

A 24.2-MB DELETION OF 4q12→q21.21 CHARACTERIZED BY ARRAY CGH IN A 13½-YEAR-OLD GIRL WITH SHORT STATURE, MENTAL RETARDATION, DEVELOPMENTAL DELAY, HYPEROPIA, EXOTROPIA, ENAMEL DEFECTS, DELAYED TOOTH ERUPTION AND DELAYED PUBERTY

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Summary: A 24.2-Mb deletion of 4q12→q21.21 characterized by array CGH in a 13½-year-old girl with short stature, mental retardation, developmental delay, hyperopia, exotropia, enamel defects, delayed tooth eruption and delayed puberty: We report molecular and cytogenetic characterization of proximal deletion of chromosome 4q, del(4)(q12→q21.21) in a 13½-year-old girl with short stature, mental retardation, developmental delay, hyperopia, exotropia, enamel defects, delayed tooth eruption and delayed puberty. We speculate that haploinsufficiency of the *AMTN*, *ENAM* and *AMBN* genes is most likely responsible for dental disorders, haploinsufficiency of the *BMP2K* genes is most likely responsible for ocular disorders, and haploinsufficiency of the *REG*, *AREG* and *BTC* genes is most likely responsible for delayed puberty in this patient.

Key-words: *AMBN* – *AMTN* – *AREG* – *BMP2K* – *BTC* – *ENAM* – *REG* – Eye – Monosomy 4q (4q12→q21.2) – Proximal 4q deletion – Teeth.

INTRODUCTION

Clinical reports associated with interstitial deletions of proximal 4q are uncommon. To date, only 14 cases of proximal 4q interstitial deletions that share a common proximal breakpoint at 4q12 including del(4)(q12q13.1) (24), del(4)(q12q21) (6, 13, 28), and del(4)(q12q21.1) (1, 2, 5, 9-10, 21, 23, 25-27, 29); and 5 cases of proximal 4q interstitial deletions that share a common proximal breakpoint at 4q13 including del(4)(q13q21) (16), del(4)(q13.2q21.3) (27), del(4)(q13q22) (17), del(4)(q13.2q23) (18), and del(4)(q13.2q21.22) (4) have been reported. The common features of proximal 4q deletions include short stature, postnatal growth restriction, mental retardation, craniofacial abnormalities such as a prominent forehead, microcephaly, a high frontal hairline, a depressed nasal bridge, low-set ears, epicanthus, small hands

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and feet, microphthalmia, coloboma involving iris and optic disk, hypotonia, seizures and piebaldism (4, 22, 25-26). Here, we report a new case of proximal interstitial deletion of chromosome 4q.

CLINICAL REPORT

The 13½-year-old girl was the second child of a 34-year-old mother and a 48-year-old father. The parents were healthy and non-consanguineous. The family history was unremarkable. She was delivered uneventfully at 38 weeks of gestation with a birth weight of 2,500 g (3rd centile), a body length of 46.5 cm (3rd centile) and a head circumference (HC) of 32 cm (3rd centile). When examined at 6 months of age, she manifested short stature, hypotonia and minor facial anomalies such as large low-set ears, a prominent forehead, a high frontal hairline, hypertelorism, a depressed nasal bridge, and ophthalmologic disorders such as exotropia, hyperopia, astigmatism and amblyopia. Her body weight was 2.5 Kg (< 3rd centile), body length 52.5 cm (< 3rd centile) and HC 39.8 cm (3rd centile). Cytogenetic analysis at the age of 6 months revealed a karyotype of 46,XX. At the age of 4 years, she underwent surgical correction for exotropia. Brain and cardiac ultrasound findings were unremarkable. When examined at 6 years of age, she manifested psychomotor delay, learning difficulty, delayed tooth eruption and multiple caries with enamel defects, mental retardation and short stature. Her body weight was 17 Kg (15th centile), and body length was 97 cm (< 3rd centile). When examined at 13½ years of age, she manifested short stature, small hands and feet, pubertal delay, developmental delay, mental retardation, and facial dysmorphism (Fig 1). There was neither a white forelock on the hair nor hypopigmented streaks on the skin. Endocrinological and biochemical studies were unremarkable. Her body weight was 30 Kg (< 5th centile), and body length was 127



Figure 1: Anterior view and lateral view of the proband at age 13½ years.

cm (< 5th centile). Array comparative genomic hybridization (aCGH) analysis identified a 24.2-Mb deletion of 4q12-q21.21 with the first abnormal clone located at 58,105,424 bp and the last abnormal clone at 82,276,629 bp (NCBI Build 36, March 2006) (Fig. 2). The cytogenetic analysis revealed a karyotype of 46,XX,del(4)(q12q21.2) (Fig. 3). The parental karyotypes and aCGH results were normal. Polymorphic DNA marker analysis using an informative DNA marker D4S3243 specific for 4q21.21 revealed a paternal origin of the deletion.

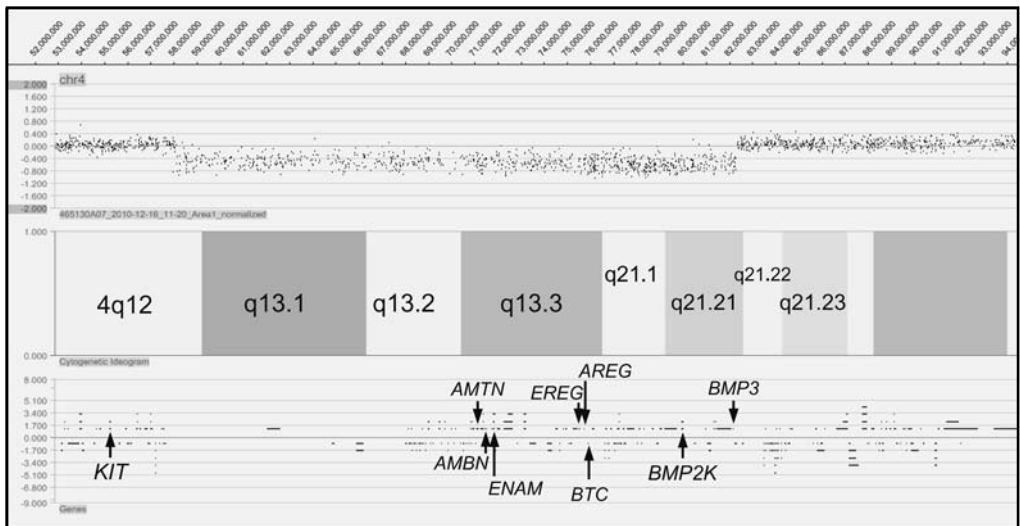


Figure 2: High-resolution comparative genomic hybridization (HR-CGH) analysis of proband's DNA using NimbleGen's 3×720K high-density tiling array V3.1 (Roche, NimbleGen, USA) shows a deletion of 4q12→q21.21 encompassing the region from 58,105,424 to 82,276,629 bp.



Figure 3: Partial G-banded karyogram shows a normal chromosome 4 and an aberrant chromosome with del(4)(q12q21.2) in the proband.

DISCUSSION

This presentation provides evidence for the association of dental and ocular disorders, and delayed puberty with proximal interstitial deletion of chromosome 4q. The present case was associated with dental and ocular disorders and pubertal delay in addition to the common observed abnormalities of short stature, developmental delay and mental retardation. Dental disorders such as disturbances of tooth eruption and multiple caries with enamel defects, and ocular defects such as hyperopia, astigmatism and exotropia as presented in this case have been occasionally described in the cases with del(4)(q12q21) or del(4)(q13q21). Delayed tooth eruption was first noted in a 3½-year-old boy with del(4)(q12q21) (6). Hoo *et al.* (9) reported a 6½-year-old boy with del(4)(q12q21.1), delayed dentition, enamel defects and abnormal retina. Mascari *et al.* (16) reported a 14-year-old girl with del(4)(q13q21), multiple caries with enamel defects, hyperopia and astigmatism. Schinzel *et al.* (21) reported a 2-year-old girl with del(4)(q12q21.1), delayed tooth eruption and bone maturation. Strehle and Middlemiss (27) reported a 2½-year-old girl with del(4)(q12q21.1), squint, delayed tooth eruption and enamel defects, and a 5-year-old boy with del(4)(q13.2q21.3) and abnormal teeth.

The present case had haploinsufficiency of the genes of *AMTN* (OMIM 610912), *ENAM* (OMIM 606585) and *AMBN* (OMIM 601259) at 4q13.3. Normal enamel formation requires ameloblast-specific proteins of enamelin (*ENAM*) and ameloblastin (*AMBN*) to be deposited in the organic enamel matrix. *AMBN* and *ENAM* are candidate genes of autosomal dominant amyogenesis imperfecta type 1B (*AI1B* or *AIH2*) (OMIM 104500), and mutations of these genes cause *AI1B* (12, 15). Amelotin (*AMTN*) is an ameloblast-specific protein and is specially expressed in maturation-stage ameloblasts (11).

The present case had haploinsufficiency of the genes of *BMP3* (OMIM 112263) and *BMP2K* at 4q21.21. Bone morphogenetic proteins (BMPs) play diverse roles in skeletal development and bone homeostasis, and belong to the members of transforming growth factor- β (*TGF β 1*) superfamily. *BMP3* is a negative regulator of bone density (3). Increased bone density has been observed in *Bmp3* *-/-* mice (3). Overexpression of *BMP3* leads to decreased mineralization and less bone (7). *BMP2* expression is essential for ocular development and retinal tissue remodeling (20). Recently, Liu *et al.* (14) found that variant of *BMP2K* gene (*BMP2*-inducible kinase), whose expression is up-regulated during *BMP2*-induced osteoblast differentiation, contributes to high myopia. Whether there is a correlation of loss of formation of the *BMP2K* gene with hyperopia is unclear and will require further study to prove.

The present case had haploinsufficiency of the genes of *EREG* (OMIM 602061), *AREG* (OMIM 104640) and *BTC* (OMIM 600345) at 4q13.3. Epiregulin (EREG), amphiregulin (AREG) and betacellulin (BTC) belong to members of epidermal growth factor (EGF) family. Park *et al.* (19) demonstrated that EGF-related growth factors are mediators of LH action in the ovulatory follicle. Delayed puberty in this case may be in part due to the haploinsufficiency of the EGF-related growth factor genes.

The present case did not show piebaldism because the proximal breakpoint of the deletion in this case was distal to the *KIT* gene (55,218,852-55,306,138 bp). Piebaldism has been reported in patients with proximal interstitial deletion of 4q involving the region of 4q12 (5-6, 9, 21, 23, 29). The *KIT* gene (OMIM 164920) is located at 4q12, and mutation of the *KIT* proto-oncogene is associated with piebaldism (8).

In summary, we have presented clinical findings and molecular cytogenetic analysis of partial monosomy 4q (4q12→q21.21) in an adolescent girl. We speculate that haploinsufficiency of the *AMTN*, *ENAM* and *AMBN* genes is most likely responsible for dental disorders, haploinsufficiency of the *BMP2K* gene is most likely responsible for ocular disorders, and haploinsufficiency of the *EREG*, *AREG* and *BTC* genes is most likely responsible for delayed puberty in this patient.

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