**KDM5C**

**Disease/Syndrome Features:**
Recent advances in comparative genomic hybridization and whole exome sequencing have revealed strong associations between X-linked Intellectual Disability (XLID) and mutations in chromatin modifying genes\(^1\-^4\). Of particular significance is lysine demethylase 5C (KDM5C, also referred to as SMCX or JARID1C), which belongs to a family of transcriptional regulators. KDM5C-associated ID, also referred to as CJ-XLID (Claes-Jensen type, X-linked Intellectual Disability; OMIM# 300534), accounts for 2.8-3.3% of XLID worldwide and is characterized by syndromic and non-syndromic forms of ID ranging from mild to severe\(^5\). To-date, 38 mutations in KDM5C have been reported segregating in families with CJ-XLID, resulting in truncated or missense KDM5C variants\(^6\-^20\). Although the majority of reported CJ-XLID cases are associated with nonsyndromic ID in males (with females only being mildly affected), syndromic features such as short stature, speech impairment, epilepsy, highly aggressive behavior, hyperreflexia, and facial dysmorphism have also been observed\(^21\-^22\). Additionally, mutations in KDM5C have also been found in some individuals to be comorbid with autism spectrum disorder (ASD)\(^21\), Huntington’s disease\(^23\), and cerebral palsy\(^24\).

**Protein/Pathway:**
KDM5C is located at Xp11.22-p11.21 and encodes a 1560-aa protein which aids in transcriptional repression. KDM5C accomplishes this by demethylating di- and trimethyl marks at lysine 4 on histone H3 (H3K4me2/3) via the enzymatic activity of its Jumonji C (JmjC) domain. KDM5 is ubiquitously expressed, with its highest levels found in brain and skeletal muscle in humans\(^5\). Within the mouse brain it is expressed within neurons and astroglia in regions including the hippocampus, cortex, amygdala, and cerebellum\(^25\). In non-neuronal cells, it has been shown to function as a transcriptional co-repressor of the RE1-silencing transcription factor (REST) complex to prevent the misexpression of neuronal genes\(^9\,^17\).

Although much work has been done clinically characterizing the cognitive and behavioral deficits of patients with KDM5-associated ID, the mechanism or mechanisms by which KDM5 dysfunction contribute(s) to ID remain(s) unknown. One hypothesis implicates decreased KDM5 demethylase activity to the pathogenesis of ID, as H3K4me3 marks are normally significantly decreased in neurons of the human prefrontal cortex, but not in non-neuronal cells, during the first year of life\(^26\-^27\). Additionally, the majority of genes associated with these decreased H3K4me3 marks belong to gene ontology categories relating to neuronal development. Indeed, previous studies in rat cerebellar granular neurons and mice pyramidal neurons of the basolateral amygdala demonstrate that Kdm5c knockout results in dendritic spine abnormalities, an anatomical feature typically observed in forms of ID such as Fragile X Syndrome\(^28\). Additionally, KDM5C knockout mice display various behavioral deficits associated with ID patients, such as increased aggression, learning and memory impairments, and decreased seizure thresholds\(^28\). Collectively, although these studies provide strong evidence that disruption of KDM5 may impact programs critical to neuronal development, either in a demethylase dependent or
independent manner, the precise mechanism(s) relating KDM5 dysfunction to intellectual disability remain largely unknown.

Publications:


**Support Groups and Information:**
KDM5C Facebook Support Group: [https://www.facebook.com/groups/kdm5c/](https://www.facebook.com/groups/kdm5c/).