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Histone Lysine Demethylase 5B Role in Autism Spectrum Disorder

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ABSTRACT

KDM5B, a histone lysine demethylase “eraser” protein, is a transcriptional repressor of active promoter regions on histone 3 lysine K4. KDM5B is crucial to regulating gene expression and development. Previously, all mutations in KDM5B were described in cancer. High-performance sequencing revealed missense, frameshift, and nonsense mutations in KDM5B that can be linked to developmental disorders like autism spectrum disorder (ASD). This review summarizes KDM5B’s role in ASD and other developmental disorders.

Background

Autism spectrum disorder (ASD) accounts for a range of early-onset development disabilities. Diagnosed individuals may present with communication and cognitive deficits, anxiety, depression, intellectual disability (ID), specialized talents or interests, delayed development, and epilepsy 1. Hundreds of risk genes have been identified by genetic studies and genome sequencing of individuals with ASD. Various gene mutations have been found to correlate to ASD; additional risk genes have been identified that are causation of ASD.

Epigenetic modulators, like KDM5B, have specific functions that control chromatin structure. Some histone modifications that regulate gene expression by modifications are acetylation, methylation, phosphorylation, ubiquitinylation, and sumoylation. Specifically, methylation of histone H3 lysine K4 (H3K4) plays a crucial role in gene expression, as its modifications initiate transcription. Genes are expressed when DNA is accessible to transcription factors, or when chromatin is in euchromatin form. On the contrary, when DNA is not accessible gene transcription will not occur, this is called heterochromatin 2. Histone demethylases are transcriptional repressors. Modifications of H3K4 most often occur near the N-terminal tails, these modifications are post-translation modifications (PTMs) 4.

One specific histone demethylase, KDM5B, can remove H3K4me3 found at promoters of active expression regions and transcription start sites 3. This modification may play a prominent role in developmental disorders 7. An influx of research is developing about variants in the KDM5B gene in relation to development and neurodevelopmental disorders (NDDs). This review will cover the possibility that KDM5B mutations cause ASD.

KDM5B Location and Function

The KDM5 histone demethylase family functions as a protein to catalyze the removal of one, two, or three methyl groups from H3K4. H3K4me3 is enriched near active promoter regions on genes, these promoter regions are the start of transcription 6, 3. Once at the promoter region, the proteins can express or repress transcription. KDM5 enzymes' interaction with transcription factors may lead them to different cell types and functions, but they all have a role in chromatin structure and gene regulation 9, 7, 8.

The KDM5B enzyme contains the catalytic Jumanji C (JmjC) domain; this domain's function is the methylation of histone three (Fig. 1) 10, 11. KDM5B is a cognitive function gene that aids development and neuronal differentiation 11. It is important to note that autism spectrum disorder presents with cognitive deficits (impairment in an individual's mental processes that lead to the acquisition of information and knowledge, and drive how an individual understands and acts in the world 13) 12. KDM5B's role in neuronal development correlates with synaptic function, neurogenesis, cell proliferation, embryogenesis, and hormone regulation 9, 14, 11. From yeast to humans, KDM5B is recognized by the gene's role in genomic stability; allowing for DNA break response and prevention of disease and neurodevelopmental disorders in animals. Ultimately, the KDM5B gene is heavily involved in development, and a mutation in KDM5B associates itself with developmental disorders.

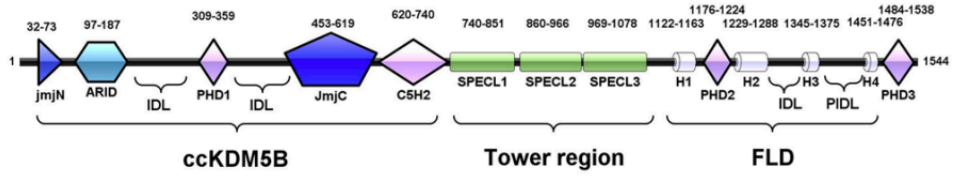

Figure 1. KDM5B. Representation of KDM5B structural domains (adapted from Dorosz et al., 2019)

KDM5B Variants Identified in Individuals with ASD and ID

Previously, KDM5B mutations were only identified in individuals with cancer: hepatocellular carcinoma, prostate cancer, colorectal cancer, esophageal cancer, and malignant melanoma 9. Recently, more and more studies are identifying KDM5B mutations in individuals with neurodevelopmental disorders (NDD). Genome studies of NDDs use animal models to research this discovery, like mice and *drosophila* (fruit fly).

Individuals with autism do not always have a KDM5B variant, but this variant can also be found in people with ID, DD, facial dysmorphia, and epilepsy. This is important as these disorders are symptoms of ASD, creating even more connections to KDM5B 2, 15. Exome-wide studies on ASD patients identified nine missense, frameshift, and nonsense KDM5B mutations in the JmjC domain 9. Nonsense and frameshift mutations result in loss of function, while missense mutations alter the transcription of genes. Two *de novo* missense and loss of function (LoF) mutations were reported in patients with either ID or ASD. One *de novo* splice mutation (c.808 + 1G > A) in one patient resulted in a decrease in KDM5B mRNA expression, this patient had ID and ASD characteristics. This study's second KDM5B de novo mutation (c.576 + 2T > C) resulted in DD and ASD 2. A different study investigated a patient with two *de novo* mutations: KDM5B frameshift mutations and deletion of 8.2 Mb. This patient was not diagnosed with ASD, but they had epilepsy, intellectual disorders, and facial dysmorphisms (common symptoms of autism) 15. In addition to nonsense, frameshift, and missense mutations, compound heterozygous and homozygous mutations in KDM5B correlate to ASD and ID 14. Compound heterozygous variants cause severe DD and homozygous variants are commonly linked to recessive intellectual disability; both present facial dysmorphism and camptodactyly 7, 16. Research from Genome sequencing, exome sequencing, etc. in people leads to the conclusion that KDM5B variants have a role in ASD.

Animal Models

As previously mentioned, KDM5B mutations in NDDs is a developing research subject; therefore few animal models have been pursued. But most animal models investigated mice and KDM5B mutations. Earlier studies in which homozygous deletion of KDM5B in mice had a high embryonic lethality, but those who survived had neural defects and irregular gene expression 17. Also in the embryonic stage, these mice experienced smaller

lungs, disorganized central nervous system nerves, and eye defects 17. This is likely due to H3K4me3's role in embryogenesis. Recent studies have come to more conclusive observations. For instance, homozygous and compound heterozygous KDM5B mutations in mice show cognitive dysfunction, facial dimension difference, increased anxiety, memory deficits, skeletal abnormalities, and more 14, 7. Ultimately, this data further supports that KDM5B LoF modulates cognitive phenotypes and development.

Conclusion and Future Perspectives

KDM5B catalyzes the demethylation of H3K4. KDM5B regulates cell functions ranging from DNA damage response to neuronal differentiation. Exome and genome sequencing revealed missense, frameshift, and nonsense mutations of the KDM5B gene in patients with ASD. Knockdown of KDM5B in mice is detrimental to development (affected learning, social interactions, and epilepsy), suggesting KDM5B variants may be the cause of developmental disorders. Although research is making great strides in coming to a conclusion, further research on KDM5B mutations in NDDs should be pursued. These studies should include vitro analyses, in vivo experiments, and knockout experiments in *Drosophila* and mice. We believe future studies could lead to therapeutics or prenatal treatments to prevent ASD and neurodevelopmental disorders alike.

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