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Case Report

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A New Case of Microdeletion 5q11.2 with Segmental 5q Isodisomy and Review of the Literature

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Abstract

Deletions of the proximal regions of long arm of chromosome 5 are rare, till date only 10 case reports describing patients with del 5q11.2 are available. Segmental UPD are estimated about 0.6% in the random/general population. Recently Snjiders Blok et al. [1] describe a new microdeletion 5q11.2 syndrome. We report a new case of microdeletion 5q11.1-q11.2 with associated segmental isodisomy 5q11.2-qter, patient presents psychomotor retardation, autism spectrum disorder, patent foramen ovale and speech delay and this case is compared with others reported cases from the literature to contribute for the better understanding of 5q11.2 microdeletion syndrome.

Keywords

Microdeletion 5q11.1-q11.2; Segmental UPD; Autism spectrum disorder; SNP-array

Abbreviations: UPD: Uniparental Disomy; ROHs: Regions of homozygosity; SNPs: Single Nucleotide Polymorphisms; CGH: Comparative Genomic Hybridization; CNV: Copy Number Variation; PFO: Patent Foramen Ovale; PHA: Phytohemagglutinin; BAFs: B Allele Frequencies

Introduction

Uniparental disomy is a genetic condition where offspring receives two chromosomal homologues from single parent. If UPD is present on a segment, interstitial or telomere, of the homologues, the condition is referred to as a segmental UPD, and if the homologues are identical (copies of a single homologue from one of the parents), the condition is known as isodisomy. Segmental UPD is estimated to effect 0.6% of the population [2].

With the introduction of new technologies using oligo-SNP studies, regions of homozygosity (ROHs) which affects all chromosomes are being found more frequently [2]. Deletions of the segment 5q11.1-q11.2 have rarely been reported and most reported cases of deletion affect the long arm of chromosome 5 involving different regions i.e. 5q11.2, 5q12.1, 5q12.3 e 5q13.2.

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Recently Snjiders Blok et al. [1] describe a new microdeletion 5q11.2 syndrome. We report an additional case with microdeletion 5q11.1-q11.2 with associated segmental isodisomy 5q11.2-qter presenting psychomotor retardation, autism spectrum disorder, patent foramen ovale (PFO) and speech delay.

This case is compared with others reported cases from the literature the segment of which is only partially superimposed (because it is broader) than the one we found to contribute for the better understanding of 5q11.2 microdeletion syndrome.

Case Presentation

We present the case of a 2-year-old male patient, the first conceived by healthy non- consanguineous parents who was born on the 36th week of gestation as a result of artificially-induced childbirth due to reduced fetal growth. During 20th week hemivertebra was detected. Birth weight was 2190g (3°-10° centile), length 45.3 cm (10°-25° centile), head circumference 31cm. Apgar score was 7-9 and 10, during the neonatal period no distinguishing features were noted and reported. Height-weight development was 3°-10° percentile. He was able to stay seated at 10 months, walk without assistance at 16 months and at about 1 year able to pronounce monosyllables. At 20 months the child was referred to our Pediatric Hospital for evaluation and diagnostic advice for cognitive retardation, autism, scoliosis, patent foramen ovale and speech delay. Physical examination showed weight 10.2 kg (3°-10° centile), height 81 cm (3°-10° centile), occipito-frontal circumference 46.5 cm (3°). No seizures were reported even during episodes of high fever, dental growth was normal. There was no presence of cutaneous marks, abdominal ultrasound was normal. No dysmorphisms were observed. The ecocardiograph showed patent foramen ovale, EEG was normal.

Patient received Autism Spectrum Disorder diagnosis based on clinical observation and according to DSM-V criteria [3]. Diagnosis was confirmed by the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2) [4] supervised by experienced clinicians trained for research reliability. Furthermore, he was operated for unilateral inguinal hernia.

Methods and Results

Conventional cytogenetic analysis

Peripheral blood lymphocytes of patient were cultured with phytohemagglutinin (PHA) and cells were harvested according standard cytogenetic techniques. Karyotype appeared normal from the analysis in metaphase chromosomes QFQ banded by standard methods (450 band stage ISCN, 2016).

SNP-array analysis

Genomic DNA was purified from peripheral-blood samples. SNP array analysis was performed using the Human Omni Express Exome-8 Bead Chip (Illumina Inc., San Diego, CA) containing 960, 919 loci derived from phases I, II and III of the International HapMap project. The array includes over 274,000 functional exonic markers, delivering unparalleled coverage of putative functional exonic variant selected from 12,000 individual exome and whole-genome sequences.

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A total of 200 ng of gDNA (50 ng/µl) was processed according to Illumina's Infinium HD Assay Super protocol. Normalization of raw image intensity data, genotype clustering and individual sample genotype calls were performed using Illumina's Genome Studio software v2011.1 (cnv partition 3.2.0). The CNVs were mapped to the human reference genome hg19 and annotated with UCSC RefGene. Allele detection and genotype calling were performed with Genome Studio software, B allele frequencies (BAFs) and log *R* ratios were exported as text files for PennCNV analysis.

Analysis conducted with SNP-array (Figure 1) detected a submicroscopic 5q11.1-q11.2 deletion (49,457,282-53,282,649) of approximately 3.8 Mb in size: arr[hg19] 5p11q11.2(46,399,093x2,49,457,282-53,282,649x1,53,282,979x2).

Moreover, an extensive homozygosity region of 127 Mb was detected (53,282,979-180,693,127) in chromosome 5q11.2-qter, leading to the suspicion of segmental UPD.

It was only possible to analyze and carry-out a comparison between the patient's and the mother's genotype, as the father was not present. This lead us to the hypothesis that the patient possesses a paternal UPD of the 5q11.2-qter segment as the deletion was present on the maternal chromosome (Tables 1 and 2).

In order to understand these results we presume that this rearrangement may be explained by a monosomy rescue mechanism of the long arm of a chromosome 5. Specifically, two different mechanisms are possible or delete the long arm of chromosome 5 in the maternal oocyte and subsequent rescue of the missed arm in the zygote using the paternal chromosome 5 as a mold, or instead deletion of the long arm of a maternal chromosome 5 in the early development zygotic stages and subsequently the rescue of the deleted arm using paternal chromosome 5 as a mold. In both hypotheses, a deletion of q11.12 segment of the maternal chromosome 5 is observed because the chromosome rescue is not completely successful.

Discussion

Deletions of the proximal regions of long arm of chromosome 5 are rare. The regions that are mostly involved in these aberrations are: q11.2, q12.1, q12.3, q13.2 [1,5-11].

Reports describing patients with del 5q11.2 consist of 10 cases [1,5,6,8-10] of which 5 have deletions of extended segments that also involve part of region q12.1 and a further (q12.3 Jalliard 3 case, q 13.2 a Jalliard 4 case), 6 cases involve part of region q11.1(of which Jalliard case 3 extends from q11 to q12.3) Three cases involve the region q12.3 (Figure 2) [7,8,11].

In 2010 De Jong et al. [6] reported a case of del 5q11.2 (3.6Mb) where they tried to define the phenotype (cardiovascular anomalies and developmental delay) of the deletion by comparing it with the first case reported by Prescott [5]. Later Snjiders Blok et al. [1] defined microdeletion syndrome 5q11.2 by analyzing four additional cases and defining the short overlap region (SRO) to 2.0 Mb and emphasizing that the phenotype of deletion 5q11.2 resembles that of deletion 22q11.2 and also to that of CHARGE syndrome. A recent report by Fontana et al. (2016) reports a case of extended deletion (8.6 Mb) in band 5q11.2 and 5q12.1 associated with a developmental delay and dismorphysms.

The case we report with del 5q11.1-11.2 has cardiophaty, scoliosis and autistic spectrum disorders (Table 3), the deletion of 3.8Mb is among the smallest reported, comparable to that reported in the De Jong'case [6], but as reported by Fontana [10], no correlation was found between the size of deletion and the severity of the phenotype, presumably dependent on the genes involved. From the comparison with the other cases reported (Table 3), we see that our case present a joint segment in common with Snjiders Block case 1, 2, 3, Prescott case, De Jong case, 3rd case of Jallard and the case of Peeters which are much more extensive. By comparing the clinical signs of these

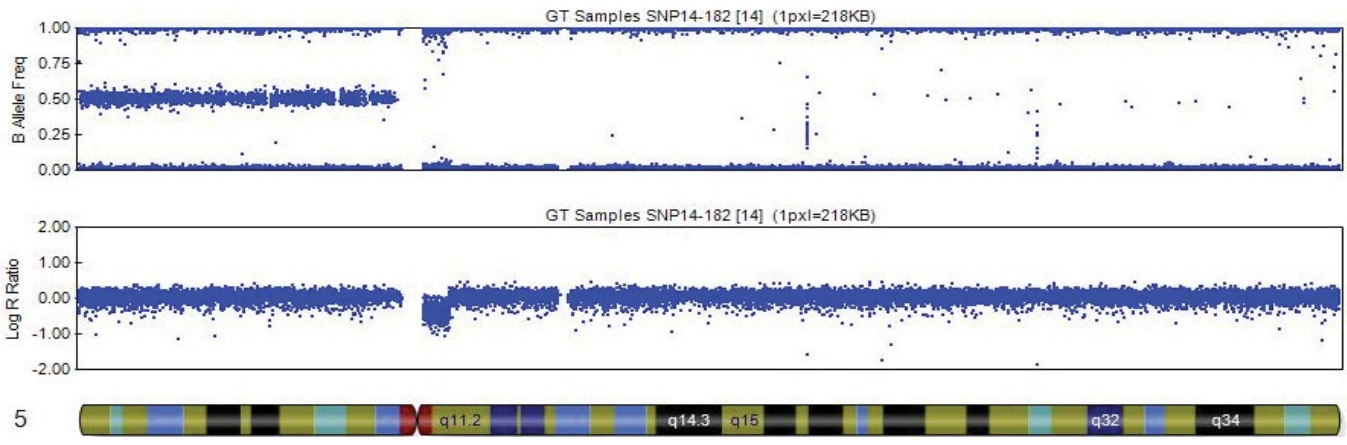

Figure 1: Analysis SNP-array (platform Illumina, Human Omni Express Exome and software GenomeStudio) of the reported case.

Table 1: Genotype comparison son and mother of markers inside the deletion 5q11.1-q11.2 (49,457,282-53,282,649).

	Patient	Mother
rs1041414	AA	BB
rs10461515	AA	BB
rs16884728	AA	BB
exm22660	BB	AA
rs13170744	BB	AA

Table 2: Compare genotype son and mother of markers inside ROH in 5q11.2-qter (53,282,979-180,693,12).

	Patient	Mother
rs4865795	AA	BB
rs788514	AA	BB
rs10940351	AA	BB
rs255754	BB	AA
rs31226	BB	AA

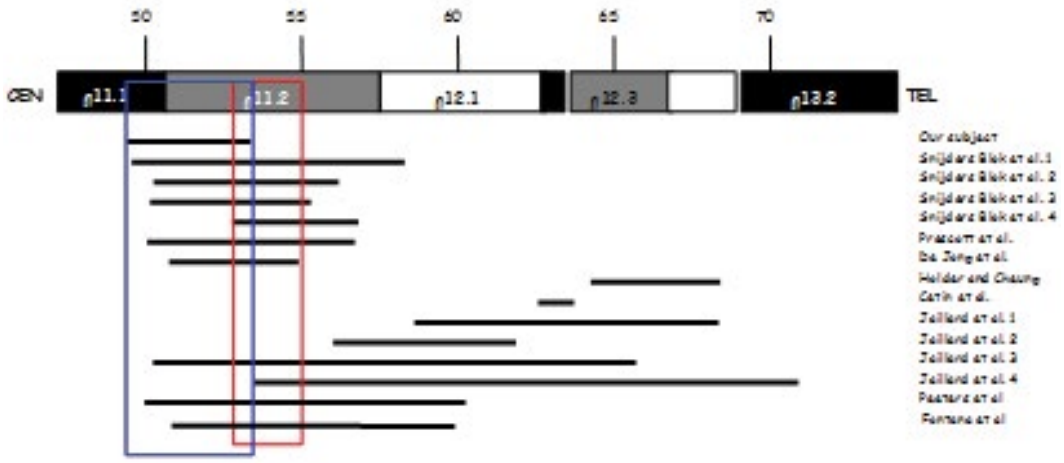

Figure 2: Overlapping regions.

Red: Snijders Blok 2014, Blue: Reported case and other cases

Table 3: Clinical and molecular comparison of all cases.

Case	Seizures	Irsutism Hypertrichosis	Strabismus	Developmental Delay	Atresia Choane	Cardiovascular anomalies	Growth Retardation	Dysmor physms	Autistic Behavior	Scoliosis	Behavioral Problems	Visual impairment	Size
Our case	-	-	-	+	-	+	-	-	+	+		-	3,8 Mb
Snijders B et al.1	-	+	+	+	+	-	+	+	+	-	+	+	8,6 Mb
Snijders B et al.2	-	+	-	+	-	-	+	+		-	+	-	5,8 Mb
Snijders B et al.3	-	-	-	+	+	-	-	+	+	-	+		5 Mb
Snijders B et al.4	+	-	-	+	-	-	-	+	NR	-	+		3,9 Mb
Prescott et al.	+	-	-	+	-	+	+	+	NR	-	+		6,5 Mb
De Jong et al.	NR	-	-	NR	-	+	NR	+	NR	-	NR		4 3,6 Mb
Holder and Cheung	-	-	-	+	-	-	+	+	NR	-	+	-	4,1 Mb
Cetin et al.	+	-	-	+	-	-	3-10 centile?	+	NR	-	NR	-	0,9 Mb
Jaillard et al.1	+	+	+	+	-	+	+	+	NR	-	NR	+	10,6 Mb
Jaillard et al.2	-	-	+	+	-	NR	-	+	NR	-	+	+	5,8 Mb
Jaillard et al.3	-	+	+	+	-	-	+	+	NR	-	NR	+	16,1 Mb
Jaillard et al.4	+	-	+	+	-	+	+	+	NR	-	NR	-	17,3 Mb
Fontana et al	-	-	-	+	-	-	+	+	NR	-	-	-	8,7 Mb
Peeters et al.	NR	-	NR	+		-	-	+	+	-	NR	NR	*8 Mb

cases it is noted that none of these presents seizures except that of Prescott's which is having a much larger segment and the fourth case of Sniders Block. All cases include developmental delay and three autistic behaviour (Snjiders 1 and 3 and the Peeters case) in addition to ours. It is difficult to correlate these features with the deletion [1,5-8].

Moreover, from the point of view of molecular analysis only partial overlapping is evident, in fact we tried to define the overlapping region of these cases, the overlap is only partially in common with the region highlighted by Sniders Block et al. [1] as shown in Figure 2.

The comparison of all these cases was carried out in order to further define the critical region of microdeletion 5q11.2 by evaluating the significance of the genes involved and their possible implication on autism.

The cardinal gene DHX29, that encodes an ATP dependent RNA helicase involved in RNA translation and is associated with CHD7 that is related to Charge syndrome, is not involved in the deleted segment of our case.

In fact in common there is only NDUFS4 whose heterozygous mutations can lead to Leigh syndrome, but our case does not show

homozygosity, but in the deleted area MIR851 can be found, which is involved in the post transcriptional gene expression and regulation. It should also be considered that the array analysis on patients reported in the literature has been carried out with a-CGH technology that does not highlight the presence of ROH or IUPD that may be responsible for the different phenotypes and could alter the phenotype due to deletion alone.

Certainly it is not possible to define the responsibility of isodisomy in the phenotype of our patient, in fact the presence of heterozygous mutations on the paternal chromosome may result in homozygosity in our patient in the analysis of the presence of pathogenetic variations.

Of course certainly, the collection of additional cases with SNP-array analysis methodology may contribute to the better definition of these phenotypes and also Exome analysis could lead to the identification of mutated genes on the 5q region responsible for the phenotype.

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