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CASE REPORT

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Familiar del3p syndrome: The uncertainty of the prognosis. A case report

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Abstract

The 3p deletion syndrome is an unusual condition. The few cases described are mainly de novo. We described a familial case detected in a prenatal diagnosis. Three members of the family had the 3p26.3-p26.1 deletion; however, only the son presented clinical features.

KEYWORDS

3p deletion, array-comparative genomic hybridization, cytogenetic, fluorescence in situ hybridization

What is already known about this topic? What does this study add?

The 3p deletion syndrome is an unusual condition with a spectrum of anomalies caused by deletions of varying lengths in the 3p25-pter region. The few cases reported thus far are mainly de novo. The authors describe a 3p deletion detected in a prenatal diagnosis. Three members of the family had the 3p26.3-p26.1 deletion; however, only the son presented with mild intellectual disability. This case highlights the clinical variability of the syndrome.

1 | INTRODUCTION

The 3p deletion syndrome is an unusual condition with a spectrum of anomalies caused by deletions of varying lengths in the 3p25-pter region. The few cases reported thus far are mainly de novo. The aim of this case report is to present a familial 3p microdeletion with different clinical manifestations. Cytogenetic analysis was performed on a pregnant woman with a normal family history because of her advanced maternal age. The results revealed a karyotype from the mother with a deletion on the terminal short arm (p26) of chromosome 3. The mother carried this same imbalance. No ultrasound anomalies were detected; therefore, after genetic counseling, the couple decided to continue the pregnancy and a phenotypically normal child was born. Six years later, the couple's first child, now aged 11 years, was referred to genetic counseling for mild intellectual disability. Array-comparative genomic hybridization was requested for the family and revealed that the same 7.4 Mb segment, involving 18 genes in 3p26.3p26.1, was deleted in all three members of the family. This rare syndrome is reported mostly in de novo cases, with few familial cases being reported. Our case represents the clinical variability of the syndrome, drawing attention to the challenge in understanding the genotype-phenotype correlation of this microdeletion. The mother, son, and daughter had the same microdeletion; however, only the son presented with mild intellectual disability and phenotypic features. Every new case should be reported to

improve our understanding of the condition and assist in genetic counseling.

Imbalances in 3p telomeric sequences are responsible for two major disorders: 3p trisomy and 3p deletion syndromes.[1] The latter, also known as the monosomy 3p syndrome or partial monosomy 3p syndrome, is a rare genomic disorder, and the major breakpoints of different sizes are mapped in the 3p25-pter region.[2] The first case of 3p25 deletion was reported in 1978 by Verjaal and Nef[3]; since then, approximately 50 cases of 3p deletion have been reported.[4]

The distal deletion of chromosome 3p25-pter causes a wide range of phenotypical characteristics, from normal to severe, including microcephaly, low birthweight, hypotonia, intellectual disability, developmental delay, delayed bone maturation, kidney defects, and dysmorphic features such as ptosis, hypertelorism, and micrognathia.[2] Other features such as congenital heart defects, namely atrioventricular septal defect, may occur in approximately one-third of patients.[4] In addition, some clinical features show phenotypic similarities with other genetic diseases, making it difficult to accurately diagnose this syndrome in some cases.[1] The spectrum and severity of the disease phenotype appear to be correlated with the overall size of the deleted fragment; individuals with a large deletion exhibit severe malformations and intellectual disability. However, there is still no consensus about this correlation.[5] The distal region of 3p contains several genes that are involved in neurodevelopmental functions.[3] Cuoco et al (2011) described a patient with 3p deletion syndrome with a 1.5 Mb minimal terminal deletion, which includes the cereblon (*CRBN*) and contactin 4 (*CNTN4*) genes in chromosome 3.[6] The cell adhesion molecule L1-like (*CHL1*) gene, which maps at 3p26.3 distally to *CRBN* and *CNTN4*, has been proposed as a candidate gene for nonspecific intellectual disability because of its high expression in the brain.[1] Because there are few cases in the literature, it is important to continue to describe each new case to better understand this syndrome. The most appropriate genetic counseling can be provided by understanding the breakpoints and genes involved, as well as their functions. In this case study, the authors describe a 3p deletion detected in a prenatal diagnosis.

2 | CLINICAL CASE

A 40-year-old pregnant woman underwent amniocentesis because of her advanced maternal age. There was no family history of congenital anomalies or intellectual disability, and the couple already had a 5-year-old healthy son. Cytogenetic analysis revealed a karyotype from the mother with a deletion on the terminal short arm (p26) of chromosome 3 (Figure 1A). Fluorescence in situ hybridization was performed in metaphase cells with a *p*-arm subtelomeric sequence (D3S4559, Vysis), according to the manufacturer's recommendations (Figure 1B). Cytogenetic analysis of the parents revealed that the mother carried the same chromosomal imbalance. The karyotype of the father was normal. After genetic counseling and a prenatal ultrasound, the findings of which were unremarkable, the couple decided to continue the pregnancy. A phenotypically normal female child was born.

Six years later, the first child of the couple, now aged 11 years, was referred to genetic counseling for mild intellectual deficit. He also presented the following phenotypic characteristics: a narrow triangular face, hypertelorism, abnormal shaped and short ears with an overfolded helix, a small mouth with a short upper lip, overcrowded teeth, a narrow palate, a small nose with hypoplastic nares, and mild micrognathia. Array-comparative genomic hybridization (CytoScan 750K, Affymetrix, Santa Clara, CA, USA) was requested for the family (performed at CGC Genetics, Porto). The mother, son, and daughter had the 3p deletion. The array analysis revealed that the same 7.4 Mb deleted segment, involving 18 genes in 3p26.3p26.1 (Figure 1C), was present in all three members of the family. The deleted genes were as follows: *CHL1*, *CNTN6*, *CNTN4*, *CNTN4-AS2*, *IL5RA*, *TRNT1*, *CRBN*, *LRRM1*, *SETMAR*, *SUMF1*, *ITPR1*, *EGOT*, *LOCI00507582*, *BHLHE40*, *ARL8B*, *EDEM1*, *MIR4790*, and *IGRM7* (Figure 1C).

3 | DISCUSSION

Abnormalities of the distal portion of the short arm of chromosome 3 are rare genomic disorders and not yet fully understood.[5] The most well-characterized anomalies are the deletions; however, even these require further understanding. They can vary from small interstitial deletions to large terminal deletions of several megabases, with variable proximal breakpoints. This syndrome is described as having a recognizable phenotype,[7,8] with delayed development, dysmorphic features, and several congenital anomalies.[1] Only few patients have had mild or no phenotypic effects, and in the last case often associated with inherited deletions.[2] Few familial cases have been described so far[2,3,9,10]; however, most cases of 3p deletions occur *de novo*.[2]

In the present case, a 3p26.3-p26.1 inherited deletion was detected in a prenatal diagnosis. The mother has normal intelligence and faced no health problems throughout her life. The daughter, now 6 years old, also shows normal development. However, an 11-year-old son exhibited mild intellectual disability and other typical phenotypic features of the disease. Among the 18 genes found to be disrupted in this family, 2 can particularly explain the mild intellectual deficit in the son. The first is the *CHL1* gene, which is located at 3p26.3 and is highly expressed in the central and peripheral nervous systems; it plays an important role in the

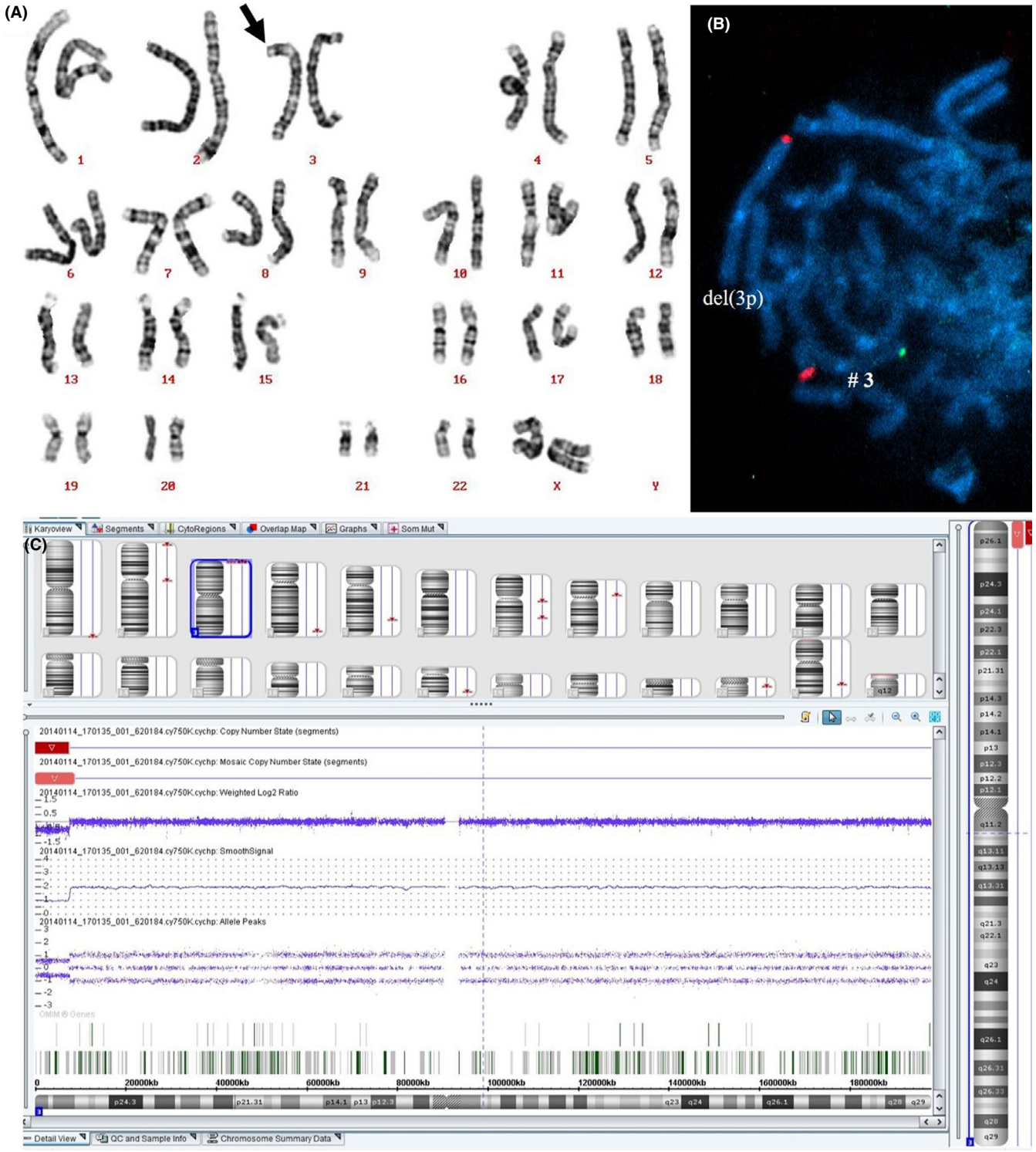

FIGURE 1 A, GTL-banded fetal karyotype (del3p marked). B, Partial metaphase with subtelomeric probe for chromosome 3 (green: p arm; red: q arm). C, Whole-genome array-comparative genomic hybridization on blood shows a 7.4 Mb deletion at 3p26.3-p26.1

development of the nervous system and synaptic plasticity[5] and has been described in individuals with learning and language difficulties.[2] The second is the *CNTN4* gene, which is also located at 3p26.3 and plays a role in the development of the nervous system and neural networks. Disrupting the *CNTN4* gene is known to cause developmental delay and learning disabilities, growth retardation, and dimorphisms in patients with 3p deletion syndrome.[7]

It is still not entirely clear why different members of the same family can be affected differently by the same chromosome deletion. In 2008, a review of the possible theories was published and reported that this difference could be because

of phenotypic variability, chromosomal nonpenetration, or genetic modification.[8] Barber (2008) proposed that chromosomal nonpenetrance or gene modification could occur if only one or some of the genes within a large imbalance were sensitive to dosage, so different phenotypic characteristics could be explained by factors that change the level of expression, time of expression or be able to compensate the reduced dosage of these genes.[8] Takagishi (2006) considering the Barber reference suggests that 3p deletion syndrome could be considered with variable penetrance like it was suggested for microdeletion syndromes 1q21.1 and 16p13.1.[11] Moreover, an apparently unaffected parent who carries the deletion could have subtle phenotypic features consistent with those in case of a deletion that would only become evident on further clinical evaluation.[6] Other possibilities that may explain phenotypic variability include differences in genetic background, epigenetic phenomena, expression or regulatory variations, and the unmasking of recessive variants (like mutations) on the other allele.[8]

This case demonstrates a family with a hereditary 3p26 deletion and represents the clinical variability of the syndrome, ranging from the complete absence of phenotypic changes to mild intellectual disability. All three affected members of the family, mother, son, and daughter, had the microdeletion; however, only the son presented with mild intellectual disability. Therefore, the transmission of hereditary deletions from phenotypically normal or mildly affected parents seems to be more common than previously thought. Thus, every new case should be reported to improve our understanding of the condition and assist in genetic counseling. The identification of the 3p deletion should be followed by a genetic study of the family, as well as a clinical evaluation of the family members, since some clinical manifestations can be only valued after the end of childhood.

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Published with written consent of the patient.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Dr Osvaldo Moutinho: followed the pregnancy. Dr Márcia Martins: accompanied the couple in genetic counseling consultation. Dr Rosário Pinto Leite: was responsible for the cytogenetics analysis. The remaining authors performed the laboratory techniques. All authors have revised and reviewed manuscript and have approved the final version.

ETHICS STATEMENT

Ethical committee approval was not required for this case report. Informed consent was obtained from the parents.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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