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고해상도 염색체 마이크로어레이법으로 확인된 4번 염색체 장완 근위부 결실의 특징: 증례보고 및 문헌검토

Characteristics of Interstitial Deletion in Chromosome 4q Confirmed by Array Comparative Genomic Hybridization: A Case Report and Literature Review

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Chromosome 4q deletion syndrome is a rare disease caused by partial deletion of the long arm of chromosome 4. Phenotypic severity and expressivity vary among patients with chromosome 4q deletions, depending on the size and region of the deletion of the affected chromosome. Although there have been many reports of proximal 4q deletion cases, very few have been confirmed by high-resolution array comparative genomic hybridization (aCGH). In the current study, we presented a new case of 4q proximal deletion, with detailed genetic and clinical characteristics, and compared these characteristics to those of six previous cases with available aCGH data. According to our review, several genes known to be associated with specific phenotypes of 4q12q21.1 deletion cannot sufficiently explain the variable phenotypes observed among the cases. These phenotypes include mental retardation, microcephaly, ocular anomalies, dental anomaly, and piebaldism. Consequently, we recommend further detailed investigations into the genes associated with 4q12q21.1 deletion to assist in identifying genotype-phenotype associations more clearly.

Key Words: Chromosome 4q- syndrome, Comparative genomic hybridization, Genetic association studies

INTRODUCTION

Chromosome 4q deletion syndrome is a rare disease caused by interstitial or terminal deletion of the long arm of chromosome 4 [1-3]. These deletions are typically *de novo*, although some cases have been found to result from an unbalanced product of parental reciprocal translocation [4]. The majority of 4q deletion cases are associated with a 2–15.1 Mb deletion of the q11–q31 region, with substantial phenotypic variation. However, only a small number of previously reported cases have been confirmed by high-resolution array comparative genomic hybridization (aCGH).

In the present study, we report the case of a patient with an interstitial deletion of a maximum, 22.8 Mb on chromosome 4q. Clinical and genetic characteristics were compared against previously reported patients with deletion of the same region, confirmed by aCGH. Further, we discuss candidate genes, associated with this syndrome, as potential markers, which could provide new insights into the phenotypic spectrum and genotype-phenotype correlation.

CASE REPORT

The present case looks at an 18-year-old male patient with an unremarkable family history. He is the third child of non-consanguineous, healthy, Korean parents and was born at a gestational age of 40 weeks, at 2.8 kg, by vaginal delivery. Upon presentation,

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his height and weight were less than 1 percentile. The patient further presented with microcephaly and clear dysmorphic facial features, including cranial asymmetry, prominent forehead protrusion, a bilateral epicanthal fold, hypertelorism, depressed nasal root with a broad or beaked nose and low-set, simple ears with preauricular dimples. No spots or piebaldism were observed. A neurological examination indicated hypotonia, but the deep tendon reflex was well preserved. Exophthalmos, ptosis, and strabismus were observed in both eyes with a cataract also present in the left eye. A dental examination revealed white plaque, due to the generalized amelogenesis imperfecta, with normal maxillomandibular growth, but bimaxillary protrusion was evident. Due to substantially delayed bone maturation, bone age was delayed (Fig. 1A). Abnormalities in the spine (Fig. 1B) and both feet (Fig. 1C) were also present. There were no abnormalities in the right hip, according to both hip radiographs; however, sequelae of Legg-Calvé-Perthes was observed in the left hip, with a short, broad left femoral head and relative shortening of the left limb with coxa magna deformity (Fig. 1D). This caused a discrepancy of 2 cm in leg length.

The patient had a no history of seizure but did present with a learning disability and speech disorder, along with severe devel-

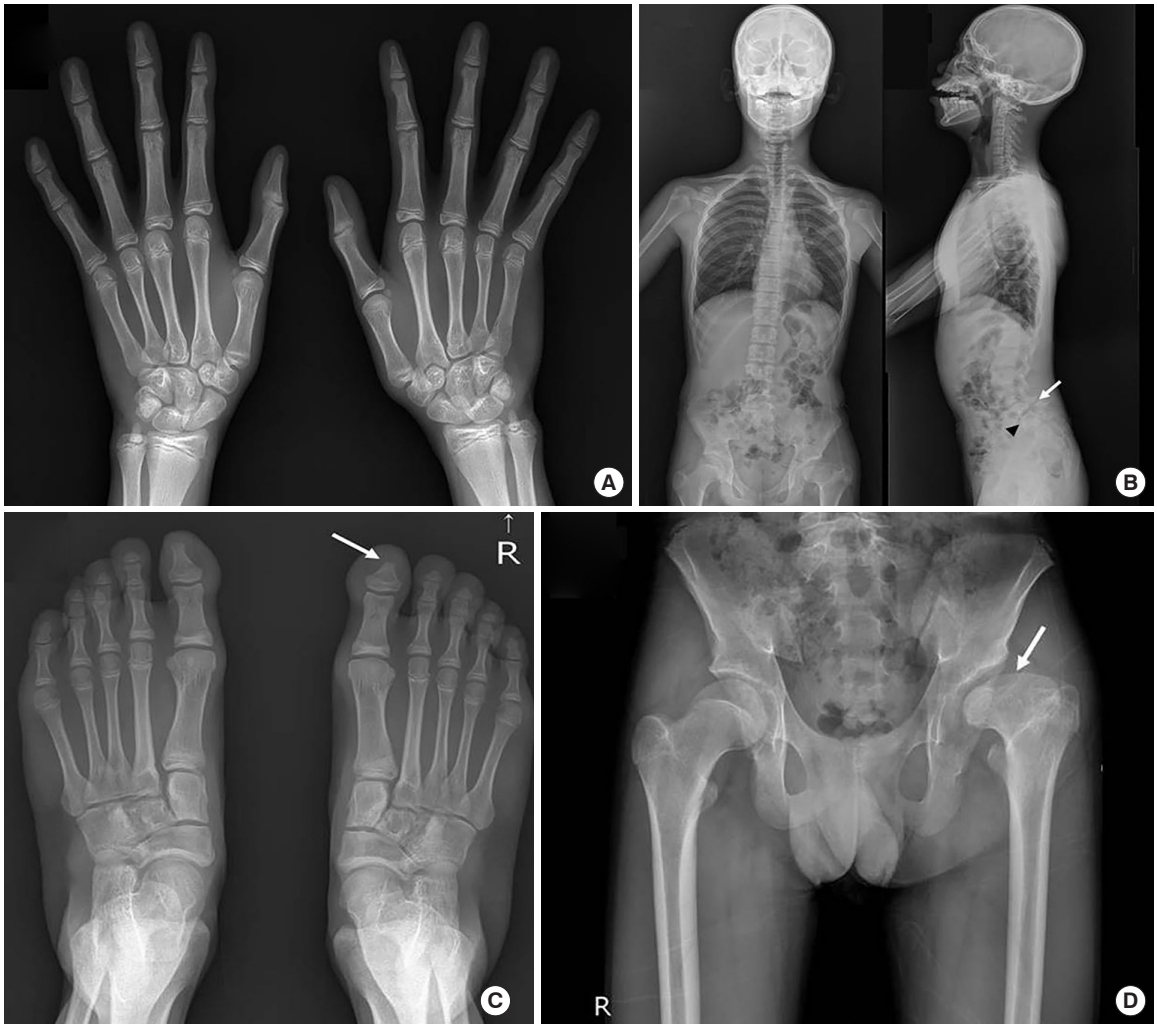

Fig. 1. Skeletal radiographs of the proband. (A) Both AP hand radiographs showed no fusion of the phalangeal physis' and the bone age was considered to be in the order of 14 years, determined by the Greulich-Pyle method at the age of 17.3 years. (B) Whole spine, AP and lateral, radiographs showed minimal scoliotic curvature of the T-L spine, loss of normal lordotic curvature of the cervical spine, moderate spondylolytic spondylolisthesis at L5 on S1 (arrow), and a deformity of the anterosuperior corner of the S1 body (arrowhead). (C) AP radiographs of both feet showed deformity of the right first distal phalangeal bone (arrow). (D) Both hip AP radiographs showed sequelae of Legg-Calve-Perthes disease in the left hip, with a short, broad femoral head (arrow) and relative shortening of the left limb, in keeping with a coxa magna deformity.

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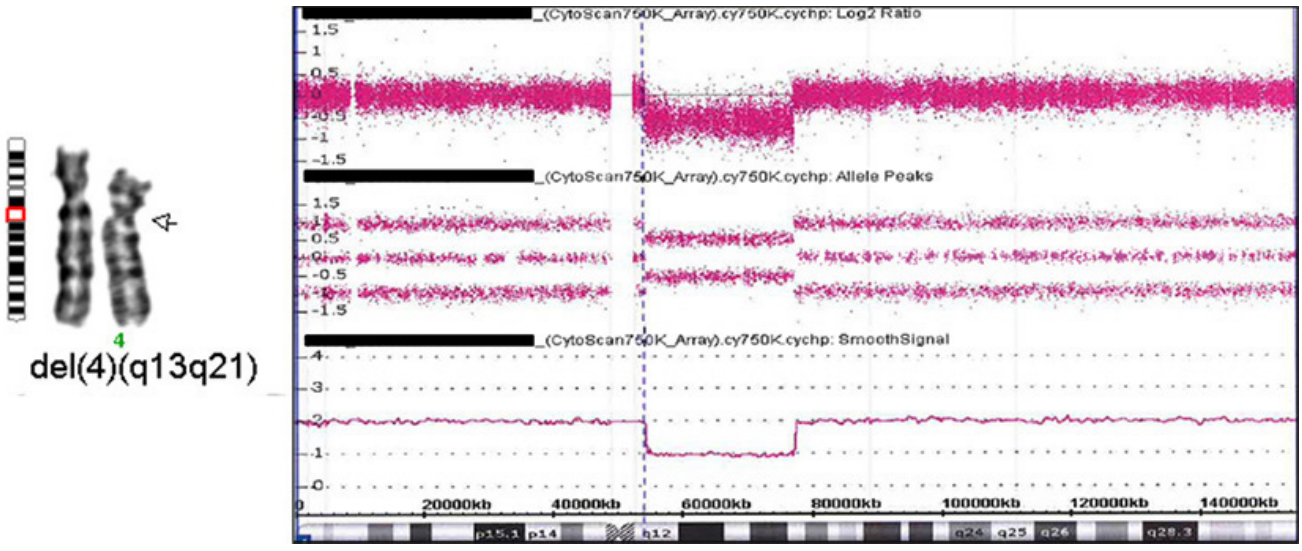

Fig. 2. GTL-banded partial karyotype and aCGH results of the proband: 46,XY,del(4)(q12q21.1).arr[GRCh38] 4q12q21.1(53575744_76379310)x1.

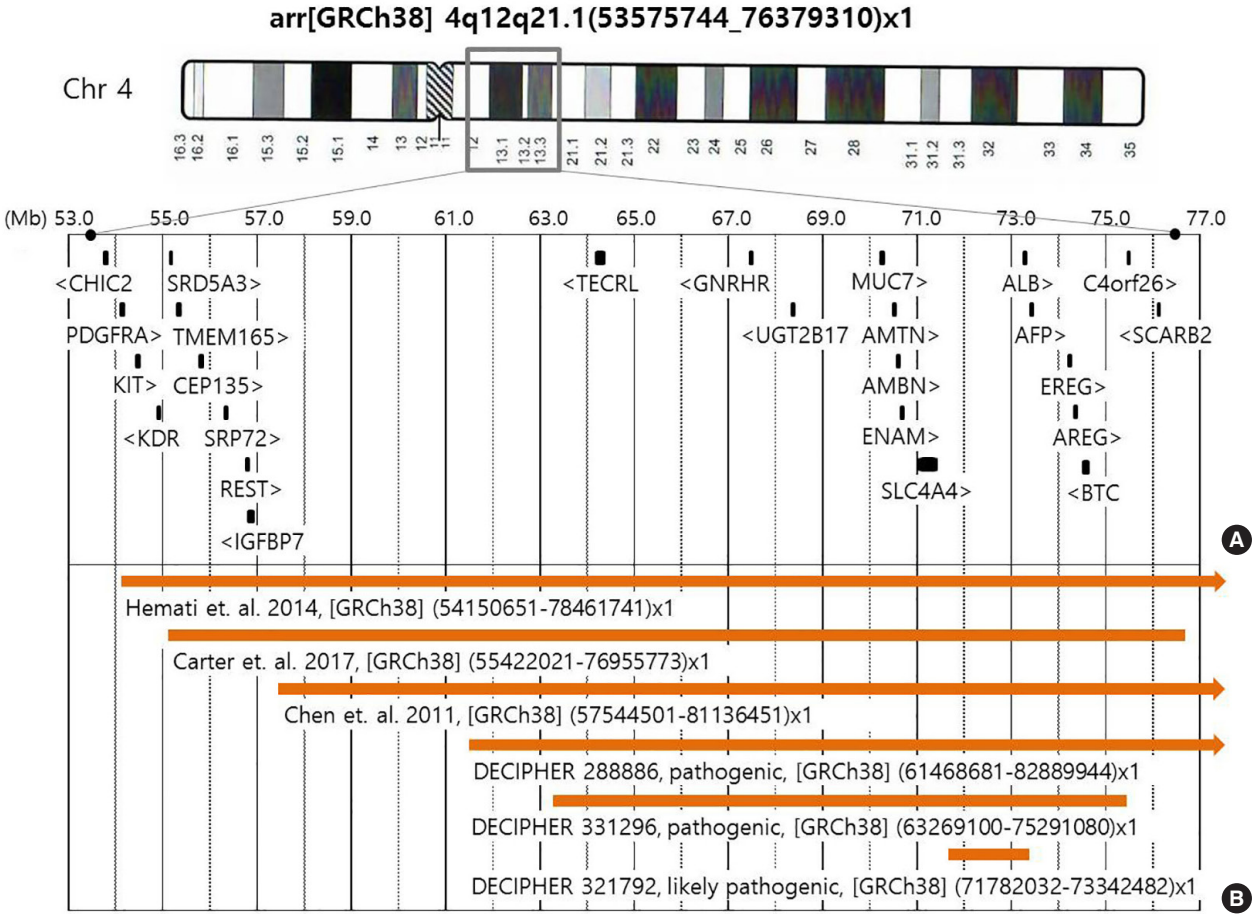

Fig. 3. The deleted region of the proband and diagrammatic comparison of previously reported cases. (A) Significant MIM genes in the region of the 22.8-Mb deletion were detected by whole-genome SNP array in the proband. (B) The regions of previously published cases, with sufficient clinical data and confirmed by aCGH at the same loci, and DECIPHER cases of pathogenic and likely pathogenic deletions, within the deleted region of the proband.

opmental delay. A psychiatric evaluation revealed signs of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). An investigation of his pubertal status showed a testes volume of 18/18 mL, pubic hair score of 4–5, genitalia score of 5 with appropriate adult external genitalia overall. His serum testosterone, luteinizing hormone and follicle stimulating hormone levels were all elevated, at 3.95 (reference range: 1.7–8.6 mIU/mL), 3.37 (1.5–12.4 mIU/mL) and 8.57 (1.88–8.82 ng/mL), respectively. No abnormal findings were observed in complete blood cell count, urinalysis, biochemical tests, hearing tests, electroencephalography, echocardiography, pelvic sonography, and the kidney-ureters-bladder sonography survey.

Cytogenetic analysis and aCGH of the patient revealed an interstitial, heterozygous deletion of chromosome 4q: 46,XY,del(4)(q12q21.1) arr[GRCh38] 4q12q21.1(53575744_76379310)x1 (Fig. 2) with the maximum length of the deleted region being 22.8 Mb. His mother had a normal karyotype, but no chromosome analysis was performed on his father. Neither parent showed any of the phenotypes of the proband. Chromosome analysis of peripheral blood lymphocytes was performed, according to standard techniques, at a 550-band level. The aCGH was performed using the Affymetrix Cytoscan 750K array. Copy number variants were compared with public databases, including the DECIPHER database (http://decipher.sanger.ac.uk) and USCS Genome Browser (http://www.genome.ucsc.edu/cgi-bin/hgGateway). No pathogenic or likely pathogenic variant was found in whole-exome sequencing using the peripheral blood sample of the proband. All exon regions of all human genes (~22,000) were captured using Agilent's SureSelect kit and the captured regions of the genome were sequenced with the Illumina sequencing platform.

The deleted region of the proband comprised 109 known Mendelian Inheritance in Man (MIM) genes, including 25 genes associated with disease phenotypes; however, few of these genes were associated with specific phenotypes (Fig. 3A). The patient and his parents provided written informed consent for the publication of patient information.

DISCUSSION

Many patients with 4q proximal deletion of various sizes have been reported to date, including 4q12q21.1. Capalbo et al. [5] summarized the clinical characteristics of 31 patients with pure 4q proximal deletions; however, detailed information on the deleted region was not provided for these patients. Only three of these cases had similar sized deletions (21.59–24.37 Mb) at the same loci as our present case, and this was confirmed by aCGH (Fig. 3B). In addition, the DECIPHER database (version 9.23, released on May 23, 2018) showed three cases recorded as "pathogenic" or "likely pathogenic", which were smaller sized deletions of this region, as pure copy number variations (DECIPHER number 288886, 321792, and 331296) (Fig. 3B). Therefore, including the present case, there are only seven cases of 4q proximal deletion confirmed with aCGH and detailed clinical information (Table 1). The common characteristics of these cases include mental retardation, learning disability, growth retardation, minor facial anomalies, hypotonia, skeletal abnormalities, and eye anomalies. Therefore, more in-depth comparisons of these cases could prove useful in understanding the genotype-phenotype relationship of the proximal 4q region.

As shown in Table 1, mental retardation and/or learning disability was a common clinical finding in all seven cases (100%). The chromosomal region currently analyzed (4q) was found to be associated with two distinct syndromes linked to mental retardation and growth retardation: Kahrizi syndrome (MIM#612713) and renal tubular acidosis, proximal, with ocular abnormalities and mental retardation (RTA-OA-MR, MIM#604278). Kahrizi syndrome, which can be caused by a homozygous mutation of *SRD5A3* (MIM*611715) [6], is an autosomal recessive, neurodevelopmental disorder characterized by mental retardation, cataracts, coloboma, kyphosis, and coarse facial features. RTA-OA-MR is also an autosomal recessive disease, and it is caused by a homozygous mutation in *SLC4A4* (MIM*603345) [7]. *SRD5A3* and *SLC4A4* are both recessively inherited genes; however, our patient, and some other patients with mental retardation and/or learning difficulties [8, 9], show heterozygous deletion of both genes. Moreover, some symptomatic patients only harbor the *SLC4A4* deletion [10], or no deletion of either gene (DECIPHER 321791), suggesting that a more complicated relationship exists between *SRD5A3, SLC4A4* or possibly other unidentified genes in this region, in the process of neurodevelopment.

The common craniofacial features of 4q deletions, which were also observed in our case, are microcephaly and ocular defects such as exophthalmos, astigmatism, strabismus, and cataracts. Microcephaly is known to be associated with *CEP135* (MIM*611423), and was identified in patients with autosomal recessive primary

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Table 1. The clinical features of the proband along with other previously reported cases

	Our case	Carter et al., 2017 [9]	Hemati et al., 2015 [8]	Chen et al., 2011 [10]	Decipher 288886	Decipher 331296	Decipher 321792
Deleted region [GRCh38]	53,575,744-76,379,310	55,422,021-76,955,773	54,150,651-78,461,741	57,544,501-81,136,451	61,468,681-82,889,944	63,269,100-75,291,080	71,782,032-73,342,482
Deleted size	22.80 Mb	21.53 Mb	24.31 Mb	23.59 Mb	21.42 Mb	12.02 Mb	1.56 Mb
Karyotype/ chromosome locus	46,XY,del(4)(q12q21.1)	46,XY,del(4)(q12q21.1)/47,idem,+r(4)	46,XX,del(4)(q12q21.21)	46,XX,del(4)(q12q21.2)	4q13.1-q21.22*	4q13.1-q13.3*	4q13.3-q13.3*
Gender/age	M/17 yr	M/6 mon, 22 mon	F/7 yr 3 mon	F/13 yr 6 mon	?/?	M/?	F/?
Inheritance	unknown	de novo	unknown	de novo	unknown	de novo	maternal
Intellectual/ learning disability	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Growth delay	Yes	Yes	Yes	Yes	ND	ND	ND
Short stature	Yes	Yes	Yes	Yes	ND	ND	Yes
Facial dysmorphism	Yes	Yes	Yes	Yes	ND	ND	ND
Microcephaly	Yes	ND	10 percentile at 18 mon, 25-50 percentile later	Yes	ND	ND	Yes
Eye anomalies	Yes	ND	Yes	Yes	ND	ND	ND
Amelogenesis defect	Yes	ND	No	Yes	ND	ND	ND
Piebaldism	No	Yes	No	No	ND	ND	ND
Hypotonia	Yes	ND	Yes	Yes	ND	ND	ND
Abnormality of the skeletal system	Yes	ND	Yes	ND	ND	ND	Yes
Other	ADHD, Autism	hepatomegaly	Hyperextensible skin, hypermobile joints	Delayed puberty			Puberty and gonadal disorders

*The loci were consistent with the reported deletion region. Their karyotypes were not described on the DECIPHER database.
Abbreviation: ND, not described.

microcephaly (MIM#614673) in homozygote form [11, 12]. The microcephaly of our case, being a heterozygous *CIP135* deletion, and some other patients, also with the same deletion, may therefore not be explained by *CEP135* alone. Haploinsufficiency for *BMP3* (MIM*112263) and *BMP2K* (MIM*617648) is the prevailing hypothesis concerning the origin of ocular anomalies [10]. However, our case did not have a deletion of either of these genes. To date, none of the genes within the deleted region associated with ocular expression have been associated with ocular abnormalities.

Dental and enamel defects, which are also common features of 4q deletions, could be ascribed to haploinsufficiency of the *ENAM* (MIM*606585), *AMBN* (MIM*601259) and *AMTN* (MIM*610912) genes, at 4q13.3. Dental enamel, a highly mineralized tissue, is rigorously controlled in ameloblasts by the interaction of several organic matrix molecules, including enamelin, encoded by *ENAM*, and ameloblastin, encoded by *AMBN*. Mutations of the *ENAM* and *AMBN* genes cause amelogenesis imperfecta type 1B (MIM#104500), 1C (MIM#204650) and 1F (MIM#616270) [13, 14]. Amelotin, an ameloblast-specific protein, encoded by *AMTN* and specifically expressed in maturation-stage ameloblasts, and partial deletion of the *AMTN* gene, was reported in amelogenesis imperfecta type 3B (MIM#617607) [15]. Our case and that reported by Chen et al. [10], both lacking variants in these genes, showed dental disorders, whereas the case reported by Hemati et al. [8] did not show any dental disorders (Table 1). These conflicting findings suggest the possibility of either incomplete penetrance, or that other genes, in the deleted region or elsewhere, likely also play strong roles in amelogenesis.

Haploinsufficiency of *KIT* (MIM*164920) is well known to be related to piebaldism [10]. Our patient, along with some previously reported patients with proximal 4q deletion, showed *KIT* deletion without piebaldism [8] (Fig. 3, Table 1). This suggests incomplete penetrance of *KIT* haploinsufficiency, or the presence of other factors that could affect the expression of piebaldism.

In summary, our review of the present case, and the few previous cases, confirmed with aCGH, indicates that the genes currently considered to be associated with specific phenotypes of 4q12q21.1 deletion cannot sufficiently explain the phenotypes observed or the variations in clinical manifestations among cases, such as mental retardation, microcephaly, ocular anomalies, dental anomaly, and piebaldism. This is in contrast with the conclusions of some previous publications [8-10] and highlights the need for ongoing

investigations into the genes associated with 4q12q21.1 deletion to assist in identifying genotype-phenotype associations more clearly.

요 약

"4번 염색체 장완(4q) 결실증후군"은 4번 염색체 장완의 일부 결실을 가진 희귀질환의 일종으로 관련유전자 및 결실크기에 따라 표현형의 중증도나 표현도에 차이를 나타낸다. 저자들은 최근 4q 근위부에 22.8Mb의 결실을 가진 환자를 진단하게 되어 관련유전자와 임상적 특징들을 자세히 조사하여 기존 증례들과 비교검토하였다. 문헌 및 DECIPHER database에 보고된 4q 근위부 결실환자들 중 고해상도 염색체 마이크로어레이법(aCGH)으로 확인된 증례는 극히 드물었고, 결실부위가 저자증례와 공통부위를 가진 증례는 6건뿐이었다. 이 중 한국인은 없었다. 관련논문들에서는 4q, 특히 근위부 결실증후군 환자들이 가진 증상인 정신지체, 소두증, 눈기형, 치아이상, 피부색소증(piebaldism) 등을 설명할 수 있는 유전자들을 각기 제시하고 있었다. 그러나 데이터베이스에 기록된 6건과 본 증례의 사례를 면밀히 검토한 결과 모두 불완전하거나 부적절했다. 저자들은 검토한 유전형-표현형 상관관계를 요약하여 표로 제시하였다. 향후 4q 근위부 결실을 가진 환자를 진단하게 된 전문의들이 본 보고서를 참고하여 기존 논문들의 주장을 보다 균형적으로 검토하게 될 수 있기를 기대한다.

Conflicts of Interest

None declared.

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