



Short communication

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Findings from ACGH in patient with psychomotor delay-case report

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Abstract

Initial testing of children with psychomotor delays considers karyotype analysis and metabolic tests. However, introduction of Array Comparative Genomic Hybridization (ACGH) has become the standard method of diagnostics worldwide. ACGH is a highly sensitive method which enables detection of unbalanced chromosomal aberrations and aneuploidies. In this case report, a patient is a sixteen year old girl born to unrelated parents with mild mental retardation and psychomotor delay, hyperacusis, epilepsy, silent nasal speech, clinodactyly of the V finger on left hand, as well as low set ears. Patient had a karyotype interpreted as normal using GTG band analysis. Array CGH was performed using Agilent SurePrint G3 custom CGH+SNP Microarray 8x60K (UCSC, hg19, NCBI Build 37, February,2009). Results were analyzed by CytoGenomics 3.0 Agilent software. Results of aCGH revealed clinically significant duplication of 17q25.1-q25.3 region with the size of ~7.96Mb. Within the duplicated region 217 genes are present, of which 36 are described as OMIM morbid. Duplications of similar size are described in DECIPHER date base in patients with psychomotor delay, hyperactivity and neoplasm of CNS. Besides duplication, a ~755kb clinically significant deletion was detected in the 17q25.3 region. Deletion involves 18 genes of which 2 are described as OMIM morbid: TBCD (MIM604649) and ZNF750 (MIM610226). Patient with similar deletion was described in DECIPHER date base with notable psychomotor delay. Based on these results FISH analysis is recommended for both parents in order to determine the possible carrier of inversion in the region of 17qter.

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Keywords

Array Comparative Genomic Hybridization, deletion, duplication

Introduction

Developmental delay (DD) and intellectual ability (ID) is characterized by a decrease in cognitive and adaptive features and affects 1-3% of the world population, with often omitted accurate diagnosis (Bartnik et al., 2014; Flint & Knight, 2003). In about 65-80% of cases the cause of the disease remains unknown. The diagnosis of DD/ID usually arises if an IQ is less than 70, which means that most of these patients are diagnosed at an early age (Uwineza et al., 2014). However, in the most cases the diagnosis is based on the motor, speech, cognitive and social stalled. When DD/ID are associated with multiple congenital anomalies, the most common cause of the disease are chromosomal aberrations (Bartnik et al., 2014). The etiology of the disease is heterogeneous and it can be caused by the genetic factors, as well as by environmental factors (Grayton et al., 2012).

Besides Mendelian DD/ID, one of the most common causes of these conditions are submicroscopic chromosomal rearrangements and copy-number variants (CNVS) (Regier et al., 2010). In the last few years' application of Array Comparative Genomic Hybridization (ACGH) significantly improved clinical diagnostics in patients with DD/ID, congenital anomalies, autism spectrum disorders, and dysmorphic features (Girirajan et al., 2012). Improvement in ACGH resolution enabled detection of CNVS ranging in size from megabases to few kilobases (Rodriguez-Revenge et al., 2007). The detection rate of clinically relevant CNVS varies between 15% and 18% (Miller et al., 2010).

Material and methods

In this case report, a patient is a sixteen year old girl born to unrelated parents with mild mental retardation and psychomotor delay, hyperacusis, epilepsy, silent nasal speech, clinodactyly of the V finger on left hand, as well as low set ears. Prior to Array CGH analysis, a cytogenetic analysis was performed using a standard method of G-banding according to the International System for Human Cytogenetic Nomenclature (ISCN 2015) (Haffer et al., 2013). ACGH was performed at the Faculty of Medicine, Institute of

Human Genetics, Belgrade, Serbia. Isolation of genomic DNA was extracted from 5 mL of peripheral blood according to (Miller et al., 1988). Array CGH was performed using Agilent SurePrint G3 custom CGH+SNP Microarray 8x60K (UCSC, hg19, NCBI Build 37, February,2009), according to the manufacturer's instructions. This platform contains 60-mer oligonucleotide probes spanning the entire human genome with 41 Kb overall median probe spacing (33 Kb in Refseq genes). After hybridization results were analyzed by CytoGenomics 3.0 Agilent software.

Results and Discussion

Patient had a karyotype interpreted as normal using GTG band analysis. Results of ACGH revealed clinically significant duplication of 17q25.1-q25.3 region with the size of~7.96Mb. Within the duplicated region 217 genes are present, of which 36 are described as OMIM morbid. Besides duplication, a ~755kb clinically significant deletion was detected in the 17q25.3 region. Also, analysis revealed a few CNVS which are described as normal variations in the Database of Genomic Variants.

In the last several years ACGH has become a first tier clinical genetic test for patients with developmental delay/intellectual disability and multiple congenital anomalies. Compared to conventional karyotyping (550 bands resolution) which is able to detect chromosomal aberrations >5-10 Mb, ACGH has increased the diagnostic yield of 15-20%. For instance, a research on 54 patients, selected according to clinical criteria, molecular and cytogenetic data 26 patients (48%) were diagnosed with structural rearrangements, while in 15 patients (28%) CNVS were proved to be clinically relevant (Iourov et al., 2012). Also, research on a sample of 318 patients with a diagnosis of mental retardation and multiple congenital anomalies described the potential pathological CNVS in 52 patients (16.4%) in size of 0.25 to 15 Mb (Gijsber et al., 2009).

In our case report ACGH revealed clinically significant duplication of 17q25.1-q25.3 region with the size of~7.96Mb. Duplications of similar size are described in DECIPHER date base in patient 254723 with psychomotor delay, hyperactivity

and neoplasm of CNS, as well as in patient 255159 with psychomotor and speech delay. Also, the research of Chong et al. 2014 reported a similar duplication of 7.10 Mb of the 17q25.1-q25.3 region in a female patient with severe developmental delay, hypotonia and failure to thrive. Besides this duplication, a clinically relevant deletion was detected. Deletion of ~755kb involves 18 genes of which 2 are described as OMIM morbid. One of them is Tubulin-specific chaperone D (TBCD; MIM604649) which is related to encephalopathy, progressive, early-onset, with brain atrophy and thin corpus callosum (Miyake et al., 2016). The second gene within this deletion is Zinc finger protein 750 (ZNF750; MIM610226) which is thought to cause Seborrhea-like dermatitis with psoriasiform elements (Birnbaum et al., 2006). Also, a patient 278987 with the deletion of this region was described in DECIPHER data base with notable psychomotor delay.

Conclusion

This case report represents a preliminary results of our research which will include 24 patients with psychomotor delays, developmental delays, congenital anomalies and dysmorphic features which do not have a final diagnosis. The patient in this case report is a sixteen year old girl with mild mental retardation and psychomotor delay, hyperacusis, epilepsy, silent nasal speech, clinodactyly of the V finger on left hand, as well as low set ears. ACGH revealed clinically significant duplication of 17q25.1-q25.3 region with the size of ~7.96Mb as well as a ~755kb clinically significant deletion in the 17q25.3 region. Also, analysis revealed a few CNVs which are described as normal variations. Characterization of the chromosomal aberrations detected by ACGH will contribute to successful diagnosis, adequate genetic counseling as well as the usage of specific therapeutic procedures. Also, this is the first study in our population, and currently there is no database of normal copy number variations which are characteristic for each population.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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