Duplication of the 15q11-13 region in a Moroccan patient with autism, intellectual deficiency, and absence of speech – a case report

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ABSTRACT

Background: The 15q11.2-q13 duplication syndrome (OMIM: 608636) is a rare autosomal dominant neurodevelopmental disorder caused by genomic rearrangements within a highly unstable chromosomal region prone to low-copy repeat–mediated duplications. This region contains imprinted genes involved in Angelman and Prader–Willi syndromes, for which parental origin has been shown to influence pathogenicity. Clinically, affected individuals present with autism spectrum disorder (ASD), intellectual disability, developmental and speech delays, seizures, and hypotonia. To date, no case has been reported in Morocco.

Case Presentation: We report an 8-year-old girl referred to our genetics department for global developmental delay, absence of speech, intellectual disability, ASD, and facial dysmorphia. Neurological examination revealed motor delay, including tiptoe walking and incontinence, while electroencephalogram, thyroid function, and auditory evoked potentials were normal. Whole exome sequencing revealed a heterozygous 9.0 Mb duplication at 15q11.2-q13.3 encompassing imprinted genes such as UBE3A, SNRPN, and GABRB3, consistent with 15q11-q13 duplication syndrome (OMIM: 608636).

Conclusion: The genotype-phenotype correlation in this syndrome is highly complex, due to incomplete penetrance. We present the first reported instance of 15q11.2-q13 duplication syndrome in Morocco. Our findings contribute to the growing body of evidence implicating genes within the 15q11-q13 region in ASD and other neurodevelopmental abnormalities.

Keywords: 15q11.2-q13 duplication syndrome, neurodevelopmental disorder, autism spectrum disorder, case report, Morocco.

Type of Article: CASE REPORT **Specialty:** Medical genetics

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Introduction

The 15q11.2-q13 duplication syndrome (OMIM:608636) is a rare genetic neurodevelopmental disorder with autosomal dominant inheritance [1]. The 15q11-q13 chromosomal region is well-known to be unstable and susceptible to genomic rearrangements due to low-copy repeats (LCRs), with specific breakpoints (BP1-BP5) that lead to deletions and duplications of variable sizes [1,2]. This particular region contains critical imprinted genes implicated in Angelman Syndrome and Prader–Willi Syndrome. Thus, the parental origin of the duplication may be key to the pathogenicity [3-6]. The prevalence of 15q11.2-q13 duplication syndrome is estimated to be 1 in 30,000 to 1 in 60,000 children, with only 134 cases reported worldwide [1,7].

The abnormal phenotype is diverse, with main clinical characteristics that include autism spectrum disorder (ASD), intellectual disability, developmental delay, speech delay, seizures, hypotonia, and minor dysmorphic features [2,8-12].

Described for the first time in 1993 [13], the 15q11.2-q13 duplication syndrome is now considered a relatively common cause of ASD, accounting for approximately 1% of cases [14]. To the extent of our knowledge, no case has been reported in Morocco. Herein, we will present the clinical and genetic features of a patient referred with autism, intellectual disability, and absence of speech.

Case Presentation

Here we describe a girl of 8 years of age born from non-consanguineous parents. The mother was 25 years old. The girl was born by normal delivery with a low birth weight of 1,800 g and a transient generalized neonatal hypotonia that did not persist beyond the neonatal period. Subtle dysmorphic features included a bulbous nose, full cheeks, broad forehead, and enophthalmos. The patient presented a complex phenotype with growth retardation including height and weight, feeding problems in the newborn period, delayed psychomotor development, absence

of speech, aggressiveness, and worsening hyperactivity. The diagnosis of ASD and intellectual disability was made based on clinical evaluation by a pediatric psychiatrist, and the severity of the intellectual disability has not been formally graded. There was no family history of a similar case. Other neurological findings include motor delay such as walking on tiptoes and involuntary leakage of urine and stool, but seizures have not been observed to date. Furthermore, the patient exhibits no sleep problems and a routine electroencephalogram (EEG) detected no anomalies. The thyroid function test, Auditory Evoked Potentials were normal.

Whole exome sequencing using read-depth Copy Number Variations (CNV) analysis identified a heterozygous pathogenic 9.0 Mb duplication at 15q11.2q13.3. Duplication at this genomic region is associated with autosomal dominant chromosome 15q11-q13 duplication syndrome (OMIM: 608636). This region spans a well-known imprinted gene cluster associated with Angelman syndrome (OMIM: 105830) and Prader–Willi Syndrome (OMIM: 176270).

The results demonstrated that the duplicated region comprises the specific position NC_000015.10:g.(?_23129470)_(32101347_?).

The variant is not observed in the gnomAD SVs v2.1.1 dataset.

In this region, we identified the following coding genes: GOLGA6L1, GOLGA8S, GOLGA6L2, MKRN3, MAGEL2, NDN, NPAP1, SNURF, SNRPN, UBE3A, ATP10A, GABRB3, GABRA5, OCA2, HERC2, GOLGA8F, GOLGA8G, GOLGA8M, APBA2, ENTREP2, NSMCE3, TJP1, GOLGA8J, GOLGA8T, CHRFAM7A, GOLGA8R, ARHGAP11B, FAN1, MTMR10, TRPM1, KLF13, OTUD7A, CHRNA7.

Methylation analysis was not performed due to unavailability at the time of testing.

In this study, the parental genetic testing to determine the inheritance pattern could not be done due to a lack of financial means. Thus, the parental origin of the 15q11-13 duplication in this patient remains unknown.

Discussion

The 15q11-q13 chromosomal region is commonly involved in the formation of structural rearrangements due to LCRs, with specific breakpoints (BP1-BP5) that are thought to involve unequal meiotic recombination between repeat sequences. This mechanism, in turn is likely to cause chromosomal fragment deletion and duplication [1,15-17]. The duplications most frequently occur in one of two forms: an isodicentric chromosome 15, abbreviated idic [15], or an interstitial duplication 15 abbreviated int dup [15,18].

The parental origin of the 15q11-13 duplication of the present case is unknown. Nevertheless, established knowledge from other studies show that 80.20% of cases that present clinically inherited their duplication from one parent, with maternally inherited accounting for 62.96% of the cases. Several de novo and paternal duplications have also been identified, although with less severe phenotypes. More often than not, the carrier parent remained phenotypically unaffected, and there are reported cases of siblings with a normal phenotype despite having the same genotype, highlighting the syndrome's reduced penetrance and variable expressivity [2,5,10]. An abnormal increase in the dosage of maternally derived genes within the 15q11q13 region is thought to disrupt normal brain development and function, likely contributing to structural and developmental anomalies [1,5,19].

The 15q11.2-q13 duplication region encompasses key imprinted genes such as *SNRPN* and *UBE3A*, which are particularly implicated in the corresponding deletion syndromes Prader–Willi Syndrome and Angelman Syndrome. Notably, in the majority of 15q11.2-q13 duplication syndrome cases, the duplicated segment is of maternal origin. This recurrent maternal inheritance observed in published cohorts suggests that maternally expressed imprinted genes, particularly UBE3A, may play a major role in the pathophysiology of neurodevelopmental manifestations [10,20-22].

In previously reported cases, the clinical severity of 15q11.2-q13 duplication syndrome has been shown to correlate imperfectly with duplication size, inheritance pattern, and gene dosage [2,10,11]. The approximately 9.0 Mb duplication identified in our patient is comparable in size to duplications reported in interstitial dup [15] cases, which are frequently associated with ASD, intellectual disability, and severe speech impairment [1,15,17]. While epilepsy is a common feature in many cohorts - particularly in patients with isodicentric duplications – seizures have not been observed to date in our patient, consistent with reports indicating variable neurological involvement even among individuals with large duplications [18,20]. Similarly, the absence of EEG abnormalities in our case aligns with observations that epileptiform activity is not universal in duplication carriers [7,10,12]. Overall, the clinical presentation of our patient falls within the broad phenotypic spectrum described in other populations, reinforcing the marked heterogeneity and incomplete penetrance associated with 15q11.2-q13 duplication syndrome.

Finally, as emphasized by previous studies, the phenotypic expression of duplication of 15q11-q13 is highly heterogeneous, with no pathognomonic features, making establishing a clinical diagnosis and medical management particularly challenging and underlining the importance of molecular findings [7,11].

Clinical management and follow-up

Management of patients with 15q11.2-q13 duplication syndrome is primarily supportive and requires a multidisciplinary approach tailored to the individual's

neurodevelopmental profile [1,11]. In the present case, the patient is followed by a pediatrician and pediatric psychiatrist, with ongoing neurodevelopmental monitoring. Supportive therapies include speech therapy, psychomotor therapy, and behavioral interventions aimed at addressing ASD, absence of speech, and behavioral difficulties [7,10,11]. Although seizures have not been observed to date, continued neurological surveillance is recommended given the increased risk of epilepsy reported in this syndrome [18,20]. Genetic counseling was offered to the family, with discussion of recurrence risk and the importance of parental testing to determine inheritance and guide future reproductive counseling [2,4]. Long-term follow-up focusing on developmental progress, behavioral regulation, and functional autonomy is essential. Early identification and sustained multidisciplinary care may help optimize developmental outcomes despite the variable and unpredictable course of the disorder [1,11].

Conclusion

In summary, the genotype-phenotype of 15q11.2-q13 duplication syndrome is highly complex. Moreover, the penetrance of this duplication seems to be incomplete for some genes, leading to variable phenotypes in patients and underlining the importance of molecular findings in such cases.

What is new?

It is the first reported case of 15q11.2-q13 duplication syndrome in a Moroccan patient with ASD, which contributes to the growing body of evidence implicating genes within the 15q11-q13 region in ASD and helps with the complex genotype-phenotype.

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List of Abbreviations

ASD	Autism spectrum disorder
EEG	Electroencephalogram
LCRs	Low-copy repeats

Conflict of interests

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Consent for publication

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Ethical approval

Written informed consent was obtained from the patient for his anonymized information to be published in this article. This case report contains no identifiable information about the patient. Our institution does not require ethical approval for reporting individual cases or case series.

Author's contribution

F.Z., B.S., D.H., and T.A. conceived of the presented idea. F.Z. collected the data and drafted the manuscript. T.A. reviewed the manuscript. D.H. supervised this work. All authors read and approved the final manuscript. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Summary of the case

1	Patient (gender, age)	8 years, female
2	Final diagnosis	15q11.2-q13 duplication syndrome
3	Symptoms	Growth retardation (height and weight) Feeding problems in the newborn period Delayed psychomotor development Absence of speech ASD intellectual disability Aggressiveness and worsening hyperactivity. Seizures: Not observed to date
4	Medications	Symptomatic treatment given
5	Clinical procedure	Symptomatic treatment given
6	Specialty	Requires multidisciplinary management