Screening for SOX2 mutations in Bulgarian patients with congenital hyposomatotropism: first results

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Background: The most common cause of congenital combined pituitary hormone deficiency (CPHD) is mutations in the transcription factor (TF) PROP1 gene, followed by PIT1 mutation. Bulgarian pituitary TF study showed an allele frequency of PROP1 mutations in 12.2% and no confirmed PIT1 mutations (1).

The TF SOX2 (sex determining region Y box 2) is a member of high-mobility group transcription factor family. It is one of the earliest TFs during the embryogenesis and therefore mutations cause very complex phenotype. SOX2 is expressed most notably in the development of the central and peripheral neuros system, pituitary (fig.1), corpus callosum, hypocampus, eye and ear (2). The first SOX2 mutation is revealed by Fantes in 2003 (3). Since then more than 40 mutations have been found. Heterozygous mutations have been associated with ocular abnormalities like anophtalmia/microphtalmia, coloboma, nistagmus, impaired anterior pituitary development with reduced levels of anterior pituitary hormones, and male genital tract anomalies (4).

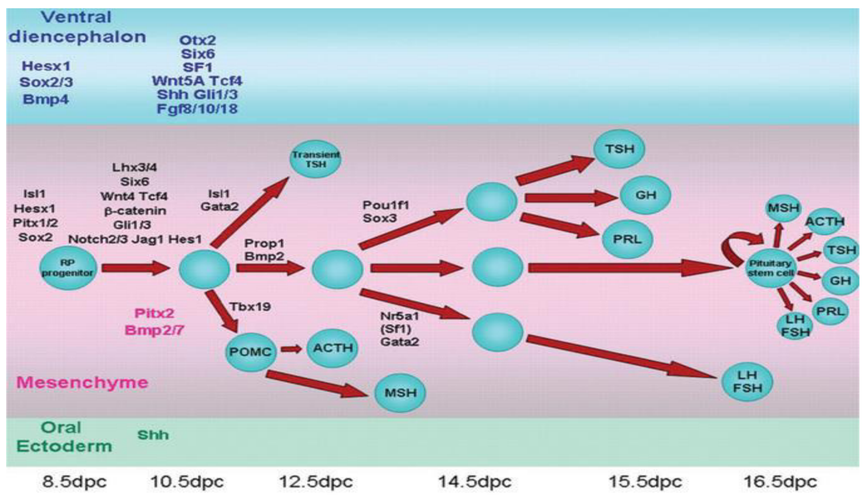
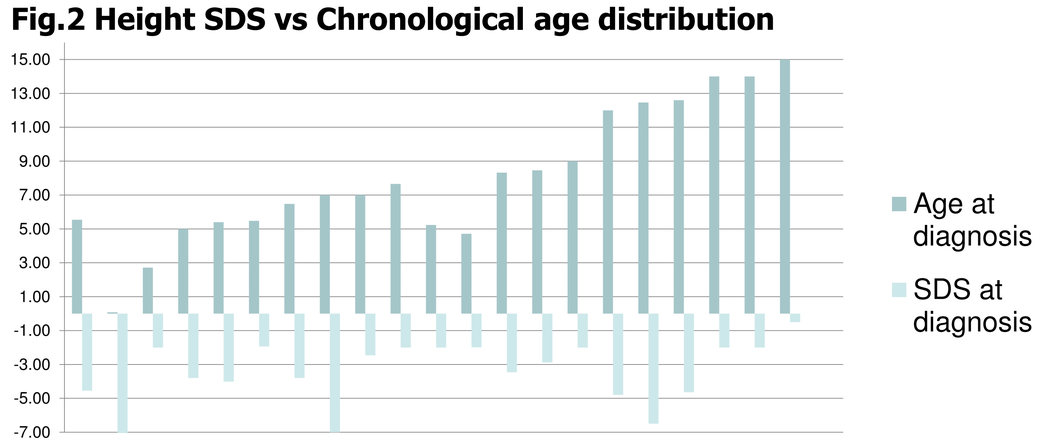


Fig.1 Place of SOX2 in the pituitary embryological development (5)

Objective: To implement a mutational screening for SOX2 as a diagnostic tool in congenital CPHD and to assess the overall allele frequency in Bulgarian hyposomatotropic patients.

Study population: 22 patients, aged (x±SD) 12.9±10.6, median 10.3 years, 13 females (12.7±10.9, median 9.3 years), 9 males (13.1±11.0, median 9.3 years).

Fig.2 Height SDS vs Chronological age distribution



1. Inclusion criteria: obligate congenital GH deficiency; additional criteria: ophthalmologic abnormalities; CPHD and pathologic findings of hypothalamus-pituitary region on MRI or CAT scan;
2. Exclusion criteria: Acquired hypopituitarism.
3. Phenotype characterization based on: auxology, bone age, hormonal tests (GH, TSH, fT4, Prl, LH, FSH, T, E2 by Delfia ®, IGF1&BP3, cortisol, AMH, Inhibin B by ELISA); Molecular genetic analysis by direct sequencing of the single exon genes SOX2.

Fig.3 Neonatal presentation in the studied population

Symptoms	N
No symptoms	7
SGA	2
Breech delivery	3
Hypoglycemia	1
Neonatal jaundice	2
Asphyxia	4
Cryptorchism	2
Micropenis	2
Monosymptomatic	3

Fig.4 Pituitary hormone deficiencies in the studied population

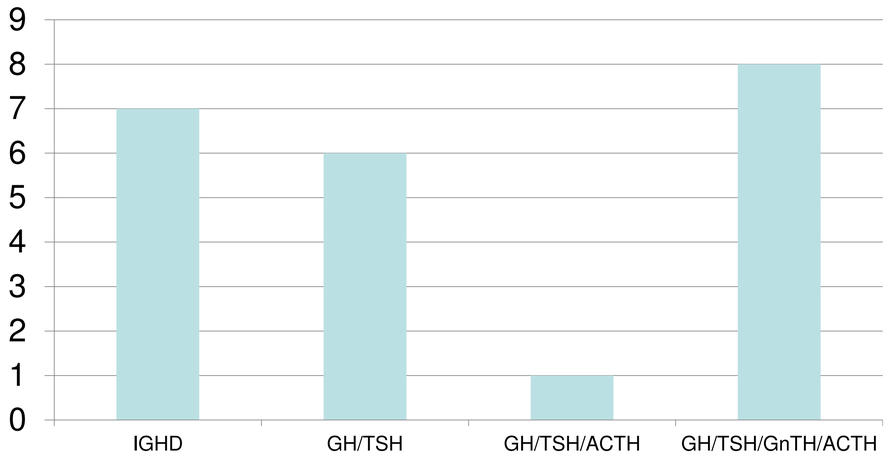


Fig.6 MRI findings in hypothalamus-pituitary region

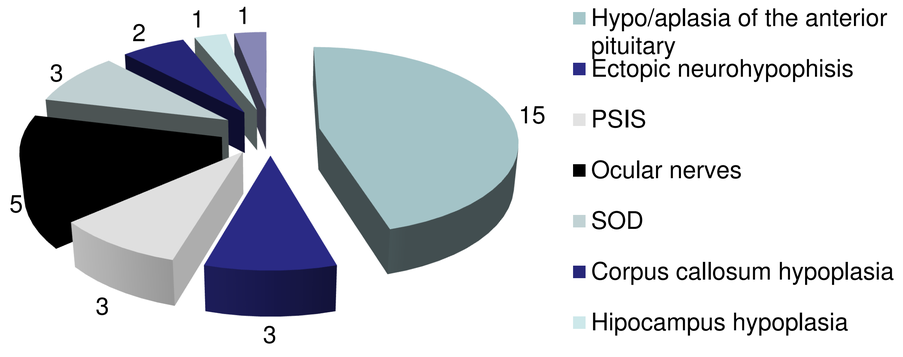


Fig.5 Ophthalmological abnormalities in the selected patients

	Abnormalities	n
Refraction errors	Myopia	3
	Hypermetropia	2
Eye bulb size	Microophthalmia	2
Anterior segment of eye ball	Congenital cataract	1
	Unilateral iris coloboma	2
	Bilateral iris coloboma	1
Posterior segment of eye ball	Retinopathy	3
	Macula hypoplasia	2
	Bilateral macula coloboma	1
Ocular nerves	Unilateral hypoplasia	4
	Bilateral hypoplasia	1
Oculomotor apparatus	Horizontal nystagmus	1
	Strabismus	2
	Reduced peripheral vision	3
	Hyperthelorism	2

Results: No mutations in SOX2 gene were verified in the selected patients.

Conclusions: Mutations in SOX2 are a rare cause of hypopituitarism. For a precise etiological diagnosis patients with complex phenotype including pituitary and extrapituitary manifestations should undergo whole genome sequencing.

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