SOX11-related syndrome: report on a new case and review

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Abstract:

The *SOX11* gene is a member of the SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and in the determination of cell fate. Recently, *SOX11* variants were linked to cases of overlapping syndromes collectively termed SSRIDDs, which are mainly associated with variants in BAF complex genes. Patients with these various syndromes exhibit a spectrum of features including developmental delay, intellectual disability, feeding difficulties, hypotonia, short stature, microcephaly, fifth finger hypoplasia, behavioural problems and seizures. We report a novel de novo mutation in *SOX11*, c.146T>A [p.Ile49Asn], found by exome sequencing in a middle eastern child with intellectual deficiency, developmental delay, microcephaly, thick scalp hairs, long eyelashes and eyebrows, and low-set ears. No abnormalities of fingers were noted. The *SOX11*-related SSRIDD and a review of *SOX11* reported cases are discussed.

Key-words: Dysmorphology; *SOX11*; Variant; Exome

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 (SRY)-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; Ninkovic et al., 2013; Mu et al., 2012; Wang et al., 2013).

Recently, defects in the *SOX11* gene were reported in 7 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, behavioural 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 developmental delay. 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 (CCS) 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 inhouse bioinformatics pipelines including base calling, primary filtering of low quality reads and probable artefacts, 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 (MAF) 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 occipito-frontal 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 7th cranial nerve paralysis, of unknown origin, that did not heal completely.

At the first examination, when he was two 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 5th digit phalanges in hands and feet, a 2nd toe longer than the hallux on the left side, and hypospadias (Figure 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 developmental delay and recurrent buccal mycoses. He was able to walk unhelped since the age of 3 and his speech was still rudimentary. His height was 104cm (10th percentile), and his OFC 49cm (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 (Figure 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 (Figure 3).

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 hypospadias. 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 high mobility group (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; Figure 3). Five out of the eight *SOX11* reported variants (including this study) fall within this HMG domain (Figure 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, 2014a, 2014b; Van Houdt et al, 2012; Wieczorek et al., 2013; 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 dysmorphia, sparse scalp hair, hypertrichosis, frequent infections

and feeding difficulties (Vergano and Deardorff, 2014; Santen et al., 2013). 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.

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Legends

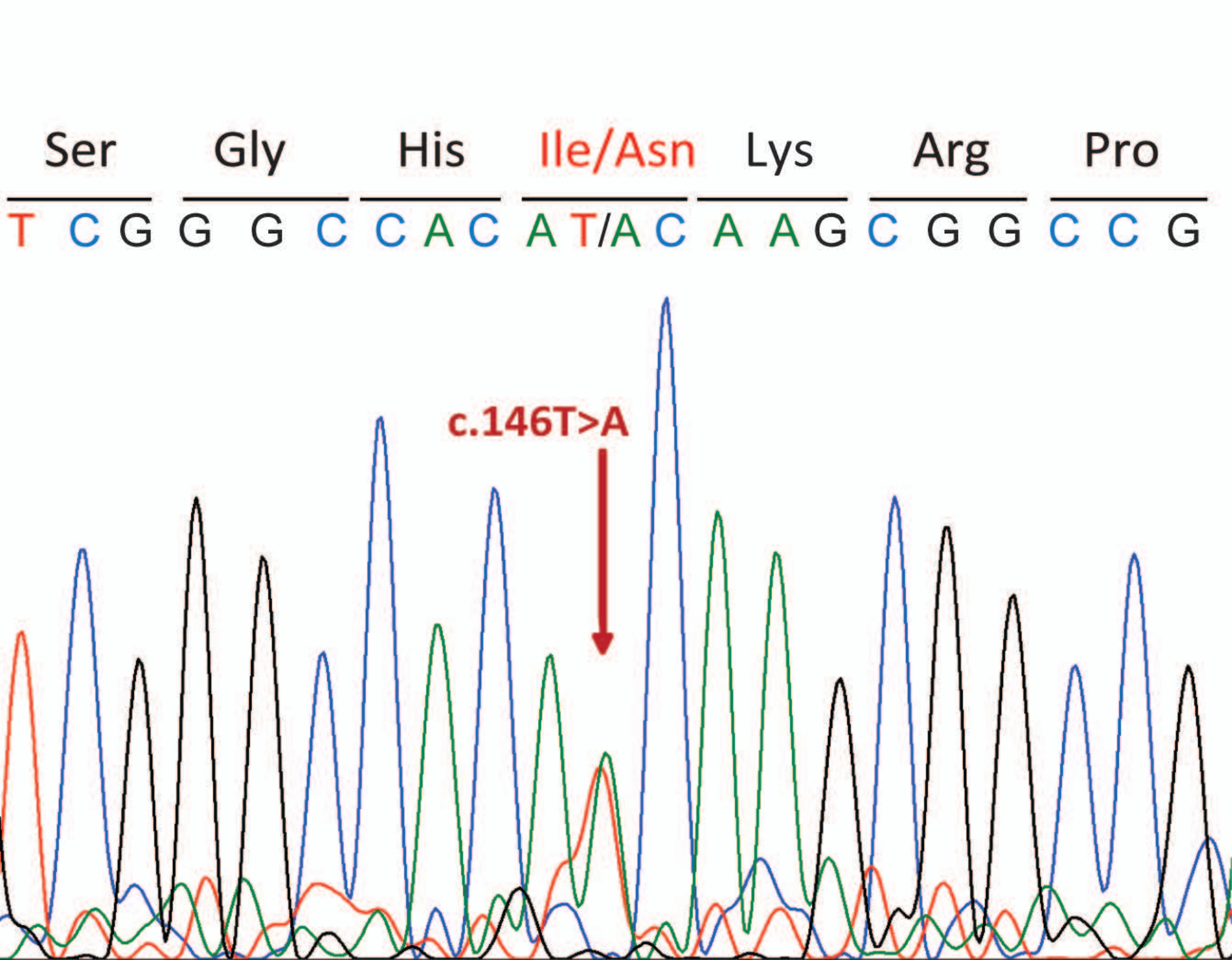
Table 1: Clinical features of reported *SOX11* patients

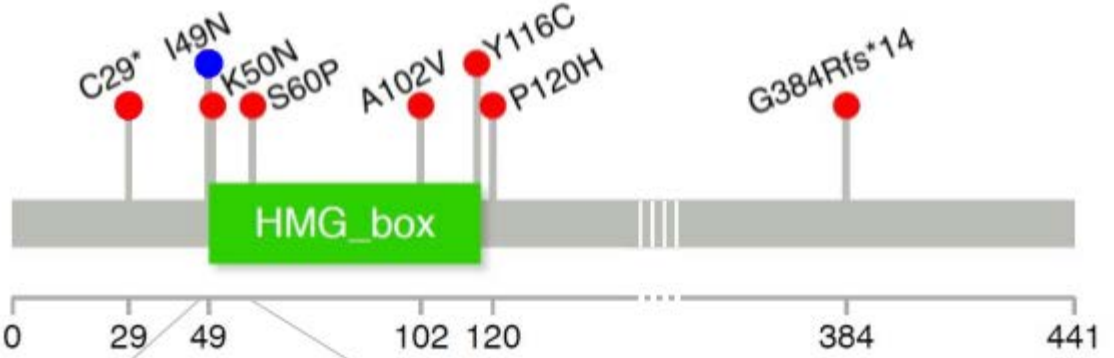
Figure 1: Images of reported patient highlighting facial features (a), hand (b) and foot (c).

Figure 2: Sanger sequencing electropherogram showing the *SOX11* variant c.146T>A in the patient.

Figure 3: Previously reported variants depicted on a linear representation of *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.


A
B
C


Ser
Gly
His
Ile/Asn
Lys
Arg
Pro
T C G G G C C A C A T/A C A A G C G G C C G
c.146T>A



H**I**KRPMNAFMVWS	H.sapiens
H**N**KRPMNAFMVWS	Reported variant
H**I**KRPMNAFMVWS	P.troglodytes
H**I**KRPMNAFMVWS	M.mulatta
H**I**KRPMNAFMVWS	M.musculus
H**I**KRPMNAFMVWS	R.norvegicus
H**I**KRPMNAFMVWS	G.gallus
H**I**KRPMNAFMVWS	D.rerio
H**I**KRPMNAFMVWS	X.tropicalis
H**I**KRPMNAFMVWS	D.melanogaster
H**I**KRPMNAFMVWS	C.elegans

Table 1: Clinical features of reported *SOX11* patients

	Tsurusaki et al. (2014)		**Hempel et al. (2016)**			**Khan et al. (2017)**	**Okamoto et al. (2018)**	**Current study**
	Subject 1	Subject 2	Subject 8	Subject 9	Subject 10			
Subject details								
Gender	Female	Female	Female	Male	Male	Male	Male	Male
Origin	Japanese	Indian	Caucasian*	Caucasian*	Caucasian*	Caucasian*	Japanese	Lebanese
SOX11 Mutation	c.347A>G (p.Tyr116Cys)	c.178T>C (p.Ser60Pro)	c.359C>A (p. Pro120His)	c.150G>C (p. Lys50Asn)	c.87C>A (p. Cys29*)	c.1148dupG (p.Gly384ArgfsTer14)	c.305C>T (p.Ala102Val)	c.146T>A (p.Ile49Asn)
Origin of Mutation	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo
CNS Features								
Developmental Delay	+	+	+	+	+	+	+	+

Intellectual Disability	+ (mild)	+ (mild)	+ (severe)	+ (severe?)	+ (mild?)	+ (mild)	+ (mild)	+ (severe)
Hypotonia	+	-	N/R	N/R	N/R	+	-	+
Microcephaly	+	+	+	+	-	-	-	+
Facial Features								
Coarse Facies	-	-	+	-	+	-	+	-
Thick Eyebrows	-	-	-	-	-	+	-	+
Long/Prominent Eyelashes	+	-	-	-	-	-	-	+
Skeletal Features								
Hypoplasia of 5th fingernail/toenail	+	+	+	+	+	+	+	-
Clinodactyly of 5th finger	+	+	+	+	+	+	+	-

Hypoplasia of 5th phalanx (hands)	+	+	-	-	-	-	-	-
Hypoplasia of 5th phalanx (feet)	+	+	-	-	-	-	-	-
Joint Laxity	-	-	N/R	N/R	N/R	N/R	N/R	?
Skin and Hair								
Hypertrichosis	+	+	-	-	-	-	+	-
Low Anterior Hairline	N/R	N/R	-	-	-	-	-	+
Sparse Scalp Hair	-	+	-	-	-	+	-	-
Others								
Frequent Infections	-	-	N/R	N/R	N/R	-	N/R	+ (Buccal Mycoses)
Hypospadias	-	-	-	N/R	N/R	-	N/R	+

* Ethnicity not reported. Subjects were presumed to be caucasian based on their photos
N/R: Not Reported