX5* gene c.1627del p.(Tyr543IlefsTer14) was identified in this patient as responsible of Lamb–Shaffer syndrome. This case contributes to understanding the genetic characteristics, clinical features, and diagnosis of LAMSHF.

Keywords LAMSH, SOX5, p.(Tyr543IlefsTer14), Developmental delay, Neurodevelopmental delay

Background

Lamb–Shaffer syndrome (LAMSHF; MIM#616803) [1, 2] is a rare neurodevelopmental disorder, described in very few patients, that is caused by heterozygous mutation or microdeletion in the *SOX5* gene. Also, deletion in 12p12 region [3–5] or chromosomal translocation [2] containing *SOX5* gene have been identified as causes of LAMSHF.

The prevalence of LAMSHF is currently unknown. According to the revised literature, LAMSHF has been only reported in less than 100 patients worldwide [6, 7], and only a small case series has been previously published [1–3, 8, 9].

LAMSHF is characterized by developmental delay, intellectual disability, poor expressive speech and mild dysmorphic facial features [1, 2, 5, 10, 11]. In addition, ophthalmological alterations and skeletal abnormalities [12, 13] can also be shown in these patients.

Located on chromosome 12p12.1, *SOX5* gene produces at least five transcript isoforms through the expression of different promoters, alternative start sites, and alternative precursor messenger RNA (m-RNA) splicing. The longer isoform (NM_006940) encodes a protein initially named L-SOX5 (now called SOX5), which is the major isoform in the brain. *SOX5* is part of the *SOX* [1, 14] gene family, which includes *SOX2, SOX4, SOX5, SOX9, SOX10*

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and *SRY*. These genes have been described to be involved in very important processes such as sex determination, chondrogenesis, skeletogenesis and neurogenesis [15–17]. Most pathogenic variants of the *SOX* gene family are de novo (except for the *SRY* gene) and cause haploinsufficiency, as it happens in the case of the *SOX5* gene causing LAMSHF. Only in a very few cases describing LAMSHF the mutation is inherited from parents [18].

We present a case of a child diagnosed with neurodevelopmental delay, sialorrhea and scoliosis. Trio-WES was conducted according to our hospital protocol for these patients, and a novel pathogenic, de novo mutation in *SOX5* gene was identified. This case is added to the reduced number of publications previously reported regarding LAMSHF.

Case presentation and genetics findings

We reported a clinical case of a two-and-a-half-year-old male, only son of non-consanguineous parents without history of genetic disease. The mother reported a well-controlled and echographically normal pregnancy and no prior abortions. Born at 38 gestational weeks and with a normal neonatal screening, he had no episodes of hospitalization during the neonatal period.

At 4 months of age, a slight right plagiocephaly was detected at a paediatric check-up, being treated with a cranial orthosis and followed up until 10 months of age.

At the age of 18 months, he was evaluated by neuropaediatrics due to peculiar facies (epicanthus, broad nose, small palpebral fissures, hypertelorism, micrognathia, synophrys and big ears), delayed psychomotor development in all areas and scoliosis. He was also evaluated by ophthalmologists, who diagnosed him of marked epicanthus with suspicion of intermittent endotropia. In addition, due to an alteration in the alignment of one foot and the difficulty in standing, he was recommended to use a dynamic ankle foot orthosis (DAFO). The child was also referred to paediatric rehabilitation and neuropaediatric consultations.

Following the protocol established in our hospital for those cases in which psychomotor retardation is evident, doctors ordered both a genetic testing for Fragile X syndrome (FRAXA) [19] and a Microarray-based Comparative Genomic Hybridization (aCGH). No pathogenic findings were revealed in any case.

At this point, with the aim of extending the study due to nonspecific dysmorphic features and a phenotype indistinguishable from many other inherited disorders with intellectual disability, a Trio-WES (whole exome sequencing) was performed in the patient and his biological parents.

The library for this technique was prepared using the Comprehensive Exome Panel technology (captures > 20,000 genes, > 99% coverage of the genes included in the RefSeq, CCDS and GENCODE databases > 85% of the alterations responsible for diseases of genetic origin and flanking splicing regions (5–20 bp), with a size of 41.2 Mb).

The sequencing was performed on a state-of-the-art mass sequencer, NovaSeq 6000 SystemTM (Illumina). The sequences were aligned against the reference genome (GRCh37/hg19), filtered according to specific quality criteria and analysed with DRAGENTM BioIT Platform software.

A heterozygous de novo frameshift variant c.1627del; p.(Tyr543IlefsTer14) was detected in exon 13 of *SOX5* gene (NM_006940.5), (GRCh37:g.23696291delA) with a probable genotype–phenotype association (Table 1), being later confirmed by Sanger sequencing. This finding in the patient was not detected in his parents.

Not having been previously reported in clinical databases (Clinvar, PubMed, LOVD) this variant was also not included in the control population databases (1Kgenome, gnomAD). However, some nonsense and frameshift mutations in this gene (Table 2) have been described as a cause of the LAMSHF with a dominant inheritance pattern [14, 20]. These patients showed, among other clinical features, language delay from a mild to severe degree.

Table 1 Variants identified in genes with a probable genotype–phenotype association

Gene	**Effect**	**Sample**			**In silico pred**		**Categorization**
	Nomenclature	**Zigosity**			**Conservation**		**OMIM inheritance**
#MIM	**Variant**	**Variant allele frequency**			**Frequency**	**ClinVar ID**	**Variant inheritance**
Coverage	**Exon**	**Depyh**			**Population**	**dbSNP**	**Interpretation**
SOX5	Frameshift deletion	Child	Mother	Father	NA	NAv	Pathogenic
604,975	Chr12(GRCh37):g.23696291delA	Heterozygosity	–	–	NA	NAv	AD
100%	(NM_006940.5): c.1627delT; p.(Tyr543fs)	45%	–	–	NA		De novo
	Exon 13	64X	162X	187X	NA		–

NA not applicable, *NAv* not available

Table 2 Pathogenic variants of the SOX5 gene case described in the ClinVar [21] and LOVD [22] databases

cDNA variant	Protein variant	GRCh37	Condition	Clinical significance (last reviewed)
c.224_225del (NM_006940.6)	p.(Gln75fs)	NC_000012.11: g.24048772_24048773del	LAMSHF	Likely pathogenic (22 June 2022)
c.352C>T (NM_006940.6)	p.(Arg118Ter)	NC_000012.11: g.23999046G>A	LAMSHF	Pathogenic (18 October 2021)
c.405dup (NM_006940.6)	p.(Lys136fs)	NC_000012.11:g.23998993dup	LAMSHF	Pathogenic (1 August 2020)
c.433dup (NM_006940.6)	p.(Thr145fs)	NC_000012.11:g.23998965dup	LAMSHF	Pathogenic (25 October 2021)
c.442C>T (NM_006940.6)	p.(Gln148Ter)	NC_000012.11: g.23998956G>A	Not provided	Pathogenic (23 October 2020)
c.518G>A (NM_006940.6)	p.(Trp173Ter)	NC_000012.11: g.23908622C>T	LAMSHF	Pathogenic (5 August 2019)
c.519G>A (NM_006940.6)	p.(Trp173Ter))	NC_000012.11: g.23908621C>T	Not provided	Pathogenic (1 September 2019)
c.559G>T (NM_006940.6)	p.(Glu187Ter)	NC_000012.11: g.23908581C>A	Intellectual disability	Likely pathogenic (10 September 2020)
c.622C>T (NM_006940.6)	p.(Gln208Ter)	NC_000012.11: g.23893920G>A	LAMSHF	Pathogenic (15 May 2018)
c.637C>T (NM_006940.6)	p.(Arg213Ter)	NC_000012.11: g.23893905G>A	LAMSHF	Pathogenic (13 May 2021)
c.747_748del (NM_006940.6)	p.(Arg250fs)	NC_000012.11: g.23887680_23887681del	LAMSHF	Pathogenic (5 August 2019)
c.755dup (NM_006940.6)	p.(Gln253fs)	NC_000012.11:g.23887673dup	LAMSHF	Pathogenic (19 June 2021)
c.757C>T (NM_152989.3)	p.(Gln253Ter)	NC_000012.11: g.23887632G>A	Not provided	Likely pathogenic
c.820C>T (NM_006940.6)	p.(Gln274Ter)	NC_000012.11: g.23818489G>A	LAMSHF	Pathogenic (5 August 2019)
c.847C>T (NM_152989.6)	p.(Gln283Ter)	NC_000012.11: g.23818423G>A	Not provided	Pathogenic
c.959delC (NM_006940.6)	p.(Pro320fs)	NC_000012.11: g.23793806del	LAMSHF	Pathogenic (10 August 2020)
c.1060G>T (NM_006910.6)	p.(Gly354Ter)	NC_000012.11: g.23757425C>A	LAMSHF	Pathogenic (31 December 2017)
c.1381C>T (NM_152989.3)	p.(Gln461Ter)	NC_000012.11: g.23716260G>A	Not provided	Pathogenic
c.1411C>T (NM_006940.6)	p.(Arg471Ter)	NC_000012.11: g.23716269G>A	LAMSHF	Likely pathogenic (7 September 2018)
c.1465dup (NM_006940.6)	p.(Leu489fs)	NC_000012.11:g.23716215dup	LAMSHF	Pathogenic (16 December 2019)
c.1477C>T (NM_006940.6)	p.(Arg493Ter)	NC_000012.11: g.23716203G>A	LAMSHF,	Pathogenic (25 September 2019)
c.1600C>T (NM_152989.3)	p.(Arg534Ter)	NC_000012.11: g.23696277G>A	Not provided	Pathogenic
c.1613C>G (NM_006940.6)	p.(Ser538Ter)	NC_000012.11: g.23696303G>C	LAMSHF	Pathogenic (23 September 2021)
c.1639C>T (NM_006940.6)	p.(Arg547Ter)	NC_000012.11: g.23696277G>A	Not provided	Pathogenic (30 September 2021)
c.1659del (NM_006940.6)	p.(Glu553fs)	NC_000012.11: g.23696258del	Not provided	Pathogenic (23 October 2020)
c.1782G>A (NM_006940.6)	p.(Trp594Ter)	NC_000012.11: g.23689593C>T	LAMSHF	Pathogenic (5 August 2019)
c.1819G>T (NM_006940.6)	p.(Glu607Ter)	NC_000012.11: g.23689556C>A	LAMSHF	Pathogenic (5 August 2019)
c.1977C>A (NM_006940.6)	p.(Tyr659Ter)	NC_000012.11: g.23689398G>T	Not provided	Likely pathogenic (18 February 2022)

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Therefore, it was then considered that this frameshift variant (c.1627del; p.(Tyr543IlefsTer14) changes the reading frame, generating a premature stop codon and causing a loss-of-function effect on the SOX5 protein.

According to the American College of Medical Genetics and Genomics (ACMG) variant classification guidelines [23], this variant should be considered pathogenic. There criteria supporting this state are the following: It is a null variant in a gene where LOF (Loss of function) is a known mechanism of disease (PVS1), it is absent from controls in Exome Aggregation Consortium (PS2), it does not exist in general population databases (gnomAD, 1000 G, ESP) (PM2) and the protein length changes as a result of in-frame deletions in a non-repeat region or stop-loss variants (PM4).

The demonstration of a de novo pathogenic variant in the *SOX5* gene in a patient with symptomatology compatible with LAMSHF, and the evidence of other nonsense and frameshift pathogenic variants reported as cause of LAMSHF, lead us to ascertain that the new mutation c.1627delT; p.(Tyr543IlefsTer14) in the *SOX5* gene, causes LAMSHF.

Other variants with low population frequency were also identified in Trio-WES (Table 3) but for them, a genotype–phenotype correlation was not possible.

Our patient was finally diagnosed with LAMSHF. He currently carries DAFO and has been performing autonomous walks and runs from 22 months of age. At the time of writing this article, the boy was two-and-a-half years old, 12.0 kg (P15) weight, 91.5 cm (P25) height and craniofacial perimeter 47.7 cm (P5). Nowadays, he is still being followed by Neuropaediatrics due to his neurodevelopmental disorder. He goes to kindergarten, eats, understands everything, points, imitates, uses propositional bisyllables and parents refer a positive evolution since the early childhood care.

Discussion

Pathogenic variants in the *SOX* genes have been proposed to cause developmental disorders [24]. Concretely, the *SOX5* gene has been described in association with developmental delay, language and motor deficit, intellectual disability, behavioural disturbance including autistic traits, and other partially penetrating features [1] (facials features, strabismus and skeletal abnormalities).

LAMSHF should be suspected in individuals with developmental delay, speech delay, intellectual disability, behavioural disturbances, ophthalmological alterations and skeletal abnormalities. According to Zawerton's [1] language delay (97%), behavioural disturbances (49%) and seizures (19%) have been described as the most frequent clinical features in affected patients. Other symptoms were hypotonia (51%) and strabismus (27%). Skeletal abnormalities (fused vertebrae, microcephaly, thoracic kyphosis, joint hyperlaxity and tooth anomalies) have also been described in LAMSHF. These percentages will presumably change as new cases are described.

Our patient presented delayed psychomotor development in all areas, epicanthus phenotype, broad nose, small palpebral clefts, hypotonia, strabismus, scoliosis

Table 3 Low population frequency variants detected in the Trio-WES without genotype phenotype correlation

Gene	cDNA variant	CRCh37	Protein variant	Categorization	Variant inheritance	OMIM heredity and phenotype
NHS (NM_198270.3)	c.926C > G (exon 4)	ChrX g.17739634C > G	p.(Pro309Arg) missense	VOUS	Hemizygosis	Syndrome Nance-Horan (XLD)
DCHS1 (NM_003737.3)	c.887G > A (exon 2)	Chr22 g.6661958C > T	p.(Arg296Gln) missense	VOUS	Heterozygous (Inherited from father)	Syndrome de Van Maldergem 1 (AR)
FKRP (NM_001039885.2)	c.928G > C (exon 4)	Chr19 g.47259635G > C	p.(Glu310Gln) missense	VOUS	Heterozygous (Inherited from the mother)	Autosomal recessive limb-girdle muscular dystrophy type 2I (AR), Congenital muscular dystrophy type 1C (AR), Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 5 (AR)
GRIN1 (NM_007327.3)	c.467G > A (exon 3)	Chr9 g.140040251G > A	p.(Arg156His) missense	VOUS	Heterozygous (Inherited from the mother)	Neurodevelopmental disorder with or without hyperkinetic movements and seizures (AR)
KIF1A (NM_004321.7)	c.4798C > T (exon 45)	Chr2 g.241658536G > A	p.(Arg1600Trp) missense	VOUS	Heterozygous (Inherited from the mother)	Hereditary sensory autonomic neuropathy type 2 (AR), Autosomal spastic paraplegia type 30 (AD; AR)

XLD X-linked dominant, *AR* autosomal recessive, *AD* autosomal dominant, *VOUS* variant of uncertain significance

and joint laxity. All these clinical features are similar to those described in the LAMSHF. Skeletal anomalies (pectoral malformations) and epileptic seizures were not evident in the patient.

Hypertelorism, small eyes, small fingers, retromicrognathia, synophrys, large and separated ear and sialorrhea were described in our patient but not included in OMIM as clinical symptoms of LAMSHF. Thus, they should also be considered in future medical reviews of the disease.

Molecular genetic testing approaches depends on hospital protocols and laboratory possibilities. In our patient, with intellectual disability and nonspecific dysmorphic features, the performance of a single-gene testing or multigene panel was intended to discard other inherited disorders with the same clinical manifestations and from which the patient's phenotype was indistinguishable. Therefore, a Trio-WES was conducted on the patient and their parents.

Variants in the *SOX5* gene have been described in association with the LAMSHF, which can be detected by array-CGH [3, 5] or WES [10]. The majority are nonsense and missense variants [1]. According to the inheritance pattern, it has been demonstrated that most patients with LAMSHF present a de novo mutation. Here, we reported a frameshift pathogenic variant de novo (loss-of-function) in exon 13 of *SOX5* gene.

Conclusion

LAMSHF is a rare genetic neurodevelopmental disorder that should be suspected in individuals with developmental delay, speech delay, intellectual disability, behavioural disturbances, ophthalmological alterations and skeletal abnormalities. Trio-WES is the technique with the best results for the diagnostic approach of these patients and so, it should be performed initially. In our patient, the presence of a pathogenic de novo variant in *SOX5* together with clinical symptoms allowed us to diagnose LAMSHF. This case is added to the reduced number of publications regarding LAMSHF and contributes to understanding the genetic characteristics, clinical features, and diagnosis of this syndrome.

Abbreviations

LAMSHF	Lamb–Shaffer syndrome
NGS	Next-generation sequencing
WES	Whole-exome sequencing
Array-CGH	Array comparative genomic hybridization
m-RNA	Messenger RNA
DAFO	Dynamic ankle foot orthosis
FRAXA	Fragile X syndrome
NMD	Nonsense Mediated Decay
ACMG	American College of Medical Genetics and Genomics
XLD	X-linked dominant
AR	Autosomal recessive
AD	Autosomal dominant
SNV	Single nucleotide variant
NA	Not applicable
NAv	Not available

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Author contributions

JCA and RGT drafted and critically reviewed the manuscript. JLPS was the principal physician in the patient's case. ECA, ESR, NGR and SIA contributed to data collection, literature search and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the parents of the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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