International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 6 Issue 9 ǁ September 2017 ǁ PP. 30-36

A case of a boy with SOD and 7q11.23 microduplication syndrome

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Abstract:*Theseptooptic dysplasia (SOD) is an extremely heterogeneous condition. The classical triad includes optic nervehypoplasia/aplasia, midline defects, and hypopituitarism. Anomalies of the visual system, CNS, and various systemsmay also be observed. Classically, mutations in HESX1 gene are associated with SOD, but other genes are also involved in the etiology: SOX2, SOX3, FGF8, FGFR1, PROK1, PROKR, SHH. We present a patient with SOD and 7q11.23 microduplication syndrome.*

Case report. *A boy, presented at 8.7 years, with short stature (SDS_h-3.46). The examination reviled: mild mental retardation, developmental delay, mutism, hearing loss, cleft lip and palate, partial IGHD (peak GH 4.1 mU/L), 4-years delayed BA, cryptorchidism, high degree hyperopia, astigmatism, cataracta, iris coloboma. APH (MRI).*

Methods. *Direct sequencing of HESX1, SOX2, SOX3, array CGH was performed.*

Results. *After negative screening of HESX1, SOX2, SOX3, four chromosomal aberrations were found by array CGH: 1. duplication in chr1:1p36.13, including the gene SPEN; 2. 698kb duplication in chr10:10p14-p13, involving the DHTKD1 gene; 3. 10:10q, including the genes DNA2, STOX1, KIAA1279. These aberrations has little, if any, influence on the phenotype. The forth one is a 3.297Mb duplication in chr7:7(q11.23q11.23)(72366111-75663082)x3[hg19], containing 59 genes. There is 87% match with the autosomal dominant 7q11.23 microduplication syndrome.*

Conclusion. *The 7q11.23 microduplication syndrome is very rare, as of today only around 120 patients have been described worldwide. To our knowledge, our patient is the first one with SODas part of the 7q11.23 microduplication syndrome.Patients with multiple organ involvement and GHD should undergo screening of the whole genome. This approach may contribute to finding new etiological insights of hypopituitarism.*

Key words:*7q11.23 microduplication syndrome, SOD, hypopituitarism, hyposomatotropism.*

Date of Submission: 06-10-2017 Date of acceptance: 14-10-2017

I. Introduction

Theseptooptic dysplasia (SOD), also known as de Morsier syndrome, was first described by Reeves in 1941[(1)]. It is an extremely heterogeneous condition with prevalence of 1:10 000 live births [(2)]. The classical triad is seen in only 30% of the patients and includes hypoplasia/aplasia of the optic nerve (bilateral in 88% of the patients), midline defects and hypopituitarism.Two of the three above-mentioned criteria must be completed for the diagnosisSOD [(3)].

The phenotype of patients with SOD is extremely variable. Anomalies of the visual system such as nystagmus, detachment of the retina, an-/microophthalmia, may also be observed.The neurological impairment varies from focal epilepsy and hemiparesis to global developmental delay. In 60% of the cases additional midline defects, such ascleft lip/palate, absent septum pellucidum, hypoplasia of corpus callosum, cerebellum, rhombocephalosynapsis, prosencephaly, etc., are evident. Hypopituitarism due to pituitary hypoplasiaobserved in 62% of the patients. Most often, growth hormone deficiency (GHD) is diagnosed, followed by deficiency of TSH and ACTH. Alternation in gonadotropin secretion is caused by hypothalamic dysregulation and may lead to precocious or delayed puberty. Rarely, diabetes insipidus is diagnosed [(2, 3, 5)]. The phenotype may also include insomnia, obesities, anosmia, sensory-neural deafness, and anomalies in the cardiovascular, respiratory, urogenital and muscular-skeletal system [(2, 3, 5)].

The etiology of SOD is multifactorial and is acombination of exogenous and genetic factors. Environmental factors include young age of the mothers, and exposure to teratogenious medications during early pregnancy (4-6 gestational week)[(2)]. Classically, mutations in *HESX1* gene are associated with SOD, but it accounts for only 1% of the SOD cases [(5)]. An increasing number of genes are involved in the etiology of SOD:

SOX2 [2, 3, 4], *SOX3*[6], *FGF8*, *FGFR1*[7, 8], *PROK1*, *PROKR* [9],*SHH*[10, 11]. There is a theory that these three conditions SOD, Kallman syndrome, and holoprosencephaly are overlapping clinically and genetically [12]. Due to the etiological heterogeneity it is challenging to find the cause of the disease, especially in patients with complex phenotype including GHD associated with extrapituitary manifestations.

In a previous study we analyzed 23 patients with hypopituitarism and associated extrapituitary abnormalities, using a candidate-gene approach. We could not find any mutations in *HESX1, SOX2* and *SOX3* genes [13, 14, 15]. In a search for new pathological regions and genes implicated in the etiology of the complex phenotype of SOD, we performed an analysis of the whole genome by competitive genome hybridization (CGH).

We present a patient with SOD, including eye anomalies, midline defects and anterior pituitary hypoplasia causing GHD [13, 14, 15]. A 7q11.23 microduplication syndrome was found by array CGH.

II. Casereport

A boy, presented at age of 8.7 years, with short stature (SDS_h -3.46) (fig. 1, 2). No available perinatal data exist. At examination he showed: mild mental retardation, developmental delay, mutism, hearing loss, cleft lip and palate, partial IGHD (peak GH 4.1 mU/L) (tabl. 1), 4-years delayed bone age, cryptorchidism, refractive anomalies – high degree of hyperopia and astigmatism (AR OD: +4,25 dsph -2,5 dcyl ax 137^0; OS: +6,25 dsph -1,25 dcyl ax 33^0), congenital cataracta, postoperative iris coloboma. Anterior pituitary hypoplasia was found by MRI (fig. 3). Recombinant human growth hormone, initially at a dosage of 0.05 U/kg/24h s.c. was instituted. No additional pituitary hormone deficits were established during follow up (tabl. 2);

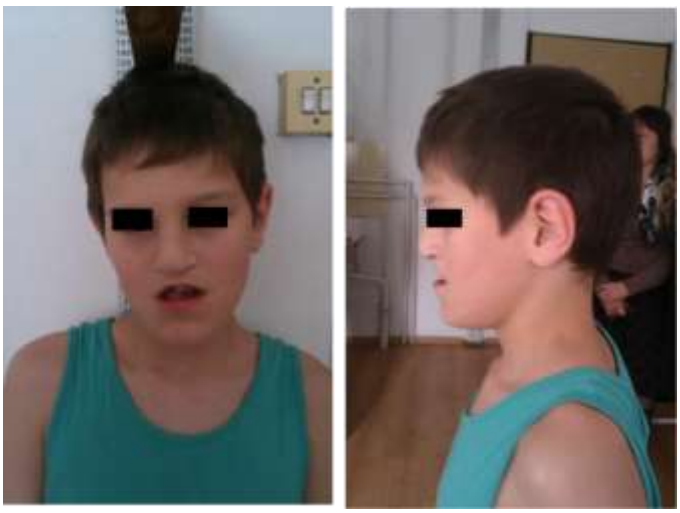

Fig. 1. Facial dysmorphism of the patient

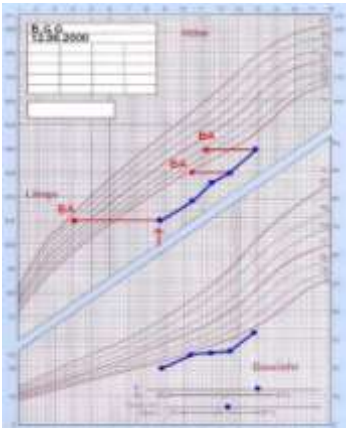

Fig. 2. Growth curve of the patient 1-18 years.

Stimulation test withArginin HCL										Physical exercise		
Minutes	-15	0	15	30	45	60	90	120	150	0	10	20
GHmU/l	3.5	2.1	**4.1**	3.8	1.5	0.8	0.3	0.3	0.2	0.25	17.0	6.3
BGmmol/l	5.5	4.9	4.7	4.2	4.5	4.5	5.3	5.9	6.0	-	-	-

Tabl. 1. Functional endocrine diagnostics of partial GHD

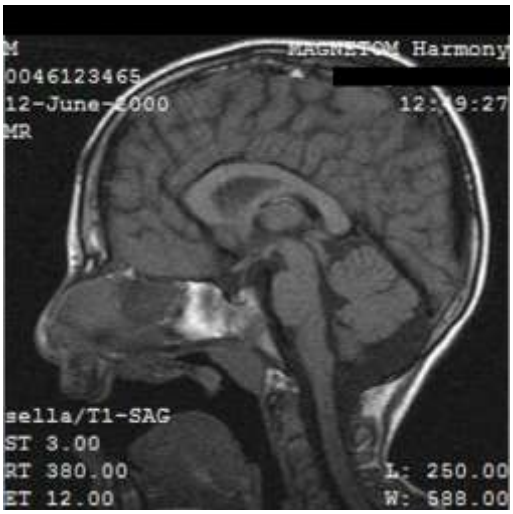

Fig. 3. MRI of hypothalamo-piruitary region

The linear growth during 6 years treatment increased by 30 cm, but height remained below the 3rd centile: the SDS_h(P) has changed from -3.46 to -1.98. An advancement in the bone maturation is observed: BA is only 2.48 years delayed from CA (Greulich&Pyle). Spontaneous and fast progressive puberty was evident.

Tabl. 2. Treatment follow up

Ade (decimals)	8.72	10.32	11.48	12.48	13.48
Height (m)	110	117.5	124.8	130.4	140
$SDSh_{Prader}$	-3.46	-3.64	-3.07	-2.75	-1.98
Treatment rhGH (IU/24h)	0.9	1.8	2.1	2.7	-
IGF-1 ng/ml	114	98	266	288	225
IGFBP3 ng/ml	2537	3083	2973	3773	1020
Growth velocity (cm/year)	-	4.5	6.3	5.6	9.6
Growth velocity (percentiles)	-	10-25th	90-97th	50th	75-90th
Pubertalstage (Tanner)	-	-	-	**12y** LT 4ml, RT 3ml; **12.48y** T 6 ml, D 18mm	T 10мл P 2-3

Tabl. 2. Treatment follow up

III. Methods

After informed consent, a sequencing analysis of exon 1-4 of HESX1, single exon SOX2 and SOX3 was performed[13, 14, 15]. Patient's DNA was extracted from peripheral leucocytes using an automated Chemagan system (PerkinElmer). Array comparative genome hybridization was performed using a DNA microarray SurePrint G3 Unrestricted CGH with format 1x1M (Agilent, Santa Clara, USA), with resolution 2,1 Kb.

IV. Results

The patient's screening of *HESX1*, *SOX2 and SOX3* [13, 14, 15] was negative. Four chromosomal aberrations were found by array CGH.The first one is duplication in chromosome 1: 1p36.13, which includes the gene *SPEN* (spen family transcriptional repressor). No studies on this gene have been performed in humans and, therefore, there are no reported mutations to date. The effect of this aberration on the patient's phenotype is unclear. The second one is a duplication of 698 kb in chromosome 10:10p14-p13, involving the DHTKD1 gene. There are two patients in DECIPHER with similar in size duplications, one with unknown pathogenicity and learning disability (288701) and the other with behavioral abnormality and mild intellectual disability.

The third one is 10:10q. It includes the genes *DNA2, STOX1 and KIAA1279.* The phenotype of patients with similar aberration partially overlaps with the index patient. We believe that this aberration has little, if any, influence on the phenotype.

The forth one is a 3.297 Mb duplication in chromosome 7: 7(q11.23q11.23)(72366111-75663082)x3[hg19], containing 59 genes and 13 pseudogenes (fig. 4). There is 87% match with the autosomal dominant 7q11.23 microduplication syndrome (tabl. 4). Up to now, none of the 7q11.23 patients are described to have hypopituitarism or SOD.

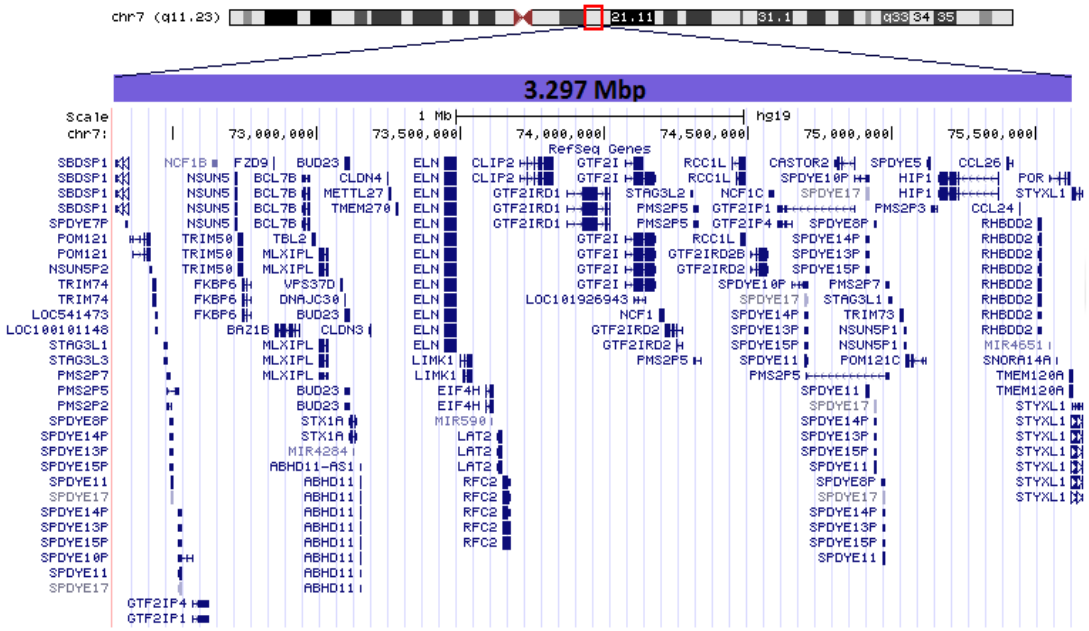

Fig. 4. Schematic representation of duplicated 7q11.23 region in the patient with gene content. The blue bar represents the ranges of the duplication. *Taken and modified from UCSC Genome Browser (University of California Santa Cruz).*

V. Discussion

The patient's phenotype is complex and includes eye abnormalities (congenital cataract, high hyperopia and astigmatism), partial GHD, caused by anterior pituitary hypoplasia, and midline defect (cleft palate)[16]. These manifestations complete the criteria for the diagnosis ofSOD [5]. In a previous study of our team, we used the phenotype-based candidate gene approach. The patient underwent sequencing of *HESX1, SOX2 and SOX3* genes, but no mutations or polymorphism were identified [13, 14, 15]. The next step was whole genome screening by array CGH.We found aberrations in three chromosomes: 1,7 and 10, that possibly contribute to the described phenotype.

The first one is duplication on chromosome 1: *1p36.13*, which includes the gene *SPEN* (Spen Family Transcriptional Repressor). This transcriptional repressor preserves its conservative structure through many species from Drosophila to human. It plays a key role in the determination of progenitor cells and interacts directly with HDAC (Histone deacetylase), a part of the transcriptional repressor complex which inhibits the Notch signal system (trough Rbp-J)[17,18].On the other hand, SPEN increases the repression activity of *HESX1* by interacting with NCoR (nuclear receptor corepressor 1), part of the HESX1/TLE/NCoR complex.

Both Notch signal system (through Rbp-J) and the TF HESX1 (through the HESX1/TLE/NCoR complex) play a critical role in the pituitary embryogenesis[19]. They regulate the temporal and special expression of PROP1 and all the pituitary cell lines [20]. Therefore, disturbances in the well-orchestrated signal transduction lead to different degree of hypopituitarism.

In the available literature to date, we were not able to find any studies on the SPEN expression in human, or mutations in this gene. Theoretically, SPEN might cause the patient's phenotype. We found duplication of the gene. There are described gain-of-function mutations in Xenopusembrios, which affect the CNS development [17]. We could speculate that there is a dose dependent effect of the gene, similar to the X-linked SOX3 and ZNF674 [21, 22].

The second chromosome involved is 10.One aberration is a 698 kb duplication 10p14-p13. Worldwide, there are two described patients with aberrations in this region and their phenotype partially overlaps with the patient's: mild mental retardation and learning difficulties (DECIPHER, patients 288701, 288627). The gene involved in this duplication is DHTKD1 (OMIM 614984). A heterozygous loss-of-function mutation in the DHTKD1 gene was reported in Chinese family with Charcot-Marie-Tooth disease type 2Q (CMT2Q) [23]. Another disease associated with DHTKD1 mutations is 2-aminoadipic and 2-oxoadipic aciduria (OMIM 204750), where compound heterozygote mutations have been described[25]. More than half of the described patients were asymptomatic, whereas others had mild to severe intellectual disability, muscular hypotonia, developmental delay, ataxia, and epilepsy [24]. Further analysis of the gene identified nine novel mutations, including three missense mutations, two nonsense mutations, two splice donor mutations, one duplication, and one deletion and insertion [6].There is currently no data about the potential effect of duplications of this gene.

A second aberration in chromosome10 was found:a duplication 10q21.3-q22.1. It includes the genes*DNA2, STOX1 and KIAA1279*. There is one described patient with cleft palate and aberration in the same region, but much greater. This led us to the conclusion that these aberrations have little, if any, influenceon the phenotype.

The third pathological region is a 3.297 Mb duplication in chromosome 7: *(q11.23q11.23)(72366111-75663082)x3 [hg19]*which encompasses49 genesand 13 pseudogenes. This locus matches with the known autosomal dominant 7q11.23 microduplication syndrome. The first patient with this syndrome was described by Somerville et al in 2005[26]. Since then, over 140 patients have been described[27, 28, 29, 30, 31, 32, 33]. The estimated prevalence is 1:13000 to 1:20000 live births[31]. In the literature, the size of the aberration is 1.5 Mb and includes between 25 and 30 genes listed on fig. 4[27, 28, 29, 30, 31, 32, 33]. Our patient harbors 26 of these 30 genes. This makes complete overlap with 7q11.23 microduplication syndrome. Our patient's duplication is larger and includes additional 22 genes with different functions (tabl.3). Much more common is the William-Beuren syndrome due to 7q11.23 microdeletion with prevalence of 1:7500 live births.

	Genes included in the 7q23.11 microduplication syndrome		**Additional duplicated genes in the index patient**	
Cytogenetic bands	**Gene**	**Name**	**Gene**	**Name**
7q23.11	HIP1	huntingtin interacting protein 1	GTF2IRD2B,	GTF2I repeatdomaincontaining 2B
	WBSCR16	Williams-Beuren syndrome chromosome region 16	TRIM73	tripartitemotifcontaining 73
	GTF2I	general transcription factor IIi	GATSL2	GATS protein-like 2
	GTF2IRD1	general transcription factor II I repeat domain-containing 1	GATSL1	GATS protein-like 1
	CLIP2	CAP-GLY domain containing linker protein 2	STAG3L2	stromalantigen 3-like 2
	LAT2	linker for activation of T cells family, member 2	NCF1	neutrophilcytosolicfactor 1
	EIF4H	eukaryotic translation initiation factor 4H	GTF2IRD2	GTF2I repeatdomaincontaining 2
	WBSCR28	Williams-Beuren syndrome chromosome region 28	MIR590	microRNA 590
	RFC2	eplication factor C (activator 1) 2, 40kDa	WBSCR26	Williams-Beurensyndromechromosomeregion 26
	ELN	Elastin	MIR4284	microRNA 4284
	LIMK1	LIM-domain containing, protein kinase	TBL2	transducin (beta)-like 2
	WBSCR27	Williams-Beuren syndrome chromosome region 27	BAZ1B	bromodomainadjacenttozincfingerdomain, 1B
	CLDN4	claudin 4	FKBP6	FK506 bindingprotein 6, 36kDa
	ABHD11	abhydrolase domain containing 11	TRIM50	tripartitemotifcontaining 50
	CLDN3	Claudin 3	NSUN5	NOP2/Sundomainfamily, member 5
	WBSCR22	Williams-Beuren syndrome chromosome region 22	POM121	POM121transmembranenucleoporin
	WBSCR18	Williams-Beuren syndrome chromosome region 18	BCL7B	B-cell CLL/lymphoma 7B
	STX1A	syntaxin 1A	TRIM74	tripartitemotifcontaining 74
	VPS37D	vacuolar protein sorting 37 homolog D	POM121C	POM121 transmembranenucleoporin C
	MLXIPL	MLX interacting protein-like	TMEM120A	transmembraneprotein 120A
	POR	P450 (cytochrome) oxidoreductase	SPDYE5	speedy/RINGO cellcycleregulatorfamilymember E5
	FZD9	frizzled class receptor 9	SNORA14A	smallnucleolar RNA, H/ACA box 14A
	CCL24	chemokine (C-C motif) ligand 24		
	CCL26	chemokine (C-C motif) ligand 26		
	RHBDD2	rhomboid domain containing 2		

Tabl. 3. Genes included in the 7q23.11 microduplication of the index patient

The phenotype manifestations are variable,but our patient's phenotype shows 87% overlap (tabl. 4). He shows facial dysmorphism, speech and language delay, sensory-neural deafness, moderate mental retardation, anddevelopmentaldelay, which are common for the syndrome. Previous studies revealed a variety of craniofacial and brain malformations [27, 28, 30, 31, 32, 33]. Morris et al. describe 5 patients with GHD in their study, performed in parallel with ours [29]. However, this is the first patient with 7q11.23 microduplication syndrome in

association with SOD.The phenotype might be influenced by the additional 22 genes duplicated in our patient, as well as the other two aberrations, which might interfere the clinical appearance.

Symptoms	7q11.23microduplication syndrome	Index patient
Facial dysmorphism	~100%	+
Speech and language delay	~100%	+
Sensory-neural deafness	25%	+
Mild to moderate mental retardation	83%	+
Developmentaldelay	70%	+
Shortstature	10-15%	+
Criptorchidism	25%	+
Cleftpalate	11%	+
Muscle hypotonia	70%	-
Behavior changes	~100%	+
Seizers	25%	-
Cardiovascular anomalies	20%	-
Ocularanomalies	27%	+
Constipation	75%	-

Tabl. 4. Comparison of the phenotype of the index patient with patients with 7q11.23 microduplication syndrome [27, 28, 29, 30, 31, 32, 33]

VI. Conclusion

The 7q11.23 microduplication syndrome is very rare, as of today only around 120 patients have been described worldwide[27, 29, 32, 33, 34]. The phenotype of the syndrome is variable. With our study we further extend the clinical manifestations associated with the syndrome. To our knowledge, our patient is the first one with SOD, including partial IGHD due to pituitary hypoplasia, as part of the 7q11.23 microduplication syndrome.
Patients with multiple organ involvement and growth hormone deficiency should undergo screening of the whole genome. Thisapproach may contribute to finding new etiological insights of hypopituitarism.

Acknowledgement

Sponsored by Medical University Sofia, "Mladizsledovatel" № 40/2013. Acknowledgment to the PhD student Valentina Peycheva, Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University Sofia.

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Ani Aroyo. “A case of a boy with SOD and 7q11.23 micro duplication syndrome.” International Journal of Pharmaceutical Science Invention(IJPSI), vol. 6, no. 9, 2017, pp. 30–36.