BRIEF COMMUNICATION

Novel variants in the *SOX11* gene: clinical description of seven new patients

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Pathogenic *SOX11* variants have been associated with intellectual developmental disorder with microcephaly, and with or without ocular malformations or hypogonadotropic hypogonadism (HH) (IDDMOH, OMIM # 615866). In this article, we report seven new patients with de novo *SOX11* variants. Five of the variants are missense, one nonsense, and one whole-gene deletion, most of them are novel variants. The main clinical features included neurodevelopmental delay (7/7) and intellectual disability (5/7), autism/attention deficit hyperactivity disorder (5/7), microcephaly (4/7), short stature (4/7), hypotonia (4/7), and clinodactyly of the 5th fingers (5/7). HH was confirmed in two female patients with primary amenorrhea, nonvisualized/prepubertal size of the uterus, and nonvisualized ovaries. Two of the male patients presented with micropenis, two had cryptorchidism, and one had decreased testicular size, which are suggestive findings of HH. This article contributes to the clinical characterization of patients with *SOX11* variants and supports the role of this gene in HH.

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INTRODUCTION

First reported by Tsurusaki and colleagues in 2014, pathogenic variants in *SOX11* were associated with a mild form of Coffin-Siris syndrome (CSS) [1]. In 2016, Hempel and colleagues reported ten individuals harbouring heterozygous deletions or sequence variants in *SOX11*, all of them showing features compatible with a mild form of CSS [2]. CSS is characterized by developmental or cognitive delay, hypoplasia of the distal phalanx or nail of the fifth digits, hypotonia, and distinctive facial features [3, 4]. However, *SOX11* variants were only identified in about 2% of patients with a clinical suspicion of CSS [1]. Further studies showed a variable phenotype, and some of the patients did not have a previous clinical diagnosis of CSS [5–9].

SOX11 gene is located at 2p25.2 and belongs to the SRY-related high-mobility-group (HMG) transcription factors family. Along with *SOX4* and *SOX12* genes, *SOX11* is a part of the SOXC group of transcription factors, characterized by a highly conserved box DNA-binding domain [10]. Most of the missense variants reported in the literature are located within the HMG domain, hypothesized to be critical to protein function. In humans, *SOX11* is expressed in the developing central nervous system and in the developing palate, considered essential for neuronal differentiation and cell proliferation [6, 10–12]

Recently, Al-Jawahiri and colleagues described the largest series of individuals with *SOX11* variants, presenting with a broad phenotypical heterogeneity. Common clinical features included developmental delay, microcephaly, and short stature. Ocular malformations (oculomotor apraxia, coloboma, and microphthalmia) and hypogonadotropic hypogonadism (HH - genital anomalies, cryptorchidism, and delayed puberty) were also reported in a subset of patients with *SOX11* variants [6]. The OMIM entry for *SOX11*-related phenotype (OMIM #615866), which was previously assigned to Coffin-Siris syndrome 9, was updated to intellectual developmental disorder with microcephaly, and with or without ocular malformations or hypogonadotropic hypogonadism (IDDMOH) [13].

To date, approximately 60 individuals with *SOX11* variants have been described in the literature, and the majority were identified via a genotype first approach, specifically whole exome or genome sequencing, and not due to a clinical suspicion of CSS [5–10]. In this study, we report on clinical features of seven patients with pathogenic or likely pathogenic variants involving *SOX11*, five of them with novel variants.

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PATIENTS AND METHODS

All patients were included in this study for having pathogenic or probably pathogenic variants in *SOX11*. Two of the patients were enrolled through a collaboration between university hospitals in Brazil (patients 1 and 2). Three patients were enrolled by contacting physicians and clinical diagnostic laboratories that submitted variants to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) (patient 3 - VCV001685451.1 – from Brazil; patient 4 - VCV001218667.6 – from USA; patient 5 - VCV000444486.26 – from Germany). One patient was enrolled through a collaboration between the State University of Campinas (Brazil) and the Radboud University Medical Center (Netherlands) (patient 6), and one patient was enrolled through personal communication with Erin Torti from GeneDX (patient 7 – from USA).

Regarding the reason for referral to genetics investigation, most of them were referred due to intellectual disability/neurodevelopmental delay and/or dysmorphic features and hypotonia. Only patient 3 was referred at birth for presenting with micropenis. None of them had a previously diagnosis of HH neither of CSS.

Since each patient was investigated in a different centre, the genetic tests applied were heterogenous and are described in the detailed case report of each patient (Supplemental material). Only patient one was investigated in a research context, and the methods are also described in supplemental material. For the remaining patients, genetic tests were performed in diagnostic laboratories and followed specific protocols from these laboratories. Six *SOX11* variants (patients 1–6) were identified using whole exome sequencing (WES). *SOX11* gene deletion (patient 7) was identified by chromosomal microarray analysis (CMA). The variants of all patients were investigated in the parents by WES trio-analysis or Sanger sequencing and were de novo in all cases. All variants were classified and revised according to the recommendations of the American College of Medical Genetics (ACMG) [14].

The phenotypes of the patients included in this study were compared with general findings described by Al-Jawahiri et al. [6] and Hanker et al. [8] (Table 1).

Protein structural analysis was performed using the model P35716 as a template to generate a homology model in the SWISS-MODEL (https://swissmodel.expasy.org/) to observe the structural characteristics of the domains where the variants are located [15].

RESULTS

Here, we describe seven additional patients, each harbouring a de novo *SOX11* variant. Five of the variants were missense, one was nonsense, and one was a whole-gene deletion (Table 1). Four missense variants were novel, and one has been previously reported in the literature, c.305 C > T (Patient 6) [16, 17]. All of the missense variants were predicted to be deleterious according to the aggregated prediction tool from Franklin by Genoox platform (https://franklin.genoox.com/clinical-db/home), and were located within the HMG-box domain (Fig. 1A, B). The nonsense variant found in Subject 5 (c.511 A > T; p.(Lys171Ter)) was also a novel variant and classified as likely pathogenic (PVS1 - Strong, PM2, PM6). This nonsense variant is not predicted to undergo nonsense-mediated mRNA decay (NMD), since the *SOX11* gene has only one exon. Nonetheless, loss of function variants in this gene were not found in the general population, this exon is present in biologically relevant transcripts, and this variant is predicted to remove more than 10% of the protein. Regarding the whole-gene deletion, it includes no protein-coding genes except for the *SOX11*. The ClinGen dosage sensitivity curation considers *SOX11* to be a haploinsufficient gene, reason why the variant was considered likely pathogenic.

The patients reported in this study present with neurodevelopmental delay (7/7) and intellectual disability (5/7), autism/attention deficit hyperactivity disorder (5/7), microcephaly (4/7), short stature (4/7), hypotonia (4/7), and clinodactyly of the 5th finger (5/7) (Table 1). Other varied clinical features were found in a few patients, including cleft lip/palate in two patients, hearing impairment in one, syndactyly in two, and seizures in one patient. In addition, two female patients showed HH, two male patients had micropenis, and two had cryptorchidism. The most consistent dysmorphisms were upslanted palpebral fissures (5/7), everted upper/lower lip vermilion (4/7), short philtrum (3/7), and epicanthal fold (3/7) (Table 1).

In patients 1 and 4, primary amenorrhea has prompted subsequent imaging of the pelvis, which did not visualize ovaries and uterus for Patient 1 and revealed a small prepubertal-sized uterus and nonvisualized ovaries for Patient 4. Complementary endocrinological investigation confirmed HH in both patients (Supplemental material). The other female patient (Patient 5) was last evaluated at 10 years of age, and no information regarding endocrinological abnormalities was available. Two of the male patients from this cohort presented with micropenis (Patients 2 and 3), two had cryptorchidism (Patients 2 and 6), and one of them (Patient 2) had decreased testicular size, which are suggestive of HH. However, endocrinological exams were not available for these patients, who were prepubertal at the time of the last examination (Patients 2 and 3) or still in an age range in which constitutional pubertal delay may not be ruled out yet (Patient 6).

DISCUSSION

This study describes the clinical phenotype of seven new patients with *SOX11* variants, contributing to the clinical characterization of this rare disorder. The main clinical features in this case series are compatible with the most common findings reported by Al-Jawahiri and colleagues [6]. In addition, five of the patients have features suggestive of HH, which was confirmed in two female patients.

Regarding genes associated with CSS and HH, only variants in *PHF6* has been previously associated with hypogonadism [18]. Interestingly, there are no previous reports of HH in patients with variants in *SOX4* (https://www.omim.org/entry/618506). It is known that the *SOX* family plays a crucial role in mammalian sex development, and other *SOX* family genes including *SOX3, SOX8, SOX9*, and *SOX10*, have a well-known contribution to the sex development process, as fundamental agents in gonad differentiation, and have been implicated in disorders of sex development [19, 20]. Pathogenic variants in *SOX2* and *SOX10* have already been confirmed to cause HH in humans [6]. The association between *SOX11* and hypogonadism was first reported in 2014, when Tsurusaki and colleagues described a female patient presenting with a *SOX11* variant and HH(1). Later, Cho and colleagues, in 2021, reported two patients with idiopathic HH harbouring pathogenic variants in the *SOX11* [5]. In 2022, Al-Jawahiri and colleagues reported eight individuals with HH, corresponding to 21% of the patients described in their cohort [6].

Considering that the patients presented in this study were not selected due to HH, but due to harbouring *SOX11* variants, the finding that 5/7 of them present with features suggestive of hypogonadism points out that HH can be a more common clinical feature in patients with *SOX11* variants than previously described by Al-Jawahiri and colleagues [6]. Therefore, the association between *SOX11* variants and HH may be underestimated. Of note, 13/29 females among the 53 patients reported by Al-Jawahiri et al. were under 12 years of age, and probably have not reached puberty yet. The underlying mechanisms of aberrant *SOX11* expression leading to HH are not well established. Nevertheless, the study by Al-Jawahiri et al. showed that *SOX11* is expressed in the developing human pituitary and hypothalamus, and may play multiple roles in development of the hypothalamic-pituitary-gonadal axis [6]. These results supports that endocrinological studies should be performed in all patients with a pathogenic variant in *SOX11* and features of delayed puberty. On the other hand, *SOX11* should also be included as a candidate gene in the investigation of patients presenting with hypogonadotropic hypogonadism.

In conclusion, the results presented here contribute to the clinical and molecular characterization of patients with *SOX11*

Table 1. Clinical features of the patients and comparison with data from the Literature.

	Present study								Literature
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Total	Al-jawahiri et al., 2022	Hanker et al., 2022
Sex	Female	Male	Male	Female	Female	Male	Male			
Age at last evaluation	23 years	7 years	2 years	18 years	10 years	13 years	4 years			
Variant	c.251 G > A	c.323 A > C	c.167 T > G	c.175 T > C	c.511 A > T	c.305 C > T	2p25.2 (5486129_5928416)x1			
Aminoacid change	p.Gly84Asp	p.Lys108Thr	p.Phe56Cys	p.Trp59Arg	p.Lys171Ter	p.Ala102Val	-			
Inheritance	de novo	de novo	de novo	de novo	de novo	de novo	de novo			
ACMG Criteria	LP (PM1, PM2, PM5, PM6, PP3)	LP (PM1, PM2, PM6, PP3)	LP (PM1, PM2, PM6, PP3)	LP (PM1, PM2, PM6, PP3)	P (PVS_strong, PM2, PM6)	LP (PM1, PM2, PM6, PP3, PP5) Previously reported by Okamoto (PMID: 28787104) and Lunke (PMID: 32573669)	LP			
Aggregated Pathogenicity Prediction (Franklin)	Deleterious (0.87)	Deleterious (0.85)	Deleterious (0.99)	Deleterious (0.99)	-	Deleterious (0.88)				
Reference Genome	hg19	hg19	hg19	hg19	hg19	hg19	hg19			
Genomic Coordinate	chr2:5833104	ch2: 5833176	chr2:5833020	chr2:5833028	chr2:5833364	chr2:5833158	chr2:5486129_5928416			
Prenatal/neonatal findings/complications	poor foetal movements	gestational diabetes, cerebral hemorrhage, and sepsis.	none	none	none	none	none			
Gestational age (weeks)	term	35	term	term	38	39	38			
Weight in kilograms/ age (Z-score)	25.2 (9 years) (−1.05)	NR	5.8 (3 months) (−0.8)	NR	25 (10 years) (−1.51)	63.5 (13 years) (+1.44)	14.2 (4 years) (−1.3)			
Stature in centimeters/ age (Z-score)	129.4 (9 years) (−0.96)	NR	59 (3 months) (−1.19)	NR	140 (10 years) (+0.21)	157 cm (13 years) (−1.28)	92.6 (4 years) (−2.47)			
Head circumference in centimeters/age (Z-score)	48.7 (9 years) (−2.79)	49 (7 years) (−2.5)	NR	NR	50 (10 years) (−1.95)	NR	48.5 (4 years) (−1.72)			
Microcephaly HP:0000252	+	+	+	+	NR	-	-	4/7 (57%)	13/53 (24%)	4/9 (44%)
Short stature HP:0004322	+	+	+	NR	NR	-	+	4/7 (57%)	NR	5/9 (55%)
Sparse scalp hair HP:0002209	NR	-	+	NR	NR	-	-	1/7 (14%)	NR	2/9 (22%)
Thick eyebrows HP:0000574	NR	-	+	NR	NR	-	-	1/7 (14%)	NR	NR

Table 1. continued

	Present study								Literature	
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Total	Al-jawahiri et al., 2022	Hanker et al., 2022
Highly arched eyebrow HP:0002553	NR	NR	+	NR	NR	-	-	1/7 (14%)	NR	4/9 (44%)
Long eyelashes HP:0000527	NR	+	+	NR	NR	-	-	2/7 (28%)	NR	1/9 (11%)
Epicanthal fold HP:0000286	+	+	+	NR	NR	-	-	3/7 (42%)	NR	NR
Upslanted palpebral fissure HP:0000582	+	+	+	+	NR	+	-	5/7 (71%)	NR	NR
Full lips/thick vermilion border HP:0012471	NR	+	NR	NR	NR	+	-	2/7 (28%)	NR	6/9 (66%)
Everted upper/lower lip vermilion HP:0010803/ HP:0000232	+	+	+	+	NR	-	-	4/7 (57%)	NR	2/9 (22%)
Wide mouth HP:0000154	-	-	+	NR	NR	+	-	2/7 (28%)	NR	2/9 (22%)
Gingival overgrowth HP:0000212	+	+	-	NR	NR	NR	-	2/7 (28%)	NR	NR
Cleft palate/cleft lip hp: 0100333	+	-	-	-	+	-	-	2/7 (28%)	6/53 (11%)	NR
Short philtrum hp:0000322	-	+	NR	+	NR	+	-	3/7 (42%)	NR	4/9 (44%)
Low-set ears HP:0000369	+	-	NR	-	NR	-	-	1/7 (14%)	NR	3/9 (33%)
Hearing impairment HP:0000365	NR	+	-	-	NR	-	-	1/7 (14%)	6/53 (11%)	1/9 (11%)
Hypoplasia/aplasia fifth fingernail HP:0008398	-	+	+	-	NR	-	-	2/7 (28%)	1/53 (1.8%)	3/9 (33%)
Clinodactyly of the 5th finger HP: 0004209	+	+	+	-	+	+	-	5/7 (71%)	11/53 (20%)	7/9 (77%)
Syndactyly HP:0001159	-	NR	+	-	NR	+	-	2/7 (28%)	1/53 (1.8%)	3/9 (33%)
Hypoplastic Toenails HP:0001800	NR	+	+	+	NR	+	+	5/7 (71%)	NR	9/9 (100%)
Hypertrichosis HP:0000998	NR	-	-	+	-	-	-	1/7 (14%)	NR	3/9 (33%)
Micropenis HP:0000054	NA	+	+	NA	NA	-	-	2/4 (50%)	1/53 (1.8%)	NR
Cryptorchidism HP:0000028	NA	+	NR	NA	NA	+	-	2/4 (50%)	5/53 (9%)	NR
Decreased Testicular Size HP:0008734	NA	+	NR	NA	NA	NR	NR	1/7 (14%)	0/53 (0%)	NR
Aplasia/Hypoplasia of the uterus HP:0008684	+	NA	NA	+	NR	NA	NA	2/3 (66%)	NR	NR

Table 1. continued

	Present study								Literature
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Total**	**Al-jawahiri et al., 2022**	**Hanker et al., 2022**
Aplasia/Hypoplasia of the ovary HP:0010462	+	NA	NA	+	NR	NA	NA	2/3 (66%)	NR	NR
Primary amenorrhea HP:0000786	+	NA	NA	+	NR	NA	NA	2/3 (66%)	1/53 (1.8%)	NR
Hypogonadotropic Hypogonadism HP:0000044	+	NA	NA	+	NR	NR	NA	2/7 (28%)	11/53 (20%)	NR
Neurodevelopmental delay HP:0012758	+	+	+	+	+	+	+	7/7 (100%)	31/53 (58%)	9/9 (100%)
HypotoniaHP:0001252	NR	+	+	+		-	+	4/7 (57%)	5/53 (9%)	3/9 (33%)
Seizure HP:0001250	+	-	-	-	NR	-	-	1/7 (14%)	5/53 (9%)	NR
Oculomotor Apraxia HP:0000657	NR	NR	+	+	NR	-	-	2/7 (28%)	4/53 (7%)	4/9 (44%)
Intellectual Disability HP:0001249	+	+	NA	+	+	+	NA	5/7 (71%)	36/53 (67%)	6/9 (66%)
Autism HP:0000717/ Attention Deficit Hyperactivity Disorder HP:0007018	NR	+	NR	+	+	+	+	5/7 (71%)	9/53 (16%)	1/9 (11%)

Variants are reported according to GRCh37/hg19.
LP likely pathogenic, *P* pathogenic, *NR* not reported, *NA* not applicable.

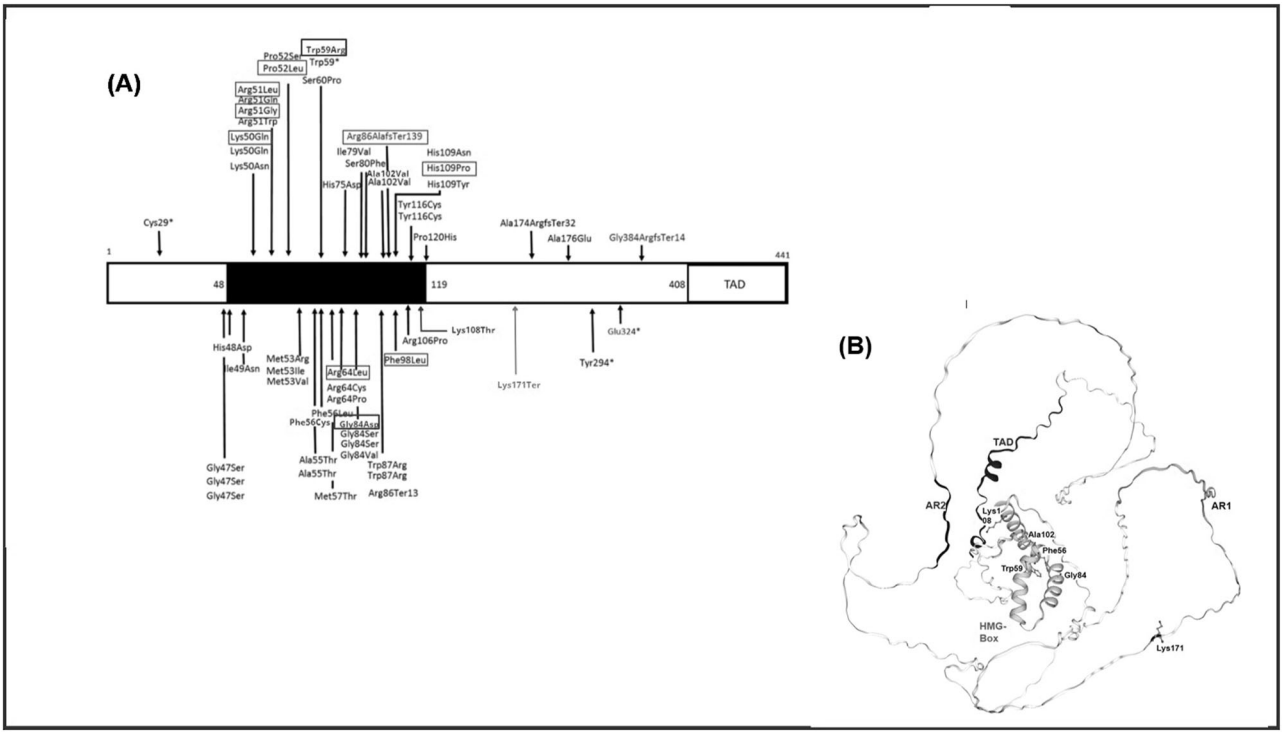

Fig. 1 Reported SOX11 variants and structural model of the SOX11 protein. A Schematic figure adapted from Al-Jawahiri et al. The published variants to date are represented in black. The missense variants from this study are represented in red and the nonsense variant from this study is represented in blue. All the variants whose patients present with hypogonadotropic hypogonadism are inside red boxes. The black box indicates the High Mobility Group (HMG-box) domain. **B** Structural model of the SOX11 protein showing the positions of the variants identified in this study. Protein domains are highlighted by colors: yellow represents the HMG-box domain, orange and dark blue indicates the two acidic regions AR1 and AR2, respectively. The red color corresponds to the C-terminal transactivation domain (TAD).

variants and support that HH can be an important feature associated with this rare disorder.

DATA AVAILABILITY

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

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AUTHOR CONTRIBUTIONS

BSM, AMS, and TPV designed the study, wrote, and revised the article. AMS, VLGSL, AP, CFMS, EC, JCH, PJ, CS, ATMG, LM, AR, MS, HZE, JM, and SB evaluated the patients and collected clinical data. BSM, HFS, and SSS performed the in silico analysis. BSM and GRCC performed experimental analysis. TPV, NL, and RP performed the WES analysis. All authors revised the manuscript and approved the final version of this document.

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COMPETING INTERESTS

HZE and MS are employees of GeneDx, LLC. The other authors declare no competing interests.

ETHICAL APPROVAL

Written consent for clinical data collection was given by legal guardians. Ethical approval was obtained by the respective institutional research ethics board for each individual.

ADDITIONAL INFORMATION

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