The Case with Short Stature and Intellectual Disability Caused by a Novel 2q12 Duplication

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ABSTRACT

Copy number variation (CNV) is a kind of malfunction of DNA polymerase to produce extra genetic material which leads to more number of repeats in genes. The CNVs have been associated with different clinical phenotypes such as learning disabilities, short stature, and intellectual disability. The chromosomal microarray analysis is an effective diagnostic method for identifying new CNVs and understanding their clinical effects. In this case report, a variation that has not been reported previously in the literature is presented. This case report will contribute to increasing the knowledge. The CNV (arr [hg19] 2q12.1q12.3 (103,368,824-107,946,062) x3) detected in the index case was also detected in her father and male sibling.

Key Words: *DNA, Copy number variation, Chromosomal duplication, Intellectual disabilities.*

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INTRODUCTION

The human genome consists of approximately 3 billion base pairs. The variations in chromosomal size that involves more than 50 bases are called Copy Number Variations (CNVs).[1,2] Gains (duplications-insertions) or losses (deletions) can be seen in the related chromosomal region in CNVs. The CNVs have been associated with different clinical phenotypes such as learning disabilities, short stature and intellectual disability (ID). We present a new CNV which has not been reported previously in the literature. This CNV was also detected in the father and the male sibling of the index case.

CASE REPORT

A female child was admitted to the clinic due to short stature at the age of 2 years and 9 months. On physical examination, there were no obvious findings other than scoliosis and microcephaly. Two-word sentences were considered as a speech delay. The clinical features and molecula results are shown in Table I.

Growth hormone (GH) stimulation tests were performed first due to insufficient growth rate (3, 4 cm/year). No GH deficiency was detected. GH insensitivity was detected with the Insulin like growth factor (IGF) generation test and GH treatment was initiated. Due to an insufficient growth rate, the treatment was discontinued in the 2nd year.

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Table I: Clinical features of the three patients.

	Case 1	Case 2	Case 3
Age at diagnosis (years)	$8^{6/12}$	$8^{9/12}$	34
Birth weight (g)	2200	2700	2900
Weight (kg)	20 (0,86SDS)	21,6 (-1,38)	90
Height (cm)	112 (-2,86SDS)	124,3 (-0,99SDS)	170
Head circumference (cm)	48 (-2,78SDS)	51 (-1,4SDS)	54,5

The patient with microcephaly, short stature, mild learning disabilities, low school performance, and behavioral abnormalities (aggressive behavior and self-harm) was referred to the genetic department for genetic testing.

arr[hg19]2q12.1q12.3(103, 368, 824-107, 946, 062)x3 were detected in chromosomal microarray analysis (CMA) using Affimetrix Optima Chips. This duplication region in 2q12 was 4577 KB in size and POU3F3 (602480), MRPS9 (611975), GPR45 (604838), TGFBRAP1 (606237), FHL2 (602633), NCK2 (604930), C2orf40 (611752), UXS1 (609749), PLGLA (612212), and RGPD3 (612706), ST6GAL2 (608472) genes were located in this region.

The above genetic variation in the index case was also detected in her sibling and father. Her brother was found to have speech delay, mild mental disorder, and attention deficit hyperactivity disorder (ADHD), while their father had ID and social communication disorder.

DISCUSSION

The genomic imbalance caused by the CNVs can cause a developmental delay (DD), ID, and different structural anomalies.

Affected individuals with similar region deletions or duplications have been described as microdeletion or duplication syndromes.[3,4]

In this report, a variation of approximately 4577 KB in the 2q12 region was detected in three individuals of the same family. While there was pathological short stature and microcephaly in our index case, the anthropometric measurements of her father and male sibling with variation were normal. All the three cases with the variations, had a learning disability, cognitive retardation, and speech delay. Although three deletions were reported previously in the literature, no duplications were reported. Syndactyly, epicanthus, behavioral disorder, learning disability and hearing anomalies were found in one case (patient 281422) defined in the DECIPHER database.

In another case (patient 283152), trigonocephaly, epicanthus, delay in speech and language development, and delay in motor skills were described. In the last case (patient 250511), syndactyly, wide nasal bridge, impaired tooth alignment, myotonia, delayed speech and language development, feeding difficulty in infancy, truncal obesity, impaired pain sensation, and ID were detected. We found cognitive retardation, learning disability, and delay in speech and language development as common features in these described cases. There are 11 genes in the reported 2q12 to 2q12.3 region of our family registered in the OMIM database. Recently, the *POU3F3* gene has been associated with the Snijders Blok-Fisher Syndrome phenotype. Main features of this syndrome are developmental delay and/or ID, neurological findings, and dysmorphic features.[5] In this case, *POU3F3* gene duplication was detected. Although its effect on protein structure is unknown, growth retardation and learning disability are common findings with Snijders Blok-Fisher syndrome. The phenotypic effect of the 10 genes registered in OMIM is unknown.

Nineteen cases with deletion and duplication in the 2q13 region have been presented and CNVs in this region are the risk factors for growth retardation and dysmorphism.[6] The CNVs in the 2q13 region are typically associated with developmental retardation with mild ID and childhood psychiatric diagnoses, particularly ADHD. In accordance with the literature, one of our two siblings cases had ADHD and the other one had aggressive and self-injurious behavior.[7]

In conclusion, CMA is an effective diagnostic method in identifying new CNVs and understanding their phenotypic effects. This case report provides an understanding of the clinical findings of variation. Genetic counselling is required for the early detection of individuals with genetic variation and to take the necessary precautions.

PATIENTS' CONSENT:

Informed consent was obtained from the patients to publish the data concerning this case.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

PK: Study design.
ACC: Case collection.
DT: Manuscript writing.
All the authors have approved the final version of the manuscript to be published.

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