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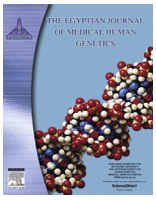

Case Report

The clinical, cytogenetics and molecular characterization of inverted duplication/deletion of chromosome 8p in a boy with mental and motor retardation: Genotype-phenotype correlation in a case report

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ABSTRACT

Background: Rearrangements that occur mainly through the non-allelic homologous recombination (NAHR) during maternal meiosis in short arms of chromosome 8 is relatively associated with various clinical spectrum.
Aim: The objective of this study was to report cytogenetics and molecular characterization of a mental and motor retarded boy with short arm of chromosome 8 rearrangements [invdupdel(8p)] in this current case report. Subjects and methods: We report an 11-year-old boy with scoliosis, intellectual disability, mental-motor retardation and characteristic facial features. Agenesis of corpus callosum was detected with brain Magnetic Resonance Imaging (MRI) analysis. Derivative chromosome 8 structure was identified after conventional cytogenetics – karyotype analysis, Multiplex Ligation-Dependent Probe Amplification (MLPA) and Microarray-based Comparative Genomic Hybridization (aCGH) techniques. Genotype-phenotype correlation in the current proband case will be discussed.
Results: Case was diagnosed as 46, XY, der (8), del (8) (p23.1) invdup (8) (p11.1-p23.1) by using advanced comparable techniques. Subtelomeric MLPA analysis showed deletion of FBXO25 gene which is located at 8p23.3 locus and FISH with subtelomeric probes for 8p shows also only deleted region. The microarray-CGH profilling showed 7,9 mb deletion for 8p23.1 and 31 mb duplication for 8p11.1 locuses.
Conclusion: Results from the current case emphasized that the cases with clinical manifestations of such disorders extremely need to be examined by combined comparable genetics techniques such as; karyotyping, FISH, MLPA and chromosomal microarray for the accurate phenotype – genotype correlation.

1. Introduction

The rearrangement of short arm of the chromosome 8 [Invdupdel, (8p)] is a well-described and uncommon chromosomal rearrangement, already known as the inverted duplication/deletion 8p syndrome, with an incidence rate of around 1 in 10,000–30,000 liveborn infants [1], and most of the cases are diagnosed in childhood period due to neurodevelopmental delay [2]. The clinical manifestations of this disorder include mental retardation, central nervous system (CNS) abnormalities including agenesis of corpus callosum, hydrocephalus, some degree of learning disability, hypotonia, orthopedic abnormalities, scoliosis/kyphosis, microphthalmia, congenital heart defects [3]; and some typical facial features including a high, rounded forehead, a pouting lower lip, a small lower jaw and large ears with an unusual shape [4]. In people with an inv dup del 8p, one chromosome 8 is normal, but there is an extra copy of the short arm of the other chromosome 8. In addition, the end of the short arm of the other chromosome is missing. The extra duplicated part runs in the opposite direction to normal and is therefore termed inverted. Barber et al. [5] have claimed that the size and the duplicated type of chromosome are not similar in all reported patients with inv dup/del 8p. With only few exceptions [6–8], there are no reported cases of normal intelligence associated with chromosome 8p deletion. There seems to be a relation between the size of the deleted region on chromosome 8, affected genes and the degree of intellectual disability [9]. It has been suggested that the critical region for producing this phenotype may lie between 8p21.3 and 8p23 because individuals with

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deletions in this region show the most severe consequences [10], while those with very distal deletions (e.g. 8p23 → 8pter) show fewer or milder features [9].

Here we aimed to present the genotype-phenotype correlation between rearranged chromosome 8p and mental - motor retardation in a boy with inverted duplication and deletion at short arm of this chromosome.

2. Case

Here we report an 11 years old boy with some distinctive facial appearance and mental motor retardation. Mother was 45 and father was 47 years old when the child was born and there was no consanguinity between the parents (Fig. 2). His mother has remarkable obstetric problems in proband's pregnancy, as polyhydramniosis, high level of alpha fetoprotein concentration at maternal blood indicating high risk for spina bifida, but parents didn't accept amniocentesis.

Our case has short stature (120 cm, <3p) with a history of scoliosis, intellectual disability (he can talk only few words, can't read or write), mental-motor retardation (started to walk at the age of 8 years), epilepsy and some characteristics of facial features such as; narrow forehead, bushy eyebrows, hypertelorism, large ears, hypoplastic alae nasi, short philtrum, thin upper lip and hypotonia. Cardiac evaluation and auscultation were normal and family didn't accept pediatric cardiology consultation because of they have to travel to another city. He has also some intestinal symptoms such as; obstipation and constipation. Cranial MRI showed Dandy Walker variant with increased dimensions of the cisterna magna in left side; cystic appearance of posterior fossa; enlargement in 3th and 4th ventricles and agenesis of corpus callosum.

The GTG banded metaphases, FISH, Multiplex Ligation-Dependent Probe Amplification (MLPA) and Array-CGH techniques were used for the chromosomal identification and genotype-phenotype correlation in the current proband [11,12]. Informed written consent was obtained from the parent of the proband. All experiments have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Heparinized peripheral blood cell cultures were used for chromosomal study and FISH (Cytocell, UK); peripheral blood-EDTA sample was used for molecular techniques for the current case. P036 Subtelomeric probemix (MRC-Holland, Amsterdam) was used for MLPA and the data was analysed with Coffalyser software. Agilent sureprint G3 HUMAN CGH 60 k Mikroarray platform and Agilent cytogenomics 4.0.2.21 software (Agilent Technologies, Santa Clara, CA, USA) were used for molecular karyotyping by using total genomic DNA from the proband [12,13].

3. Results and discussion

Trypsin GTG- banded metaphases showed duplication in short arm of the chromosome 8 and case was diagnosed as 46, X,der(8),del(8)(p23.1)invdup(8)(p11.1–p23.1) after conventional lymphocyte cell culture (Fig. 1), Pedigree diagram shows a few affected individuals with intellectual disability in the presented large family, other case was invited but was not examined yet (Fig. 2).

Heterozygous deletion in FBX025 gene was detected after MLPA peak profile (Fig. 3B), and Coffalyser software analyses in the proband (Fig. 3C); whereas, all MLPA peak profiles and Cofallyser profiles were in normal status in healthy control (Fig. 3A).

The Array-CGH profile showed 7,9 mb deletion in 8p23.1 that is encompassing the FBX025, DLGAP2, CLN8, ARHGEF10, and MYC genes, in addition to 31 mb duplication for 8p11.1 that encompass the KJAA1456, DLC1, SGCZ, TUSC3, MSR1 and FGF genes in the current case reported (Fig. 4, circles). Breakpoints were detected between (191,530–8,130,689) × 1 in 8p23.1 and between (12,467,484–43,529,733) × 3 bases in 8p11.1.

In this case, we present an 11-year-old boy with invdupdel[8p] syndrome complicated with central nervous system (CNS) abnormalities, and characteristic facial features. Various chromosomal rearrangements are associated with the distal 8p region. Among them are invdup(8p), [13], del(8p22) [14]; and del(8)(pter) [3]. The cardinal phenotypic features of the invdup(8p) are brain malformations, severe mental retardation with specific involvement of speech, and minor facial dysmorphisms [15]. A similar phenotype associated with invdupdel(8p) has been observed among individuals with a partial deletion near the telomere of chromosome 8p (del8p21), and on smaller segments (8p23.1 → pter). Digilio et al. [9], delineated the features for deletion 8p syndrome, citing growth

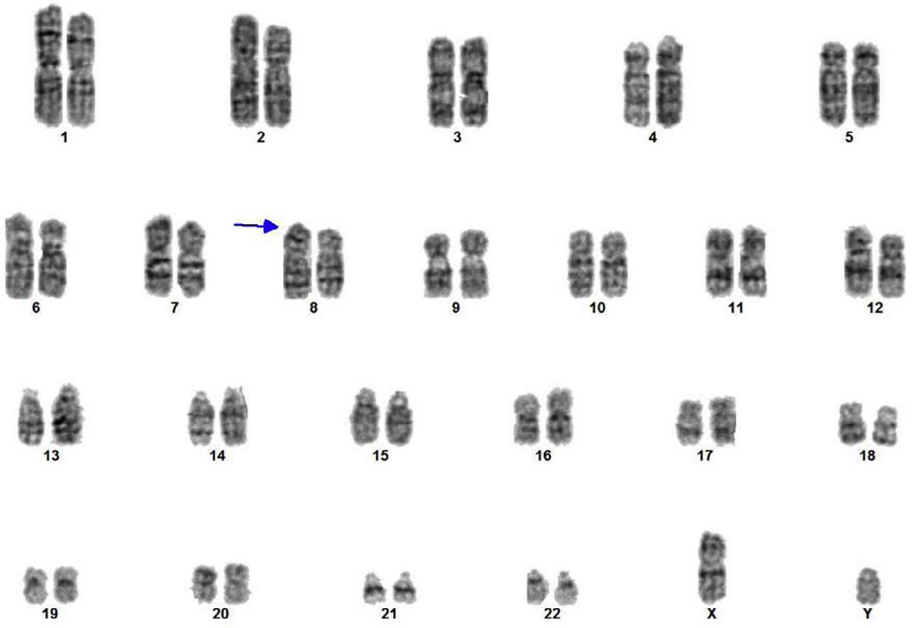

Fig. 1. The karyotype profile of the current case with chromosome 8p duplication status. Case was diagnosed as 46, XY, dup8(p23.3–23.1) cytogenetically.