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Genetic Variability of *SOX10*-Related Disorders within an Italian Family: Straddling the Line between Kallmann and Waardenburg Syndrome

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Established Facts

- *SOX10* pathogenic variants are notably associated with both Kallmann syndrome (KS) and Waardenburg syndrome (WS), often described as distinct allelic disorders.
- The genetic link between the two conditions has not yet been established and *SOX10* relevance to the etiology of both WS and KS remains uncertain.

Novel Insights

- This family report can provide insights into *SOX10*-related phenotypic spectrum, which may represent a clinical continuum, rather than distinct allelic disorders, within the frame of neurocristopathies.
- The same *SOX10* variant can be associated with inter- and intra-familiar variability. This highlights the need for careful evaluation and long-term follow-up of *SOX10* patients.

Keywords
Kallmann syndrome · Waardenburg syndrome · Family history · *SOX10* · Exome sequencing

Abstract
Introduction: Kallmann syndrome (KS) is a genetically heterogeneous developmental disorder that most often manifests hypogonadotropic hypogonadism (HH) and hypo-/anosmia due to early embryonic impairment in the migration of gonadotropin-releasing hormone neurons. *SOX10* (SRY-Box 10; MIM*602229), a key transcriptional

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activator involved in the development of neural crest cells, has been associated with KS and is identified as one of the causative genes of Waardenburg syndrome (WS). ***Case Presentation:*** A 28-year-old female patient, who was clinically diagnosed with KS in her childhood, presented with HH and anosmia, mild bilateral sensorineural hearing loss (SNHL), and pigmentation abnormalities. Next-generation sequencing analysis detected a missense heterozygous *SOX10* pathogenic variant (NM_006941.4:c.506C>T) in the proposita and in her mother, whose phenotype included exclusively anosmia and hypopigmented skin patches. The same variant has been described by Pingault et al. [Clin Genet. 2015;88(4):352–9] in a patient with apparently isolated bilateral severe SNHL. ***Conclusion:*** Our finding substantiates the extreme phenotypic variability of *SOX10*-related disorders, which range from classical KS and/or WS to contracted endophenotypes that could share a common pathway in the development of neural crest cells and highlights the need for careful evaluation and long-term follow-up of *SOX10* patients, with special focus on atypical/additional and/or late-onset phenotypic traits.

Introduction

Kallmann syndrome (KS) (MIM: PS147950) is a clinically and genetically heterogeneous disorder mainly characterized by hypogonadotropic hypogonadism (HH) and hypo- or anosmia. The estimated prevalence is about 1 in 30,000 in males and 1 in 125,000 in females [1]. The etiopathogenesis of KS is supposed to result from abnormal embryonic migration of gonadotropin-releasing hormone (GnRH) and olfactory neurons, from the olfactory placode to the hypothalamus. A deficit in the GnRH release can lead to decreased levels of luteinizing hormone and follicle-stimulating hormone, which consequently result in low testosterone in males and low estrogen and progesterone in women [2]. Typically, the diagnosis occurs after puberty, as sex hormone deficiencies can determine a lack of sexual maturation (e.g., lack of testicular development in men and primary amenorrhea in women), and the absence of secondary sexual characteristics. KS may be accompanied by non-reproductive abnormalities that can guide the diagnosis: synkinesis, craniofacial abnormalities, dental agenesis and/or skeletal anomalies, renal agenesis, neurologic defects, and hypoacusis [3]. Specifically, hearing loss occurs in approximately 5% of KS individuals, most of whom have unknown genetic features [4]. At present, more than 20 causative genes have been associated with KS [5]. The most frequent defects are found in *ANOS1* (Anosmin 1; MIM*300836) and *FGFR1* (Fibroblast Growth Factor Receptor; MIM*136350); however, in up to 35–45% of cases the underlying molecular drivers remain unknown [6]. Pingault et al. [7] demonstrated that about one-third of patients with KS and deafness have a *SOX10* (SRY-Box 10; MIM*602229) heterozygous loss-of-function pathogenic variant. This finding has been confirmed in subsequent reports of unrelated patients with KS and hearing impairment [8, 9].

SOX10 belongs to the *SOX* family, which consists of a group of genes with a sequence identity to *SRY* (Sex-determining Region Y; MIM*480000), and encodes a 466-amino acid transcriptional factor with a highly conserved DNA binding domain, called the high mobility group (HMG)-box [10]. *SOX10* plays a major role in the development and migration of neural crest cells and oligodendrocytes, through the regulation of several transcriptional targets [11]. In addition to KS, *SOX10* has been established as a causative gene for Waardenburg syndrome (WS) (type 2E and 4C; MIM# 611584 and 613266), a rare autosomal dominant disorder characterized by pigmentation abnormalities of the hair, skin and iris and sensorineural hearing loss (SNHL), and for Peripheral Demyelinating Neuropathy, Central Demyelinating Leukodystrophy, WS, Hirschsprung disease syndrome (PCWH; MIM#609136) [12, 13]. Incomplete penetrance of associated clinical features has been observed, and rare *SOX10* variants have been identified in patients who presented with isolated Hirschsprung disease or hearing impairment, representing possible endophenotypes of WS [14]. Nonetheless, the genetic link between KS and WS has not yet been established and *SOX10* relevance to the etiology of both phenotypes remains uncertain [5].

In the present case study, we identified a heterozygous NM_006941.4(*SOX10*):c.506C>T; p.Pro169Leu missense variant by exome sequencing, in an Italian patient who was diagnosed with KS in childhood and presented with HH, anosmia, pigmentation abnormalities, and progressive mild bilateral SNHL. The variant was inherited from the mother, who presented with anosmia and hypopigmented skin patches, and has been previously described in medical scientific literature in a patient with congenital severe bilateral SNHL and normal pubertal development [15].

Case Report

The proposita (III-2) (shown in Fig. 1a) was born to non-consanguineous Italian parents after an uncomplicated pregnancy. Her mental development was normal. She had no Hirschsprung disease or episodes of constipation. Her hearing screening test at birth through otoacoustic emissions was negative. The patient's older brother (III-1) was diagnosed with KS during puberty, as hyposmia, HH, and olfactory bulbs hypoplasia at brain magnetic

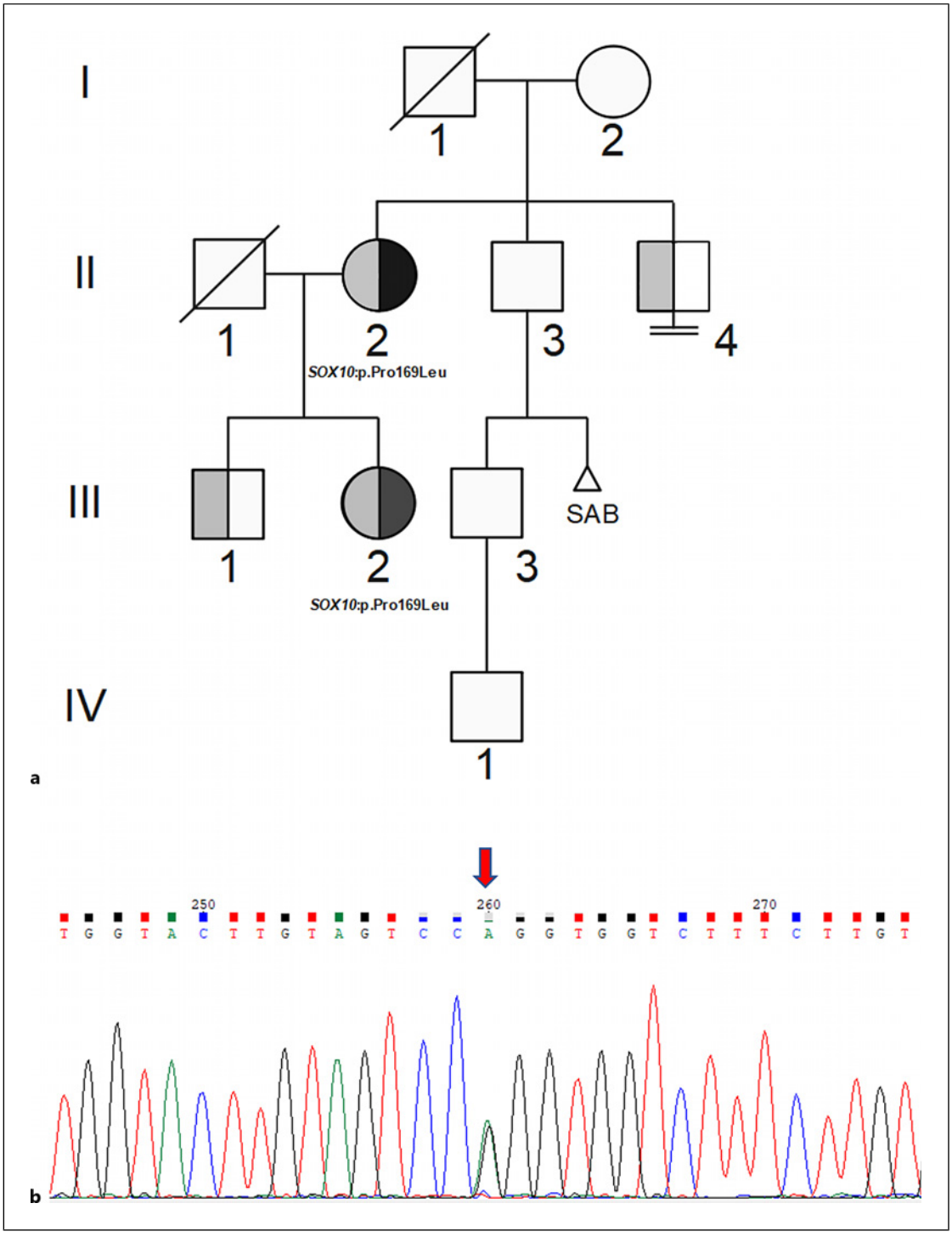

Fig. 1. a Clinical characterization of the four-generation pedigree of the family. Gray-filled individuals presented with Kallmann syndrome (KS) clinical features, which included anosmia/hyposmia, HH, or both. Black-filled individuals presented with Waardenburg syndrome (WS) clinical features, which included SNHL, pigmentation abnormalities, or both. The proposita (III-2) and her mother (II-2) were screened for the p.Pro169Leu variant in *SOX10* (SRY-Box 10). SAB, spontaneous abortion. **b** Sanger sequencing validation of the c.506C>T variant in *SOX10* gene in the proband (III-2).

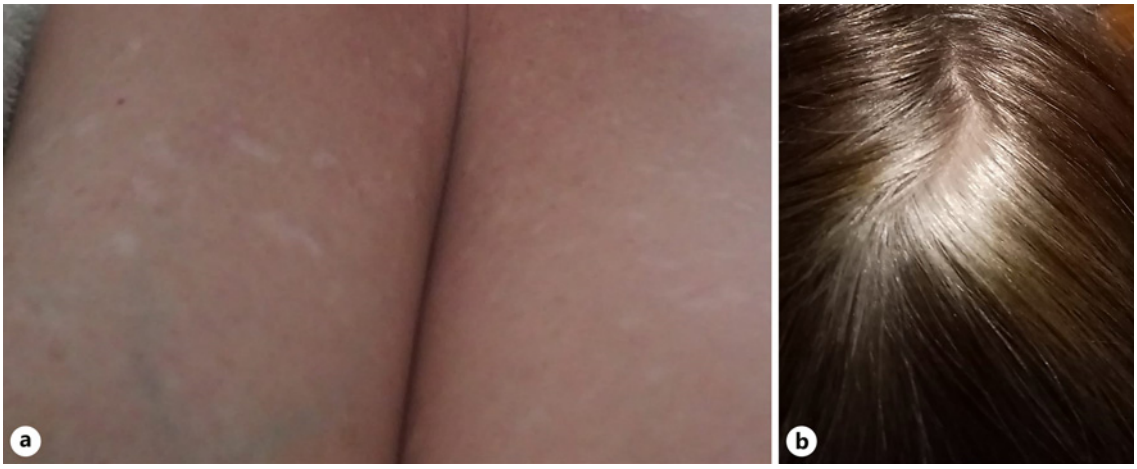

Fig. 2. a Hypopigmented skin patches of the right arm and chest in the proband's mother (II-2). **b** Isolated patchy heterochromia of the scalp hair in the proposita (III-2).

resonance imaging were documented; his audiogram showed bilateral normoacusis. The patient's parents had normal height and age-appropriate pubertal development. Nonetheless, the mother (II-2) of the proposita presented with anosmia at olfactory test and with hypopigmented skin patches (shown in Fig. 2a), and her brother (the patient's uncle) was diagnosed with infertility of unknown etiology. The patient's father (II-1) passed away at age 60 from myocardial infarction (shown in Table 1).

At 11 years and 6 months old, the proposita was referred to endocrinological evaluation due to growth retardation, pubertal development delay, and hyposmia. At physical examination, her height and weight were 134 cm (−2.09 SD) and 27 kg (1.83 SD), respectively. Decreased bone maturation was noticed, with the patient matching the skeletal age of a 9-year-old according to Greulich and Pyle standards. Ophthalmological evaluation was normal. Brain magnetic resonance imaging demonstrated bilateral agenesis of olfactory tract and bulb, and pituitary hypoplasia. The basal secretion of the pituitary hormones was normal, but gonadotropin-releasing stimulation test revealed poor gonadotropin response. Therefore, she received hormone replacement therapy, and menarche was induced at the age of 16 years due to primary amenorrhea.

At 28 years of age, the proposita was referred to our Endocrinological Unit for re-evaluation due to osteoporosis and absence of menstruation. She complained of absent sex drive and tinnitus of recent onset. At physical examination, multiple freckles and an isolated patchy heterochromia of the scalp hair were noted (shown in Fig. 2b). Her height was 166 cm (0.57 SD). Previous bone density scan of the spine at 23 years of age demonstrated a Z-score in the range of osteoporosis (−2.0 SD) [16]; pelvic ultrasound examination was normal. Repeat pelvic ultrasound examination at 28 years of age documented decreased ovary size bilaterally. The first presumed audiological examination performed at 28 years of age showed mild bilateral SNHL. At the time of the examination, the patient was taking combined oral estroprogestinic therapy (levonorgestrel, 0.1 mg and ethinyl-estradiol, 0.02 mg) and cholecalciferol oral supplement (25,000 IU per 15 days). Basal luteinizing hormone, follicle stimulating hormone, prolactin and adrenocorticotropic hormone levels in the blood were 0.6 mIU/mL (normal range, 0.4–4.1), 1.2 mIU/mL (normal range, 4.8–10.4), 3.0 μg/L (normal range, 0–25), and 8.0 pg/mL (normal range, 10–60), respectively; low plasma estradiol level was demonstrated (10.0 pg/mL; reference range, 11.0–172). Low-dose estroprogestinic therapy was suspended and hormone substitutive therapy (17-β estradiol, 100 mg/die; progesterone, 200 mg/die) was prescribed to the patient.

At 12-month follow-up medical examination, the proposita reported normal sex drive and regular menstrual cycles. Low basal plasmatic adrenocorticotropic hormone levels persisted (0.4 mIU/mL; reference range 0.4–4.1), and thus urinary-free cortisol dosage was performed (34 μg/24 h, expected value >70): secondary hypoadrenalism was diagnosed and subsequently treated with oral cortisone acetate (12.5 mg/die). The secretion of the other pituitary hormones and plasma estradiol levels were within range. Repeat bone density scan of the spine demonstrated a Z-score in the range of osteopenia (−1.5 SD) [16].

After genetic counselling, informed consent was obtained from the patient and her mother for venous blood sampling. Karyotype and fluorescence in situ hybridization (FISH) analysis were performed on metaphase chromosome preparations of the patient. Exome Sequencing of the proposita and her mother was performed on genomic DNA using ClinEX pro kit (4bases, Manno, Switzerland) on the NovaSeq6000 platform (Illumina, San Diego CA, USA). In silico analysis was performed for coding regions and exon-intron junctions of the genes associated with KS (*ANOS1*, *CHD7*, *FGF8*, *FGFR1*, *GNRH1*, *GNRHR*, *KISS1*, *KISS1R*, *LEP*, *LEPR*, *NSMF*, *PROK2*, *PROKR2*, *SOX10*, *TAC3*, *TACR3*).

Analysis of the karyotype (46,XX) and of *ANOS1* (Anosmin 1) (MIM*300836) gene deletion with FISH in the proposita was normal. The NGS analysis detected a heterozygous variant in the *SOX10* gene (NM_006941.4:c.506C>T) in both the subjects tested; the result was confirmed through polymerase chain reaction amplification and Sanger sequencing (shown in Fig. 1b). This variant results in a missense mutation Pro169Leu and is classified as "likely pathogenic" according to the American College of Medical Genetics and Genomics (ACMG) guidelines (shown in online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000536574) [17].

Table 1. Clinical features of the proposita (III-2), her mother (II-2), and her brother (III-1), in comparison with the unrelated patient described by Pingault et al. [15]

Individual	III-2	III-1	II-2	Pingault et al. [15] (2015)
Age	28	33	63	18
Gender	F	M	F	M
Pubertal development	Delayed	Delayed	Normal	Normal
Olfaction	Anosmia	Hyposmia	Anosmia	Hyposmia
Olfactory bulb (MRI)	Agenesis	Hypoplasia	NA	NA
SNHL	Progressive, mild, bilateral	ND	ND	Congenital, severe, bilateral
Hair PA	Patchy heterochromia of the scalp hair	ND	ND	ND
Skin PA	Multiple Freckles	ND	Hypopigmented skin patches	ND
Other	Hypopituitarism	ND	ND	Vestibule dilatation, lat SCC hypoplasia
SOX10 screening	c.506C>T; p.Pro169Leu	NT	c.506C>T; p.Pro169Leu	c.506C>T; p.Pro169Leu

MRI, magnetic resonance imaging; NA, not available; ND, not determined; NT, not tested.

Discussion

In this study, we identified a heterozygous pathogenic *SOX10* variant (NM_006941.4:506C>T) in an Italian family, determining a variable phenotypic expression within its members. A missense substitution in exon 4 (c.506C>T) that predicted a proline substitution (p.Pro169Leu) was found in our proposita, who exhibited HH and anosmia, which are characteristics of KS. Interestingly, she also manifested pigmentation anomalies and bilateral SNHL, which are consistent features of WS. The p.Pro169Leu *SOX10* variant was inherited from the patient's mother, who had normal pubertal development and two natural pregnancies, and presented with anosmia, skin heterochromia, and normoacusis. The patient's brother (who was not available for diagnostic testing) was clinically diagnosed with KS during puberty due to HH and olfactory bulbs hypoplasia, and his audiological and dermatological evaluations were normal. The p.Pro169Leu variant has been previously described in an unrelated patient with profound bilateral SNHL, bilateral vestibule malformation, hyposmia, and normal pubertal development [15].

In recent years, *SOX10* pathogenic variants have been documented in unrelated WS patients presenting with anosmia; likewise, WS features (e.g., abnormal pigmentation and SNHL) co-segregated in numerous cases ascertained by the KS phenotype [18]. Most patients with WS are diagnosed in childhood, due to congenital hearing impairment and/or abnormal pigmentation, while KS patients are more frequently diagnosed after puberty due to lack of sexual maturation. Nonetheless, the significance of *SOX10* abnormalities in the etiology of neither WS nor KS has been fully established yet. Previous studies demonstrated that *SOX10* loss-of-function heterozygous variants concur to KS developmental defects [7, 19]; similarly, the very large majority of *SOX10* anomalies in WS patients are either frameshift or nonsense variants encompassing the entire gene [12]. Thus, haploinsufficiency has been indicated as a possible shared mutational mechanism [18].

Sox10 knockout mice models demonstrated a defective differentiation of olfactory ensheathing cells, a distinct subset of neural crest-derived glial cells, which would lead to disrupted olfactory axon targeting and GnRH neuron migration [11]. Besides, defects in distinct neural crest-derived cells such as melanocytes and enteric nervous system cells, which reflect the haploinsufficiency for *SOX10*, have been described in association with WS critical features, in both humans and animal models [20]. Therefore, it has been speculated that both phenotypes might represent a single phenotypic continuum in the spectrum of neurocristopathies, due to a biological and molecular overlap of *SOX10*-related disorders [21].

Although the majority of *SOX10* disease-associated variants predict a truncation of the main functional domains of the protein, the proportion of missense variations has increased with time, and missense *SOX10* damaging variants have been recently described in the literature in both KS and WS cases [22]. However, it has been observed that missense variants are proportionally more frequent in KS patients, whereas the proportion of truncating variants increases in WS cases [18]. These results suggest that the highly variable phenotypic expressivity and/or penetrance of *SOX10*-related disorders could be partially attributable to variant severity, within a shared pleiotropic mutational spectrum [21]. As often happens in the case of transcriptional factors, most *SOX10* pathogenic missense variants are found in the HMG DNA-binding domain of the protein and modify relatively conserved amino acids within it [23]. The HMG domain is made up of three alpha helices that fold into an L-shaped module maintained by a hydrophobic core for structural shape. When bound to the minor groove of DNA, the HMG domain induces a large conformational change in the DNA, bending the DNA molecule and mediating protein-protein interactions [24]. Because of the ability to alter DNA conformation, SOX proteins are believed to exert part of their function as architectural proteins [25]. The HMG domain also contains two nuclear localization signals (NLSs) and one nuclear export signal (NES) enabling intracellular transport regulation [26]. Therefore, variants located in the NLS and the NES sequences within the HMG domain could affect the subcellular localization of the resulting mutant protein, as previously described for variants found in the NLSs of *SRY* and *SOX9* [27]. For some specific missense variations, a dominant-negative effect was also proposed, based on the observation that these mutants lead to the recruitment and consequent accumulation of the wildtype SOX10 protein in mutant-induced nuclear foci in in vitro experiments [23].

The nonconservative Pro169Leu amino acid substitution described in our patient – and previously reported in an unrelated patient by Pingault et al. [15] – is located in the C-terminal distal part of the HMG domain of SOX10 (amino acids 133–203) and is most likely to produce a full-length protein with a single amino acid change. The distal half of the HMG domain is believed to be essential for protein-protein interactions and transcription factor recruitment and may thus be crucial for synergistic regulation of gene expression [25]. In a three-dimensional analysis, Palasingam et al. [28] showed that proline 169 induced a curve in the loop between the third α-helix and the C-terminus of the HMG domain of similar SOX proteins. Therefore, any alteration of proline 169 can potentially modify the position of the HMG C-terminus, as well as of the distal part of the protein, and impair SOX10 function by leading to loss of DNA-binding capacities, cytoplasmic and/or subnuclear redistribution and incorrect folding of the protein. Indeed, in vitro functional studies of several missense variants localized in the HMG domain show how some mutants exert their deleterious effects by altering subcellular localization and some others by disrupting DNA binding and transactivation capacities for different tissue-specific target genes, possibly accounting for the phenotypic variability observed [23]. Previous in vitro analysis of transfected HeLa cells demonstrated that SOX10: p.Pro169Leu mutant protein partly relocalizes to the cytoplasm, even if neither the NLSs nor the NES regions are involved [15]. Interestingly, it was observed that cytoplasmatic redistribution of several other missense mutant proteins may be due to an indirect effect of abnormal protein configuration induced by variants not necessarily located within the NLSs, as reported in the closely related SOX9 transcription factor [23, 29]. Notably, no evidence of phenotypic distinction between KS and WS patients conferred to specific HMG domain residues due to *SOX10* missense variants has been demonstrated to date [18].

The intrafamilial variability observed suggests that environmental factors and/or gene-to-gene interaction could explain this phenomenon [30]. As outlined in several earlier studies, most *SOX10* patients exhibit SNHL, indicating that the auditory system is highly sensitive to *SOX10* impairment [8]. The hearing impairment is most frequently prelingual, non-evolutive, profound, and bilateral in *SOX10* patients [18]. Nonetheless, patients with mild, asymmetric, and/or progressive hearing impairment have been reported [31]. This highlights the need for long-term follow-up of individuals with *SOX10* pathogenic variants, as evidenced in our patient.

In conclusion, these findings support the notion that *SOX10*-related disorders, including KS and WS, may represent a single phenotypic spectrum of developmental defects rather than distinct allelic entities. Provided that further studies in larger cohorts are needed, we suggest carefully evaluating additional phenotypic features in *SOX10* patients to allow recognition of both early pubertal phenotypes and hearing impairment, which may arise late in life. The presence of atypical clinical presentation in family medical history might as well guide the inclusion of *SOX10* genetic screening in patients with either KS or WS clinical features.

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Statement of Ethics

Ethical approval was not required for the studies involving humans because the submitted report is derived from a hospital case of a patient with developmental defects, which was sent to our institution by the attending physician. Therefore, Ethical Committee approval was unnecessary since no supplementary analysis was performed on the patient, except for the diagnostic genetic test for developmental defects. The internal Ethical Committee grants approval for entire research projects and not for reports based on single cases. Ethical approval was not required for this study in accordance with local/national guidelines. The study was conducted according to the guidelines of the Declaration of Helsinki. We obtained written consent from the patient beforehand, as required by our regulations. The human samples used in this study were acquired from a by-product of routine care or industry.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: L.G. and M.L.C.; methodology: L.G.; software: C.M.; validation: A.N., R.R., and G.N.; formal analysis: R.R.; investigation: F.P.; resources: A.N.; data curation: A.A.; writing – original draft preparation: L.G., M.L.C., and F.P.; writing – review and editing: M.B. and D.L.; visualization: A.B.; supervision: G.N. and D.L.; project administration: G.N.

Data Availability Statement

All datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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