It's all in their eyes: a three-generation family with branchio-oculo-facial syndrome (BOFS) reveals a heterozygous novel mutation in TFAP2A gene.

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Introduction

Ocular defects are important semiological clues for the internist, leading sometimes to diagnose a familial disease. Branchio-oculo-facial syndrome (BOFS) is a rare congenital disorder characterized by ophthalmic malformations, branchial skin defects and craniofacial anomalies. Ocular features include coloboma of choroid and/or iris, microphtalmia, cataract, ptosis and strabismus. We herein describe a new three-generation non consanguineous family with BOFS.

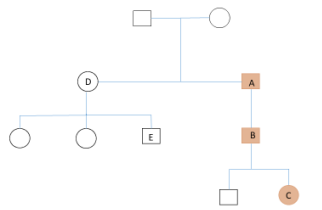
Patients

The proband (A) was the 67 years-old grandfather. He presented with a left eye coloboma and microcornea. His 39 years-old son (B) was diagnosed as a baby with a left coloboma and microphtalmia, right preaxial polydactily. At the age of 35, B had a craniopharyngioma treated with surgery and radiotherapy. The 6 years-old grand daughter (C) presents with a left coloboma and microphtalmia and a right kidney hydronephrosis. The sister of the proband (D) presented a branchial fistula and a melanoma and his son (E) had a prolactinoma. Because of this intriguing phenotype, an inherited anomaly closest to BOFS was suspected in this non consanguineous family.

Genetic Studies

A syndromic microphthalmia type 6 (OMIM #607932) was first considered because association with digital and pituitary anomalies. However, no mutation was found in the *BMP4* gene. No mutations were identified in the *PAX2* (coloboma-kidney syndrome) and *PAX6* (coloboma and anterior segment dysgenesis) genes. Then, a panel of ocular developmental genetic anomalies was screened, eventually showing a heterozygous frameshift duplication of 19 bp in exon 2/7 of the *TFAP2A* gene in A, B and C: c.38-56dup. This likely pathogenic variant (type IV), induces protein truncation (p.Ala20Argfs*149) in exon 2.

	Patient A mut+	Patient B mut+	Patient C mut+	Patient D Mut -	Patient E Mut-
Branchial Anomalies				Neck branchial fistula	
Cervical cutaneous anomalies	no	no	no	no	no
Ectopic tymus	no	no	no	no	no
Ocular anomalies			no		
coloboma	Yes (left)	yes	yes	no	no
microphtalmia	Yes (left)	no	yes	no	no
Heterochromia irides	no	no	no	no	no
cataract	no	no	no	no	no
strabismus	no	no	no	no	no
Facial anomalies					
Auricular anomalies	no	no	no	no	no
Cleft lip/palate	no	no	no	no	no
Other	no	CRANIOPHARYNGIOMA 41 mm	no	Melanoma	Prolactinoma 8 mm
Hearing loss	no	no	no	no	no
Kidney anomalies	yes	no	no	no	no
polydactilia	no	yes	no	no	no



Branchio ocular facial syndrome associated with TFAP2A gene mutation

Coloboma Facts

- Coloboma is a rare eye malformation (1/10 000 births) presenting as a a hole in one of the structures of the eye, such as the iris, retina, choroid, or the optic disc.
- It is caused by failure of the optic fissure to close during 5th ti 7th weeks of fetal life.
- Coloboma is linked to eye abnormalities: microphtalmia, cataracts, glaucoma, myopia, nystagmus and retinal detachment.
- The most common syndromic form of coloboma is **CHARGE** syndrome (**C**oloboma, **H**eart, **A**tresia choanae, **R**etarded growth, **G**enitourinary and ear nomalies/deafness)

We are the key to Coloboma Awareness

Discussion

TFAP2A mutations have been related with BOFS and anophthalmia-microphthalmia syndromes. Reported BOFS associated malformation are diverse and heterogeneous, like in most dominant diseases.

We report a novel *TFAP2A* mutation in a three-generational BOFS affected family. ***TFAP2A*** is a **retinoic acid inducible transcription factor** implicated in ocular morphogenesis, localized on the minus strand of chromosome 6. In addition, two antisense non-coding RNA molecules have been identified. *TFAP2A* also regulates gene expression during embryogenesis of the ear, face, body wall, limbs, kidney and neural tube in humans as well as in Tfap2 knockout mice embryos.

A, B and C presented with coloboma whereas B had also right preaxial polydactily. We thought to study B and D for a *TFAP2A* mutation, because there is a down-regulation of AP-2α in some tumors (like hepatic carcinoma), with an impact on Wnt/β-catenin pathway (like in craniopharyngiomas), and there is abolition of *TFAP2A* expression in melanoma. Intriguingly, D did not have the familial *TFAP2A* mutation although she had a melanoma and a branchial fistula. Moreover, the presence of two unrelated pituitary tumors in B and E remain unexplained.