American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Case Report

Novel KMT5B Variant c.889A>G: p. (Ile297Val) Associated with Autism Spectrum Disorder in a 9 Years-Old Brazilian Boy

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To Cite This Article: *Stefan Bittmann*, Elisabeth Luchter, Marco Castilho and Renata Moldenhauer Minillo. Novel KMT5B Variant c.889A>G: p. (Ile297Val) Associated with Autism Spectrum Disorder in a 9 Years-Old Brazilian Boy. Am J Biomed Sci & Res. 2025 25(4) AJBSR.MS.ID.003345,*

DOI: 10.34297/AJBSR.2025.25.003345

Received: January 17, 2025; **Published:** January 24, 2025

Abstract

Lysine Methyl Transferases (KMT`s) play an important role in various neurodevelopmental syndromes and synaptic function. These protein structures add und remove methyl groups to histones H3 and H4 to change transcription process. High throughput gene sequencing has identified lysine methyl transferase 5B as a high impact neurodevelopmental disorder risk gene in humans. Until 2024, at least around 60 individuals with KMT5B-related syndrome have been described in medical literature. The first case of KMT5B-related syndrome was reported in 2012. Genetic screening identified KMT5B as a high-risk gene for autism due to its role in histone modification in the prefrontal cortex. The specific function of KMT5B in the brain and its connection to autism are not well understood. The effects of KMT5B deficiency in the prefrontal cortex on behaviour, synaptic transmission, and molecular mechanisms are to date, unclear. Mice with KMT5B deficiency shows social deficits, a hallmark of autism, and impaired glutamatergic synaptic transmission in the prefrontal cortex. This was associated with reduced expression of glutamate receptor subunits and proteins. KMT5B deficiency also disrupted DNA repair mechanisms, leading to increased p53 expression and synaptic impairment. RNA-sequencing data revealed changes in genes related to cellular stress response and protein degradation. These findings suggest that KMT5B plays a crucial role in synaptic function and gene regulation in the prefrontal cortex, and its deficiency may contribute to autistic phenotypes through synaptic dysfunction and transcriptional changes. Studies reveal a close correlation of KMT5B alterations and autism. We present the first case of a 9 years-old boy KMT5B gene alteration associated with autism spectrum disorder.

Keywords: KMTB5-Alteration-Variant-Gene-Autism-Child

Introduction

The KMT5B-related syndrome is a genetic condition, meaning it is caused by variants in the genes (1-26). Research shows that the KMT5B-related syndrome is often the result of a de novo variant in KMT5B (4,7,9). Many parents who have had their genes tested do not have the KMT5B gene variant found in their child with the syndrome. In some cases, the KMT5B-related syndrome occurs because

the genetic variant was passed down from a parent. The KMT5B-related syndrome is an autosomal dominant genetic condition. This means that a person who has one harmful variant in KMT5B is likely to exhibit symptoms of the KMT5B-related syndrome. For someone with an autosomal dominant genetic syndrome, there is a 50% chance with each child of passing on the same genetic variant and a 50% chance of not passing on the same genetic variant.

Case Report

A father, an intensive care practioner, focussed on autism spectrum disorder starting seven years ago when his son was diagnosed with the condition. Despite intense ABA therapy, little progress has been made. To date of publication, the boy is still non-verbal at nearly 10 years of age. Various off-label therapies were applicated, such as sulforaphane, curcumin, coenzyme Q10, vitamin D, folinic acid, glutathione, omega-3, zinc, resveratrol, magnesium, among others, but without success. As an intensivist, the father had never been an advocate for off-label therapies, but due to the limited number of effective treatments and his son`s poor development, he used to try. A genetic test, however, revealed a variant in the KMT5B gene of uncertain significance.

Molecular Testing from Hospital Israelite, Albert Einstein Diagnostic Medicine Goiania Unit, Brazil

a) Method: SNP-array (Affymetrix 750k platform); Microarray chromosomal analysis Clinical Summary Developmental disorder characterized by ASD, in association with hypotonia/ligament laxity.

b) Karyotype with Normal Result: 46, XY

Summary of Results

No pathogenic CNV or LOH/AOH variations were identified that define the molecular diagnosis related to the clinical presentation. Chromosomal microarray analysis did NOT identify copy number alterations (CNVs) that are pathogenic or known to be associated with known chromosomal microduplication or microdeletion syndromes in the sample evaluated. Segments in Loss/Absence of Heterozygosity (LOH/AOH) were also not identified in regions that suffer from imprinting effects suggestive of Uniparental Disomy (UPD) or common ancestry detectable by the methodology and level of resolution applied in the sample studied.

Benign copy number changes (CNVs) that may be present in this patient are not reported in this report. The test followed the recommendations of the American College of Medical Genetics (ACMG) for interpretation and reporting of postnatal Copy Number Variations (CNVs).

Reference Values Female: arr (1-22, X) ×2 Male: arr (1-22) ×2, (X, Y) ×1.

Additional Findings

a) Gain Change Locus: No. 213 Probes Size 423 kb

b) Summary of Results: arr[GRCh37] 15q13.3(32020856_32444043)×315q13.3 Intervale Chr15:32020856-32444043

Additionally, a gain of chromosomal material was identified on the long arm of chromosome 15 (15q13.3). The gain is approximately 423 kb in size containing 213 chip makers and involving 2 genes (2 OMIM® genes). This CNV (Copy Number Variation) was classified as a variant of clinical contribution of UNCERTAIN significance (VUS-variant of uncertain significance). Genes involved: CHRNA7 (118511), OTUD7A (612024).

Observations

The presence of any other alteration, pathogenic or not, present in gene regions not studied by the present test cannot be excluded. The classification and interpretation of the variants identified in this test reflect the current state of scientific understanding at the time of issuing the result. In some cases, the classification and interpretation of such variants may change as new scientific information becomes available.

Methodology

Microarray chromosomal analysis is a technique that allows the simultaneous investigation of thousands of genomic sequences for the detection of Copy Number Variations (CNVs), including changes in gains (duplications) and losses (deletions) of chromosomal segments that are not visualized in conventional karyotype examination. The platform used is CS3000 from Affymetrix and the chip used in this test was CytoScan® 750K Cytogenetics Solution, which contains 750,000 oligonucleotides distributed throughout the human genome, consisting of 200,000 SNPs and 550,000 non-polymorphic markers. In clinically significant regions there is a greater density of probes, even allowing the identification of CNVs that partially or totally cover a single gene. The platform used allows the detection of alterations greater than 100Kb and the identification of practically al microdeletion and microduplication syndromes already reported in the current specialized medical literature. The analysis of the results is carried out using the Chromosome Analysis Suite (ChAS software)-Thermos Fisher Scientific, version 4.0.0.385, r28959).

The following are considered in the analysis: (a) losses or gains of genomic segments greater than 150 Kb; (b) deletions and duplications affecting genes known to be associated with genetic diseases when mutated, regardless of the size of the alteration. In these cases, they will be reported only when the genetic alterations are consistent with the clinical picture reported to the laboratory. In the absence of clinical information, these changes will not be reported; (c) segments with Loss of Heterozygosity (LOH) greater than 10MB; (d) segments with Loss of Heterozygosity (LOH) >3Mb along the genome that, when added together, represent more than 3% of the genome; (e) segments with Loss of Heterozygosity (LOH) in regions known to be influenced by genomic imprinting, regardless of size. Variations in copy numbers less than 4Mb commonly found in the general population, classified in the literature or in databases for available, tolerated, or benign human chromosomal variants, will not be reported due to the strong evidence that these alterations do not contribute

Variants of uncertain clinical significance, also known as VUS

(Variant of Unknown Significance) smaller than 500Kb were not reported, taking into account the absence of information that allows the association of these variants with the phenotype presented by the patient. The classification and interpretation of the variants identified in this examination reflect the current state of scientific knowledge available in the literature at the time of the issuance of the report. The classification and interpretation of such variants may change as new scientific information and advances in research in the area become available. Standardized and validated protocol was performed at the Special Techniques Laboratory of the Department of Clinical Pathology of Hospital Israelite Albert Einstein in partnership with Genomic Diagnostics. Result described according to ISCN 2016 (International System for Human Cytogenetic Nomenclature).

Overall Results

VARIANT: c.889A>G: p. (Ile297Val) POSITION: chr11:67938570-67938570 The variant c.889A>G: p. (Ile297Val) was found in exon 9 of the KMT5B gene, in heterozygosis, in this individual. This variant replaces an Isoleucine with a Valine at codon 297 of the translated protein. The accumulation of evidence allows its current classification as a variant of uncertain significance.

Criteria for Variant Classification

Variant absent in population databases (gnomAD=0, 1000Genomes=0, ABraOM=0) (PM2), non-synonymous variants are a common cause of alteration in this gene (PP2) and computational tools are contradictory regarding the prediction of the variant's impact on the structure and/or function for the final protein. The variant was investigated by orthogonal methodology (Sanger sequencing) in the patient and his biological parents, and it was found that the variant is present in the patient and is absent in both parents; thus, it is likely that it has occurred again in the patient.

Recommendations

It is recommended that these findings be correlated with the clinical phenotype and genetic counselling for the best interpretation of this result. This report is limited to genes predicted to be related to the clinical phenotype (according to the HPO terms used from the clinical information provided) and to variants in additional genes that cause significant medical effects on the health of the individual and family members (incidental findings recommended by the ACMG). With the advancement of genetic studies, new information on the frequency and clinical effect of these variants may become available. For this reason, for cases in which the test did not obtain a conclusive result, a new analysis of the data may be requested, at the discretion of the attending physician.

Interpretation of Incidental Findings

The test did not identify genetic variants that are responsible for other diseases not associated with the clinical summary presented by this patient.

Report of Incidental Findings

Following the recommendations of the American College of Medical Genetics and Genomics (ACMG), in this section we analyse the presence of pathogenic variants in 59 genes recommended by the ACMG and that may or may not be related to the patient's clinical condition. Only variants known to be pathogenic or likely pathogenic are reported. Variants found can be confirmed by another methodology according to clinical indication.

Methodology

Whole exome sequencing testing evaluates 95% or more of the bases of al exons in the human genome, with a depth greater than or equal to 10x. The gene regions of interest were captured using the Agilent Sure Select Al Exon V6 kit, and sequenced in an Illumina sequencer. Paired-end reads of 150bp were aligned against the UCSC reference genome (hg19) using the Burrows Wheeler Aligner (BWA) aligner, and variants were called using the Genome Analysis Tool Kit (GATK) and Free Bayes and annotated using ANNOVAR and in-house developed and validated tools. The transcript is numbered from base A of the ATG initiation codon.

Detected Variants

Detected variants are filtered using the following criteria: (1) variants in disease-related genes in databases such as OMIM, ClinVar, and ClinGen; (2) variants in coding and splicing regions; (3) variants that are not located in duplication areas segmental (without pseudogenes). Each variant is evaluated using information available in public and internal databases. In addition, the relevant published literature is reviewed in the light of clinical data. Variants are described using the HGVS nomenclature (www.hgvs.org/mutnomen). The genes of interest are selected according to the HPO terms related to the clinical picture described. Detected variants are classified as Pathogenic, Probably Pathogenic, Benign, Probably Benign, and Variants of Uncertain Significance, according to the criteria of the American College of Medical Genetics and Genomics. Variants that do not reach the standards established in internal validation will be confirmed by a second methodology, as detailed in the report. Sanger sequencing of the c.889A>G: p. (Ile297Val) variant of the KMT5B gene was performed in Arthur and both parents.

Observations

The report was issued according to current scientific knowledge. The interpretation of data and results and classification of variants may change in the future, with the advancement of medical knowledge or improvement of data analysis tools. Benign, probably benign, intronic, and synonymous variants with no evidence of pathogenicity are not reported. The absence of pathogenic variants cannot be considered as a reference value due to the complexity of the analysis. We suggest correlating the clinical finding with laboratory data. Genetic tests are not definitive tools for the diagnosis of the disease(s) studied. It should be understood that there are rare, but possible, sources of error, including screening contamination, technical errors, and rare genetic variants capable of interfering with the analysis. This exam should be one of the many aspects used by the physician in charge to assist in diagnosis and treatment, and not serve as the only one diagnostic source. This test was devel-

oped and validated by Genomic Diagnostics S.A and the Laboratory of Special Techniques of the Department of Clinical Pathology of Hospital Israelite Albert Einstein (in-house methodology).

Discussion

KMT5B-related neurodevelopmental disorder is an autosomal dominant genetic disorder caused by a mutation in the KMT5B gene [1-26]. The KMT5B gene is associated with intellectual deficit 51 [OMIM: 617788], of autosomal dominant inheritance, characterized by neurodevelopmental disorder with neuropsychomotor delay mainly in speech, attention deficit, autism spectrum disorder, and other variable manifestations that include cognitive deficit, phenotypic deviations, febrile seizure, cryptorchidism, tall stature, macrocephaly, and immunodeficiency [5,9,14,20]. Additionally, the KMT5B gene is classified as category 1 (high confidence) for autism spectrum disorder in the SFARI database. It is characterized by macrocephaly, intellectual disability, failure to thrive, unique facial and foot features, neurobehavioral psychiatric problems, absent speech or language deficiency, and coordination difficulties [1-26]. Patients typically range in age from 5 to 19 years and may also exhibit non-neurological abnormalities such as dysmorphic facial features, cryptorchidism, foot deformities, and sleep difficulties [14,18,20,23]. Some patients may have a tendency toward tall stature or experience febrile seizures. The disorder is caused by heterozygous loss-of-function and missense variants in the KMT5B gene located on chromosome 11q13.2 [1-26]. The KMT5B gene encodes histone-lysine N-methyltransferase KMT5B, which plays a crucial role in various cellular processes [1].

KMT5B-related neurodevelopmental disorder is characterized by significantly below-average general intellectual functioning and impairments in adaptive behaviour typically seen during the developmental period [4,8,14,25]. Patients aged 5 to 19 years exhibit various clinical phenotypes, including developmental delays, mild-to-moderate intellectual disability, speech difficulties, motor delays, coordination issues, and a high prevalence of ASD [15,20,23,24]. Additional features such as dysmorphic facial characteristics, cryptorchidism, foot deformities, and sleep problems are also common. Some patients show mild brain abnormalities on MRI. KMT5B, encoding lysine N-methyltransferase 5B (SUV420H1), plays a crucial role in DNA transcription, replication, and repair. Mutations in KMT5B account for over 80% of cases of KMT5B-related neurodevelopmental disorder [1]. The protein functions as a lysine methyltransferase involved in various physiological processes, including transcription and genomic integrity maintenance [1,5,8,9,13]. The mutation affects the SET domain, leading to diverse pathological effects at the molecular and cellular levels [5,9].

Until 2024, less than 100 individuals with KMT5B-related syndrome have been described in medical research [1-26]. The first case of KMT5B-related syndrome was reported in 2012. Scientists believe that with improved access to genetic testing, more individuals with the syndrome will be identified. Individuals with KMT5B-related syndrome may look different. Currently, there are no medications to treat the syndrome [14,17]. A genetic diagnosis can help affected individuals determine the best course of action to manage the condition and undergo therapies. Doctors may refer individuals to specialists for physical examinations and brain evaluations, genetic consultations, developmental and behavioural studies.

Additional Data

Limitations

This test detects>99% of SNV variants and small deletions and duplications up to 20bp. Variants larger than 20bp and smaller than an exon can be detected with reduced sensitivity. Variants may not be reported if they are present in gene regions that are not properly sequenced, repeat-rich regions, deep intronic regions, and areas with pseudogenes. Sequencing performed in this panel does not detect major structural changes such as translocations, deletions, duplications, and inversions. For situations in which the report is not conclusive, it is recommended that a new analysis of the data be requested periodically, it is suggested annually, given the large volume of regularly published scientific data.

Data Availability Statement

A few datasets for this article are not publicly available due to concerns regarding patient anonymity. Requests to access the dataset should be directed to the corresponding author.

Ethical Compliance

The patient`s parents provided written consent to participate in this case report study with the declaration of Helsinki.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this manuscript.

Funding

None.

Acknowledgement

We are grateful to the patient and his family for participation in this study.

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