Septo-Optic Dysplasia – Novel Insights into the Aetiology

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Key Words

HESX1 • *SOX2* • *SOX3* • Septo-optic dysplasia • Pituitary

Abstract

Septo-optic dysplasia (SOD) is a highly heterogeneous condition comprising a variable phenotype of optic nerve hypoplasia, midline brain abnormalities and pituitary hypoplasia with consequent endocrine deficits. The majority of cases are sporadic and several aetiologies have been suggested to account for the pathogenesis of the condition. However, a number of familial cases have been described and the identification of mutations in key developmental genes including *HESX1*, *SOX2* and *SOX3* in patients with SOD and associated phenotypes suggests that a genetic causation is likely in the more common sporadic cases of the condition. The precise aetiology of SOD is most likely multifactorial involving contributions from environmental factors in addition to an important role for crucial developmental genes. The variability of the penetrance and phenotypes within a single SOD pedigree may also suggest a complex interaction between genetics and the environment, and at present, the understanding of these interactions is rudimentary. Further study of these critical factors may shed light on the aetiology of this complex disorder. We have reviewed recent literature selecting relevant references based on the keywords *HESX1*, *SOX2*, *SOX3*, Septo-optic dysplasia, genetics and pituitary development.

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Septo-Optic Dysplasia

Septo-optic dysplasia (SOD), often referred to as de Morsier syndrome, is a rare, highly heterogeneous condition initially described by Reeves [1] in a 7-month-old baby with absence of the septum pellucidum and optic nerve abnormalities. The condition is defined loosely by any combination of the triad of optic nerve hypoplasia (ONH), midline neuroradiological abnormalities (such as agenesis of the corpus callosum and absence of the septum pellucidum) and pituitary hypoplasia with consequent hypopituitarism [1, 2]. The reported incidence of SOD is 1/10,000 live births [3] and it is thought to be equally prevalent in males and females. Although the condition is generally sporadic, familial cases have been described. Neurological deficit is common ranging from global retardation to focal deficits such as epilepsy or hemiparesis [4, 5], with other features including cavum septum pellucidum, cerebellar hypoplasia, schizencephaly and aplasia of the fornix. Approximately 75–80% of patients exhibit ONH, which may be unilateral or bilateral although bilateral involvement is more common (88% as compared with 12% unilateral cases) and may be the first presenting feature with later onset of endocrine dysfunction [6–9]; in rare cases, the eye abnormality may be more severe, resulting in microphthalmia or anophthalmia. Pituitary hypoplasia may manifest as variable endocrine deficits ranging from isolated growth hormone (GH) deficiency to panhypopituitarism, and there

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has been a suggestion that abnormalities of the septum pellucidum and hypothalamo-pituitary axis on neuroimaging can predict the severity of endocrine dysfunction [10]. GH deficiency is the most common endocrinological feature followed by deficiencies of thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH) [11], whereas gonadotrophin secretion may be retained in the face of other pituitary hormone deficiencies; however the endocrinopathy may evolve with a progressive loss of endocrine function over time. Either sexual precocity or failure of pubertal development may occur, with abnormal hypothalamic neuroanatomy or function [12–14]; other features such as hypoglycaemia and diabetes insipidus are less commonly associated [15].

The phenotype is highly variable, and a diagnosis of SOD usually made if two or more of the triad of ONH, hypopituitarism or midline brain defects are present. According to Morishima and Aranoff [16], approximately 30% of SOD cases have complete manifestations, 62% have the complication of hypopituitarism and 60% have an absent septum pellucidum. The condition is thought to be more frequent in children born to younger mothers (mean maternal age 22 years) [17], although this has been disputed [9] and in some studies there is a preponderance of primigravida mothers [9]. Recently, cases of both isolated ONH as well as SOD have been shown to cluster in high population density, inner city areas with high rates of unemployment and teenage pregnancy [3].

The development of the forebrain is highly complex, occurring at a very early stage of embryogenesis; any insult at this critical stage of embryonic development could account for the features of SOD. Such developmental insults would have to take place during the critical period of morphogenesis for these structures, corresponding to between 4 and 6 weeks of gestation in humans, during which two significant developmental events occur. First, the telencephalic optic vesicles and retinal ganglion cells differentiate, and secondly, the lamina terminalis thickens, and its subsequent differentiation results in formation of the corpus callosum, anterior commissure, and fornix. Any insult arising at this stage has the potential to produce failure of ganglion cell formation with subsequent hypoplasia of optic nerves and chiasm in the first instance and lack of commissural or septal formation in the second instance. It is important to stress that hypoplasia can result from an incomplete commitment of progenitor cells, or a failure to commit adequate numbers of precursors, which could then give rise to variable degrees of hypoplasia, as well as aplasia, of forebrain structures.

Congenital midline defects encompass a large array of clinical phenotypes, ranging from those that are incompatible with life to severe palato-facial cleft associated with neuroanatomical defects. The conditions include various forms of holoprosencephaly, SOD and agenesis of the corpus callosum, with isolated cleft lip or palate at the less severe end of the spectrum. As the pituitary is a midline structure, the association between hypopituitarism and extensive congenital midline brain defects has long been recognized, of which SOD phenotypes are the most common [18, 19].

Genetic Aetiology of SOD

Several aetiologies have been postulated to account for the sporadic occurrence of SOD, such as viral infections, environmental teratogens, and vascular or degenerative damage [14, 20]. However, the precise aetiology of the condition still remains unknown and is most likely to be multifactorial, with a combination of genetic and environmental factors. Familial cases of SOD are rare, but implicate a genetic defect underlying the developmental mechanisms involved, and are more frequently associated with an autosomal recessive manner of inheritance [21, 22] although dominant inheritance has also been reported [23–25]. The identification of mutations in key developmental genes in patients with SOD and associated phenotypes provides evidence for a genetic aetiology in sporadic cases of the condition.

HESX1

Hesx1 is a member of the paired-like class of homeobox genes and functions as a transcriptional repressor, with repression domains within the N terminal region and the DNA binding homeodomain [26, 27]. It is one of the earliest markers of murine pituitary development, being initially expressed during gastrulation in a region fated to form the forebrain. Subsequently, *Hesx1* expression is restricted to the ventral diencephalon by embryonic day (E) 9.0, and also in the thickened layer of oral ectoderm that will give rise to Rathke's pouch, the primordium of the anterior pituitary. *Hesx1* continues to be expressed in the developing anterior pituitary until E12 when expression is attenuated corresponding to progressive pituitary cell differentiation, finally becoming undetectable by E13.5.

Homozygous disruption of *Hesx1* in mice is associated with a phenotype closely resembling that of SOD. Abnormalities are fully penetrant, although variable, in *Hesx1*

Fig. 1. A Sagittal MRI scan of the head of a normal child showing the corpus callosum (CC), the optic chiasm (OC), the anterior pituitary (AP), the pituitary stalk (PS) and posterior pituitary (PP) in the normal sella turcica. Note the well-formed corpus callosum, optic chiasm, and the posterior pituitary which appears as a bright spot within the sella turcica. **B** Sagittal MRI scan of a patient with a homozygous R160C mutation in *HESX1*. The corpus callosum (CC) is severely hypoplastic, as is the optic chiasm (OC)

and the anterior pituitary (AP) located in a well-formed but empty sella turcica. Note the ectopic posterior pituitary (PP) and the lack of a visible pituitary stalk. **C** Sagittal MRI scan of sibling, also homozygous for the R160C mutation in *HESX1*. Note that the splenium of the corpus callosum is more hypoplastic than the rest of the structure and that the sella turcica is shallow as compared with the MRI scan of the first patient (**B**). The posterior pituitary (PP) appears to be partially descended.

null mice and features include a reduction in prospective forebrain tissue, absence of developing optic vesicles, markedly decreased head size, craniofacial dysplasia with a short nose, severely reduced forebrains with no sign of telencephalic vesicle or infundibulum development, absence of olfactory placodes, hypothalamic abnormalities and aberrant morphogenesis of Rathke's pouch [28]. Further analysis of neonatal and adult mutants revealed hypoplastic nasal cavities, hypoplastic olfactory bulbs, microphthalmia and anophthalmia, with abnormalities of the septum pellucidum and corpus callosum. A more detailed analysis of the *Hesx1*-null mutants revealed that a proportion of mice (5%) exhibited a more severe phenotype in which no anterior pituitary gland was formed, although thickening of the oral ectoderm was detected [26]. However, in the majority of the mice, pituitary development proceeded beyond formation of Rathke's pouch and showed a milder phenotype with an overall reduction of forebrain epithelium and ventral midline defects of the hypothalamus. The majority of these mice showed multiple invaginations of the oral ectoderm, and aberrant morphogenesis of Rathke's pouch which displayed abnormal bifurcations resulting in the apparent formation of multiple pituitary glands.

In light of the similarity between the phenotype of *Hesx1* null mice and SOD, we investigated the role of the human homologue of *HESX1* (OMIM 601802) in patients with SOD. A homozygous missense mutation in the homeobox of *HESX1* was initially identified in a highly

consanguineous family in which 2 affected siblings presented with ONH, a hypoplastic corpus callosum, and hypoplasia of the anterior pituitary gland with an undescended/ectopic posterior pituitary and consequent hypopituitarism (fig. 1) [21, 28]. The mutation identified in the affected siblings resulted in the substitution of a highly conserved arginine at residue 160 (position 53 of the homeodomain) by cysteine (R160C) which leads to a loss of DNA binding of the mutant protein. The parents were heterozygous for the mutation and phenotypically normal, consistent with an autosomal recessive mode of inheritance. Four additional homozygous mutations have subsequently been identified (table 1). A homozygous substitution (I26T) was identified in a girl presenting with GH and gonadotrophin deficiency, with evolving ACTH and TSH deficiency. Magnetic resonance imaging (MRI) revealed anterior pituitary hypoplasia with an undescended posterior pituitary, however she had normal optic nerves and no midline forebrain defects. This mutation lies in a highly conserved region in the N-terminus of *HESX1*, the engrailed homology domain (eh-1) crucial for transcriptional repression [27], and was associated with partial loss of repression [29]. A third recessive mutation was identified in 2 siblings from a consanguineous family, involving an Alu-element insertion in exon 3 of *HESX1*, which encodes the homeodomain of the protein [30]. Homozygosity for the mutation was associated with a severe phenotype including undetectable levels of all anterior pituitary hormones as a result of aplasia of the

Table 1. Reported mutations in *HESX1*

Mutation	Inheritance	Endocrine phenotype	Neuroradiological findings	Ref.
Q6H	Dominant	GH, TSH, LH, FSH deficiency	AP hypoplasia, ectopic PP	23
I26T	Recessive	GH, LH, FSH deficiency; evolving ACTH, TSH deficiency	AP hypoplasia, ectopic PP, normal ON	29
c.306_307insAG	Dominant	GH, LH, FSH deficiency; hypothyroidism	AP hypoplasia, ON hypoplasia	25
Q117P	Dominant	GH, TSH, ACTH, LH, FSH deficiency	AP hypoplasia, ectopic PP	32
c.357+2T>C	Recessive	GH, TSH, ACTH, PRL deficiency	AP aplasia, normal PP, normal ON	31
Alu insertion (exon 3)	Recessive	Hypopituitarism	AP aplasia, hypoplastic sella, normal PP and infundibulum	30
E149K	Dominant	GH deficiency	AP hypoplasia, ectopic PP, infundibular hypoplasia	17
c.449_450delAC	Recessive	GH, TSH, ACTH deficiency	AP aplasia, normal PP, normal ON, thin CC, hydrocephalus	31
R160C	Recessive	GH, TSH, ACTH, LH, FSH deficiency	AP hypoplasia, ectopic PP, ON hypoplasia, ACC	28
S170L	Dominant	GH deficiency	Normal AP, ON hypoplasia, ectopic PP, partial ACC	23
K176T	Dominant	GH deficiency, evolving ACTH, TSH deficiency	Ectopic PP	32
g.1684delG	Dominant	GH deficiency	AP hypoplasia, ON hypoplasia, ACC, absent PP bright spot	24
T181A	Dominant	GH deficiency	AP hypoplasia, normal ON, absent PP bright spot	23

AP = Anterior pituitary; PP = posterior pituitary; ON = optic nerve; (A)CC = (agenesis of the) corpus callosum.

anterior pituitary (as observed in 5% of homozygous null mice), together with hypoplasia of the sella turcica. Conversely, the posterior pituitary and pituitary stalk were both normal. One sibling had a coloboma of the right optic nerve resulting in unilateral blindness, whilst the other had no ophthalmic abnormalities but displayed a left-sided diaphragmatic hernia and aortic coarctation and died shortly after birth. Sobrier et al. [31] have recently reported two additional patients with novel recessive mutations (c.449_450delAC, c.357 + 2T>C) in *HESX1* associated with anterior pituitary aplasia in the absence of an ectopic posterior pituitary or optic nerve abnormalities, features typically associated with *HESX1* mutations. The patient with the 2-bp deletion (c.449_450delAC) had additional midline abnormalities including a thin corpus callosum and hydrocephalus.

To date, reports of screening patients with sporadic SOD have yielded eight novel heterozygous mutations within *HESX1* (table 1). These heterozygous mutations are generally associated with milder phenotypes than the homozygous mutations, leading to GH deficiency with or without an undescended posterior pituitary [23], although ONH as well as midline forebrain abnormalities may be associated [24]. The penetrance may be variable, and the presence of a mutation is not always associated with a phenotype. We have now screened over 800 patients with SOD and hypopituitarism, and identified mutations in less than 1% of individuals confirming the rarity of *HESX1* mutations [17]. As a result of this screening we have identified a number of sequence variants, including a change of unknown functional importance in a highly conserved base in a known *cis*-regulatory region

upstream of *HESX1*. Whether these variants contribute to the pathogenesis remains to be proven. The overall frequency of *HESX1* mutations is low suggesting that mutations in other known or unknown genes contribute to this complex disorder, together with a likely contribution from environmental factors [3, 32].

SOX3

SOX3 (OMIM 313430) is a member of the SOX (SRY-related HMG box) family of transcription factors, which were initially identified based on homology to the conserved binding motif of the high mobility group (HMG) class, present in the mammalian sex-determining gene, *SRY* [33]. Approximately 20 different SOX genes have been identified in mammals and variation in homology exhibited within the HMG box between different members allows them to be grouped into different subfamilies [34, 35]. SOX3 was among the first of the SOX genes to be cloned, and together with SOX1 and SOX2, belongs to the SOXB1 subfamily exhibiting the highest degree of similarity to *SRY* [33]. SOX3 is encoded by a single exon producing a transcript with a coding region of approximately 1.3 kb, mapping to chromosome Xq27. The SOX3 protein consists of a short 66 amino acid N-terminal domain of unknown function, the 79 amino acid DNA binding HMG domain and a longer C-terminal domain, containing four polyalanine stretches, shown to be involved in transcriptional activation [33, 36].

Members of the SOXB1 subfamily of genes are expressed throughout the developing central nervous system (CNS) and are some of the earliest neural markers that are believed to play a role in neuronal determination.

Sox3 is expressed in the earliest stages of development, with its main site of expression within the CNS and has been strongly implicated in neurogenesis [37]. Subsequently, *Sox3* is expressed along the full length of the developing CNS, including the brain and spinal cord, in actively dividing undifferentiated neural progenitor cells where expression is maintained throughout development [38]. High levels of expression have also been noted in the ventral diencephalon, including the infundibulum and presumptive hypothalamus [39].

Targeted disruption of *Sox3* in mice results in mutants that have a variable and complex phenotype including craniofacial abnormalities, midline CNS defects, and a reduction in size and fertility [39]. *Sox3* mutant mice of both sexes are born with expected frequency showing no evidence for embryonic lethality, and approximately one third of mutant mice are viable and fertile with no gross abnormalities. Heterozygous females are mosaic with respect to the mutation due to X inactivation and generally appear normal, although some display a mild craniofacial phenotype. However, approximately 43% of *Sox3* null mice do not survive to weaning, and the most severely affected mice exhibit profound growth insufficiency and general weakness with craniofacial defects including overgrowth and misalignment of the front teeth and abnormality of the shape of the pinna which was completely absent in some animals [39].

Rizzotti et al. [39] analysed the pituitary gland and brain of *Sox3* mutant mice in detail, revealing the mutants to have a variable endocrine deficit, the extent of which was correlated with body weight. Pituitary levels of GH, luteinizing hormone (LH), follicle-stimulating hormone and TSH were all lower in mutant compared to wild-type mice at 2 months of age. Histological analysis of the pituitary gland at this stage revealed a hypoplastic anterior lobe with the presence of an additional abnormal cleft disrupting the boundary between the anterior and intermediate lobes. Further examination of *Sox3* mutant embryos revealed that Rathke's pouch displayed an abnormally expanded and bifurcated appearance in mutant embryos which possibly results in the additional cleft observed at later stages of development and in the adult pituitary. *Sox3* is not expressed in Rathke's pouch, however it is expressed at high levels in the ventral diencephalon including the infundibulum which provides necessary inductive signals for the formation of the anterior pituitary [40]. In *Sox3* mutants, the evagination of the infundibulum was less pronounced than observed in wild-type mice and the presumptive hypothalamus thinner and shorter [39]. This suggests that the hypopituitary pheno-

type observed in mutant mice arises as a secondary consequence of the absence of *Sox3* in the ventral diencephalon [39].

In humans, tandem duplications involving chromosome Xq26-27 have been identified in several pedigrees with mental retardation and hypopituitarism [41–43]. By using array comparative genomic hybridization, Solomon et al. [43] defined a critical duplication region of 3.9 Mb between Xq26.1 and Xq27.3 containing 18 annotated transcripts including *SOX3*. The phenotypes of affected males with X-linked hypopituitarism involving duplications within this region are variable. All affected males manifest GH deficiency and varying degrees of developmental delay or mental retardation [41, 43]. Some individuals have been reported to have varying combinations of deficiencies of other hormones including ACTH, TSH or gonadotrophins, and complete anterior pituitary hormone deficiency has been documented in some cases [42]. Unaffected carrier females in these pedigrees show preferential inactivation of the duplicated X chromosome; however, a rare family with 5 affected females presenting with short stature secondary to hypopituitarism, speech and language problems, hearing impairment and facial dysmorphism has also been reported with a 7.5-Mb duplication of chromosome Xq26.2-q27.1 [44]. The authors suggested that the duplication may disrupt *SOX3* resulting in hemizygosity in affected females, although this was not confirmed at the molecular level. Woods et al. [45] described a pedigree with 2 half-brothers manifesting evidence of X-linked hypopituitarism, in the absence of developmental delay, harbouring a submicroscopic duplication on chromosome Xq27.1, further refining the critical interval to approximately 690 kb. The first child manifested GH deficiency and borderline low FT4 concentrations, with hypoplasia of the lower half of the infundibulum and an abnormal corpus callosum which contained a cyst within the splenium. The second sibling manifested a more severe phenotype of combined pituitary hormone deficiency, with complete absence of the infundibulum and hypoplastic genitalia; however his corpus callosum appeared normal. Both patients had anterior pituitary hypoplasia and an undescended posterior pituitary as revealed by MRI. The duplication identified in this family is the smallest described to date encompassing *SOX3* and two additional transcripts of unknown function, neither of which is expressed in the developing infundibulum [45] suggesting that the phenotype in these patients is due to the presence of an additional copy of *SOX3*.

Further implication of *SOX3* in X-linked hypopituitarism comes from the identification of patients harbour-

Fig. 2. Polyalanine tract expansion mutations within *SOX3*.

ing an expansion of one of the polyalanine tracts within the gene (fig. 2) [45, 46]. Laumonnier et al. [46] identified an in-frame duplication of 33 bp occurring between nucleotides 711 and 743 and co-segregating in affected males in a large family with X-linked mental retardation and GH deficiency. This mutation encodes an additional 11 alanine residues and is predicted to cause expansion of the normal polyalanine tract from 15 to 26 residues. Additionally, a second novel expansion of seven alanine residues within the same tract has been identified in 3 siblings of a consanguineous pedigree presenting with profound hypopituitarism in association with anterior pituitary hypoplasia, an absent or hypoplastic infundibulum and an undescended posterior pituitary. There was no evidence of mental retardation or craniofacial dysmorphism in these individuals.

In vitro analysis of the *SOX3* +7 alanine expansion identified by Woods et al. [45] revealed that the expansion leads to partial loss of function possibly due to impairment of nuclear localization as the mutant protein was largely excluded from the nucleus, compared to wild-type *SOX3* which is predominantly localized within the nucleus of the cell. Similar findings have also been shown for the mutant *SOX3* protein containing the +11 alanine expansion which forms aggregates within the cytoplasm [47]. Furthermore, expansion mutations in *HOXA13* and *RUNX2* show a similar effect, suggesting that expanded polyalanine tract mutations in transcription factors are associated with loss of function as a result of cytoplasmic aggregation of the mutant protein [47].

In summary, both duplications of Xq27 encompassing *SOX3* and loss-of-function polyalanine expansion mutations are essentially associated with similar phenotypes, predominantly infundibular hypoplasia, suggesting that

gene dosage of *SOX3* is critical for normal development of the diencephalon and infundibulum and, consequently the anterior pituitary.

SOX2

SOX2 (OMIM 184429) is also a member of the same *SOXB1* subfamily as *SOX3* and *SOX1* (OMIM 602148). In the mouse, initial expression of *Sox2* is detected at 2.5 dpc at the morula stage, and then in the inner cell mass of the blastocyst at 3.5 dpc. Later expression of *Sox2*, following gastrulation, is restricted to the presumptive neuroectoderm and by 9.5 dpc it is expressed throughout the brain, CNS, sensory placodes, branchial arches, gut endoderm and the oesophagus and trachea [48, 49]. Homozygous loss of *Sox2* results in peri-implantation lethality, whereas *Sox2* heterozygous mice appear relatively normal but show a reduction in size and male fertility [50]. Further studies that have resulted in the reduction of *SOX2* expression levels below 40% compared to normal levels result in anophthalmia in the affected mutants [51].

Given the observation of growth retardation and reduced fertility, we have recently investigated the role of *Sox2* in murine pituitary development, showing that a proportion of heterozygous animals manifested a variable hypopituitary phenotype, with hypoplasia and abnormal morphology of the anterior pituitary gland with concomitant reduction in levels of GH, LH, ACTH and TSH [52]. Like its murine counterpart, the human *SOX2* gene is composed of a single exon encoding a 317 amino acid protein containing an N-terminal domain of unknown function, a DNA binding HMG domain and a C-terminal transcriptional activation domain. Twelve heterozygous de novo mutations in *SOX2* were previously

Fig. 3. Pathogenic mutations and sequence variants identified within the coding region of *SOX2*.

reported in 14 human patients associated with bilateral anophthalmia or severe microphthalmia with additional abnormalities including developmental delay, learning difficulties, oesophageal atresia and genital abnormalities [49, 53–56]. All of these mutations (fig. 3) occurred de novo and included 5 nonsense, 4 frameshift, 1 deletion, and 2 missense mutations. We have subsequently reported 6 patients harbouring de novo heterozygous mutations in *SOX2* resulting in loss-of-function of the mutant protein, 4 of which were previously unreported (c.60insG, c.387delC, Y160X and c.479delA). Clinical evaluation revealed that in addition to anophthalmia/microphthalmia, *SOX2* mutations were also associated with anterior pituitary hypoplasia and hypogonadotropic hypogonadism, which resulted in the absence of puberty in all 6 patients and genital abnormalities in males. All affected individuals exhibited learning difficulties with other variable manifestations including hippocampal abnormalities, defects of the corpus callosum, oesophageal atresia and sensorineural hearing loss [52]. The mutations were associated with significant loss of function that included loss of DNA binding, nuclear localization, and transcriptional activation, suggesting these phenotypes arise as a result of haploinsufficiency of *SOX2* in development. More recently, Sato et al. [57] have reported an additional patient with a missense mutation in the HMG domain (L75Q) resulting in decreased DNA binding affinity of the mutant protein. The affected individual manifested unilateral right-sided anophthalmia and isolated hypogonadotropic hypogonadism, with a normal anterior pituitary and normal mental development, further supporting a critical role for *SOX2* in the regulation of correct gonadotrophin production in addition to eye development [57].

Conclusions

SOD is now known to be due to disordered development of the forebrain and related structures. It has previously been speculated that SOD is due to an environmental effect, however it is now clear that mutations in the gene encoding the transcriptional repressor *HESX1* may play a role in the pathogenesis of some rare familial forms of SOD [28–31] in addition to a suggestive role for this gene in some cases of the more frequently occurring sporadic form of SOD [23, 25, 27]. Nevertheless, the majority of patients screened in our studies show no mutation of *HESX1*. As observed with holoprosencephaly, SOD may have a multigenic basis, and mutations in as yet unidentified genes could contribute to some cases. Mutations identified in *SOX2* and *SOX3* are associated with rarer SOD variant phenotypes that include severe bilateral eye defects and abnormalities of the infundibulum and corpus callosum respectively. To date, the targets and partners of these transcriptional factors involved in the development of forebrain structures remain unknown and investigation and identification of these may shed further light on the molecular basis of not only SOD, but of various other pituitary disorders. The variability of the phenotypes within a single SOD pedigree may also suggest a complex interaction between genetics and the environment, and at present, the understanding of these interactions is rudimentary. Further study of these critical factors may shed light on the aetiology of this complex disorder.

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