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Case Report

Novel ANKRD11 Variant in a Lebanese Girl with KBG Syndrome: An 11-Year Follow-Up

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Abstract

KBG syndrome is a rare autosomal dominant neurodevelopmental disorder caused by pathogenic variants in the *ANKRD11* gene. The clinical presentation is highly variable and may include characteristic craniofacial features, developmental delay, learning disabilities, behavioral abnormalities, and growth impairment. Here we describe a Lebanese female patient who was followed for 11 years because of failure to thrive, developmental delay, attention deficit, behavioral difficulties, and persistent learning disabilities. Longitudinal follow-up documented gradual neurocognitive improvement with multidisciplinary interventions and pharmacological treatment for attention and behavioral difficulties. Whole Exome Sequencing (WES), performed at the age of 11 years, identified a novel heterozygous frameshift pathogenic variant in the *ANKRD11* gene (p.Tyr808fs), confirming the diagnosis of KBG syndrome. To our knowledge, this is the first reported Lebanese patient carrying this specific *ANKRD11* variant. This case expands the molecular spectrum of KBG syndrome and highlights the importance of genomic testing in children presenting with developmental delay, learning difficulties, and subtle dysmorphic features, particularly when the diagnosis remains uncertain during early childhood.

Keywords: *KBG syndrome, ANKRD11, Developmental delay, Learning disability, Attention deficit hyperactivity disorder, Synophrys, Whole Exome Sequencing, Lebanese patient.*

Introduction

KBG syndrome is a rare autosomal dominant neurodevelopmental disorder first described in 1975 and named after the initials of the first families reported with the condition [1]. It is mainly caused by heterozygous pathogenic variants in *ANKRD11* or by chromosomal deletions involving 16q24.3 that include *ANKRD11*, leading to ANKRD11 haploinsufficiency [1,2]. The clinicals presentation vary but it has a typical presentation which includes macrodontia of the permanent upper central incisors, characteristic craniofacial features such as triangular face, synophrys or bushy eyebrows, prominent ears and nasal bridge, short stature, skeletal abnormalities, developmental delay, learning difficulties, seizures or EEG abnormalities, and attention-related problems [1,3].

Before the eruption of the permanent incisors' diagnosis can be delayed due to different causes like symptoms overlapping and non-specificity. The importance of testing can be seen in children where symptoms and diagnosis can be mistaken with other dysmorphic neurodevelopmental syndromes, including Cornelia de Lange syndrome [1,4]

Here, we report a girl from Lebanon with long-term follow-up for growth and neurodevelopmental delay, attention and learning difficulties, and dysmorphic craniofacial features, in whom whole-exome sequencing identified a heterozygous likely pathogenic frameshift variant in *ANKRD11* .This case highlights the value of genomic testing in children with persistent learning difficulties and subtle syndromic features and adds regional and longitudinal data to the reported *ANKRD11*/KBG syndrome spectrum.

Case Presentation

We hereby report the case of an 11-year-old Lebanese girl, who first presented at the age of 1 year and 4 months for developmental delay and failure to thrive. She was initially evaluated for poor weight gain and delayed neurodevelopmental milestones. The patient was noted to have thick bushy eyebrows with synophrys, raising the suspicion of Cornelia de Lange syndrome at that time.

From the age of 3 to 6 years, the patient developed persistent learning difficulties with poor concentration and significant academic delay. She repeated first grade and required continuous psychomotor, speech, and educational therapies. The patient particularly struggled with reading and writing skills and had difficulty connecting letters and maintaining attention during school activities. Despite these challenges, she maintained good social interaction and was described as intelligent and cooperative, although extremely shy during medical evaluations.

Past medical history was remarkable for hypermetropism. Brain MRI was reported as normal and PEA testing was also normal.

Physical examination revealed synophrys with thick bushy eyebrows, triangular facies, prominent ears, and a broad nasal bridge. Neurological and cardiac examinations were unremarkable. Head circumference measured 50 cm. During early evaluations, the patient weighed 18 kg and continued to demonstrate failure to thrive throughout childhood.

The child was followed in a Lebanese schooling system, and was exposed to 3 languages in parallel, Arabic, French and English. At the age of 6 years and a half, the patient was noted to have severe learning difficulties with inability to properly write her name or perform basic counting. She had a very short attention span and poor concentration. The TOVA test showed and attention comparison score of -3.42. A treatment by atomoxetine was started and led to a partial improvement in attention and school performance. The patient showed persisting behavioral problems, tantrums, hyper-excitability and needed a regular treatment by risperidone until the age of 8 years.

During follow-up visits, gradual academic improvement was noted. At the age of 8 years, the patient became better in class participation and writing skills, although she continued to have reading difficulties and required constant encouragement and assistance. At that age, the patient was unable to continue learning three languages simultaneously and therefore pursued her education in Arabic and French only. Greater progress was observed in reading and writing using the Latin alphabet compared with Arabic script, where each letter may assume up to four different forms depending on its position within the word. The patient's learning difficulties were mainly characterized by dyslexia and dyspraxia. Although she remained academically delayed compared with her peers, she demonstrated clear improvement in social interaction, communication skills, and overall classroom participation.

At the age of 10 years, she was able to perform mental addition and subtraction as well as written multiplication. Physical examination remained stable and unremarkable throughout follow-up. At the age of 10 years the patient was socially independent and was comparable to her peers.

Whole Exome Sequencing (WES), performed at the age of 11 years identified a heterozygous novel pathogenic frameshift variant in the ANKRD11 gene, p.Tyr808fs, confirming the diagnosis of KBG syndrome. The patient's clinical features including synophrys, triangular face, developmental delay, learning disability, behavioral difficulties, and failure to thrive were consistent with the phenotypic spectrum of this syndrome. To our knowledge, this represents the first reported Lebanese patient with KBG syndrome carrying this pathogenic *ANKRD11* variant, further expanding the clinical and molecular spectrum of the disease in the Lebanese population.

Discussion

KBG syndrome (OMIM #148050) is a rare autosomal dominant neurodevelopmental disorder caused by haploinsufficiency of the *ANKRD11* (Ankyrin Repeat Domain-containing protein 11) gene, located on chromosome 16q24.3, or by microdeletions at the same locus. Since its initial description by Herrmann et al. in 1975, the clinical recognition of the syndrome has expanded significantly, yet it remains underdiagnosed due to its phenotypic overlap with other developmental syndromes [5]. In the present case, we describe an 11-year longitudinal follow-up of a Lebanese girl carrying a novel frameshift variant in *ANKRD11*, highlighting the evolving nature of the neurocognitive phenotype and the challenges of early clinical differentiation.

The classic clinical triad of KBG syndrome includes macrodontia of the upper central permanent incisors, characteristic craniofacial dysmorphism, and skeletal anomalies, particularly of the hands [6]. Our patient exhibited several hallmark facial features, including a triangular face, broad nasal bridge, prominent ears, and synophrys with thick, bushy eyebrows. Interestingly, the initial clinical suspicion at one year of age was Cornelia de Lange syndrome (CdLS), a common diagnostic pitfall noted in the literature [7]. Parenti et al. emphasized that the "bushy eyebrows" and synophrys seen in *ANKRD11* variants frequently mimic the CdLS phenotype, though KBG syndrome typically lacks the severe limb reductions and significant growth retardation often associated with *NIPBL* or *SMC1A* variants [8].

The genetic finding in our patient, a heterozygous c.2424_2425delTA (p.Tyr808Ter) variant in *ANKRD11*, results in a premature termination codon. *ANKRD11* is a critical chromatin regulator that recruits histone deacetylases to modify gene expression during neural development [2]. Most pathogenic variants reported in KBG syndrome are located in the large exon 9, similar to our patient's variant [9]. Ockeloen et al. demonstrated that these truncated protein products fail to properly regulate p53-mediated transcription, leading to the global developmental delay and skeletal anomalies observed in affected individuals [10].

A notable aspect of this 11-year follow-up is the progression of the neurobehavioral phenotype. While the patient was initially referred for failure to thrive and motor delay, her primary challenges shifted toward cognitive and behavioral domains as she reached school age. Global developmental delay and intellectual disability are reported in nearly all patients with KBG syndrome, often accompanied by expressive language deficits and behavioral issues such as ADHD, anxiety, and autism spectrum disorder [3]. Our patient's struggles with concentration, poor attention span, and difficulties in mathematical reasoning are consistent with the "learning difficulty profile" described by van Dongen et al., who noted that children with KBG syndrome often require specialized educational support despite being "social and intelligent" in interaction [11].

Management of ADHD symptoms in KBG syndrome remains a clinical challenge. Our patient showed a significant improvement in school performance and social integration following the initiation of Atomoxetine at a dose of 1.2 mg/kg/day. This aligns with emerging evidence that pharmacotherapy for ADHD, when tailored to the neurodevelopmental profile of the child, can significantly enhance the quality of life and academic outcomes in patients with *ANKRD11* variants [12]. Furthermore, the use of Risperidone in our patient to address behavioral regulation highlights the multi-modal approach often required in these cases [13].Our patient exhibited consistent improvement in language acquisition over time despite simultaneous exposure to three languages and later to two. This observation suggests that early exposure to multiple linguistic and orthographic systems, particularly the complexity of abjad languages, may positively influence cognitive development and learning abilities in children with special needs, alongside the established advantages of bilingual exposure [14].

To our knowledge, this case represents one of the longest documented clinical follow-ups of a Lebanese patient with KBG syndrome. The use of Whole Exome Sequencing (WES) was pivotal in establishing the definitive diagnosis, especially given the atypical presentation in infancy where skeletal anomalies and macrodontia (which depends on the eruption of permanent teeth) may not yet be evident [15]. This underscores the recommendations by Low et al. that *ANKRD11* should be included in first-tier genetic testing panels for children presenting with unexplained developmental delay and characteristic facial features [3].

Conclusion

In conclusion, this case expands the genetic spectrum of KBG syndrome by describing a novel frameshift variant in a Lebanese girl. It illustrates the importance of longitudinal monitoring to manage the shifting needs of these patients, from early nutritional and motor support to later behavioral and educational interventions. As genetic testing becomes more accessible in the Middle East, the identification of similar cases will further refine our understanding of the genotype-phenotype correlations in this rare but likely under-recognized population.

Conflict of Interest

The authors declare no competing financial or personal interests.

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