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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

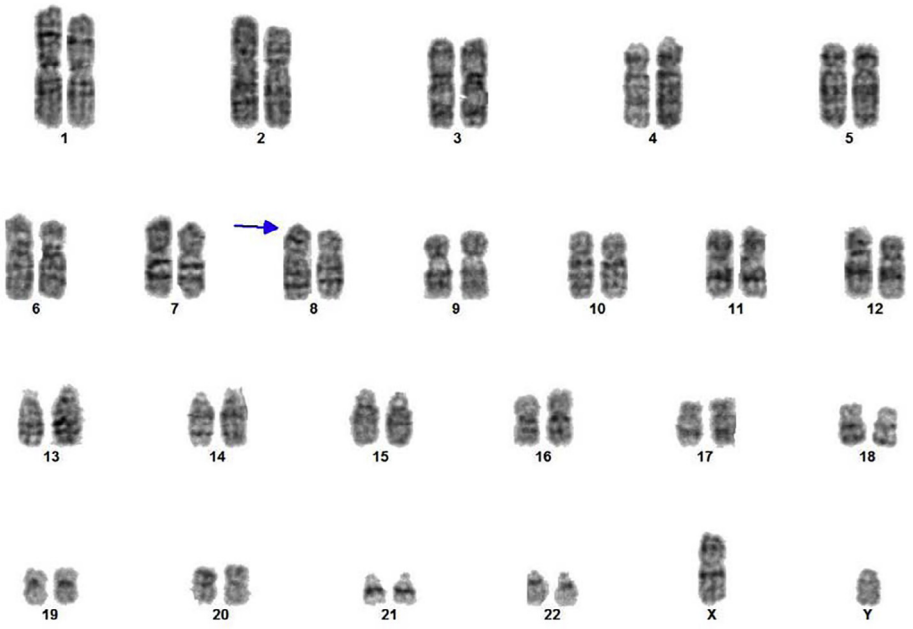

Fig. 1. The karyotype profile of the current case with chromosome 8p duplication status. Case was diagnosed as 46, XY, dup8(p23.3–23.1) cytogenetically.

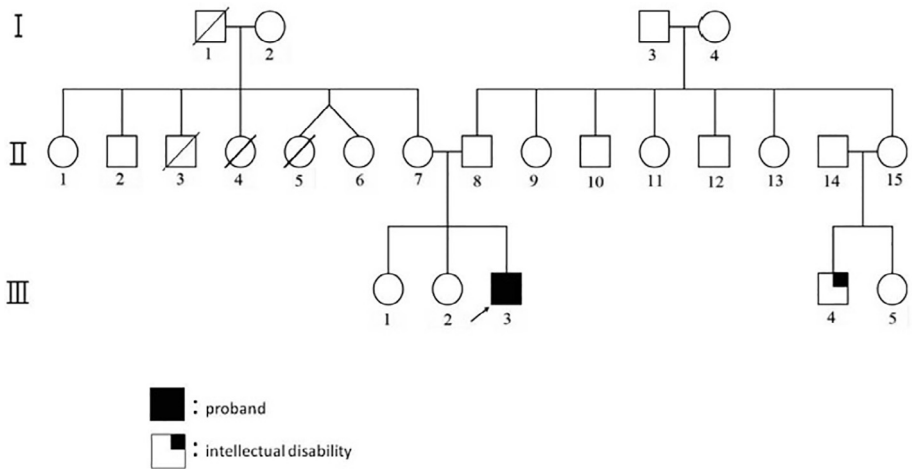

Fig. 2. Pedigree diagram for the presented case proband (arrow).

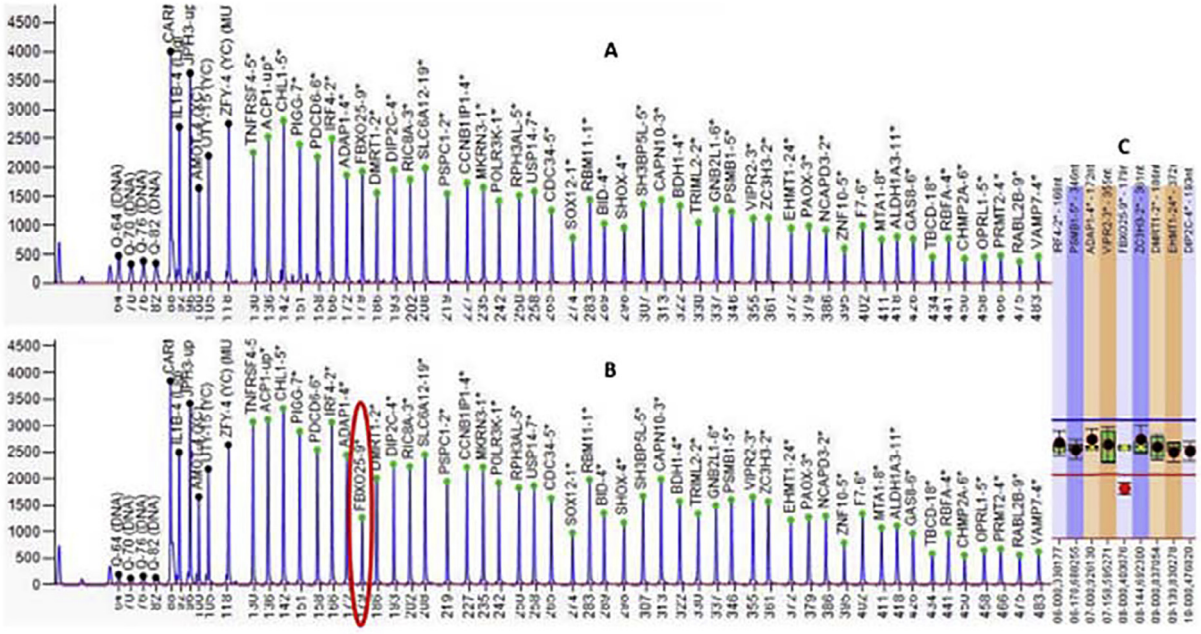

Fig. 3. MLPA P036 Subtelomeric kit peaks and Coffalyser diagram for the case (B and C) and a healthy control individual (A). Heterozygous deleted peak (B, red circle) and Coffalyser profile was detected for the target FBX025 gene in proband (C).

impairment, craniofacial anomalies, congenital heart defects, genital anomalies, and varying degrees of intellectual disabilities, characteristics found in the invdupdel(8p) phenotype.

The facial traits of children with inv dup 8p strongly resemble those of patients with mosaic trisomy 8 syndrome, especially at a young age. However, psychomotor retardation in patients with inv dup 8p is severe-to profound, whereas moderate retardation is the rule in mosaic trisomy 8 syndrome [4]. Molecular analysis of both 8p duplications and 8p interstitial deletions showed that all cases shared similar chromosomal breakpoints. This finding led to the hypothesis that these rearrangements were caused by ectopic recombination at misaligned duplicons [16]. Floridia et al. [11] found two types of rearrangements: A duplication from the centromere to D8S552, with a deletion from D8S349 to the telomere; second, a duplication from 8p11.2 or 8p21 to D8S552, with a deletion from D8S349 to the telomere. They categorized these two types, respectively, as dicentric inverted duplication (dicinvdup(8p)) and inverted duplication (inv dup(8p)). They hypothesised that the causes of inv dup(8p) rearrangement might also account for some of the 8p deletions. The detection of both the inv dup(8p) and the large terminal deleted chromosome del(8p) in their patient led them to assume that this 8p− was the complement of the 8p+ derived after breakage of an intermediate dicentric chromosome at anaphase I. Contrary to this assumption, they discovered that the del (8) contains sequences which are duplicated on the inv dup(8p) [17]. Rooms et al. [18], argued From their analysis of subtelomeric rearrangements, that no single mechanism seemed to account for these breakpoints, but that diverse molecular processes may produce these outcomes. Other researchers have observed that causes for the high proportion of intellectual disability in subtelomeric regions may be due to gene-rich loci residing at the telomeres, concurrent with higher than expected occurrences

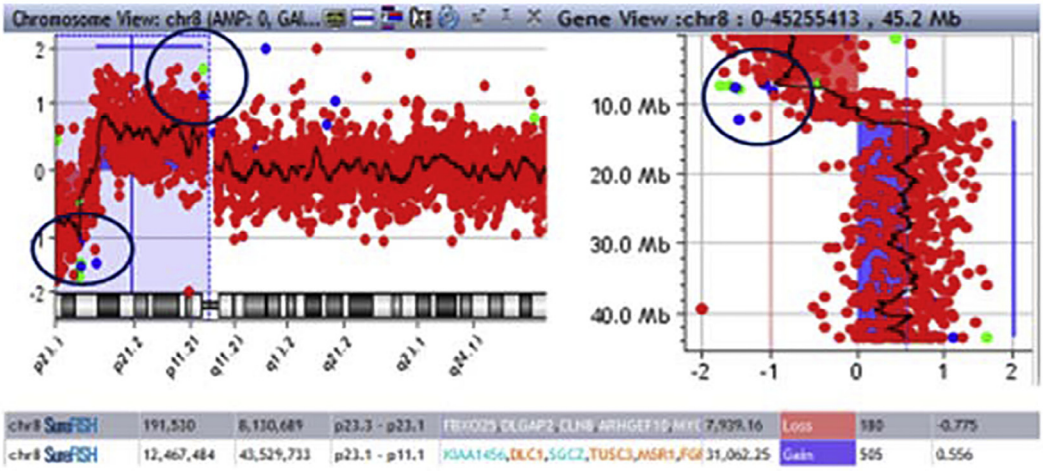

Fig. 4. 60 k microarray-CGH profile for inverted duplication/deletion of the chromosome 8p in the current case. An interstitial 31 kb duplication in p23.1–p11.1 that encompass KJAAI 456, DLC1, SGCZ, TUSC3, MSR1 AND FGF genes (black arrow) and 7.9 kb deletion in p23.3–p23.1 locus that encompassing FBX025, DLGAP2, CLN8, ARHGEF10 and MYC genes were detected in the current mentally retarded boy (blue circles).

of chromosomal rearrangements [19]. Giglio et al. [20] showed the presence of olfactory gene clusters (OR clusters) at the sites where the interstitial 8p deletions occur. Whereas these interstitial deletions could thus be explained by misalignments of the OR clusters during meiosis, they also presented an elegant explanation for the origin of the 8p duplications. An inversion polymorphism between these OR clusters, present in 20% of the population, abrogates correct pairing between the OR clusters which causes susceptibility for an intrachromosomal crossover between the OR repeats. Ectopic recombination at these sites can lead to a dicentric intermediate which on breakage can lead to a duplicated chromosome 8p, the inv dup(8p). The complement of this breakage event speculated to be a terminal deleted chromosome del(8p) [20]. Published deletions involving chromosome 8p23.1 range from large terminal deletions, that are easily detectable by routine chromosome analysis to small interstitial deletions which are best identified using fluorescence in situ hybridization (FISH) or molecular techniques such as array comparative genomic hybridization (aCGH) [21].

In literature, about 50 cases of invdupdel[8p] have been reported in the postnatal period. The majority of these cases were diagnosed during childhood after identification of postnatal neurodevelopmental problems including speech delay, mental retardation, facial dysmorphism, and relatively mild CHD [1,21,22]. In addition to its previously identified clinical features, inversion duplication on the short arm of chromosome 8 was found to be associated with autism [23]. Ozgen et al. [24] cytogenetically examined 4 patients diagnosed with autism and found copy number variants in the invdupdel(8p) region 8p23.1 → p21.1. In their study, Fisch et al. [21] examined the molecular-genetic and cognitive-behavioral features of 2 male and 2 female children, aged 3–15 years, initially diagnosed cytogenetically with invdupdel (8p23). Of the 4 participants they tested using array CGH, 2 exhibited classic invdupdel(8p), the rearrangement in one participant was more complex than a "classical" invdupdel(8p). The break point for the deleted region from 8p22 → pter was the same for all 3 participants with the deletion, but was not associated with severity of cognitive deficit. On the other hand, the size of the duplicated region did correlate well with the degree of cognitive deficit. Sireteanu et al. [25] diagnosed invdupdel[8p] in a 5-year-old girl via conventional cytogenetic analysis followed by SNP Array (Human CytoSNP-12 v2.1 Bead Chip platform (Illumina Inc., San Diego, CA)). An additional material on chromosome 8 was identified by standard G-banding analyses. The authors proceeded with a SNP array and detected both a terminal deletion (8p23.3–8p23.1) and a duplication (8p23.1–8p11.1). Soler et al. [26] first reported prenatal diagnosis of inv dup(8p) with deletion of the distal 8p23 region and duplication of the remaining 8p in a fetus with clubfeet, clenched left hand, subcutaneous edema, and bilateral hydrocephalus. In addition, Chen et al. [27], reported molecular cytogenetic characterization of inv dup del(8p) in a fetus with ventriculomegaly, hypoplastic left heart, polyhydramnios, and intestinal obstruction. In their report, Akkurt et al. [2], present the first prenatal microarray diagnosis of invdupdel[8p] syndrome mimicking trisomy 18 due to similar sonographic features. Contrary to reported cases with invdupdel[8p] syndrome, their case had severe polyvalvular dysplasia and the infant deceased at day 12 of life.

Although karyotyping, FISH, MLPA and Array CGH could be used to detect chromosomal deletions and duplications; our case demonstrated that first two methods has some limitations (FISH and MLPA showed only deletions because of probe locations) and array CGH provided accurate diagnosis.

4. Conclusion

It is possible that only children with apparent delays or anomalies are being referred for cytogenetic analysis, while those with few or subtler effects remain undiagnosed and unreported in the literature. Array CGH technology would allow for the detection of microdeletions and micro-duplications, which will allow for the provision of proper counseling before and during pregnancy. CGH microarray technology can associate the molecular-genetic features invdupdel(8p) to its cognitive-behavioral phenotype, and be a systematic investigation of the cognitive-behavioral features associated with invdupdel(8p).

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