A NOVEL *OTX2* MUTATION IN A CHILD WITH GROWTH HORMONE DEFICIENCY

Delvecchio M, Lonero A, De Palma F, Luce V, Faienza MF, Cavallo L

Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy

Background

OTX2 is expressed in the human brain and plays a key role in the eye development. OTX2 mutations are reported in patients with ano/microphthalmia, optic nerve or optic chiasm hypoplasia, ocular coloboma and retinal dystrophies, associated in some cases with brain or pituitary abnormalities.

Case presentation

We describe a child with microphtalmia and GH deficiency carrying a novel *OTX2* heterozygous mutation. The patient, a female, was the second child born from non-consanguineous Italian parents after 40 weeks of uncomplicated gestation. Birth weight was 2800 g.

AT BIRTH ➡ **right microphtalmia**

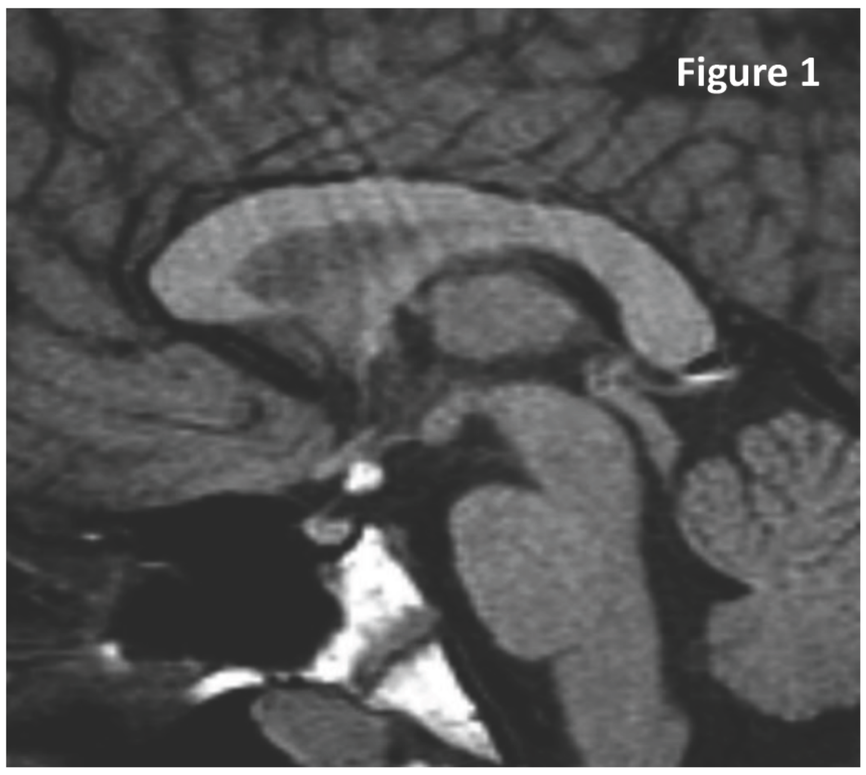
9 MONTHS ➡ **ocular examination** under general anaesthesia "absence of retinal vascularization, vitreal spots and optic nerve hypoplasia in the right eye and mild macular dystrophy in the left eye." **Electroretinogram** and **p-VEP** confirmed the *right nerve hypoplasia*. A **brain MRI** showed normal midline structures and cerebral parenchyma, mild hypoplasia of the anterior corneal segment, *dysmorphic cristalline* with increased posterior convexity and thin optical nerve in the right eye. Left nerve eye was normal (pituitary gland not evaluated)

2 YEARS ➡ exotropia, fusion maldevelopment nystagmus, and hence an anomalous head posture. A **right ocular prosthesis** was implanted. **Sialotransferrins isoelectrofocusing** and **CGH Array** resulted normal. Infectious causes of microphthalmia were ruled out

3.7 YEARS ➡ **genetic testing** for *SOX2* and *OTX2* showed a ***heterozygous c.402del OTX2 mutation.*** Both parents were negative

3.8 YEARS ➡ referred to the Paediatric Endocrine Unit because of *short stature*. She was prepubertal, height -2.13 SDS, body mass index -1.0 SDS, cranial circumference 47 cm (normal), TH -0.6 SDS, BA 3 years. Routine biochemistry was normal as well as thyroid and adrenal function, while GH provocative test showed **GH deficiency** and normal IGF1 (10^{th}-25^{th} centile) (Table 1). A pituitary MRI delineated an **ectopic hypoplasic pituitary** placed behind the tuber cinereum (figure 1). rhGH treatment was started at the dose of 33 mcg/kg/day.

Table 1	Stimulus (dose)	Basal	Peak
GH (ng/mL)	Clonidine (100 mg/mq)	0.08	3.46
	Arginine (0.5 g/kg)	0.34	5.24
TSH (µIU/ml)	TRH (10 µg/kg)	3.42	9.6
PRL (mg/mL)	TRH (10 µg/kg)	7.48	15.68
ACTH (pg/ml)		6.77	
Cortisol (ug/dl)	ACTH (0.25 mg)	6.82	32.37
IGF-1 (ng/mL)		47.55	
Free T4 (ng/dl)		1.08	
Free T3 (pg/ml)		5.38	
LH (mIU/ml)	Decapeptyl (100 µg/m^2)	<0.2	1.98
FSH (mIU/ml)	Decapeptyl (100 µg/m^2)	2.74	22.46



Discussion

Most of *OTX2* mutations are nonsense or frameshift introducing a premature termination codon and resulting in a truncated protein. More rarely missense mutations occur. In this paper, we report **a novel *OTX2* heterozygous mutation (c.402del)**, never described before, in a patient with microphthalmia and GH deficiency. This frameshift mutation (p.S135Lfs*43) causes a premature codon stop 43 amino-acids downstream which is predicted to generate a premature truncation and thus a non-functional protein. Parental analysis indicated that it is a de novo mutation.

We do not know if the patient will develop any other pituitary hormone deficiency, and thus appropriate clinical and biochemical follow-up is mandatory.

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GH and IGF Treatment

Maurizio Delvecchio

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