BJCR
Brazilian Journal of Case Reports

PCAA
Publicações Científicas de Acesso Aberto

Case Report

6q2.31q23.3 Interstitial Deletion: A Rare Prenatal Diagnosis

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Abstract: Interstitial deletions in the proximal region of the long arm of chromosome 6 are a rare finding, and only a few cases were published. The severity of the condition and the signs and symptoms depend on the size and location of the deletion and which genes are involved. These cases are mainly diagnosed with children or adults presenting various signs and symptoms, such as intellectual disability, developmental delay, growth retardation, cardiac anomalies, and dysmorphic features. Its diagnosis at a prenatal level is an even more rare finding. We present a case of a 29-year-old pregnant woman who was submitted to a chorionic villus biopsy due to a nuchal translucency above the 99th centile. The Array Comparative Genomic Hybridization revealed a pathogenic interstitial deletion of the chromosome 6 at 6q22.31q23.3, involving the *EYA4* gene.

Keywords: Chromosome 6; Array Comparative Genomic Hybridization; Chorionic Villi Biopsy.

Citation: Palmeira B, Torrão MM, Ferreira M. 6q2.31q23.3 Interstitial Deletion: A Rare Prenatal Diagnosis. Brazilian Journal of Case Reports. 2025 Jan-Dec;05(1):bjcr72.

https://doi.org/10.52600/2763-583X.bjcr.2025.5.1.bjcr72

Received: 31 January 2025
Accepted: 26 February 2025
Published: 4 February 2025

1. Introduction

Interstitial deletions on a chromosome are a rare finding, and in the case of chromosome 6 are divided into proximal (6q11q16), medial (6q15q25), and terminal (6q25qter) based on conventional cytogenetics [1-2]. In this type of deletion, there's loss of a segment of genetic material in a specific region of the chromosome, without any loss of its ends. The severity of the condition, and the signs and symptoms associated with it, depend on the size and location of the deletion and which genes are involved. Regarding chromosome 6, there have been described interstitial deletions for several regions of the long arm, with phenotypes such as intellectual disability, developmental delay, growth retardation, cardiac anomalies, dysmorphic features, upper limb malformations [3-4]. In this article, we will describe the case of an interstitial deletion on the long arm of the chromosome 6 diagnosed at the prenatal level, highlighting the importance of the early diagnosis of these conditions.

2. Case Report

A 29-year-old woman presented at our hospital to perform the routine first trimester scan, which revealed a nuchal translucency above the 99th centile (Figure 1). After counselling, a chorionic villus biopsy (CVB) was performed at 12 weeks + 4 days without complications. The Array Comparative Genomic Hybridization (aCGH) revealed a pathogenic interstitial deletion of the chromosome 6 at 6q22.31q23.3, involving the *EYA4* gene, as is shown in Figure 2. The follow up scan after the CVB, at 14 weeks + 3 days, demonstrated a reduced volume of amniotic fluid, evidence of retrognathism, and a fetal growth below the expected (Figure 3). After discussing the results with the medical team, including the Geneticist, the couple requested for medical termination of the pregnancy, which was accepted by the ethics committee.

Figure 1. First trimester ultrasound, showing a nuchal translucency above the 99th centile.

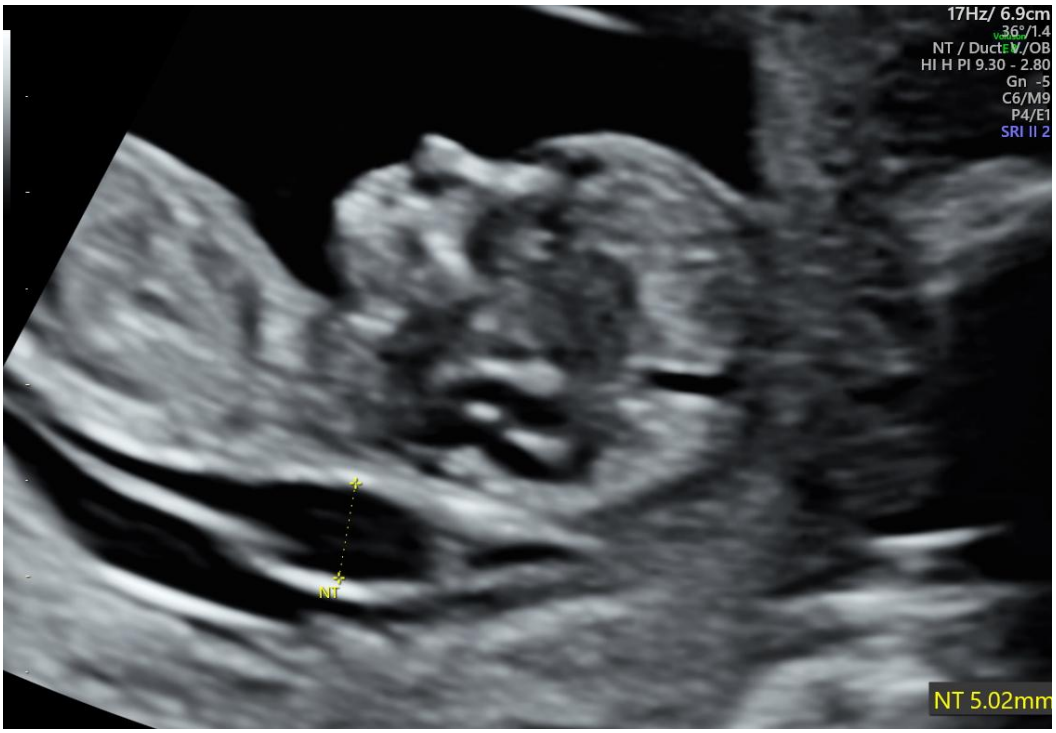
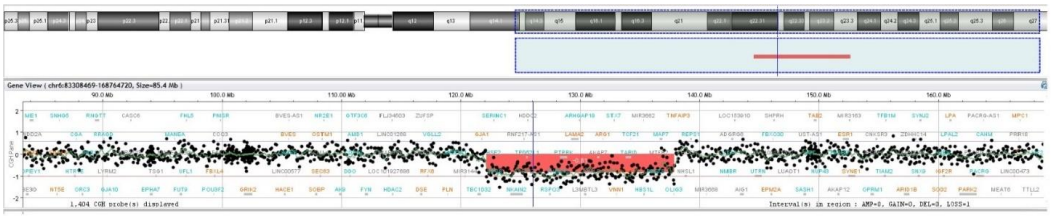


Figure 2. Array Comparative Genomic Hybridization (aCGH) result of this case. The affected region (6q22.31q23.3) is shown in red, including the *EYA4* gene.



3. Discussion

The chromosome 6 is one of the biggest of the human genome, constituting about 6% of it. This chromosome houses the major histocompatibility complex (MHC), a crucial region for the immune system, and it plays vital roles in immunity, disease susceptibility, and various physiological processes [5]. Even though being a rare finding, there have been various interstitial deletions of the long arm of the chromosome 6 identified, mainly on children or adults presenting with various signs and symptoms, such as intellectual disability, developmental delay, growth retardation, cardiac anomalies, dysmorphic features [6].

At prenatal level, these findings are even more rare, with scarce information in literature, and chromosome abnormalities still constitute a challenge in genetic counselling. In the case that we describe here, the interstitial deletion of the chromosome 6 diagnosed during the first trimester screening was located at 6q22.31q23.3, being considered a terminal interstitial deletion having in consideration the conventional cytogenetics. The findings described in this report are consistent with the information available in the literature, as shown in Table 1, mainly regarding the evidence of retrognathism and the fetal growth restriction. Additionally, the bibliographic consultation carried out during the study identified an individual with a superimposable deletion, whose phenotype included developmental delay, craniosynostosis and other minor anomalies [7].

Figure 3. Control ultrasound post CVB. Reduced volume of amniotic fluid and evidence of retrognathism (arrow).

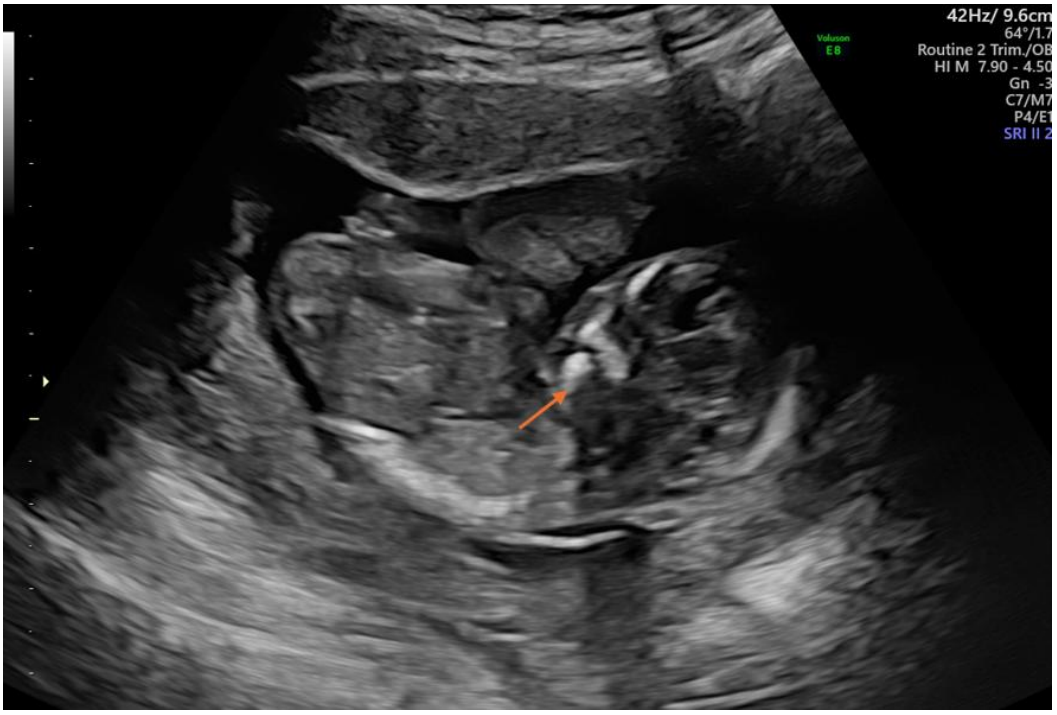


Table 1. Literature review of 6q deletions associated with phenotypes and clinical outcomes.

Reference	Breakpoints	Associated phenotype	Clinical outcome
[1]	6q13q14.2	Hypertelorism; Upslanting palpebral fissures; Bilateral epicanthic folds; Flat nasal bridge; Thin lips; Low-set ears.	Intellectual disability and developmental delay; Unable to speak.
[4]	6q15q16.3	Small pituitary gland; Ankyloglossia; High and narrow palate; Tapered fingers due to proximal obesity; Bilateral grade II vesicoureteral reflux.	Gastroesophageal reflux disease; Sleep apnea; Hypothyroidism; Morbid obesity.
[5]	6q15q21	Patent ductus arteriosus; Atrial septal defect; Broad forehead; Scaphocephaly; Broad nasal bridge; Bilateral mild ptosis; Small hands and feet; Right bundle branch bloc; Arnold-Chiari malformation type 1.	Intellectual disability and developmental delay; Poor articulation; Wide-based gate; Obesity.
[4]	6q16.1q21	Left arachnoid cyst; Borderline ventriculomegaly; Prominent forehead; Highly arched and disrupted eyebrows; Anteverted nares; Flat nasal bridge; Bifid uvula; Submucosal cleft palate; Poor dentition; Flat philtrum; Small hands and feet; Fifth finger clinodactyly; Brachydactyly; Flat feet; Left kidney smaller than right; Left undescended testicle.	Profound intellectual disability and developmental delay; Hyperreflexive bladder; Morbid obesity.

[8]	6q16.1q22.32	Flat occiput; Hypertelorism; Downslanting palpebral fissures; Retromicrognathia; Short neck; Ectrodactyly of the left hand; Tetralogy of Fallot.	Prolonged hospitalization at Neonatal Intensive Care Unit, with need for heart surgery. Need for tracheostomy and gastrostomy tubes even after discharge. Severe developmental delay.
[4]	6q16.2q16.3	Thin corpus callosum; Mildly enlarged posterior fossa; Small ears; Midfacial hypoplasia; Wide nasal tip; Hypoplastic alae nasi; Hypoplastic philtrum with thick upper lip; Small feet; First toe angled upward.	Hand flapping; Hyperreflexia; Ankle clonus.
[4]	6q16.3q22.31	Underdeveloped genu of corpus callosum; Cerebellar vermis hypoplasia; Brachycephaly; Prominent nasal tip; Thick alae nasi; Downturned mouth corners; Thick upper maxillary frenulum; Mildly short philtrum; Middle finger camptodactyly; Hyperconvex nails; Narrow feet with jumbled toes; Minimal pectus excavatum; Patent ductus arteriosus.	Poor visual processing; Poor head control; Recurrent ear infections; Delayed gastric emptying; Gastroesophageal reflux disease; Nasolacrimal duct stenosis; Decreased muscle mass.
[2]	6q21q22.1	Cerebellar vermis hypoplasia; Exotropia; Hypertelorism; Hypertelorism; Pectus excavatum, chest asymmetry, thoracic scoliosis and vertebral rotation; Absence of the pectoralis major and minor muscles.	Intellectual disability; Developmental delay.
[4]	6q21q22.1	Partial agenesis of the corpus callosum; Small cerebellum; Generally underdeveloped brain; Bilateral colobomas; Small anterior fontanelle; Mild brachycephaly; Bitemporal narrowing; Small, posteriorly rotated, cupped ears with unraveled helices; Hypertelorism; Small jaw; Camptodactyly at the proximal finger interphalangeal joints; Double outlet right ventricle; Dysplastic pulmonary valve; Pulmonary atresia; Large ventricular and atrial septal defects; Small chest wall musculature; Hydronephrosis.	Intellectual disability and developmental delay.
[4]	6q22.1	Cerebellar vermis hypoplasia; Periventricular leukomalacia; Thick corpus callosum; Mildly arched eyebrows; Pointed chin with dimples; Multiple flame nevi on face and back; Undescended testes.	ADHD.
[4]	6q21q22.31	Bitemporal hollowing; Bilateral ear pits; Highly arched and disrupted eyebrows; Extra creases on fingers and toes.	Severe ADHD; Ataxic gait.

[1]	6q21q22.31	Mild cerebellar vermis atrophy; Two hair whorls (cutis verticis gyrata); Oval facies; Small forehead with low frontal hairline; Incomplete folded helix of left ear; Mild retrognathia; High and narrow palate; Broad feet; Hypoplastic 5th toenails; Pectus excavatum; Scoliosis; Pronounced gynecomastia; Hyperextensible joints.	Mild-moderate intellectual disability and developmental delay; Adult-onset reticular myoclonus, dysmetria, poor tandem walking, fine tremor of upper extremities.
[4]	6q22.1q22.2	Thick corpus callosum; Epicanthal folds; Upslanting palpebral fissures; Prominent fingertip pads; Tapered fingers; Flat feet; Hip laxity.	High pain tolerance; Hyperphagia; Phonological difficulties; Poor coordination; Poor balance; Toe-heel walking; Baseline tremor.
[5]	6q22.1q22.33	Microcephaly; Sparse hair at the vertex; Short forehead; Oval facies; Hypotelorism; Long thin nose; Protruding columella; Short philtrum; Micrognathia; Partial 2–3 toe syndactyly; Humped neck; Congenital hypoplastic left kidney; Bifid uterus.	Mild-moderate intellectual disability and developmental delay.
[4]	6q22.2q23.1	Craniosynostosis; Plagiocephaly; Hydrocephalus; Cerebral atrophy; Small hands; Mild aortic stenosis.	Obesity; Mental retardation.
[8]	6q22.33	Mild motor delay; Behavioural abnormalities; Microcephaly; Congenital heart disease (sinus venosus defect with a partial anomalous pulmonary venous connection); Cleft lip and palate; Facial minor anomalies.	Mild-moderate intellectual disability and developmental delay.
[4]	6q25.2	Wide and full anterior fontanel; Straight palpebral fissures; Lacrimal duct stenosis; Telecanthus; Prominent nasal bridge; Broad nasal tip; Anteverted nares; Redundant nuchal skin; Hydrocephalus; Ventriculoseptal defect with pulmonary valve stenosis.	Profound intellectual disability and developmental delay; Severe sensorineural hearing loss; Recurrent infections; Need for oxygen supplementation; Congestive heart failure. Passed at two years old of respiratory failure secondary to pulmonary hypertension.

Furthermore, the deletion identified in the case described in this case report included the *EYA4* gene, which is linked to autosomal dominant non-syndromic hereditary hearing loss and to Otofaciocervical syndrome, which is characterized by facial dysmorphisms (long and narrow facies, high arched palate, narrow nose, and narrow mandible), ear abnormalities with hearing loss, and shoulder girdle anomalies [8-9].

During genetic counselling, the couple was informed of the various phenotypes associated with a 6q interstitial deletion, according to the available literature, including the possibility of occurrence of profound intellectual disability and developmental delay. With all the available information, and taking also into account the reduced amniotic fluid, which could lead to additional pulmonary atresia, the couple opted for medical termination of the pregnancy.

4. Conclusion

Interstitial deletions on a chromosome are a rare finding, with a wide range of signs and symptoms associated depending on the size and location of the deletion and which genes are involved. These deletions are mainly diagnosed in children or adults presenting with those symptoms, making its diagnose on a prenatal level an even more rare. Our results enrich the spectrum of manifestations of chromosome 6 deletions known to date and highlight the complexity of prenatal counselling in these cases.

Funding: None.

Research Ethics Committee Approval: We declare that the legal guardian authorized the study, as it involved a gestational fetus, by signing an informed consent form. The study followed the ethical guidelines established by the Declaration of Helsinki.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflicts of interest.

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