Severe congenital cutis laxa: Identification of novel homozygous LOX gene variants in two families

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Abstract

We report three babies from two families with a severe lethal form of congenital cutis laxa. All three had redundant and doughy-textured skin and two siblings from one family had facial dysmorphism. Echocardiograms showed thickened and poorly contractile hearts, arterial dilatation and tortuosity. Post-mortem examination in two of the babies further revealed widespread ectasia and tortuosity of medium and large sized arteries, myocardial hypertrophy, rib and skull fractures. The presence of fractures initially suggested a diagnosis of osteogenesis imperfecta. Under light microscopy bony matrices were abnormal and arterial wall architecture was grossly abnormal showing fragmented elastic fibres. Molecular analysis of known cutis laxa genes did not yield any pathogenic defects. Whole exome sequencing of DNA following informed consent identified two separate homozygous variants in the LOX (Lysyl Oxidase) gene. LOX belongs to the 5-lysyl oxidase gene family involved in initiation of cross-linking of elastin and collagen. A mouse model of a different variant in this gene recapitulates the phenotype seen in the three babies. Our findings suggest that the
1 | INTRODUCTION

Cutis laxa syndromes encompass a large group of rare connective tissue disorders associated with reduced skin elasticity. Subtyping is based on the mode of inheritance and extra-cutaneous manifestations. Autosomal recessive cutis laxa type I (ARCL type I) is associated with pulmonary and/or vascular complications and can be caused by variants in LTBP4, FBLN5 or FBLN4. LTBP4- and FBLN5-related cutis laxa results in prominent pulmonary emphysema, diaphragmatic hernia, and diverticulosis of the genitourinary and gastrointestinal tract.1,2 FBLN4-related cutis laxa is associated with arterial tortuosity and aneu-rysm formation3 and closely relates to arterial tortuosity syndrome.4 Currently about one third of all ARCL type I cases are molecularly explained, suggesting that there are additional genes to be identified (Unpublished data, B. Callewaert, 2017).

We report the finding of homozygous variants in LOX (Lysyl Oxidase - OMIM *153455) in two unrelated families as a cause for a severe lethal form of ARCL type I associated with both pulmonary failure and arterial tortuosity. LOX encodes an extracellular copper enzyme that has a pivotal role in lysine and hydroxylysine cross-linking of collagen and elastin in the extracellular matrix of the cardiovascular, respiratory, skeletal and cutaneous systems. A previously reported knockout mouse model (Lox−/Lox−) closely recapitulates the phenotype reported herein.

1.1 | Clinical report

1.1.1 Patient 1

This male baby was the first child born to consanguineous (first cousin) Indian parents. The maternal age at delivery was 22 years and the paternal age was 33 years. Delivery was vaginal at 39 weeks gestation following an uneventful pregnancy. Meconium stained amniotic fluid was noted following spontaneous rupture of membranes. Birth weight was 3170 g (25th – 50th percentile). The baby had relatively poor Apgar scores of 3, 4 and 4 at 1, 5 and 10 min, respectively. The baby soon developed significant respiratory distress with low oxygen saturations despite intubation and ventilation with 100% oxygen, addition of nitrous oxide, high frequency oscillation and full circulatory support. A chest drain was inserted when a small left sided pneumothorax developed. A stressed, poorly contractile heart with thickened myocardium and the presence of extremely dilated vessels arising from it was identified on echocardiography. Clinical examination identified redundant and lax skin, and facial dysmorphic features, including a convex nasal ridge and lax and overfolded ear helices. Radiography of the thorax indicated variably aged rib fractures, which initially raised the possibility of osteogenesis imperfecta (Figure 1). Despite extensive resuscitation efforts he died at 10 h of respiratory failure. Renal ultrasound prior to death was normal. A diagnosis of ARCL type I was suspected.

1.1.2 Patient 2

Given the severe presentation in their first baby, close ultrasound surveillance was undertaken in the second pregnancy with a low probability first trimester screen and normal anatomical scans at 19, 24 and 27 weeks gestation. There were no fetal anomalies noted at 33 weeks; however, the amniotic fluid volume was mildly reduced (amniotic fluid index [AFI] 9.0 cm). At 34 weeks, the amniotic fluid volume was further reduced (AFI 5.0 cm) and redundant neck skin and an enlarged heart (occupying 50% of the thorax) were seen. Fetal echocardiography confirmed cardiomegaly and noted dilated and tortuous great arteries. Follow-up at 35 and 36 weeks gestation confirmed these findings and an emergency caesarean section was undertaken at 37.2 weeks gestation for fetal compromise. The male baby weighed 3370 g (75th – 90th percentile), with a length of 49 cm (75th percentile) and head circumference of 35 cm (75th percentile). Apgar scores were 9 at 1 and 5 min. The initial echocardiogram demonstrated good biventricular function with mild to moderate mitral and tricuspid regurgitation and evidence of ectatic coronary arteries. The baby developed rapidly progressive respiratory distress with evidence of persistent pulmonary hypertension and poor oxygenation despite ventilation, nitrous oxide and prostaglandin treatment. Rib fractures were demonstrated on radiology. Death occurred within hours of birth.

Neither parent has a history of skin, cardiac or vascular issues. Both had formal cardiovascular assessments with no evidence of vascular abnormalities based on transthoracic echocardiogram and abdominal ultrasound (mother) and CT angiogram (father). The mother conceived for the third time while the pathogenicity of the LOX variant was being debated. Although its causal nature could not be definitively confirmed at that time a decision was made to offer prenatal diagnosis. Testing identified the baby as a heterozygous carrier of the LOX variant and the pregnancy continued with subsequent delivery of a healthy boy. A fourth pregnancy was ended in the early second trimester following identification of homozygous LOX variants on

LOX gene is a novel cause of severe congenital cutis laxa with arterial tortuosity, bone fragility and respiratory failure.

KEYWORDS
ARCL1 (autosomal recessive cutis laxa type 1), cutis laxa, LOX, Lysyl oxidase
prenatal diagnosis with chorionic villus sampling. Post mortem was declined.

1.1.3  |  Patient 3

This female baby was the sixth child born to reportedly non-consanguineous parents of Middle Eastern descent. Three older siblings were reportedly healthy, however the other two died in the first months of life with internal malformations, including diaphragmatic hernia in one. Based on prenatal ultrasound transposition of the great arteries had been suspected however adequate visualisation of the outflow tracts was challenging. Delivery was by planned caesarean section at 38.4 weeks gestation. Birth weight was 3300 g (50th percentile) and length was 50 cm (50th – 75th percentile). Oxygen supplementation was needed from the first minutes and throughout life, resulting in an average oxygen saturation of approximately 80%. Evidence of pulmonary emphysema was present on x-rays. The initial echocardiogram demonstrated biventricular hypertrophy, bilateral branch pulmonary artery stenosis, a long and very tortuous ductus arteriosus with bidirectional shunt and an abnormally tortuous and elongated aortic arch. Clinical examination identified redundant and lax skin although the presence of specific dysmorphic facial features was difficult to assess. Coarctation did not develop on closure of the ductus arteriosus but over time the branch pulmonary artery stenosis increased in severity and the right ventricle particularly became extremely dilated and hypertrophic. This was considered inoperable due to the presence of multiple and severe peripheral branch pulmonary artery stenoses, combined with an extreme degree of generalised vascular malformation and the child died at 6 months of age due to a combination of pulmonary atelectasis and right heart failure.
Neither parent has a history of skin, cardiac or vascular issues; however, no cardiac or vascular imaging was able to be performed.

2 | MATERIALS AND METHODS

Genomic DNA was extracted from blood leukocytes using standard procedures. Chromosomal microarray analysis was performed using the illumina CytoSNP-12 BeadChip and Karyostudio software version 1.4 (Illumina) (genome assembly GRCh 37/hg19). For whole exome sequencing in Patients 1 and 2, libraries were prepared using the Ion Ampliseq Exome RDY Kit (Life Technologies, Carlsbad, CA) with sequencing on the Ion Proton Sequencer (Life Technologies, Carlsbad, CA). Alignment and variant calling were performed using Torrent Suite software (Life Technologies), and variants were annotated, filtered, and analysed in Bench Lab NGS (Cartagenia, Leuven, Belgium). In Patient 3, exome sequencing (AmpliSeq Exome; Life Technologies) was undertaken. Details of the LOX variants have been submitted to the ClinVar database (ClinVar Accession numbers: SCV001468319 and SCV001478878). Considering LOX as a candidate gene for arterial tortuosity, an independent cohort of 32 patients presenting with arterial tortuosity was screened. Previous EFEMP2 (or FBLN4, Genbank accession number NM_016938.5) and SLC2A10 (Genbank accession number NM_030777.3) sequencing was performed in the cohort, without identification of any pathogenic variants. LOX was amplified by polymerase chain reaction (primers available on request) and polymerase chain reaction products were sequenced using next-generation sequencing (MiSeq, Illumina, San Diego, CA, USA) and compared with the wild-type sequence as submitted by the Genbank accession number NM_002317.5. Identified variants and polymorphisms, as well as regions with insufficient coverage were confirmed using Sanger sequencing. Informed consent was obtained for whole exome sequencing. Institutional ethics permission was not required.

3 | RESULTS

Postnatal investigations in Patient 1 included acylcarnitine assay, chromosomal microarray and TORCH serology, all of which were normal apart from the presence of multiple regions of loss of heterozygosity (LOH) on the array, consistent with the known parental consanguinity. One of the known autosomal recessive cutis laxa genes, PYCRI (NM_001282280), was located within one of these LOH regions.

Post-mortem examination in Patients 1 and 2 identified dysmorphic facial features, including an ovoid shaped head with marked occipital oedema, convex nasal ridge, hypoplastic alae nasi and large, lax and dysplastic ears. The skin appeared pale, lax and wrinkled and had a dough-like consistency. Multiple posterior rib fractures of varying ages were present in both babies and Patient 2 also had an occipital fracture with associated haemorrhage (Figure 1). There was marked dilatation of the aorta and medium sized systemic arteries including the umbilical, coronary and carotid arteries, which appeared tortuous with varicosities (Figure 2). Similar abnormalities were noted in the pulmonary arteries whose walls were thickened and collapsed into the arterial lumens. The annuli of the pulmonary and aortic valves were dilated. The lungs were small by weight and showed appropriate maturation in Patient 1, but were normally grown in Patient 2.

![Marked tortuosity of coronary arteries (A). 3D image of heart and associated tortuous vessels with arrow indicating ascending aorta (B). Histology of normal control aortic wall (C) compared to aortic wall from Patient 1 (D) showing disorganisation and fragmentation of elastic fibres. Lung histology (E) demonstrating abnormal thickening of the media of pulmonary arterial walls (arrows) [Colour figure can be viewed at wileyonlinelibrary.com]](image-url)
The large systemic and pulmonary arteries appeared dysplastic histologically. The wall of the aorta was poorly organised, with a haphazard arrangement of myofibroblastic cells and poor organisation and formation of elastic laminae. The elastic fibres in the inner portion of the muscular wall had a concentric arrangement, but appeared thickened. In the mid portion the wall was acellular with thin elastin fibres, and external to this the elastin had an irregular pattern. The smaller arteries were better organised with a subendothelial fibroconnective tissue layer and an irregular elastic lamina, but the muscle in the wall was disorganised. Arterioles appeared normal. The pulmonary arteries were abnormally formed with markedly thickened walls which had collapsed into the lumens, which were narrowed and sometimes almost obliterated (Figure 2).

There was patchy, poor intramembranous ossification in the skull, with thick trabeculae consisting of woven bone, a normal complement of osteocytes but little osteoblastic rimming. The ossification process was delayed and incomplete. Sections from the femoral epiphysis showed normal ossification. Sections taken from the posterior rib showed woven bone. Some ribs showed callus formation.

The aorta, a branch of the coronary artery and skin were examined ultrastructurally. These showed poorly developed internal elastic laminae with concentrated elastic fibre microfibrils and little elastin moiety in between. The elastic fibres in the deep reticular dermis were poorly developed and displayed irregular outlines. The amorphous elastin content in these fibres was reduced but the microfibrillar component was present in normal concentration both within the fibre and in its immediate periphery. Foci of collagen fibres showed poor or absent bundling (Figure 3). There was neither loss nor aggregation of microfibrils as seen in other examples of cutis laxa.

In Patients 1 and 2, molecular analysis of genes known to cause congenital cutis laxa (FBLN4, FBLN5, LTBP4, PYCR1, ATP7A, ATP6V0A2 and ALDH18A1) was inconclusive. Subsequent “quad” whole exome sequencing (DNA analysis in both affected babies and both parents) confirmed the absence of pathogenic variants in any of the known genes but identified a homozygous missense variant in LOX (NM_002317.5(LOX): c.[1021A > C];[1021A > C] p. [Thr341Pro];[Thr341Pro]), which was heterozygous in both parents and confirmed by Sanger sequencing. This was classified as a variant of uncertain significance based on the absence of previous reports in the medical literature or available databases, although it was not present in any of the WES datasets generated locally, is not present in population databases (1000G, dbSNP, ExAC, ESP6500, GnomAD) and is predicted to be deleterious in Polyphen2, SIFT, Provean and Mutation Taster. The CADD-PHRED score was 31. The variant alters a highly conserved amino acid residue in the lysyl oxidase protein (catalytic) domain (Figure 4). Exome sequencing in Patient 3 revealed a homozygous missense variant in the LOX gene (NM_002317.6): c. [749A > G];[749A > G] p.[Tyr250Cys];[Tyr250Cys] after earlier testing failed to identify any abnormalities or homozygous regions in or nearby previously published ARCL1 genes (FBLN4, FBLN5, LTBP4) and SLC2A10. This variant changes a highly conserved nucleotide and amino acid and is not present in any databases (gnomAD, dbSNP) or in inhouse generated databases. The variant is also located in the catalytic domain and in silico predicted to be deleterious (CADD-PHRED Score: 26). Screening for biallelic LOX variants in a cohort of 32 additional patients with arterial tortuosity and no variants in known genes associated with arterial tortuosity did not reveal causal variants in any of the patients.

4 | DISCUSSION

Lysyl oxidases are extracellular copper enzymes that initiate the formation of lysine and hydroxylysine crosslinks in elastin and collagen fibres. These crosslinks are essential for the stability and elasticity of elastin and collagen fibres that respectively provide resilience and

![FIGURE 3](image-url)  
**FIGURE 3** Electron micrograph of dermis in Patient 1. The elastic fibres are poorly developed. Their microfibrillar component is well represented but there is minimal elastin deposition. Note also the wide separation of the various connective tissue components as well as the focal poor bundling of several collagen fibres

![FIGURE 4](image-url)  
**FIGURE 4** LOX (lysyl oxidase) showing location of the Tyr250 and Thr341 variants within the catalytic domain of the C-terminal motif, which is highly conserved across species. LOX-family catalysis is vital for elastin and collagen crosslinking in multiple tissues

[Colour figure can be viewed at wileyonlinelibrary.com]
strength to extracellular matrix of connective tissues. There are five known human lysyl oxidases: LOX and LOXL1-4. Lysyl oxidase (encoded by LOX) is responsible for 80% of the lysyl oxidase activity in mouse aorta. Other lysyl oxidase enzymes are unable to compensate for the absence of LOX activity in mice.5,6 Lysyl oxidase activity is important for the fibrillar organisation of collagen and elastin fibres in various connective tissues. So far, two entities that affect lysyl oxidase function have been reported and result in elastic fibre degeneration along with neurological symptoms. These include the spectrum of occipital horn syndrome and Menkes disease (due to \(\text{ATP7A}\) variants) and (osteo)lathyrism (due to inhibition of lysyl oxidase function by \(\beta\)-aminopropionitrile).7,8

We report two families with homozygous variants in LOX, presenting with a cutis laxa phenotype within the severe spectrum of ARCL type 1B. Table 1 compares the phenotypic features of the cases presented here and the three known subtypes of ARCL type 1. The associated vascular dilatation and tortuosity, along with bone fragility, resemble most closely the \(\text{FBLN4}\)-associated subtype (ARCL1B, OMIM #614437),\(^{1,3,9-11}\) while the pulmonary hypoplasia resulting in early lethality indicates overlap with ARCL1A and ARCL1C due to \(\text{FBLN5}\) (OMIM #604850) and \(\text{LTBP4}\) (OMIM #604710) variants respectively. There was no obvious emphysema present in Patients 1 and 2, which is similar to ARCL1B (Unpublished data, B. Callewaert, MD, PhD & A. Beyens, MD, 2020), although X-ray features of emphysema were present in Patient 3. This is a more consistent finding in ARCL1A and ARCLC subtypes. In addition, cardiomegaly and heart failure, fractures, and spontaneous haemorrhages complemented the clinical picture. Patients 1 and 2 both had variably aged rib and other fractures despite vaginal and then caesarean delivery respectively, while no fractures were reported in Patient 3 (caesarean). This is consistent with what is known about other bone fragility conditions like osteogenesis imperfecta, where the mode of delivery seems to bear no relationship to the rate of fracture.12

Several lines of evidence support the pathogenicity of the LOX variants in the patients’ phenotype. First, both variants are located in the catalytic domain, absent in control databases and predicted deleterious by all in silico prediction algorithms including Polyphen2, SIFT, Provean and Mutation Taster. Second, Lysyl oxidase directly interacts with Fibulin-4 (\(\text{FBLN4}\)), the protein deficient in ARCL1B, with similar clinical effects on the vasculature, skin (cutis laxa), skeleton and respiratory system (including diaphragmatic abnormalities).9,10,13,14 Third, several LOX knockout mouse models (\(\text{Lox}^{−/−}\)) have been generated that presented with a very similar clinical phenotype to that seen in our patients.5,6,15 Fourth, the ultrastructural findings can be

<table>
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<th>Disorder</th>
<th>Patients 1 and 2</th>
<th>Patient 3</th>
<th>ARCL1A</th>
<th>ARCL1B</th>
<th>ARCL1C</th>
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<td>Gene</td>
<td>LOX</td>
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<td>(\text{FBLN4 (EFEMP2)})</td>
<td>(\text{LTBP4})</td>
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<td>Infancy</td>
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<td>Infancy to adulthood</td>
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<td>Redundant ++</td>
<td>Redundant +</td>
<td>Hyperextensible redundant +</td>
<td>Redundant +++</td>
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<td>Craniofacial</td>
<td>Ovoid head shape, occipital oedema, convex nasal ridge, antverted nares, hypoplastic alae nasi, large, flexible and overfolded ears</td>
<td>No specific dysmorphic features noted</td>
<td>Large ears, long ear lobules, sagging cheeks, micrognathia</td>
<td>Hypertelorism, highly arched palate, micrognathia</td>
<td>Bitemporal hypotrichosis, receding forehead, periorbital fullness, sagging cheeks, antverted nares, micrognathia</td>
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TABLE 1  Comparison of clinical features in our patients and other subtypes of ARCL type 1
interacted as showing a significant fault in elastogenesis: the microfi-
brillar scaffolding of the elastic fibre is forming but the actual assem-
blv of elastin in its interstices is minimal, all of which is consistent with
a lysyl oxidase anomaly.6

Mice knocked-out for LOX die shortly after birth with a normal
gross appearance but with cyanotic skin and in poor condition. Fre-
quent findings are large aortic aneurysms with aortic wall dysplasia,
diaphragmatic hernias, and large intrathoracic haemorrhages. Pulmo-
mary findings included impaired development of distal and proximal
airways with distal airway dilatation and wall thickening and reduced
numbers of proximal airways with reduced branching. These findings
became apparent before the development of diaphragmatic hernia,
precluding the latter as the main cause of the respiratory immaturity.

Electron microscopy of the aorta obtained from knockout mouse
models demonstrated a discontinuous smooth muscle layer, fragmen-
ted elastic laminae and normal collagen fibres similar to the observa-
tions made in our patients. There were no overt ultrastructural heart
abnormalities, suggesting a secondary effect on cardiac function. Lung
tissue showed reduced elastin staining from late gestation with thin-
er, irregular and fragmented elastin fibres in the pulmonary artery
walls and mesenchyme. Skin elastin showed similar features and there
were abnormalities of collagen present. Lox enzyme activity in Lox+/−
mice was <20% in skin fibroblasts and aortic smooth muscle cells
compared to Loxwt/wt mice.5,6,15

Interestingly, recent work identified likely pathogenic heterozy-
gous LOX variants in a total of 6 familial thoracic aortic aneurysms and
dissections, now designated AAT10 (aortic aneurysm, familial thoracic
10).16,17 The clinical phenotype has involved aneurysm/dissection of
the ascending aorta at younger than average ages (ranging from 11
years to the 70s) and arterial tortuosity. Affected individuals have
been otherwise mostly non-syndromic, however some have presented
with additional marfanoid features (pectus excavatum, highly arched
palate, dental crowding, myopia, tall stature, hernias) without fulfilling
the diagnostic criteria for a formal diagnosis of Marfan syndrome. Hist-
opathology (where available) demonstrated cystic medial necrosis
and fragmented elastic lamellae. Most of the LOX variants identified
have been missense variants located in the catalytic domain, along
with several truncating variants predicted to halve normal enzyme
activity. The heterozygous carrier parents of Patients 1 and 2 had no
vascular or cardiac abnormalities when assessed, however this does
not preclude development of these issues at some point.

In congruence with these data, a mouse model of the variant
identified by Lee et al (c.[893 T > G]; p.[Met298Arg)]) showed that
heterozygotes survived normally but had abnormal aortas with
increased length and discontinuous elastic lamellae, while homozy-
gous mice died shortly after birth with a phenotype similar to
homozygous knockout mice.16

5  |  CONCLUSIONS

In summary, we show that biallelic LOX variants are a novel cause of
severe lethal congenital cutis laxa with severe arterial and pulmonary
dysplasia. The clinical phenotype most closely resembles ARCL1B due
to FBLN4. Although the presence of multiple fractures raised the pos-
sibility of a severe form of osteogenesis imperfecta in Patients 1 and
2, the other clinical features should reliably differentiate these two
conditions. As these are the only cases reported to date the full clini-
cal spectrum is as yet unclear. However, the early postnatal lethality
in Patients 1 and 2, loss of Patient 3 in infancy and the poor survival
in mouse models supports this being a severe condition that should
be considered in the differential diagnosis of ARCL type 1.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
All authors were involved in drafting and/or revising the manu-
script for important intellectual content and have given final
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Callewaert, Gareth Baynam, Jan E. Dickinson, Jesper Norman
Steensberg and Birgitte Rode Diness provided clinical information.
Kym Mina and Jakob Ek undertook the molecular work that identi-
fied the LOX variants, while Bert Callewaert and Aude Beyens
were involved with the additional molecular studies. Gareth
Baynam and John Papadimitriou provided details and images of
the relevant pathology.

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The peer review history for this article is available at https://publons.

DATA AVAILABILITY STATEMENT
Data available from the authors on reasonable request.

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REFERENCES
1. Callewaert B, Su CT, Van Damme T, et al. Comprehensive clinical and
molecular analysis of 12 families with type 1 recessive cutis laxa. Hum
Mutat. 2013;34:111-121.
2. Beyens A, Boel A, Symoens S, Callewaert B. Cutis laxa: a comprehen-
sive overview of clinical characteristics and pathophysiology. Clin


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