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SOX2: Not always eye malformations. Severe genital but no major ocular anomalies in a female patient with the recurrent c.70del20 variant

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ABSTRACT

SOX2 variants have been identified in multiple patients with severe ocular anomalies and pituitary dysfunction, in addition to various systemic features.

We investigated a 26-year-old female patient suffering from spastic paraparesis, hypoplasia of corpus callosum, hypogonadotropic hypogonadism (HH) and intellectual disability, who was monitored for over 20 years, allowing a detailed genotype-phenotype correlation along time. Whole exome sequencing on the patient and her relatives identified a *de novo SOX2* c.70del20 variant, which has been frequently reported in individuals with SOX2-related anophthalmia. Importantly, our patient lacked major ocular phenotype but showed vaginal agenesis, a feature never reported before. Although the involvement of male urogenital tract (cryptorchidism, hypospadias, small penis), is a well known consequence of *SOX2* variants, their effect on the female genitalia has never been properly addressed, even considering the paradoxical female excess of SOX2 cases in the literature. Our findings emphasize the importance of testing for *SOX2* variants in individuals with HH and genital anomalies even though anophthalmia or microphthalmia are not observed. Moreover, our case strengthens the role of SOX2 as a master regulator of female gonadal differentiation, as widely demonstrated for other SOX genes related to 46, XX sex reversal, such as *SOX3* and *SOX9*.

1. Introduction

SOX2 (OMIM 206900), a SOX1B-HMG box transcription factor involved in early embryonic development with a critical role in eye, forebrain, and hypothalamo-pituitary development, has been shown to cause uni- and bilateral anophthalmia/microphthalmia (A/M) as well as related disorders such as anophthalmia/esophageal-genital syndrome (AEG) or A/M and esophageal atresia (AMEA). In addition, *SOX2* variants are associated with a wide range of extra-ocular manifestations: intrauterine growth restriction, postnatal growth retardation, male hypogenitalism, hypogonadotropic hypogonadism (HH), hypoplasia of the corpus callosum, seizures, sensorineural hearing loss, learning disability with speech delay, spastic diplegia/quadriplegia, vertebral and dental anomalies (Fantes et al., 2003; Williamson et al., 2006; Kelberman et al., 2008; Schneider et al., 2009; Numakura et al., 2010; Chacon-Camacho et al., 20015). Aside from the infrequent mosaic cases, SOX2-positive cases without or only with minor eye phenotypes have been very rarely reported (Dennert et al., 2017).

Surprisingly, the intra-familial recurrence of deleterious *SOX2* variants is extremely infrequent. One explanation might be the occurrence of genital tract abnormalities, plausibly related to reduced hypothalamic-pituitary-gonadal axis hormones, or direct effect of *SOX2* haploinsufficiency on the germ cells (Bakrania et al., 2007). In the mouse, *Sox2* is expressed in both male and female genitalia, and *Sox2* heterozygotes show male (but not female) reduced fertility, associated with testicular abnormalities, diminished epididymal sperm count and motility (Avilion et al., 2003; Kelberman et al., 2006). In keeping with these findings, *SOX2* gonosomal mosaicism has been specifically detected in the maternal samples (Faivre et al., 2006; Chassaing et al., 2007; Schneider et al., 2008), suggesting that female gametogenesis is

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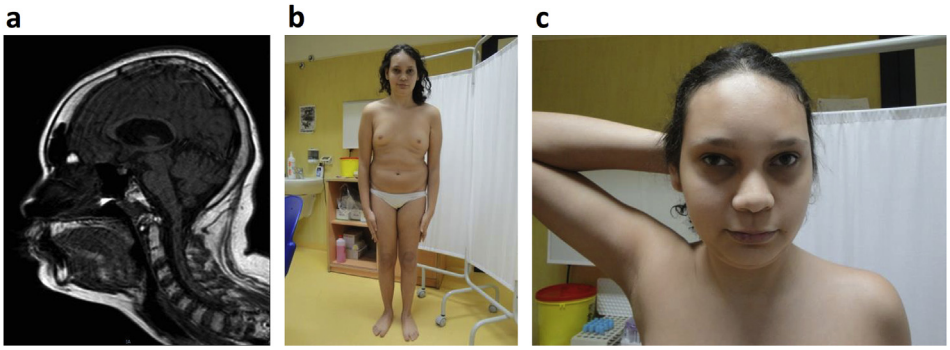
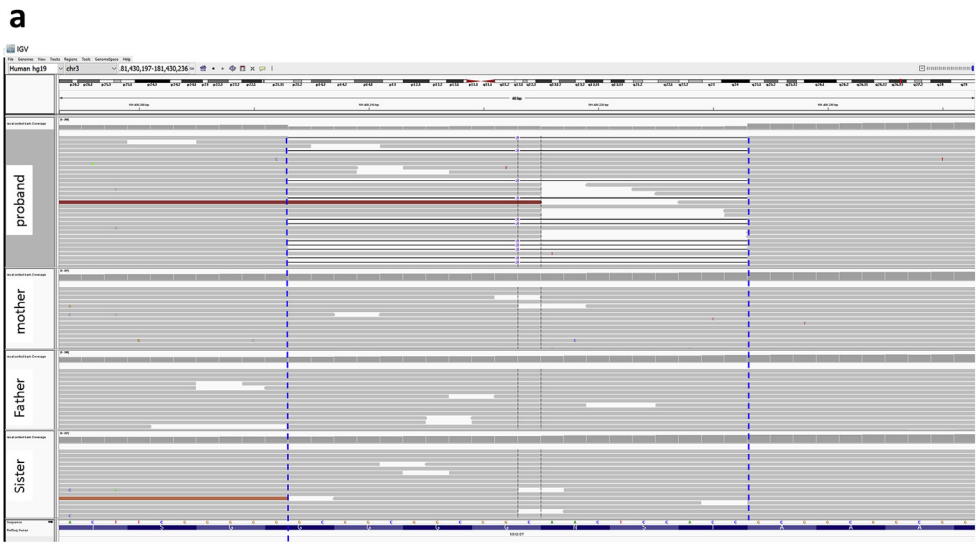


Fig. 1. Clinical features of the 26-year-old proband. (a) Brain MRI showing atrophy of corpus callosum. (b) Patient's picture showing large chest, widely spaced nipples, and thin lower limbs. (c) Facial dysmorphisms: high forehead and frontal hairline, wide sparse eyebrows, upslanted palpebral fissures, hypertelorism, squint, long filtrum, thin upper lip.



b

	Proband	Mother	Father	Sister
Read Depths (DP)	99	113	120	119
Allelic Depths (AD)	37	0	0	0
Alt Allele Freq	0.42	0.00	0.00	0.00

c

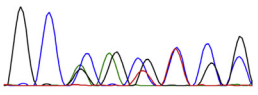


Fig. 2. WES analysis in the family. (a) IGV (Integrative Genomics View) visualization of the *SOX2* c.70del20 variant in the patient and relatives. The deletion's boundaries are delimited by dashed blue lines. (b) Read depths (DP), Allelic Depths (AD) and Mutation Allelic Fraction (Alt Allele Freq) of the *SOX2* variant. (c) Sanger sequencing validation, showing the heterozygous frameshifting alteration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

more tolerant of reduced *SOX2* dosage than is spermatogenesis.

The involvement of male urogenital tract (cryptorchidism, hypospadias and micropenis) is a well known consequence of *SOX2* variants in humans (Fantes et al., 2003; Williamson et al., 2006; Kelberman et al., 2006; Bakrania et al., 2007). Neverthless, their effect on female genitalia has never been properly addressed, although slight female excess of SOX2 cases have been reported in the literature.

We studied a female patient with a *SOX2* variant showing severe genital anomalies, HH, spastic paraparesis, but no major ocular phenotype. We also provided an extensive revision of SOX2 patients carrying the recurrent c.70del20 variant with a specific focus on females showing similarly rare genital anomalies.

1.1. Clinical report

The patient, a 26-year-old woman, was diagnosed with focal frontal lobe epilepsy, spastic paraparesis and HH. She is second child of healthy non-consanguineous parents, born after uneventful pregnancy. Family history was unremarkable. At birth, weight was 3100 g and length 50 cm (50th centile). During infancy, speech development was normal, while motor development was delayed. Hypertonia of the lower limbs was diagnosed when she was 18 months and she is presently wheelchaired due to spastic gait. At the age of 20, she manifested stereotyped episodes characterized by deviation of the eyes to the right followed by sudden loss of consciousness with reduction of muscle tone and traumatic falls. Video-EEG revealed no abnormalities, while brain MRI showed normal pituitary gland, corpus callosum hypoplasia and agenesis of the septum pellucidum (Fig. 1a). Neurological examination revealed dysarthria, spastic-ataxic gait, spasticity of the upper and lower limbs, and intellectual disability. At the last anthropometric evaluation, weight was 57.6 Kg (50-75th centile), height 158 cm (25th centile), head circumpherence 53 cm (25th centile), and arm span 166 cm (45th centile). Physical examination detected various facial dysmorphisms: high forehead and frontal hairline, wide sparse eyebrows, upslanted palpebral fissures, hypertelorism, wide nasal bridge, long filtrum, thin upper lip, large ears. Curiously, she had two supernumerary teeth with persistence of deciduous central lower incisors. In addition, we observed large chest, widely spaced nipples, thin lower limbs, cervical lordosis, truncal obesity and flat feet (Fig. 1b and c). Cardiological evaluation (ECG, echo, Holter) did not identify anomalies. Endocrinological and gynecological assessment revealed primary amenorrhea and oedematous labia, while abdominal ultrasounds detected vaginal agenesis, hypoplastic uterus, and rudimentary gonads. At the last hormonal evaluation, FSH was 0.2 mUI/ml, LH 0.1 mUI/ml, oestradiol < 5.0 pg/ml, and testosterone 0.003 mg/ml; TSH, FT3, FT4 and PRL were in the normal range. Ophthalmological examination revealed hypermetropia of +1.25D sphere in the right eye and +0.75D sphere in the left eye, and only minor ocular alterations: bilateral