Introduction

In 2000, Fryns and Aftimos described the Fryns-Aftimos Syndrome for the very first time in two separate men with intellectual disability (1). During following years other scientists reported similar cases (2,3). In 2012, Reviere mentioned that there are major overlapping features between Fryns-Aftimos Syndrome and Baraitser-Winter syndrome including trigonocephaly, hypertelorism, ptosis, high arched palate, skeletal problems (short stature, short fingers, flat feet) and mild intellectual disability. Parents are not relatives and there is no similar case in family. Based on positive clinical findings Fryns-Aftimos syndrome was suspected and genetic testing of ACTB gene was performed identifying a heterozygous c.220G>A mutation. Both parents were checked and did not harbor this mutation.

Case presentation

Proband is a five-year-old boy, referred to our genetics center for evaluation of psychomotor retardation.

Abstract: Fryns-Aftimos Syndrome is a rare autosomal dominant disorder characterized by craniofacial signs, anterior neuronal migration disorder (pachygryria, lissencephaly), skeletal deformities and mental retardation. We describe a five-year-old boy with abnormal facial features (hypertelorism, ptosis, high arched palate), skeletal problems (short stature, short fingers, flat feet) and mild intellectual disability. Parents are not relatives and there is no similar case in family. Based on positive clinical findings Fryns-Aftimos syndrome was suspected and genetic testing of ACTB gene was performed identifying a heterozygous c.220G>A mutation. Both parents were checked and did not harbor this mutation.

Keywords: Fryns-Aftimos Syndrome; Craniofacial Abnormalities; Mental Retardation.
He is the first child of non-consanguineous parents. Parents are healthy. The proband was delivered by caesarean section, due to placental detachment at 37th weeks of pregnancy. His birth weight was 3000 gm (<25th percentile), head circumference was 48 cm (both 25th percentile). At 5 years his measurements were as follows: weight 15 kg (<10th centile), head circumference 49 cm (<50th centile) and height 97 cm (<3rd centile).

He held his head up at 2 months, sat at 7 months, stood at 15 months, walked at 18 months and said his first word at 2 years. Now, he can say full sentences.

Major clinical findings were hypertelorism, telecanthus, ptosis, facial edema, short and upturned nose, large and squared nose tip, grooved nasal tip, prominent nasal root, long philtrum, prominent cheeks, thin upper lip, thick lower lip, large mouth, high arched palate, small teeth, posterior and low set ears, short neck, inverted and widely spaced nipples (Figure 1a), sacral dimple (Figure 1b), broad thumbs, short fingers (Figure 1c), cavernous hemangioma on right upper limb, flat feet and small phallus.

He has very friendly behavior. Lymphedema was present until 6 months which resolved by the age of 1 year. His IQ was borderline normal. He had normal brain sonography at 1 year and normal abdominal ultra sonography. Brain MRI has been requested to rule out brain abnormalities which has been seen in many patients with Fryns-Aftimos syndrome. Cortical renal scan with DMSA showed possible damaged at right renal pole. Cytogenic study by GTG banding technique at 450-500 band resolution showed a normal 46,XY pattern. Based on positive signs and symptoms including dysmorphic facial features (hypertelorism, telecanthus, epicanthus, ptosis, facial edema, thickened oedematous eyelids, short and upturned nose, large and squared nose tip, grooved nasal tip, prominent nasal root, long philtrum, prominent cheeks, thin upper lip, thick lower lip, large mouth, high arched palate, small teeth), broad thumbs, short stature the proband was suspected to have Fryns-Aftimos syndrome.

Genetic analysis of ACTB gene was requested which identified a heterozygous c.220G>A mutation in the ACTB (NM_001101.3) gene, confirming the diagnosis of Fryns-Aftimos syndrome.

Discussion
Fryns-Aftimos Syndrome is a rare genetic disorder characterized by facial anomalies, skeletal problems and most important of all, problems in structure and development of brain. Patients have a wide range of mental disability from mild to severe. Many patients suffer from intractable seizures due to structural problems of brain which cause mental development regression and severe mental retardation. Pachygyria (or thickening of brain cortex and as a result, decrease and largening of brain gyri)—especially in frontal lobe— is commonly seen (6). Most patients have also facial edema, arched eyebrows, bilateral ptosis, hypertelorism, broad nasal bridge, wide mouth with thin upper lip and inverted lower lip, inverted hypoplastic ears. Some of them appear to have short webbed neck, low posterior hairline, inverted hypoplastic widely spaced nipples.

Our case was a 5-year old boy diagnosed with Fryns-Aftimos Syndrome who—like most patients with this disease— had developmental delay, short stature, and mild limb anomalies (short fingers, flat feet). Dysmorphic facial features consisted of ptosis, downslanting palpebral fissures, facial edema, short upturned nose, broad nasal tip, prominent nasal bridge, thin upper lip, thick lower lip, large mouth, short nose and hypertelorism. This child did not have seizures and severe mental retardation—like most patients with Fryns-Aftimos Syndrome—and on the other hand had a very friendly and sociable behavior.
Additional features seen in Fryns-Aftimos cases such as microcephaly, limited joint movement and pterygia, coloboma.

It has been suggested that patients carrying mutation in ACTB gene have a more severe phenotype than mutations in ACTG1(7). Our case has a mutation in ACTB mutation but has relatively mild features. Intellectual disability is mild, and in fact the patient is very sociable and friendly. Unfortunately brain MRI is not available to evaluate brain abnormalities, but based on mild intellectual abnormality we can safely assume that no major structural brain abnormality is present. It is possible that modifier genes and environmental factors play a role in dictating the severity of the phenotype. In cases, the same mutation has been described in two families with considerable variability in the phenotype (5,7).

References