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CLINICAL REPORT

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# Hypotrichosis-lymphedema-telangiectasia syndrome: Report of ileal atresia associated with a *SOX18* de novo pathogenic variant and review of the phenotypic spectrum

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## Abstract

Hypotrichosis-lymphedema-telangiectasia syndrome (HLTS) is a rare condition caused by pathogenic variants in the *SOX18* gene. SOX18 plays a key role in angio- and lymphangiogenesis due to its expression in venous endothelial cells from which the lymphatic system develops. It is also expressed in embryonic hair follicles, heart, and vascular smooth muscle cells. The main clinical symptoms of HLTS include sparse hair, alopecia totalis, lymphedema, most often affecting lower limbs, and telangiectatic lesions. Only 10 patients with a *SOX18* pathogenic variant have been described that presented with additional features such as hydrocele, renal failure, arterial or pulmonary hypertension, aortic dilatation, and facial dysmorphism. Here, we summarize these phenotypic variations and report an additional HLTS patient, with a 14-nucleotide de novo duplication in *SOX18* and congenital ileal atresia, a feature not previously associated with HLTS.

**KEYWORDS**
genetic, HLTRS, HLTS, lymphangiogenesis, phenotype, transcription factor

## 1 | INTRODUCTION

Hypotrichosis-lymphedema-telangiectasia syndrome (HLTS, OMIM 607823) is a very rare syndrome that associates lack of bodily hairs with lymphedema and cutaneous telangiectasias (Irrthum et al., 2003). Pathogenic variants have been discovered in *SOX18*, encoding a transcription factor, in both heterozygous (dominant) and homozygous (recessive) states. Only 10 individuals with *SOX18* pathogenic variants from eight distinct families have been described to date (Table 1) (Bastaki et al., 2016; Devriendt et al., 2002; Glade et al., 2001; Irrthum et al., 2003; Moalem et al., 2015; Proesmans et al., 1989; Valenzuela et al., 2018; Wangberg et al., 2018; Wünnemann et al., 2016). Some patients have additional signs, such as aortic dilatation (Wünnemann et al., 2016) or renal dysfunction leading to end-stage renal disease, necessitating renal transplantation (Moalem et al., 2015).

In two consanguineous families (Patients 1–3, Table 1), the pathogenic variants were homozygous *c.283T>A* (p.W95R) or *c.310G>C* (p.A104P) substitutions that were present in heterozygous state in the unaffected parents. In all other families, the pathogenic variants were heterozygous premature stop codons or a 14-nucleotide duplication, all leading to truncation in the *trans*-activation domain. These pathogenic variants likely have a dominant-negative effect by inhibiting compensatory transcription factor binding (Brouillard et al., 2016).

In this article, we report a new patient with a de novo pathogenic variant in *SOX18*, presenting with HLTS and life-threatening ileal atresia, a possible new phenotypic feature of HLTS.

  

## 2 | CASE PRESENTATION

The patient (Patient 11, Table 1) is a white male born to a 27-year-old mother and 38-year-old father (Figure 1a). Both parents are healthy Caucasians and there was no evidence of consanguinity. The patient has an elder brother and a maternal half-brother who are asymptomatic. During pregnancy, the mother took pro re nata Tylenol (acetaminophen), Valtrex (valacyclovir) for mouth blisters and prenatal vitamins. She denied tobacco, alcohol, and recreational drug use. Her prenatal glucose tolerance test was normal. She gained 14 kg during pregnancy. Fetal movements were normal, with onset at around 18 weeks of gestation. At 5 months, prenatal ultrasound imaging showed possible hydronephrosis and subsequent ultrasounds showed polyhydramnios with fetal anasarca, pericardial effusion, ascites, and dilated bowels. No other pregnancy complication was noted.

The patient was born at 33 weeks and 5 days of gestation by an urgency caesarean section for nonimmune hydrops fetalis (NIHF). His Apgar scores were 9–9-9, but he had to be intubated in the first hour

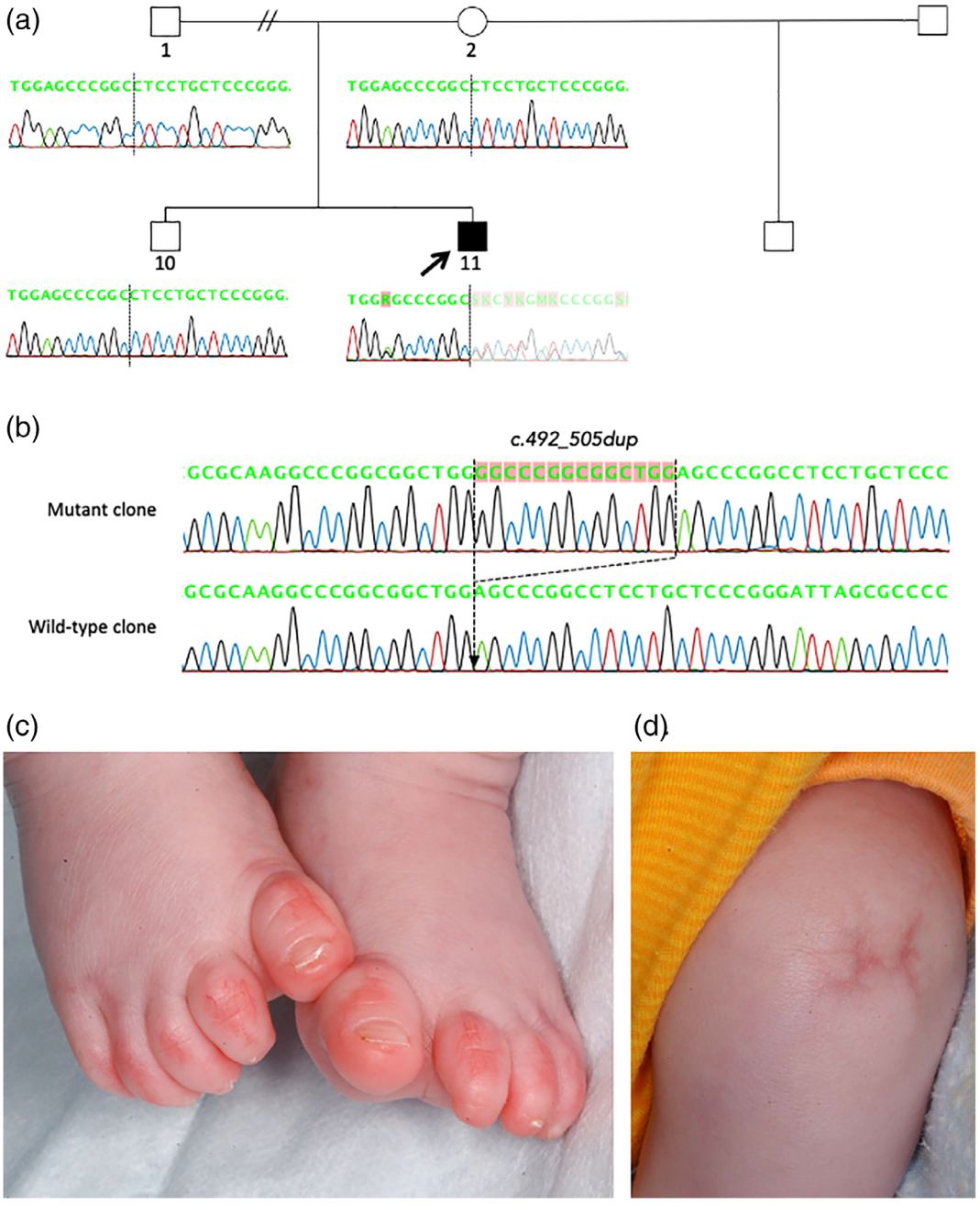


**FIGURE 1** A new family with a *SOX18* pathogenic variant. (a) Pedigree and gDNA sequences of *SOX18* exon 2. Double sequence seen only in index patient (arrow). (b) Sequences of cloned amplicons showing the 14 nt insertion resulting from duplication of nucleotides 492 to 505 (*GGCCCGGCGGCTGG*). (c, d) Index at birth: (c) telangiectasias on toes and hypoplastic nails; (d) telangiectasia on knee [Color figure can be viewed at wileyonlinelibrary.com]

of life and treated with surfactant following the occurrence of respiratory distress. His birth weight was 2613 g, one *SD* above the average for his gestational age. The prenatal pericardial effusion was postnatally confirmed and resolved within 8 weeks. On the first day of life, the patient developed abdominal distention and sepsis. Exploratory laparoscopy showed ileal atresia with perforation, requiring a 5 cm bowel resection and ileostomy with mucous fistula. He passed his hearing test. He had almost absent hair on his scalp, absent eyebrows and eyelashes, red nose, red lines on the toes (Figure 1c), knees (Figure 1d), elbows and knuckles, toenail hypoplasia (Figure 1c), mottled skin on the back, and bilateral large hydroceles. Chromosomal analysis showed 46, XY normal male genotype at the band resolution of 675, in a total haploid set.

By the age of 2 months, the patient had a mottled rash on the torso and back, mild dysmorphic facial features and persistent bilateral hydroceles. His weight was 3640 g (10th-25th percentile), height 51.7 cm (10th–25th percentile), and head circumference 34.5 cm (5th-10th percentile). All growth parameters were adjusted for prematurity. Oral examination revealed a mild retrognathia.

The patient had a revision of his ileal surgery at 4 months of age. At the age of 9 months, the patient had red streaks with mild depression and dimples on both knees and cutis marmorata-like mottled rash on his back and abdomen. He was noted to sweat profusely. The second toenails were absent. His weight was 8.8 kg (25th percentile), height 68 cm (25th–50th percentile), and head circumference 44.5 cm (50th percentile), all adjusted for prematurity. Alopecia was obvious, and ears were normal in size and position, with slight over-folding of the left ear helix. Mild retrognathia was still present. Bilateral hydroceles had resolved, but the scrotal skin had multiple telangiectatic lesions. Cranial ultrasound and echocardiography were normal.

By 10 years of age, the patient had not had additional hospitalization or surgery. He was in 4th grade at school, had normal intellect, but needed reading tutoring and speech therapy for articulation. He took no medication, had headaches and seasonal allergies. He wore glasses. He had been followed by a cardiologist for a history of elevated triglycerides with normal echocardiography. His systolic and diastolic blood pressure, as well as heart rate, were within standards: 108/83 mmHg and 83 bpm. He had recurrent epistaxis, which had become more frequent during winter months. Endocrinological follow-up was put in place due to poor growth, low weight, and delayed bone age: height 125.7 cm (± 3rd percentile), head circumference 50 cm (± 3rd percentile), weight 23.65 kg (10th percentile). Gastrointestinal, renal, and urinary anamneses were normal. Hydroceles had remained absent, but scrotal telangiectasias and angiokeratomas were observed. Hypotrichosis persisted. The patient had poor wound healing, poikiloderma of central face, thighs, and acral extremities and telangiectatic lesions on extremities. Nails had abnormal ridging and second toenails were hypoplastic bilaterally. Atrophic scars due to mosquito bites (parental note) were visible on the skin of the feet. He had brachycephaly, a widened nasal bridge, normal dentition but hypertrophic gums.

Now, at 15 years of age, hypotrichosis and telangiectasia are still present. There is no lymphedema, but hydrocele is observed again. Aortic root dilatation has been detected on echocardiography. There is no arterial hypertension, but the patient takes daily Lisinopril for proteinuria. Serum biomarkers for kidney function are normal: nitrogen urea 14 mg/dL and creatinine 0.58 mg/dL. Growth development is within standards.

## 3 | GENETIC ANALYSIS

The coding part of *SOX18* (two exons) was Sanger-sequenced on blood-derived genomic DNA from the patient, his elder brother, and the parents. Only the index patient's DNA showed a double-sequence in exon 2 (Figure 1a), decoded after cloning and sequencing as a 14-nucleotide duplication (*c.492_505dup*) resulting in protein truncation (p. Glu169Glyfs*14) (Figure 1b). Parentality was ascertained using the Powerplex 16 HS System (Promega), confirming that the pathogenic variant occurred de novo.

## 4 | DISCUSSION

As our patient is clearly heterozygous for the *SOX18* pathogenic variant, the de novo event happened either in the gametes of one of the parents (gonadal mosaicism) or very early in the zygote. The same *c.492_505dup* de novo pathogenic variant has been reported in a Jordanian boy (Patient 8, Table 1) (Bastaki et al., 2016). That patient had total alopecia, toenail anomalies, and distinct craniofacial features including microcephaly. No lymphedema was noted but he had ascites and chylothorax in utero. Our patient (Patient 11, Table 1) has similar features, namely sparse or absent hair, absent second toenail, brachycephaly, and retrognathia. Lymphatic disease manifested in utero as polyhydramnios and at birth as puffy eyelids and hydrocele. In addition, he had life-threatening ileal atresia, a feature that has not yet been reported in patients with HLTS.

Summarizing the clinical features described in the 11 cases (Tables 1 and 2), we notice that the diagnostic triad of hypotrichosis, lymphedema, and cutaneous telangiectasia is not always present. Hypotrichosis is the key to diagnosis. It was present in all the patients except Patient 4, where it has not been determined.

Signs of lymphatic dysfunction (NIHF; face, eyelid, or limb edema; hydrocele) were also frequent (all except Patient 7) (Table 1). NIHF (minimum two of the following: skin edema, pericardial or pleural effusion, or ascites [Mardy et al., 2019]) has been highlighted by prenatal ultrasound in Patients 4, 8, and 11 (Table 2), one of whom died in utero (Patient 4). Of note, Patients 8 and 11 carry the same *c.492_505dup* pathogenic variant. In the most recent clinical report (Wangberg et al., 2018), a postnatal chylothorax, not detected by prenatal ultrasonography, was described in Patient 10, who also suffered from pulmonary hypertension. All males but Patients 8 and 9 had bilateral hydroceles (Patient 4, aborted male fetus, not determined). Primary lymphedema was not always present at birth (Patients 1, 2, 3).

**TABLE 1** Clinical features of the 11 patients with a *SOX18* pathogenic variant

| Patient | 1—(family I) | 2—(family II) | 3—(family II) | 4—(family III) | 5—(family III) | 6—(family IV) | 7—(family V) | 8—(family VI) | 9—(family VII) | 10—(family VIII) | 11—(family IX) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender | Female | Male | Female | Male fetus † | Male | Male | Female | Male | Male | Male † | Male |
| References | Glade et al., 2001<br>Irrthum et al., 2003 | Devriendt et al., 2002<br>Irrthum et al., 2003 | Irrthum et al., 2003 | Irrthum et al., 2003<br>Moalem et al., 2015 | Irrthum et al., 2003<br>Moalem et al., 2015 | Proesmans et al., 1989; Moalem et al., 2015 | Wünnemann et al., 2016 | Bastaki et al., 2016<br>Overman et al., 2019 | Valenzuela et al., 2018 | Wangberg et al., 2018 | This case |
| *SOX18* pathogenic variant | *c.283T>A*<br>p.Trp95Arg<br>Homozygous | *c.310G>C*<br>p.Ala104Pro<br>Homozygous | *c.310G>C*<br>p.Ala104Pro<br>Homozygous | *c.720C>A*<br>p.Cys240*<br>Heterozygous | *c.720C>A*<br>p.Cys240*<br>Heterozygous | *c.720C > A*<br>p.Cys240*<br>Heterozygous | *c.481C>T*<br>p.Gln169*<br>Heterozygous | *c.492_505dup*<br>p.Glu169Glyfs*14<br>Heterozygous | *c.712G>T*<br>p.Glu238*<br>Heterozygous | *c.541C>T*<br>p.Gln181*<br>Heterozygous | *c.492_505dup*<br>p.Glu169Glyfs*14<br>Heterozygous |
| Inheritance | Recessive | Recessive | Recessive | Dominant, de novo | Dominant, de novo | Dominant, de novo | Dominant, de novo | Dominant, de novo | Dominant, de novo | Dominant, de novo | Dominant, de novo |
| Ethnicity | Turkish | Caucasian (Belgian) | Caucasian (Belgian) | n/a | n/a | n/a | Caucasian | Jordanian | Caucasian | n/a | Caucasian |
| Consanguinity | + | + | + | – | – | – | – | – | – | – | – |
| Prenatal ultrasound | n/a | n/a | n/a | NIHF (chylous peritoneal and pleural effusions) | None | None | None | NIHF (pericardial effusion, ascites and chylothorax) | None | Bilateral hydroceles | NIHF (pericardial effusion + ascites)<br>Dilated bowels<br>Polyhydramnios<br>Possible hydronephrosis |
| Delivery (cause) | n/a | 32 w | 36 w | Died in utero at 30 w | n/a | n/a | C/S at term | Vaginal delivery at term | C/S at 34 w (fetal distress) | Induced at 41 w (post maturity) | C/S at 33 w (hydrops fetalis) |
| HYPOTRICHOSIS | | | | | | | | | | | |
| *Scalp hair* | Sparse | Very sparse | Very sparse | n/a | Very sparse | Very sparse | Sparse | Absent | Sparse | Absent | Very sparse |
| *Eyebrows* | Sparse | Absent | Absent | | Absent | Absent | Absent | Absent | Absent | Sparse | Absent |
| *Eyelashes* | Absent | Absent | Absent | | Absent | Absent | Absent | Absent | Absent | Sparse | Absent |
| *Pubic and axillary hair* | Sparse | n/a | Absent | | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| *Earliest onset* | Birth | 6 mo | 2 yo | | 6 mo | Birth | Birth | Birth | Birth | Birth | Birth |
| LYMPHATIC DYSFUNCTION | | | | | | | | | | | |
| *Face edema (onset)* | - | - | - | n/a | +/– (episodes in infancy) | + (birth) | - | - | - | - | - |
| *Eyelid edema (onset)* | - | - | - | n/a | + (birth) | + (birth) | - | + (11 mo) | + (birth) | - | + (birth) |
| *Leg/feet edema (onset)* | + (4 yo) | + (15 yo) | + (puberty) | n/a | +/– (episodes in infancy) | - | - | - | + (birth) | + (birth) | - |
| *Hydrocele (onset)* | | + (12 yo) | | n/a | + (birth) | + (birth) | | - | - | + (birth) | + (birth) |
| CUTANEOUS RED STAINS | | | | | | | | | | | |
| *Telangiectasia* | + (palms, soles) | n/a | n/a | n/a | + (scalp, scrotum, legs) | + (hands, knees, elbows, nasal, gingival) | + (face, limbs, torso) | n/a | - | + (scalp, legs) | + (scrotum, palms, soles) |
| *Cutis marmorata (like)* | + | n/a | n/a | n/a | n/a | n/a | + | + | n/a | + | + |
| *Other* | Angiomas | n/a | Vascular nevus | n/a | Eczema on cheeks | Hemangioma | Livedo reticularis at birth | Hemangiomas | n/a | n/a | Poikiloderma |

**TABLE 1** (Continued)

| Patient | 1—(family I) | 2—(family II) | 3—(family II) | 4—(family III) | 5—(family III) | 6—(family IV) | 7—(family V) | 8—(family VI) | 9—(family VII) | 10—(family VIII) | 11—(family IX) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neurologic | n/a | n/a | n/a | n/a | n/a | Learning difficulties<br>Brain calcifications | Brain calcifications | Learning difficulties | Normal development | Normal exam | Reading difficulties<br>Headaches |
| Head and neck | Mongoloid slanting | n/a | n/a | n/a | Broad root and tip<br>Epistaxis<br>Full lips<br>Prognathism | Oval face<br>Right eye naevus<br>Broad root and tip<br>Epistaxis (since transplantation)<br>Full lips<br>Long and narrow nose | Epistaxis | Microcephaly<br>Red thick everted lips | Broad nose tip<br>Full lips | None | Brachycephaly<br>Widened nose bridge<br>Epistaxis<br>Retrognathism<br>Gingival hypertrophy |
| Cardiovascular | No arterial hypertension | n/a | n/a | n/a | Arterial hypertension | Arterial hypertension<br>On statin therapy | Arterial hypertension<br>Ascending aorta dilatation | No arterial hypertension<br>Pericardial effusion | No arterial hypertension<br>Normal echocardiography | Pulmonary hypertension<br>Bidirectional patent ductus arteriosus | No arterial hypertension<br>Pericardial effusion<br>Aortic root dilatation<br>Elevated triglycerides |
| Respiratory (onset) | n/a | Respiratory distress (birth) | n/a | n/a | Episodes of pulmonary edema (infancy) | n/a | n/a | Normal examination | n/a | Respiratory distress (birth)<br>Interstitial lung disease<br>Chylothorax | Respiratory distress (birth) |
| Gastrointestinal | n/a | n/a | n/a | n/a | n/a | Ileocolic invagination | Asymptomatic carcinoid tumor | Reducible inguinal hernia | n/a | n/a | Sepsis on intestinal perforation with ileal atresia |
| Renal / urinary (onset) | n/a | n/a | n/a | n/a | Renal failure (5 yo)<br>MPGN<br>Renal transplantation (14 yo) | Renal failure (18 yo)<br>MPGN<br>Renal transplantation (27 yo)<br>MPGN | None | None | None | None | Proteinuria |
| Endocrine | None | n/a | n/a | n/a | n/a | Short stature at birth (3rd centile) | n/a | None | None | None | Short stature at birth<br>Delayed bone age |
| Integumentary | Normal nails | Normal nails<br>Thin skin | Normal nails<br>Thin skin | n/a | Normal nails | n/a | Dysplastic toenails | Hypoplastic toenails | Normal nails | Indurated thighs<br>Short umbilical cord | Absent toenails<br>Profuse sweating |

*Note:* †, deceased patient; n/a, no data available; +, present; –, absent.

Abbreviations: C/S, caesarean section; do, day(s) of life; mo, month(s) old; MPGN, membranoproliferative glomerulonephritis; NIHF, nonimmune hydrops fetalis; w, weeks (gestational age); yo, year(s) old.

**TABLE 2** Frequencies of the clinical features observed in 11 HLT (R)S patients with a *SOX18* pathogenic variant

| Sign or symptom | Number of cases | Patients (see Table 1) |
|---|---|---|
| Hypotrichosis * | 10/11 (90%) | 1, 2, 3, 5, 6, 7, 8, 9, 10, 11 |
| Lymphatic dysfunction * | 10/11 (90%) | 1, 2, 3, 4, 5, 6, 8, 9, 10,11 |
| *Hydrocele* | 5/8 males (62%) | 2, 5, 6, 10, 11 |
| Cutaneous red stains * | 8/11 (72%) | 1, 3, 5, 6, 7, 8, 10, 11 |
| Facial dysmorphism | 6/11 (54%) | 1, 5, 6, 8, 9, 11 |
| Epistaxis | 4/11 (36%) | 5, 6, 7, 11 |
| Nail abnormality | 3/11 (27%) | 7, 8, 11 |
| Arterial hypertension | 3/11 (27%) | 5, 6, 7 |
| Kidney dysfunction | 3/11 (27%) | 5, 6, 11 |
| Non-immune hydrops fetalis | 3/11 (27%) | 4, 8, 11 |
| Aortic dilatation | 2/11 (18%) | 7, 11 |

*Note:* Signs of the diagnostic triad of HLT(R)S are indicated with an asterisk. Lymphatic dysfunction include NIHF, face, eyelid or limb edema, and hydrocele.

Cutaneous red stains detected in HLTS patients include vascular lesions formed by clearly visible small vessels (telangiectasias) (Patients 1, 5–7, 10, 11), cutis marmorata-type lesions (thin and transparent skin with visible blood vessels or varicosities) (Patients 1, 7, 8, 10, 11), (hem) angiomas (Patients 1, 6, 8), mild eczema (Patient 5), livedo reticularis (Patient 7) and poikiloderma of central face, thighs, and acral extremities (Patient 11). Moreover, multiple atrophic scars and poor wound healing were highlighted in the patient of this report (Patient 11), which might be explained by the expression of *SOX18* during neovascularization associated with wound healing (Downes et al., 2009). All these observations confirm the phenotypic variability of HLTS.

There are other similarities between the HLTS diagnosed patients (Table 2). Facial dysmorphism was frequent: micro- or brachycephaly, broad nasal root or widened nasal bridge, full lips, and pro- or retrognathism have been described (Patients 1, 5, 6, 8, 9, 11), which suggests that SOX18 has an impact on facial morphogenesis through one of its multiple target genes. Patients 5, 6, 7, and 11 suffered from epistaxis, maybe due to telangiectatic lesions on the nasal mucosa. Three patients had hypoplastic or absent toenails (Patients 7, 8, 11). So far, two patients have also been described with dilatation of ascending aorta (Patients 7, 11). Two patients carrying the same p.Cys240* pathogenic variant (Patients 5, 6) experienced arterial hypertension and renal defects, leading to normo-complementaemic membranoproliferative glomerulonephritis (MPGN) that necessitated renal transplantation. These clinical signs led to the definition of a related phenotype, hypotrichosis-lymphedema-telangiectasia-renal defect syndrome (HLTRS; OMIM 137940) (Moalem et al., 2015). Our patient (Patient 11) is treated with Lisinopril for proteinuria and has an otherwise normal renal function. This medication could also hide arterial hypertension. Follow-up studies of all *SOX18* patients are needed to clarify genotype–phenotype correlation in HLTS and HLTRS.

In the gastrointestinal tract, an ileocolic invagination (Patient 6) successfully operated at 10 years old, an asymptomatic carcinoid tumor (Patient 7) and a small left reducible inguinal hernia (Patient 8) have been described. Here we add (Patient 11) a congenital ileal atresia that required a 5 cm bowel resection and ileostomy on the first day of life. Restoration of intestinal continuity was performed at 4 months of age.

Jejuno-ileal atresia (JIA) occurs in 1 in 5000 to 1 in 14,000 live births. Dilated bowel, ascites and polyhydramnios can be detected antenatally by ultrasonography, like in our patient (Adams & Stanton, 2014). Medication during pregnancy, such as the combination of acetaminophen and pseudoephedrine, has been associated with a nearly threefold increase in small intestine atresia (SIA). However, acetaminophen alone, as it is the case for our patient (Patient 11), has not been associated with fetal SIA (Werler et al., 2002). The causes of JIA are mostly unknown, with only 3.8% associated with an identified genetic defect (Best et al., 2012). A vascular basis has been suggested (Louw & Barnard, 1955). SOX18 may play such a role or be directly involved in gut differentiation.

HLTS patients are deprived of an effective treatment. However, Overman and coll. suggested that propranolol could alleviate some symptoms of these patients (Overman et al., 2019). They proposed that an antihypertensive propranolol treatment in Patient 7 explained his milder HLTS clinical features. In addition, they treated Patient 8 with propranolol at the age of 17 months for a recurrent pericardial effusion resistant to ibuprofen and prednisone. After 53 weeks of oral propranolol at a maximum dose of 4.1 mg/kg/day the effusion resolved completely (Overman et al., 2019). This sounds promising but further propranolol testing in HLTS patients is required.

## 5 | CONCLUSION

In conclusion, the phenotypic diversity among patients with a *SOX18* pathogenic variant reflects the pleiotropic functions regulated by this transcription factor. It strongly indicates that numerous clinical parameters have to be examined and followed-up in patients with HLTS symptoms. Further genetic and functional studies are anyhow required to dissect the specific effects of the different *SOX18* mutants during vasculogenesis, angiogenesis, and lymphangiogenesis, as well as their effects in disease progression and outcome.

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## AUTHOR CONTRIBUTIONS

Richard Coulie, Elodie Fastré, and Pascal Brouillard carried out the genetic analysis. Dmitriy M. Niyazov and Michael J. Gambello made the clinical diagnosis and follow-up. Richard Coulie, Dmitriy M. Niyazov, Pascal Brouillard, and Miikka Vikkula drafted the manuscript. All authors read and approved the final manuscript.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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