The FEBS Journal

FEBS PRESS science publishing by scientists

STATE-OF-THE-ART REVIEW

Molecular and cellular events linking variants in the histone demethylase KDM5C to the intellectual disability disorder Claes-Jensen syndrome

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Keywords
animal models of disease; autism spectrum disorders; CJ-XLID; Claes-Jensen syndrome; histone demethylase; intellectual disability; KDM5C; KDM5C-RD; MRXSCJ; neurodevelopmental disorders

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(Received 9 August 2021, revised 2 September 2021, accepted 16 September 2021)

doi:10.1111/febs.16204

The widespread availability of genetic testing for those with neurodevelopmental disorders has highlighted the importance of many genes necessary for the proper development and function of the nervous system. One gene found to be genetically altered in the X-linked intellectual disability disorder Claes-Jensen syndrome is *KDM5C*, which encodes a histone demethylase that regulates transcription by altering chromatin. While the genetic link between *KDM5C* and cognitive (dys)function is clear, how KDM5C functions to control transcriptional programs within neurons to impact their growth and activity remains the subject of ongoing research. Here, we review our current knowledge of Claes-Jensen syndrome and discuss important new data using model organisms that have revealed the importance of KDM5C in regulating aspects of neuronal development and function. Continued research into the molecular and cellular activities regulated by KDM5C is expected to provide critical etiological insights into Claes-Jensen syndrome and highlight potential targets for developing therapies to improve the quality of life of those affected.

Genetic variants in the *KDM5C* gene lead to the intellectual disability disorder Claes-Jensen syndrome

Neurodevelopmental disorders (NDDs) are a group of related conditions that alter the functioning of the nervous system of affected individuals and include intellectual disability (ID), autism spectrum disorders (ASD), communication disorders, and developmental delay (DD). Environmental factors such as maternal stress during pregnancy or preterm birth can increase the risk of NDDs [1–3]. In addition, many genetic variants have been etiologically linked to NDDs using genome-wide approaches such as comparative genomic hybridization and whole-exome sequencing [4]. These NDD-associated changes to DNA can range from

Abbreviations
ARID, A/T-rich interaction domain; ASD, autism spectrum disorder; CJ-XLID, Claes-Jensen X-linked intellectual disability; DD, developmental delay; DSM, diagnostic and statistical manual of mental disorders; H3K4me3, histone H3 trimethylated at lysine residue at amino acid position 4; ID, intellectual disability; IQ, intelligence quotient; JmjC, jumonji C-terminal domain; JmjN, jumonji N-terminal domain; KDM5, lysine demethylase 5; KDM5C-RD, KDM5C-related disorder; KMT2A, lysine methyltransferase 2A; KO, knock out; MRI, magnetic resonance imaging; MRXSCJ, mental retardation, X-linked, syndromic, Claes-Jensen type; NDD, neurodevelopmental disorder; NMJ, neuromuscular junction; OMIM, online Mendelian inheritance in man.

single base pair changes to large deletions and can either display a familial inheritance profile or occur *de novo* in affected individuals. While genes with roles in a range of cellular processes have been associated with NDDs, many variants affect transcriptional regulators, clearly demonstrating the importance of regulated gene expression to the proper development and functioning of the brain [5,6]. This review focuses on one transcriptional regulator, KDM5C, which is found to be genetically altered in individuals with the NDD intellectual disability, X-linked, syndromic, Claes-Jensen type (OMIM#300534) (Fig. 1A; Table 1). We will refer to this disorder as Claes-Jensen syndrome, although it should be noted that it has also been referred to as CJ-XLID, MRXSCJ, and KDM5C-RD [7–10].

KDM5C is one of four paralogous genes, *KDM5A-D*, that encode structurally similar proteins that function to regulate transcription (Fig. 1B). *KDM5* genes are expressed in a broad range of tissues, although it is notable that *KDM5C* is expressed at high levels within the brain, consistent with it playing a critical role in cognitive function [11]. The most characterized means by which KDM5C regulates gene expression is via its enzymatic demethylase activity. This function is mediated through its Jumonji N (JmjN) and Jumonji C (JmjC) domains, which enzymatically removes, di- and trimethyl marks from lysine 4 of histone H3 (H3K4me2/3) (Fig. 1) [12–15]. The target of KDM5C protein demethylation, H3K4me2/3, is found primarily surrounding promoter regions of genes and correlates with transcriptional activation [16]. Consistent with its ability to regulate the activity of promoters, KDM5C binds to these regulatory elements to alter transcription [7,8,17,18].

Clinically, males with pathogenic genetic variants in *KDM5C* are almost universally diagnosed with ID (Table 1). According to the most recent DSM-5 release, a diagnosis of ID is defined by an intelligence quotient (IQ) of less than 70 along with deficits in two or more adaptive behaviors that significantly affect daily functioning by the age of 18 [19]. Adaptive behaviors include conceptual skills related to language and problem solving, in addition to social proficiencies in interpersonal communication, social judgment, and empathy [19–21]. Also considered in a diagnosis of ID is the ability of affected individuals to independently carry out tasks required for self-care, to maintain employment, and be fiscally responsible. The degree of ID observed in males with Claes-Jensen syndrome

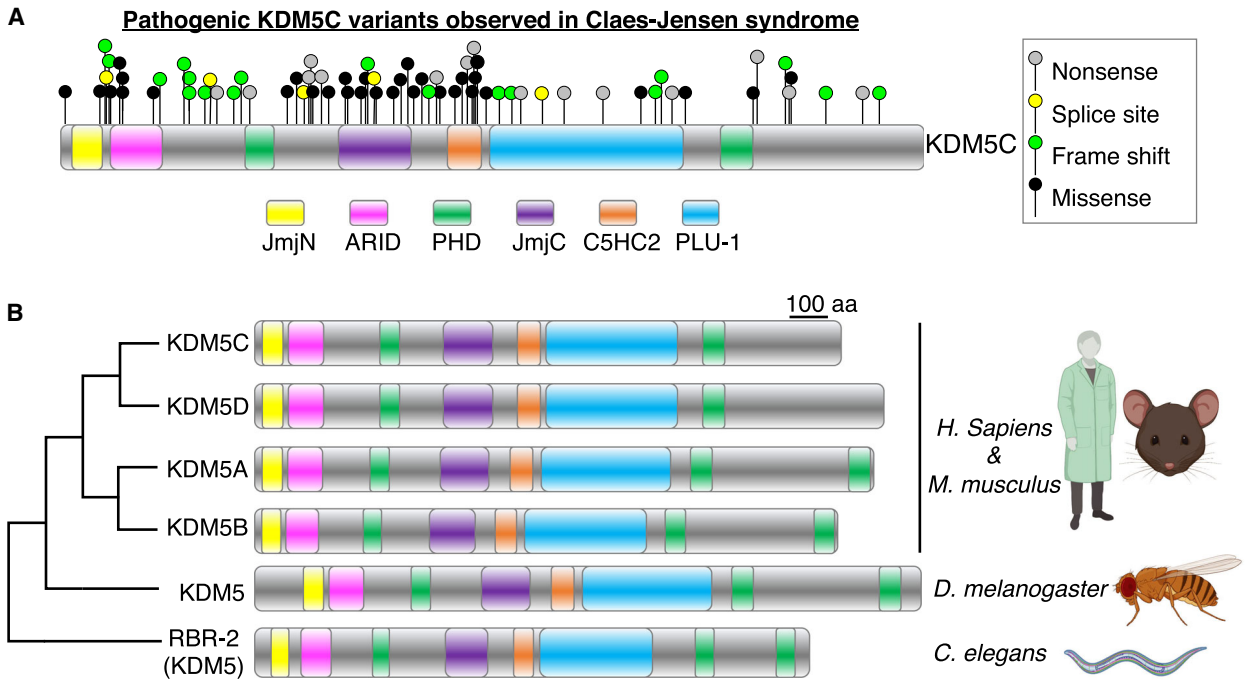

Fig. 1. The *KDM5C* gene that is genetically altered in individuals with Claes-Jensen syndrome encodes a conserved protein. (A) Genetic variants observed in individuals with Claes-Jensen syndrome. Types of genetic change are indicated by colored circles, with missense in black, frameshift in green, splice site in yellow, and nonsense variants in gray. Details of each variant can be found in Table 1. (B) Phylogenetic relationship between the four paralogous KDM5 family proteins in humans and the single orthologs in flies and worms. Domains are shown by colored boxes. Animal images generated using Biorender.com.

Table 1. *KDM5C* variants observed in individuals with Claes-Jensen syndrome. Type of variants and corresponding change to the encoded protein observed in males and/or females with Claes-Jensen syndrome. For missense variants, predicted domain(s) affected by the change in amino acid are indicated. Effects to *in vitro* demethylase activity are also indicated, if applicable. The "–" symbol indicates unknown or not determined.

Missense variants	NDD	KDM5C domain	Enzymatic activity	Frameshift variants	NDD
M1T [28]	ID	-	-	A50Rfs*23 [26]	ID
W52C [26]	ID	JmjN	-	R68fs*7 [10]	ID
A77T [22]	ID	ARID	-	G170Efs*64 [88]	ID/DD
Y85F [89]	ID/DD	ARID	-	L197fs*23 [26]	ID/DD
D87G [26,90] (2 families)	ID	ARID	No defect [91]	R211fs*23 [88]	ID/DD
Y164N [92]	ID	ARID	-	R211fs*22 [88]	ID/DD
A388P [10]	ID	PHD/JmjC	Reduced [14]	L257Afs*4 [93]	ID
D402Y [10]	ID	PHD/JmjC	Reduced [91,94]	T270fs*2 [95]	ID
S451R [96]	ID	PHD/JmjC	-	W534Gfs*15 [92]	ID
P480L [97]	ID	PHD/JmjC	Reduced [94]	A683fs*81 [25]	ID
Y503C [89]	ID/DD	JmjC	-	R795fs*5 [26]	ID
V504 M [22]	ID	JmjC	-	E810Cfs*5 [98]	NDD
S522F [23]	ID	JmjC	-	V1075fs*2 [94]	ID
K532N [99]	ID	JmjC	-	K1087fs*43 [24]	ID
P554T [24]	ID	JmjC	Reduced [24]	A1292Qfs*7 [27]	ID
R599C [26,89]	ID/DD	JmjC	-	L1336Pfs*11 [100]	ID
E613K [26]	ID	JmjC	-	R1481Gfs*9 [22]	ID
W622C [26]	ID	JmjC	-	Nonsense variants	NDD
C640Y [101]	ID	JmjC	-	Q237* [102]	ID
F642L [90]	ID	JmjC/C5HC2	Reduced [14]	R322* [90]	ID
E698K [10]	ID	C5HC2	-	E424* [103]	ID
T713M [104]	ID	C5HC2	-	E433* [105]	ID
A718P [105]	ID	C5HC2	-	E467* [89]	ID/DD
L731F [10,106]	ID	C5HC2	Reduced [14]	R694* [10]	ID
R750W [90]	ID	C5HC2	-	C724* [36]	ID
Y751C [90]	ID	C5HC2	Reduced [14]	R828* [107]	ID
R766W [108]	ID/ASD	C5HC2/PLU-1	-	Q970* [92]	ID
E1024D [109]	ID	PLU-1	-	C1095* [90]	ID
R1115H [35]	ID/ASD	-	No defect [35]	W1288* [10]	ID
A1277T [89]	ID/DD	-	-	E1299* [110]	ID
D1300V [80,111]	ASD	-	-	E1468* [99]	ID

Splice site variants	NDD
c.160G > T [112]	ID
c.1243-2A > G [26]	ID
c.658-1G > T [113]	ID/DD
c.1583 + 5G > A [22]	ID
c.2243 + 2T > C [92]	ID
c.2622 + 2dupT [26]	ID

varies from mild to severe, with children often also displaying and an increased incidence of epilepsy, aggression, and motor delays. Individuals may also present with physical characteristics such as short stature and craniofacial features [22–25]. Typically, those with mild ID have an IQ of 50–70 and have difficulty with speech, reading and writing, straightforward arithmetic, and/or adapting to societal norms. Those with moderate and severe ID have IQs of 35–50 and 20–40, respectively, and show greater deficits to adaptive behaviors. They may additionally require daily assistance with tasks involving self-care and social interaction.

Unlike males hemizygous for pathogenic *KDM5C* variants, the clinical presentation of heterozygous females varies widely and is only now beginning to be characterized in detail. While up to 50% of females have no overt deficits, others show intellectual disability, developmental delay, learning and speech difficulties, hormonal imbalance, and anxiety [9,23,26–29]. The basis for the incomplete penetrance of symptoms

is not clear, though for other genetic causes of X-linked cognitive disorders such as Fragile X syndrome, skewing of X-chromosome inactivation can impact the severity of symptoms in females [30,31]. Despite initially being thought to escape X-inactivation [32], the extent to which *KDM5C* is expressed from the inactive X-chromosome appears to vary widely [33,34]. It is therefore likely that variability in *KDM5C* inactivation contributes to disease severity in females with Claes-Jensen syndrome [26,28,35].

Pathogenic *KDM5C* variants alter neuronal structure and function

Very little published literature exists detailing the anatomical and functional changes to the brain that occur in those with Claes-Jensen syndrome. A subset of individuals has been documented to have microcephaly, and, in one case, an MRI revealed a disproportionately small cerebellum [27,36]; however, overall changes in brain size and structure do not appear to be common features of this disorder. To better understand the links between KDM5C function and brain development, several powerful genetic model systems have been employed. These include the mouse *Mus musculus*, the vinegar fly *Drosophila melanogaster*, and the nematode worm *Caenorhabditis elegans*. Studies using these animal models suggest that KDM5C plays vital roles in several different aspects of neuronal development and function, all of which could contribute to the clinical manifestations seen in those with Claes-Jensen syndrome.

The first *in vivo* model developed to study the molecular and cellular mechanisms underlying Claes-Jensen syndrome utilized mice. Like humans, mice encode four paralogous *Kdm5* genes and genetic knockout of the X-linked *Kdm5c* ($Kdm5c^{KO}$) results in features that resemble those observed in patients. For example, hemizygous male $Kdm5c^{KO}$ mice are smaller than their wild-type littermates and show deficits in learning and memory and motor control while displaying increased aggression and seizure susceptibility [7,8]. Heterozygous female $Kdm5c^{KO}$ mice have milder phenotypes than hemizygous males, being only slightly smaller than expected and exhibiting mild learning deficits [8]. While the brains from $Kdm5c^{KO}$ adult mice did not show any overall cytoarchitectural defects, cellular studies revealed that pyramidal neurons from the basolateral amygdala and the ventral hippocampus showed dendritic spine defects [7,18]. Dendritic spines receive synaptic signals from the axons of adjacent neurons and can change based on synaptic strength [37]. Notably, individuals with a range of different NDDs have been shown to have alterations in dendritic spine number and morphology [38–40]. Whether the changes to dendritic structure seen in *Kdm5c* knockout mice are the result of altered synaptic transmission or whether such morphological defects occur in other neuronal subtypes remains important and open questions.

The subject of whether KDM5C regulates gene expression programs necessary for synaptic activity has been investigated using another animal model, *Drosophila*. In contrast to mice and humans, *Drosophila* has a smaller genome that encodes a single KDM5 protein-containing conserved domains from all four mammalian paralogs (Fig. 1). Because ~70% of human disease-causing genes are conserved in *Drosophila*, it is widely used to provide fundamental insights into many disorders, including NDDs [41–43]. *Drosophila* has recently been developed as a model for Claes-Jensen syndrome, with KDM5 being shown to be necessary for associative learning and memory in adult flies [44,45]. The *Drosophila* larval neuromuscular junction (NMJ) is a glutamatergic synapse that is functionally similar to an excitatory synaptic connection in the human brain [46]. Analyses of genetic null animals have shown that KDM5 is essential in motor neurons to regulate the size and number of synaptic boutons at the NMJ, as well as for proper synaptic transmission [44]. Because altered glutamatergic signaling has been implicated in a range of NDDs [5,47], KDM5C-mediated regulation of synaptic signaling could contribute to the cognitive changes seen in Claes-Jensen syndrome.

Studies from *Drosophila* and *C. elegans* suggest that KDM5C is also likely to alter neuronal connectivity through its regulation of axonal growth and guidance. Whereas the *Drosophila* larval NMJ is an excellent system to examine synaptic morphology and function, the mushroom body, a key learning and memory structure within the adult brain, is a well-established model for studying axonal growth and guidance [46]. Animals lacking the *kdm5* gene show significant structural defects that are caused by failure of the neurons that comprise the mushroom body (Kenyon cells) to properly project their axons [48]. A similar phenotype has been described in worms with mutations in the single *kdm5* gene (*rbr-2*), where the axons of inter- and motoneurons show altered trajectory [49]. The repertoire of neurons affected by these growth and guidance defects in the fly and worm systems remains to be determined, as does the extent to which KDM5C regulates this process within mammalian brains. Combined, these data do provide compelling evidence that KDM5C controls more than one aspect of neuronal development across multiple cell types and developmental stages (Fig. 2).

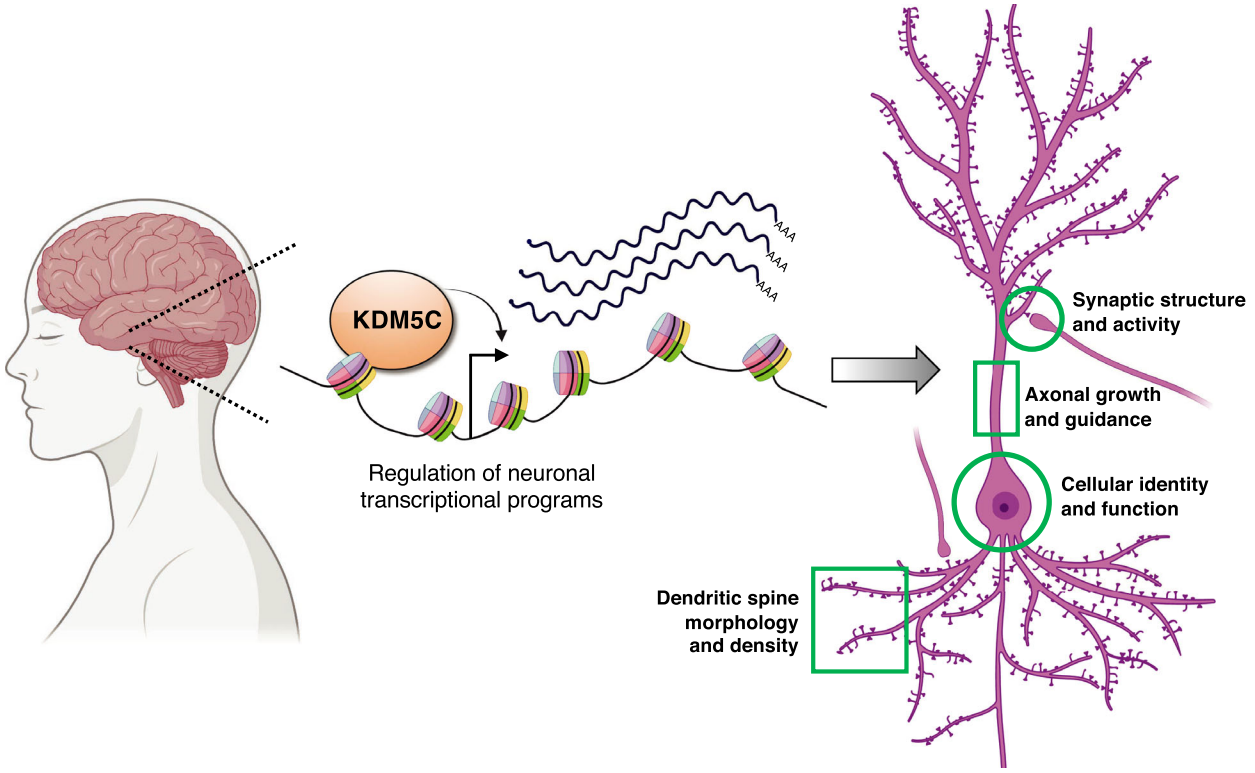

Fig. 2. Neuronal functions of KDM5C that could contribute to Claes-Jensen syndrome. KDM5C is a transcriptional regulator required for several distinct aspects of neuronal development and function based on studies in animal models (mice, flies, and worms). See text for details. Model created using Biorender.com.

KDM5C variants alter transcriptional programs in neurons

Because KDM5 family proteins regulate gene expression, changes to critical transcriptional programs are likely to lie at the heart of the clinical features seen in individuals with Claes-Jensen syndrome. Across species, KDM5 family proteins act primarily as modulators of gene expression, with their loss leading to modest (mostly < 2-fold) changes to the expression of downstream target genes [17,44,45,48–56]. This observation suggests that the phenotypes caused by alleles of *KDM5C* are due to the combined impact of many, relatively small, changes to gene expression. Pathogenic variants in KDM5C are thus likely to contribute to the neurodevelopmental features seen in Claes-Jensen syndrome by affecting multiple key transcriptional programs. This can make it challenging to define the *in vivo* transcriptional targets of KDM5C, particularly when comparing human samples that can be genetically heterogeneous. This challenge is highlighted by a study that used cells from patients with Claes-Jensen syndrome [11]. Because the human brain is not amenable to direct assays to define KDM5C functions, transformed lymphoblastoid cells from patients hemizygous for *KDM5C* alleles were used for genome-wide and targeted transcriptional analyses. While this led to the identification of a handful of genes that were dysregulated across all patient-derived cell lines, it did not lead to testable models of how variants in *KDM5C* could affect cognition and behavior. Although easy to access and culture, the use of lymphoid cells may complicate the interpretation of these data, since they may only partially recapitulate all the gene regulatory activities of KDM5C in the brain. In addition, differences in genetic background between individuals with Claes-Jensen syndrome and controls could make it difficult to detect small changes in gene expression. It is also notable that many key transcriptional changes are likely to occur during development, and thus may be missed by studies using mature cell types collected from patients.

Model organisms provide genetically controlled systems that are amenable to studies aimed at

understanding how KDM5C regulates gene expression in neuronal cell types. Indeed, transcriptomic analyses from mice and flies have revealed interesting insights into possible mechanisms contributing to Claes-Jensen syndrome. In-keeping with the range of neuronal functions found to be phenotypically altered by loss of *Kdm5c* in mice or its orthologs in *Drosophila* and *C. elegans*, KDM5C can regulate different distinct transcriptional programs. In some contexts, the gene expression changes seen upon loss of KDM5C appear to fit expectations based on the observed nervous system deficits. For example, consistent with its role in synaptic structure and function in mice and flies, KDM5C regulates the expression of genes involved in synaptic plasticity and neurotransmitter release [7,44,57]. Similarly, known regulators of axonal growth, such as the actin cytoskeleton binding protein Wasp-1 and the transcriptional regulator Prospero, have been found to be key mediators of the neuronal guidance defects observed in worms and flies [48,49].

Other changes to gene expression programs regulated by KDM5C have been more surprising. For example, gene expression changes in the hippocampus of $Kdm5c^{KO}$ mice revealed the derepression of a significant number of genes whose expression is normally limited to the germline [8]. This gene expression signature has the potential to be significant for the neuropathology of Claes-Jensen syndrome, as germline-enriched genes are found to be derepressed in mouse models of other NDDs such as Kleefstra syndrome and Rett syndrome [58–60]. An additional cellular process that was uncovered through analyses of a *Drosophila* strain harboring a patient-associated variant in the fly ortholog of *KDM5C* was the regulation of ribosomal protein genes [55]. Proper control of translation is critical to neuronal function, with deficits in this process being observed in individuals with other inherited forms of cognitive impairment, including Fragile X syndrome, ASD, and Alzheimer's disease [61–70]. This suggests that altered translation may be a common pathogenic mechanism of a subset of cognitive disorders that includes Claes-Jensen syndrome. Consistent with the possibility that the regulation of translation may be conserved in vertebrate animals, ChIP data from cultured embryonic mouse cortical neurons show that KDM5C binds to the promoter region of most ribosomal protein genes [7]. Both the inappropriate expression of germline genes and altered expression of ribosomal protein genes have the potential to interfere with neuronal structure and function, thereby contributing to the cognitive changes seen in those with Claes-Jensen syndrome.

Leveraging model organisms to uncover disrupted KDM5C regulatory mechanisms in Claes-Jensen syndrome

It is generally assumed that the histone demethylase activity of KDM5C is the primary means by which it regulates gene expression and that loss of this activity leads to cognitive impairment. This hypothesis is appealing since it points toward a potential means for targeted therapies for individuals with Claes-Jensen syndrome. The most compelling data in support of this model come from a study showing that the learning and memory phenotypes of hemizygous $Kdm5c^{KO}$ mice are attenuated by genetically reducing the levels of one of the enzymes that deposits the H3K4me3 mark, KMT2A [18]. Corroborating evidence comes from studies using a *Drosophila* model of Claes-Jensen syndrome. Analyses of a fly strain specifically lacking KDM5 histone demethylase activity have revealed that this enzymatic function is essential both for proper synaptic function at the larval NMJ and for learning and memory in adults [44,45,55]. Similarly, the axonal guidance defects observed in *C. elegans* are caused by the loss of the catalytic activity of KDM5 [49]. Importantly, these data are consistent with the general observation that tight regulation of H3K4me3 levels appears to be critical in the brain, as mutations in other regulators of this chromatin mark are also observed in individuals with NDDs [71].

There is, however, accumulating evidence that KDM5C may affect transcriptional programs critical for normal neuronal development and function via nonenzymatic means. While some missense mutations in human KDM5C attenuate its *in vitro* enzymatic activity to some extent, this is not universally true, as two patient-associated mutations do not result in reduced demethylase function (Table 1) [14,15,35]. Interestingly, the missense variants that do not affect KDM5C's *in vitro* demethylase activity occur in two different regions of the protein. The D87G variant is at the N-terminal extreme of the A/T-rich interaction domain (ARID) that can bind both A/T- and C/G-rich DNA sequences *in vitro* [72,73]. While this change could alter the ability of KDM5C to be recruited to some target genes, structural modeling studies suggest that this variant is unlikely to affect ARID-mediated DNA binding [74]. Instead, this change could affect protein–protein interactions necessary for KDM5C to regulate the expression of its target genes. The other variant, R1115H, occurs in a region of unknown function toward the C terminus of KDM5C. Like D87G,

this change could alter critical protein–protein interactions. Additional evidence supporting nonenzymatic roles comes from *Drosophila*, where the regulation of axonal growth and guidance by KDM5 in Kenyon cells occurs independently of its demethylase activity [48]. Precisely how KDM5 family proteins regulate neuronal gene expression via nonenzymatic mechanisms is still not clear. However, the involvement of additional mechanisms of gene regulation by KDM5C in neuronal lineages is unsurprising given the multidomain nature of this family of proteins (Fig. 1). Indeed, there is now considerable evidence that all KDM5 family proteins can regulate gene expression by multiple mechanisms, such as by interacting with lysine deacetylases and chromatin remodelers [49,75,76]. These data highlight the complex nature of KDM5-regulated gene expression and suggest that there may be more than one way that mutations in KDM5 family genes can lead to cognitive phenotypes.

Conclusions and perspectives

Since the first molecular identification of *KDM5C* variants in patients with ID in 2005 [10], many additional pathogenic alleles have been identified in individuals with NDDs. More recently, it has also become clear that a more general feature of KDM5 paralogs may be to regulate critical neuronal functions. Most notably, variants in KDM5B have recently been observed in individuals with NDDs and can result in clinical features that overlap with, but are not identical to, those observed in individuals with Claes-Jensen syndrome [5,77–81]. Despite the clear link between KDM5 proteins and cognition, we still have much to learn about how these proteins function molecularly to orchestrate gene expression programs that are needed for brain development. For example, we still lack a basic understanding of how KDM5 proteins are recruited to their target promoters, in addition to which proteins they interact with that facilitate their transcriptional regulatory functions. It is also possible that KDM5C acts through nontranscriptional means to affect neuronal development and function. Key to these fundamental discoveries will be the use of animal model systems. In addition, there is a great deal of excitement about the development of organoid models generated from human induced pluripotent stem cells. Cerebral organoids recapitulate some of the structural and molecular aspects of brain development and are increasingly used to understand the basis of NDDs [82–87]. Analyses of organoids are therefore expected to complement studies in model organisms to provide a more complete understanding of the effects of specific patient alleles on neuronal development and function. This fundamental knowledge will, in turn, lead to the development of targeted therapies to help individuals with Claes-Jensen syndrome.

Acknowledgments

We thank members of the Secombe lab for helpful discussions and feedback on this review. JS is supported by National Institutes of Health (NIH) R01GM112783, R01AG053269, and P50HD105352 in addition to an Irma T. Hirschl career award, and HAMH is supported by NIH Ruth L. Kirschstein National Research Service Award F31NS110278.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

JS drafted the manuscript, JS and HAMH edited the manuscript.

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