

A CASE REPORT OF 6P25P22 DUPLICATION ASSOCIATED WITH BOFs CLINICAL FEATURES

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BACKGROUND

Branchio-Oculo-Facial syndrome (BOFs, MIM 113620) is a rare autosomal dominant disorder caused by haploinsufficiency of the transcription factor AP-2 alpha gene (*TFAP2A*) [1]. *TFAP2A* is known to activate gene transcription crucial to embryo development, in particular, embryogenesis of the eye, ear, face, body wall, limbs and neural tube [2].

Clinical

Three major clinical indications may assist a clinical diagnostic of BOFs: branchial cleft sinus defects, ocular anomalies, and characteristic facial anomalies, such as cleft or pseudo-cleft lip and palate. In addition to this, a first-degree relative who has been independently affected with BOFs or ectopic thymus can also be considered as a diagnostic criteria of BOFs [3]. Nevertheless, this disorder has been characterized with variable expression between patients. Other common features include psychomotor development delay, such as visual and/or hearing disabilities, intellectual disability (moderate to severe), amongst others. More rarely, severe hearing loss and structural renal abnormalities, pre/postnatal growth restriction and ectodermal anomalies (dental and hair) have been reported [1, 4, 5, 6].

Genetics

The genetic makeup of individuals with BOF syndrome always compromises *TFAP2A* function and normally is presented in the form microdeletion [7, 8], complex deletion/*de novo* insertion [5] or point mutation within *TFAP2A* [1, 9].

CASE REPORT

We report a 2yo boy with classic clinical features of BOF syndrome and an interstitial duplication on 6p25.2p22.3 (Figure 1). To the best of our knowledge, so far no patient with BOF syndrome has been reported to carry a duplication on 6p25.2p22.3.



Figure 1. Clinical photographs of patient demonstrating clinical phenotype of BOFs. Proband at (A) 1 month of age and (B) 6 months of age showing several facial dysmorphic features, such as thin and sparse hair, set high; bilateral frontal humps, severe blepharophimosis; epicanthus; hypertelorism; small nose with bulbous tip; long smooth philtrum; thin upper lip; small/"folded" pinna, rotated out and with low insertion.

As no formal diagnostic criteria exist for the clinical identification of BOF syndrome, we followed clinical manifestations based on reported literature [1, 6, 11]. Patient's examination demonstrated clinical manifestations typical of BOF syndrome, including branchial, ocular and facial anomalies, such as right cervical branchial cyst, blepharophimosis and dysmorphic features. Table 1 summarizes clinical features described for this patient.

Table 1. Clinical features from patient with BOF syndrome.

Clinical Features	Observations	
Branchial (cutaneous) anomalies	Right cervical branchial cyst	Small pinna
Ocular anomalies	Blepharophimosis	
Facial anomalies	Dolichocephaly	
	Hypertelorism	
	Telecanthus	
	Broad nasal tip	
	Horizontal palpebral fissures	
Additional Features	Psychomotor performance	Severe psychomotor developmental delay
		Delay in speech and walking abilities
		Chewing difficulties
	Intellectual disability	Autism spectrum disorder
	Growth restriction	

Array CGH was performed on an Affymetrix platform, Cytoscan 750K. Data analysis was performed on ChAS Software, Affymetrix (reference NCBI_hg19). Karyotype was performed on peripheral blood following standard protocols.

Array CGH revealed a 13.9 Mb duplication at 6p25.2-p22.3 (breakpoints Chr 6: 4,066,234 - 18,025,300, hg19), resulting in a complete duplication of *TFAP2A* and 75 other genes (Figure 2).

Karyotype analysis allowed definition of the type of structural rearrangement present in the patient [46,XY,dup(6)(p25.2p22.3)].

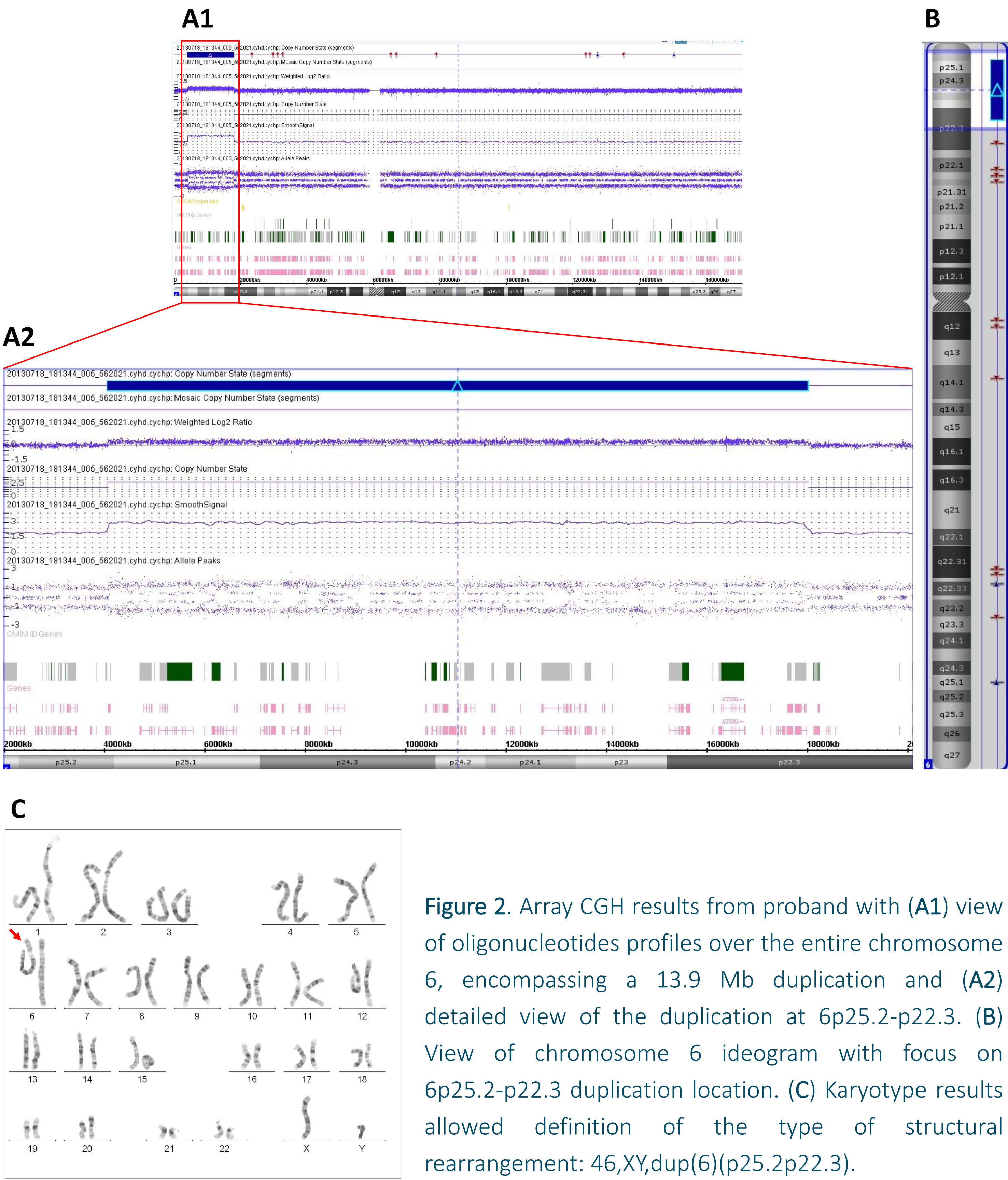


Figure 2. Array CGH results from proband with (A1) view of oligonucleotide profiles over the entire chromosome 6, encompassing a 13.9 Mb duplication and (A2) detailed view of the duplication at 6p25.2-p22.3. (B) View of chromosome 6 ideogram with focus on 6p25.2-p22.3 duplication location. (C) Karyotype results allowed definition of the type of structural rearrangement: 46,XY,dup(6)(p25.2p22.3).

CONCLUSION

BOF syndrome is a rare disorder mainly characterized by branchial, ocular and facial distinctive clinical features and is due to the haploinsufficiency of *TFAP2A* gene. Up to date, individuals with this syndrome have comprised *TFAP2A* gene function either due to deletion/microdeletion event involving *TFAP2A* [5, 7, 8] or a point mutation in *TFAP2A* gene [1, 9]. The present report describes for the first time a patient with classic clinical features of BOF syndrome and an interstitial duplication on 6p25.2p22.3.

REFERENCES

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