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Exome Sequencing Expands the Mechanism of SOX5-Associated Intellectual Disability: A Case Presentation with Review of Sox-Related Disorders

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The *SOX5* haploinsufficiency syndrome is characterized by global developmental delay, intellectual disability, language and motor impairment, and distinct facial features. The smallest deletion encompassed only one gene, *SOX5* (OMIM 604975), indicating that haploinsufficiency of *SOX5* contributes to neuro developmental delay. Although multiple deletions of the *SOX5* gene have been reported in patients, none are strictly intragenic point mutations. Here, we report the identification of a de novo loss of function variant in *SOX5* identified through whole exome sequencing. The proband presented with moderate developmental delay, bilateral optic atrophy, mildly dysmorphic features, and scoliosis, which correlates with the previously-described *SOX5*-associated phenotype. These results broaden the diagnostic spectrum of *SOX5*-related intellectual disability. Furthermore it highlights the utility of exome sequencing in establishing an etiological basis in clinically and genetically heterogeneous conditions such as intellectual disability.
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INTRODUCTION

Recent publications have delineated a clinically-significant 12p12.1 microdeletion area, which has been refined to the critical deletion region involving only the *SOX5* gene. There were 11 reported patients with cytogenetic abnormalities involving only *SOX5*. These patients shared a phenotype of mild to severe developmental delay with more severely affected speech, dysmorphic features including down slanting palpebral fissures, frontal bossing, crowded teeth, auricular abnormalities, and prominent philtral ridges, hypotonia, strabismus, and behavioral abnormalities [Soysal et al., 2011; Lee et al., 2013; Schanze et al., 2013]. It became clear through multiple reports that haploinsufficiency of *SOX5* was responsible for these features, yet no reports of patients with intragenic point mutations in the *SOX5* gene have been published.

In this paper we report on the first patient with a de novo stop gain variant in *SOX5*, who presented at age 15 years with moderate developmental delay, mildly dysmorphic features, scoliosis, bilateral optic atrophy, and behavioral issues. An extensive genetic and metabolic evaluation was unrevealing. Subsequently, exome sequencing identified a heterozygous de novo variant in nucleotide

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position 1021 of the *SOX5* gene (c.1021G>T; NM_152989.3), resulting in a premature stop codon (p. (G341*)) (Fig. 1). We compared the clinical features of our patient to the previous reports and found strong clinical correlation in the phenotype. These results further establish the role of haploinsufficiency of *SOX5* as a cause of intellectual disability.

MATERIALS AND METHODS

Clinical Report

The patient was a 17-year-old female who presented with developmental delay, scoliosis, bilateral optic atrophy, and mild dysmorphisms. The parents were healthy and unrelated. The patient's 14-year-old brother presented with mild pectus carinatum, but otherwise was in good health with a normal EKG. Additional history includes a maternal aunt with a sternal cleft and tetralogy of Fallot, who died at age 39 years. The rest of the patient's family history was unremarkable.

The patient was the product of a naturally-conceived singleton pregnancy born by induced vaginal delivery at 40 weeks to a then 33-year-old G1P1 mother. She weighed 2835 g (25th centile) at birth and was 49.5 cm long (25th centile). There were no complications or exposures during the pregnancy, and she was discharged home with her mother on the second day of life. Her development was delayed, and she started physical, occupational, and speech therapy around 18 months. She did not walk until 23 months of age and she did not say her first words until 2 years of age. She also has a history of infantile gastro–esophageal reflux and poor feeding with late transitioning to solid foods in early childhood; she continued to have difficulty gaining weight throughout her childhood.

Around age 10, the patient was diagnosed with non-progressive bilateral optic atrophy after a retinal exam revealed small optic nerves with temporal pallor bilaterally. She additionally has a history of exotropia and moderate myopia, for which she was prescribed yoked prism glasses. In addition, she also has a history of thoracic kyphoscoliosis, lumbar lordosis, and pectus carinatum. Scoliosis was first diagnosed at age 11; bracing was insufficient, so spinal fusion from T3-L1 was performed at age 13. She has no history of fracture or joint dislocation.

She underwent normal menarche at the age of 12 years. She had an echocardiogram at age 14 because of a concern for connective tissue disease, which showed only mild mitral regurgitation. She does not have a history of pneumothorax or pulmonary blebs. At age 15 she was seen by a connective tissue specialist for concern of Marfan syndrome, for which she did not meet criteria. As part of her evaluation she had a normal whole genome SNP microarray, plasma amino acids (with free homocystine), homocystine, urine organic acids, acylcarnitine profile, and lactate/pyruvate. She was also referred to a general pediatric geneticist. There she was found to be mildly dysmorphic, including a prominent maxilla with a midline groove on the tongue (Fig. 2). Also, she has a history of a narrow palate with overcrowded teeth and a small lower jaw, which necessitated a palate expander for one year. She was noted to have 2–3 toe syndactyly bilaterally. Her weight was 42 kg (5–10th centile), height was 166.8 cm (75th centile), head circumference was 53.5 cm (25th centile), her armspan to height ratio was 0.98 (normal) and upper segment to lower segment ratio was 0.95 (normal.) At the time of publication, she was doing well in 11th grade in a full time learning support class. Her overall IQ was 50, she read at a 4th grade level, and could add, subtract, multiply, and divide, but was unable to perform higher math. She also had significant anxiety, which has responded to therapy and medication.

Whole Exome Sequencing (WES) and Data Analysis of the Proband:

Genomic DNA was extracted from blood with the AutoGen DNA extraction kit following manufacturer's guidelines (QIAGEN). The whole exome library was prepared using the SureSelectXT Human All Exon V5 kit following standard manufacturer protocol (Agilent Technologies) and sequenced on the Illumina HiSeq 2,500 using the 2×100 bp kit with the targeted average coverage of 150x. Alignment and variant calling were performed with an in-house bioinformatics pipeline. Variants with a minor allele frequency of <0.03 in the 1,000 Genomes project [Abecasis et al., 2012] and the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/ 2011) databases and expected to affect coding/splicing of the protein, or were present in the Human Gene Mutation Database (HGMD) [Stenson et al., 2003] were included in the analysis using the Bench Lab NGS software (Cartagenia).

Sanger Validation

Target amplification PCR was performed on DNA from the proband, parents, and the proband's brother using gene specific primers tailed by M13 sequences (forward primer 5′- GTAAAACGACGGCCAGTGTGGCAAGACAGTGGCTTCT-3′ and reverse primer 5′- CAGGAAACAGCTATGACTCCAGTGCACTAAACAAAATGC-3′) under the following conditions: 95° for 5 mins; 35x cycles of 5 sec at 98°, 5 sec at 58°, and 40 sec at 68°; followed by 1 min at 72°. PCR product was purified using ExoSAP (Affymetrix) and Centri-SEP columns (Princeton Separations), then sequenced with M13 primers on an ABI 3,700 DNA Analyzer (Applied Biosystems) using BigDye Terminator v1.1 Cycle Sequencing Kit (Life Technologies) following standard manufacturer protocols.

RESULTS

Exome Sequencing

Whole exome sequencing of the proband produced an average coverage depth of 165x for the target regions. Filtration was performed using Cartagenia Bench Lab NGS software. Of the initial 301,678 sequence variants obtained from WES, 1,227 remained for further analysis. Detailed data analysis and clinical correlation studies led to the identification of a heterozygous stop gain variant (c.1021G>T, p. (G341*)) in exon eight of *SOX5*. This variant is expected to result in premature termination of the mRNA and subsequent nonsense mediated mRNA decay, causing haploinsufficiency of SOX5 [Popp and Maquat, 2013]. This variant has not been previously reported in three publicly available databases: NHLBI Exome Sequencing Project, 1,000 Genomes project and Exome Aggregation Consortium (ExAC) databases (Exome Ag-

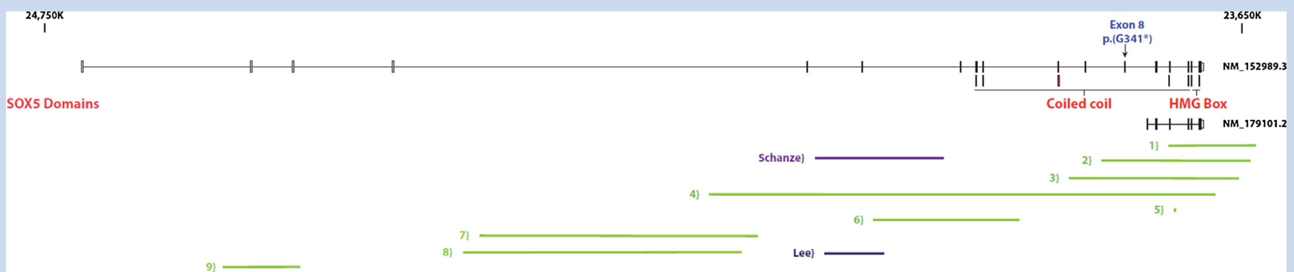

FIG. 1. Location of the *SOX5* p. (G341*) stop gain in the affected proband is shown in blue. Previously identified genomic alterations involving only *SOX5* are in green (Table II: Lamb *et al* 2012), purple [Schanze et al., 2013] and navy [Lee et al., 2013]. Functional domains are in red (Uniprot: P35711). Note: the first four exons of NM_152989.3 are UTR's, for the purpose of our study, exon one is the first coding exon. NM_179101.2 is the short form of the gene. Positions are approximate and based on genome build GRCH37(hg19).

gregation Consortium (ExAC) April 2015). In addition, we were unable to find evidence of incontestable *SOX5* loss of function variants in the NHLBI Exome Sequencing Project, 1,000 Genomes project and Exome Aggregation Consortium (ExAC) databases, making this an extremely rare sequence variation (Table SI). A comparative analysis of the proband's characteristics revealed similarities with regards to the presence of developmental delay and distinct physical dysmorphisms seen with heterozygous deletions of *SOX5* (Table I). Sanger sequencing was performed on the proband, the parents and the proband's male full sibling. Testing of the proband confirmed that the *SOX5* variant was present in the heterozygous state. Testing of the parents and brother showed that they did not carry the *SOX5* variant, which was therefore a de novo sequence change (Fig. 3).

DISCUSSION

SOX5 Functional Domains and Role in Development

The *SRY-related HMG Box 5* (*SOX5*) gene is part of a family of transcription factors involved in regulation of embryonic development [Kamachi and Kondoh, 2013]. SOX5 contains a C-terminal high-mobility-group (HMG) domain and two N-terminal coiled-

FIG. 2. Patient with *SOX5* p. (G341) at 17 years of age, note the prominent maxilla, blepharoptosis, low-set, and posteriorly rotated ears, retrognathia, long fingers and long halluces, 2–3 toe syndactyly bilaterally, and a marfanoid appearance of hands and feet.

coil domains. The HMG domain functions in site-specific DNA-binding and is a highly conserved motif seen in other transcription factors including the *TCF*, *HMG*, and *UBF* genes [Laudet et al., 1993]. The coiled-coil domain allows for interactions between homologous SOX proteins. In addition, *SOX5* produces several tissue-specific alternate transcripts: the long forms which encompass the proband's stop gain variant, and a short form which does not. The short form, lacking the N-terminal coiled-coil domain, is transcribed only in testes [Ikeda et al., 2002]. The long form, occasionally referred to as *L-SOX5*, contains all domains and is present in the other SOX5-regulated tissues (Fig. 1).

SOX5 plays a critical role in chondroblast and neuronal progenitor development by regulating the timing of differentiation, which is vital to the specialization of tissue [Lefebvre et al., 2001; Lai et al., 2008]. In the murine brain, loss of Sox5 results in precocious maturation of cortical projection neurons, preventing the production and migration of intermediate cell types and leading to failure of cortical layer V and VI development [Lai et al., 2008]. In chondrocytes, loss of SOX5 results in defects of endochondrial ossification, the process in which bone is formed to replace cartilage [review in Lefebvre et al., 2001]. In the absence of SOX5, chondrogenic cells do not secrete extracellular matrix and thus cartilage does not form [Smits et al., 2001]. To this effect, SOX5 has been demonstrated to be crucial during skeletal development and bone healing [Uusitalo et al., 2001; Ikeda et al., 2005]. Furthermore, *Sox5* null mice die postnatally with respiratory distress, cleft palate and a

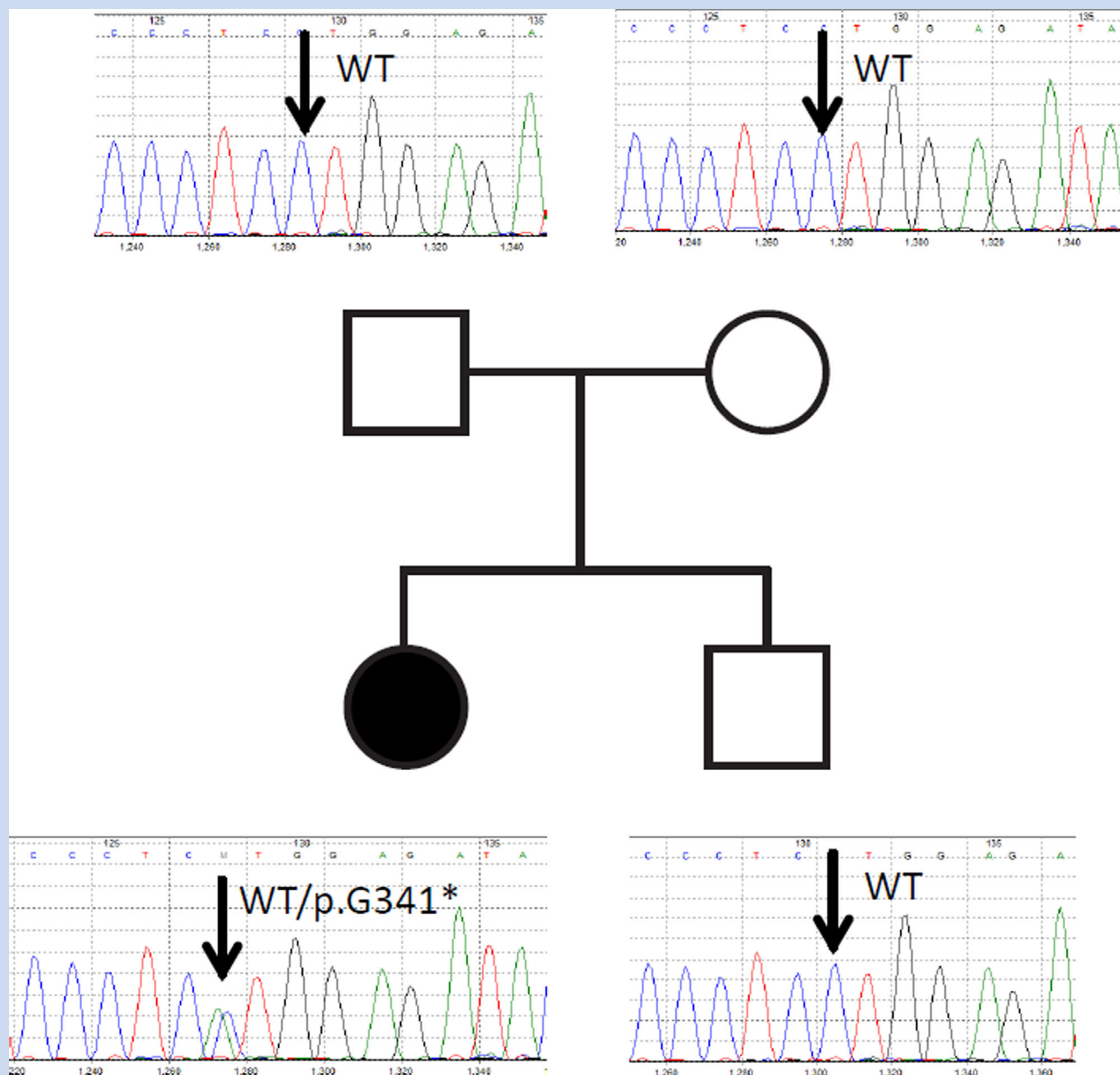

FIG. 3. Sanger traces of a de novo nonsense mutation identified in exon eight of *SOX5*, producing a premature stop codon (p.(341*)) in the affected proband.

TABLE I. Shared Features Between the Proband and SOX5 Deletion Cases. The Patient Presented Here Shares Many Features, Such as Developmental Delay, Neuropsychiatric Issues, and Minor Facial Dysmorphisms, However, She Also Has Signs of a Minor Connective Tissue Disorder, Such as Pectus Carinatum, Which Are Not Usually Found in Patients With SOX5-Related Disorders

Feature Type	Features seen in patient with SOX5 p.G341*	Previous patients reported with isolated sox5 del (n = 11)	Percentage Affected
Motor development	Moderate delay, walked at 23 months	11/11	100%
Cognitive development	IQ of 50	Ranged from mild to severe 10/11	91%
Speech	Delayed, first word at 2 years	10/11	91%
Neuropsych	Anxiety	6/11	55%
Hypotonia	Moderate	5/11	45%
Seizures	None	2/11	18%
Dysmorphisms	Prominent maxilla, midline tongue groove, narrow palate, overcrowded teeth, small lower jar, 2-3 toe syndactylyl bilaterally	8/11	73%
Musculoskeketal	Thoracic kyphoscoliosis, lumbar lordosis, and pectus carinatum with spinal fusion	7/11	64%
Opthomologic	Non-progressive bilateral optic atrophy, exotropia and moderate myopia	5/11	45%
Other	Infantile gastro-esophageal reflux with poor feeding, mild mitral regurgitation	Genital, renal, cardiac, hepatomegaly, thyroglossal duct cyst	

small thoracic cage, demonstrating the impact of SOX5 on developmental regulation [Smits et al., 2001].

SOX Gene Family: Roles in Disease

Pathogenic point mutations have been reported in the *SOX* family of genes (*SOX2*, *SOX9*, *SOX10*, and *SRY*); these genes are postulated to play an important role during cell fate determination of developmental programs including sex determination, chondrogenesis, and neurogenesis [McElreavey et al., 1992; Meyer et al., 1997; Touraine et al., 2000; Fantes et al., 2003]. Phylogenic analysis of the HMG super family suggests that *SRY* (Sex Determining Region Y) evolved from the *SOX* genes, with *SOX9*, *SRY*, and potentially *SOX3* all involved in primary sex determination [Nagai, 2001]. Despite this shared regulatory function, the HMG box gene family predates the existence of sex chromosomes; therefore many *SOX* genes remain involved in regulation other than sexual development. Additionally, while some *SOX* genes are more diverged than others, they still function together in the same differentiation programs. For instance, although SOX5, and SOX6 can form heterodimers due to their highly conserved coiled-coil domain, which is absent in SOX9, all three proteins are vital for proper chrondrocyte differentiation [Ikeda et al., 2005]. As such, mutations of *SOX* and related genes have been implicated in several overlapping, yet distinct, genetic disorders. Haploinsufficiency of *SOX9* results in XY sex reversal and a severe form of chondrodysplasia, resulting in fatal respiratory distress soon after birth; a condition known as Campomelic dysplasia (OMIM 114290) [Meyer et al., 1997]. Loss of function of the Y-linked *SRY* is responsible for type 1 XY sex reversal (OMIM 400044) [McElreavey et al., 1992]. Mutations of the X-linked *SOX3* gene are a cause of intellectual disability and panhypopitutarism (OMIM 300123 and 312000) [Laumonnier et al., 2002; Woods et al., 2005]. *SOX2* is involved in syndromic anophthalima, and microphthalmia (OMIM 206900) [Fantes et al., 2003], while *SOX10* is responsible for Waardenburg Syndrome (OMIM 609136, 611584, and 613266) [Touraine et al., 2000]. In addition, a translocation disrupting *SOX6*, a gene with high homology to *SOX5*, was reported in a case of congenital craniofacial dysmorphisms [Tagariello et al., 2006].

Overall, these disorders demonstrate the importance of the *SOX* family of genes across multiple areas of developmental regulation, with both deletions and point mutations as mechanisms of pathogenicity. The comparable functions of the *SOX* gene family in neurogenesis and chrondogenesis is reflected in the similarities seen between the proband's phenotype, *SOX5* deletion cases, animal models, and several other instances of mutations in the *SOX* genes.

SOX5 and Its Role in Human Disease

To date, there have been three separate publications describing isolated *SOX5* haploinsufficiency due to intragenic disruption, with a total of eleven patients. There is considerable variability between these patients, even those with only *SOX5* involvement. This may be explained by variable expressivity or differential effects on the transcript by deletions of various sizes and locations. The most common findings in all the patients with haploinsufficiency of *SOX5* include developmental delay (mild to severe), speech delay, hypotonia, strabismus, behavioral abnormalities, and dysmorphic features (Table I). The dysmorphic features were variable and typically mild; common findings included frontal bossing, down-slanting palpebral fissures, prominent philtral ridges, crowded teeth, and auricular abnormalities. In comparing this reported phenotypic data to the current patient, we observed

several shared features including developmental delay with an IQ of 50, mild dysmorphic features including dental crowding and strabismus, and a behavioral abnormality manifesting as anxiety. Although not as common, all the additional major features in the proband have also been previously reported in patients with isolated *SOX5* haploinsufficiency: scoliosis in 2/11 patients and bilateral optic atrophy in 1/11 patients. She has some additional features that have not been seen in the previous *SOX5*-haploinsufficiency patients, such as a marfanoid habitus and arachnodactyly. As her unaffected brother has a pectus carinatum deformity, it is possible that there is also an unrelated mild connective tissue disease phenotype in the family.

This is the first reported patient with a point mutation in the *SOX5* gene. This patient has clinical findings that are consistent with the clinical features in previously reported instances of patients with *SOX5* disruptions. Additionally, parental analysis revealed this variant to be a de novo germline mutation, which is in keeping with most reported cases of SOX5 haploinsufficiency. These results highlight that haploinsufficiency of *SOX5* is caused by a number of molecular mechanisms including large copy number changes, translocations, and point mutations.

Intellectual disability is genetically heterogeneous and presents challenges for molecular diagnosis using traditional approaches such as Sanger sequencing. Given that deletion and a gene-disrupting translocation were the only previously known mechanisms for *SOX5* haploinsufficiency, *SOX5* would not have been a likely candidate for assays which detect SNPs and small indels, despite the similarities between this proband and *SOX5* deletion patients. Therefore, it is unlikely this proband's disease-causing mutation would have been identified by traditional genetic testing modalities such as single gene sequencing. In addition, due to both the absence of reported pathogenic sequence variants and the variable nature of the phenotype, this is likely an under diagnosed syndrome. Sequencing and deletion/duplication testing of *SOX5* should be considered when a patient presents with developmental delay, dysmorphia, and other syndromic features. The ability to sequence the exome provides an opportunity to detect novel modes of pathogenicity in disease genes, making exome sequencing a powerful tool for diagnosing conditions that are genetically heterogeneous.

REFERENCES

Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. 2012. An integrated map of genetic variation from 1,092 human genomes. Nature 491:56–65.

Exome Aggregation Consortium (ExAC) C, MA (URL: http://exac.broadinstitute.org) April 2015.

Fantes J, Ragge NK, Lynch SA, McGill NI, Collin JR, Howard-Peebles PN, Hayward C, Vivian AJ, Williamson K, van Heyningen, V, FitzPatrick DR. 2003. Mutations in SOX2 cause anophthalmia. Nat Genet 33:461–463. http://evs.gs.washington.edu/EVS/.

Ikeda T, Kawaguchi H, Kamekura S, Ogata N, Mori Y, Nakamura K, Ikegawa S, Chung UI. 2005. Distinct roles of Sox5, Sox6, and Sox9 in different stages of chondrogenic differentiation. J Bone Miner Metab 23:337–340.

Ikeda T, Zhang J, Chano T, Mabuchi A, Fukuda A, Kawaguchi H, Nakamura K, Ikegawa S. 2002. Identification and characterization of the human long form of Sox5 (L-SOX5) gene. Gene 298:59–68.

Kamachi Y, Kondoh H. 2013. Sox proteins: Regulators of cell fate specification and differentiation. Development 140:4129–4144.

Lai T, Jabaudon D, Molyneaux BJ, Azim E, Arlotta P, Menezes JR, Macklis JD. 2008. SOX5 controls the sequential generation of distinct corticofugal neuron subtypes. Neuron 57:232–247.

Laudet V, Stehelin D, Clevers H. 1993. Ancestry and diversity of the HMG box superfamily. Nucleic Acids Res 21:2493–2501.

Laumonnier F, Ronce N, Hamel BC, Thomas P, Lespinasse J, Raynaud M, Paringaux C, Van Bokhoven H, Kalscheuer V, Fryns JP, Chelly J, Moraine C, Briault S. 2002. Transcription factor SOX3 is involved in X-linked mental retardation with growth hormone deficiency. Am J Hum Genet 71:1450–1455.

Lee RW, Bodurtha J, Cohen J, Fatemi A, Batista D. 2013. Deletion 12p12 involving SOX5 in two children with developmental delay and dysmorphic features. Pediatr Neurol 48:317–320.

Lefebvre V, Behringer RR, de Crombrugghe B. 2001. L-Sox5, Sox6, and Sox9 control essential steps of the chondrocyte differentiation pathway. Osteoarthritis Cartilage 9 Suppl A S69–S75.

McElreavey K, Vilain E, Boucekkine C, Vidaud M, Jaubert F, Richaud F, Fellous M. 1992. XY sex reversal associated with a nonsense mutation in SRY. Genomics 13:838–840.

Meyer J, Südbeck P, Held M, Wagner T, Schmitz ML, Bricarelli FD, Eggermont E, Friedrich U, Haas OA, Kobelt A, Leroy JG, Van Maldergem L, Michel E, Mitulla B, Pfeiffer RA, Schinzel A, Schmidt H, Scherer G. 1997. Mutational analysis of the SOX9 gene in campomelic dysplasia and autosomal sex reversal: Lack of genotype/phenotype correlations. Hum Mol Genet 6:91–98.

Nagai K 2001. Molecular evolution of Sry and Sox gene. Gene 270:161–169.

Popp MW, Maquat LE. 2013. Organizing principles of mammalian nonsense-mediated mRNA decay. Annu Rev Genet 47:139–165.

Schanze I, Schanze D, Bacino CA, Douzgou S, Kerr B, Zenker M. 2013. Haploinsufficiency of SOX5, a member of the SOX (SRY-related HMG-box) family of transcription factors is a cause of intellectual disability. Eur J Med Genet 56:108–113.

Smits P, Li P, Mandel J, Zhang Z, Deng JM, Behringer RR, de Crombrugghe B, Lefebvre V. 2001. The transcription factors L-Sox5 and Sox6 are essential for cartilage formation. Dev Cell 1:277–290.

Soysal Y, Vermeesch J, Davani NA, Hekimler K, Imirzalioglu N. 2011. A 10. 46Mb 12p11. 1–12. 1 interstitial deletion coincident with a 0.19Mb NRXN1 deletion detected by array CGH in a girl with scoliosis and autism. Am J Med Genet A 155A:1745–1752.

Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, Abeysinghe S, Krawczak M, Cooper DN. 2003. Human gene mutation database (HGMD): 2003 update. Hum Mutat 21:577–581.

Tagariello A, Heller R, Greven A, Kalscheuer VM, Molter T, Rauch A, Kress W, Winterpacht A. 2006. Balanced translocation in a patient with craniosynostosis disrupts the SOX6 gene and an evolutionary conserved non-transcribed region. J Med Genet 43:534–540.

Touraine RL, Attie-Bitach T, Manceau E, Korsch E, Sarda P, Pingault V, Encha-Razavi F, Pelet A, Auge J, Nivelon-Chevallier A, Holschneider AM, Munnes M, Doerfler W, Goossens M, Munnich A, Vekemans M, Lyonnet S. 2000. Neurological phenotype in Waardenburg syndrome type 4 correlates with novel SOX10 truncating mutations and expression in developing brain. Am J Hum Genet 66:1496–1503.

Uusitalo H, Hiltunen A, Ahonen M, Gao TJ, Lefebvre V, Harley V, Kahari VM, Vuorio E. 2001. Accelerated up-regulation of L-Sox5, Sox6, and Sox9 by BMP-2 gene transfer during murine fracture healing. J Bone Miner Res 16:1837–1845.

Woods KS, Cundall M, Turton J, Rizotti K, Mehta A, Palmer R, Wong J, Chong WK, Al-Zyoud M, El-Ali M, Otonkoski T, Martinez-Barbera JP, Thomas PQ, Robinson IC, Lovell-Badge R, Woodward KJ, Dattani MT. 2005. Over-and underdosage of SOX3 is associated with infundibular hypoplasia and hypopituitarism. Am J Hum Genet 76:833–849.

SUPPORTING INFORMATION

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