Supplementary Material

Supplementary Table S1: *SOX* gene variants associated with NDDs

Genetic Aetiology	Clinical presentation	References
***SOX3* deletion** Xq26.2-27.2 deletion (comprising the *Factor IX* gene and *S0X3*)	intelectual disability, haemophilia B	(Stevanovic et al., 1993)
***SOX3* deletion** 2.1 Mb Xq27.1-q27.2 deletion (comprising the entire *SOX3* gene)	mild intellectual disability, language delay, dysarthria, behavior problems, minor facial anomalies, hyperphagia	(Helle et al., 2013)
***SOX3* duplication** Xq26.3-27.3 duplication	intellectual disability, growth hormone deficiency, ocular dyspraxia	(Stagi et al., 2014)
***SOX3* duplication** 323.8 kb Xq27.1 duplication (breakpoints 139,261,842–139,585,653)	severe intellectual disability, hypoglycemia, prolonged jaundice, failure to thrive, micropenis, small-volume testes, adrenal insufficiency, central hypothyroidism, hypoplastic anterior pituitary, growth hormone deficiency, ventricular septal defect, patent ductus arteriosus, trivial mitral regurgitation	(Arya et al., 2019)
***SOX3* duplication** 396 kb Xq27.1 duplication (breakpoints 139,347,578–139,743,254)	severe intellectual disability, neuropathic bladder, lumbar myelomeningocele, hydrocephalus, agenesis of the corpus callosum, hypoglycaemia, micropenis, small-volume testes, growth hormone deficiency, bilateral optic atrophy, left temporal lobe epilepsy, Arnold-Chiari malformation, limited mobility	(Arya et al., 2019)
***SOX3* duplication** 11 Mb Xq27.1 duplication (breakpoints 139,055,504–150,083,888)	mild intellectual disability, short stature, growth hormone deficiency, borderline TSH deficiency, hypoplastic anterior pituitary	(Arya et al., 2019)
***SOX3* duplication** 481 kb Xq27.1 duplication (breakpoints 139,261,841–139,743,254)	moderate intellectual disability, short stature, pubertal delay, low testicular volumes, moderate learning difficulties, growth hormone deficiency, partial agenesis of the corpus callosum, absent septum pellucidum, presence of heterotopic grey matter	(Arya et al., 2019)
SOX3 missense variant c.449C>A (p.Ser150Tyr)	mild intellectual disability, microphthalmia, coloboma, hypopituitarism, facial dysmorphology, dental anomalies, microcephaly, retrognathia, solitary median maxillary central incisor	(Jelsig et al., 2018)
SOX3 in-frame duplication of 33 bp	intellectual disability, growth hormone deficiency	(Laumonnier et al., 2002)

encoding for 11 alanines in a polyalanine tract of the *SOX3* gene		
SOX4 heterozygous missense variants: c.198C>A (p.Phe66Leu); c.334G>C (p.Ala112Pro); c.176T>G (p.Ile59Ser); c.315G>T (p.Lys105Asn)	common features: developmental delay, intellectual disability, mild facial and digital morphological abnormalities	(Zawerton et al., 2019)
- ***SOX5*** intragenic heterozygous deletions ranging from 72 kb to 466 kb; - balanced *de novo* translocation with breakpoint within ***SOX5*** [46,XX,t(11;12)(p13;p12.1)dn]; - ***SOX5*** deletions 12p12 deletions ranging from 1.4 Mb to 12.1 Mb, encompassing multiple genes including *SOX5*	common features: intellectual disability, prominent language delay, behavior abnormalities, dysmorphic appearance	(Lamb et al., 2012)
SOX5 deletion heterozygous 12p12.1 deletions ranging from 120 kb to 4.9 Mb	common features: intellectual disability, moderate delay in motor development, delayed speech development	(Schanze et al., 2013)
SOX5 heterozygous stop gain variant in exon eight (c.1021G>T, p. (G341*))	intellectual disability, moderate developmental delay, bilateral optic atrophy, mildly dysmorphic features, scoliosis, behavioral issues	(Nesbitt et al., 2015)
SOX6 heterozygous variants – CNVs (partial deletions of *SOX6* which did not involve any other gene), SNVs (nonsense, frameshift, missense variants), balanced reciprocal translocation 46,XY,t(2;11)(p11.2;p15.2)	common features: intellectual disability, developmental delay inconstant features: attention-deficit/hyperactivity disorder, autism, mild facial dysmorphism, craniosynostosis, multiple osteochondromas	(Tolchin et al., 2020)
SOX11 heterozygous missense mutations localize within the HMG domain: c.347A>G (p.Tyr116Cys); c.178T>C (p.Ser60Pro)	common features: mild intellectual disability, dysmorphic facial features, microcephaly, growth deficiency, hypoplastic fifth toe nails	(Tsurusaki et al., 2014)