Short Report

Hypotrichosis-lymphedema-telangiectasia-renal defect associated with a truncating mutation in the SOX18 gene


SOX18 mutations in humans are associated with both recessive and dominant hypotrichosis–lymphedema–telangiectasia syndrome (HLTS). We report two families with affected children carrying a SOX18 mutation: a living patient and his stillborn brother from Canada and a Belgian patient. The two living patients were diagnosed with HLTS and DNA analysis for the SOX18 gene showed that both had the identical heterozygous C>A transversion, resulting in a pre-mature truncation of the protein, lacking the transactivation domain. Both living patients developed renal failure with severe hypertension in childhood for which both underwent renal transplantation. To our best knowledge this is the first report of renal failure associated with heterozygous mutations in the SOX18 gene. We conclude that this specific mutation results in a new, autosomal dominant condition and propose the acronym HLT-renal defect syndrome for HLTRS.

Conflict of interest

The authors declare that they have no conflict of interest.
Over the past few years, many of the molecular underpinnings of the formation of the lymphatic architecture and system have started to be elucidated (1). The mechanisms responsible for the molecular control of the lymphatic endothelial cell fate include key transcription factors: SRY-related HMG box-containing protein 18 (SOX18) (2), COUP-TFI, and prospero-related homeobox 1 (PROX1) (3).

SOX18 is the human homolog of the gene mutated in the spontaneous mutant mouse strains Ragged for which four different mutations in Sox18 were identified: Ra, RaJ, Rag1 and Ragop. SOX18 has been shown to directly induce Prox1 gene expression to initiate lymphangiogenesis (1, 2, 4). The mutant form of SOX18 can also interfere with the transcriptional activity of SOX-F family members including SOX7, SOX17 and SOX18 (5). The transcription factor SOX18 was shown to play a role in the development of hair, blood vessels and lymphatic vessels and when mutated, results in hereditary lymphedema, with unique clinical association of hypotrichosis, lymphedema, and telangiectasia (6). Heterozygous (dominant) or homozygous (recessive) mutations in SOX18 were originally described in three families with hypotrichosis–lymphedema–telangiectasia syndrome (HLTS) and included one of the two cases reported here (7). We report two unrelated patients with identical de novo heterozygous C>A mutation in the SOX18 gene with HTLS who developed renal failure requiring renal transplantation.

Case reports

Family I

This family was first reported by Irrthum et al. (7) and the parents were healthy and non-consanguineous. The proband’s older brother was the product of their first pregnancy. The pregnancy was complicated with non-immune hydrops fetalis and resulted in an intrauterine fetal death at 30 weeks gestation. The autopsy showed pericardial and pleural effusions and generalized vascular congestion with pulmonary lymphangiectasia. The proband was the result of the couple’s second pregnancy and the pregnancy with him was uncomplicated. He had large bilateral hydroceles that required surgical repair at 3 months of age, and scrotal telangiectasia (7). At 6 months of age, he experienced progressive hair loss, resulting in alopecia universalis by the age of two. As an infant and toddler, he experienced multiple episodes of facial, peripheral and pulmonary edema and recurrent epistaxis. He was originally diagnosed with HLTS.

Subsequently to the original report by Irrthum et al. (7), at 5 years of age, he presented with renal failure and severe hypertension (207/155 mmHg). Renal biopsy including electron microscopy (EM) showed a chronic microangiopathy involving the glomerular and extra-glomerular vasculature. On EM the podocytes showed microvillus hyperplasia and effacement of foot processes. He required almost a year of peritoneal dialysis but recovered sufficient renal function to discontinue dialysis for 9 years. During that time, he had a slow progressive deterioration in renal function requiring renal transplantation at age 14. Renal allograft function has been stable since transplantation and he is on enalapril (ACE-I). His facial features were dysmorphic (Fig. 1a) with puffy eyelids, broad nasal root and tip, full lips and prognathism. The parents of the proband went on to have a healthy daughter.

Family II

This case was originally described by Proesmans et al. (8). The proband was born to a healthy and non-consanguineous couple who had a healthy older child. The proband was born with hydrocele surgically corrected at 2.5 years. He was first referred at 9 years of age with a 2 year history of sparse hairs, absent eyebrows and eyelashes, cutaneous, nasal and gingival telangiectasia, low subcutaneous fat and normocomplementemic membranoproliferative glomerulonephritis (MPGN) (8). Repeat renal biopsy showed glomerular hypercellularity and mesangial expansion with prominent glomerular basement membranes (Fig. 2). Of note, the histological characteristics of a MPGN can also be found in many cases of thrombotic microangiopathy, the renal histopathological findings in the proband in family I. Thus, both cases are compatible with a MPGN type of glomerulonephritis against the background of a thrombotic microangiopathy. He had facial dysmorphism with an ovale face, full lips, puffy eyelids, a long and narrow nose with a broad nasal root and tip and prognathism as well as facial oedema. Scalp hair electron

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Fig. 1. (a) Index case of family I at 14 years of age. (b) Index case of family II at 38 years of age.
microscopic examination was normal and brain computed tomography (CT) scan showed calcified choroid plexus and abdominal ultrasound showed renal artery arteriosclerosis reminiscent of pre-mature aging. He did not have peripheral lymphedema. At age 10 he underwent abdominal surgery for ileocolic invagination. He had learning difficulties and at the age of 18 years, he developed progressive chronic renal failure with proteinuria and hypertension. Renal biopsy revealed MPGN and at the age of 25 he required peritoneal dialysis.

Ophthalmological examination revealed a right-sided naevus (2–3 mm) and a few central drusen. He had a successful renal allograft from a live donor at the age of 27. Since transplantation the patient has suffered from recurrent epistaxis and a unilateral idiopathic peripheral facial nerve palsy (Bell’s palsy), which resolved completely with corticosteroid treatment. Renal allograft function has been normal and stable since transplantation and he is not on ACE-I or ARB therapy. A recent brain magnetic resonance imaging (MRI) was suggestive of right-sided hippocampal sclerosis and his electrocardiogram (EEG) was normal. He was also diagnosed with facial basal cell carcinoma, which was resected. At 38 years of age, the patient looks older than his age with a reddish facial skin complexion and alopecia universalis (Fig. 1b). He is on immunosuppressive medication and a statin.

Genetic analysis

The SOX18 gene was sequenced on blood-derived genomic DNA of the two index cases and the stillborn brother in family I and all were found to have the same heterozygous nucleotide change (c.720C > A). This mutation results in the creation of a termination codon instead of the cysteine at position 240 (p.C240*). This residue is located in the second exon of SOX18, corresponding to the transactivation domain of the transcription factor [Fig. 4 in (7)]. Parental mutation analysis in both families showed no detectable mutation in the SOX18 gene (Figs 3 and 4). Parentality was ascertained in both families [Fig. 3 and (7)]. To exclude the possibility of combined mutations in our patients, we sequenced the two exons of SOX17 in all samples of both families and no mutation was detected.

Discussion

Over the past few years, many of the molecular mechanisms that underpin the formation of the lymphatic vascular tree and function have started to be elucidated (1). The SOX18 gene has a major role in the formation of blood and lymphatic vessels and mutations in this gene are known to results in HLTS. However, renal defects have never been reported in patients with this condition who had other mutations in the gene (6) nor in the Ragged or the Sox18 knockout mice (9). In contrast,
the double-knockouts Sox17+/−; Sox18−/− present with reduced neovasculature in the liver and kidneys (10). To our knowledge this is the first report of two patients with HLTS associated with progressive, severe renal dysfunction which required transplantation with both patients being heterozygous for the c.720C>A mutation in the SOX18 gene which resulted in a pre-mature truncation of the protein at the 240th amino acid (p.C240*) instead of the usual 384 residues. This mutation differs from the two other reported (p.A104P and p.W95R) which were associated with an autosomal recessive mode of inheritance and homozygosity because of parental consanguinity.

In contrast, the mutation reported in our patients was because of the same de novo mutation for which both of the patients were heterozygous. Interestingly, the same mutation was also found in the deceased fetus in family I. The presence of the mutation in both affected offspring in family I suggests gonadal mosaicism in one of the parents.

In family II, the older sib male was unaffected. In both families, the parentality was ascertained. We believe that this specific mutation is acting in a dominant-negative manner with a clearly distinct genotype/phenotype correlation.

Sox18−/− does not have a similar phenotype in the mice who present with only mild coat defect (5). In contrast, renal alterations were visible in Sox17/Sox18 double heterozygotes (10). Moreover, mutations in SOX17 gene in humans were also found to cause congenital renal anomalies and vesicoureteral reflux-1 (OMIM #19000) and 3 (OMIM #613674) (13). We screened SOX17 in the patients and their parents and found no mutations. Thus, the role of the SOX18 gene and the redundancy between the SOX proteins might differ between mice and man, as in the latter, a single truncated allele seems sufficient to display the renal phenotype. It is therefore very likely that the interaction with the SOX17 gene is altered in our patients. SOX18 might also play a role in the context of vascular development in the kidney through its interaction with other genes.

Fig. 4. Sequencing of the mutation in individuals of family II.

For example, matrix metalloproteinase-7 (MMP7) has also been found to be a target of SOX18 and the two genes are co-expressed in blood vessels of human skin (14). In contrast, MMP7 was overexpressed in a microarray gene expression analysis of patients with congenital renal dysplasia (15) characterized by disruption of normal renal development, cyst formation, impaired renal growth and reduced or absence of nephrons. It is thought that MMP7 inhibits formation of branching structures in certain cells that are stimulated by bone morphogenetic protein-7 (BMP7), which is essential for normal kidney development. Thus, the renal phenotype seen in our patients could also result from altered MMP7 function, or a combination of it with altered SOX17 signaling. Thus, we believe that this specific mutation in both our patients might be acting in a dominant-negative manner with a clearly distinct genotype/phenotype correlation. This is the first report of renal failure associated with a heterozygous SOX18 gene mutation, most probably because of abnormal glomerular lymph angiogenesis. Because it highlights are yet unreported renal manifestations associated with SOX18 mutations, we propose to call the disease caused by mutations in the SOX18 gene HLTRS, for hypotrichosis–lymphedema–telangiectasia–renal defect syndrome. In a clinical setting, this renal aspect linked to the c.720C>A mutation is very important as it leads to renal failure and the need for transplantation.

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References

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