folia medica

Folia Medica 63(1): 138-41
DOI: 10.3897/folmed.63.e52763

Case Report

16p11.2 Duplication Syndrome – a Case Report

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Received: 31 Mar 2020 ♦ **Accepted:** 18 May 2020 ♦ **Published:** 28 Feb 2021

Citation: Levkova M, Stoyanova M, Staneva R, Hachmeriyan M, Angelova L. 16p11.2 Duplication Syndrome – a case report. Folia Med (Plovdiv) 2021;63(1):138-41. doi: 10.3897/folmed.63.e52763.

Abstract

16p11.2 duplication syndrome is a rare disorder, often associated with intellectual disability, attention deficit, hyperactivity disorder, and a predisposition to epilepsy and schizophrenia. There are no specific dysmorphic features for this genetic condition, but microcephaly, micrognathia and hypertelorism could be present. We report a case of 16p11.2 duplication syndrome which has the typical clinical presentation – slight facial dysmorphism, impaired intellectual development, and autistic behavior. Whole-exome sequencing was performed, but no pathogenic or likely pathogenic mutations were identified. Array comparative genomic hybridization analysis established the diagnosis of 16p11.2 duplication syndrome, which illustrates the importance of this method when diagnosing children with unexplained intellectual disability.

Keywords

16p11.2 duplication, array CGH, autistic behavior, intellectual disability

INTRODUCTION

16p11.2 duplication syndrome is characterized by impaired intellectual development, attention deficit hyperactivity disorder and microcephaly.[1] Although this disorder is rare in the general population, it affects approximately 1% of the patients with autistic behaviour.[2] That is why the identification of this duplication could be important when establishing the genetic reason for intellectual disability. In the present article we report a case of 16p11.2 duplication syndrome, which has the typical clinical presentation and is confirmed by array comparative genomic hybridization (array CGH).

CASE REPORT

Our patient was a 4-year-old girl, born per vias naturales after a second uneventful pregnancy. The pregnancy was not followed up by an obstetrician. The birth weight of the patient was 2900 gr, birth length – 49 cm, head circumference – 32 cm. Apgar score was 8 points at 1 minute and 9 points at 5 minutes. A foramen ovale together with a pulmonary stenosis was found after birth, which did not require surgical correction. At the age of around one year the biological mother of the patient abandoned her and the child was raised by foster parents.

The patient demonstrated delayed motor and neurological development: she started walking at the age of 1 year and 6 months and could not talk. When the girl was two years old, the foster parents noticed that she had a vacant stare together with sudden hand movements, but no seizures. She was admitted to hospital and diagnosed with petit mal epilepsy.

On admission, the girl presented with microcephaly, craniosynostosis, hypertelorism, epicantic folds, depressed nasal bridge and wide nose, micrognathia, low set ears and a helix deformity of the right ear ***(Fig. 1)****. She also had a single pal-*

mar crease on both hands, clinodactily of the 2nd and 3rd finger of the hands and pes equinovarus congenitus of the left foot. She also presented with lack of coordination and an unsteady gait.

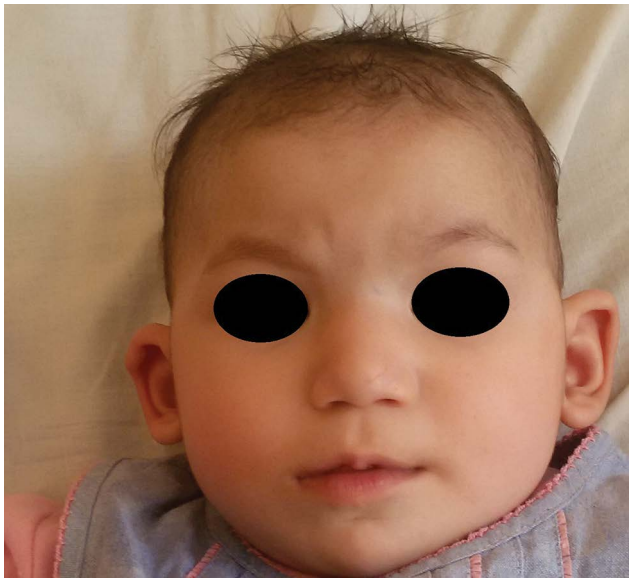

Figure 1. Phenotype of the patient presenting with dysmorphic features.

A brain MRI showed no abnormal findings. The computed tomography showed coronal and sagittal craniosynostosis. An abdominal ultrasound exam showed agenesis of the left kidney and a compensatory hypertrophy of the right one.

The girl was admitted several times to hospital because she underwent surgical correction of the craniosynostosis. There was no significant improvement in her general condition. She was hyperactive and had stereotypic movements. At the age of 4, she was not able to speak and communicated only with nonsensical speech sounds and had attention deficit.

Cytogenetic analysis of peripheral lymphocytes was performed using Giemsa staining. Informed consent was obtained from the foster parents prior to the genetic testing. A normal 46,XX karyotype was observed in all analyzed metaphase spreads.

Whole-exome sequencing (WES) with HiSeq4000 (Illumina) was performed in the Institute of Human Genetics, Goettingen as part of an on-going research project. No pathogenic or likely pathogenic mutations were identified, which could explain the phenotype of the patient. WES found a heterozygous splice-site variation c.3085-3C>G in intron 18 of the CTNND2 gene, but this is a variant of uncertain significance. Unfortunately, parental DNA was not available to further proof this finding.

Because of the dysmorphic syndrome with intellectual disability of unknown etiology the next genetic diagnostic step was applied. An array CGH was performed with oligonucleotide microchips 4×44K (CytoSure ISCA version 2, Oxford Gene Technology). As a result a changed number of copy number variation (CNV) was found – Arr[hg19] 16p11.2 (295500252_30240067×3). The patient was diagnosed with 16p11.2 duplication syndrome. There was a gain of approximately 739 kilobases at the 16p11.2 location ***(Fig. 2)****. The parents could not be tested in order to check if it was a de novo mutation.*

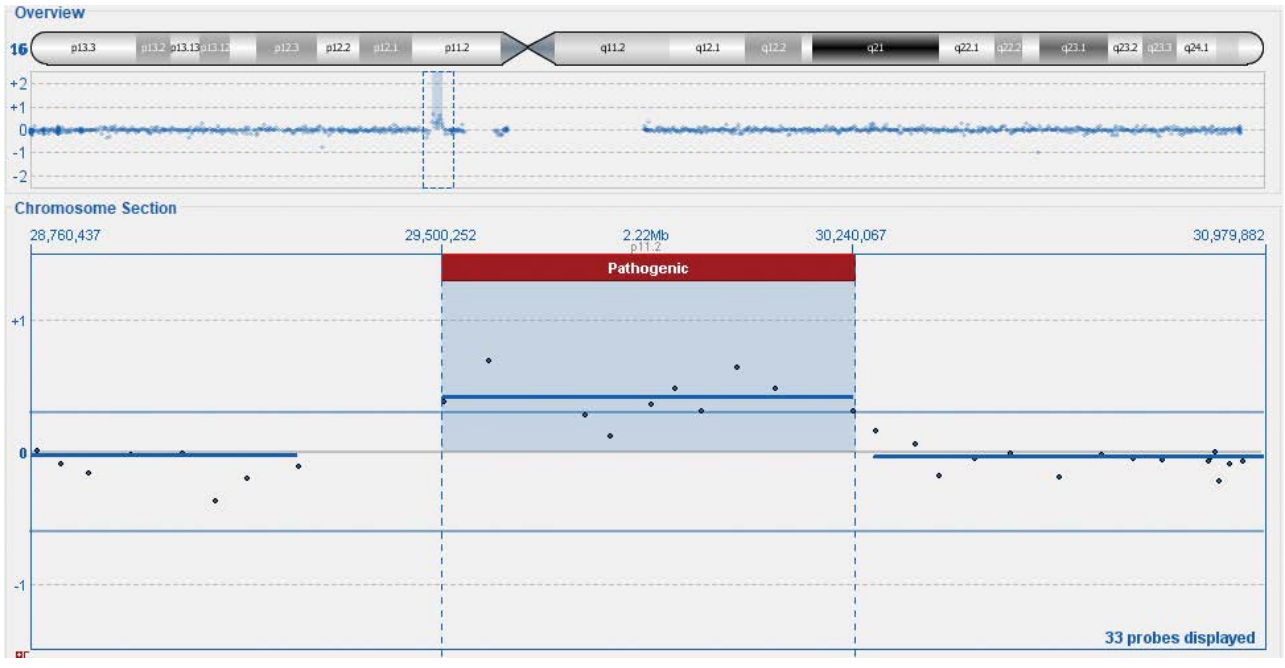

Figure 2. Array-CGH analysis showing the duplication located within the 16p11.2 region.

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DISCUSSION

16p11.2 duplication syndrome is associated with leading manifestation of intellectual disability and especially hyperactivity and speech delay, which was also observed in our case.[2] The intellectual disability, which is the leading symptom, could be due to an impaired transmission of Gamma aminobutyric acid in the synapses in animal models.[3] Also, there is an increased incidence of epilepsy and schizophrenia.[2]

However, there are no specific dysmorphic features for this genetic condition, but microcephaly, micrognathia and hypertelorism have been documented in other patients with this disorder.[4,5] Moreover, there could be also a deletion in this region and similar phenotype is observed, which makes the clinical diagnosis very hard to recognize.[6,7]

That is why in patients with leading symptoms of delayed mental development, psychiatric disorders no matter the absence of specific dysmorphic features the array-CGH should be a first method of choice.[8] However, in our case we started with WES as a part of an on-going research project for craniosynostosis.

CTNND2 gene has not been described as a cause for a genetic disorder, but it may be related to severe mental retardation in patients with 5p deletion.[9] Unfortunately, we were not able to test for de novo occurrence of this variant of yet uncertain significance as this child was adopted and we did not have access to parental DNA. Nevertheless, this might be a good candidate gene and an additional cause for intellectual disability.

The presented case of 16p11.2 duplication illustrates the need for routine array-CGH testing in patients with autistic behavior/attention deficit disorder because there is no evident phenotype of this condition. With the help of this analysis there could a major improvement in the diagnostic process of patients with delayed mental and motor development.

REFERENCES

1. D'Angelo D, Lebon S, Chen Q, et al. Defining the effect of the 16p11.2 duplication on cognition, behavior, and medical comorbidities. JAMA psychiatry 2016; 73(1):20–30.
2. Steinman KJ, Spence SJ, Ramocki MB, et al. Simons VIP Consortium. 16p11. 2 deletion and duplication: characterizing neurologic phenotypes in a large clinically ascertained cohort. Am J Med Genet A 2016; 170(11):2943–55.
3. Rein B, Tan T, Yang F, et al. Reversal of synaptic and behavioral deficits in a 16p11.2 duplication mouse model via restoration of the GABA synapse regulator Npas4. Mol Psychiatry 2020:1-3.
4. Filges I, Sparagana S, Sargent M, et al. Brain MRI abnormalities and spectrum of neurological and clinical findings in three patients with proximal 16p11.2 microduplication. Am J Med Genet A 2014; 164A(8):2003–12.
5. Shim YJ, Park SY, Jung N, et al. First Korean case of 16p11.2 duplication syndrome diagnosed by chromosomal microarray analysis. J Int Gen 2019; 1(1):10–3.
6. Avdjieva-Tzavella D, Hadjidekova S, Rukova B, et al. Detection of genomic imbalances by array-based comparative genomic hybridization in Bulgarian patients with autism spectrum disorders. Biotechnology & Biotechnological Equipment 2012; 26(6):3389–93.
7. Shinawi M, Liu P, Kang SH, et al. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet 2010; 47(5):332–41.
8. Peycheva V, Kamenarova K, Ivanova N, et al. Chromosomal microarray analysis of Bulgarian patients with epilepsy and intellectual disability. Gene 2018; 667:45–55.
9. Chen CP, Huang JP, Chern SR, et al. Prenatal diagnosis and molecular cytogenetic characterization of de novo distal 5p deletion and distal 22q duplication. Taiwan J Obstet Gynecol 2020; 59(1):140–5.

Синдром дупликации 16p11.2 – клинический случай

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Дата получения: 31 марта 2020 ♦ **Дата приемки:** 18 мая 2020 ♦ **Дата публикации:** 28 февраля 2021

Образец цитирования: Levkova M, Stoyanova M, Staneva R, Hachmeriyan M, Angelova L. 16p11.2 Duplication Syndrome – a case report. Folia Med (Plovdiv) 2021;63(1):138-41. doi: 10.3897/folmed.63.e52763.

Резюме

Синдром дупликации 16p11.2 – редкое заболевание, часто связанное с психическим урегулированием, синдромом дефицита внимания и гиперактивности и предрасположенностью к эпилепсии и шизофрении. Нет никаких специфических дисморфических особенностей этого генетического состояния, но могут присутствовать микроцефалия, микрогнатия и гипертелоризм. Мы сообщаем о случае синдрома дупликации 16p11.2, который имеет типичную клиническую картину – лёгкий лицевой дисморфизм, нарушение умственного развития и аутичное поведение. Было выполнено полное экзоматическое секвенирование, но патогенных или возможно патогенных мутаций обнаружено не было. Сравнительная геномная гибридизация микрочипов (массив CGH) позволила поставить диагноз синдрома дупликации 16p11.2, что показывает важность этого метода в диагностике детей с необъяснимыми умственными нарушениями.

Ключевые слова

дупликация 16p11.2, массив CGH, аутичное поведение, умственная отсталость