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Review

The Crucial Roles of the Lysine Acetyltransferases KAT6A and KAT6B in Development and Neurodevelopmental Disorders

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Abstract

KAT6A and KAT6B are central acetyltransferases that acetylate histone H3 and non-histone proteins, thereby regulating the expression of many transcription factors and developmental genes, and modulating a wide array of key signaling pathways, such as Wnt/β-catenin and MAPK, as well as cellular pathways. These include chromatin organization, cell cycle regulation, proliferation, differentiation, maintenance of mesenchymal, hematopoietic and neural stem cells, as well as orchestration of multiple developmental programs, including hematopoietic, neurogenic, skeletal, and craniofacial development. Consistent with these key roles, heterozygous pathogenic variants in *KAT6A* and *KAT6B* result in neurodevelopmental syndromes. These syndromes are characterized by mild to severe intellectual disability, developmental delay including motor and speech delay, and a variety of malformations. This review provides a comprehensive summary of current evidence highlighting the impact of KAT6A and KAT6B on developmental programs and neurodevelopmental disorders resulting from pathogenic variants in *KAT6A* and *KAT6B*. Moreover, we describe the cellular and animal models of KAT6A and KAT6B syndromes, which are essential for studying and deciphering the molecular etiologies underlying the manifestation of the clinical phenotypes of these syndromes. An in-depth understanding of the molecular and cellular pathways impaired in KAT6A and KAT6B syndromes is essential for guiding future development of possible therapeutic interventions.

Keywords: KAT6A, KAT6B, lysine acetyltransferase, acetylation, epigenetics, gene expression, neurodevelopmental syndromes

Introduction

Epigenetic modifications are reversible chemical alterations of DNA or histones that regulate chromatin remodeling and gene expression [1–3]. Histone modifications include the extensively studied methylation and acetylation, as well as a multitude of histone acylations including propionylation, butyrylation, crotonylation, lactylation, succinylation, malonylation, glutarylation, 2-hydroxy isobutyrylation, and β-hydroxybutyrylation [3–5]. Accurate orchestration of histone modifications is essential for precise levels and spatiotemporal regulation of gene expression [6,7]. Proper cell proliferation, differentiation, and development rely on high levels of regulatory control over gene expression, which is crucial for various developmental processes, including skeletogenesis, craniofacial morphogenesis, hematopoiesis, and neurogenesis [7–10]. Accordingly, pathogenic variations in genes encoding histone-modifying enzymes that result in aberrant epigenetic regulation are frequently associated with neurodevelopmental disorders, which predominantly exhibit dominant inheritance [6,7,11–13]. These disorders are collectively called Mendelian disorders of epigenetic machinery (MDEM) or Mendelian disorders of chromatin machinery (MDCM) [11,14,15]. Among the histone-modifying enzymes are lysine acetyltransferases (KATs), including KAT6A and KAT6B, which catalyze ε-lysine acetylation on histone

tails as well as on non-histone proteins [16]. Histone lysine acetylation promotes transcription by neutralizing the positive charges on histones, thereby weakening their interaction with negatively charged DNA and facilitating an open chromatin state. Similarly, post-translational acetylation of non-histone proteins neutralizes the positive charge of lysine residues, thereby resulting in modulation of protein conformation and function, stability, protein-protein or protein-DNA interaction and subcellular localization. Consequently, acetylation of histone and non-histone proteins impacts multiple cellular and physiological processes, including transcription, mitosis, autophagy, liquid-liquid phase separation, differentiation, and neural function [16].

KAT6A was first identified as part of a fusion transcript to CREB binding protein (CBP) in acute myeloid leukemia (AML) [17]. Its homolog KAT6B was subsequently identified a few years later [18]. In the past 3 decades, both KAT6A and KAT6B have been identified in chromosomal translocations and as aberrantly expressed in a multitude of cancer types, mostly overexpressed and operating as oncogenes [19,20]. While the role of KAT6A and KAT6B in malignancies is well-documented, pathogenic heterozygous *KAT6A* and *KAT6B* variants have subsequently been identified and linked to neurodevelopmental and intellectual disability syndromes, which have been studied in the past 15 years [19–21].

The role of KAT6A/KAT6B in cancer, as well as advances in the development of KAT6A/KAT6B inhibitors and their evaluation in preclinical and clinical trials, were recently described in detailed reviews [20,22,23]. In the current review, we focus on the roles of KAT6A and KAT6B in development and discuss findings from recent studies that explored how these central acetyltransferases regulate developmental programs, and specifically neurodevelopment, as well as the role of heterozygous pathogenic variations in *KAT6A*/*KAT6B* in neurodevelopmental disorders.

KAT6A and KAT6B: Structure and acyltransferase function

KAT6A (formerly named MOZ and MYST3) and KAT6B (*aka* MORF and MYST4) are two key members of the KAT family of lysine acetyltransferases, including KAT2A (GCN5), KAT2B (PCAF), KAT3A (CBP), KAT3B (p300), KAT5 (TIP60), KAT7 (HBO1, MYST2) and KAT8 (MOF, MYST1) [24]. The KAT family of lysine acetyltransferases is categorized into three principal families, GNAT, MYST, and p300/CBP, based on their conserved structural domains and function. KAT6A, KAT6B, and KAT7, which belong to the MYST family (along with KAT5 and KAT8), serve as alternating catalytic subunit components of a multi-subunit complex comprised of BRPF1/2/3, ING4/5, and MEAF6 (Figure 1A-B) [25–27]. This complex, when comprised of KAT6A or KAT6B, acylates histone H3 on lysine residues 9 and 23 (H3K9 and H3K23), as well as diverse non-histone proteins (Figure 1C). Among these proteins are p53, SMAD3, and COP1 (constitutive photomorphogenesis protein 1) [28–30]. Through these post-translational modifications, KAT6A and KAT6B regulate a broad range of key physiological and pathological processes, including transcription, cell cycle progression, differentiation (e.g., hematopoiesis, neurogenesis, skeletogenesis), DNA repair, maintenance of hematopoietic and neuronal stem cells, developmental programs, and tumorigenesis [20,27]. KAT6A and KAT6B possess identical domain architecture, as shown in Figure 1A, and high sequence homology, sharing 60% amino acid identity and 66% similarity [18]. They bind Acetyl-CoA through their conserved MYST domain [18,31]. The zinc finger domain and helix-turn-helix motifs within the MYST domain enable the binding of the MYST domain of KAT6A to DNA [32]. The conserved region in the N-terminal domain is called the NEMM (N-terminal part of Enok, MOZ or MORF) domain. The NEMM contains a region that is essential for the nuclear localization of the acetyltransferases, as well as two winged helix motifs (WH1 and WH2) and a double plant homeodomain (PHD) zinc finger domain, which interacts with histone H3 [33–35]. It was demonstrated that while both WH1 and WH2 motifs, located in the NEMM, bind to DNA, WH1 specifically enables binding of KAT6A/KAT6B to unmethylated CpG motifs and colocalizes with H3K18ac-rich CpG regions [36–38]. H3K18 is the acetylation substrate of the acetyltransferase p300, and notably, KAT6B was shown to interact with the TAZ domain of p300 via a hydrophobic motif within its WH1 domain [38]. This interaction suggests a functional cooperation of KAT6B and p300 in transcriptional regulation. KAT6A/KAT6B recruitment to the promoters of their target genes and subsequent acetylation activity relies on the DNA-binding capacity of the WH domain [37]. The unstructured C-terminal segment contains a glutamate/aspartate-rich region and serine/methionine-rich region. Within its serine/methionine-rich region, KAT6A contains a 55 amino acid stretch composed solely of proline and glutamine residues, which is absent in KAT6B [31,39]. In this respect, this intrinsically disordered region appears to contribute to liquid-liquid phase separation and the formation of biomolecular condensates of KAT6A in the nucleus of ovarian cancer cells [40]. The serine/methionine

domain is essential for the interaction with transcription co-activators and the transcription activation capacity of KAT6A/KAT6B [31,35,41]. KAT6A/KAT6B recognize (i.e. 'read') and bind to specific histone acylation marks through their double PHD finger domain [42–44]. This interaction promotes their enzymatic activity (i.e. 'writing') and transcription at specific loci. Specifically, KAT6A recognizes unmodified H3R2 and H3K14ac, the latter of which is the acetylation substrate of KAT7 [42,45]. The association of the PHD finger domain with H3K14ac contributes to the localization of KAT6A to the promoter of *HOXA9* in HEK-293 cells. In addition to acetylated H3K14, KAT6A also binds H3K14 harboring other acyl modifications such as crotonyl, butyryl, and propionyl groups, with a preference to crotonylated H3K14 [43]. Similarly, KAT6B recognizes H3K14 acylation, which promotes its role in H3K23 acetylation at specific loci [44,46]. While most studies describe the acetyltransferase function of KAT6A/KAT6B, both enzymes, as well as other members of the MYST family of lysine acetyltransferases, exert propionyl transferase activity as well [47,48].

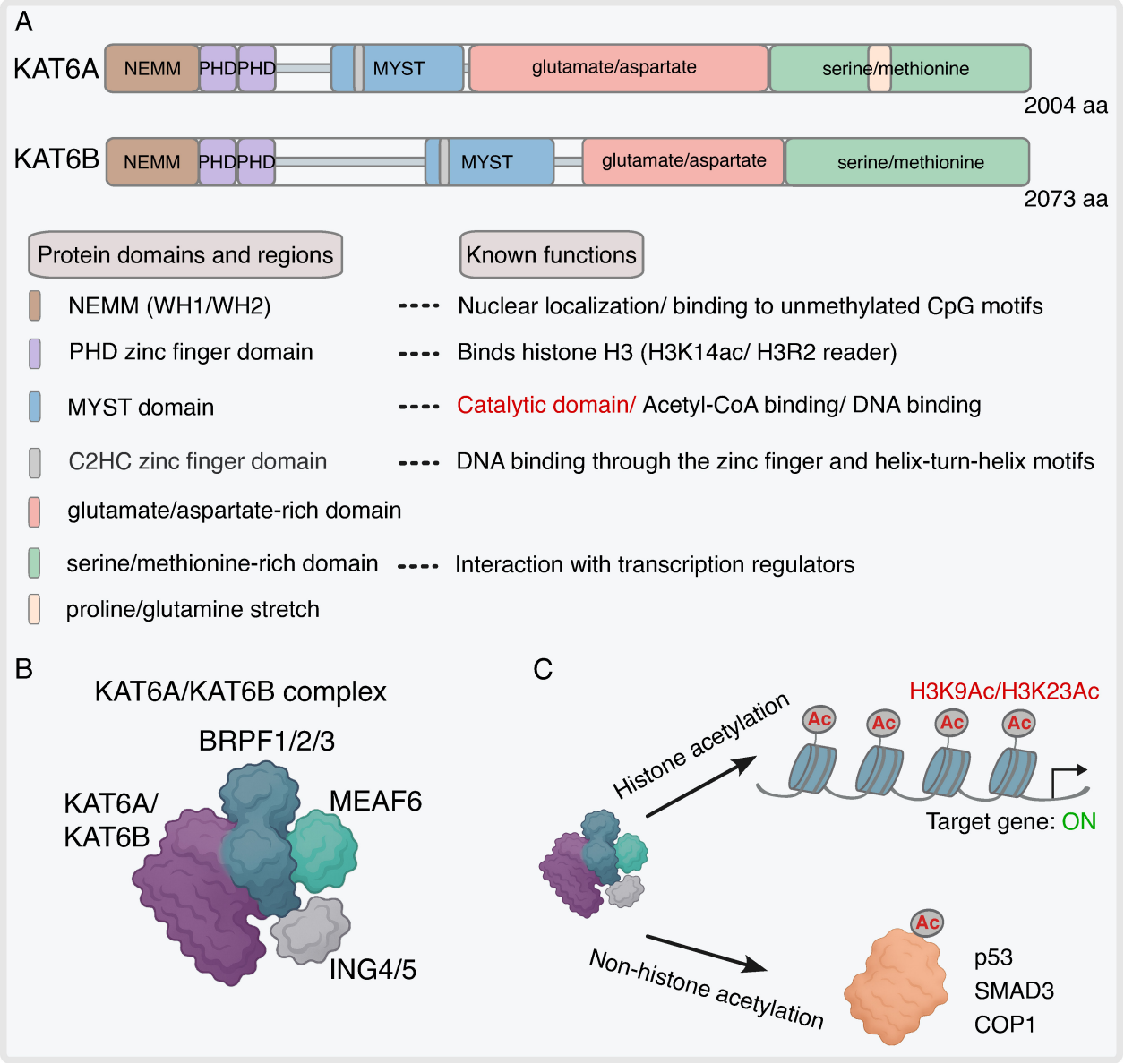


Figure 1. KAT6A/KAT6B lysine acetyltransferases: structure and enzymatic function. A) Schematic representation of KAT6A/KAT6B's protein domain architecture, including representation of color-coded domains and regions: the N-terminal NEMM (contains two highly conserved winged-helix domains, WH1/WH2), double plant homeodomain (PHD) zinc finger domains, catalytic MYST domain (contains a C2HC zinc finger and helix-turn-helix motifs), and, in the C-terminal region, the acidic-rich and serine/methionine-rich domains. Domain coordinates were derived from UniProt (KAT6A (Q92794) (NEMM, 1-205; PHD-type 1, 206-265; PHD-type 2, 266-313; catalytic/MYST domain, 488-778; C2HC MYST-type, 537-562; acidic-rich domain, 787-1420; serine/methionine-rich domain 1421–1996; proline/glutamine stretch, 1647-1701). KAT6B (Q8WYB5) (NEMM, 1-212; PHD-type 1, 213-272; PHD-type 2, 273-320; catalytic/MYST domain, 715-1008; C2HC MYST-type, 748-773; acidic-rich domain, 1069-1529; serine/methionine-rich domain 1530–2073). A description of the functions of each domain is included. B) The 4-subunit KAT6A/KAT6B complex is composed of the catalytic subunit KAT6A/KAT6B and the scaffolding subunit BRPF1/2/3 that interacts with the ING4/5 and MEAF6 subunits. C) The KAT6A/KAT6B complexes acylate lysine residues K9 and K23 on histone H3 tails as well as non-histone proteins. KAT6A/KAT6B histone acetylation is associated with a transcriptionally active chromatin state.

Developmental roles of KAT6A and KAT6B

Embryonic and tissue development

According to the Human Protein Atlas [49] and the Harmonizome 3.0 [50] databases, both *KAT6A* and *KAT6B* are ubiquitously expressed in human adult tissues, including the heart, brain, lung, intestine, muscles, and hematopoietic system, underscoring their roles in diverse developmental and adult tissue pathways [17,18,20]. Both acetyltransferases play crucial roles in maintaining adult tissue homeostasis through regulation of stem cells and the immune system [20]. Mouse *Kat6b* is expressed as early as the embryonic stem (ES) cell stage and within the inner cell mass of blastocysts [51,52]. KAT6B modulates chromatin compaction and influences the interactions of Oct4 and Nanog with chromatin targets in ES cells [51]. *Kat6a* and *Kat6b* are both expressed from early mouse developmental stages, with transcripts detected in whole embryos at E8.5, E9.5, and E10.5, as well as in mouse embryonic fibroblasts (MEFs) and fetal hematopoietic progenitors [53]. Notably, *Kat6a* mRNA is expressed at higher levels than *Kat6b* mRNA in embryos at E8.5-E10.5 as well as in several embryonic tissues including the heart, pharyngeal arches (transient embryological structures in vertebrates that develop into the face, jaw, ears, and neck) [54], and in LSK cells (a population of hematopoietic stem and progenitor cells) [53].

Depending on the genetic background, homozygous *Kat6a*-deficient mice display embryonic lethality or die at birth [55,56]. KAT6A is a regulator of the expression of diverse homeodomain transcription factor (TF) genes, which serve as master regulators of fundamental developmental programs [19,20,27]. KAT6A was found to regulate the expression of HOX family genes, which regulate body segment identity [57–60], DLX genes, which modulate craniofacial development [61], as well as the T-box TFs TBX1 and TBX5, which are involved in heart development [62,63]. In line with the attenuated expression of *Tbx1* and *Tbx5* in *Kat6a*-deficient mice, these mice display heart defects including interrupted aortic arch and ventricular septal defects [62,63]. Unlike *Kat6a*-deficient mice, *Kat6b* deficiency in mice is not embryonic lethal. However, *Kat6b*-deficient mice display growth retardation when compared to control littermates [52,64] and do not survive past weaning [65,66].

Remarkably, a point mutation that abrogates the catalytic acetyltransferase activity of KAT6A leads to a milder phenotype in mice compared to the complete loss of the KAT6A protein [67]. This finding suggests that KAT6A possesses non-catalytic functions presumably mediated by interactions with other proteins. These mice survive to term, albeit exhibiting postnatal lethality characterized by reduced survival rates post-weaning. Mice harboring the point mutation in the catalytic domain exhibit only a few differentially expressed genes compared to the null phenotype at embryonic stage E9.5. KAT domain mutant mice display abnormal development of a thinner atlas vertebra of the axial skeleton and diminished fetal liver hematopoietic stem cell activity, albeit not complete elimination of hematopoietic stem cells as in the null phenotype. Moreover, unlike the null phenotype, they do not exhibit homeotic transformations or aortic arch defects, and only one out of five fetuses displayed ventricular septal defects.

A point mutation that abolishes the acetyltransferase activity of KAT6B did not lead to differentially expressed genes, cardiac abnormalities, or hematopoietic stem cell activity. However, the combined mutation of both the catalytic domains of KAT6A and KAT6B resulted in more severe phenotypes than the mutation in the KAT6A catalytic domain alone, yet less severe than that of the KAT6A-null mutation.

In a surprising and remarkable recent paper, it was demonstrated that *Kat6b* overexpression (4-fold upregulation) rescues embryonic lethality in homozygous null *Kat6a* mice, thereby restoring embryonic vitality [53]. *Kat6b* overexpression restored acetylation at histone H3 lysine 9 and 23 and reversed critical gene expression anomalies in *Kat6a* mutant mice. These findings imply that the target gene specificity of KAT6A can be substituted, at least in part, by the related paralog KAT6B, despite differences in amino acid sequence, as long as KAT6B is expressed at sufficiently high levels. The authors suggested that KAT6B overexpression in the absence of KAT6A yields a more favorable stoichiometry of complex subunits compared to endogenous levels of KAT6B, or KAT6B overexpression in the presence of KAT6A, enabling KAT6B to functionally substitute for KAT6A. Notably, KAT6B does not normally regulate critical processes which depend on KAT6A, as evidenced by distinct individual knockout phenotypes: *Kat6a*-null mice display embryonic lethality and hematopoietic stem cell loss, whereas *Kat6b*-deficient mice primarily display neurogenesis defects [52,53,55,56]. The clear phenotype observed in haploinsufficient *Kat6a* and *Kat6b* mouse models suggests that there is no compensation between KAT6A and KAT6B when they are expressed at endogenous levels [65,68]. Additionally, endogenous *KAT6B* expression levels were not upregulated following *KAT6A* deficiency to compensate for *KAT6A*

loss in SH-SY5Y cells or neural progenitor cells (NPCs) differentiated from iPSCs derived from a KAT6A patient [69]. Collectively, these findings highlight the crucial role that these two central acetyltransferases play in development. Their roles in various developmental processes are discussed in greater detail in the subsequent sections.

Craniofacial and skeletal development

The zebrafish ortholog of KAT6A was found to be essential for the segment identity of pharyngeal arches two to four [58]. The impact of Kat6a deficiency on segment identity in zebrafish was attributed to the Kat6a-dependent regulation of *hoxa2b* and *hoxb2a* expression [58]. These genes function as "selector genes" which instruct this tissue to generate the support skeleton for the jaw instead of duplicating the lower jaw structure. Interestingly, in contrast to mice in which loss of a single *Hoxa2* gene results in severe deformities, these genes in zebrafish function redundantly, and only when both genes are knocked down simultaneously severe developmental defects occur, specifically the transformation of second-arch cartilages into duplicate jaw structures. Similarly, *Kat6a*-deficient mouse embryos displayed homeotic transformation of anterior body segments that give rise to the neck and trunk region [57]. *Kat6a* deficiency in mice led to reduced expression of multiple *Hox* genes, which was accompanied by decreased H3K9 acetylation at these genes' loci [57,60]. Loss of function (LoF) of KAT6A in mice results in craniofacial anomalies in the jaws, including cleft palate [62]. Among the differentially expressed genes, 19 genes were related to cleft palate, including *Dlx1*, *Dlx2*, *Dlx3* and *Dlx5*, as well as several genes regulated by DLX TFs [61]. KAT6A was shown to directly bind to the *Dlx5* locus and maintain its H3K9 acetylation. In addition to the downregulation of multiple genes involved in craniofacial and specifically palate development, several bone collagen genes as well as genes involved in osteoblast differentiation, such as *Runx2* and *Nkx3-1,* were upregulated in the pharyngeal arches and palatal shelves [61]. The upregulation of these genes could result from premature osteogenic lineage differentiation during palatal shelf development [61].

KAT6A was suggested to play a role in tooth formation via the regulation of odontoblast differentiation [70]. KAT6A overexpression increased the expression of the TFs *Runx2* and *Sp7*, which are essential for commitment and differentiation, as well as genes encoding early and late markers of odontoblast maturation and mineralization, *Alp*, *Col1a1*, *Ocn*, *Dspp*, and *Dmp1*, in rat MDPC-23 dental pulp cells. The authors further demonstrated that KAT6A and RUNX2 are recruited to the promoters of *Dspp* and *Dmp1* in MDPC-23 cells, and KAT6A overexpression synergistically increased *Dspp* promoter activity with RUNX2 in HEK-293T cells. Notably, both KAT6A and KAT6B interact with RUNX2 via their C-terminal serine/methionine-rich domain [41]. KAT6A also binds and promotes H3K9 acetylation on the chromatin of *RUNX2* in HEK-293 cells, suggesting a role for KAT6A in regulating *RUNX2* expression, in addition to functioning as its co-activator [36].

KAT6A expression is reduced in human aging bone marrow-derived mesenchymal stem cells (BM-MSCs), leading to impaired stemness characterized by decreased proliferation, self-renewal, and osteogenic differentiation [71]. BM-MSCs are essential for bone and cartilage formation, and decreased stemness of BM-MSCs has been associated with osteoporosis [72–74]. Using gain- and LoF experiments in young and old BM-MSCs, it was found that KAT6A promotes proliferation, colony formation, and osteogenic differentiation of BM-MSCs through the regulation of the Nrf2/ARE antioxidant signaling axis and inhibition of reactive oxygen species (ROS) accumulation [71]. KAT6A regulated the expression of the osteogenic-related genes *RUNX2*, *OCN*, and *BMP2* following osteogenic differentiation of BM-MSCs.

Consistent with a broader role in bone remodeling, KAT6A is elevated in RANKL-induced osteoclast cell cultures and in the serum of patients with osteoporosis [75]. Knockdown of KAT6A in an *in vitro* model of osteoclast differentiation from mouse bone marrow-derived macrophages (BMDMs) and RAW264.7 cells revealed reduced capacity of osteoclast differentiation following stimulation [75]. Mechanistically, KAT6A binds the Tet1 promoter, increases H3K9 acetylation and RNA Pol II recruitment, resulting in upregulated Tet1, which promotes the transcription of TRPV4 (Transient Receptor Potential Cation Channel Subfamily V Member 4). TRPV4 is a nonselective calcium-permeable channel that is essential for osteoclast differentiation, function, and bone resorption [76].

Collectively, these findings indicate that KAT6A plays an important role in bone homeostasis by maintaining BM-MSCs, regulating the expression of key osteogenic genes, such as *RUNX2* and *DLX*, and regulating osteoclastogenesis.

Interestingly, in addition to its functions during skeletal development, KAT6A has also been implicated in degenerative cartilage pathology. KAT6A was identified as a major driver of cartilage senescence in osteoarthritis [77]. In this respect, the long noncoding RNA ELDR mediates the formation of a protein complex consisting of KAT6A and hnRNPL,

thereby altering chromatin accessibility. Specifically, this complex regulates histone modifications at the promoter region of IHH (Indian Hedgehog), a crucial regulator of osteoarthritis, thereby activating the Hedgehog signaling axis, resulting in chondrocyte senescence and cartilage degradation.

During mouse embryogenesis, *Kat6b* expression is upregulated within the developing craniofacial and dental structures, including the frontonasal and maxillary prominences at E11.5 and E12.5, eyelids at E15.5, and in tooth primordia [52,64,78]. Similar to *Kat6a*, *Kat6b* deficiency in mice results in craniofacial abnormalities, including microphthalmia (smaller eyes) and more ventrally positioned ears [52,64]. Mice homozygous for a *Kat6b* hypomorphic allele (90% *Kat6b* deficiency) exhibited irregular development of calvarial bones (i.e., the skullcap bones, including the frontal, parietal, and occipital bones) without an observed craniosynostosis [52]; the latter is defined as the premature fusion of the cranial sutures, hence causing an abnormal head shape. Additionally, mice homozygous for a *Kat6b* null allele presented shorter frontal bones and jaws [65].

The irregular craniofacial development in *Kat6a*- and *Kat6b*-deficient mice is consistent with craniofacial abnormalities presented by individuals harboring monoallelic pathogenic variants in *KAT6A* and *KAT6B* [19,20,79,80]. *KAT6B* pathogenic variants frequently lead to additional skeletal malformations, such as in the spine, patella, and digits [19,81]. In this respect, *KAT6B* was found to be epigenetically silenced in patients with congenital scoliosis (CS) [82]. CS is characterized by perturbations in spine development. KAT6B downregulation in chondrocytes from CS patients led to their reduced proliferation, presumably due to the observed decreased RUNX2 expression. It is well established that RUNX2 is a master TF that regulates the entire skeletal developmental program [83,84]. In this respect, RUNX2 is crucial for the differentiation of osteoblasts and the maturation of chondrocytes. It further plays a complex and significant role in their proliferation. Hence, RUNX2 is important during cartilage and bone formation. *Kat6b*-deficient mice exhibited an impaired femur growth plate, suggesting a role of KAT6B in chondrocyte differentiation [64]. Consistently, KAT6B was highly expressed in the undifferentiated mesenchyme of the skull and in the mesoderm surrounding cartilage of the limbs [52,64]. *Kat6b* deficiency in mice led to increased chondrocyte hypertrophy and premature ossification, resulting in increased bone density in the skull, shortened skeletal elements, and thickened bone [85]. *Kat6b* deficiency did not alter chondrocyte proliferation in growth plate regions. Chondrocyte hypertrophy is the process of an increase in the chondrocyte volume prior to a shift from a collagen-rich to a calcified matrix in the remodeling of cartilage into bone tissue [86]. The phenotype observed in *Kat6b*-deficient mice is consistent with skull malformations and craniosynostosis observed in some individuals harboring pathogenic heterozygous *KAT6B* variants [81,87,88]. In line with the observed premature ossification, *Kat6b*-deficient MEFs that were induced to differentiate into osteoblast-like cells (pre-osteoblasts), displayed increased expression of genes associated with osteoblast development, compared to control MEFs [85]. Among the upregulated genes were several genes whose gain-of-function is associated with craniosynostosis in humans. Consistent with the above findings, *Runx2* was upregulated following osteogenic induction. Conversely, unlike wild-type (WT) pre-osteoblasts, *Sox9* was not upregulated in *Kat6b*-deficient pre-osteoblasts. Notably, SOX9 and RUNX2 are antagonistic regulators of chondrocyte fate during growth plate maturation and ossification [89]. Additionally, SOX9 and RUNX2 can physically interact and reciprocally inhibit each other's transactivation [90,91]. SOX9 is an essential key regulator of chondrocyte lineage commitment and is downregulated during chondrocyte dedifferentiation/osteoblastic redifferentiation [86,89,92]. SOX9 maintains chondrocyte identity and prevents premature hypertrophy, dedifferentiation, and transition towards an osteoblast fate, whereas RUNX2 promotes chondrocyte hypertrophy and osteoblast differentiation. [89,93].

Maintenance of hematopoietic stem cells and the development of the immune system

Both KAT6A and KAT6B acetyltransferases were found to function in the maintenance of hematopoietic stem cells (HSCs) [55,56,94–98]. Deletion of *Kat6a* or a mutation that results in catalytic inactivation of KAT6A leads to a reduced number of fetal and adult HSCs and loss of quiescent adult HSCs [55,56,99,100]. KAT6A suppresses senescence via inhibition of the INK4A-ARF pathway in hematopoietic and neural progenitors, as well as in fibroblasts [97,101].

While most studies described the significant role of KAT6B in relation to neural stem cells, KAT6B was also found to regulate hematopoietic stem cells [95]. In this respect, KAT6A haploinsufficiency reduced H3K23ac, whereas KAT6B haploinsufficiency diminished H3K9ac in fetal hematopoietic stem cells and progenitor cell populations. Similar to the loss of KAT6A, KAT6B deficiency led to a reduced number of HSCs as well as a reduced number of quiescent cells and a greater number of cells in G_1 phase of the cell cycle. While KAT6A exerted a predominant regulatory impact, both KAT6A and KAT6B cooperatively

regulated the transcription of hematopoiesis-associated genes including *Pbx1*, *Meis1*, *Erg*, *Flt3*, and genes belonging to the HOXA and GATA families [95]. HSCs harboring combined monoallelic loss of both *Kat6a* and *Kat6b* (*Kat6a*$^{+/-}$*Kat6b*$^{+/-}$) exhibited more severe transcriptional deficits than loss of either alone. Notably, among the downregulated genes in *Kat6a*$^{+/-}$ *Kat6b*$^{+/-}$ HSCs were *Pbx1*, *Tie2* and *Mpl*, which are essential to maintain the quiescence of HSCs, as well as *Meis1*, *Hoxa9,* and *Erg,* which are implicated in self-renewal of HSCs [95]. These findings support cooperative functions *in vivo*. However, chromatin co-occupancy data for KAT6A and KAT6B are currently limited to leukemia models [102], leaving normal tissues uncharacterized regarding direct target-gene overlap. While global histone marks (like H3K23ac or H3K9ac) were mapped using the CUT&TAG (Cleavage under targets and tagmentation) technique in normal mouse primary tissues such as MEFs and neural stem and progenitor cells (NSPCs) [53,66,103], direct binding profiles for KAT6A/KAT6B were presumably limited by the lack of high-quality, reliable and specific antibodies against KAT6A and KAT6B, which often necessitates the use of a tagged fusion protein [66,68].

Interestingly, the above study revealed 126 genes co-occupied by both KAT6A and KAT6B in human AML MOLM-13 cells [102]. Among these genes were *HOXA*-cluster genes and *MEIS1*, suggesting that these genes are directly regulated by both KAT6A and KAT6B. Moreover, this study revealed that *KAT6B* loss had modest effects on leukemia cell growth compared to *KAT6A* KO, further suggesting the functional dominance of KAT6A over KAT6B in hematopoietic cells [102]. Studies in AML cell lines have demonstrated that KAT6A cooperates with the nuclear chromatin reader protein ENL (eleven-nineteen leukemia) [104,105]. The acetyl-lysine reader ENL binds H3K9ac catalyzed by KAT6A at gene promoters and cooperates with a network of chromatin factors to drive transcriptional elongation. While this cooperative writing-reading function was identified in malignant cells, whether this epigenetic crosstalk occurs under physiological conditions remains to be elucidated. Notably, KAT6A colocalized with ENL at promoter-proximal regions of *HOXA5* and *HOXA9* in HEK293T cells [105], suggesting that this functional interaction may occur under physiological conditions as well.

In addition to their role in the maintenance of HSCs, both KAT6A and KAT6B regulate lineage differentiation. KAT6A deficiency and downregulation of KAT6B reduced erythroid differentiation capacity, resulting in enhanced myeloid lineage differentiation [55,94]. KAT6A is crucial for the differentiation of monocytes into macrophages and is further implicated in their polarization into M1 macrophages [106,107]. M1 macrophages are essential for proinflammatory responses, whereas M2 macrophages have a role in anti-inflammatory responses and promote tissue repair [108]. In this respect, *Kat6a* was upregulated in mouse macrophages stimulated to induce M1 polarization [107], in macrophages that participate in inflammatory processes such as periodontitis [109] and sepsis-induced acute lung injury [110] in mouse models, as well as in peripheral blood samples of sepsis patients [110]. Conversely, *Kat6a* was downregulated in IL-4-stimulated (to induce M2 polarization) primary mouse BMDMs [106]. *Kat6a* downregulation in stimulated (to induce M1 polarization) mouse macrophage-like cell line and BMDMs led to impaired phosphorylation of AKT, ERK, p38, and JNK, which are involved in signaling pathways that are essential for the polarization of M1 macrophages [106,111]. Additionally, *Kat6a* downregulation resulted in reduced expression of pro-inflammatory cytokines, including IL-1β, tumor necrosis factor (TNF) α, and IL-6 [106,109,110]. A recent study has further demonstrated that inhibition of KAT6A in mouse peritoneal macrophages and BMDMs, using the KAT6A/KAT6B inhibitor WM1119, as well as KAT6A knockdown in M1-induced RAW264.7 macrophages, reduced multiple glycolytic genes, including *Glut1, Hk2*, *Pkm*, *Eno1, and Ldha* [110]. Consequently, glucose uptake and glycolysis were reduced, whereas mitochondrial respiration was increased. KAT6A inhibition led to the reduced expression of both HIF1α and c-Myc, which regulate the expression of genes encoding glycolytic enzymes and pro-inflammatory factors [110,112,113]. Moreover, KAT6A inhibition was associated with diminished PI3K-AKT-mTORC1 pathway, a central signaling axis supporting macrophage activation and M1 polarization. The PI3K-AKT-mTORC1 axis is associated with glucose uptake and glycolysis as well as regulation of the TFs MYC and HIF-1α [114]. In this respect, KAT6A drives *MYC* expression in AML cells, thus promoting tumorigenesis [104].

In contrast to KAT6A, KAT6B is downregulated following the activation of M1 macrophages, suggesting that KAT6A and KAT6B may serve different roles in the context of M1 macrophage polarization [107].

Apart from KAT6A's role in the differentiation of cells of the myeloid lineage, KAT6A was found to regulate processes in cells of the lymphoid lineage, such as B cells and T cells. B cell progenitor proliferation is dependent on KAT6A, which was shown in mice to directly bind the *Meis1* locus and

regulate the expression of TFs that are critical for hematopoietic cell proliferation, such as *Hoxa7*, *Hoxa9*, *Pbx1*, and *Meis1* [115].

Consistent with its function in hematopoietic self-renewal and differentiation, KAT6A binds to and co-activates TFs implicated in hematopoiesis, such as Runt-related transcription factor 1 (RUNX1 aka AML1) and PU.1, which are critical TFs for HSC maintenance, lineage specification, and differentiation [35,55,116–118].

KAT6A is also essential for the immune response by regulating crucial processes in memory B- and T-cell formation and function [119–121]. Specifically, KAT6A-deficient B cells displayed increased differentiation into IgM and low-affinity IgG1 memory B cells during primary response and decreased secondary high-affinity antibody-secreting cells [121]. By directly acetylating H3K9 in the promoter and E8I enhancer at the *Cd8* locus, KAT6A regulates its expression in $CD8^+$ T cells [119]. Consequently, KAT6A deficiency reduced CD8 coreceptor expression, which was associated with diminished T cell receptor signaling and effector-like memory T cells. KAT6A is also essential for the proliferation of $CD4^+$ T cells and the differentiation of a subset population of pro-inflammatory Th1 and Th17 cells [120]. KAT6A exerts its role in $CD4^+$ T cells via the regulation of expression of cell cycle- and glucose metabolism-related genes. KAT6A regulation of glucose metabolic reprogramming was dependent on the binding of MYC and HIF-1α TFs to these genes.

These data lend support to the importance of both KAT6A and KAT6B in the maintenance of hematopoietic stem cells as well as in the differentiation of several hematopoietic cell lineages.

Maintenance of neural stem cells and neurodevelopment

In addition to their role in the maintenance of hematopoietic stem cells, KAT6A and KAT6B also support the maintenance of neural stem cells (NSCs) [66,97,98,122]. Reduced proliferation and increased senescence of neural cells were identified both *in vivo* in the brain of mouse embryos harboring catalytically inactive KAT6A and *ex vivo* in cells isolated from the telencephalon of these mice to generate neurospheres [97]. Importantly however, a recent study revealed that while homozygous loss of *Kat6a* expression in mouse embryonic NSPCs from the dorsal telencephalon led to reduced proliferation, haploinsufficiency of *Kat6a* impacted the differentiation of NSPCs but not their proliferation [103]. Complete loss of *Kat6a* expression resulted in a moderate reduction in global H3K23ac in NSPCs. In-depth chromatin profiling revealed a *Kat6a* dose-dependent reduction in H3K9ac and H3K23ac in promoters, enhancers, and gene bodies in differentiating NSPCs. Proliferating NSPCs exhibited a similar trend of reduced H3K23ac, whereas H3K9ac was reduced only in *Kat6a*-deficient cells. KAT6A deficiency in differentiating NSPCs led to a decreased expression of multiple genes associated with nervous system development. The list of downregulated genes includes SOX family genes and TF-encoding genes that were previously shown to be downregulated following KAT6A deficiency in other cell types; these include *Myc* [104,110], DLX family members [61], and MEIS genes [104,115]. Interestingly, KAT6A deficiency was associated with diminished recruitment of the methyltransferase MLL1 (Mixed-Lineage Leukemia protein-1, KMT2A) to its target genes, accompanied by reduced H3K4 methylation at these loci. These alterations were positively correlated with observed changes in gene expression levels. Importantly, MLL1 is a central epigenetic regulator, acting as a transcriptional activator that is essential for hematopoiesis, neural progenitor proliferation and neuronal differentiation [123–125]. Consistently, KAT6A was previously shown to impact MLL1 recruitment to *HOX* gene loci in mouse embryos [57]; moreover, KAT6A and MLL1 cooperatively regulate the expression of *HOX* genes in human cord blood $CD34^+$ cells [126]. Evidence for the cooperative regulation of gene expression by KAT6A and MLL1 was additionally demonstrated in B-cell progenitors [115] and HEK-293T cells, where they colocalized at the promoters of many transcriptionally active genes, including *MYC* and *HOXA9* [127], in REH acute lymphoblastic leukemia (ALL) cells [127], AML MOLM-13 cells [102], and in gastrointestinal stromal tumor cells [128].

Kat6b-deficient mouse embryonic stem cells (mESC) exhibit reduced capacity of neuronal differentiation [51,129]. Recently it was shown that KAT6A and KAT6B are essential for the activation of genes at bivalent chromatin during an *in vitro* neuronal differentiation from ESCs [129]. Bivalent nucleosomes are asymmetric for the repressive histone mark H3K27me3 and the activating histone mark H3K4me3 [130]. A possible role for these bivalent domains in ESCs is to poise genes for timely activation or repression upon cell-lineage specification and differentiation. Histone bivalency also occurs in NPCs and in neurons, albeit to a lesser extent [130,131]. KAT6B and its complex subunits BRPF1/2 and ING5 specifically bind asymmetric bivalent nucleosomes in ESCs [129]. Moreover, KAT6B preferentially binds bivalent over monovalent H3K4me3 at promoter sites. The recruitment of the KAT6B complex to bivalent nucleosomes is presumably mediated by the ability of

the MYST domain of KAT6B to act as an H3K27me3 reader and the recognition of the H3K4me3 mark by the PHD finger domain of ING5 [129,132]. H3K23ac was markedly reduced in *Kat6b*-deficient mESC and to a lesser extent in *Kat6a*-deficient mESC [129]. However, KAT6A- or KAT6B deficiency did not affect the proliferation and maintenance of mESC, nor the expression of genes in ESCs. Sequential differentiation of mESC towards glutamatergic neurons revealed that KAT6A and KAT6B are essential for glutamatergic neuronal differentiation. The expression of neural progenitor as well as early and mature neuronal marker genes was preferentially downregulated in genes associated with bivalency at their promoters. Loss of KAT6A/KAT6B preferentially affected bivalent genes that are activated during neuronal differentiation, indicating that these acetyltransferases preserve a poised chromatin state that is required for proper developmental gene induction.

KAT6B expression increases during cerebral cortex development, and KAT6B was found to be crucial for neurogenesis and the development of the cerebral cortex [52,66]. Loss of KAT6B in embryonic NSPCs derived from the dorsal telencephalon of mice impaired neuronal differentiation and neurite outgrowth, in addition to reducing proliferation and self-renewal of NSPCs *in vitro* [66]. Conversely, *Kat6b* overexpression promoted neurite outgrowth in cortical neurons [133]. Consistently, *Kat6b*-deficient mouse embryos displayed a smaller cortical plate and adult cortex with fewer layer V pyramidal neurons and GAD67-positive interneurons [52]. Apart from embryonic neurogenesis, KAT6B displays a role in adult neurogenesis too. KAT6B gene expression is high in the neurogenic subventricular zone of adult mice, and *Kat6b* deficiency in mice resulted in reduced self-renewal of NPCs, a reduced number of neuroblasts in the subventricular zone, as well as diminished capacity for neuronal differentiation *in vitro*, along with smaller olfactory bulbs [122]. Conversely, overexpression of *Kat6b* in mice led to enhanced self-renewal of subventricular zone-derived NSPCs and skewed differentiation towards a neuronal rather than an astrocytic fate *in vitro* and *in vivo* [133].

The molecular function and gene targets of KAT6B in neurogenesis have only recently begun to be deciphered. Using *Kat6b*-deficient and -overexpressing mice, KAT6B was found to catalyze global H3K9ac in embryonic NSPCs and global H3K9ac and H3K23ac in the dorsal telencephalon, at E12.5 [66,133]. H3K23ac was reduced at promoters, gene bodies, and active enhancers at specific genomic sites in *Kat6b*-deficient NSPCs. Transcriptomic profiling of *Kat6b*-deficient NSPCs revealed a reduction in the expression of nervous system development-associated genes and neural precursor proliferation genes, which was positively correlated with a reduction in H3K9ac. This gene list included early regulators of neuroepithelium, brain development, and NSC function, including *Sox1*, *Sox2*, *Pax6*, and *Id2*, and genes related to neurite elongation [66]. Loss of KAT6B also led to downregulation of brain and neuronal development genes in the dorsal telencephalon, which was established to give rise to the cerebral cortex, at E12.5. Among the downregulated genes in both NSPCs, E12.5 dorsal telencephalon, and E15.5 cortex were many SOX family genes, which are implicated in neural precursor proliferation and brain development [134]. KAT6B was found to bind the genomic loci of SOX2 and PAX6 and directly regulate their gene expression.

Congruently, many upregulated genes in *Kat6b*-overexpressing NSPCs and dorsal telencephalon were associated with nervous system, neuronal development and maturation genes [133]. Interestingly, fewer genes were detected as differentially expressed in more mature areas, i.e., the cortex at E15.5, when KAT6B was deficient or overexpressed, suggesting a possible role in early developmental stages of neurogenesis or an increased cell type complexity, which masks differential expression of genes in specific cell types [66].

Collectively, these studies reveal that KAT6B is a key epigenetic regulator of neurodevelopment, controlling neural stem/progenitor proliferation, neuronal differentiation, and cortex formation. While KAT6A was shown to be essential for NSPCs proliferation and early differentiation, as stated above, its role during the early stages of neurogenesis has just begun to be elucidated and is further discussed later in this review.

A critical goal in understanding KAT6A and KAT6B syndromes involves resolving KAT6A/KAT6B cell-type-specific functions within the developing brain. Bulk assays used in the studies described above mask cell-type-specific perturbations, particularly given the complex cellular heterogeneity of the developing brain [135]. Future studies leveraging single-cell RNA sequencing (scRNA-seq) and scATAC-seq (single-cell assay for transposase-accessible chromatin with high-throughput sequencing) could potentially determine whether impaired function of KAT6A/KAT6B impacts specific cell types, progenitor subtypes, and neural lineages. Importantly, the utilization of a combined approach of several omics, as was done with dermal fibroblasts obtained from KAT6A patients [136] and NSPCs obtained from *Kat6b*-deficient mice [66], is beneficial in order to comprehensively profile the epigenome and transcriptome changes caused by *KAT6A* and *KAT6B*

deficiency in neurodevelopment. This multi-omics approach, including the utilization of scATAC-seq and CUT&RUN (Cleavage under targets and release using nuclease) or CUT&TAG followed by sequencing, combined with scRNA-seq, could profile chromatin accessibility and link epigenomic alterations with transcriptional changes at specific loci within specific cell types.

KAT6A/KAT6B-associated neurodevelopmental disorders

The established roles of KAT6A and KAT6B as pivotal epigenetic modifiers, particularly in regulating NSC homeostasis and neurodevelopment, underscore why their dysregulation has been linked to serious neurodevelopmental disorders. While pathogenic *KAT6A* variants are associated with KAT6A syndrome, *aka* Arboleda-Tham syndrome (ARTHS, OMIM#616268) [137–139], pathogenic *KAT6B* variants are associated with Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome (SBBYSS, OMIM #603736) [78], Genitopatellar syndrome (GTPTS, OMIM #606170) [140,141], Noonan syndrome-like phenotype [64] and intermediate or combined phenotypes [81,142,143], which are now collectively referred to as "KAT6B disorders" [80,81,88]. Pathogenic *KAT6A* and *KAT6B* variants are predominantly heterozygous *de novo* truncating variants [79,81,144,145], although a few inherited variants were reported as well (Figure 2; Supplementary Tables S1, S2) [81,144,146–151]. Missense variants are less common and are often located within functionally critical domains, such as the MYST acetyltransferase domain or the acidic and serine/methionine-rich domains, where they are predicted to impair enzymatic activity or protein-protein interactions (Figure 2A) [19,79]. Several splice variants were reported as well (Figure 2B) [80,81,139,144,148,152–155]. The pathogenic variants of *KAT6A* that were described to date occur throughout the gene, although there is an evident clustering of truncating variants (64%, 61/95 truncating variants) in the glutamate/aspartate region of KAT6A, which is encoded by the last exons (exon 15 through the proximal region of exon 17) (Figure 2A; Supplementary Table S1). As for *KAT6B*, pathogenic variants that were previously reported predominantly reside in the glutamate/aspartate and serine/methionine regions, which are encoded by exons 16-18 (Figure 2A; Supplementary Table S2). Interestingly, all GTPTS-associated variants cluster within the distal part of exon 17 and the proximal region of exon 18 (reported variants mapped between amino acids 1194–1515 in the acidic domain; Supplementary Table S2) [81,88,156].

Common phenotypic features of KAT6-associated disorders include varying degrees of intellectual disability (ID), developmental delay (DD), and multisystemic anomalies (Figure 3) [80,81,144,157]. Additional common features include facial dysmorphisms, speech delay, hypotonia, seizures, microcephaly, feeding difficulties, as well as congenital heart defects. The most consistent facial features in KAT6A syndrome include a broad nasal tip and a thin, tented upper lip. Other characteristic features may include strabismus, bitemporal narrowing, a prominent nasal bridge and a flat philtrum. Some patients present epicanthic folds and low-set and posteriorly rotated ears, which are occasionally folded, and micro/retrognathia [144,157]. The hallmark of SBBYSS is the "mask-like" facies, blepharophimosis and ptosis. Lacrimal duct anomalies (e.g., dacryostenosis) are also more specific to this subtype of KAT6B syndrome [80,81]. Common KAT6B spectrum features include a nose with a bulbous end or a broad nasal bridge, low-set and posteriorly rotated ears, prominent cheeks, downslanting palpebral fissures, long philtrum, thin upper lip, thin lip vermilion, and micro/retrognathia [81,158]. While KAT6A and KAT6B syndromes exhibit some phenotypic overlap, each presents additional distinct clinical manifestations that further diverge between patients with GTPTS and with SBBYSS (Figure 3). Some individuals with KAT6A syndrome display digestive problems, sleep disturbances, motor disorders, visual problems, and autism features [144,152]. Common features of individuals with KAT6B syndrome include craniofacial and skeletal anomalies, such as a cleft palate; with some features that are more common in GTPTS patients, including patellar hypoplasia, contractures of the hips and knees, as well as genital anomalies [80,81,88,158]. Long thumbs or long great toes are seen particularly in the SBBYSS subtype. Similar to KAT6A syndrome patients, gastrointestinal complications, including gastroesophageal reflux and constipation, were reported for patients with KAT6B syndrome [79,81,88]. Sleep disturbances are not frequently reported in patients with KAT6B syndrome, but several patients were reported to have obstructive sleep apnea [88,143].

Magnetic resonance imaging (MRI) of the brain did not reveal structural anomalies in most KAT6A syndrome patients [144,157,159]. However, reported variations include microcephaly and infrequent malformations such as craniosynostosis, thinning of the corpus callosum, cisterna magna enlargement, Chiari malformation (i.e., the pushing of the cerebellum downwards into the spinal canal), and white matter hyperintensities. Conversely, KAT6B

syndrome patients were more frequently reported to have structural malformations [81]. Approximately one-third of SBBYSS patients were found to bear microcephaly, and a few displayed agenesis or hypoplasia of the corpus callosum [80,158]. Structural anomalies reported for the majority of GTPTS patients included agenesis or hypoplasia of the corpus callosum and microcephaly. Some GTPTS patients were also reported to exhibit cortical malformations, hydrocephaly, or ventriculomegaly [158].

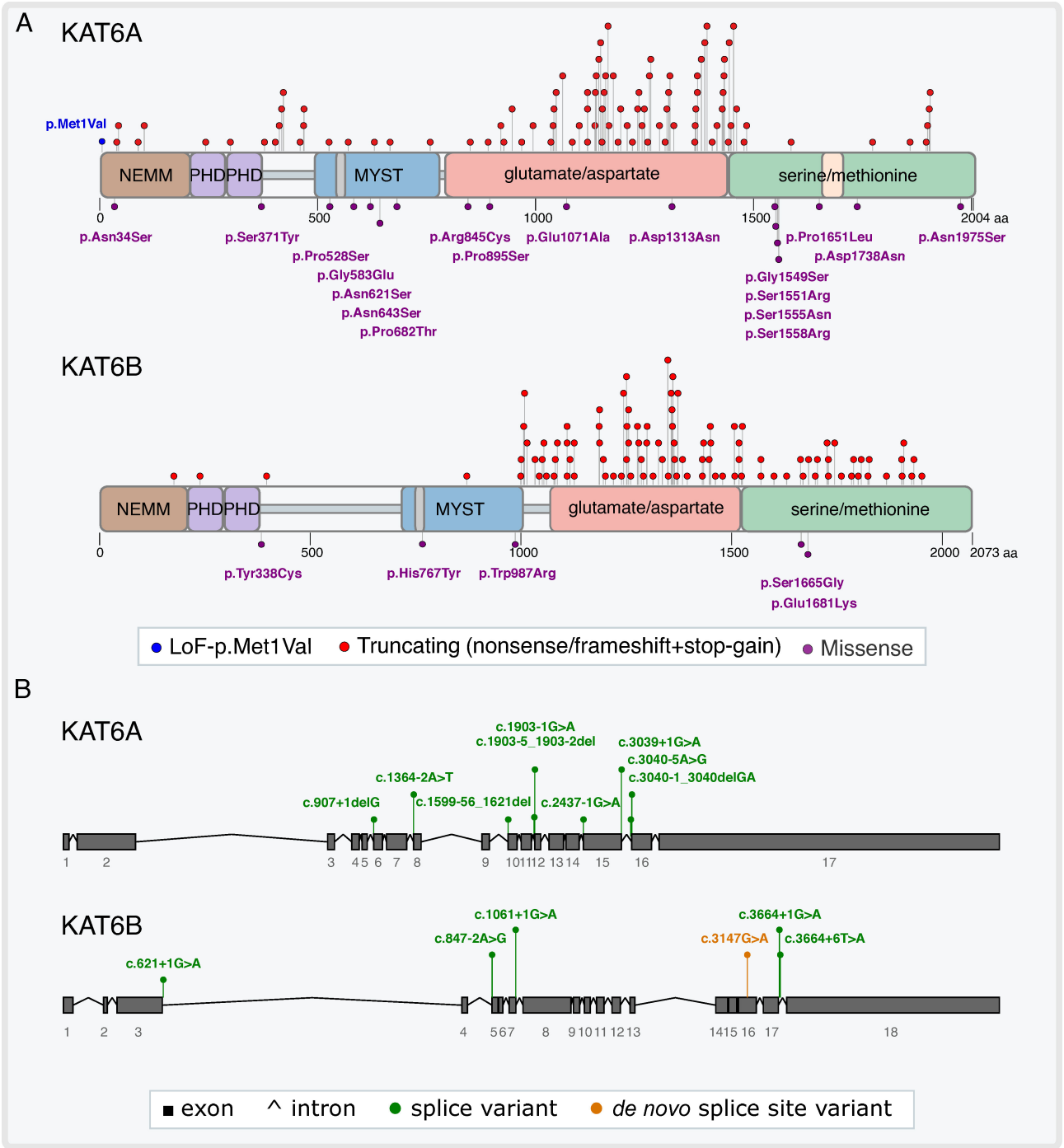


Figure 2. Distribution of pathogenic variants associated with KAT6A/KAT6B neurodevelopmental syndromes. A) Pathogenic variants associated with KAT6A- and KAT6B-related neurodevelopmental disorders are plotted according to their relative position along the schematic representation of the protein domains. A loss of function variant (p.Met1Val) abolishing *KAT6A*'s start-codon is indicated by a blue lollipop and label. Truncating variants (nonsense and frameshift variants that lead to a premature stop codon) are shown above the protein (red lollipops); missense variants are shown below the protein (purple lollipops and labels). B) Splice site variants (green lollipops and labels) are plotted along the exon-intron gene structure (exons/introns are scaled according to their relative size). Recurrent *de novo* alterations of the synonymous variant c.3147G>A (orange lollipop and label) (n=8) indicate the presence of a mutation hotspot, which is predicted to result in a protein truncation (p.Ala1008Argfs*62) through an aberrant, newly created cryptic splice site [185–189]. Pathogenic *KAT6A*/*KAT6B* variants that were previously reported for KAT6A/KAT6B syndromes are summarized in Supplementary Tables S1 and S2. Recurrent variants are plotted in the figure only once to maintain figure clarity and to avoid redundancy of pathogenic variants in individuals that were described more than once in the literature.

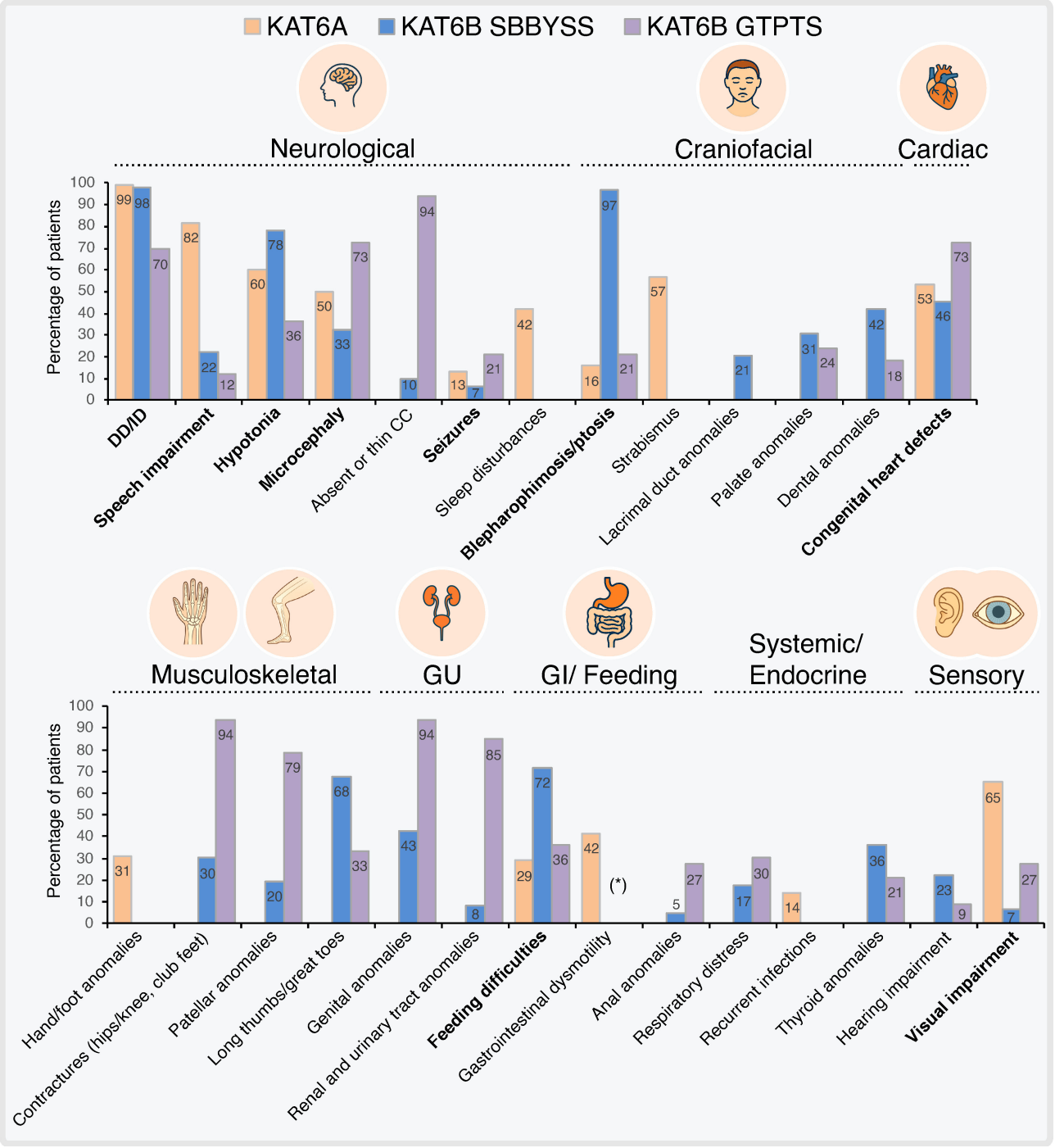


Figure 3. Phenotypic spectrum and prevalence of clinical features associated with KAT6A, KAT6B-SBBYSS, and KAT6B-GTPTS syndromes. The bar graph depicts the percentage of individuals presenting with major clinical features across KAT6A and KAT6B syndromes (including the SBBYSS and GTPTS subtypes), highlighting both shared and syndrome-specific phenotypic profiles. Shared clinical features across KAT6A and both KAT6B subtypes are indicated in bold. Clinical features are categorized into organ system domains: neurological, craniofacial, cardiac, musculoskeletal, genitourinary (GU), gastrointestinal (GI)/feeding, systemic/endocrine, and sensory. Percentages for each clinical feature are indicated within the bars. CC denotes corpus callosum. DD/ID denotes developmental delay/intellectual disability. (*) Gastrointestinal complications, including gastroesophageal reflux and constipation, were also reported in patients with KAT6B syndromes [81,88,158]. Data for the figure were collated from previous publications [79–81,157].

Several studies addressed the evaluation of the cognitive and behavioral functions of KAT6A syndrome patients in recent years [152,160–163], while one study also compared the cognitive profile of 13 KAT6B syndrome patients to that of 15 KAT6A syndrome patients [160]. These studies reported that both KAT6A and KAT6B patients exhibit difficulties in adaptive functioning as well as impaired non-verbal cognition and receptive language skills. KAT6A syndrome patients were also found to display impaired expressive language skills, while this skill remains to be systematically evaluated in KAT6B

syndrome patients [12,152,160]. Notably, while both groups shared autism-related behaviors with low rates of externalizing behavior problems, only KAT6B syndrome patients exhibited reduced social motivation [160].

Two studies investigating the impact of distal versus proximal truncating variants in KAT6A on the severity of the phenotype reported a correlation between the position of the pathogenic variant and the level of ID [144,152]. Individuals carrying truncating variants in the last two exons exhibited a shift towards a more severe degree of ID than those with variants in the first 15 exons, including lower standard scores of adaptive behaviors, such as communication, daily living skills, and socialization [152]. However, two other studies did not find a correlation between early versus late truncating variants and the neuropsychological phenotype, due to the small number of participants [161,163]. Nevertheless, the authors suggested a trend towards relatively higher cognitive functioning in individuals carrying missense variants compared to those harboring truncating variants. Notably, specific missense variants in *KAT6A* and *KAT6B* were associated with milder phenotypes compared to truncating variants [19]. Across major cohorts, missense variants exhibit a reduced prevalence or complete absence of congenital heart defects [79,144]. A point mutation that abrogates the catalytic acetyltransferase activity of KAT6A was shown to lead to a milder phenotype in mice compared to *KAT6A* null mice, revealing that KAT6A possesses non-catalytic functions too [67]. Similarly, missense variants within the MYST domain of human KAT6A may selectively impair its catalytic activity, while preserving its non-catalytic functions. Additionally, KAT6A and KAT6B physically bind to the N-terminal region of the BRPF1/2/3 scaffolding subunit through their catalytic MYST domain [25]. BRPF1/2/3 acts as the structural core of the complex by binding both KAT6A/KAT6B and the ING4/5 and MEAF6 subunits. Consequently, missense variants located in the MYST domain may disrupt both KAT6A/KAT6B's catalytic acetyltransferase activity and BRPF1-mediated complex assembly. Conversely, missense variants in non-catalytic domains are more likely to disrupt scaffolding functions or specific protein-protein interactions. Missense variants in KAT6A or KAT6B located outside the MYST domain, such as those within the N-terminal NEMM domain, the double PHD fingers, or the C-terminal acidic and serine/methionine-rich regions, can selectively impair chromatin recruitment, histone/DNA binding, transactivation, and TF interactions [27,144]. Preserving partial functional integrity might account for the milder phenotypes observed with certain missense *KAT6A* variants. Clearly, additional studies with a larger sample size are warranted to determine whether there is a statistically significant correlation between the variant type and the resulting phenotype [161,163].

In vitro and *in vivo* modeling of KAT6A and KAT6B syndromes

In order to decipher the molecular and cellular mechanisms underlying KAT6-associated disorders, it is imperative to implement disease models, such as transgenic mice and patient-derived induced pluripotent stem cells (iPSCs). The advantages and limitations of each *in vitro* and *in vivo* model are summarized in Table 1. While the roles of KAT6A/KAT6B in development, and neurodevelopment in particular, could be explored in KAT6A/KAT6B-deficient or -overexpressing animal and cell models [51,52,57,66,97,103,122,133], KAT6A/KAT6B disorders result from pathogenic heterozygous mutations. Hence, these cells presumably express at least 50% WT transcript, and animal and cell models of these disorders should be heterozygous for the pathogenic *KAT6A/KAT6B* variants or present haploinsufficiency. By recapitulating the environment of cells harboring pathogenic *KAT6A/KAT6B* variants, these models could enable the systematic identification of molecular perturbations and dysfunctional regulatory networks and possibly the validation of potential therapeutic targets. In this respect, two recent studies explored the impact of *Kat6a* haploinsufficiency in mice on neurogenesis, cognitive function, and behavior [68,164]. The researchers used mice harboring a deletion of exon 4 or exons 4-8 in one *Kat6a* allele, which resulted in a premature stop codon, mirroring the genotype of *KAT6A* in patients harboring early truncating pathogenic variants [68,164], as well as mice with KAT6A haploinsufficiency restricted to the neocortex and hippocampus ($Kat6a^{NEX\text{-}cKO}$ mice) [164]. In contrast to the embryonic or perinatal lethality and early developmental arrest observed in complete *Kat6a* deficiency models, *Kat6a*-haploinsufficient mice survived to adulthood, although they displayed smaller body size [68,164]. *Kat6a*-haploinsufficient mice displayed impaired cognitive function, a deficit in memory, and reduced anxiety levels. A difference between these two studies was that while one study observed normal social behavior of *Kat6a*-haploinsufficient mice [164], the other study reported a slightly reduced preference for interaction [68].

Similar to the study on KAT6A, the impact of *Kat6b* haploinsufficiency on cognitive function and behavior was also explored in mice [65]. Unlike the homozygous *Kat6b* KO mouse models, which failed to

survive past weaning, *Kat6b*-haploinsufficient mice survived to adulthood [65]. *Kat6b*-haploinsufficient mice exhibited impaired learning and memory as well. These mice also displayed reduced social recognition and interaction, resembling KAT6B syndrome patients [160]. Interestingly, KAT6B overexpression in mice resulted in aggression, anxiety, and seizures [133].

Similar to the majority of KAT6A syndrome patients, who were not reported to have structural anomalies of the brain, *Kat6a*-haploinsufficient mice had normal morphology of the brain, cerebral cortex, cortical layers, and ventricles [68]. Similarly, *Kat6a*$^{NEX\text{-}cKO}$ mice exhibited normal cortical morphology and hippocampal cell density [164].

The study by Liu *et al.* [164] revealed that *Kat6a*-haploinsufficient CA3 hippocampal neurons display decreased spine density and impaired synaptic activity. The impaired synaptic activity and cognitive function of the mice were mainly attributed to a reduction in *Rspo2*, whose expression is directly regulated by KAT6A, and consequently, RSPO2-mediated Wnt signaling was downregulated [164].

Consistent with the observations in fetal hematopoietic stem cells, *Kat6a* haploinsufficiency caused a reduction of H3K23ac in the brain and peripheral white blood cells of mice, as well as in human HEK-293T cells carrying several pathogenic heterozygous *KAT6A* variants [68]. In contrast, *Kat6b* haploinsufficiency induced a reduction of H3K9ac in the cortex of mice at 2 weeks of age (but not at 3 weeks of age) and in peripheral white blood cells of the mice [65]. These findings suggest that although both KAT6A and KAT6B were shown to acetylate histone H3K9 and H3K23 [19], each of them acetylates a preferential H3 lysine residue.

Table 1: Summary of advantages and limitations of *in vitro* and *in vivo* modeling of KAT6A and KAT6B syndromes.

Model Type	Key Features	Advantages	Limitations	Ref. for KAT6 syndromes modeling
HEK293 cell line	-Heterologous mammalian *in vitro* expression system. -Enables transient or stable transfection/CRISPR gene editing to express wild-type or mutant KAT6A/KAT6B constructs. -Standard tool for investigating enzyme biochemistry and protein-protein interactions.	-Easy to culture, expand, and transfect efficiently. -Ideal for rapid biochemical assaying (e.g., measuring H3K9/H3K23 acetylation). -Enables straightforward structural and domain-function mechanistic studies (e.g., testing BRPF1 complex interactions)	-Lacks patient-specific physiological, genomic, and chromatin architecture background. -Does not capture complex neurodevelopmental or tissue-specific pathology. -Overexpression can lead to non-physiological protein stoichiometry.	[64,65,68,88]
Patient-derived cells (e.g., dermal fibroblasts, iPSCs, peripheral blood cells)	-Derived directly from individuals with KAT6A or KAT6B neurodevelopmental syndromes. -Preserves patient-specific heterozygous variants (nonsense, frameshift, or missense) and background genome. -Can be differentiated into target cell types (e.g., neural progenitor cells, cortical neurons).	-Highly clinically relevant human physiological model. -Useful for identifying disease-relevant downstream target genes and epigenetic biomarkers (e.g., histone acetylation status in blood/cells). -Provides a translationally relevant platform for testing therapeutic interventions.	-High patient-to-patient variability and line-to-line heterogeneity. -iPSC reprogramming and neuronal differentiation protocols are labor-intensive and costly. -Cannot replicate systemic whole-organism physiology or behavioral deficits.	[48,64,69,136,190]
In vivo models (e.g., *Kat6a/Kat6b* transgenic mouse lines)	-Whole organism genetic models (e.g., haploinsufficient *Kat6a*$^{+/-}$ or *Kat6b*$^{+/-}$ mice). -Models complex gene-dosage effects (haploinsufficiency vs. full KO), systemic development, and neurocircuitry.	-Captures full systemic phenotypes, including neurodevelopment, craniofacial features, heart, and hematopoiesis defects. -Allows evaluation of motor and cognitive skills, as well as social behaviors. -Essential for testing preclinical systemic efficacy, pharmacokinetics and pharmacodynamics of potential therapeutic compounds.	-Interspecies differences between mouse and human genetic/developmental networks. -Resource-intensive, longer experimental timelines, and high maintenance costs.	[65,68,103,164]

In line with the reduced H3K9ac levels resulting from *Kat6b* haploinsufficiency, *Kat6b*-deficiency in mouse embryonic dorsal telencephalon and adult cerebral cortex, as well as a lymphoblastoid cell line derived from a patient with a *KAT6B* variant, implicated dysregulation of the MAPK signaling pathway [64]. Specifically, expression analyses in the *Kat6b*-deficient mouse model revealed altered expression of genes related to the MAPK pathway. Moreover, the patient-derived cells exhibited hyperactivation of this pathway, specifically characterized by increased phosphorylation of MEK1/2, ERK1/2, and AKT. Clinically, this individual presented a Noonan syndrome-like phenotype. Noonan syndrome (OMIM #163950) shares several features with *KAT6B*-related disorders, including cognitive impairment, developmental delay, facial dysmorphism, cardiac defects, genitourinary anomalies, and skeletal abnormalities [165]. Notably, similar to the findings observed in the KAT6B patient-derived cells, Noonan syndrome is caused by pathogenic variants in the RAS/MAPK pathway genes that increase MEK1/2 and ERK phosphorylation. These results suggest a functional relationship between *KAT6B* deficiency and dysregulated MAPK/AKT signaling.

A recent study utilized KAT6A patient-derived iPSCs differentiated into NPCs and cortical neurons to model the KAT6A disorder [69]. This study revealed a significantly altered transcriptome in *KAT6A*-mutant NPCs and cortical neurons compared to their healthy counterparts. Interestingly, a great number of the dysregulated genes were found to be associated with autism spectrum disorder (ASD). *KAT6A*-mutant cortical neurons exhibited premature elevation of many key neuronal development genes at an early stage of the differentiation. This altered transcriptome apparently led to a precocious maturation, as demonstrated by the hyperexcitability and increased spatial coverage, dendritic arbor complexity, neurite width, and soma size of the *KAT6A*-mutant neurons at an early stage of the differentiation. Notably, these neurons exhibited a markedly lower percentage of GABA (gamma-aminobutyric acid)-positive neurons. *KAT6A*-mutant cortical neurons that were differentiated for a longer time became hypoexcitable compared to control neurons, apparently due to downregulation of key ion channel genes [69]. In line with these observations, *Kat6a*-haploinsufficient mice displayed upregulation of neuronal development and maturation genes, including axon guidance and synapse organization-related genes, in the developing dorsal telencephalon at E12.5, compared to control mice [68]. Strikingly, a similar phenotype of early maturation, hyperexcitability, and a reduced percentage of GABA-positive neurons was previously also found in neurons differentiated from iPSCs obtained from patients with ASD- and ID-related variants [69,166–168]. Collectively, these findings suggest that *KAT6A* downregulation impacts the timely maturation of neurons, leading to an early maturation of cortical neurons.

Evaluation of potential treatments in mouse models of KAT6A and KAT6B syndromes

To date, there is no direct treatment for KAT6A or KAT6B syndromes; patients therefore receive symptomatic and supportive care. These treatments include physical, feeding, speech and language therapies, as well as treatment against sleep disturbances and seizures [144,147,157,158,161,163, 169]. Histone acetylation deficiency could potentially be treated by inhibition of histone deacetylases (HDAC), which are the epigenetic erasers of acetyl groups [170]. In this respect, treatment with HDAC inhibitors (HDACi) like valproic acid (VPA) was found to be neuroprotective in mouse models of brain injury and neurodegenerative diseases [170].

VPA is a well-established HDACi used as an FDA-approved treatment for various types of epilepsy and as a mood stabilizer, especially in the manic phase of bipolar disorder [171,172]. However, a major limitation of broad epigenetic drugs (such as HDACi like VPA) is their lack of organ and locus-specificity. Since they broadly alter global histone acetylation, they carry high risks of systemic toxicity [173]. Indeed, the clinical utility of VPA has been limited by substantial side effects, including neurotoxicity, especially when taken at certain developmental stages of a child's brain, hepatotoxicity and teratogenicity [173]. VPA's neurotoxic effects result from its ability to increase ROS production, cause mitochondrial dysfunction, alter epigenetics, influence signaling pathways and neurotrophic cascades, as well as shift the balance between excitatory/inhibitory neurotransmission. Additionally, HDACi administration causes gastrointestinal disturbances, immune dysregulation, and off-target effects [174]. Thus, VPA is currently serving as a scaffold for drug development of analogs aimed at augmenting treatment efficacy while diminishing untoward toxicity [175]. Notably, a precise balance of histone acetylation and deacetylation is crucial in neurodevelopment [176]. Similar to acetyltransferases, HDACs play essential roles during neurodevelopment, synaptic transmission, plasticity, and cognition [177,178]. Consequently, aberrant expression of HDACs leads to neurodevelopmental

syndromes [179–181]. Mechanistically, treatment with HDACi such as VPA during specific postnatal periods significantly decreases neural stem cell progeny production in the dentate gyrus, rostral migratory stream, and olfactory bulb [182].

Another treatment approach is to increase the levels of Acetyl-CoA, the canonical acetyl donor substrate of acetyltransferases, in order to enhance histone acetylation. Following this rationale, *Kat6b*-haploinsufficient mice were treated with VPA, or with acetyl-carnitine (ALCAR), which is an acetyl donor [65]. Both VPA and ALCAR treatments resulted in increased acetylation levels of H3K9, H3K14 and H3K23 in the adult cortex. Notably, *vitro* treatment with VPA as well as with ALCAR partially restored gene expression in cortical neurons, which were isolated from *Kat6b*-haploinsufficient mice. While both VPA and ALCAR treatment partially reversed sociability deficits, ALCAR treatment further rescued learning and memory deficits in *Kat6b*-haploinsufficient mice. *Kat6b*-deficient mice displayed reduced GABAergic neurons [52], and the improved sociability could possibly be attributed to the reported ability of VPA to increase GABA levels, which is essential for social behavior [65,183]. Notably, while VPA treatment elicited some beneficial effects, it also exerted adverse effects on the motor skills of these mice. Similarly, in addition to cognitive and language delays, developmental motor delays are reported in children who were exposed to VPA during prenatal development [173].

Similar to the treatment of *Kat6b*-haploinsufficient mice, supplementation of ALCAR was found to restore H3K23ac levels in the brain of *Kat6a*-haploinsufficient mice and significantly improved their learning and memory, as well as reduced their hyperactivity [68]. However, in contrast to *Kat6b*-haploinsufficient mice, ALCAR treatment did not improve the sociability of *Kat6a*-haploinsufficient mice. It should be noted that KAT6A syndrome patients exhibit social motivation, and another *Kat6a*-haploinsufficient mouse model did not exhibit impaired sociability, as stated above [160,164].

Importantly, given that ALCAR and VPA exert pleiotropic effects, they could potentially ameliorate the phenotype of *Kat6a*- and *Kat6b*-haploinsufficient mice through compensatory mechanisms, rather than through the mere restoration of normal acetylation levels at specific gene loci [65,68]. Such mechanisms include the elevation of the neurotransmitters GABA, acetylcholine, noradrenaline and serotonin, as well as elevation of a glutamatergic receptor. Elevation of acetylcholine could result in the improvement of learning and memory [68,184].

In summary, the above findings reveal that treatment with an acetyl donor had beneficial outcomes in mouse models of KAT6A and KAT6B syndromes. However, additional studies are warranted to carefully examine and assess this treatment option for KAT6A and KAT6B patients.

While the efficacy and safety of treatment with epigenetic modulators constitute major concerns [174], utilizing *in vitro* and *in vivo* models of KAT6A and KAT6B syndromes aims to uncover specific downstream molecular perturbations. Pinpointing these molecular pathways could reveal novel targets for therapeutic interventions. Moreover, this downstream approach could be beneficial and circumvents the risks of gene overexpression, which has been shown to cause adverse effects with *Kat6b* overexpression [133].

Furthermore, establishing a precise therapeutic window is essential. As stated above, early postnatal treatments yielded favorable therapeutic effects in mouse models of KAT6A and KAT6B syndromes, ameliorating specific phenotypes such as hyperactivity and improving learning and memory [65,68]. Future studies must determine whether these neurobehavioral rescues are restricted to a specific window, during early critical periods of neurodevelopment in early childhood, and whether a specific intervention remains beneficial in adulthood.

Concluding remarks and future directions

KAT6A and KAT6B lysine acetyltransferases are essential for a multitude of key signaling cascades, cellular functions and developmental pathways, as shown in Figures 4 and 5. These include chromatin landscape, proliferation, differentiation, support of mesenchymal, hematopoietic, and neural stem cell maintenance, metabolic pathways such as glycolysis, and orchestration of developmental programs. Abnormal acetylation of histone and non-histone proteins disrupts chromatin dynamics and leads to imbalanced gene expression programs and aberrant regulation of various key cellular processes. Collectively, the role of KAT6A/KAT6B in a wide range of central developmental pathways, including neurogenesis, provides a mechanistic framework for understanding how their aberrant expression leads to neurodevelopmental syndromes. However, the pathogenic molecular mechanisms have only begun to be deciphered by using cellular and animal models of KAT6A and KAT6B syndromes in recent years. Additional studies are warranted to further uncover the aberrantly expressed genes and defects in molecular and cellular pathways that lead to the clinical phenotypes of these syndromes. Elucidating the molecular and cellular pathways impaired by

aberrant expression and function of KAT6A and KAT6B in these disorders is critical for the possible rational development of targeted therapeutic interventions.

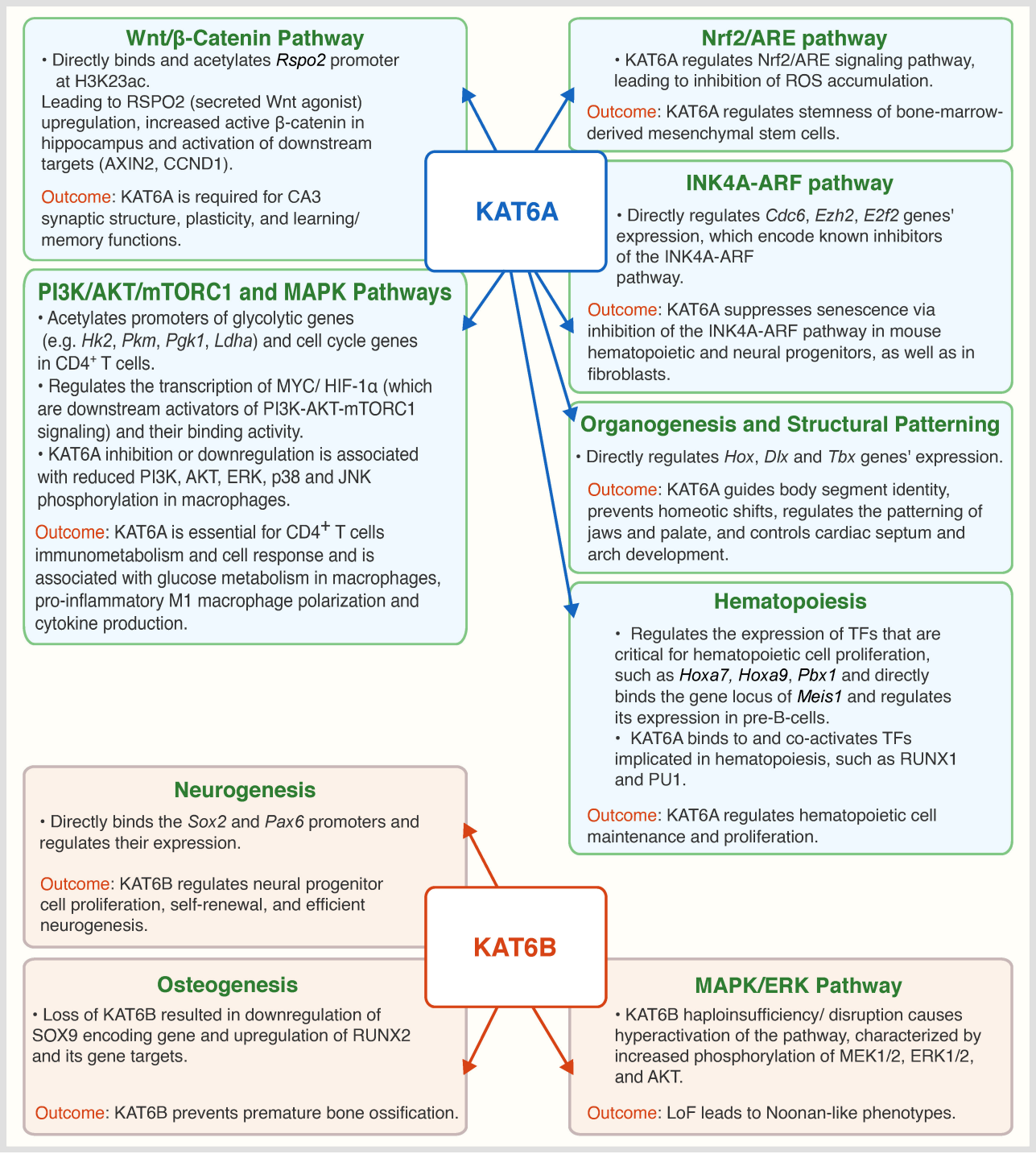


Figure 4. KAT6A and KAT6B orchestrate key physiological molecular pathways. A schematic overview of KAT6A- and KAT6B-dependent regulation across major molecular pathways (signal transduction, metabolic, and gene regulatory/epigenetic pathways), presenting epigenetic targets, downstream signaling cascades, and physiological outcomes. Data for KAT6A were collated from references: [164] (Wnt/β-catenin signaling), [106,110,120] (PI3K-AKT-mTORC1/ glycolysis in CD4+ T cells and macrophages), [71,109] (inflammatory and stress axes), expression of *Hox* [57–60], *Dlx* [61] and *Tbx* genes [62,63], [97,101] (INK4A-ARF pathway), [55,115,116] (hematopoiesis). Data for KAT6B were derived from references: [66] (neurogenesis), [85] (bone ossification), [64] (MAPK/ERK pathway).

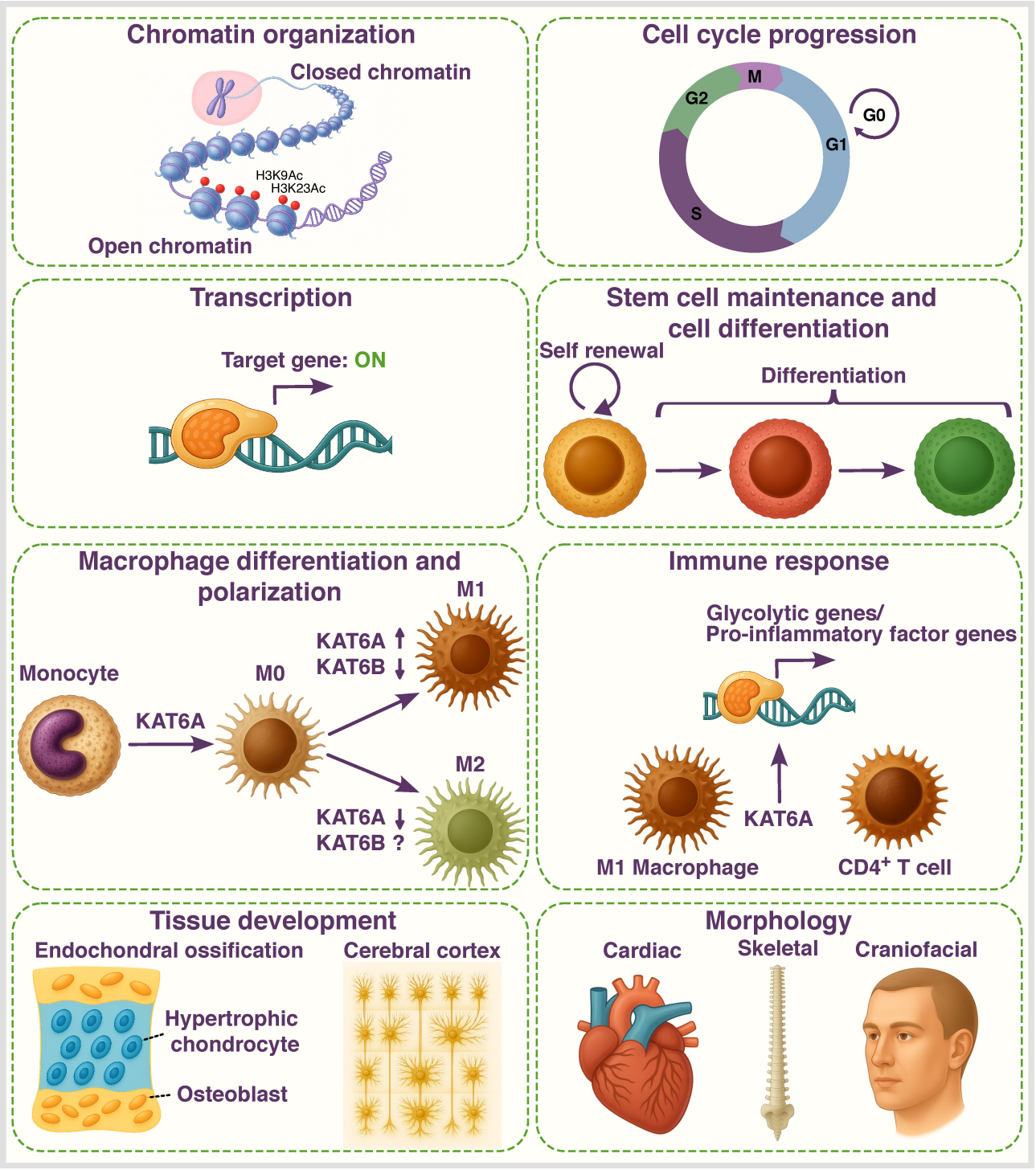


Figure 5. KAT6A and KAT6B acetyltransferases regulate a broad spectrum of essential cellular and developmental processes. At the cellular level, they regulate chromatin organization, transcription regulation, cell cycle progression, stem cell maintenance including mesenchymal, hematopoietic, and neural stem cells, and lineage differentiation. Moreover, KAT6A, in particular, has been linked to modulating immune responses, including macrophage differentiation and polarization, immune cell function and metabolic programming. It plays an important role in the formation and function of memory B- and T cells, and promotes glycolytic gene expression programs in activated $CD4^+$ T cell sub-populations, as well as glycolytic and pro-inflammatory transcriptional programs in M1 macrophages. At the tissue and organ level, KAT6A and KAT6B are key regulators of multiple developmental processes, including hematopoiesis, neurogenesis, skeletogenesis, body segment identity, cerebral cortex formation, as well as craniofacial and cardiac development.

Abbreviations

ALCAR: acetyl-carnitine; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; ARTHS: Arboleda-Tham syndrome; ASD: autism spectrum disorder; BMDMs: bone marrow-derived macrophages; BM-MSCs: bone marrow-derived mesenchymal stem cells; CBP: CREB binding protein; CS: congenital scoliosis; CUT&RUN: cleavage under targets and release using nuclease;

CUT&TAG: cleavage under targets and tagmentation; DD: developmental delay; ES: embryonic stem; GABA: gamma-aminobutyric acid; GTPTS: Genitopatellar syndrome; HDAC: histone deacetylase; HDACi: histone deacetylase inhibitors; HSCs: hematopoietic stem cells; ID: intellectual disability; iPSCs: induced pluripotent stem cells; KATs: lysine acetyltransferases; LoF: loss of function; MDCM: Mendelian disorders of chromatin machinery; MDEM: Mendelian disorders of the epigenetic machinery; MEFs: mouse embryonic fibroblasts; mESC: mouse embryonic stem cells; MLL1: Mixed-Lineage Leukemia protein-1; MRI: Magnetic resonance imaging; NEMM: N-terminal part of Enok, MOZ or MORF; NPCs: neural progenitor cells; NSCs: neural stem cells; NSPCs: neural stem and progenitor cells; PHD: plant homeodomain; ROS: reactive oxygen species; RUNX1: Runt-related transcription factor 1; SBBYSS: Say-Barber-Biesecker-Young-Simpson syndrome; scATAC-seq: single-cell assay for transposase-accessible chromatin with high-throughput sequencing; scRNA-seq: single-cell RNA sequencing; TF: transcription factor; TNF: tumor necrosis factor; VPA: valproic acid; WH: winged helix; WT: wild-type.

Supplementary Material

Supplementary tables.
https://www.ijbs.com/v23p0077s1.xlsx

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Microsoft 365 Copilot was used to generate individual images within the Figures.

Competing Interests

The authors have declared that no competing interest exists.

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