

SOX3 gene duplication (OMIM 313430) associated with midline CNS malformations, hypopituitarism and neurodevelopmental abnormalities: five unrelated cases

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Poster number:
P2 – P318

Background

Duplications of the SOX3 gene at Xq27.1 are known to be associated with a spectrum of forebrain midline defects, isolated or multiple pituitary hormone deficiencies, spina bifida and sometimes learning difficulties (1-3). We report 5 cases of SOX3 duplication with hypopituitarism and/or neurodevelopmental issues and differing presentations.

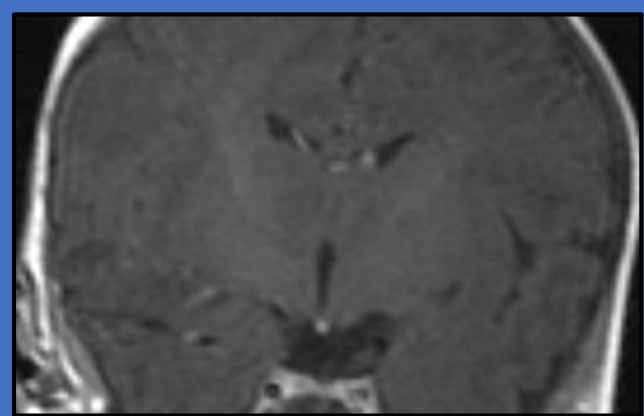
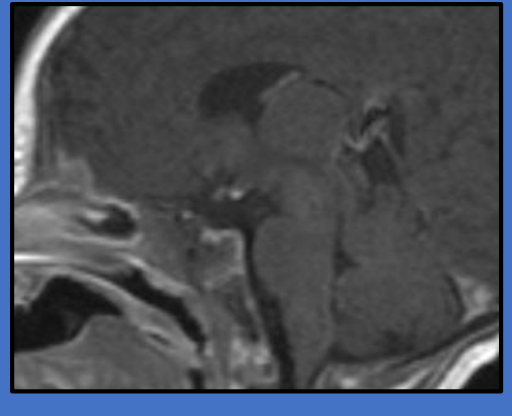
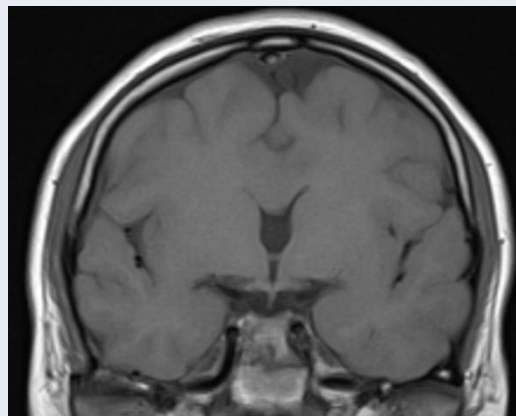
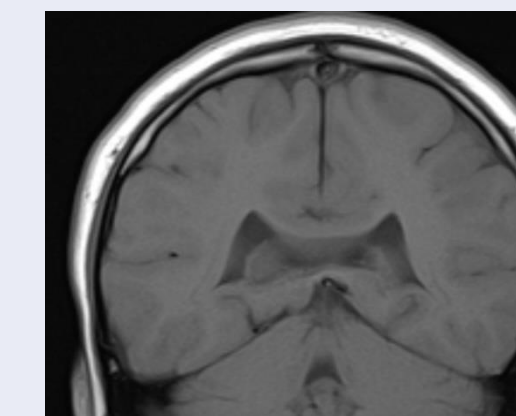
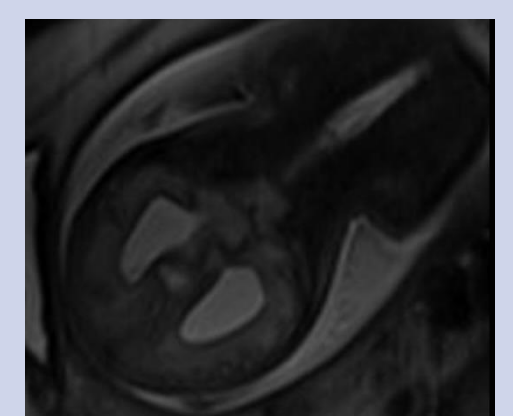
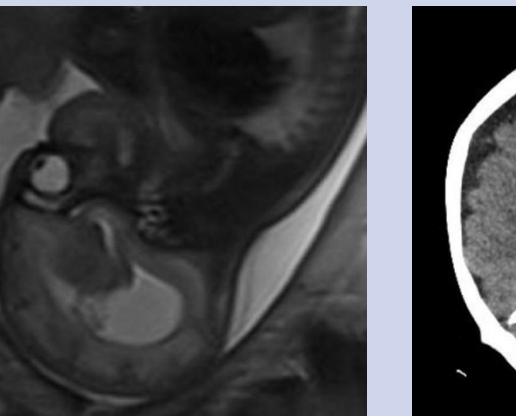
Presenting Demographics and Clinical Features

Feature	Case 1	Case 2	Case 3	Case 4	Case 5
Age at presentation	Neonatal period	15yr	Neonatal period	4.9yr	5yr
Birth weight/gestation	2810 g/ 37 weeks	3628 g/ 40 weeks	3220 g/ 34 weeks	2800 g/ 40 weeks	3170 g/ 40 weeks
Presenting complaints	Neonatal jaundice, hypoglycaemia, failure to thrive	Short stature, pubertal delay	Neonatal hypoglycaemia, micropenis, small testes	Short stature, mild developmental delay	Obesity and developmental delay
Family History	Maternal male cousin with hypopituitarism and Diabetes Insipidus. Another maternal male cousin with spina bifida	No known pituitary defect in the family Sister carrying Xq27.1 duplication	No known pituitary defect in the family	No known pituitary defect in the family	No known pituitary defect in the family
Visual symptoms	None	None	Severely impaired (optic atrophy)	None	None
Seizures	None	None	Left temporal lobe epilepsy	None	None
Intellectual disability	Moderate	Dyspraxia Language delay Moderate LDs	Severe developmental delay	Mild delay	Mild delay
Other	None	Hyposmia, brachycephaly	Lumbar meningomyelocele and hydrocephalus	Clinodactyly, hypoplasia of right thumb, brachycephaly, hyperextensible fingers	None
SOX3 duplication inheritance	Maternally derived	Maternally derived	De novo	Maternally derived	De novo

Biochemical Evaluation

Case	Basal IGF-1 (nmol/L)	FT4 (pmol/l)/ TSH (mIU/L)	Peak GH (mcg/L) (Glucagon)	Peak cortisol (nmol/l) (SST)	Pituitary hormone deficiencies
1	5 (4 – 37)	8.0 / 6.4	0.1	179	GH, ACTH, TSH, ?gonadotrophin
2	20 (60 -90)	Normal	6.1	Normal	GH, ?gonadotrophin
3	4 (4-15)	Normal	4.4	452	GH, ?gonadotrophin
4	Normal	Normal	26.0	Normal	None
5	6 (4 – 41)	12.6 / 2.9	Undetectable	Normal	GH, ?TSH

Imaging

	Case 1	Case 2	Case 3	Case 4	Case 5
Imaging:	 <i>Coronal</i>  <i>Sagittal</i>	 	 <i>Antenatal MRI</i>  <i>Post-shunt</i>	Picture not available	Picture not available
Interpretation:	<i>Pituitary hypoplasia and ectopic posterior pituitary with normal septum pellucidum and corpus callosum</i>	<i>Partial agenesis of corpus callosum Absent septum pellucidum Heterotopic grey matter adjacent to lateral Ventricles</i>	<i>Hydrocephalus and Agenesis of Corpus Callosum / Septum Pellucidum. CT scan after post-natal shunt placement showing improvement in hydrocephalus</i>	<i>Normal</i>	<i>Anterior pituitary hypoplasia and ectopic posterior pituitary</i>

Endocrine Management

Case	1	2	3	4	5
Treatment	Hydrocortisone, Thyroxine, Growth Hormone	Testosterone	None (parents declined GH)	Nil	Growth Hormone and Thyroxine

Discussion

We believe these cases represent the largest series of unrelated index patients (with related but genetically unconfirmed relatives with SOX3 duplication). Their age at presentation and diagnosis range from newborn to adolescence. This demonstrates the variable combinations of pituitary hormone deficiencies, CNS anatomical abnormalities and neurodevelopmental phenotype between and within family pedigrees. Array CGH can readily identify the genetic basis of these associated but variable features and permit appropriate counselling to female carriers.

Reference:

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