A New 3p14.2 Microdeletion in a Patient with Intellectual Disability and Language Impairment: Case Report and Review of the Literature

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Abstract

Interstitial deletions of chromosome 3p are rare, and specific genotype-phenotype correlations cannot always be assessed. We report the case of a 3p14.2 proximal microdeletion in a 60-year-old female patient with mild intellectual disability, severe speech delay, and mild dysmorphism. An array-CGH analysis detected a 500-kb deletion in the 3p14.2 region, including *FEZF2*, *CADPS*, and *PTPRG*. *FEZF2* and *CADPS* are known to network within the neurodevelopmental pathways. It is possible that their rearrangements lead to the phenotypic features observed in the patient, and therefore, they can be considered candidate genes responsible for such abnormalities.

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Cases of 3p proximal deletions are rarely reported in the literature. The described rearrangements vary in size, overlapping on a wide region, starting from 3p12.1 and ending at 3p14.3. The subregions involved in these rearrangements contain several candidate genes responsible

for common features such as intellectual disability (ID), neurocognitive development delay, and dysmorphisms. There are also other candidate genes responsible for more specific disorders such as autism or behavioral spectrum disorders, epilepsy, malformations affecting the brain, limbs etc., and for other abnormalities such as hypotonia. Some authors focused on the deletions of centromeric sequences, i.e., 3p14.2p14.1 [Kogame and Kudo, 1979; Neri et al., 1984; Lalli et al., 2007; Schwarzbraun et al., 2007; Morales et al., 2009; Pariani et al., 2009; Carr et al., 2010; Hamdan et al., 2010; Horn et al., 2010; Tuțulan-Cunită et al., 2012; Palumbo et al., 2013]. Only a few reports describe the rearrangements involving 3p14 and mainly proximal subbands [Tao et al., 2011; Schwaibold et al., 2013; Okumura et al., 2014; de la Hoz et al., 2015].

In a recent paper, de la Hoz et al. [2015] described a patient with a 3p14 interstitial deletion of about 8 Mb and reviewed some overlapping deletions, suggesting a core region, on the basis of a common phenotype, able to produce the characteristic defects described in the 3p proximal interstitial deletion syndrome. This core region of about 2.3 Mb, approximately starting from the gene *FEZF2* (chr3:62,355,347–62,359,190, hg19) to the locus *ADAMTS9* (chr3:64,501,330–64,673,676, hg19) (<http://dgv.tcag.ca/dgv/app/home>), includes 19 genes, 6 of which

are considered responsible for the phenotype observed in their patients (*FEZF2*, *CADPS*, *SYNPR*, *ATNX7*, *PRICKLE2*, and *MAGI1*). However, the authors underlined that a clear genotype-phenotype correlation is still not fully established and that the description of new clinical cases of deletions, restricted either to a single or a few genes, could be of great importance for this purpose.

We report the case of a small 500-kb proximal interstitial deletion in the 3p14.2 region, containing only a few genes, in a 60-year-old female. The patient has severe speech delay, mild ID, and slight facial dysmorphism, but no other major malformations. Our case was compared to previously described patients with overlapping deletions that presented similar clinical features.

The phenotype is suggested to be related to haploinsufficiency of the *FEZF2*, *CADPS*, and *PTPRG* genes, supporting the hypothesis that a novel 3p14.2 core region in 3p proximal deletions is associated with neurodevelopmental disorders.

Fig. 1. Family pedigree. The patient is indicated by a black circle.

Case Report

The patient was a 60-year-old Italian woman. Her family history is unremarkable except for her mother's reported premature ovarian failure at 27 years of age (Fig. 1). Her parents are unrelated, and she is their only child, born at term by normal delivery after an uneventful pregnancy. Normal auxological parameters were present at birth: length 50 cm (25th centile), OFC 34 cm (25th centile), and weight 3,000 g (10–25th centile). Her physical development was normal during the neonatal period and infancy, and she had normal puberty. She presented with psychomotor developmental delay (sitting without support at 1 year) and severe speech delay with a limited number of words and very simple phrasing until she was about 9 years old. No neurological problems were detected and no motor deficits were present.

During her life, she did not suffer from severe health problems. She attended primary school until 13 years of age with special educational needs teachers and had difficulties with different simple employments (e.g., as a waitress and shop assistant). She was diagnosed as having mild ID. The patient had a healthy son. No miscarriages were reported. She suffered from premature ovarian failure at the age of 33.

Dysmorphology evaluation revealed a broad forehead, arched thick eyebrows, hypertelorism, wide bulbous nasal tip, short columella, a broad and large mouth with slightly downturned corners, thick lips, prominent chin, and brachydactyly of the hands (Fig. 2). There was a small disproportion between span and height.

Methods

Genetic Analysis

A conventional chromosomal analysis (400 bands) was performed on the patient. We carried out a molecular analysis of the *FMR1* gene by means of a PCR specific for the CGG trinucleotide repeat (Amplidex *FMR1* PCR kit, Asuragen).

Following, we performed array CGH using standard procedures on a 4x44K slide (Cytochip oligo ISCA, Bluegenome LTD) with a resolution of ~150–250 kb and the results were confirmed by FISH using probes RP11-32J15 (62,368,620–62,534,278) localized in 3p14.2 (Bluegenome). The data were analyzed by means of the software BlueFuse Multi (Bluegenome LTD).

Fig. 2. a, b Facial appearance of the patient.

Reference DNA was a normal human female genomic DNA. FISH analysis with the same specific probes used in the patient was performed on both her mother and her son, in order to confirm array-CGH results. A conventional chromosomal analysis was also performed on the patient's son.

Fig. 3. FISH with the specific probe RP11-32J15 which maps within the chromosome 3 deletion. The signal is absent in 1 of the 2 chromosomes (arrow).

Results

The karyotype was normal (46,XX). Molecular analysis of the *FMR1* gene also was normal. Array-CGH analysis revealed a 500-kb deletion in the 3p14.2 region of the patient (from position 62,145,855 to 62,648,232 bp; hg19), and this result was confirmed by FISH analysis (Fig. 3). The microdeletion was not found in the patient's mother nor son; this was confirmed by FISH.

It was only possible to test the patient's mother (the father had died), and her son had a normal karyotype (46,XY).

In the deleted region, there were 3 OMIM genes: a 3' part of *PTPRG* (OMIM 176886; <https://decipher.sanger.ac.uk/>), *FEZF2* (OMIM 607414), and a 5' part of *CADPS* (OMIM 604667) (Fig. 4) (UCSC Genome Browser on Human Feb. 2009 [GRCh37/hg19] Assembly). No additional pathological CNVs were identified.

Discussion

In recent years, submicroscopic deletions/duplications (less than 10 Mb) have been evidenced using array CGH in cases of ID, multiple congenital defects, and dys-

Fig. 4. The array-CGH profile of chromosome 3 showing the deletion. In the upper part, chromosome 3, generated by Cyto-Chip, is shown. The red bar shows the patient's deletion. The breakpoint of the 3p14.2 deletion is from position 62,145,855 to 62,648,232 bp. The size of the deletion is ~500 kb. In the lower part of the figure, the 3p14.2 deleted region and genes included as generated by the UCSC Genome Browser are shown. The *PTPRG*, *FEZF2*, and *CADPS* genes, partially or completely deleted, are indicated by red circles.

Fig. 5. Interactome network (STRING database). The red circles represent the gene network involved in the development of the nervous system. *FEZF2* interacts indirectly with *PTPRG* through *SEMA5A* and *CNTN4*, while *PTPRG* and *FEZF2* indirectly act very loosely with *CADPS*.

morphisms. The delineation of their size and breakpoints helps to understand the genotype-phenotype correlations of small genomic imbalances [Rauch et al., 2006].

Our patient, with moderate ID, severe speech delay, and mild dysmorphic features, shows a 500-kb deletion in the 3p14.2 region, spanning from position 62,145,855 to 62,648,232 and containing 3 OMIM genes: *FEZF2*, *CADPS* (partially), and *PTPRG*. *C3orf14* was also deleted. The respective codified proteins proved to be linked to brain development and function. The *FEZF2* gene (FEZ family zinc finger protein 2) encodes a transcriptional factor necessary for the specification of corticospinal neuron and connectivity [Yang et al., 2012; Wolf and Ryu, 2013]. The *CADPS* gene (calcium-dependent activator protein for secretion 1) encodes a neuroendocrine-specific cytosolic and peripheral membrane protein that is required for Ca^{2+} -regulated exocytosis of the secretory vesicle. This protein is expressed in fetal and adult brain as well as in neuroendocrine tissues, and it is an essential regulator of the synaptic and large core vesicles priming in mammalian neurons as well as in neuroendocrine cells [Brunk et al., 2009; Farina et al., 2015]. The *PTPRG* gene (protein tyrosine phosphatase, receptor type G) encodes

a protein that is a member of the protein tyrosine phosphatase (PTP) family. PTPs are signaling molecules that regulate many cellular processes, including cell growth, differentiation, mitotic cycle, and oncogenic transformation. *PTPRG* is frequently deleted in renal cell carcinoma and lung carcinoma; thus it is thought to be a candidate tumor suppressor gene [Lamprianou et al., 2006].

Considering the roles that these 3 genes play in central nervous system development, it is conceivable that their loss may be causative of the pathologic phenotype seen in our patient via haploinsufficiency. This is also supported by assessments with biostatistical analysis [Huang et al., 2010]. A possible interactome network of these 3 proteins is shown in Figure 5, based on a STRING database search (<https://string-db.org/>).

In order to substantiate a correlation between genotype and phenotype, we compared our deletion to those already reported in the literature for the same region and in the DECIPHER database (<https://decipher.sanger.ac.uk/>) [Tao et al., 2011; Schwaibold et al., 2013; Okumura et al., 2014; de la Hoz et al., 2015] (Table 1).

Our patient shares developmental delay, ID, typical mild facial dysmorphism, and language impairment with

Table 1. Summary of patients with overlapping 3p14.2 deletions characterized by array CGH in the same region reported in the literature and in the DECIPHER database

Patient	hg19 start-end deletion	Size	Inherited	<i>PTPRG</i> deletion	<i>FEZF2</i> deletion	<i>CADPS</i> deletion	Developmental delay/ID	Speech delay/impairment	Autism/behavioral anomalies	Facial dysmorphism/limb anomalies	Other features
Present case	62,145,855 – 62,648,232	500 kb	not maternal	+, partially	+	+, partially	+, mild	+/+, severe	–/–	+/–	POF
255918	62,749,576 – 63,021,934	272 kb	unknown	–	–	+	+	–/–	–/–	+/+	scrotal hypoplasia
Tao et al., 2011; pat 3	62,690,487 – 64,915,076	2.22 Mb	unknown	–	–	+	+, severe	–/–	+/–	–/–	epilepsy
282444	60,522,634 – 63,534,765	3.01 Mb	unknown	+	+	+	+, moderate	–/–	–/+	–/–	obesity
304622	62,197,343 – 66,026,643	3.83 Mb	unknown	+	+	+	+, severe	+/+	+/–	+/+	generalized hypotonia
Schwaibold et al., 2013; pat 3	59,443,171 – 64,162,112	4.76 Mb	de novo	+	+	+	+	+/+	+/–	+/+	brain anomalies in MRI
260004	59,813,606 – 65,296,648	5.48 Mb	unknown	+	+	+	+	+/+	–/–	+/+	–
Schwaibold et al., 2013; twins	58,224,794 – 64,571,699	6.55 Mb	de novo	+	+	+	+	+/+	+/–	+/+	severe feeding problems, small stature, hypoplasia of corpus callosum, hydrocephalus
291797	61,865,579 – 68,646,642	6.78 Mb	de novo	+, partially	+	+	+	+/+	–/–	–/–	abnormality of the ventricular septum, defect in the atrial septum
Okumura et al., 2014	60,472,496 – 67,385,119	6.88 Mb	de novo	+	+	+	+, severe	+/+	+/–	+/+	ventriculomegaly, intestinal malrotation
de La Hoz et al., 2015	60,461,316 – 68,515,453	8 Mb	de novo	+	+	+	+, severe	+/+	+	+/–	motor developmental delay

ID, intellectual disability; pat, patient; POF, premature ovarian failure.

all reported cases, but lacks other pathological characteristics such as hypotonia, obesity, autism, or epilepsy which are present in some other deletions.

The 3p14 deletion of our patient is relatively small compared to the majority of the reported cases in this chromosomal region (Fig. 6); only *FEZF2* and *CADPS* (partially) are deleted among the genes of the suggested core 3p14.2 region that is considered crucial for the signs and symptoms present in our patient. Haploinsufficiency of the 2 genes in the suspected critical zone [de La Hoz et al., 2015], alone or in conjunction with the partial loss of *PTPRG*, whose function is considered important for neurodevelopment, should be sufficient to result in the following characteristics of the 3p-deletion phenotype: developmental delay, ID, mild facial dysmorphisms, and language impairment. Our patient has no autistic features or epilepsy because these disorders could be due to the additional loss of other genes, such as *PRICKLE2* and *MAGII* [Okumura et al., 2014].

The premature ovarian failure present in our patient and her mother was probably due to genetic mutation(s) of other gene(s) in chromosomal loci different from the deleted one in 3p14.2.

Furthermore, considering the smaller size of the deletion involving only *CADPS*, reported in DECIPHER number 255918, it seems possible that this is sufficient to lead to ID and dysmorphisms, but other similar cases are required to confirm such observation. There is no reported case of a deletion *only* in the *FEZF2* gene with ID and/or other phenotypic features that could support its importance in pathogenicity. However, the importance of *FEZF2* for ID and developmental delay is shown in a recently described patient with a homozygous point mutation in the gene presenting with brain atrophy, suspected Dandy-Walker malformation, and microcephaly detected by cerebral MRI [Anazi et al., 2017]. Finally, the *PTPRG* tumor suppressor gene, which is outside of the suggested critical region [de la Hoz et al., 2015] and does

Fig. 6. Schematic representation of the 3p14.2 deletion identified in our patient and in previously described patients in the literature and in the DECIPHER database. The dotted lines contain the region in which the candidate genes are located and the overlapping deleted regions of the other cases.

not seem to be relevant in the determination of ID and dysmorphisms (with a few exceptions) [Kranz et al., 2016], is also partially involved in our deletion. In our case, there is no behavior alteration, even if the gene is considered a relevant predisposition factor for this [Cresant et al., 2017].

In conclusion, we believe that the 3p14 microdeletion identified in our patient leads to the observed phenotype due to the loss of at least 2 genes (*FEZF2* and *CADPS*) included in the region, already suspected to be responsible for neurological disorders. The deletion of these genes is sufficient to result in ID, speech delay, and mild dysmorphisms, but not autism or epilepsy.

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Statement of Ethics

The authors hereby declare to have no ethical conflicts to disclose. Written informed consent was obtained from the patient for the publication of this case report and all accompanying images.

Disclosure Statement

The authors declare to have no conflicting or competing interests to disclose.

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