SOX11-related syndrome: report on a new case and review
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List of key features
Intellectual disability
Microcephaly
Low-set ears
Hypotonia
Fifth finger hypoplasia

Introduction
The differentiation of embryonic stem cells to neuronal progenitor cells (NPCs) and the subsequent generation of mature neurons and glial cells from these NPCs is a complex process directed by the sequential activation of gene expression by the SOX [sex-determining region Y-related high-mobility-group (HMG) box] family of transcription factors. SOX11, a member of this family, is required for the differentiation of mature neurons (Bergsland et al., 2011; Kavyanifar et al., 2018) and plays a critical role in axonal projection, radial migration and dendritogenesis (Shim et al., 2012).

This transcriptional regulator, encoded by a 9002-nucleotide-long, intronless gene, is highly expressed in the human fetus, in the gastrointestinal tract, lung, spleen, pancreas, kidneys, and gonads, but particularly in the nervous system (Sock et al., 2004; Potzner et al., 2010; Wang et al., 2013), illustrating its key role in embryonic development. Moreover, it has also been shown to be essential for adult neurogenesis (Jankowski et al., 2006; Salerno et al., 2012; Mu et al., 2012; Ninkovic et al., 2013; Wang et al., 2013).

Recently, defects in the SOX11 gene were reported in seven patients, whose conditions fall into the class of the SWI/SNF-related intellectual disability disorders (SSRIDDs), a collective term suggested by Bögershausen and Wollnik (2018) to describe disorders related to BAF complex (also known as the mammalian SWI/SNF complex) genes. This term encompasses Coffin–Siris Syndrome (CSS; OMIM 135900), Nicolaides–Baraitser syndrome (OMIM 601358) and other overlapping syndromes. Collectively, these disorders exhibit a spectrum of features that includes developmental delay (DD), mild intellectual disability (ID), dysmorphic facial features, feeding difficulties, hypotonia, microcephaly, fifth digit nail/finger hypoplasia, prominent interphalangeal joints, brachydactyly, sparse hair, short stature, behavioral problems and seizures.

Here we report on a male Lebanese child with DD, ID and dysmorphic features, presenting a novel de-novo mutation in SOX11. The SOX11-related SSRIDD and a review of SOX11 reported cases are discussed.

Materials and methods
Case study
The male patient was referred for genetic counseling and genetic workup because of DD. His parents were not related, and the child was born after two miscarriages. An extensive clinical and paraclinical workup was done on the patient including EEG, EKG, brain MRI and whole exome sequencing (WES).

Molecular analysis
Informed consent for genetic analysis was obtained from the family in compliance with national ethics regulations. Genomic DNA was isolated from peripheral blood samples collected from the patient and his parents using standard techniques.

WES was performed on the patient. The analysis covered 99% of the exome with an average of 30 reads for the whole exome.

The parents were tested by Sanger sequencing for the analysis of a specific somatic mutation present in their affected son. The mutation was also confirmed in the patient by Sanger sequencing.

Whole exome sequencing
Approximately 37 Mb (214,405 exons) of the Consensus Coding Sequences were enriched from fragmented genomic DNA by >340 000 probes designed against the human genome (Nextera Rapid Capture Exome,
Illumina) and the generated library sequenced on an Illumina NextSeq or HiSeq 4000 platform (Illumina) to an average coverage depth 70-100X. An end to end in-house bioinformatics pipeline including base calling, primary filtering of low-quality reads and probable artifacts, and annotation of variants was applied. All disease-causing variants reported in HGMD, in ClinVar or in CentoMD (class 1) as well as all variants with minor allele frequency of less than 1% in ExAc database were considered. Evaluation was focused on exons and intron boundaries ±20. All relevant inheritance patterns were considered, provided family history and clinical information were used to evaluate eventually identified variants.

**Bioinformatic analysis**

In order to predict the effect of the identified sequence variations, different bioinformatics tools were applied; such as MutationTaster (http://www.mutationtaster.org/) (Schwarz et al., 2010), SIFT (http://sift.bii.a-star.edu.sg/) (Kumar et al., 2009), PROVEAN (http://provean.jcvi.org/index.php/) (Choi et al., 2012), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) (Adzhubei et al., 2010), and CADD (https://cadd.gs.washington.edu/) (Rentzsch et al., 2019). Homologene was used to study the conservation of the protein (https://www.ncbi.nlm.nih.gov/homologene) (Sayers et al., 2011). Lollipops was used to visualize the localization of the different variants along SOX11 (https://joiningdata.com/lollipops/index.html) (Jay and Brouwer, 2016).

**Results**

**Case report**

The patient, a boy, is the first-born child of healthy non-consanguineous Lebanese parents. He was born at full-term following an uneventful pregnancy and normal delivery, weighing 3250 g (42nd percentile). Although the patient’s length and occipitofrontal circumference (OFC) at birth were not available, they were considered normal by the parents. At the age of 6 months, parents noted a delay in developmental milestones. At the age of 15 months, he had a seventh cranial nerve paralysis, of unknown origin, that did not heal completely.

At the first examination, when he was 2 years old, he was unable to walk unhelped and could only say a few words. His length was 71 cm (15th percentile), OFC 48 (35th percentile) and weight 11.8 Kg (40th percentile). He had long eyelashes, a synophrys, thick eyebrows, low set ears, short but normal fifth digit phalanges in hands and feet, a second toe longer than the hallux on the left side, and hypospadias (Fig. 1). Laboratory investigations, including genetic tests, were refused by the family.

He was seen again at the age of 5 years. The major complaint of the parents was his severe DD and recurrent buccal mycoses. He was able to walk unhelped since the age of three and his speech was still rudimentary. His height was 104 cm (10th percentile), and his OFC 49 cm (12th percentile). Clinically, he had the same features seen before. Small 2–4 toenails were noted, similar to his father. The brain MRI of the patient as well as the EEG, and EKG were normal.

**Molecular results**

WES analysis showed a novel missense variant in SOX11, c.146T>A [p.Ile49Asn]. This likely pathogenic variant was confirmed in the patient by Sanger sequencing (Fig. 2) and not found in either parent. The detected variant was neither found in gnomAD nor 1000G and was predicted to be deleterious by SIFT (score = 0), probably damaging by PolyPhen2 (score = 0.998), disease-causing by MutationTaster (score = 194), deleterious by PROVEAN (score = -6.469) and deleterious by CADD (score = 34). The affected residue was shown to be conserved across several species (Fig. 3).

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Images of reported patient highlighting facial features (a), hand (b) and foot (c).
Fig. 2

Sanger sequencing electropherogram showing the \textit{SOX11} variant c.146T > A in the patient.

Fig. 3

Previously reported variants depicted on a linear representation of \textit{SOX11}, with the variant reported here, p.Ile49Asn, shown in blue. Alignment of residues around the affected amino acid (highlighted in yellow), showing conservation across several species.
Discussion

SOX11 is an essential regulator of embryogenesis and cell fate determination. It regulates the expression of multiple target genes, involved in various cellular processes (Wegner, 2010; Sha et al., 2012). Its expression has been found to be misregulated in several types of cancer tissues (Grimm et al., 2019).

We report here a male child with DD, severe ID, microcephaly, recurrent infections, thick eyebrows, long eyelashes, thick scalp hair and hypoesthesia. Exome sequencing uncovered a novel likely pathogenic de-novo variant in SOX11, a gene in which mutations were recently associated with SSRIDDs, two cases of which were classified by authors as CSS (Tsurusaki et al., 2014).

The residue affected in this SOX11 variant is located within the HMG domain, a motif shared by SOX proteins (Bowles et al., 2000; Schepers et al., 2002). This DNA-binding domain is essential for SOX11’s role as a transcriptional regulator, and thus affects various developmental processes (Dodonova et al., 2020). This domain, including the residue affected in the patient reported here, has been shown to be conserved across several species (Bowles et al., 2000; Schepers et al., 2002; Fig. 3). Five out of the eight SOX11 reported variants (including this study) fall within this HMG domain (Fig. 3). The four variants which localize in this domain have been found to affect downstream transcriptional activity in vitro (Hempel et al., 2016; Tsurusaki et al., 2014). The variant reported here is similarly expected to affect expression of downstream SOX11 targets, especially considering that the HMG domain is predicted to be lost due to this mutation by the in silico tools we used.

Interestingly, all reported SOX11 related cases, including the current study, are de novo mutations. Moreover, the mutations reported in genes of the BAF complex and related proteins that have been associated with SSRIDDs are also mainly de novo variants (Bögershausen and Wollnik, 2018). This is consistent with the finding that de novo mutations play a major role in neurodevelopmental, early-onset and rare disorders (Veltman and Brunner, 2012; Acuna-Hidalgo et al., 2016).

SSRIDDs are a genetically and phenotypically heterogeneous class of disorders caused by pathogenic variants in the BAF complex genes including SMARCA2, SMARCB1, SMARCA4, SMARCE1, ARID1A, ARID1B, DPF2, as well as PHF6 and SOX11 (Hoyer et al., 2012; Santen et al., 2012; Tsurusaki et al., 2012; Van Houdt et al., 2012; Wieczorek et al., 2013; Tsurusaki et al., 2014a, 2014b; Vasileiou et al., 2018). The BAF complex is an ATP-dependent chromatin remodeling complex required for regulating gene expression. While this complex has biologically diverse functions, it is particularly critical in embryonic neural development as it promotes the proliferation of neural progenitor cells, neurogenic cell division, migration of immature neurons and dendritic morphogenesis (Yoo et al., 2009; Sokpor et al., 2017). SOX11 expression is regulated by the BAF complex pathway, specifically through the transcription factor PAX6 (Wurm et al., 2008; Ninkovic et al., 2013) which could explain the overlapping symptoms of SOX11-related disorders with those of other SSRIDDs.

CSS is a rare autosomal dominant, multiple malformation SSRIDD resulting in numerous features including ID, DD, facial dysmorphism,Sparse scalp hair, hypertrichosis, frequent infections and feeding difficulties (Santen et al., 2013; Vergano and Deardorff, 2014). However, its defining characteristic appears to be hypoplasia of the fifth digit nails, followed by hypoplasia of the fifth digit phalanges, earning it the moniker of ‘fifth digit syndrome’ (Mannino et al., 2018). Tsurusaki et al. (2014) studied 92 CSS patients and identified two cases amongst them with SOX11 mutations. Three other individuals with SOX11 mutations were identified by Hempel et al. (2016) and were reported as having a ‘Neurodevelopmental disorder with CSS features’ rather than being diagnosed with CSS. A similar diagnosis was reported by Okamoto et al. (2018) for an individual with a SOX11 variant, while Khan et al. (2017) described a child with a SOX11 mutation as having a ‘phenotype resembling mild CSS’. Interestingly, a recent study reported a SOX4 variant in a patient exhibiting overlapping features as patients with SOX11 variants (Zawerton et al., 2019). This is consistent with the fact that SOX4 and SOX11 belong to the same subgroup of SOX proteins and share a similar expression pattern (Schepers et al., 2002). Whether or not SOX4 patients should be classified as SSRIDDs will become more clear as more reports of SOX4 variants emerge.

The clinical features of these seven subjects (shown in Table 1) vary widely, but fall within the spectrum of SSRIDDs phenotypes. Based on the clinical features described here, in particular the absence of fifth digit hypoplasia and of classic CSS facial features (such as coarse facies, sparse scalp hair and hypertrichosis), and in accordance with other reported cases of SOX11 mutations (Hempel et al., 2016; Khan et al., 2017; Okamoto et al., 2018), this patient does not fit the CSS clinical profile. Instead, as proposed by Bögershausen and Wollnik (2018), individuals with SOX11 variants, like the patient reported here, should be classified as having a distinct SOX11-related SSRIDD.
## Table 1 Clinical features of reported SOX11 patients

| Subject details | Tsurusaki et al. (2014) | Hempel et al. (2016) |
|-----------------|-------------------------|----------------------|
| **Sex**         | Female                  | Female               |
| **Origin**      | Caucasian               | Caucasian            |
| **SOX11 mutation** | c.347A>G (p.Tyr116Cys) | c.87C>A (p. Cys299G) |
| **Clinical features** | Developmental delay: + | +                    |
| CNS features    | Intellectual disability: + (mild) | + (mild) |
|                | Hypoplasia of 5th phalanx (hands): + | + |
| Facial features | Palpable capillary telangiectasia: + | + |
|                | Coarse facies: - | - |
| Skeletal features | Hypoplasia of 5th phalanx (feet): + | + |
| Others          | Hypoplasia of 5th finger: + | + |
|                | Hypertelorax: + | + |
|                | Hypertrichosis: + | + |
|                | Joint laxity: N/R | N/R |
|                | Hyperimmune infections: | |
|                | Nystagmus: - | - |
|                | Hypoplasia of 5th phalanx (toes): + | + |
|                | Extremities: | |

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**Conflicts of interest**

There are no conflicts of interest.

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SOX11-related syndrome

Wakim et al.

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