Neurodevelopmental delay associated with a de novo 11q13.2 microdeletion: a case report

Retard neurodéveloppemental associé à une micro-délétion de novo 11q13.2 : à propos d'un cas

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RÉSUMÉ

Introduction : La délétion de la région chromosomique 11q13.2, également connue sous le nom de syndrome oto-dentaire, est une anomalie génétique autosomique dominante extrêmement rare, caractérisée par une grande hétérogénéité phénotypique. Moins d'une dizaine de familles ont été rapportées dans la littérature à ce jour. Cette région renferme plusieurs gènes impliqués dans le neurodéveloppement, les fonctions sensorielles et la morphogenèse cranio-faciale.

Observation : Nous rapportons le cas d'un garçon âgé de 2 ans, suivi pour un retard global des acquisitions psychomotrices associé à une dysmorphie cranio-faciale. L'examen clinique retrouvait une trigonocéphalie, un hypertélorisme, un aplatissement de la racine du nez, des oreilles mal ourlées et une micrognathie. L'IRM cérébrale objectivait un kyste de la poche de Rathke avec une ventriculomégalie minime. Le bilan neurosensoriel mettait en évidence une surdité de perception. Le séquençage de l'exome a identifié une délétion hétérozygote de novo de 1,5 Mb au niveau de la région 11q13.2, classée probablement pathogène selon les critères ACMG/ClinGen 2020. L'exploration hormonale de l'axe hypothalamo-hypophysaire était normale.

Conclusion : Ce cas contribue à élargir le spectre phénotypique associé aux délétions 11q13.2 et renforce les corrélations génotype–phénotype. Une analyse génomique fine associée à une évaluation clinique détaillée est essentielle pour améliorer le diagnostic, le conseil génétique et la prise en charge personnalisée des patients.

Mots clés : Délétion 11q13.2, Retard psychomoteur, Dysmorphie cranio-faciale, Surdité neurosensorielle

ABSTRACT

Background : Deletion of the 11q13.2 chromosomal region, also known as oto-dental syndrome, is an exceptionally rare autosomal dominant genetic anomaly characterized by marked phenotypic heterogeneity. Fewer than ten families have been reported worldwide. This region harbors several genes involved in neurodevelopment, sensory functions, and craniofacial morphogenesis.

Case report : We report the case of a 2-year-old boy presenting with global psychomotor developmental delay and craniofacial dysmorphism. Clinical examination revealed trigonocephaly, hypertelorism, flattened nasal bridge, poorly folded auricles, and micrognathia. Brain MRI showed a Rathke's cleft cyst associated with mild ventriculomegaly. Audiological evaluation demonstrated sensorineural hearing loss. Whole-exome sequencing identified a de novo heterozygous 1.5 Mb deletion at chromosome 11q13.2, classified as likely pathogenic according to ACMG/ClinGen 2020 criteria. Hormonal assessment of the hypothalamic–pituitary axis was normal.

Conclusion : This case further expands the phenotypic spectrum associated with 11q13.2 deletions and strengthens genotype–phenotype correlations. High-resolution genomic analysis combined with detailed clinical evaluation is essential to improve diagnostic accuracy, genetic counseling, and individualized patient management.

Keywords : 11q13.2 deletion, psychomotor developmental delay, craniofacial dysmorphism, sensorineural hearing loss

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INTRODUCTION

Deletion of the 11q13.2 region, also known as oto-dental syndrome, is an extremely rare autosomal dominant craniofacial anomaly. To date, only nine families affected by this syndrome have been reported in the literature [1]. This rare but clinically significant anomaly involves the long arm of chromosome 11 (region 1, band 3, sub-band 2) and results in the loss of a chromosomal segment containing several genes essential for the regulation of cellular development, tissue differentiation, and intracellular signaling. This region is of particular interest because the genes it harbors are involved in fundamental biological processes, including cell cycle regulation, apoptosis, and cellular growth.

Clinically, the condition presents with a heterogeneous phenotypic spectrum. Depending on the extent and precise localization of the chromosomal loss, affected individuals may exhibit a variety of congenital anomalies, motor and cognitive developmental delays, growth disturbances, and an increased predisposition to certain malignancies.

From a genetic standpoint, identification of the 11q13.2 deletion relies on conventional cytogenetic techniques such as karyotype analysis, as well as more recent molecular methods including comparative genomic hybridization and high-throughput sequencing. These tools have improved the characterization of the frequency, extent, and functional implications of this anomaly while highlighting the significant interindividual variability of associated phenotypes [2]. Despite recent advances, knowledge of the clinical consequences of the 11q13.2 deletion remains incomplete, largely due to the rarity of reported cases and the heterogeneity of clinical manifestations. A comprehensive understanding of this anomaly is nevertheless essential to improve early diagnosis, clinical follow-up, personalized management, and genetic counseling for patients and their families.

We report here a new case of 11q13.2 deletion, adding to those previously described in the literature, with the aim of further refining the clinical and phenotypic characterization of this chromosomal abnormality.

CASE REPORT

A 2-year-old boy was followed for delayed psychomotor development associated with craniofacial dysmorphism. He is the second child in the family, born to non-consanguineous parents, and has a 5-year-old older sister with normal development and no medical history. There was no notable family history of neurological, genetic, or congenital disorders.

He was born at term with good adaptation to extrauterine life. Psychomotor delay was characterized by acquisition of sitting at 12 months and production of only a few syllables by the age of 2 years. At the time of evaluation, he had not yet acquired standing or independent walking.

Clinical examination revealed trigonocephaly with facial dysmorphism, including hypertelorism, flattening of the nasal bridge, poorly folded auricles, and micrognathia. Growth parameters were appropriate for age. Visceral examination was normal, with no abnormalities of dentition or extremities.

Brain MRI revealed a Rathke's cleft cyst associated with mild ventriculomegaly. Neurosensory assessment demonstrated sensorineural hearing loss. Hormonal evaluation of the hypothalamic–pituitary axis was normal. Genetic analysis by whole-exome sequencing identified a de novo 1.5 Mb deletion at chromosome 11q13.2.

DISCUSSION

Deletion of the 11q13.2 region represents a rare chromosomal abnormality with variable and clinically significant implications. In our case, a heterogeneous phenotypic spectrum was observed, including craniofacial dysmorphism—characterized by trigonocephaly, hypertelorism, flattened nasal bridge, poorly formed auricles, and micrognathia—as well as delayed psychomotor development. These findings confirm and extend previously reported data, highlighting the phenotypic variability associated with this deletion [3].

Clinical features reported in the literature include dental anomalies such as large, globular molars (globodontia), small or absent premolars, and delayed tooth eruption; hearing impairment, predominantly high-frequency sensorineural hearing loss; ocular anomalies; facial dysmorphism; and psychomotor developmental delay or intellectual disability [4]. Additional anomalies may be present depending on the size of the deletion.

Whole-exome sequencing in our patient revealed a heterozygous 1.5 Mb deletion at 11q13.2, encompassing 48 genes, including 37 protein-coding genes. This deletion is classified as likely pathogenic according to the ACMG/ClinGen 2020 criteria [5]. It includes genes associated with haploinsufficiency, notably KMT5B (confirmed haploinsufficiency) and LRP5 (probable haploinsufficiency).

The 11q13.2 region contains several genes of clinical relevance whose loss may contribute to the observed phenotype. PC (pyruvate carboxylase) plays a central role in mitochondrial metabolism, and partial loss may contribute to neurological or metabolic manifestations. CABP2 and CABP4, encoding calcium-binding proteins, are involved in auditory function and retinal synaptic transmission, respectively; their haploinsufficiency may explain sensory impairments such as hearing loss or visual abnormalities [6,7]. KMT5B, a lysine methyltransferase, has been associated with neurodevelopmental disorders, and its loss may contribute to cognitive delays and dysmorphic features [8]. TCIRG1, involved in osteoclast formation, may play a role in skeletal or bone abnormalities when deleted.

Haploinsufficiency or deletion of chromosomal segments including CCND1 and/or FGF3 may result in altered tissue development, contributing to growth or maturation delays. Similarly, loss of FGF3 may affect morphogenetic or differentiation processes, corresponding to congenital anomalies or impaired development [9]. Thus, the exact extent of the deletion and the combination of genes involved likely determine phenotypic variability, with some clinical manifestations potentially modulated by yet unidentified genetic or environmental factors.

Reported cases in the literature remain very limited (Tableau 1).

Tableau 1. Clinical features associated with 11q13 subregion deletions.

Segment	Key genes	Dominant phenotypes
11q13.1	KMT5B, CABP4, MEN1	NDD, macrocephaly, hypotonia, possible visual impairment
11q13.2	CABP2, PPP2R5B	Sensorineural hearing loss, developmental delay
11q13.2–q13.3	SHANK2, FGF3/FGF4	Autism, ID, dental anomalies, hearing loss
11q13.3–q13.4	CCND1, CNIH2, GAB2	Mild delay, language disorders
Large deletions	Multiple	Severe combined phenotype

NDD : Neurodevelopmental Disorder ; ID : Intellectual Disability.

From a clinical perspective, detailed knowledge of the phenotypic spectrum associated with the 11q13.2 deletion is essential for genetic counseling and personalized patient management [10]. However, several limitations must be acknowledged. The rarity of this anomaly and the heterogeneity of reported cases limit the generalizability of conclusions. Moreover, some clinical features may not be directly attributable to the deletion itself but rather to concomitant genetic or environmental variations.

These findings open perspectives for future studies aimed at better understanding the functional roles of genes within the 11q13.2 region, identifying underlying pathogenic mechanisms, and developing adapted management strategies. The establishment of a centralized database of reported cases could further improve phenotypic characterization and facilitate long-term patient follow-up.

CONCLUSION

The 11q13 region occupies a distinctive place in clinical genetics due to the diversity of genes it contains and the phenotypic heterogeneity associated with its deletions. Our work highlights the importance of distinguishing critical subregions, each associated with a specific clinical spectrum ranging from neurodevelopmental disorders (notably involving SHANK2 and KMT5B), to sensory impairments such as hearing loss or visual abnormalities (CABP2, CABP4), and to dental or craniofacial features linked to FGF3/FGF4. These findings underscore the necessity of high-resolution genomic analysis (aCGH, NGS) combined with systematic clinical evaluation. The accumulation of published cases, supplemented by our contribution, strengthens genotype–phenotype correlations and enhances understanding of critical region delineation. Ultimately, these clinical and functional data will improve diagnostic accuracy, genetic counseling, and individualized patient management.

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