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REVIEW

Epigenetic regulation of *autophagy-related* genes: Implications for neurodevelopmental disorders

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ABSTRACT

Macroautophagy/autophagy is an evolutionarily highly conserved catabolic process that is important for the clearance of cytosolic contents to maintain cellular homeostasis and survival. Recent findings point toward a critical role for autophagy in brain function, not only by preserving neuronal health, but especially by controlling different aspects of neuronal development and functioning. In line with this, mutations in autophagy-related genes are linked to various key characteristics and symptoms of neurodevelopmental disorders (NDDs), including autism, micro-/macrocephaly, and epilepsy. However, the group of NDDs caused by mutations in autophagy-related genes is relatively small. A significant proportion of NDDs are associated with mutations in genes encoding epigenetic regulatory proteins that modulate gene expression, so-called chromatinopathies. Intriguingly, several of the NDD-linked chromatinopathy genes have been shown to regulate autophagy-related genes, albeit in non-neuronal contexts. From these studies it becomes evident that tight transcriptional regulation of autophagy-related genes is crucial to control autophagic activity. This opens the exciting possibility that aberrant autophagic regulation might underly nervous system impairments in NDDs with disturbed epigenetic regulation. We here summarize NDD-related chromatinopathy genes that are known to regulate transcriptional regulation of autophagy-related genes. Thereby, we want to highlight autophagy as a candidate key hub mechanism in NDD-related chromatinopathies.

Abbreviations: ADNP: activity dependent neuroprotector homeobox; ASD: autism spectrum disorder; ATG: AutTophaGy related; CpG: cytosine-guanine dinucleotide; DNMT: DNA methyltransferase; EHMT: euchromatic histone lysine methyltransferase; EP300: E1A binding protein p300; EZH2: enhancer of zeste 2 polycomb repressive complex 2 subunit; H3K4me3: histone 3 lysine 4 trimethylation; H3K9me1/2/3: histone 3 lysine 9 mono-, di-, or trimethylation; H3K27me2/3: histone 3 lysine 27 di-, or trimethylation; hiPSCs: human induced pluripotent stem cells; HSP: hereditary spastic paraplegia; ID: intellectual disability; KANSL1: KAT8 regulatory NSL complex subunit 1; KAT8: lysine acetyltransferase 8; KDM1A/LSD1: lysine demethylase 1A; MAP1LC3B: microtubule associated protein 1 light chain 3 beta; MTOR: mechanistic target of rapamycin kinase; MTORC1: mechanistic target of rapamycin complex 1; NDD: neurodevelopmental disorder; PHF8: PHD finger protein 8; PHF8-XLID: PHF8-X linked intellectual disability syndrome; PTM: post-translational modification; SESN2: sestrin 2; YY1: YY1 transcription factor; YY1AP1: YY1 associated protein 1

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Introduction

The term autophagy (Greek for "self-eating") encompasses a fundamental lysosome-mediated degradation pathway that is active at basal levels in all cells to maintain cellular homeostasis [1]. Neurons appear to be particularly dependent on autophagy because of multiple reasons. First, their complex and polarized neuronal architecture requires specialized intracellular vesicle trafficking for efficient cargo recycling [2,3]. Second, their postmitotic nature makes them highly sensitive to the accumulation of toxic proteins and damaged organelles. Accordingly, autophagy is constitutively active in healthy neurons, while decreased autophagy, with subsequent accumulation of toxic proteins and damaged organelles, rapidly reduces cell viability and affects neuronal function [4–7]. Neuron-specific knockout of the *Atg5* (autophagy related 5) or *Atg7* genes, which are involved in the autophagy core machinery, in mice cause abnormal protein aggregation and eventual neurodegeneration leading to motor dysfunction, corroborating that autophagy is essential for neuronal homeostasis [4,8,9]. Similarly to these observations, interference with several core *ATG* genes causes reduced survival and early-onset progressive neurodegeneration [10–12]. Defective autophagy is therefore strongly linked to neurodegeneration, and a hallmark of different neurodegenerative disorders [13–16].

Autophagy is known to be cytoprotective, but prolonged autophagy eventually leads to cell death [17], which reveals the importance of balanced control of autophagic activation and inhibition for cell survival. In the past, numerous studies have been conducted to understand what distinguishes the life-or-death decision in various cells [17–20]. It has become evident that distinct transcription factors and epigenetic

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networks rapidly and tightly regulate transcription of the 30 core *ATG*s in response to autophagic stimuli, but also determine the long-term outcome of autophagy with respect to cell death versus survival [21–23]. Thereby epigenetic and transcriptional regulation of *ATG* and autophagy-related genes becomes an inevitable part of the autophagic pathway (Figure 1). Specific chromatin-modifying enzymes catalyze epigenetic modifications, including DNA methylation of cytosine residues and post-translational modifications (PTM) of histone tails. These modifications affect chromatin state and thereby gene accessibility for transcription factors to either activate or repress transcription of autophagy-related genes. To give an example in the perspective of autophagy, EHMT2/G9a (euchromatic histone lysine methyltransferase 2) is associated with promotor sites of core *ATG* genes like *MAP1LC3B* (microtubule associated protein 1 light chain 3 beta) [24]. To prevent excess cytoplasmic degradation, EHMT2 dimethylates H3K9 in order to inhibit autophagy-related gene transcription. Therefore, EHMT2 serves as a negative feedback regulator to control autophagy-related gene transcription. Several reviews summarize how different PTMs facilitate the regulation of autophagy-related gene transcription and thereby autophagic activity [21,25–27].

Besides its role in maintaining cellular homeostasis in neurons, autophagy is also an important mechanism during neurodevelopmental processes [28] (Figure 1). The link between mutations in autophagy-related genes resulting in deregulated autophagic activity and causing a neurodevelopmental phenotype is well established. A small group of NDDs (around 20 disorders), characterized by, among others, structural brain abnormalities, intellectual disability (ID), and developmental delay, is known to be caused by mutations in autophagy-related genes [28–30]. Although many chromatinopathy genes have been identified, it is unclear which downstream pathways are affected and whether there is any convergence. Many studies speculate that NDD-linked chromatinopathy genes would specifically affect transcriptional regulation of genes involved in synaptogenesis [31–34]. Here, we examined several NDD-related chromatinopathy genes that have previously been found to modulate autophagy-related protein expression, mostly in a non-neuronal context. The list encompasses 20 genes whose corresponding protein products have a catalytic function in introducing histone PTMs (writers), removing histone modifications (erasers) or have chromatin remodeling activity (remodelers). We will review their function in regulating autophagy-related gene expression and, where possible, provide supporting evidence for their role in autophagic

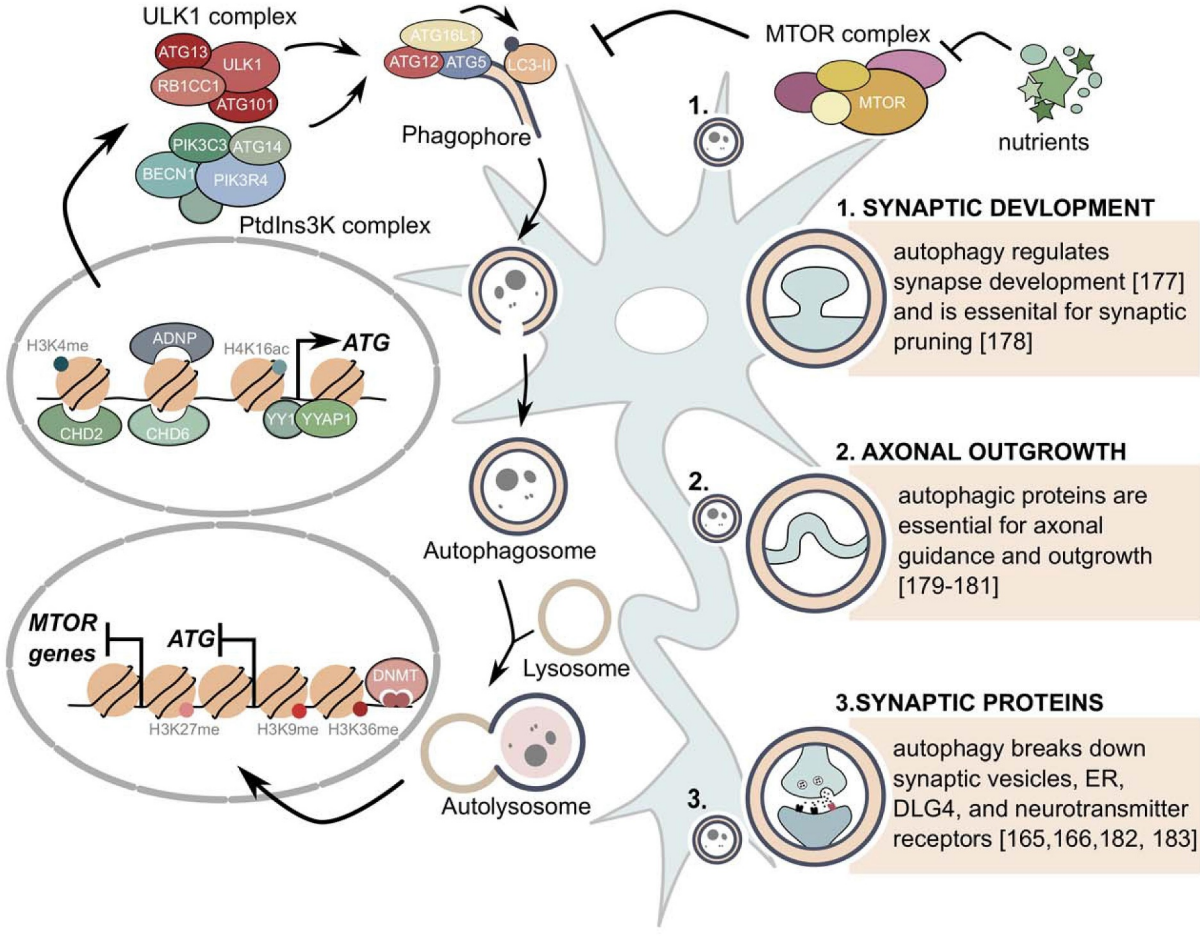

Figure 1. Different levels of autophagy regulation and its' effect on neuronal development and function.

regulation that potentially underlies the associated neurodevelopmental phenotypes.

Histone modifications regulate autophagy-related gene expression

Epigenetic modifiers alter gene accessibility and thereby regulate gene expression in different ways. One way is through PTMs including phosphorylation, methylation, acetylation, and ubiquitination by a variety of histone modifying enzymes. Histone PTMs are most common on the histone N-terminal tails where they affect the local chromatin structure and thereby modulate the accessibility of DNA for transcription factors which contributes to transcriptional regulation and elongation. Mutations in various genes encoding for histone modifying enzymes are associated with neurodevelopmental phenotypes (reviewed in [35,36]). Below we review all the histone modifiers that have been shown to regulate autophagy-related gene expression (Figure 2).

Histone modifiers associated with repressed autophagy-related gene expression

Mutations in the *EZH2* gene lead to various NDDs, including autism spectrum disorder (ASD) and Weaver syndrome [37]. Patients diagnosed with Weaver syndrome are characterized with tall stature, mild to severe ID, and a characteristic facial appearance [38] (Table 1). In addition, a few individuals with pathogenic variants in *EZH2* show brain MRI abnormalities [39]. The respective protein, EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), is a critical regulator of numerous developmental genes [40]. It mediates the trimethylation of H3K27, a repressive histone mark which is also known to inhibit autophagy-related gene transcription [41,42]. EZH2 controls the induction of autophagy through transcriptional repression of MTOR (mechanistic target of rapamycin kinase) -related genes, such as *TSC2, RHOA, DEPTOR, FKBP11, RGS16*, and *GPI* in different human cancer cell lines [42] (Figure 2). Interestingly, RNA interference of EZH2 leads to overexpression of TSC2. Given that TSC2 inhibits MTOR at the lysosomes in response to nutrient shortage [43], one can hypothesize that increased TSC2 leads to overactivation of autophagy potentially affecting neuronal development in EZH2-deficient cells.

Methylation of H3K9 is another repressive histone mark associated with silenced autophagy-related gene expression [44–46]. As an illustration, the HMT EHMT2 is essential to epigenetically repress autophagy related genes, such as *MAP1LC3*, *WIPI1*, and *TP53INP2*, through dimethylation of H3K9 under normal conditions in naive T cells [45] (Figure 2). During nutrient starvation, G9a-repressive histone marks are removed at the *ATG* promoter sites leading to induction of autophagy (Figure 2) [45]. Interestingly, EHMT2 functions in a heteromeric complex with EHMT1 [47], and pathogenic variants in *EHMT1* cause Kleefstra syndrome [48,49]. Characteristic features of Kleefstra syndrome include developmental delay with ID, severely limited or absent speech, and weak muscle tone (hypotonia) (Table 1). Experimental data demonstrating that EHMT1 mediates histone 3 lysine 9 dimethylation (H3K9me2) at *ATG* promoter sites and thereby represses *ATG* expression is missing. However, on protein level it was shown recently that siRNA mediated knockdown of EHMT1 in RPE1 and HeLa cells causes increased size and abundance of LAMP1-positive vesicles, pointing toward altered lysosomal function in EHMT1-deficient cells [50]. Its' association with EHMT2 suggests that in Kleefstra syndrome patients heterozygous loss of EHMT1 would result in reduced levels of EHMT1-EHMT2 complex. This in turn would cause decreased H3K9me2 levels, and hence increased expression of lysosomal genes, and potentially also *ATG* expression.

Histone modifiers associated with increased autophagy-related gene expression and activity

Loss-of-function variants in *SETD2*, are associated with Luscan-Lumish syndrome, in which the patients are characterized by macrocephaly, ID, speech delay, and behavioral problems [51] (Table 1). *SETD2* encodes for a histone methyltransferase (HMT) that trimethylates H3K36 [52] and thereby promotes transcriptional elongation as well as RNA splicing [53] (Figure 2). In the latter, loss of SETD2 leads to alternative splicing of *ATG12* [54], which is required for autophagosome formation and expansion through the ATG12–ATG5-dependent conjugation system [55]. Mechanistically, the resulting short isoform of *ATG12* leads to an increased expression of free ATG12 and accumulation of aberrant ATG12-containing complexes, in addition to the conventional ATG12–ATG5 covalent complex [54]. SETD2 deficiency is therefore associated with a defect in autophagy initiation, thereby leading to reduced autophagic degradation activity. The effect of *SETD2* haploinsufficiency on autophagy was solely examined in context of clear renal cell carcinoma [54,56], meaning that potential autophagic defects in a neuronal model for Luscan-Lumish syndrome patients remain to be explored.

Haploinsufficiency of *PHF8 (PHD finger protein 8)* causes Siderius X-linked ID syndrome (hereafter called PHF8-XLID) [57]. Characteristics of PHF8-XLID include developmental delay, ID, learning difficulties and craniofacial dysmorphology (Table 1). *PHF8* encodes for a histone lysine demethylase, which specifically removes the methyl groups of multiple methylated histone marks [44,58,59]. PHF8 acts as a positive regulator for autophagy through its binding to promoter regions of *RB1CC1/FIP200* [60] (Figure 2). RB1CC1 is a binding partner of ULK1, which, as a complex, localizes to phagophores in order to initiate autophagosome formation under nutrient deprivation [61]. Knockdown of *PHF8* has been shown to suppress autophagy through reduced expression of RB1CC1 in hepatocellular carcinoma cells [60]. Interestingly, exogeneous expression of RB1CC1 in these PHF8 depleted cells leads to increased numbers of autophagosomes and autolysosomes, meaning that overexpression of RB1CC1 is capable to reverse the autophagy inhibiting effect of PHF8 deficiency. Up to now, studies investigating whether PHF8-XLID causing mutations in *PHF8* affect autophagosome biogenesis in a neural model are still missing.

Other histone lysine demethylases that are associated with NDDs and have shown to play a role in autophagy are KDM6B and KDM6A. Patients with pathogenic variants in either *KDM6B* or *KDM6A* suffer from developmental delay with

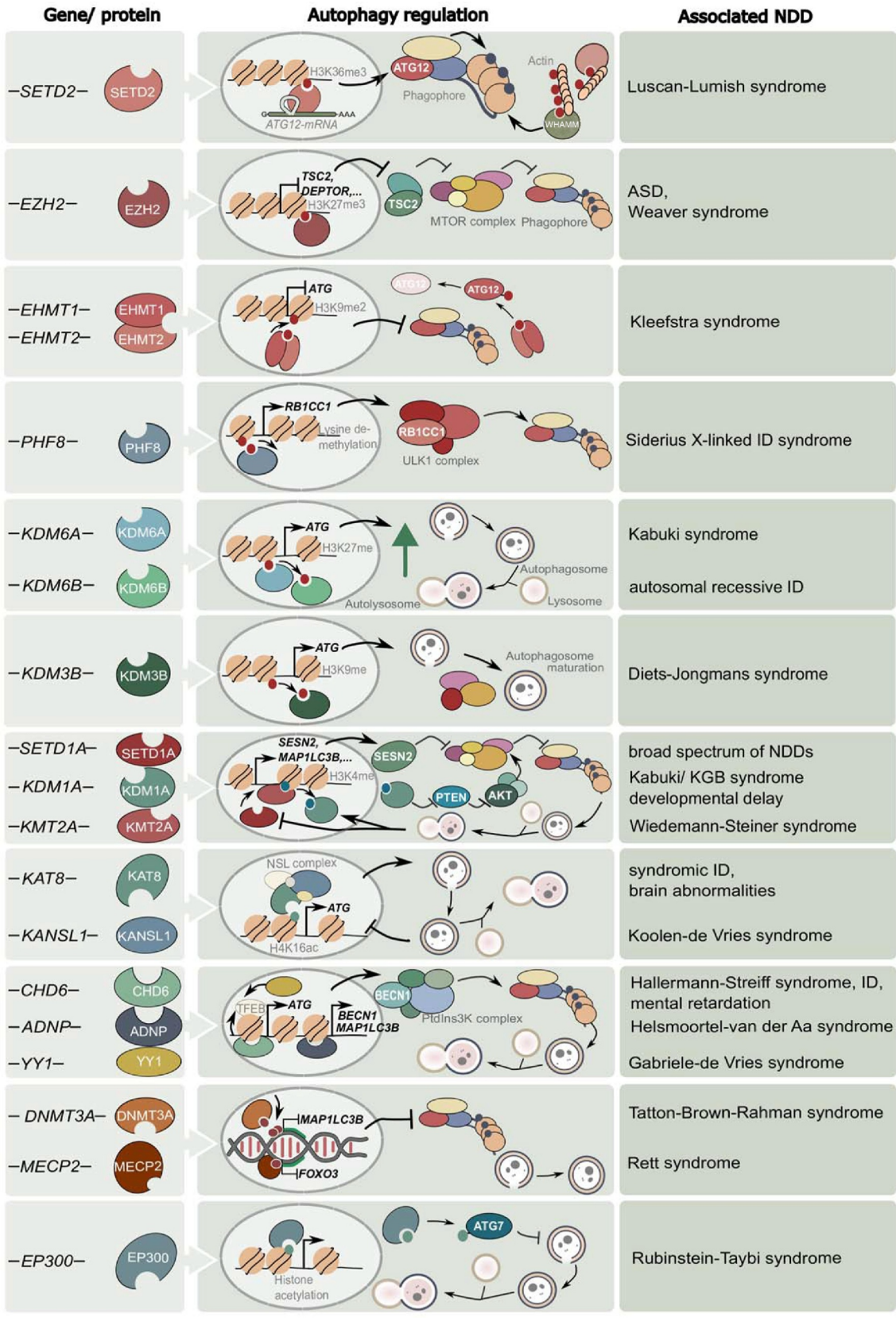

Figure 2. Overview of how the different epigenetic modifiers regulate autophagy and the associated NDDs.

Table 1. Chromatinopathy causing genes associated with altered autophagy regulation and the respective clinical phenotypes.

Gene	Autophagy switch	Associated disorder	Clinical phenotype *(overlap with common symptoms of congenital disorders of autophagy)
Histone modifiers			
EZH2	OFF	ASD Weaver syndrome (OMIM # 277590)	Tall stature, mild to moderate ID*, developmental delay*, macrocephaly, characteristic facial appearance*, mild to severe scoliosis, hypo-/hypertonia*, poor coordination
SETD2	ON	Luscan-Lumish syndrome (OMIM # 616831)	Macrocephaly, speech delay, ID*, ASD*, distinctive facial appearance, postnatal overgrowth, epileptic seizures*
KAT8	ON	Syndromic ID Li-Ghorbani-Weisz-Hubshman syndrome (OMIM # 618974)	Global developmental delay*, mild to moderately ID*, language delay, mild dysmorphic features*, epilepsy*, and structural brain abnormalities* (e.g. enlarged ventricles, thin corpus callosum, and gray matter nodular heterotopia)
KANSL1	ON	Koolen-de Vries syndrome (OMIM # 610443)	Hypotonia*, developmental (speech) delay*, mild to moderate ID*, epileptic seizures*, dysmorphic facial features, structural brain abnormalities* (e.g. corpus callosum hypoplasia/aplasia, enlarged ventricles, hydrocephalus, and/or heterotopias), congenital heart, renal, urologic anomalies, musculoskeletal problems (e.g. scoliosis, short stature), a friendly/amiable disposition
KDM6A	ON	Kabuki syndrome 2 (OMIM # 300867)	Mild to moderate ID*, hypotonia*, congenital heart anomalies, short stature, skeletal anomalies, characteristic facial features*
KDM6B	ON	NDD with coarse facies and mild distal skeletal abnormalities (OMIM # 618505)	Developmental delay*, poor speech acquisition, hypotonia, variable behavioral abnormalities* (e.g. ASD, hyperactivity, ADHD), coarse facial features*
PHF8	ON	PHF8-XLID (OMIM # 300263)	Developmental delay*, mild to borderline ID*, learning difficulties, craniofacial dysmorphology* (cleft lip/palate)
SETD1A	ON(?)	NDD with speech impairment and dysmorphic facies (OMIM # 619056)	Schizophrenia, global developmental delay*, and/or ID*, speech impairment, behavioral and psychiatric problems, subtle facial dysmorphisms*
KMT2A	ON(?)	Wiedemann-Steiner syndrome (OMIM # 605130)	Developmental delay*, mild to moderate ID*, hypotonia*, behavioral problems (ASD*, anxiety features), short stature, facial dysmorphism*, growth hormone and immune deficiency, hypertrichosis
KDM3B	ON	Diets-Jongmans syndrome (OMIM # 618846)	Mild to moderate ID*, distinctive facial dysmorphisms*, behavioral problems (e.g. ADHD, ASD*) short stature, epilepsy*, hearing loss, childhood hypotonia*
EHMT1	OFF	Kleefstra syndrome (OMIM # 610253)	ID*, childhood hypotonia*, severe expressive speech delay, ASD*, characteristic facial features, congenital heart malformations, renal defects, epilepsy*, recurrent infections, behavioral problems (abrupt behavioral changes around adolescence, e.g., regression, bipolar mood disorder, autistic features)
KDM1A	OFF	Cleft palate, psychomotor retardation, and distinctive facial features (OMIM # 616728)	ID*, developmental and speech delay*, cleft palate*, hypotonia*, various structural brain abnormalities*
DNA methyltransferases			
DNMT3A	OFF	Tatton-Brown-Rahman syndrome (OMIM # 615879) Heyn-Sproul-Jackson syndrome (OMIM # 618724)	Mild to moderate ID*, overgrowth, macrocephaly*, distinctive facial appearance*, hypotonia, seizures*, scoliosis, hypotonia*, increased susceptibility to the development of acute myeloid leukemia Microcephaly*, short stature, impaired intellectual development*
MECP2	OFF	Rett syndrome (OMIM # 312750)	Developmental stagnation at 6–18 months of age followed by regression of acquired skills, loss of speech, jerky truncal ataxia*, autism, 'acquired' microcephaly*, seizures*, and mental retardation
Chromatin remodelers			
CHD6	ON	Hallermann-Streiff syndrome (OMIM # 234100)	Short stature, hypotrichosis, characteristic facial features*, mental retardation*
CHD2	ON(?)	Developmental and epileptic encephalopathy (OMIM # 615369)	Epilepsy*, developmental delay*, cognitive regression, ID*, ASD*
Transcription factors			
ADNP	ON	Helsmoortel-Van Der Aa syndrome (OMIM # 615873)	Developmental delay*, behavioral problems (e.g. ASD, ADHD, obsessive compulsive behavior)*, facial dysmorphisms*, ID*, hypotonia*, congenital heart defects, short stature, dysmorphic features, seizures*, recurrent infections
YY1	ON	Gabriele-de Vries syndrome (OMIM #617557)	Delayed psychomotor development, ID*, speech delay, behavioral problems*, abnormal movement, dysmorphic facial features*, brain abnormalities* (e.g. enlarged ventricles, white matter abnormalities).
YY1AP1	ON	Grange syndrome (OMIM #602531)	Early-onset vascular disease, learning disabilities*
Cytoplasmic protein modifiers			
EP300	OFF	Rubinstein-Taybi syndrome 2 (OMIM #613684)	Mental retardation*, postnatal growth deficiency, microcephaly*, dysmorphic facial features*
EHMT1	ON	See above	See above
SETD2	OFF	See above	See above

autosomal recessive ID or Kabuki syndrome, respectively [62–64] (Table 1). These epigenetic modifiers specifically demethylate the repressive marks on histone 3 lysine 27 di-, or trimethylation (H3K27me2/H3K27me3) and thereby activate gene transcription [65,66]. In hepatocytes it has been shown that activation of KDM6B upregulates several core *ATG*s and autophagy-related genes, including *Tfeb*, *Atg7*, *AtgI*, and *Fgf21* resulting in increased autophagy-mediated degradation [67] (Figure 2). Mechanistically, KDM6B is phosphorylated when cells are nutrient deprived, which increases its nuclear localization. There it binds to the nuclear receptor PPARα to activate transcription [67]. Likewise, demethylation of H3K27me3 by

the Drosophila KDM6A ortholog Utx is required for transcription of several *Atg*s, such as *Atg3, Atg5* and *Atg9* during ecdysone-mediated programmed cell death [68] (Figure 2). Consequently, *KDM6B* and *KDM6A* play important roles in maintaining the correct temporal regulation of *ATG*s and autophagy-related gene transcription in response to nutritional needs. Reduced activity of *KDM6B* and *KDM6A* could lead to imbalanced energy homeostasis in patients with *KDM6B* or *KDM6A* haploinsufficiency, which might, at least partially, underly the neuronal phenotype observed in the patient group.

Loss-of-function variants in *KDM3B* are associated with Diets-Jongmans syndrome, which is a NDD characterized by ID and distinctive facial dysmorphisms [69] (Table 1). KDM3B is a Jumonji C domain-containing protein that catalyzes the demethylation of H3K9me1 and H3K9me2 resulting in transcriptional gene activation [70]. Depletion of KDM3B impairs the maturation stage of autophagy in a human colon cancer cell line (Figure 2) [71]. However, direct correlation of haploinsufficiency of *KDM3B* affecting neuronal autophagy still needs to be investigated.

Histone modifiers involved in negative feedback-loops to prevent prolonged autophagy

Histone 3 lysine 4 trimethylation (H3K4me3) is generally associated with transcriptionally active promoter sites. Induction of autophagy has been related to a reduction in H3K4me3 [23] and hence represses gene transcription. In this way, demethylation of H3K4 functions as a regulatory feedback loop to prevent overactivation of autophagy by repressing autophagy-related gene transcription. Three NDD-related histone methyltransferases are known to be involved in the trimethylation of H3K4. The first HMT is SETD1A, for which heterozygous variants are associated with a broad spectrum of NDDs, including schizophrenia, global developmental delay, and/or ID, as well as behavioral and psychiatric problems [72] (Table 1). Although the role of SETD1A in autophagy is unknown, KDM1A/LSD1A (lysine demethylase 1A), a major counteracting demethylase for SETD1A, is known to regulate the initiation of autophagy also through H3K4 demethylation [73]. Pathogenic variants in *KDM1A* are associated with ID [74] (Table 1), and, in combination with a *ANKRD11* mutation, with mixed features of Kabuki and KGB syndrome [75]. Mechanistically, KDM1A binds to *SESN2* (sestrin2) promoter sites and represses its' transcription. SESN2 inhibits MTOR complex 1 (MTORC1) activity through the GATOR complex, thereby suppresses the RRAG-dependent recruitment of MTORC1 to the lysosomal membrane [73,76,77]. Inhibition of KDM1A leads to active gene transcription of *SESN2*, which increases autophagy activation through decreased MTOR activity [77] (Figure 2). The effect of haploinsufficiency of *KDM1A* on autophagy in a neuronal context remains to be explored. The interplay between SETD1A and KDM1A could then emerge as a critical regulator of autophagy outcome. One may speculate that haploinsufficiency of *KDM1A* hampers MTOR activity leading to enhanced autophagy, while haploinsufficiency of *SETD1A* could lead to repressed autophagy activation. Lastly, the HMT KMT2A, for which pathogenic variants are associated with Wiedemann-Steiner Syndrome [78], also mediates H3K4me3 (Figure 2). Wiedemann-Steiner Syndrome patients are characterized with a subtype of ASD, and behavioral problems [78] (Table 1). However, nothing is known about the role of KMT2A in autophagy regulation. Haploinsufficiency of *KMT2A* could globally reduce H3K4me3 levels, which consequently would impair the negative feedback loop regulating autophagy-related gene expression.

Pathogenic variants in the encoding genes for KAT8 (lysine acetyltransferase 8) or KANSL1 (KAT8 regulatory NSL complex subunit 1) have been shown to cause syndromic ID and Koolen-de Vries syndrome, respectively [79–82] (Table 1). Patients with Koolen-de Vries syndrome show a strong cognitive phenotype including developmental delay, mild to moderate ID, and epileptic seizures [82]. KAT8 functions within the nonspecific lethal (NSL) complex in which KANSL1 is known to be an important scaffold protein. The complex localizes to gene promoters and enhancers in order to acetylate various histone H4 residues, among which H4K16 [83,84]. This histone mark plays a crucial role in a negative feedback loop for autophagy [23] (Figure 2). More precisely, autophagy induction causes downregulation of KAT8 leading to reduced H4K16ac [23]. We recently identified the formation of autophagosomes as a trigger for activating the negative feedback-loop, and hence, the reduction in H4K16ac [85]. Thereby, autophagy-related gene transcription is repressed and prolonged autophagic activity is prevented [23]. However, in Koolen-de Vries syndrome patient-derived neurons prolonged oxidative stress-mediated autophagy does not lead to H4K16ac reduction. Autophagy-related gene expression is not repressed in these cells, which results in the continuous formation of autophagosomes. This is accompanied with reduced synapse formation and aberrant neuronal network activity [85]. By reducing oxidative stress, autophagosome accumulation could be prevented and, at the same time, neuronal phenotypes, such as reduced synapse formation and network activity, could be rescued [85]. These findings demonstrate the importance of H4K16ac-mediated changes in chromatin structure for balanced autophagy regulation and its' essential role in synapse development and function.

ATP-dependent chromatin remodelers and transcription factors controlling autophagy-related gene expression

Another class of epigenetic modifiers are chromatin remodeling enzymes that utilize energy derived from ATP hydrolysis to catalyze nucleosome mobilization to regulate DNA accessibility [86]. Chromodomain helicase DNA (CHD) binding proteins form one subgroup of this chromatin remodeler class. Members of the CHD family belong to the SNF2 superfamily of ATP-dependent chromatin remodelers. They contain two N-terminal chromodomains (chromatin organization modifier) that allow surface interaction for a variety of chromatin components to alter histone-DNA contacts within the nucleosome. In addition, the CHD family is divided into three subfamilies according to the presence or absence of additional domains. The first subfamily (CHD1-CHD2) contains

a DNA-binding domain located in the C-terminal region, which preferentially binds to AT-rich DNA motifs [87–89]. The second subfamily (CHD3-CHD4) specifically harbors a N-terminal PHD Zn-finger-like domain that mostly binds to methylated histones [90–93]. The third subfamily (CHD5-CHD9) is defined by additional motifs in the C-terminal, such as a SANT-like (switching-defective protein 3, adaptor 2, nuclear receptor co-repressor, transcription factor IIIB) domain [94]. This domain couples histone binding to enzyme catalysis [95].

Haploinsufficiency of CHD encoding genes are implicated in several human pathologies [36]. For instance, pathogenic variants in *CHD6* were identified in patients with ID [96], mental retardation [97,98], and Hallermann-Streiff syndrome (HSS) [99] (Table 1). The latter study not only identifies a *de novo* missense variant in *CHD6* in a patient with HSS, but also reveals an important role for CHD6 as a major housekeeping regulator of autophagy-related genes [99]. CHD6-bound sites are enriched for TFEB and TFEB3 recognition sequences, which are known as a major autophagy and lysosomal gene regulator [100] (Figure 2). Functionally, starvation-induced autophagy in CHD6-deficient human induced pluripotent stem cells (hiPSCs) did not lead to an increase of autophagosomes and lysosomes compared to healthy hiPSCs. The data indicates a reduced capacity to activate autophagy in response to starvation [100]. There are several other CHDs that are linked to NDD phenotypes, including CHD1, CHD2, CHD3, CHD4, CHD7, and CHD8 [36]. Interestingly, CHD6 promotor binding sites overlap with some CHD2-bound positions. Further studies will be needed to elucidate whether CHD2, as well as the other named CHDs play synergistic roles in regulating autophagy-related genes in response to cell stress or nutrient starvation, and whether reduced autophagic activation underlies neurodevelopmental phenotypes observed in patients with CHD haploinsufficiency.

De novo mutations in *ADNP* result in Helsmoortel-Van Der Aa syndrome in which the patients are characterized by a syndromic form of ASD as well as cognitive and motor deficits [101,102] (Table 1). ADNP (activity dependent neuroprotector homeobox) is a master regulator that controls more than 400 genes during embryonic development [103,104]. The role of ADNP in autophagy has been examined in a NDD-related brain model of *adnp* haploinsufficient mice [105]. The pathophysiology of ADNP-related NDD reflects a reduction of BECLIN1 expression, an ATG protein involved in formation of autophagosomes by membrane recruitment, and a simultaneous increase in ADNP binding with MAP1LC3 that may reflect a compensatory mechanism to attempt reduced BECLIN1 expression (Figure 2) [105].

Individuals with *de novo* mutations or deletions of *YY1* are associated with Gabriele-de Vries syndrome, which is characterized by cognitive impairments including ID and behavioral alterations [106] (Table 1). The zinc-finger transcription factor YY1 has the unique property of multiple functions. It can act as a transcriptional repressor or as an activator, depending on its spatial and temporal context [107–109]. With regard to autophagy, YY1 directly interacts with TFEB and thereby modulates the transcription of various *ATG*s and autophagy-related genes (e.g., *MAP1LC3*, *BECN1*, and *UVRAG)* and lysosomal related genes (e.g., *LAMP1* and *ATP6V1H*) in melanoma cells [110] (Figure 2). In addition, *YY1AP1 (*YY1 associated protein 1) enhances the transcriptional activation through YY1 responsive promotors [111]. However, it remains unclear whether YY1AP1 binds to TFEB to support YY1-induced transcriptional activation of autophagy- and lysosomal related genes. Compound heterozygous nonsense variants in *YY1AP1*, and homozygous nonsense or frameshift variants have been linked to Grange syndrome, which is characterized by early-onset vascular disease and learning disabilities [112]. Further studies are required to explore the role of YY1 and YY1AP1 in the regulation of autophagy in a brain-related context.

DNA methyltransferases and their role in autophagy-related gene repression

Another level of autophagy-related gene transcription regulation is presented by DNA methylation. A methyl group is covalently added at the 5-carbon of the cytosine ring resulting in 5-methylcytosine [113]. This occurs almost exclusively at cytosine-guanine dinucleotide (CpG) sites and is catalyzed by so-called DNA methyl transferases (DNMTs) [113]. Methylation of CpG islands near promoter sites recruits gene repressor proteins and proteins that prevent transcription factor binding to repress transcription of the respective gene [114]. While histone PTMs are considered to primarily promote reversible repression of specific genes, DNA methylation contributes to long-lasting effects [115].

De novo variants in *DNMT3A* are associated with Tatton-Brown-Rahman syndrome, or also known as DNMT3A-overgrowth syndrome [116,117]. Tatton-Brown-Rahman syndrome patients are characterized with ID, overgrowth, and there are some cases in which patients show specific facial appearance with low-set, heavy, horizontal eyebrows and prominent upper central incisors [117] (Table 1). In the context of autophagy-related gene transcription regulation, DNMT3A establishes an epigenetic memory on *MAP1LC3* gene expression by which MAP1LC3 is persistently downregulated in previously autophagy-exposed cells (tested in different cell lines, including HeLa or U1810 cancer cells and mouse embryonic fibroblasts) [118] (Figure 2). This epigenetic memory is important as autophagy can be stimulated upon different forms of cellular stress, ranging from nutrient starvation to exposure to drugs. Accordingly, DNA methylation initiates a heritable epigenetic mechanism associated with reduced basal-autophagy that otherwise leads to excessive autophagy resulting to loss of cell viability. Assuming that DNMT3A is important to establish a heritable epigenetic mark to suppress basal autophagy, the question remains whether *DNMT3A*-deficient cells exhibit excessive basal autophagy due to impairments of DNA methylation on autophagy-core associated genes.

Pathogenic variants in the *MECP2* (methyl-CpG binding protein 2) gene are the major cause of Rett syndrome [119], a neurodevelopmental disorder characterized by a wide range of neurologic and behavioral features [120] (Table 1). MECP2 binds to methylated DNA and histones, thereby can exert both repressive and active gene transcription [121,122]. In

context of autophagy-related gene regulation, MECP2 is enriched on the *FOXO3/FOXO3a* promoter site, leading to methylation of the *FOXO3* promotor in endothelial progenitor cells [123] (Figure 2). FOXO3 is a transcription factor that regulates induction of autophagy [124]. Therefore, binding of MECP2 results in the inhibition of *FOXO3* transcription and consequently reduced autophagic activity [123]. Hence, MECP2 is a crucial protein that fine-tunes autophagy-related gene expression. MECP2 is highly expressed in the brain. Furthermore, it was shown previously that it accelerates FOXO3 methylation in neuronal cells [125], however, the exact consequences of MECP2 deficiency for autophagy regulation in a neural model still needs to be elucidated.

NDD-linked epigenetic modifiers in cytoplasmic autophagy regulation

Several histone modifying complexes also have non-histone targets in the cytosol, which presents an additional level of autophagy regulation by these complexes. As an illustration, SETD2, for which haploinsufficiency is linked to Luscan-Lumish syndrome, not only regulates alternative splicing of ATG12 in the nucleus, but also methylates cytoskeletal proteins essential for autophagy initiation [126]. More specifically, it trimethylates actin lysine at position 68 that interacts with the Arp 2/3 nucleation promoting factor WHAMM, which is essential for actin polymerization during initiation of autophagy [56,126]. Loss of SETD2 leads to decreased interaction between WHAMM and its target actin, resulting in impaired initiation of autophagy in hypertriploid renal cell carcinoma cell lines [126].

Novel variants in *EP300* are associated with Rubinstein-Taybi syndrome [127,128]. These patients are characterized by ID, short stature and skeletal abnormalities [127,128] (Table 1). *EP300* encodes for the histone acetyltransferase E1A binding protein p300, which has been demonstrated to negatively control autophagy [129]. Under basal-autophagy, EP300 colocalizes with ATG7 within the cytoplasm resulting in acetylation of ATG7 that, in turn, represses autophagy [129] (Figure 2). Induction of autophagy leads to the deacetylation of ATG7 through the NAD^+-dependent deacetylase sirtuin 1 [130]. These observations are extended by the use of a specific sirtuin 1 inducer, resveratrol, and an EP300 acetyltransferase inhibitor, spermidine, that synergize the induction of autophagy [131]. This synergistic effect is also associated with deacetylation of autophagy core components such as ATG5 and MAP1LC3 [132]. Loss of EP300 in Rubinstein-Taybi syndrome-associated patients would result in excessive neuronal autophagic degradation. However, further investigations will be necessary to elucidate how autophagy is regulated in *EP300*-deficient neurons.

As already mentioned previously, pathogenic variants in *EHMT1* cause Kleefstra syndrome [48,49]. While experimental evidence for a role in transcriptional regulation of autophagy-related genes is missing for EHMT1, a recent study has shown that EHMT1, in complex with EHMT2, inhibits autophagy initiation through direct methylation of ATG12 in mouse embryonic fibroblasts [133]. Upon methylation, ATG12 undergoes ubiquitin-mediated protein degradation. When autophagy needs to be activated, the EHMT1/2 complex is degraded, which stabilizes ATG12 protein levels and initiates autophagosome formation through the ATG12–ATG5 conjugation system (Figure 2) [133]. Haploinsufficiency of *EHMT1* would lead to a reduction of methylated ATG12, and thereby increase autophagic activity under basal conditions.

The lysine demethylase KDM1A is not only controlling MTOR activity through transcriptional regulation of the MTOR repressor SESN2, but also through direct protein interaction with PTEN [134]. PTEN is a well-known AKT-MTORC1 repressor and thereby mediates autophagic induction. KDM1A interacts with PTEN to enhance protein ubiquitination and degradation. Subsequently, the destabilization of PTEN increases AKT and MTORC1 activity and hence reduces autophagic activity. In skeletal muscle cells, the inhibition of KDM1A activity shows to stabilize PTEN levels and to activate autophagy [134]. As experimental evidence is missing, it can only be speculated that mutations in *KDM1A* result in increased autophagy induction in neuronal cells through a similar mechanism.

Defective autophagy as a contributor to neurodevelopmental phenotypes?

While the above summarized studies provide evidence for a critical role of chromatinopathy associated genes in regulating autophagy, there is only little known about how mutations in these genes affect autophagy and autophagy-dependent cellular processes in neuronal cell types. Insights into how deregulated autophagy alters neuronal development and function can be gained when looking at congenital disorders of autophagy. Causal mutations in this group of disorders have been identified in various autophagy-related genes, such as *EPG5*, *WDR45*, *SNX14*, *SPG11*, *ZFYVE26*, and *TECPR2*, that affect different stages of the autophagic pathway ranging from early induction phases up to autolysosome formation [135–143]. An example for this class of disorders is Vici syndrome, a severe progressive neurodevelopmental, multisystemic disorder caused by recessive mutations in *EPG5* [144,145]. The EPG5 protein plays an essential role in fusion of autophagosomes with late endosomes and lysosomes and thereby affects the late stages of autophagy [145]. Furthermore, mutations in *WDR45* have been shown to cause the neurodegenerative disease β-propeller protein-associated neurodegeneration [146]. Patients associated with β-propeller protein-associated neurodegeneration are characterized with static encephalopathy in childhood, and develop sudden-onset dystonia-parkinsonism and dementia in adulthood [137,146]. WDR45 is required for the early steps of autophagosome formation [147]. Haploinsufficiency of *WDR45* leads to lower autophagic activity and accumulation of aberrant early autophagic structures in neurons leading to swollen axons [137,138]. In addition, truncating mutations in *SNX14* are associated with pediatric-onset ataxias. SNX14-related patients often present with developmental delay and ID [139]. SNX14 localizes to lysosomes where it associates with phosphatidylinositol(3,5)P2, and therefore plays an essential role in the late stages of autophagy [139]. SNX14-patient derived

materials from cerebellar parenchyma show enlarged lysosomes and slower autophagic activity upon starvation, suggesting a crucial role for SNX14 in neuronal functioning [139]. Another example for congenital disorders of autophagy is hereditary spastic paraplegia (HSP) in which the patients are characterized by degeneration of corticospinal axons leading to progressive weakness and spasticity of the legs [148]. HSP is caused by mutations in *SPG11*, which respective protein is essential for the recycling of lysosomes from autolysosomes [140]. Deficient SPG11 therefore leads to a reduced number of available lysosomes for fusion with autophagosomes, resulting in the accumulation of autophagic waste shown in cortical neurons and Purkinje cells [141]. Besides, mutations in the *ZFYVE26* and *TECPR2* gene, which are also associated with HSP, show accumulation of immature autophagosomes, indicating that both proteins are key determinant of autophagosome maturation in primary neurons harboring *ZFYVE26* mutations [142] and in fibroblasts derived from TECPR2-related patients [143]. These studies provide evidence for deregulated autophagy that might underlie clinical neurodevelopmental phenotypes, such as structural brain abnormalities, developmental delay, ID, ASD and epilepsy [30,149,150]. When comparing these symptoms with clinical phenotypes of the here examined chromatinopathies (Table 1) it becomes striking how similar the two groups are regarding their clinical presentation. In line with this, it would also be highly interesting to see whether the epigenetic modifiers mutated in chromatinopathies regulate the gene expression of those genes associated with congenital disorders of autophagy.

However, considering that epigenetic regulatory proteins have a very wide range of downstream effects, autophagic deficits are unlikely to be a specific or exclusive contributor to neurodevelopmental phenotypes. Especially during early brain development epigenetic changes are essential to create neuronal circuits and connections between neurons as they develop their adult functional properties in response to the surrounding environment. As a result, many studies have linked NDD-linked chromatinopathy genes to transcriptional changes of gene sets involved in neurodevelopmental processes like, neuronal differentiation, dendritic maturation, and synaptic function. For instance, the histone demethylase PHF8 has been shown to regulate the expression of genes involved in cell adhesion and cytoskeleton organization by demethylating H4K20me1 at corresponding promoters [151]. Depletion of PHF8 in primary neuronal cultures derived from mouse cerebral cortex leads to downregulation of cytoskeleton genes and thereby causes deficits in neuronal differentiation [151].

Time course transcriptomic and epigenomic analyses of the repressive mark H3K27me3 in transgenic mouse models harboring *Ezh2* conditional KO alleles show a significant dysregulation of molecular networks affecting the glutamatergic differentiation trajectory [152]. Likewise, loss-of-function mutations in *SETD1A* altered gene expression profiles that are associated with synaptic function, glutamatergic neurotransmission, and neurite outgrowth, leading to increased dendritic complexity and neuronal network activity in SETD1A-deficient hiPSC-induced neuronal cultures [153]. Furthermore, we have previously shown that mutations in *EHMT1* cause deficits in the methylation of the repressive H3K9me2 mark leading to upregulation of GRIN1/NMDAR1 (glutamate ionotropic receptor NMDA type subunit 1) [154]. Changes in NMDAR expression leads to deficits in neuronal networks differentiated from Kleefstra syndrome patient-derived hiPSCs [154]. Additionally, we identified an EHMT1-dependent gene repression program that is required for synaptic scaling in an EHMT1-deficient mouse model [155]. Lastly, neuronal ablation of the H3K4-specific methyltransferase KMT2A in mouse postnatal forebrain and adults prefrontal cortex is associated with impaired working memory due to loss of *Arc* expression, which is critical for synaptic plasticity [156].

In summary, depending on the needs of neuronal cells in time (e.g., stage of neurogenesis) and space (e.g., neural progenitor cells versus post-mitotic mature neurons), the epigenetic regulatory proteins exert their modification on specific (histone) marks to fine-tune genes required for neuronal development and function, but also to fine-tune the autophagic pathway by regulating transcriptional expression of autophagy-related genes. Several recent researches start to report an essential role for autophagy in several of these aspects of neuronal development, such as neuronal differentiation [157,158] and synaptic function[159–172]. However, for most of the NDD-related chromatinopathy genes experimental evidence is required to show that deficient autophagic activity affects neuronal development and function.

Conclusions and perspectives

Epigenetic machineries emerge as a crucial part of the autophagic pathway by regulating autophagy-related gene transcription. This is important to prevent excessive cytoplasmic degradation in various cell types. Many of the described epigenetic modifiers are associated with NDD-related chromatinopathy genes. Loss-of-function mutations in NDD-related chromatinopathy genes are therefore likely to impede the autophagic pathway affecting neuronal development, function and survival. While there is already some experimental evidence for altered epigenetic regulation resulting in aberrant autophagy regulation causing neuronal deficits [85], this link remains hypothetical for most of the NDDs described here. Future studies that provide additional experimental evidence for deregulated autophagy causing neuronal deficits within the large group of chromatinopathies will increase our understanding of how a common key “hub” signaling pathway similarly affects protein-protein interactions and synaptic function and help to explain the comorbidities observed within the group of NDDs. Current research in neuronal autophagy mainly focusses on the importance for cellular homeostasis and hence protection against neurodegeneration. However, there is increasing evidence from the literature reporting an essential role for autophagy in different neuron-specific mechanisms related to differentiation [157,158] and synaptic function [159–172], which guarantees the formation of appropriate neuronal

connections. Summarizing the literature, we here show that a significant number of chromatinopathy-related genes play an essential role in the transcriptional regulation of autophagy-related proteins and thereby play key roles in the regulation of autophagic activity (Figure 2). This suggests that mutations in those genes significantly impair the tight regulation of autophagic activity and thereby could affect neuronal differentiation and function. Although this implies deregulated autophagy being part of the respective NDD-underlying pathophysiologies, for most of the chromatinopathy-related genes their role in the regulation of autophagy, specifically during neuronal development and function, remain very poorly explored. Additionally, autophagy does not only play an important role in neurons, but also in other brain cells, such as astrocytes and oligodendrocytes [173–182]. Elucidating the autophagic interplay between different brain cell types and how autophagy is regulated in this context would provide new insights in brain function in general, but also increase our understanding of the respective NDD pathophysiology. This will provide promising starting points for the development of new and refined therapeutic approaches.

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