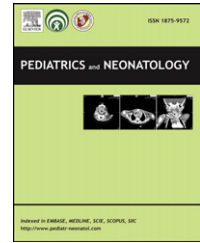


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CASE REPORT

Interstitial Deletions of the Short Arm of Chromosome 4 in a Patient With Mental Retardation and Focal Seizure

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Key Words

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Interstitial deletion of the proximal short arm of chromosome 4 has rarely been described. This defect is associated with variable clinical manifestations, including mental retardation, unusual facial appearance, and minor limb abnormalities. We describe a girl diagnosed with moderate mental retardation and seizures with an interstitial deletion of the short arm of chromosome 4 [46, XX, del(4)(p12p15.2)].

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1. Introduction

Interstitial deletions in chromosome 4p are relatively rare.^{1–3} Terminal deletion of the short arm of chromosome 4 seen in Wolf-Hirschhorn Syndrome (WHS, OMIM 190190) is characterized by marked growth retardation, severe mental retardation, microcephaly, seizure, characteristic

facial anomalies, and multiple minor anomalies.^{4,5} The syndrome requires the deletion of band 4p16, and the crucial deletion for WHS is in 4p16.3.^{6,7} Interstitial deletions of 4p12 to 4p15 have been described in few cases in the literature.^{1–3} The main clinical features in the previously reported cases were mild-to-moderate mental retardation and multiple minor dysmorphic features. Two previously reported cases with 4p15.2 deletions suffered from epilepsy.^{8,9} Electroencephalogram (EEG) abnormalities and single seizure episodes have been reported in two additional cases.¹⁰ We describe cytogenetic interstitial deletion of the 4p12p15.2 region in a girl with multiple minor anomalies, mental retardation, and focal seizures.

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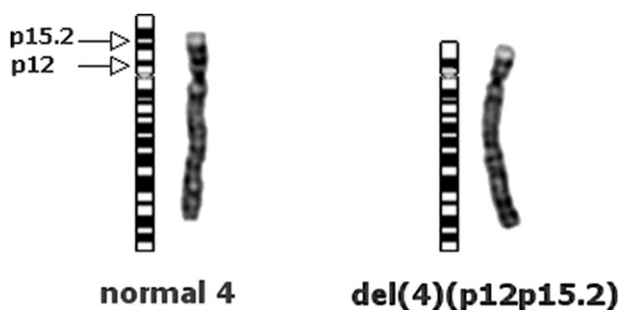


Figure 1 Standard chromosome analysis revealed the karyotype 46,XX,del(4)(p12p15.2).

We also described the array comparative genome hybridization (CGH) of her chromosomal samples from the interstitial deletion 4p12p15.2.

2. Case Report

The proband was born to a 30-year-old mother and a 32-year-old father. The family history was negative for consanguinity, congenital anomalies, recurrent miscarriages, or the presence of other individuals with mental retardation. The pregnancy was complicated by vaginal

spotting in the early part of the first trimester, and the delivery was by Cesarean section because of fetal breech position. The birth weight was 3200 g. The girl began walking at 24 months and spoke her first word at 30 months. She was clinically evaluated at 36 months because of unusual physical findings and developmental delay. Physical examination showed a short girl with abnormal facial features, dull facial expression, and generalized hypotonia. Brain magnetic resonance imaging (MRI) revealed poor myelination. Therefore, she received serial rehabilitation to improve balance, cognitive skills, and auditory skills. At the age of 7 years, she presented to the genetic clinic for evaluation of short stature. Her weight was 16 kg and height was 110 cm, which was in the third percentile for growth in her age group. She had puffy eyes, epicanthal folds, and upslanted palpebral fissures. Her nose was wide, with lateral flaring of the nostrils. She had a short philtrum, a pronounced lower lip, a prominent mandible with a mandibular overbite, and a short neck. She had an emotionless face and some degree of motor incoordination. Standard chromosome analysis revealed the karyotype 46,XX,del(4)(p12p15.2) (Figure 1), and this was confirmed with array CGH analysis (Figure 2). The reverse transcriptase polymerase chain reaction was amplified with primers for the mRNA expressions on β -actin (as a control) and *GABRB1* genes. *GABRB1* was detected in the patient

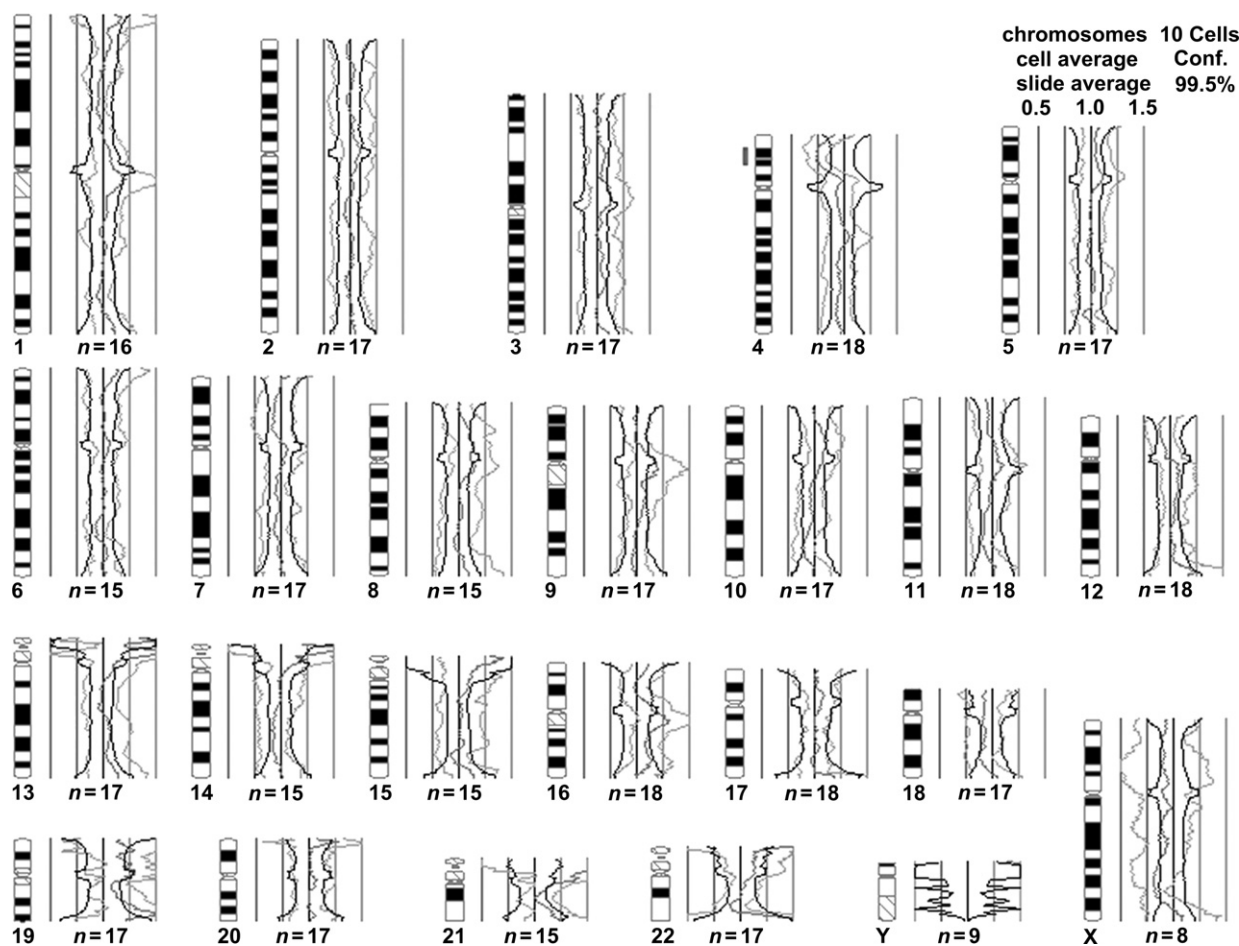


Figure 2 Array CGH analysis revealed the 46,XX,del(4)(p12p15.2). CGH = comparative genome hybridization.

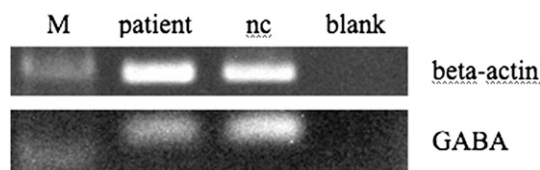


Figure 3 Lane1 (M): 100 bp marker; Lane 2: patient in this case; Lane 3 (nc): normal control; Lane 4 (blank): The RT-PCR performed without template. RT-PCR = reverse transcriptase polymerase chain reaction.

(Figure 3). The parents had normal karyotypes; and therefore, this was a *de novo* case. At the age of 9 years, the patient experienced four focal seizures within a 2-month period. EEG revealed foci of partial seizures over the right central area of the brain. Brain MRI revealed a corpus callosum atrophy and an ectopic posterior pituitary gland (Figure 4). Results of IQ testing were as follows: (1) verbal IQ, 45; (2) performance IQ, 45; and (3) full IQ, 40 according to Wechsler Intelligence Scale for Children, third edition (WISC-III).

3. Discussion

There are varying symptoms of minor anomalies and of developmental status in patients with deletions in the short arm of chromosome 4 in the literature. Patients with similar interstitial deletions (4p12p15.32) similar to this case report and the combination of severe mental retardation, upslanted palpebral fissures, epicanthal folds, a large beaked nose, and a flattened midface have been previously described.^{2,3,11} Francke et al¹ described a woman with tall, thin body composition, a long face, a large nose, a high-arched palate, a broad neck, a narrow trunk, and broad

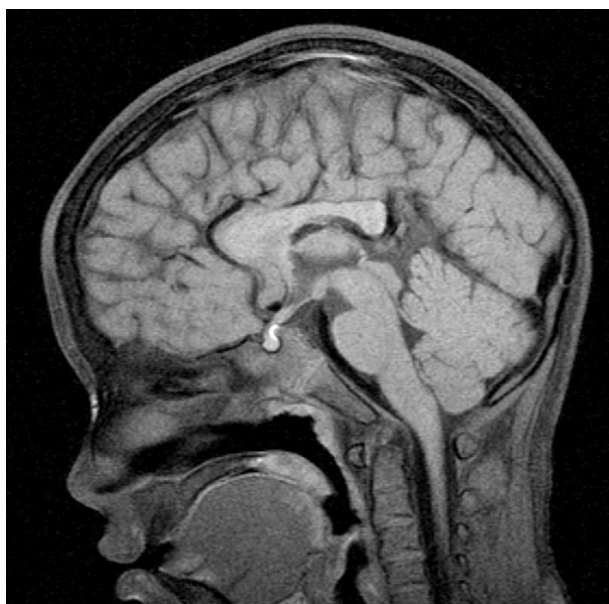


Figure 4 Brain MRI revealed a corpus callosum atrophy and an ectopic posterior pituitary gland. MRI = magnetic resonance imaging.

hands. She had severe mental retardation, a history of genitourinary malformation, and a history of poor feeding in infancy. Her deletion involved bands 4p11p15.2. Davies et al¹² described an adolescent with only minimal limb anomalies and a deletion limited to 4p15.3. A similar adult with only minimal limb anomalies had a deletion of 4p15.2p15.33.¹³ Previous investigators have localized the deletion essential for WHS to band 16.3.^{10,14} The unusual facial appearance does not have unique and significant characteristics to fully clarify the phenotype of the interstitial deletion of 4p12p4p15, and this is why early diagnosis of the interstitial deletion of 4p12p15 is so difficult. Array CGH detects both submicroscopic chromosomal imbalance and allows accurate delineation of deleted or duplicated chromosomal segments. The present case was diagnosed with WHS in childhood because of identification of the 4p deletion, although the individual's phenotype was not fully compatible with WHS. The high-resolution chromosome analysis and array CGH were performed for an accurate genetic diagnosis.

Vincent et al¹⁵ discussed two brothers with autism and neonatal seizures who had paracentric inversions of 4p (p12p15.3), which directly interrupted the *GABRG1* gene, one of the γ -aminobutyric acid (GABA) receptor subunit genes. Neonatal seizures improved during childhood. The association between the seizures in our patient and the disrupted GABA neurotransmission was considered. Despite lack of *GABRB1* analysis, *GABRB1* was detected in the present case report; however, the *GABRG1* gene was not disrupted; and therefore, epileptic changes seen in this patient will require further evaluation. Seizures of the presenting case with focal paroxysmal discharges in EEG was associated with brain corpus callosum anomaly, which indicated a probable cortical microdysgenesis that was not ever detected by MRI examination. It is noteworthy that most cases having autism has never been identified with a genetic background before. Only about 6% of autistic children were reported to be associated with chromosomal aberrations.¹⁶ Until recently, genomic alteration of some GABA receptor subunit genes were identified in a Japanese girl and in some Caucasians,^{17,18} strengthening seizure being correlated with *GABRG1*. However, a molecular investigation did not prove seizures of the case attributed to loss of expression of GABA receptor subunit genes.

In summary, we report a case of interstitial deletion of the proximal short arm of chromosome 4 involving bands p12p15.2 identified by cytogenetic analyses and array CGH analysis. This individual demonstrated an unusual facial appearance, moderate mental retardation, and focal seizures, which have not yet been reported in the cases with interstitial 4p deletions. This interstitial deletion was distinct from WHS and represents a novel 4p interstitial deletion syndrome.

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