Unlocking the Genetic Link between Kabuki Syndrome and Schizophrenia: Implications for Diagnosis and Treatment

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ABSTRACT: This review article highlights the potential role of KMT2D mutations in developing neurodevelopmental disorders, specifically Kabuki syndrome and schizophrenia. Neurodevelopmental disorders are complex conditions with a multifactorial etiology, but genetic mutations have been shown to play a crucial role in their pathogenesis. Recent studies suggest that KMT2D mutations may contribute to the development of these disorders by interfering with enhancer function and histone monomethylation, which are essential epigenetic mechanisms involved in brain development and function. The review article explores the hypothesis that KMT2D mutations may be a cause or a risk factor for Kabuki syndrome and schizophrenia. The article discusses potential areas of interest, such as the characterization of KMT2D mutations in patient populations and the investigation of their functional impact on gene expression and brain development. Additionally, the article proposes research methods to investigate further the relationship between KMT2D mutations and these disorders, including animal models and the use of cutting-edge technologies such as CRISPR/Cas9. Identifying KMT2D mutations in both Kabuki syndrome and schizophrenia may provide a new avenue for understanding the underlying mechanisms of these disorders and developing new treatments. The potential impact of this research is significant, as it may lead to the development of targeted therapies for individuals with Kabuki syndrome and schizophrenia who harbor KMT2D mutations. Additionally, identifying KMT2D mutations as a risk factor for these disorders may facilitate early detection and intervention, improving outcomes and quality of life for affected individuals and their families. In summary, this review article provides valuable insights into the potential role of KMT2D mutations in the pathogenesis of Kabuki syndrome and schizophrenia. It highlights the importance of further research in this area.

KEYWORDS: Biomedical and Health Science, Epigenetics; KMT2D; Kabuki Syndrome; Schizophrenia; genetic mutations.

Introduction

The study of genetics and genomics has revolutionized our understanding of human biology and the development of various diseases. Neurodevelopmental disorders are prime examples of conditions heavily influenced by genetic factors. These disorders encompass a wide range of conditions that arise from abnormal brain development and often manifest as cognitive, behavioral, or motor impairments. Autism spectrum disorder, schizophrenia, and Kabuki syndrome are just a few examples of such disorders that can have profound impacts on affected individuals and their families.

Over the past few decades, advances in genomic technologies, such as whole-genome sequencing and genetic screening, have allowed scientists to identify many gene mutations that contribute to the pathogenesis of neurodevelopmental disorders. This has opened up new avenues of research into the underlying mechanisms of these disorders and has provided hope for the development of more effective treatments. Moreover, it has also led to the discovery of unexpected links between apparently distinct disorders, such as Kabuki syndrome and schizophrenia, which appear to share a common genetic etiology.

Kabuki syndrome is a rare genetic disorder first described in Japan in 1981. It is named after the traditional Japanese dance-drama known as Kabuki due to the distinctive facial features and other physical characteristics that individuals with the syndrome often display. Kabuki syndrome affects multiple organ systems and can cause various medical and developmental issues, including intellectual disability, growth delays, skeletal abnormalities, heart defects, hearing loss, and vision problems.

Mutations cause Kabuki syndrome in one of two genes: KMT2D or KDM6A. These genes play essential roles in regulating gene expression, and mutations in either can disrupt normal development and lead to the characteristic features of Kabuki syndrome. While the exact prevalence of Kabuki syndrome is not well established, it is thought to affect roughly 1 in 32,000 to 86,000 live births. Despite its rarity, Kabuki syndrome has garnered significant attention from the medical and research communities due to its unique features and the insights it has provided into the molecular mechanisms of human development.

Schizophrenia is a chronic and severe mental illness affecting approximately 20 million people worldwide. It typically develops in late adolescence or early adulthood. It is characterized by a range of symptoms, including delusions, hallucinations, disorganized thinking and speech, and abnormal behaviors. Schizophrenia can be a devastating illness that significantly impacts a person’s ability to function in daily life, leading to social isolation, unemployment, and poor quality of life.
The exact cause of schizophrenia is not fully understood. Still, it is thought to be the result of a complex interplay between genetic, environmental, and neurodevelopmental factors. Research has identified several genetic risk factors that may contribute to the development of schizophrenia, including mutations in genes involved in neurotransmitter signaling, brain development, and immune system function. While there is no cure for schizophrenia, many treatments can help manage symptoms and improve the quality of life for individuals with the illness.

KMT2D mutations have been extensively studied in the context of Kabuki syndrome (Figure 1). The gene, KMT2D, has been identified as one of the most mutated genes in individuals diagnosed with Kabuki syndrome. The discovery of KMT2D mutations has led to a better understanding of the mechanisms underlying Kabuki syndrome, and this has helped clinicians and researchers devise more targeted and effective therapies. Despite the advances in understanding Kabuki syndrome, the genetic basis of schizophrenia remains poorly understood. While specific genes such as DISC1, NRG1, and COMT have been identified as potentially involved in schizophrenia, no single gene has been definitively associated with the disorder. However, recent studies have suggested that KMT2D mutations may be involved in the pathogenesis of schizophrenia and Kabuki syndrome.

A recent study by Rees et al. published in Nature has provided evidence for the involvement of KMT2D mutations in schizophrenia. The study identified rare protein-altering variants in KMT2D in schizophrenia patients, suggesting that these mutations may play a role in the development of the disorder. Additionally, the study found that variants in other genes, such as NF1 and AUTS2, may also be implicated in schizophrenia. AUTS2, a gene involved in transcriptional regulation and neurodevelopment, is consistent with the notion that schizophrenia is a neurodevelopmental disorder. Identifying KMT2D mutations in schizophrenia patients is unexpected, given that the disorder was not previously associated with Kabuki syndrome or mutations in KMT2D. Therefore, identifying KMT2D mutations in schizophrenia patients provides an exciting new avenue of research for understanding the pathogenesis of schizophrenia and Kabuki syndrome and developing new treatments.

This review paper aims to delve deeper into the relationship between KMT2D mutations and Kabuki syndrome and schizophrenia. While KMT2D mutations have been extensively studied in the context of Kabuki syndrome, recent evidence suggests that they may also play a role in the development of schizophrenia. Therefore, we hypothesize that KMT2D mutations may be a potential cause of Kabuki syndrome and schizophrenia or, at the very least, increase the risk of developing these conditions. We will explore the possible areas of interest and methods for further research. By shedding light on the connection between KMT2D mutations and these neurodevelopmental disorders, we hope to contribute to a better understanding of the molecular mechanisms underlying these conditions and to pave the way for more effective targeted therapies.

**Discussion**

***Functions of KMT2D:***

![Figure 1: Visual representation of the role of KMT2D in histones. Methyl groups (Me) are added to the Lys-4 position (K4) of histone H3.](image)

The KMT2D gene is a crucial component of the cellular machinery that regulates gene expression. The protein encoded by KMT2D, lysine-specific methyltransferase 2D (KMT2D), is an enzyme that functions as a histone methyltransferase. Histones are proteins that play a key role in packaging DNA into a compact structure called chromatin, which is necessary for proper gene regulation. KMT2D specifically adds a single methyl group to the Lys-4 position of histone H3, a process known as monomethylation, abbreviated as H3K4me1. This modification is associated with gene enhancers, which are DNA regions that help regulate the expression of nearby genes. Adding the H3K4me1 mark to gene enhancers, KMT2D helps recruit other proteins necessary for gene activation and proper cell-type specific gene expression.

KMT2D mutations can take various forms, including changes in the DNA nucleotides that lead to a different amino acid in the polypeptide chain, deletions of genetic material, or forming a premature stop signal. While the exact mechanisms by which these mutations lead to the neurodevelopmental features of Kabuki syndrome and other disorders are not yet fully understood, they are thought to disrupt the normal function of KMT2D and its associated protein complexes, leading to altered gene expression and abnormal development. In this paper, we will examine the potential role of truncated mutations in KMT2D in both Kabuki syndrome and schizophrenia. Specifically, we will investigate whether these mutations disrupt normal gene expression patterns in a way that could contribute to the development of these disorders. We will also explore potential mechanisms underlying the association between KMT2D mutations and these disorders and discuss the implications of our findings for future research and clinical practice.

**Clinical features of Kabuki syndrome and schizophrenia:**

Kabuki syndrome and schizophrenia are distinct types of neurodevelopmental disorders that differ in the age of onset and clinical manifestations. Kabuki syndrome typically presents in early childhood with significant physical symptoms,
including distinctive facial features, minor skeletal anomalies, mild-to-moderate intellectual disability, and postnatal growth deficiency.⁷ In contrast, schizophrenia typically presents in late adolescence or early adulthood and is characterized by mental symptoms, such as delusions, hallucinations, disorganized speech, and abnormal motor behaviors.²⁴

Despite the differences between the two conditions, there are some overlapping features. One similarity is that both disorders involve neuropsychiatric problems, particularly cognitive difficulties. Patients with Kabuki syndrome often have mild-to-moderate intellectual disabilities, and those with schizophrenia frequently experience cognitive impairments, including deficits in attention, memory, and executive function. The second similarity is the involvement of mutations in the KMT2D gene. While KMT2D mutations have been identified as the cause of Kabuki syndrome, recent research has implicated these mutations in the development of schizophrenia.²⁴,²⁵

Understanding the shared genetic factors in these two disorders may provide insights into the underlying mechanisms of cognitive dysfunction and neuropsychiatric symptoms. Furthermore, developing more effective treatments for these disorders is crucial, especially for Kabuki syndrome, which currently does not have a specific treatment. Investigating the potential similarities between Kabuki syndrome and schizophrenia may offer new avenues for developing targeted therapies for these disorders.

**Potential role of KMT2D in Kabuki syndrome and schizophrenia:**
Recent research has suggested that Kabuki syndrome and schizophrenia are related to mutations in the KMT2D gene.⁷ While these two conditions are distinct and have different clinical features, they share common underlying genetic mechanisms that affect the development and function of the brain. KMT2D plays a critical role in regulating gene expression by controlling enhancer action through its ability to perform monomethylation of histone proteins. As a result, if mutations in KMT2D are related to Kabuki syndrome and schizophrenia, abnormal monomethylation and enhancer action would be expected to be observed in patients with either of these conditions.²⁶

Emerging evidence suggests that KMT2D mutations may contribute to the pathogenesis of schizophrenia.²⁷ Several recent studies have identified KMT2D mutations in schizophrenia patients, and some of these mutations have been shown to disrupt histone methylation and enhancer function. These findings suggest that abnormal gene regulation due to KMT2D mutations may contribute to the development of schizophrenia and provide a potential mechanism for the disorder's observed cognitive and behavioral symptoms. By studying the relationship between KMT2D mutations and schizophrenia, we may better understand the underlying causes of this complex and debilitating disorder and identify new targets for therapeutic interventions.

Scientific research suggests that KMT2D loss-of-function may be responsible for the craniofacial malformations characteristic of Kabuki syndrome by inhibiting specific steps of neural crest (NC) development.¹⁵ The neural crest consists of multipotent stem cells at the side of the neural tube near the epidermal layer after neurulation.¹⁵ These stem cells differentiate into various cell types, similar to other multipotent stem cells. However, the biological consequences and molecular mechanisms of KMT2D mutations that cause Kabuki syndrome remain unclear.²⁸ Kabuki syndrome is primarily driven by single-nucleotide variants, short insertions, and deletions in the KMT2D and KDM6A genes, which can result in missense, nonsense, frameshift, and splice-site mutations that produce truncated or inactivated proteins.²⁹ The neural crest (NC) development process relies on this protein, making it a crucial factor in the development of Kabuki syndrome.

**Future Perspectives / Future Work**

5.1 KMT2D and schizophrenia:
It is essential first to determine if KMT2D mutations are significantly related to schizophrenia. By obtaining cells from schizophrenia patients and observing whether abnormal monomethylation at enhancers is present, it can be concluded whether KMT2D mutations are associated with schizophrenia.

Various types of cells can be utilized in this experiment, including blood cells. However, the most effective approach would be to procure skin cells and convert them into induced pluripotent stem (iPS) cells through reprogramming with different transcription factors.³⁰ iPS cells offer a distinct advantage, as the differentiated cells will retain the genetic information of patients affected by genetic mutations or neuropsychiatric disorders.³¹ Somatic cells may be differentiated explicitly into brain cells to observe how neurons respond and function in the presence of gene mutations. Additionally, postmortem brain tissues from individuals diagnosed with schizophrenia may be obtained to examine whether abnormal enhancer action and monomethylation are present.³²

Just as Ng et al. used ChIP sequencing to investigate the link between KMT2D mutations and Kabuki syndrome, this technique could be used to identify KMT2D mutations in a random sample of individuals with schizophrenia.³³ Additionally, CRISPR genome editing could introduce these mutations into iPS cells, enabling researchers to observe their impact on the gene's function and the cell's overall behavior. CRISPR has the potential not only to introduce mutations but also to correct them. By using CRISPR to repair KMT2D mutations in a cell taken from a schizophrenia patient, researchers could also determine whether abnormal monomethylation has been corrected.³⁴

By focusing specifically on differences in H3K4me1, which is highly impacted by KMT2D mutations, it is possible to infer the relationship between KMT2D mutations and the development of schizophrenia.²⁸ However, it is essential to note that abnormal monomethylation activity may be observed in schizophrenia patients, even without KMT2D mutations. This suggests that other factors may be responsible for this outcome. Further experiments are needed to determine whether KMT2D mutations directly cause schizophrenia or if H3K4me1 mutations play a more significant role, regardless of their genetic cause. The outcome of these experiments will

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help to clarify the relationship between KMT2D mutations, H3K4me1 mutations, and the development of schizophrenia.

5.2 Schizophrenia and Kabuki syndrome:

To better understand potential similarities and causes between schizophrenia and Kabuki syndrome, further research could be conducted using mouse models. Specifically, mouse models with loss of function mutations in KMT2D could be used to model Kabuki syndrome, while mouse models associated with schizophrenia could also be studied. This experiment would allow comparing the two models to identify shared features and potential causes.

The function of H3K4me1 modification in mouse models of schizophrenia and Kabuki syndrome can be observed to determine the impact of KMT2D or other mutations on both conditions. Various mouse models are currently available for schizophrenia, including developmental, drug-induced, and genetic models. Another model with MTHFR mutations, linked to abnormal methylation patterns and schizophrenia, is also available. If the mouse models exhibit similar methylation patterns, the research can be expanded to observe whether the mouse models share any behavioral symptoms. This may suggest an association between a mutation and a specific symptom or phenotype. By comparing the mouse models that mimic schizophrenia and Kabuki syndrome, it may be possible to identify similarities between the two conditions.

If the two conditions have similarities, there may be an opportunity to restore certain functions in patients with either condition. For example, studies have shown that histone deacetylase inhibition can positively treat Kabuki syndrome by restoring structural and brain functions in mouse models. Further research is needed to explore the potential benefits of histone deacetylase inhibition for treating schizophrenia. Preclinical studies using mouse models of schizophrenia could provide valuable insights into the mechanisms underlying the condition and the potential therapeutic effects of histone deacetylase inhibition. Ultimately, the goal of such research would be to develop safe and effective treatments for patients with Kabuki syndrome and schizophrenia and to improve our understanding of the genetic and epigenetic factors that contribute to the development of these disorders.

Conclusion

Kabuki syndrome and schizophrenia are two distinct mental disorders with different clinical presentations, and some similarities have been identified. Kabuki syndrome is a rare genetic disorder that typically arises in early childhood and is characterized by developmental delays, facial abnormalities, and skeletal malformations. On the other hand, schizophrenia is a chronic and severe mental illness that typically develops in late adolescence or early adulthood. A range of cognitive, emotional, and behavioral symptoms, such as delusions, hallucinations, and disordered thinking, characterizes it.

Recent research has suggested that KMT2D mutations, which are widely known as the cause of Kabuki syndrome, could be associated with the development of schizophrenia. While the mechanisms underlying this potential association are poorly understood, identifying shared genetic factors between Kabuki syndrome and schizophrenia could have important implications for both disorders' diagnosis, treatment, and prevention. Specifically, the proposed studies could be an opportunity to identify common pathophysiological mechanisms underlying both diseases, providing new insights into potential therapeutic targets.

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References


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Minkyoung Sung is a senior at American School of Johannesburg, South Africa. She is interested in biochemistry and bioengineering. She has participated in research programs and clubs related to this field and gained more practical experience through iGEM, an international synthetic biology competition.