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Review

Research Themes in KAT6A Syndrome: A Scoping Review

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Abstract: Pathogenic variants in the *KAT6A* gene cause KAT6A syndrome, a neurodevelopmental disorder characterised by intellectual disability (ID), developmental delay, speech and language challenges, feeding difficulties, and skeletal abnormalities. This scoping review synthesises current knowledge on KAT6A syndrome, identifies key research themes, and supports the mission of advocacy groups like the KAT6 Foundation. A systematic search of five databases (Ovid MEDLINE, Ovid EMBASE, PubMed, Web of Science, and Scopus) was conducted from 1990 to 2024, including peer-reviewed articles, preprints, and conference abstracts published from 2022 onward. Of 771 citations retrieved, 111 full-text articles were reviewed, with 62 meeting the inclusion criteria. Data were synthesised into six themes: (1) the genotype and phenotype map, revealing a broad phenotypic spectrum with common features like ID, absent speech, and craniofacial dysmorphism, as well as rare features such as severe aplastic anaemia and pancraniosynostosis; (2) the neurodevelopmental profile, detailing communication deficits, sleep disturbances, and impaired adaptive functioning; (3) the epigenetic and developmental roles of *KAT6A*, highlighting its critical function in histone acetylation, chromatin remodelling, and gene regulation; (4) molecular biomarkers, identifying distinct DNA methylation episignatures and dysregulated cellular pathways; (5) drug discovery, with preliminary studies suggesting that pantothenate and L-carnitine may mitigate mitochondrial dysfunction and histone acetylation deficits, while RSPO2 overexpression reverses cognitive impairment in animal models; (6) phenotypic overlap with Rett syndrome and *KAT6B*-related disorders. This review underscores the complexity and variability of KAT6A syndrome, highlighting the need for multidisciplinary approaches to improving diagnosis, management, and development of therapies. Future research should focus on longitudinal studies, underrepresented phenotypes, biomarker identification, and robust therapeutic trials to enhance outcomes for affected individuals and their families.

Keywords: KAT6A syndrome; intellectual disability; syndromic disorders; speech and language challenges and phenotypic variability

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1. Introduction

KAT6A syndrome (OMIM: 616268), also known as Arboleda–Tham syndrome, is a rare autosomal dominant neurodevelopmental disorder caused by variants in the *KAT6A* gene [1]. *KAT6A* (also known as *MOZ* and *MYST3*) encodes lysine acetyltransferase 6A, a key regulator of gene expression and chromatin remodelling, which is critical to cell development, differentiation, and organogenesis. It belongs to the MYST family of histone acetyltransferase

genes and is evolutionarily conserved across eukaryotes, indicating a common function across species. The KAT6A protein consists of a highly conserved winged helix (WH) domain in the N-terminal region, a double PHD finger motif, a MYST histone acetyltransferase domain, and a disordered C terminus containing acidic-, serine-, proline/glutamine-, and methionine-rich regions (see Figure 1). *KAT6A* is widely expressed in the brain, heart, lung, intestine, and hematopoietic systems, underscoring its role in diverse biological processes and its association with neurodevelopmental disorders and cancer [2].

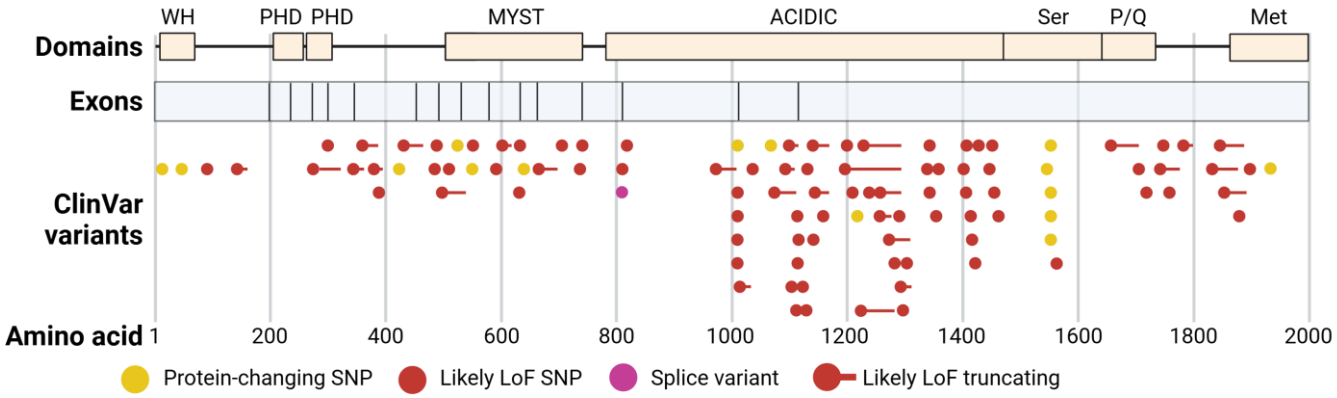

Figure 1. A schematic overview of the *KAT6A* gene, protein domains, and pathogenic variants. The displayed ClinVar variants of the *KAT6A* gene represent identified pathogenic variants within the ClinVar database. Figure created with BioRender (https://www.biorender.com).

KAT6A was linked to acute myeloid leukemia in the 1990s, but more recent research has highlighted its role in embryonic development and organogenesis [2]. The KAT6A protein forms part of the multi-subunit MOZ/MORF complex, which regulates chromatin structure by acetylating histone proteins, thereby activating the transcription of a range of genes essential to cellular function [3]. The epigenetic regulatory function of *KAT6A* is dose-dependent, and heterozygous loss-of-function variants lead to KAT6A syndrome and associated developmental deficits [1].

Genetic syndromes that result from variants that disrupt epigenetic modifiers, such as *KAT6A*, are classified as Mendelian disorders of the epigenetic machinery (MDEMs). MDEMs are increasingly recognised as a significant cause of syndromic intellectual disability [3]. MDEMs are potentially amenable to treatment using metabolic supplements or medications that prevent the removal of histone modifications [4]. Some preclinical studies on other MDEMs, including Kabuki syndrome and Rett syndrome, have shown promising improvements in cognitive and neurological deficits with treatments such as histone deacetylase inhibitors, ketogenic diets, and epigenetic editing technologies. The observed postnatal malleability in these disorders highlights the potential for developing interventions to address deficits caused by MDEMs, including KAT6A syndrome [3,5–7].

Individuals with KAT6A syndrome typically present with developmental delay, intellectual disability, and challenges in feeding, speech, and language [1,8] (see Figure 2). Other common features include neonatal hypotonia, microcephaly, gastrointestinal problems, cardiac malformations, and vision abnormalities (e.g., strabismus). Dysmorphic facial features, including a broad nasal tip and thin, tented upper lip, are commonly observed. Additional frequent characteristics include facial bitemporal narrowing, prominence of the nasal bridge, and a short and flat philtrum [1,8]. The phenotypes associated with *KAT6A* gene variants exhibit high variability in expression, influenced by the type and location of the genetic variation, as well as gene–environment interactions [1].

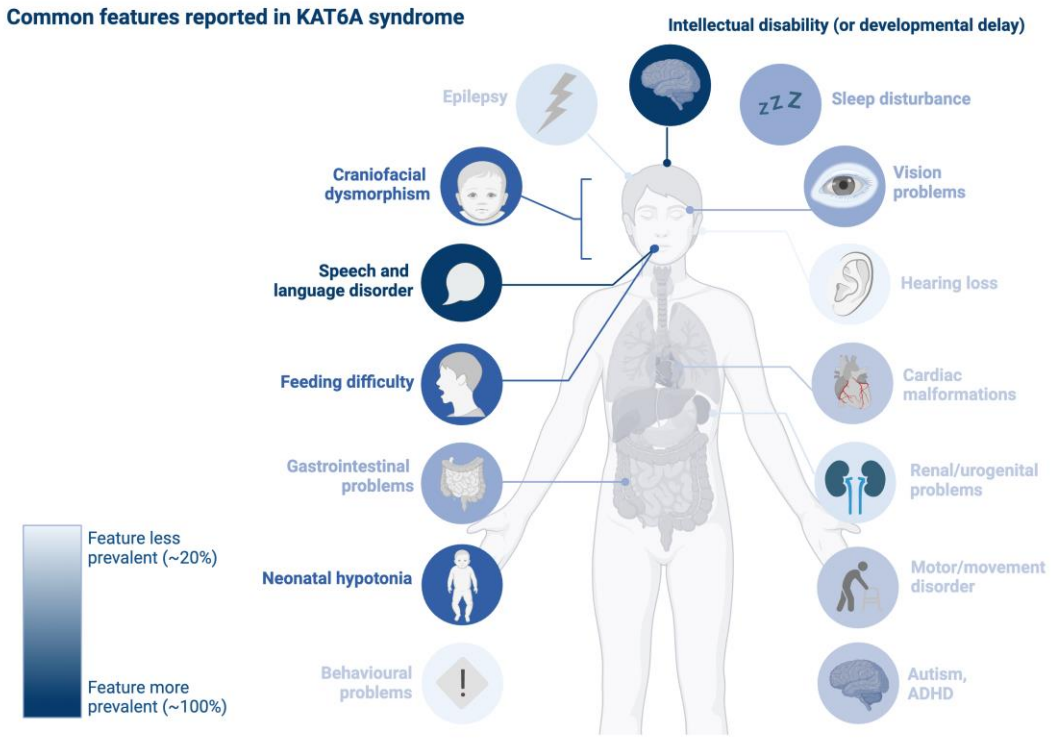

Figure 2. Common clinical features associated with KAT6A syndrome. The features are colour-coded to distinguish the most frequently reported features from the less frequently reported features. Figure created with BioRender (https://www.biorender.com).

The diagnosis of KAT6A syndrome is based on clinical phenotypes and results of genetic testing, with whole-exome sequencing being the most common diagnostic tool. The diagnostic age of individuals with KAT6A syndrome varies widely, with the youngest identified at 4 weeks old [9] and the oldest reported at 38 years old [10]. The prevalence of KAT6A syndrome is not well defined; however, as of 2024, approximately 400 individuals with KAT6A syndrome are known to the KAT6 Foundation, a parent-led advocacy group supporting affected individuals and their families [8]. The KAT6 Foundation emphasises the need to establish research priorities to develop treatments and improve outcomes for those with KAT6A syndrome.

Since the first identification of KAT6A syndrome in 2015, the literature has been largely limited to small studies and case reports, resulting in a fragmented knowledge base. A scoping review is necessary to consolidate this information and document the current state of research. This review aims to summarise available evidence on KAT6A syndrome, identify knowledge gaps, and outline future research trajectories critical to addressing unmet needs.

2. Materials and Methods

2.1. Database Search

Five databases (Ovid MEDLINE, Ovid EMBASE, PubMed, Web of Science, and Scopus) were systematically searched from 1 January 1990 to 18 July 2024. To extract the relevant literature, following subject headings and keywords were combined by using appropriate Boolean operators: *KAT6A*, lysine acetyltransferase, histone acetyltransferase, *KAT*, *MOZ*, and *MYST3* (Appendix A).

2.2. Inclusion and Exclusion Criteria

This scoping review included original peer-reviewed articles (including case reports, case series, cohort studies, case–control studies, experimental studies, and treatment trials), preprints, and peer-reviewed conference abstracts published from 2022 onward that met the following criteria: (a) focused on the *KAT6A* gene in the context of syndromic developmental disorders or specific gene ontology processes, such as chromatin remodelling, gene expression regulation, and epigenetic modification relevant to developmental biology, and (b) published in English. Studies that exclusively investigated the role of *KAT6A* as an oncogene, without addressing developmental implications, were excluded from the review. While *KAT6A* is known to play a role in cancer biology, its mechanisms and pathways in cancer may differ from those involved in developmental processes. By excluding oncogene-focused studies, this review aimed to provide an analysis dedicated to the role of *KAT6A* in developmental disorders and related gene ontology processes.

2.3. Article Selection

Search results were imported into Covidence [11], a web-based systematic review platform, in four stages. In stage 1, all articles obtained from database searchers were imported into Covidence, and the platform was used to detect and remove duplicates. In stage 2, any remaining duplicates not detected by Covidence were removed manually. In stage 3, all article abstracts were screened by the first and second authors, based on the criteria outlined above, and any abstract where it was not clear whether the inclusion criteria were met was automatically passed through to the full-text screening stage. Stage 4 involved full-text screening by the first and second authors. Conflicts were resolved by discussion.

2.4. Data Charting

The extraction process followed a structured framework that categorised studies under predefined themes: genotype and phenotype map in KAT6A syndrome, neurodevelopmental profile in KAT6A syndrome, epigenetic and developmental roles of *KAT6A*, molecular biomarkers derived from individuals with KAT6A syndrome, drug discovery and development, and phenotypic overlap between KAT6A syndrome and related disorders. These themes were developed iteratively through consensus between the first and second authors during the full-text review stage. Table 1 provides a detailed description of each theme.

Table 1. Research themes in KAT6A syndrome.

Theme	Description
Genotype and phenotype map in KAT6A syndrome	This theme includes case reports, case series, and cohort studies that expand the genotype and phenotypic spectrum of KAT6A syndrome. These studies either report novel *KAT6A* variants and their associated clinical phenotypes, validate previously reported variants, or identify correlations between the type, location, and nature of *KAT6A* variants and the clinical manifestations in affected individuals.
Neurodevelopmental profile in KAT6A syndrome	This theme focuses on studies that investigate specific phenotypic aspects of individuals already diagnosed with KAT6A syndrome. Unlike Theme 1, which centres on identifying new variants and expanding genotype–phenotype correlations, Theme 2 delves into the detailed characterisation of particular phenotypic features, such as intellectual disability, speech and language disorders, motor development, and behavioural traits. Studies may report both strengths and deficits and explore links between specific *KAT6A* variants and the severity of the phenotype. The purpose is to better understand the phenotypic spectrum of *KAT6A* variants, to support personalised interventions.

Table 1. *Cont.*

Theme	Description
Epigenetic and developmental roles of *KAT6A*	This theme explores how *KAT6A* influences gene expression through epigenetic mechanisms, such as histone acetylation. Studies focus on understanding *KAT6A*'s role in regulating key developmental processes, including cell differentiation, growth, and neurodevelopment. Researchers aim to uncover how variants in *KAT6A* disrupt these processes and contribute to developmental disorders, with a particular focus on the impact on brain development and function.
Molecular biomarkers derived from individuals with KAT6A syndrome	This theme includes studies aimed at identifying reliable molecular biomarkers linked to variations in *KAT6A*. By analysing biological samples (such as blood, tissue, or saliva) from affected individuals, the researchers aim to better understand how *KAT6A* variants influence molecular pathways and contribute to the clinical phenotype.
Drug discovery and development	This theme includes studies focused on validating potential therapeutic targets, addressing dysregulated pathways, and testing the effectiveness of compounds in correcting the effects of *KAT6A* variants. These include preclinical studies using animal models, cellular systems, and patient-derived samples to explore pharmacological and metabolic interventions that may mitigate the effects of *KAT6A* dysfunction.
Phenotypic overlap between KAT6A syndrome and related disorders	This theme includes studies identifying shared clinical features between KAT6A syndrome and other genetic disorders. By comparing the phenotypic and molecular characteristics of these conditions, the researchers aim to uncover shared pathways and mechanisms, which can inform differential diagnosis, therapeutic strategies, and a deeper understanding of the biology underlying these disorders.

The data charting framework allowed for the systematic organisation and mapping of study characteristics, such as the first author, year of publication, country of origin, research objectives, methods, phenotypic and genotypic details, diagnostic approaches, and key findings. To maintain consistency, terminologies describing phenotypic and genotypic information—such as "mutation" versus "variation" or "ocular abnormalities" versus "vision abnormalities"—were reported as they appeared in the original studies. This ensured the preservation of the original language used by the authors, providing an accurate representation of the literature.

2.5. Data Synthesis

The extracted data were synthesised through a narrative approach to provide a comprehensive overview of research themes and trends. Studies were grouped by predefined themes to identify areas of overlap and divergence. Key findings were summarised in descriptive tables for each theme, highlighting study characteristics and outcomes. The synthesis included a comparative analysis of methodologies and objectives across studies, enabling the discussion on underexplored research areas.

2.6. Ethics

This study involved neither human participants nor unpublished secondary data. As such, approval from a human research ethics committee was not required.

3. Results

The search strategy yielded 2234 studies for review. Covidence automatically removed 1396 duplicates, and a further 66 duplicates were removed manually. A total of 771 studies were screened for title and abstract, and 111 full texts were screened. Of the 49 studies

excluded from the full-text review, 17 studied *KAT6A* as an oncogene without implications for development, 16 were conference abstracts published before 2022, 6 were review studies, and 2 full texts were not in English. Overall, 62 studies were included in the scoping review (see Figure 3).

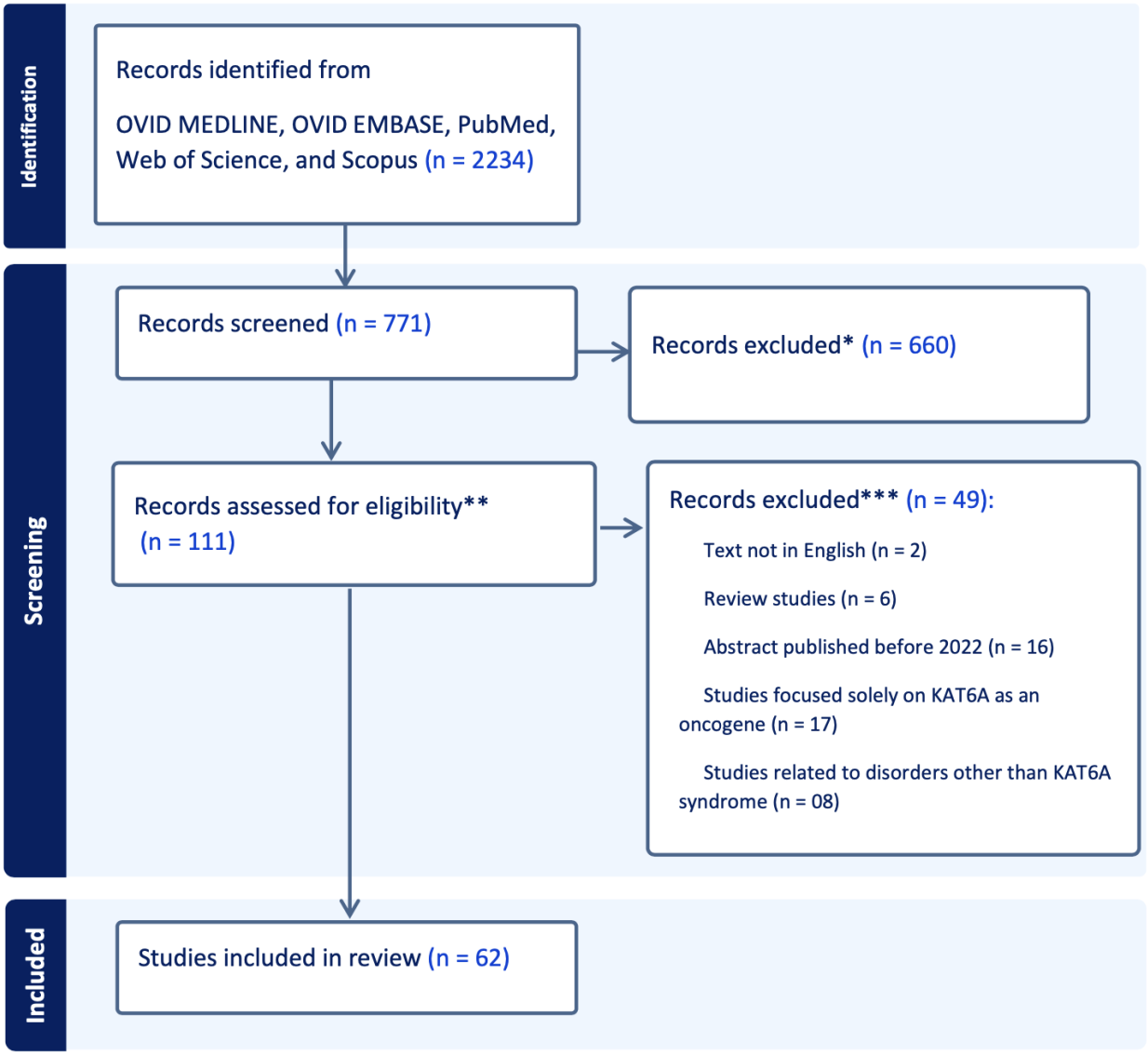

Figure 3. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram. * Records excluded based on their title and abstract review. ** Records eligible for full text review. *** Records excluded following full-text screening.

3.1. Theme 1—Genotype and Phenotype Map in KAT6A Syndrome

Of the 60 included studies, 42 focused on the *KAT6A* gene and its associated phenotypes (Table S1) [8,9,12–52]. Conducted between 2015 and 2024, these studies comprised mostly case reports (n = 23) [9,15–21,23–29,31,32,34–39], case series (n = 7) [12–14,20,30,33], and cohort studies [40–52]. Participants originated from diverse geographic regions, including North America, Europe, Australasia, and the Middle East, with two studies involving international collaborations. Case numbers ranged from a single individual to cohorts of up to 76, with ages from 4 weeks to 38 years.

Exome sequencing was the primary diagnostic method, often confirmed by Sanger sequencing. Some studies incorporated advanced research techniques such as RNA sequencing, functional studies, and protein modelling to refine the genotype–phenotype

map [35,39,43]. Reanalysis of exome data proved critical in some previously undiagnosed cases [31,37]. A limited number of case reports employed standardised measures to assess cognitive and development impairment. Scales used to quantify global development delays were the Denver Development Screening Test, the Gesell Development Scale [26,39], and the Bayley Scale of Infant Development [25].

Most case reports documented consistent core features including intellectual disability [10,12–15,17–20,22,24,26,27,34,37,39,40,46,47], communication and development delays (often with absent speech) [9,12–29,31,34–40,42–44,46,47], and neonatal hypotonia [9,10,12,14–20,23,31,35,40,43,44]. Feeding difficulties were common, with some patients requiring feeding tubes or gastrostomies during infancy [9,12,13,15–22,30,32,35,38,40,43,44]. Craniofacial dysmorphism was frequently observed, and included bitemporal narrowing, a broad nasal tip, a thin upper lip, and low-set or posteriorly rotated ears [9,12–16,19–29,31,34,35,37–40,43,44,47]. Microcephaly was common, occasionally accompanied by craniosynostosis [10,12,13,15,16,20,22,23,27,29,32,38,43,44,46,47]. Congenital heart defects, particularly septal defects, were reported frequently [12,13,15,16,22,23,25,33,36,38,43,44]. Other anomalies included ocular abnormalities such as estropia [19,28], severe myopia [23], and strabismus [10,12,28,43]. Less common features included genital anomalies, such as cryptorchidism [9,26,44].

Neurological presentations included epilepsy, including infantile spasms [20,30,46] and drug-resistant focal seizures [27,30]. Brain imaging findings were generally normal, though Chiari I malformation [29] and pituitary malformations leading to hormone deficiencies [17,18] were reported. Sleep disturbances, including obstructive sleep apnoea, were also reported, occasionally requiring continuous positive airway pressure (CPAP) therapy [38]. Rare, life-threatening complications included aplastic anaemia [36], bone marrow failure [34], bowel obstruction/malrotation [35], and severe neutropenia [40]. Rare features included pancraniosynostosis [27], megalopapilla [28], and paroxysmal startle response [20]. One study reported wheat and milk protein allergy, with gastrointestinal symptoms resolving upon an elimination diet [16].

Prenatal findings were reported in some cases. A foetus with nuchal translucency >99th percentile was postnatally confirmed to have a pathogenic *KAT6A* variant [45]. Moderate-to-severe foetal anaemia was linked to *KAT6A* [48], as were liver calcifications detected on prenatal ultrasound at 31 weeks of gestation, confirmed postnatally by abdominal ultrasound [38]. In two cases, prenatal ultrasounds identified congenital heart defects and cranial abnormalities, leading to pregnancy termination following the detection of *KAT6A* variants by exome sequencing [33].

Rare genetic mechanisms were reported, including parental germline mosaicism in one family where three siblings shared the same *KAT6A* variant despite unaffected parents [19]. Inherited missense variations were documented in a father and daughter with differing phenotypes [10] and in a mother and son, where the mother had mild intellectual impairment and the son presented with core features of KAT6A syndrome [9].

Reports of *KAT6A* gene variants were identified in eight cohort studies [40–42,44,46,47,50,52] that aimed to determine the genetic aetiology of conditions such as congenital neutropenia with intellectual disability [40], radiographically confirmed vein of Galen malformations [41], childhood apraxia of speech (marking the first reported instance of isolated speech impairment without global developmental delay present in a case of *KAT6A* gene variation) [42], syndromic craniosynostosis [44,52], paediatric epilepsy [46], multiple malformation syndrome [47], and coloboma of the optic nerve with visual impairment [50], further expanding the phenotype of KAT6A syndrome.

Three studies [43,48,51] provided insights into the phenotype spectrum of KAT6A syndrome, with two offering detailed genotype–phenotype correlations [43,48]. Intellec-

tual disability and communication delay were universal, with other common features including feeding difficulties (78–90%), neonatal hypotonia (76%), gastrointestinal issues (reflux, 60%; constipation, 51%), congenital heart defects (46–51%), motor/movement disorders (46%), recurrent infections (47%), behavioural issues (23–39%), sleep disturbances (37–65%), diagnosis of autism (28–32%), and attention deficit-hyperactivity disorder (28%). Additional features included facial dysmorphism such as a broad nasal tip (85%), a thin upper lip (67%), microcephaly (33%), renal/urogenital problems (23%), epilepsy/seizures (22%), and hearing loss (18%). Ng et al. [51] reported that all participants (n = 15) had received occupational therapy and speech language therapy, most received physiotherapy (87%), and only 27% reported behaviour therapy. Most *KAT6A* variants were truncating, followed by missense variants and splice-site mutations [43,48,51]. Late-truncating variants (located within exons 16–17) were associated with higher prevalence of intellectual disability, microcephaly, neonatal hypotonia, and cardiac defects, suggesting distinct mechanisms—haploinsufficiency for early truncating variants and dominant-negative effects for late-truncating variants [43,48]. Kennedy et al. [43] provided clinical advice and general guidelines for clinicians to help guide the clinical workup for patients with KAT6A syndrome, acknowledging the wide variability of the clinical presentation and the need for individual patients to have a personalised plan to reflect their own clinical features.

3.2. Theme 2—Neurodevelopmental Profile in KAT6A Syndrome

Four studies [48,51–53] investigated the neuropsychological, adaptive function, communication, behaviour, and sleep profile of individuals with KAT6A syndrome (Table S2). Across all studies, individuals with KAT6A syndrome demonstrated profound impairment in adaptive functioning. Domains including communication, daily living skills, socialisation, and motor skills were significantly delayed, forming a "flat" adaptive profile [53,54]. Despite low adaptive abilities, behavioural problems were reported infrequently, with relatively intact social drives and lower occurrence of internalising and externalising issues [51].

Speech and language impairment was prominent, with 73% of participants being minimally verbal or nonverbal [48]. Verbal participants exhibited complex speech disorders, such as childhood apraxia of speech, dysarthria, and phonological impairment, severely affecting intelligibility [48]. Both receptive and expressive language abilities were impaired across the cohort. Feeding difficulties affected over 90% of affected individuals and persisted into adolescence and adulthood in some [48]. Children with KAT6A syndrome consistently demonstrated the ability to greet others, attract attention, seek comfort, express dislike, make requests or choices, convey basic emotions (happy/sad), and respond to communication attempts from the caregiver. However, they often lacked clear ways to ask for clarification or information, request assistance with dressing or toileting, or react to disruptions in their routine [48]. Augmentative and alternative communication (AAC) (i.e., sign language and communication devices) was utilised by some but across limited communicative functions, with researchers emphasising the need for early individualised AAC approaches in those with KAT6A syndrome [48].

Global cognitive impairment was observed, with deficits in both nonverbal cognition and receptive language, as evidenced by comparable performance scores in these areas [51]. Autism-related features, including restricted interests and repetitive behaviours, were common, contrasting with strong social motivation.

Disordered sleep emerged as a major issue, with high rates of restless sleep, night awakenings, and long sleep latency [53]. The need for sleep medication and daytime drowsiness was frequently reported; however, sleep-disordered breathing, such as snoring and apnoea, was less common.

When genotype–phenotype trends were explored, the results varied. St John et al. found that late-truncating variants were associated with more severe impairment in intellectual disability, communication, and socialisation compared with early-truncating variants [48]. Conversely, Ng et al. [51] reported comparable cognitive profiles between early- and late-truncating variants, suggesting that both variant categories yield significant global impairment. Protein-truncating variants appeared to have more pronounced cognitive effects than missense variants, though the difference was statistically significant only for some specific neuropsychological measures [51].

3.3. Theme 3—Epigenetic and Developmental Roles of KAT6A

Twelve studies [55–66] explored the epigenetic and developmental functions of the *KAT6A* gene, emphasising its role in regulating histone modifications, gene expression, and organ development (Table S3). The studies utilised diverse animal models, including mouse [55–57,59,60,62,65,66] and zebrafish [56], and cell culture models, including mouse odontoblasts, primary human dental pulp cells [59], cardiac tissue samples [61], patient-derived induced pluripotent stem cells (iPSCs) differentiated into cerebral organoids [63], and dermal fibroblasts obtained from KAT6A syndrome patients [64].

KAT6A is a member of the MYST domain family of histone acetyltransferase proteins. It functions within a large, multi-protein complex called the MOZ/MORF complex, containing two histone acetyltransferase proteins—KAT6A and KAT6B. KAT6A preferentially acetylates histone H3 residues H3K9 and H3K14 [55,58]. Structural studies revealed KAT6A's dual role as both a reader and writer of histone marks, particularly H3K14 acetylated residues which have been shown to interact with the double PHD fingers (Figure 1). This demonstrates that the location of variants in *KAT6A* may disrupt histone acetyltransferase functionality of the MYST domain or the correct positioning of these marks on the genome during development [58]. Additionally, Weber et al. elucidated the DNA-binding mechanism of KAT6A, demonstrating its preference for unmethylated CpG-rich regions [65]. Variants in the WH1 domain impaired KAT6A's DNA-binding capability, leading to reduced histone acetylation and altered gene expression, particularly in genes regulating heart and neuronal development. This study provided mechanistic insights into how variants in the WH1 domain may contribute to KAT6A syndrome.

To understand the importance of these molecular functions during development, mouse knockout studies found that KAT6A was required to maintain H3K9 acetylation at the loci of *Hox* genes, influencing their expression and body segment identity during embryogenesis [55]. Specifically, *Kat6a*-deficient embryos exhibited H3K9 hypoacetylation at Hox gene loci (including promoters and regulatory regions), leading to the reduced transcription of these genes and resulting in the homeotic transformation of the axial skeleton and nervous system [55]. Furthermore, widespread chromatin accessibility and histone modification changes, such as increased H3K23 acetylation at posterior *HOXC* clusters, were observed in fibroblasts derived from KAT6A syndrome patients, correlating with dysregulated gene expression [64]. To extrapolate how KAT6A's role in gene regulation influences development, mouse models have underscored *Kat6a*'s essential role during organogenesis and early development. The loss of *Kat6a* disrupted the expression of transcription factors such as *Dlx5*, *Gbx2*, and *Tbx1*, leading to craniofacial abnormalities, including cleft palate, and ventricular septal defects [60,62]. The abnormalities were attributed to the downregulation of distal-less homeobox (*Dlx*) genes and premature osteoblast differentiation in *Kat6a*-deficient embryos.

In brain development, *KAT6A* variants caused transcriptomic dysregulation and delayed neural differentiation in iPSCs and cerebral organoids derived from patients with KAT6A syndrome [64]. The disruption of pathways involving cell cycle regulators (such as

E2F transcription factors), RNA-binding proteins (like PTBP1), and synaptic development genes (such as protocadherins (*PCDHs*)) impacted neural circuitry [63]. In *Kat6a*-knockout mice, heterozygous loss of function led to significant deficits in spatial learning and memory, reduced synaptic plasticity, and altered dendritic spine morphology [66].

Beyond craniofacial and neural development, *KAT6A* variants impacted other organs. Elevated *KAT6A* expression was observed in abdominal aortic aneurysm tissues, correlating with endothelial cell dysregulation [61]. Additionally, KAT6A was linked to odontoblast maturation and dentinogenesis, underscoring its role in dental development [59].

Collectively, these studies map KAT6A's involvement in critical developmental processes, including *Hox* gene regulation, craniofacial and cardiac development, and neurodevelopment.

3.4. Theme 4—Molecular Biomarkers Derived from Individuals with KAT6A Syndrome

Six studies [13,34,63,64,67,68] investigated molecular biomarkers associated with KAT6A syndrome, focusing on transcriptomic and epigenomic profiling, mitochondrial function, and diagnostic tools (Table S4). Patient-derived fibroblasts were used to study histone acetylation patterns, DNA methylation, and mitochondrial function [13,64,67]. Genome-wide DNA methylation profiles were analysed by using blood samples from individuals with *KAT6A* variants with a novel diagnostic tool, Episign, to identify unique DNA methylation patterns or episignatures which correlate specifically to KAT6A syndrome [34,68]. Distinct DNA methylation profiles associated with *KAT6A* variants were identified as diagnostic biomarkers comprising 114 differentially methylated probes exhibiting high sensitivity and specificity in distinguishing patients with KAT6A syndrome from controls and patients with other neurodevelopmental disorders [68]. Although shared pathways with *KAT6B*-related disorders (Genitopatellar syndrome and Say–Barber–Biesecker–Young–Simpson syndrome) were observed, the episignature effectively differentiated these conditions. Its clinical utility was validated by using the EpiSign assay [34].

Transcriptomic analysis from KAT6A syndrome-derived fibroblasts identified 60 differentially expressed genes, including the upregulation of posterior *HOXC* cluster genes, which correlated with increased H3K23 acetylation [65]. To identify transcription changes in neural cell types and provide insights into which neurodevelopmental pathways are affected, iPSC-derived cerebral organoids were generated from KAT6A syndrome individuals to investigate transcriptomic dysregulation in *KAT6A*-related conditions [63]. RNA sequencing revealed global transcriptomic dysregulation, with over 6000 genes affected across various stages of neural differentiation. Disrupted pathways involving cell cycle regulation (*E2F* transcription factors), RNA-binding proteins (PTBP1), and synaptic development (*PCDH*) contributed to delayed neural differentiation and impaired synaptic function [63].

The disruption of histone acetylation patterns, such as decreased H3K9 acetylation and increased H3K18 acetylation, were reported in fibroblasts, alongside alterations in the p53 signalling pathway [13]. Similarly, reduced H3 acetylation (H3K9 and H3K14) was observed in fibroblast cultures, indicating compromised epigenetic regulation [67].

KAT6A variants were also linked to mitochondrial dysfunction, including the reduced expression of respiratory chain proteins (NDUFA9 and COX4), decreased ATP production, and the downregulation of proteins involved in iron metabolism and antioxidant defences (SOD1 and SOD2) [67]. These findings highlight the systemic impact of *KAT6A* variants on cellular bioenergetics.

Overall, the studies collectively demonstrated that *KAT6A* variants lead to disruptions in histone acetylation, DNA methylation, gene expression, and cellular bioenergetics. DNA methylation episignatures emerged as a promising diagnostic tool, while transcriptomic and functional analyses provided insights into key molecular pathways implicated in KAT6A syndrome.

3.5. Theme 5—Drug Discovery and Development

Two studies [66,67] explored potential therapeutic interventions targeting epigenetic dysregulation and cognitive deficits associated with KAT6A syndrome (Table S5).

Munuera-Cabeza et al. [67] investigated the therapeutic potential of pantothenate and L-carnitine in fibroblasts derived from KAT6A syndrome patients with different heterozygous variants (frameshift, premature stop codon, and amino acid substitution). RNA sequencing revealed extensive transcriptomic dysregulation, with the downregulation of acetylation-related genes and the upregulation of neuronal regulation genes. Supplementation with pantothenate and L-carnitine improved cell survival, restored mitochondrial protein levels, and corrected histone acetylation deficits under nutritional stress conditions.

The rationale behind these treatments is based on their metabolic roles: L-carnitine is essential to mitochondrial function, while pantothenate serves as a precursor to acetyl-CoA, the acetyl donor for histone acetylation by KAT6A. Increased acetyl-CoA availability may enhance mutant KAT6A enzymatic activity, thereby restoring histone acetylation. Additionally, L-carnitine supplementation may modulate type 1 histone deacetylases (HDACs), promoting mitochondrial biogenesis via PGC1α activation. Both compounds also corrected NAD+/NADH levels and improved mitochondrial parameters, including membrane potential, maximal respiration, and respiratory capacity, highlighting their potential for treating KAT6A-associated metabolic and epigenetic dysfunctions.

Liu et al. [66] conducted a proof-of-concept study investigating RSPO2 overexpression as a potential therapeutic approach for KAT6A-related cognitive impairment. RSPO2 is an activator of Wnt signalling and was identified to be positively regulated by KAT6A in CA3 pyramidal neurons of the hippocampus. By using *Kat6a*-knockout mice, the study demonstrated that adeno-associated virus (AAV)-mediated RSPO2 delivery into the hippocampal CA3 region successfully restored spatial learning and memory in the Morris Water Maze test and improved contextual memory in the fear conditioning test. These findings highlight the essential role of RSPO2 in KAT6A-mediated synaptic and cognitive function and suggest that enhancing Wnt signalling may be a viable therapeutic strategy for reversing memory deficits in KAT6A syndrome.

3.6. Theme 6—Phenotypic Overlaps Between KAT6A Syndrome and Related Disorders

Two studies examined the overlapping and distinct features of KAT6A syndrome in relation to Rett syndrome [69] and *KAT6B*-related disorders [70]. The first study [69] evaluated seven individuals with de novo heterozygous variants in exon 17 of *KAT6A*, who exhibited clinical features overlapping with Rett syndrome (Table S6). Of the seven, two were classified as having atypical Rett syndrome, based on Neul's revised diagnostic criteria, while the remaining five were diagnosed with KAT6A-related intellectual disability presenting with Rett-like features. The study highlights phenotypic overlap between KAT6A syndrome and Rett syndrome, emphasising the importance of including KAT6A gene analysis in genetic evaluation of girls with suspected Rett syndrome.

The second study [70] compared the neurocognitive and behavioural profiles of individuals with *KAT6B*-related disorders to previously published data on individuals with KAT6A syndrome [54]. Syndromes associated with both genes demonstrated severe deficits in adaptive functioning, nonverbal cognitive impairment, and challenges in receptive language. Autism-related behaviours, such as restricted interests and social communication difficulties, were prevalent in both groups. However, individuals with *KAT6B*-related disorders showed more pronounced autistic features and reduced social motivation compared with those with KAT6A syndrome.

These findings underscore the phenotypic overlaps and distinctions among KAT6A syndrome, Rett syndrome, and *KAT6B*-related disorders, improving our understanding of shared and unique clinical characteristics across these conditions.

4. Discussion

This scoping review presents the current status of research on KAT6A syndrome, focusing on clinical, molecular, and therapeutic dimensions. Six primary research themes emerged: the genotype and phenotype map in KAT6A syndrome, the neurodevelopmental profile in KAT6A syndrome, the epigenetic and developmental roles of *KAT6A*, molecular biomarkers derived from individuals with KAT6A syndrome, drug discovery and development, and phenotypic overlap between KAT6A syndrome and related disorders. The findings highlight the complexity and variability of KAT6A syndrome.

Studies under the theme of 'genotype and phenotype map in KAT6A syndrome' emphasised the importance of detailed characterisation of genetic variations—such as their location, type, inheritance pattern, and predicted effects on protein—and their associated phenotypes. Common features, including intellectual disability, communication delay and craniofacial dysmorphisms were frequently identified. Additionally, novel findings revealed rarer phenotypes, such as pancraniosynostosis, severe aplastic anaemia, pituitary hormone deficiencies, structural pituitary malformations, and optic nerve malformations.

Neurodevelopmental profiling has uncovered deficits in cognition, adaptive functioning, and speech and language abilities that are frequently severe [48,51,53,54]. These impairment types, previously grouped under the broader category of intellectual disability, were clarified through standardised tools and parent-reported questionnaires. A significant finding is the comparable impairment of receptive and expressive language, as well as nonverbal cognition, which challenges earlier reports suggesting relatively preserved receptive communication skills [14,43]. Communication impairment, including severe deficits in speech production and language comprehension and expression, represents one of the most critical and debilitating features of KAT6A syndrome. This highlights an urgent need for studies that explore the specific neural and molecular pathways impacted in this population, which could help guide targeted interventions. Tailored AAC interventions should be implemented early to optimise communication outcomes and improve the quality of life.

Despite profound intellectual and adaptive deficits, individuals with KAT6A syndrome exhibit low levels of problematic behaviours [51,53]. Studies report limited internalising and externalising concerns juxtaposed with a strong social drive, suggesting that regulation and social potential can serve as a foundation for interventions aimed at improving developmental outcomes [51,53]. These findings underscore the importance of interventions that address severe communication and adaptive deficits while leveraging behavioural strengths to foster engagement and learning. Future research should focus on refining communication supports, investigating the mechanisms underlying this unique behavioural profile, and developing strategies that capitalise on strengths to address challenges.

Innovative data collection methods in some studies offer a promising approach for rare disease research, where generating large datasets is inherently challenging. Online family surveys and telehealth methods, as employed by St John [48], enabled detailed phenotypic evaluations. Unique approaches, such as asking families to submit recent photographs to assist in assessing dysmorphic features, were particularly effective in overcoming potential barriers in understanding medical terminology. These methods highlight the importance of adaptive approaches to improving data quality and accessibility in rare disease research.

Research into the epigenetic and developmental roles of *KAT6A* has established it as a critical component of the chromatin machinery, functioning as both a "writer" and "reader" of histone modifications. As a lysine acetyltransferase, it adds acetyl groups to

specific lysine residues on histone tails, such as H3K9 and H3K14, modulating chromatin structure and promoting gene transcription [55,58]. Additionally, the KAT6A protein recognises and binds to specific histone marks, ensuring the proper regulation of gene expression [57,64]. These functions are essential to developmental processes such as cell differentiation, neural development, and synaptic plasticity [62,63]. Variants in the *KAT6A* gene disrupts chromatin dynamics, leading to dysregulated gene expression and neurodevelopment deficits characteristic of KAT6A syndrome [65,66,68]. Studies using models such as patient-derived organoids and mouse knockouts have provided insights into the neurodevelopmental functions of KAT6A. However, further research is needed to explore the broader implications of these disruptions.

Molecular biomarker identification is critical to advancement in understanding KAT6A syndrome and includes the identification of distinct DNA methylation episignatures that show promise as diagnostic tools. Transcriptomic studies have revealed widespread dysregulation in key cellular pathways, offering valuable therapeutic targets. Additionally, the expression levels of specific proteins, such as those involved in histone acetylation, mitochondrial function, and antioxidant defence, have the potential to serve as reliable biomarkers for assessing disease severity and monitoring the effectiveness of therapies. However, rigorous validation is critical to establishing the clinical utility of these biomarkers.

Therapeutic research remains underdeveloped, with limited studies exploring intervention strategies. Preliminary evidence suggests that pantothenate and L-carnitine supplementation may mitigate mitochondrial dysfunction and histone acetylation deficits in patient-derived models [67]. However, these findings are in early stages, and more robust therapeutic research is urgently needed.

Phenotypic overlaps between KAT6A syndrome and two other MDEMs—Rett syndrome [69] and *KAT6B*-related disorders [70]—emphasise the importance of comprehensive genetic testing for accurate differential diagnosis. Further, comparative analyses of neurocognitive and behavioural profiles in KAT6A syndrome and *KAT6B*-related disorders revealed shared deficits in adaptive functioning, nonverbal cognition, and receptive language, alongside common autism-related behaviours such as restricted interests and social communication difficulties. However, individuals with *KAT6B*-related disorders exhibited more pronounced autistic features and reduced social motivation compared with those with KAT6A syndrome [70]. These phenotypic overlaps underscore shared molecular pathways between these disorders and highlight the potential for comparative research to uncover underlying mechanisms, which may inform the development of targeted therapies and personalised clinical management strategies.

Despite advancements, several research gaps remain. Longitudinal studies are needed to better understand the natural history and long-term outcomes of KAT6A syndrome. There is a lack of standardised neurodevelopmental and behavioural assessment tools, limiting comparability across studies. Additional research into underexplored phenotypes, such as motor development, gastrointestinal complications, and feeding difficulties, is critical, as these issues significantly impact quality of life and, in some cases, result in life-threatening complications. Insights into the lived experiences of affected individuals and their families are also limited, yet such data are essential to identifying unmet needs and shaping research priorities.

To address these research gaps, future research should focus on expanding cohort diversity, integrating longitudinal designs, and standardising methodologies. Collaborative efforts, such as utilising patient registries, like the one maintained by the KAT6 Foundation [71], could support larger studies and enhance data quality. Crowdsourcing initiatives involving families and advocacy groups such as the KAT6 Foundation could also provide valuable insights into

care priorities. Additionally, iPSC banks may facilitate access to advanced research models, enabling larger sample studies and accelerating therapeutic discoveries.

In conclusion, this scoping review highlights significant advancements in understanding KAT6A syndrome while identifying critical gaps that need to be addressed. Multidisciplinary collaborations and innovative approaches are necessary to bridge these gaps, improve diagnostics, and develop targeted therapies. By leveraging these opportunities, the field can move closer to improving outcomes and quality of life for individuals and families affected by KAT6A syndrome.

Limitations

This scoping review has several limitations. First, the review was limited to studies published in English, which may have excluded relevant research available in other languages, potentially introducing language bias. Additionally, the inclusion criteria focused on peer-reviewed articles, preprints, and conference abstracts, which may have excluded valuable information from grey literature or unpublished studies. This could result in an incomplete synthesis of the available evidence.

The heterogeneity of the included studies also poses a challenge, as variability in study designs, assessment tools, and reporting methods makes it difficult to directly compare or integrate findings. Furthermore, many of the data were derived from case reports or small cohort studies, which restricts the ability to draw robust conclusions or identify broad trends. The reliance on secondary data from studies with varying methodological rigor may have introduced inconsistencies in this review's findings.

Finally, while this scoping review aimed to provide a comprehensive synthesis of the research landscape, it did not assess the quality or risk of bias of the included studies. This is a common limitation of scoping review methodologies, as their primary objective is to map the breadth and scope of available evidence rather than critically appraise individual studies. This approach aligns with established scoping review frameworks, which do not require formal quality assessment. Therefore, while this limitation should be considered when interpreting the findings, it does not detract from the validity or purpose of the review, which is to provide an overview of the current research landscape and identify areas for further investigation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/dna5020021/s1, Table S1: Research theme—genotype and phenotype map in KAT6A syndrome, Table S2: Research theme—neurodevelopmental profile in KAT6A syndrome, Table S3: Research theme—epigenetic and developmental roles of *KAT6A*, Table S4: Research theme—molecular biomarkers derived from individuals with *KAT6A* syndrome, Table S5: Research theme—drug discovery and development, Table S6: Research theme—phenotypic overlaps between KAT6A syndrome and related disorders.

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Abbreviations

The following abbreviations are used in this manuscript:

AAC	augmentative and alternative communication
CPAP	continuous positive airway pressure
DNA	deoxyribonucleic acid
Dlx	distal-less homeobox
HDACs	histone deacetylases
iPSCs	induced pluripotent stem cells
MDEMs	Mendelian disorders of the epigenetic machinery
PCDHs	protocadherins
RNA	ribonucleic acid

Appendix A

Search strategy

Pubmed
("KAT6A"[Title/Abstract] OR (("lysine acetyltransferase*"[Title/Abstract] OR "lysine acetyl transferase*"[Title/Abstract] OR "histone acetyltransferase*"[Title/Abstract] OR "histone acetyl transferase*"[Title/Abstract] OR "MOZ"[Title/Abstract] OR "MYST"[Title/Abstract] OR "MYST3"[Title/Abstract]) AND ("KAT"[Title/Abstract] OR "KATs"[Title/Abstract]))) AND ("NOTNLM"[All Fields] OR "publisher"[Filter] OR "inprocess"[Filter] OR "pubmed-notmedline"[Filter] OR "indatareview"[Filter] OR "pubstatusaheadofprint"[All Fields]) = 341

Scopus
#1 Title/Abstract
KAT6A OR OR KAT-6A
#2 Title/Abstract
lysine-acetyltransferase* OR lysine-acetyl-transferase* OR histone-acetyltransferase* OR histone-acetyl-transferase* OR MOZ OR MYST OR MYST3
#3 Title/Abstract
KAT or KATs = 2665
#4 #2 AND #3 = 245
#5 #1 OR #4 = 470

Web of Science
#1 Title/Abstract
KAT6A OR KAT-6A = 203
#2 Title/Abstract
lysine-acetyltransferase* OR lysine-acetyl-transferase* OR histone-acetyltransferase* OR histone- acetyl-transferase* OR MOZ OR MYST OR MYST3 = 8927
#3 Title/Abstract
KAT or KATs
#4 #2 AND #3
#5 #1 OR #4 = 407

Medline-Ovid
(KAT6A or KAT-6A).tw,kf. = 188
lysine acetyltransferases/or exp histone acetyltransferases/ = 13,692
(lysine-acetyltransferase* or lysine-acetyl-transferase* or histone-acetyltransferase* or histone-acetyl-transferase* or MOZ or MYST or MYST3).tw,kf,hw. = 9411
(KAT or KATs).tw,kf. = 1276
(2 or 3) and 4 = 220
1 or 5 = 400

EMBASE-Ovid
(KAT6A or KAT-6A).tw,kw,dq. = 347
lysine acetyltransferase/ = 539
histone acetyltransferase/ = 7894
(lysine-acetyltransferase* or lysine-acetyl-transferase* or histone-acetyltransferase* or histone-acetyl-transferase* or MOZ or MYST or MYST3).tw,kw,dq,hw. = 11056
(KAT or KATs).tw,kw,dq. = 1567
(2 or 3 or 4) and 5 = 284
1 or 6 = 616

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