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Pathogenic *KDM5B* variants in the context of developmental disorders

Jack Harrington [a], Gabrielle Wheway [b], Sandrine Willaime-Morawek [c], Jane Gibson [a], Zoë S. Walters [a,*]

[a] School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, UK
[b] School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, UK
[c] Clinical Neurosciences, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, UK

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ABSTRACT

Histone modifying enzymes are involved in the posttranslational modification of histones and the epigenetic control of gene expression. They play a critical role in normal development, and there is increasing evidence of their role in developmental disorders (DDs). DDs are a group of chronic, severe conditions that impact the physical, intellectual, language and/or behavioral development of an individual. There are very few treatment options available for DDs such that these are conditions with significant unmet clinical need. Recessive variants in the gene encoding histone modifying enzyme KDM5B are associated with a DD characterized by developmental delay, facial dysmorphism and camptodactyly. KDM5B is responsible for the demethylation of lysine 4 on the amino tail of histone 3 and plays a vital role in normal development and regulating cell differentiation. This review explores the literature on KDM5B and what is currently known about its roles in development and developmental disorders.

1. Introduction

Epigenetics revolves around the concept of regulating gene expression without changes to the nucleotide sequence itself. It was first described by Waddington [1] as "above genetics", whose original definition has evolved over the years and has ultimately become a key avenue of research in numerous fields [2]. DNA methylation, histone modification and non-coding RNA are all mechanisms behind epigenetic control of genes, transforming the genetic sequence into displayed phenotypes. Over the past two decades the role of epigenomics in diseases has been the focus of research, where an aberrant modulation of gene expression and epigenetic landscape ultimately impacts on health and disease [3]. Epigenetic abnormalities have been observed in cancers and have been linked to obesity, diabetes and autoimmune diseases [4]. Primarily driven by oncology, epigenetic-based therapy is beginning to emerge [5].

Developmental disorders (DDs) are a heterogeneous group of chronic, often severe, conditions that impact the physical development, learning, language or behavior of an individual. The diverse etiology and range of clinical manifestations in DDs poses a challenge in understanding the underlying molecular mechanisms behind the disorders and determining any novel therapeutic interventions. Large scale studies exploring the molecular mechanisms behind DDs have implicated histone modifying enzymes (HMEs) in the pathogenesis of DDs [6], enzymes involved with the epigenetic regulation of gene expression. The mechanisms behind the overall function of these HMEs is complex, often working in a tightly regulated balance of co-factors to finely control an epigenetic landscape for normal development. It is often through studying these disease-causing aberrations that the mechanisms of normal function can be explored. This review explores the histone modifying enzyme KDM5B, its functions in development and the associated disorders as a result of damaging variants.

2. Epigenetics

2.1. Histones and histone modifications

Histones are a highly conserved family of proteins that are

Abbreviations: AAV, Adeno-associated viruses; AON, Antisense oligonucleotide; ADHD, Attention deficit hyperactivity disorder; ASD, Autism spectrum disorders; Chip-seq, Chromatin immunoprecipitation – sequencing; DD, Developmental disorders; ES, Embryonic stem cell; HME, Histone modifying enzyme; ID, Intellectual disability; LoF, Loss of function; KDM, Lysine demethylases; KMT, Lysine methyltransferases.

* Corresponding author.
E-mail address: z.s.walters@soton.ac.uk (Z.S. Walters).

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responsible for the condensing of DNA in the nucleus of eukaryotic cells into chromatin [7]. While DNA is packaged densely in chromatin, genes are inaccessible to the transcriptional machinery and are silenced. For genes to be expressed, the nucleosome needs to undergo structural changes [8]. These alterations in chromatin structure have a key role in many biological processes including development [9].

All four core histone proteins contain lysine rich histone tails that extend away from the nucleosome and that can be modified by post-translational modifications, particularly the amino termini of histone H3 and H4 and both amino and carboxyl termini of histones H2A, H2B and H1 [9]. The type and level of modification is controlled by histone modifying enzymes (HMEs). Each of these post translational modifications (marks) alters the structure of chromatin and influences the accessibility of DNA. As a result, these HMEs and their respective marks play a key role in gene regulation.

Until relatively recently, acetylation was the most widely studied histone modification [10]. In short, the addition of a negatively charged acetyl group to lysine residues on histone tails neutralizes the positive charge of histones and reduces its affinity for DNA [11]. This alters the chromatin structure to increase DNA accessibility for transcription. However, with the discovery of the first histone demethylase, Lysine-specific demethylase 1 (LSD1), the dynamic nature of histone

Table 1
A list of the characterized lysine methyltransferases and lysine demethylases, cytogenetic band, the histone and lysine residue targeted, and the developmental disorders associated with aberrant variants [14,26].

Histone modifying enzyme	Chromosome	Target	Function	Associated developmental disorder
SUV39H1	Xp11.23	H3K9	Methyltransferase	
SUV39H2	10p13	H3K9	Methyltransferase	ASD
EHMT2	6p21.33	H3K9	Methyltransferase	Kleefstra syndrome
EHMT1	9q34.3	H3K9	Methyltransferase	Kleefstra syndrome
SETDB1	1q21.3	H3K9	Methyltransferase	ASD, Schizophrenia; ID
SETDB2	13q14.2	H3K9	Methyltransferase	ID; ASD
KMT2A	11q23.3	H3K4	Methyltransferase	Wiedemann-Steiner syndrome
KMT2B	19q13.12	H3K4	Methyltransferase	Kleefstra syndrome
KMT2C	7q36.1	H3K4	Methyltransferase	Kleefstra syndrome
KMT2D	12q13.12	H3K4	Methyltransferase	Kabuki syndrome
KMT2E	7q22.3		Methyltransferase	O'Donnell-Luria-Rodan syndrome
SETD1A	16p11.2	H3K4	Methyltransferase	Schizophrenia
SETD1B	12q24.31	H3K4	Methyltransferase	Intellectual developmental disorder with seizures and language delay
ASH1L	1q22	H3K36	Methyltransferase	Intellectual developmental disorder, autosomal dominant 52
SETD2	3p21.31		Methyltransferase	Luscan-Lumish Syndrome
NSD1	5q35.3	H3K36	Methyltransferase	Beckwith-Wiedemann syndrome; Sotos syndrome 1
SMYD2	1q32.3	H3K4, H3K36	Methyltransferase	
SMYD1	2p11.2	H3K4	Methyltransferase	
SMYD3	1q44	H3K4	Methyltransferase	
NSD3	8p11.23	H3K36	Methyltransferase	
NSD2	4p16.3	H3K36	Methyltransferase	Wolf-Hirschhorn Syndrome; Rauch-Steindl Syndrome
DOT1L	19p13.3	H3K79	Methyltransferase	
KMT5A	12q24.31	H4K20	Methyltransferase	Meier-Gorlin syndrome 1
KMT5B	11q13.2	H4K20	Methyltransferase	Intellectual developmental disorder, autosomal dominant 51
KMT5C	19q13.42	H4K20	Methyltransferase	
EZH2	7q36.1	H3K27	Methyltransferase	Weaver syndrome
EZH1	17q21.2	H3K27	Methyltransferase	
SETD7	4q31.1	H3K4	Methyltransferase	
PRDM2	1p36.21	H3K9	Methyltransferase	
PRDM9	5p14.2	H3K4, H3K36	Methyltransferase	
PRDM6	5q23.2	H4K20	Methyltransferase	Patent ductus arteriosus 3
PRDM8	4q21.21	H3K9	Methyltransferase	Epilepsy, progressive myoclonic, 10
MECOM	3q26.2	H3K9	Methyltransferase	Radioulnar synostosis with amegakaryocytic thrombocytopenia 2
PRDM16	1p36.32	H3K9	Methyltransferase	Cardiomyopathy, dilated, 1LL; Left ventricular noncompaction 8
KDM1A	1p36.12	H3K4, H3K9, H4K20	Demethylase	KBG syndrome
KDM1B	6p22.3	H3K4	Demethylase	
KDM2A	11q13.2	H3K36	Demethylase	
KDM2B	12q24.31	H3K26	Demethylase	Schizophrenia; Intellectual developmental disorder with seizures and language delay
KDM3A	2p11.2	H3K9	Demethylase	
KDM3B	5q31.2	H3K9	Demethylase	Diets-Jongmans syndrome
JMJD1C	10q21.3	H3K9	Demethylase	Rett syndrome; ID
KDM4A	1p34.2-p34.1	H3K9, H3K36	Demethylase	
KDM4B	19p13.3	H3K9, H3K36	Demethylase	Intellectual developmental disorder, autosomal dominant 65
KDM4C	9p24.1	H3K9, H3K36	Demethylase	
KDM4D	11q21	H3K9	Demethylase	
KDM4E	11q21	H3K9	Demethylase	
KDM4F	11q21	H3K9	Demethylase	
KDM5A	12p13.33	H3K4	Demethylase	ASD; ID
KDM5B	1q32.1	H3K4	Demethylase	Intellectual developmental disorder, autosomal recessive 65
KDM5C	Xp11.22	H3K4	Demethylase	Intellectual developmental disorder, X-linked syndromic, Claes-Jensen type
KDM5D	Yq11.223	H3K4	Demethylase	Potentially ASD through association with *Engrailed Homeobox 2*
KDM6A	Xp11.3	H3K27	Demethylase	Kabuki syndrome
KDM6B	17p13.1	H3K27	Demethylase	Neurodevelopmental disorder with coarse facies and mild distal skeletal abnormalities
UTY	Yq11.221	H3K27	Demethylase	
KDM7A	7q34		Demethylase	
PHF8	Xp11.22	H3K9, H4K20	Demethylase	Intellectual developmental disorder, X-linked, syndromic, Siderius type
PHF2	9q22.31	H3K9, H4K20	Demethylase	
KDM8	16p12.1	H3K36	Demethylase	

methylation was revealed [12]. As a result, over the past decade the focus of histone research has shifted to methylation, the pattern and regulation of which, across various gene elements, is now known to be important in many biological processes.

2.2. Histone methylation

There are 6 major lysine residues that have the ability to be methylated; H3K4, H3K9, H3K27, H3K36, H3K79 and H4K20, where the ammonium group on the residues are able to accept up to three methyl groups [13]. Two groups of histone modifying enzymes (HMEs) are responsible for the addition (lysine (K) MethylTransferases, KMTs) and removal (lysine (K) DeMethylases KDMs) of these methyl marks. There are currently 34 characterized chromatin modifying KMTs and 24 KDMs (listed in Table 1) [14], however there are potentially more SET domain containing proteins yet to be fully characterized [15]. These enzymes have a high degree of specificity for the specific lysine and degree of methylation [16]. For example, KDM5B specifically targets tri- and di-methylated lysine 4 of histone 3 (H3K4me2 and H3K4me3) to remove methyl groups from these (Fig. 1) [17].

An extensive effort utilizing chromatin immunoprecipitation followed by sequencing (ChIP-seq) across tissue and cell types has revealed a complex pattern of histone methylation distribution. Depending on which lysine is methylated, and to what degree, it can influence the degree of gene expression or repression (reviewed [13]). For example, H3K4me3 has been specifically associated with gene activation, marking the promoters of active genes [18]. Approximately 80 % of promoters in embryonic stem cells with the H3K4me3 mark are actively transcribed [19]. More specifically, as an example, this distribution has been mapped in the human prefrontal cortex, displaying a H3K4me3 enrichment at the promoter of genes associated with synaptic control and other neuron-specific genes [20]. They found transcriptional start sites of neuropsychiatric susceptibility genes trimethylated in neuronal compared to non-neuronal cells including *DPP10*, *CNTN4* and *CHL1*.

2.3. The KDM5 family of H3K4 demethylases

The KDM5 family, also known as the JARID1 family, is characterized by the presence of a catalytic Jumonji domain catalyzing the removal of methylation marks (tri-, di- or mono-methylation) from lysine 4 of histone 3 [21]. It is a highly evolutionary conserved through nature, where in mammals the family encompasses four paralogs; KDM5A, KDM5B, KDM5C and KDM5D [22]. All member of the family consists of multiple domains including an N-terminal Jumonji N, Jumonji C, a DNA binding ARID domain, a C5HC2 zinc finger, and a number of histone binding PHD domains, but differ greatest at the C-terminal region and the number and composition of the PHD domains [23]. The association of H3H4me3 at transcriptional start sites indicates members of the KDM5 family act generally as gene repressors [24].

The transforming histone methylation landscape has an important role in human development, and through the utilization of high-resolution next generation sequencing and large scale studies, HMEs have been identified as the genetic basis of a number of DDs (Table 1) [6]. More specifically, each of the four members of the KDM5 family have been associated with a neurodevelopmental disorder [25]. To explore the functions of KDM5 in normal development and in disorders, mouse, fruitfly (*Drosophila melanogaster*) and nematode worm (*Caenorhabditis elegans*) have previously been used [22].

3. Developmental disorders

3.1. Clinical features and disease burden

The term developmental disorder (DD) encompasses a range of diagnoses that include intellectual disability (ID), hearing and vision impairment, autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), cerebral palsy and epilepsy, where neurodevelopmental conditions, including neuromuscular conditions are most common. In 2016, 52.9 million children younger than 5 years old had a diagnosed DD; 8.4 % of children worldwide [27]. These conditions usually manifest during the developmental period, from birth to early adulthood, and continue indefinitely throughout adult life [28]. Across the range of conditions, vision loss is the most prevalent DD, followed by hearing loss, ID and ASD [27]. However, these disorders frequently co-occur [29,30]. Comparatively, children with DDs are at a greater risk of health issues, lower educational attainment, reduced wellbeing and suboptimal development [31]. As such, the life expectancy of people with DDs is usually lower than in the general population [32].

Environmental conditions, like gestational infection and maternal alcohol consumption can sometimes be attributed to the development of DDs [33], however DDs are predominantly inherited genetic conditions. Between 50 and 80 % of cases have a genetic etiology including chromosomal abnormalities, copy number variants or mutations [34,35]. As well as being a highly phenotypically heterogeneous group of disorders,

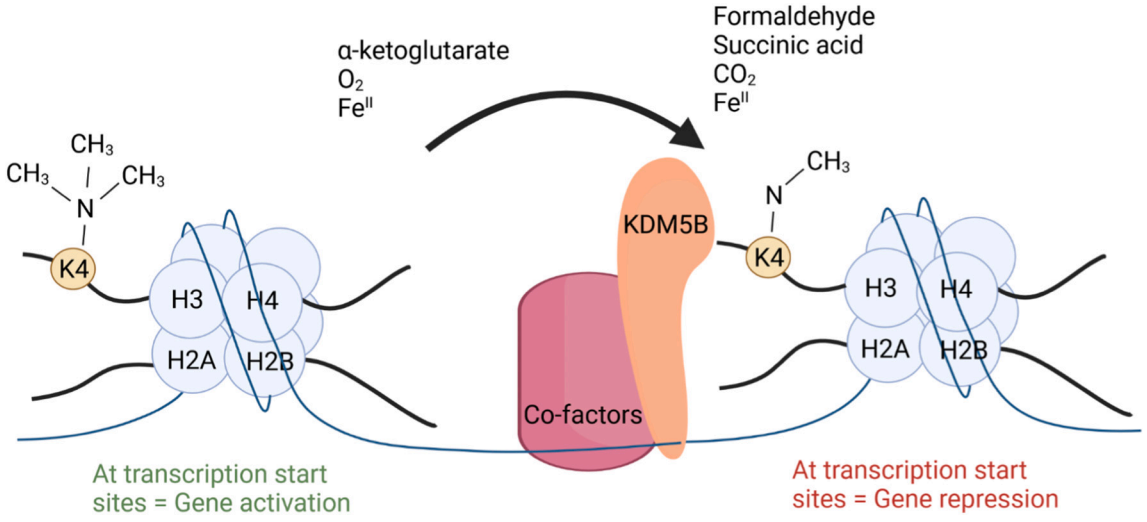

Fig. 1. The KDM5B histone demethylation reaction as a mechanism for mediating gene repression. From recruitment to the genome through the ARID domain or association with co-factors, KDM5B mediates the removal of Tri- and di-methyl groups on H3K4 in a Fe(II) and 2-oxoglutarate dependent reaction. (Created with BioRender.com, accessed April 2022).

they are extremely genetically heterogeneous. The 'Intellectual Disability' Panel App gene panel, developed as a virtual gene panel for targeted analysis of whole genome sequencing data in the 100,000 Genomes Project lists 1139 genes confidently concluded to be causes of ID [36]. This list contains a number of histone methyltransferases and demethylases notably including *KDM5B* and *KDM5C*.

3.2. Diagnosis

There is great difficulty in diagnosing DDs as they often manifest in a range of heterogeneous phenotypes affecting multiple systems, where each condition often has comorbidities and overlaps phenotypically [37]. Standard clinical approaches have a poor success rate in determining accurate diagnosis of DDs [38]. In 2013, neurodevelopmental disorders were introduced into the Diagnostic and statistical manual of mental disorders: DSM-5 [39], yet there is still a large overlap between diagnoses. An accurate and early diagnosis is crucial for the effective clinical management of the patient and is associated with improved long-term outcomes and significant positive psychosocial impacts on the individual and their family [34,40]. Whereas lack of a clear diagnosis has a detrimental effect [41]. However, due to the complex diagnosis, the length of time taken to gain a diagnosis could last up to 7 years, often referred to as the diagnostic odyssey [42]. This has improved over recent decades with the advancement of molecular and cytogenetic techniques, and as they become routine practice in the clinic [37]. Genetic diagnosis also has the additional benefit of the potential inform clinical care, and aid family planning decisions. There has been a growing implementation of genetic counsellors to provide education to both patients and the parents of patients and aids with making informed treatment decisions [43].

3.3. Treatment

Due in part to the complex multi-system nature of most DDs, they are difficult conditions to treat as well as diagnose. Although cataract surgeries and Cochlear implants have improved outcomes for some vision and hearing impairments, there is currently no cure for many features of DDs with most treatments aimed at symptom management. A range of psychotropic medications may be useful in combating some of the behavioral symptoms [44], but options are limited, and as a result the majority of DD patients require long-term supportive care. This highlights the financial cost associated with DDs with an estimated lifetime cost of $1–2 million for a child born with ID, cerebral palsy, hearing loss or vision impairment [45]. A focused exploration into targeted treatment of the underlying biology of the disorders may reveal novel avenues for treatment.

The development of antisense oligonucleotide (AON) therapy is a promising avenue to address monogenetic or multifactorial conditions. Initially approved for treating genetic eye conditions, AON have now been developed to treat other Mendelian diseases including Duchenne muscular dystrophy and spinal muscular atrophy [46]. This highlights the importance of identifying the genetic cause behind these disorders and underlying mechanisms and how it can be translated into the clinic for novel treatment avenues.

4. Histone modifying enzymes in developmental disorders

With the advent of next generation sequencing, there has been a greater focus on genetic factors behind undiagnosed DDs. Over the past decade, the Deciphering Developmental Disorders study has improved genetic diagnosis of DDs and explored the underlying molecular mechanisms behind DDs [38]. This is a concerted effort to understand the genetic mechanisms behind the development of this heterogeneous group of disorders with an aim to improving diagnosis and tailoring treatments to these children. There is a growing number of damaging *de novo* mutations identified in developmentally important genes linked to DDs [47]. In particular, whole-genome (WGS) and whole-exome sequencing (WES) have revealed an enrichment of histone modifying enzymes harboring mutations in developmental disorders [48], opening an avenue for further research.

In patients exhibiting developmental disorders, pathogenic variants of KMTs and KDMs have been identified that result in haploinsufficiency and abnormal histone methylation [6]. Mutations in the histone methyltransferase *KMT2D,* a H3K4 mono-methyltransferase, are associated with Kabuki syndrome, a disorder characterized by facial, cardiac and skeletal abnormalities with ID [49]. Mutations in the histone methyltransferase *KMT2A,* a H3K4 tri-methyltransferase, have been associated with Wiedemann-steiner syndrome, a rare disorder displaying hypertrichosis cubiti, short stature, intellectual disability and distinctive facial features [50]. Additionally, homozygous LoF mutations have also been observed in H3K4 KDMs, where *KDM5A* has been linked to ASD [51,52] and *KDM5C* linked with X-linked mental retardation [53] and ASD [54]. It is therefore unsurprising that another H3K4 KDM; KDM5B is also associated with a recognizable developmental disorder.

5. KDM5B has key functions in development and is linked to disease

5.1. KDM5B, a histone demethylase

Early development is controlled in part through coordinated epigenetic regulation. With the relevant signal, embryonic stem (ES) cells are capable of indefinitely self-renewing or differentiating into the multitude of different cell types of the three germ layers [55]. As these cells differentiate in the developing embryo, the patterns of which genes are active and which are repressed transform, dictating cell identity and fate. The coordinated patterns of histone methylation, that control the accessibility of gene promoters and enhancers, is one of the key mechanisms that regulate these processes [48]. Specifically, the methylation of H3K4 and H3K27, which are associated with gene activation and repression respectively, are key marks of gene expression mediation [19]. The general transcription factor TFIID binds to this H3K4me3 mark [56].

The histone demethylase, KDM5B (also known as Jarid1B or PLU-1), is known to regulate gene expression and has a key function in development. It was first identified as a transcriptional repressor that was over expressed in breast cancer cell lines [57], but has since gained interest in cancer initiation and progression and mammalian development. It belongs to the JHDM family of KDMs, characterized by the presence of a catalytic Jumonji-domain, and catalyzes the removal of tri- and di-methylation of H3K4 [17]. As H3K4me3 is a chromatin mark that is associated with the promoters of actively transcribed genes, KDM5B and other H3K4me3 demethylases that remove this mark were shown to act as transcriptional repressors to silence genes [58].

5.2. Structure of KDM5B

KDM5B is a large nuclear protein that is highly conserved in nature [21]. In humans, it is 1544 residues long and contains three PHD domains, and a JmjN, ARID, JmjC and C-terminal zinc finger domain crucial for its activity [59]. The JmjN and JmjC fold together to form the catalytic Jumonji domain responsible for the removal of histone tail methyl groups. A Fe(II) and α-ketoglutarate dependent reaction occurs to produce a hydroxymethyl intermediate which immediately degrades producing formaldehyde and the demethylated lysine (Fig. 1) [60]. Within the amino-acid sequence, an ARID and a PHD domain lies between both halves of the Jumonji domain, which differs from other histone demethylases outside the KDM5 family [61]. The ARID domain allows for binding to GC-rich DNA sequences and the PHD domains allow for interaction with histones [61,62]. It is these PHD domains that allow for the specificity to target distinct genomic regions [63]. Removal of either the ARID, JmjN or JmjC domains removes the ability of KDM5B

to demethylase [64].

5.3. KDM5B in development

KDM5B is largely expressed during development, whereas in healthy adults it is generally only found significantly expressed in the testes, ovaries, brain, eye, spleen and thymus [65]. However, it is often upregulated in a range of leukemias and other cancers including breast, prostate, bladder, lung and cervical cancer [66]. In development, it is observed to be highly expressed in stem cells including ES cells, neural progenitors, trophoblast stem cells and blood lineages, influencing the gene expression and differentiation of these cells [67]. In ES cells, there is some evidence that KDM5B is essential for self-renewal, where the usual transcriptional repressor, KDM5B, paradoxically functions as an activator to self-renewal genes [68]. KDM5A has also been observed to function as both an activator or repressor depending on the context [69], and the KDM5B ortholog in Drosophila positively regulates gene expression [70]. However, this contradicts another report where it was concluded that KDM5B is dispensable for self-renewal [65]. This suggests ES cell pluripotency is regulated by the chromatin modelling of KDM5B but the specific mechanisms are complex and unknown. Subsequent experiments demonstrated a depletion of KDM5B results in an extended self-renewal in the absence leukemia inhibitory factor, the cytokine that inhibits differentiation [71]. Using short hairpin RNA knockdown of *KDM5B,* Kidder et al. [71] also revealed KDM5B acting as a barrier to the reprogramming process in induced pluripotent stem (iPS) cells and was seen to be involved with silencing pluripotency genes during differentiation. As the shKDM5B cells differentiate, there was a greater level of H3K4me3 at bivalent genes, where it has been suggested that KDM5B co-localizes with H3K4me3 near the promoters and enhancers of active genes in ES cells [67]. Here it can function in focusing H3K4me3 at the promoter regions, preventing the spread of methylation to surrounding histones [67].

KDM5B also plays a direct role in cell fate decisions, notably neuronal differentiation. Overexpression of KDM5B in ES cells reduces the expression of differentiation markers, including *Egr1*, *p27* and *BMI1*, genes that are associated with differentiation and neural lineages [72]. Equally, knockdown of KDM5B resulted in an enrichment of these genes. These cells were blocked from terminal neural differentiation as observed through the absence of neural markers, yet maintained expression of self-renewal markers, such as *Oct4* [72]. Subsequent studies observed similar findings, highlighting the essential role of KDM5B in differentiation towards the neural lineage [65]. In adults, inhibition of KDM5B is seen to promote neurogenesis and decrease proliferation of adult neural stem cells [73].

5.4. Interactions in gene repression

Independent of its demethylase activity, KDM5B has been shown to regulate transcription *via* interactions with other protein partners [74]. It has been observed to associate with the transcription factors PAX9, FOXC2 and FOXG1 [75] *via* its PLU domain (Fig. 2), a Trp/Tyr/Phe Cys-rich region, that is found conserved across a number of other proteins [76]. These transcription factors are members of Groucho-mediated transcriptional repression, a group involved in embryonic and neural stem cell decisions [77]. PAX9 and FOXG1 are observed to repress transcription but combined with KDM5B, repression activity is significantly enhanced [78]. PAX9 deficient mice die soon after birth but exhibit a range of abnormalities including facial and limb deformities [79], and additionally, truncating mutations of FOXG1 are associated with ASD [80].

KDM5B is also known to directly interact with histone deacetylases (HDACs), histone modifying enzymes that decrease gene expression through a compaction of chromatin. Mammalian HDACs can be classified into four classes depending on their homology to HDACs in yeast (Reviewed in [81]). KDM5B is observed to physically interact with class I and class IIa through two of the PHD domains on KDM5B [82]. The class IIa HDACs have a crucial role in the differentiation of neural cells through binding to members of the MEF2 family of transcription factors and enhancing gene repression [83]. Pathogenic mutations in MEF2C result in MEF2C Haploinsufficiency Syndrome, a rare disorder characterized by ID, ASD, and seizures [83]. There are a number of repression complexes that contain HDACs and the nuclear receptor co-repressor (N-CoR) [81]. KDM5B was also observed to indirectly interact with N-CoR [82], potentially enhancing repression through recruiting these HDAC complexes.

KDM5B also acts as a corepressor for AP-2 mediated gene expression [84], a family of transcription factors important in embryogenesis and the development of limbs and neural tube among others [85]. KDM5B is a co-repressor dependent on a complex of TFAP2C and Myc and has been observed to repress the universal cell cycle inhibitor p21 (*CDKN1A)*.

5.5. Interactions in gene activation

Despite its usual gene repressive properties, evidence indicates KDM5B is also an essential co-activator for retinoic acid (RA) mediated genes [86]. RA signaling regulates transcription through binding to nuclear receptors that are bound to DNA at RA response elements (RAREs) (reviewed in [87]). This signaling pathway is crucial for the normal development of many organs including the brain, spinal cord and forelimbs among others (reviewed in [88]), and deregulation has been associated with cancer, metabolic disease, eye disease as well as DDs [89]. In the absence of the RA ligand, co-repressors including N-CoR

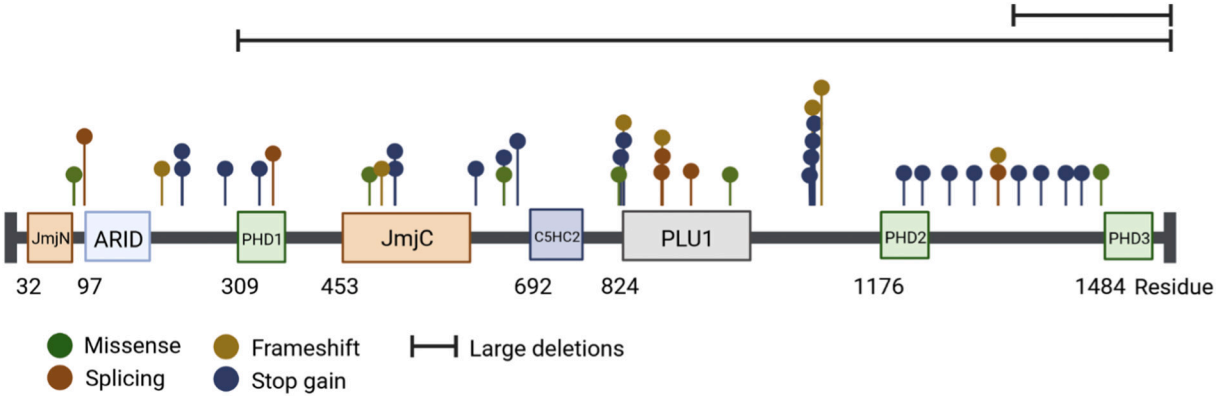

Fig. 2. A lollipop figure demonstrating the positions of likely damaging mutations found in patients. The corresponding domains of the protein that the gene encodes for are displayed. Also shown are the type of mutation as indicated through color of the lollipop. Data obtained from [94] (Created with BioRender.com, accessed April 2022).

bind to the receptor. This allows the recruitment of HDACs, the polycomb repressive complex 2 and KDM5B resulting in high H3K27me3, low level of H3K4me2/3 and low histone acetylation, marks of gene repression. In the presence of the RA ligand, co-repressors are attenuated but KDM5B is then free to bind to the retinoic acid receptor itself, acting as a co-activator enabling transcription [86]. Silencing KDM5B under treatment of RA results in a drop in HOXA1 expression, a RA mediated gene that is important for neurodevelopment.

5.6. KDM5B in developmental disorders

Like many previously mentioned HMEs, damaging variants of the *KDM5B* gene have been implicated in the pathogenesis of developmental disorders. First observed in 2014, where whole exome sequencing revealed a cohort of 2500 ASD patients contained a number of *de novo* missense and nonsense variants of *KDM5B* (Fig. 2) [90]. Further whole exome studies produced evidence again associating *KDM5B de novo* mutations with ASD [91,92], however interestingly, two unaffected siblings in the study also had *de novo* LoF KDM5B variants but did not exhibit ASD. Similarly, another 29 protein truncating variants have also been described from the Exome Aggregation Consortium [93], a collaborative aggregation of exome sequencing data from a range of projects. This suggests that haploinsufficiency is not the mechanism of the associated disease, a common mechanism seen in other HME associated DDs [6].

It was through the Deciphering Developmental Disorders Study that damaging *KD5MB* variants were first associated with a recognizable syndrome. Faundes et al. [6] observed homozygous or compound heterozygous KDM5B LoF mutations in three unrelated males, aged 10, 11 and 18 years, in two cohorts of 4293 and 5332 DD patients with whole exome sequencing [47]. All three patients exhibited moderate to severe developmental delay and ID, with two patients having facial dysmorphism and camptodactyly of the fourth and fifth fingers. An additional 7-year-old male has also been reported, again displaying developmental delay and ID as well as ADHD, sleep disturbance and joint laxity [94]. Recently a further case study has described a 25-year-old male with a heterozygous *de novo* frameshift variant in the JmjC domain alongside an 8.2 Mb of chromosome 2q. The patient displaying similar ID and facial and finger dysmorphic symptoms [95].

A further case study focused on a girl and a terminated sibling, both with compound heterozygous damaging variants, where the girl displayed the recognizable dysmorphic features [96]. Both siblings exhibited Ageness of the corpus callosum (ACC), detected on prenatal imaging. ACC is a common cerebral malformation where the corpus callosum is partially or fully absent [96] and has a wide spectrum of symptoms of from unnoticeable to severe impairments [97]. The post-mortem of the terminated sibling revealed mild ocular hypertelorism but no other dysmorphic features [98]. The presence of ACC in one previously mentioned case [6] suggest that ACC could be an additional symptom of this disorder.

This recognizable disorder has subsequently been given the name Intellectual developmental disorder, autosomal recessive 65; MRT65 [26]. Heterozygous mutations have also been recorded from the aforementioned studies. Nine patients exhibited *de novo* heterozygous mutations, of which six were LoF and three missense, and 22 inherited LoF mutations where patients exhibited moderate developmental delay but not the physical deformities [94]. The majority of the parents of the patients did not display any of the clinical features observed in the affected children, despite passing on an aberrant copy of the gene. It appears that KDM5B is a recessive developmental disorder gene where heterozygous LoF variants are incompletely penetrant. Additional *de novo* splice variants of *KDM5B* have been linked to patients with ID and ASD [93], where they concluded similarly that KDM5B is likely an autosomal recessive disorder but also with dominant disease associated variants. Interestingly, one of these variants exhibited as mild ID and ASD with reduced KDM5B expression but did not significantly change the H3K4me3 patterns. It has been suggested that this varying degree of severity of heterozygous mutations may be influenced by compensation from other members of the KDM5 family [99], similar to the upregulation of KDM5B expression observed in the presence of a KDM5C LoF mutation [100].

5.7. Mouse models

There have been several attempts at generating *KDM5B*-knockout mice, with varying degrees of success. Early attempts indicated that homozygous *KDM5B*-knockout resulted in early embryonic lethality [101]. A replacement of exon 1, containing the JmjN region, with a neomycin-resistance gene appeared to be lethal at the late blastocyst stage (E4.5) at the time of implantation, whereas heterozygous mice were viable and fertile with no apparent abnormalities [101]. Subsequent attempts have been more viable, through producing a deletion of exon 6 and a resultant frame shift and premature termination [65,102]. These mice did not result in significant prenatal mortality but did neonatally with 50 % of homozygous mice dying in the first two hours after birth. This is thought to be as a result of a failure to establish proper respiratory function, but the exact mechanisms remain unclear. The surviving homozygous adults exhibited increased incidents of exencephaly, eye defects, disorganized cranial and spinal nerves, and a reduced response to pinching [102]. Similarly, Martin et al. [94] generated a deletion of exon 7 using CRIPSR/CAS9 and were able to create homozygous *KDM5b*-null mice, albeit sub-viable when compared to heterozygous in-crosses. The heterozygous mice again appeared normal and fertile, however, homozygous mice displayed vertebra defects. Interestingly, behavioral abnormalities with *KDM5B*-null mice displaying increased anxiety, reduced sociability, and memory impairment were also observed [94]. Recently, a strain of mice has been generated with the ARID domain and five amino acids from the JmjN region spliced out. These ΔARID mice were viable and fertile but lacked demethylase activity, demonstrating that KDM5B has crucial functions in development but the demethylase activity is not necessarily required [64]. A ΔARID *KDM5B* variant has yet to be observed in humans. In conclusion from these mouse models, it is clear KDM5B has a crucial role in the development of healthy mice, both through its function to demethylase and through other interactions. How this exactly relates to human patients exhibiting KDM5B LoF is unclear, yet could provide suitable models for the development of novel treatment targeting these underlying mechanisms.

5.8. Potential avenues for treatment

As with most DDs, current treatment options for aberrant *KDM5B* associated DDs are limited with a focus on the management of individual symptoms or comorbidities rather than the underlying mechanisms. Pharmacological interventions are limited, although they may help in managing the lack of attention and insomnia that is described with the condition [94]. In recent years, there has been increasing interest in exploring targeted gene therapy for DDs.

Viral mediated gene transfer is a promising avenue for the precision therapy of DDs. The use of adeno-associated viruses (AAVs) is the leading vector for the delivery of gene therapy [103]. AAVs have been used to replace the damaging genes, making it ideal for the treatment of monogenic DDs. A recent review on the potential use of AAVs in neurodevelopmental disorders focused on the more common Rett Syndrome, Fragile X syndrome, Angelman syndrome as well as two rare DDs associated with the genes *SLC13A5* and *SLC6A1* [104]. Highlighting this progress is a review of small molecule drugs in clinical or pre-clinical development targeting an aberrant *UBE3A* gene that results in the neurodevelopment disorder Angelman syndrome [105].

Other ongoing developments for pharmacological treatment of DDs primarily focus on correcting downstream cellular pathways that are disrupted as a consequence of the aberrant genes. For example, Kabuki

syndrome, often with mutations in *KMT2D*, develop defects through abnormal regulation of the RAS/MAPK signaling [106] a hyper-activation of MEK within the RAS pathway. Utilizing small molecule inhibitors developed for a variety of cancers, MEK inhibition in zebrafish has been shown to mitigate some of the Kabuki syndrome associated phenotypes [106]. Equally, activating PI3K-AKTt-mTOR and Ras-MAPK-ERK pathways have been hypothesized to have a potential benefit for Angelman syndrome [105]. As KDM5B has been demonstrated to affect signaling pathways such as retinoic acid or AP-2 transcriptional regulation, therapeutic modulation of these could restore signaling to non-mutant *KDM5B* levels.

In order to successfully pursue these avenues of treatment, an improved understanding of the disorder is needed. Questions still remain around the influence of KDM5B on the histone methylation landscape during development, and its other functions independent of demethylation activity. There is also a need for suitable models for pre-clinical trials, where it is notoriously difficult to recreate the human phenotype of DDs in animal models. Difficulties are highlighted through the varied responses from the afore-mentioned *KDM5B* knock out mouse studies. Despite these challenges, targeting of KDM5B, either directly or indirectly, offers a promising avenue for therapeutic intervention for the treatment of DDs harboring pathogenic *KDM5B* mutations.

6. Conclusion

As focused large-scale studies come to fruition, the role of HMEs in the development of DDs is becoming more apparent [6,47,94], however the molecular mechanisms of these disease-causing aberrations remains unclear. The loss of function of KDM5B displays as developmental delay, facial dysmorphism and camptodactyly, however in heterozygous patients it is incompletely penetrant. Studies have shown that KDM5B has important functions in development, with essential roles in moderating the histone methylation landscapes [107] and interacting with transcription factors [78]. Highlighting KDM5B's role in normal development are several knockout studies, where its essential functions in early embryonic development and neuronal differentiation are apparent.

KDM5B is not unique among HMEs. With ongoing studies, more epigenetic regulators are being associated with DDs. Through studying the damaging aberrations in DDs and cancer, there will be a greater understanding of the molecular mechanisms of their actions. With continued efforts exploring these molecular mechanisms, novel therapeutic avenues could be revealed with a hope to translate into clinical applications.

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Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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