**European Journal of Medical Genetics**

**Short report**

**A 785 kb deletion of 3p14.1p13, including the FOXP1 gene, associated with speech delay, contractures, hypertonia and blepharophimosis**

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**Abstract**


1. Methods of detection

Microarray analysis using the Signature GenomicsWG BAC array with 4685 BAC clones detected an abnormality characterized by a de novo single copy loss of 3 BAC clones from the short arm of chromosome 3 at del(3)(p14.1p13) (~400 kb in size). The deleted clones at del(3)(p14.1p13) were RP11-766C13, RP11-120N20, and RP11-794B13. The nearest distal and proximal BACs that are not deleted are RP11-1005P22 (800 kb distal to the deleted region) and RP11-16C21 (4.9 Mb proximal to the deleted region) respectively. The deletion was confirmed by fluorescence in situ hybridization (FISH) analysis (Fig. 1).

Oligonucleotide array investigation by Signature Genomics refined the deletion to 795 kb between nucleotides 71,164,161 and 71,958,845 (Fig. 2). This corresponds to a deletion of 89% of the gene through the N-terminus of FOXP1 and a complete deletion of EIF4E3, PROK2 and GPR27. The FOXP1 deletion results in a deletion of the important N-terminal DNA binding domain, likely rendering the transcription factor functionless and a target for lysosomal destruction. Parental FISH analyses were performed and neither parent was found to carry a deletion or other rearrangement of the 3p14.1p13 region. Thus, the deletion identified in the patient appears to be de novo in origin.

2. Clinical description

We present a case of a 23 month-old Caucasian boy who is the product of an uneventful 39-week pregnancy. He is the only child of a 28 year-old mother and a 28 year-old father. At birth, he was under the 5th percentile for his gestational age (3123 g) and was found to have contractures of his hands and feet (similar to that seen in Trisomy 18), blepharophimosis, and hypertonia. Since birth, he had intermittent muscle spasms throughout the day. Subsequent EEG and brain MRI studies were normal. He required a tonsillectomy and adenoidectomy at age 17 months for obstructive sleep apnea and feeding difficulties. At 10 months, the child was babbling and making vowel sounds, but had not developed words. The child was...
small for his age with a height of 76 cm (below 2nd percentile) and weight of 11.5 kg (below 10th percentile). He was normocephalic with a head circumference of 48 cm (50th percentile). He had epicanthal folds and blepharophimosis (Fig. 3). Ophthalmologic evaluation revealed hypermetropia. His face was symmetric with prominent cheeks and small upturned alae nasi (Fig. 3). He had single transverse palmar creases bilaterally, persistent ulnar deviation of the proximal phalanges and persistent flexion of the distal phalanges with the 3rd and 5th fingers persistently overriding the 4th. The thumb was clasped against the flexed index finger. The child’s hallux was cocked bilaterally with dorsiflexion of the proximal phalanx and plantar flexion of distal phalanx. There was also persistent flexion and medial deviation of the 2nd, 3rd and 4th toes. He exhibited increased tone in all of his limbs that became more severe distally. His reflexes are normal. His genital exam revealed a normal-sized penis and bilateral cryptorchidism. MRI imaging of the brain showed mild asymmetric enlargement of the ventricles and sulci, consistent with minor atrophy. The olfactory bulbs were visualized and there was no evidence of hypoplasia.

His clinical picture was initially thought to be consistent with Schwartz–Jampel syndrome type 1A. A subsequent skeletal survey was normal, and his neurophysiologic examination did not reveal the typical complex, repetitive discharges of Schwartz–Jampel syndrome. As a result, we elected not to perform HSPG2 sequence analysis. Initial karyotype results were 46,XY. A bone survey revealed no evidence of skeletal dysplasia and MRI of the brain was normal. We were concerned that his clinical picture might represent blepharophimosis/ptosis/epicanthus inversus syndrome (BPES). FISH of the region containing the FOXL2 gene was therefore performed and the results were normal. Sequence analysis of FOXL2 was not performed.

3. Discussion

This is the first reported case of a patient with muscle contractures, hypertonia, blepharophimosis, speech delay, and developmental delay, who has a documented deletion of FOXP1. Deletions of EIF4E3, PROK2 and GPR27 were also present. There have been cases with large deletions of 3p reported in the literature that may also include deletions in FOXP1, but to our knowledge, this is the first time it has ever been confirmed using modern cytogenetic techniques.

The forkhead-box family of genes, to which FOXP1 belongs, consists of over 40 human genes; all of which encode 80–100 amino acids, which form a DNA binding winged helix or a forkhead domain. These genes code for a class of proteins that serve a wide array of roles including development, metabolism, immunology.

Fig. 1. A BAC clone from the deleted region (RP11-120N20) and the 3q subtelomere probe (RP11-23M2) confirmed the loss of the region covered by the RP11-120N20 probe. One signal was observed from the BAC clone and two signals were observed from the control probe.

Fig. 2. (a) Oligonucleotide-based microarray analysis using a 105 k-feature whole-genome microarray with one probe every 10 kb in targeted regions showing a 795 kb deletion between the nucleotides 71,164,161 and 71,958,845; (b) region of 3p14.1p13 (70.5–73.0 Mb) with the genes and the deletion of the present patient and of the patient of Petek indicated (hatched bars). The distal breakpoint of Petek’s patient is located between 71.6 and 71.9 Mb (dotted bar), the deletion extends into the centromeric region.
and cell cycle control [19]. The FOXP protein subfamily has four members — FOXP1, FOXP2, FOXP3, FOXP4 — and is characterized by a DNA binding dependent N-terminal transcriptional repression domain which encompasses both a zinc finger and a leucine zipper motif [9,13]. FOXP1 and FOXP2 are homologous structures that share a similar N-terminal domain. Both proteins are active in the developing human foregut and brain [14,16,18]. FOXP1 forms homodimers and heterodimers with FOXP2 and FOXP4 [9]. The FOXP transcription factors are made up of two subdomains. The first is a leucine zipper motif essential for binding and repression; the second is a co-repressor protein known as C-terminal binding protein 1 that represses transcription. FOXP4 only contains the first domain.

The FOXP1 gene is located on chromosome 3p14.1 and is 628 kb in length. It codes for a protein with four isoforms; the most common is 677 amino acids in length. The FOXP1 protein is a key transcription factor which functions in tissue and cell-specific gene transcription during early development and adulthood. Recently, researchers have shown that FOXP1 plays a critical role in defining the columnar identity of motor neurons at each axial position, as well as organizing motor axon projections [12]. A disruption of this function may explain our clinical finding of arthrogryposis and hypertonia. Though we can only speculate, the limitations of movement in the finger joints of a case with a deletion of 3p11p14.1 described by Crispino et al. [1] may also represent arthrogryposis associated with a deletion in FOXP1.

Three other cases have been described which may include a deletion of FOXP1 [1,5,15]. Sichong et al. [15] described a case of a girl with a de novo deletion of the proximal segment of short arm of chromosome 3 (46,XX, del(3)(p11p14.2)). The child had growth delay, psychomotor delay, dysmorphic facies and hearing impairment. Crispino et al. [1] described an infant with a reciprocal translocation between chromosome 3 and 20 with an interstitial deletion of 3p 46XX,t(3;20)(p14.2;p12.2)del(3)(p11p14.1). This infant was small for gestational age (<3rd percentile), with dysmorphic facies, ulnar deviation of the wrists, transverse palmar creases and limitations of movement in the finger joints. A third case described by Hertz et al. [5] reports a male fetus with an interstitial deletion of the short arm of chromosome 3 with a karyotype of 46,XY,del(3)(p14.2p11). The fetus was described as having dysmorphic facies, ulnar deviation of the wrists, transverse palmar creases and a cardiac defect. Because these cases were only described by using classical cytogenetic techniques, the breakpoints were not well defined. As a result, it is unclear whether any of these cases truly represent deletions in FOXP1. Nevertheless, there are similarities in some of the clinical findings that might indicate a deletion of FOXP1. Conversely, the above cases represent large deletions that contain many genes, and may also represent deletions in other genes such as EIF4E3, PROK2 and GPR27 (see Table 1).

Deletions of EIF4E3, PROK2 and GPR27 were also present in our patient. EIF4E3 interacts with the 5-prime mRNA cap and delivers mRNA to the ribosome [7]; mutations in this gene have not been linked to a human condition, however. PROK2 was also deleted and heterozygous mutations of PROK2 have been implicated in Kallmann syndrome type 4 [3]. As cryptorchidism can be a sign of hypogonadotropic hypogonadism, testing is planned to rule this out in our patient. A previous patient was reported with a deletion of both PROK2 and GPR27 and other genes in the del(3)(p13p11) region [11]. This case was not diagnosed with Kallman syndrome, but did have an enlarged frontal subarachnoid space and hypoplasias, as well as growth retardation, dysmorphic features, and
language abnormalities. It is unclear what clinical findings we can attribute to a deletion of GPR27. GPR27 is a highly conserved G-protein receptor, which is expressed in the central nervous system and genital organs. Its exact function and link to human pathogenesis is still unknown [10].

Although FOXP1 mutations or deletions have eluded researchers, other genes in the FOX family have been implicated in disorders featuring blepharophimosis (FOXL2) [2] and speech delay (FOXP2) [8] (Table 1). The FOXL2 protein is a transcription factor active in the early gonad prior to sex differentiation, the mature ovary, and the eyelid. Haploinsufficiency of the FOXL2 gene results in blepharophimosis, epicanthus inversus, and low nasal bridge and amenorrhea or premature ovarian failure in females. Although the blepharophimosis FOXL2 phenotype is similar to that seen in our patient with a FOXP1 deletion, the timing and expression of these transcription factors do not share overlap or interact with the same proteins. FOXL is a class I FOX protein member with a wing helix DNA binding domain and a forkhead domain, whereas FOXP is a class II member with the wing helix domain, forkhead domain, and an additional zinc finger domain. The FOXP2 protein is a transcription factor with many targets in the brain. In 1990, a family with autosomal dominant transmission of oral motor and speech dyspraxia caused by haploinsufficiency of FOXP2 was discovered. The FOXP2 arginine553histidine missense mutation of the forkhead domain is linked to speech and language abnormalities in humans [4]. The homologous region of FOXP1 was completely deleted in our patient.

FOXP3 and FOXP4 are also members of the FOX family of genes. FOXP3 is located at Xp11.23 and serves as a master regulator of T cell development and function. Mutations in FOXP3 have been linked to IPEX syndrome (immunodysregulation, polyendocrinopathy, and enteropathy, X-linked). FOXP4 is located at 6p21.1. Although no human mutations in FOXP4 have been found, expression has been seen in the developing rat forebrain along with FOXP1 and FOXP2 [17]. Heterozygous mice displayed no obvious defects, however, homozygous mice died at embryonic day 12. The homology between the two genes, coupled with the observation that FOXP1 and FOXP2 form dimers, leads us to hypothesize that the clinical phenotype of the two conditions may overlap. Much like cases of FOXP2 deletion, FOXP1 mutations may also lead to speech delay. Our patient’s clinical picture leads us to believe that mutations in FOXP1 may result in disordered motor neuron development, resulting in hypertonnia and contractures. As a result of our observations in this case, we feel that a deletion of FOXP1 should be a part of any differential diagnosis when evaluating a patient with speech delay, developmental delay, blepharophimosis, and arthrogryposis.

References


