Review



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*Review*

# Differential Ubiquitination in Phenotypic Heterogeneity of Neurodevelopmental Disorders

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**Abstract**

Neurodevelopmental disorders (NDDs) are characterized by remarkable phenotypic heterogeneity, in which individuals harboring mutations in the same gene display divergent clinical manifestations, ranging from mild cognitive impairment to severe neurodevelopmental deficits. Advances in neurogenetics and neurogenomics have rapidly expanded the catalog of genes associated with NDDs and have provided unprecedented insight into the genetic architecture of these conditions. However, how identical or similar genetic variants give rise to such diverse phenotypic outcomes remains largely unknown. Ubiquitin-mediated protein regulation is a central mechanism controlling diverse processes essential for neural development, including chromatin regulation, transcriptional dynamics, protein turnover, and synaptic function. Importantly, ubiquitination is a multilayered regulatory process governed by multiple determinants, including the availability of ubiquitination sites on substrates, the activity of ubiquitin ligases, the opposing actions of deubiquitinases, and priming post-translational modifications such as phosphorylation or acetylation. These regulatory layers create a dynamic ubiquitination landscape that may vary across individuals, cell types, developmental stages, and environmental contexts. In this review, we discuss how insights from neurogenetics and neurogenomics can be integrated with knowledge of ubiquitin signaling to better understand the molecular basis of phenotypic heterogeneity in NDDs. We propose that differential ubiquitination represents an important mechanistic framework through which genetic variation is translated into diverse molecular and cellular outcomes. Understanding the interplay between neurogenetic variation and ubiquitin-dependent regulatory networks may provide new perspectives on disease mechanisms and inform future therapeutic strategies for neurodevelopmental disorders.

**Keywords:** neurodevelopmental disorders; phenotypic heterogeneity; ubiquitination; $\beta$-catenin; MeCP2; SHANK3

## 1. Introduction

Neurodevelopmental disorders (NDDs) encompass a diverse group of conditions characterized by impairments in cognitive, behavioral, and social functions that arise from disrupted brain development [1,2]. Advances in neurogenetics and neurogenomics have dramatically expanded our understanding of the genetic architecture underlying these disorders, such as identification of numerous causative or risk-associated genes [3,4].

A striking feature of NDDs is the remarkable phenotypic heterogeneity observed among affected individuals [5–7]. Patients carrying identical or highly similar genetic variants frequently exhibit widely divergent clinical manifestations, ranging from mild cognitive impairment to severe intellectual disability or autism spectrum–related phenotypes. This variability poses a major challenge for both mechanistic understanding and clinical management, and the molecular principles that translate genetic variation into diverse phenotypic outcomes remain largely unresolved.

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One possible explanation for such phenotypic diversity lies in the multilayered regulatory networks that control protein function in developing neurons. Among these regulatory systems, ubiquitin-mediated protein modification has emerged as a central mechanism governing diverse aspects of cellular physiology, including protein stability, signal transduction, and transcriptional regulation [8–11]. In the nervous system, ubiquitin signaling plays essential roles in neural progenitor proliferation, neuronal differentiation, and synapse formation [12–15]. Consistent with these functions, mutations in components of the ubiquitin system have been increasingly linked to NDDs through neurogenetic studies.

Importantly, ubiquitination is not a simple on–off modification but rather a highly dynamic process regulated at multiple levels. The extent of substrate ubiquitination is determined by several factors, including the availability of lysine residues on substrate proteins, the activity and specificity of ubiquitin ligases, the opposing actions of deubiquitinases (DUBs), and priming post-translational modifications such as phosphorylation or acetylation that influence ubiquitin conjugation (Figure 1) [16–19]. These regulatory layers generate a flexible ubiquitination landscape that may vary among cell types, developmental stages, and environmental contexts. Consequently, even subtle differences in these regulatory mechanisms may alter the ubiquitination status of key substrates, leading to divergent molecular and cellular consequences.

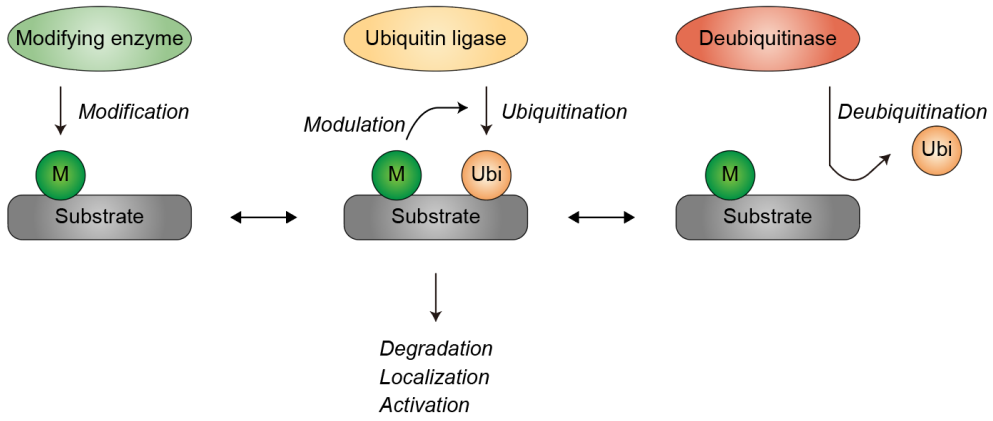


**Figure 1.** Regulation of ubiquitination by substrate modification, ubiquitin ligases, and deubiquitinases. Protein-modifying enzymes, such as kinases and acetyltransferases, modify substrate proteins, thereby modulating their susceptibility to subsequent ubiquitination. Deubiquitinases remove ubiquitin moieties from substrates, thereby counteracting the activity of ubiquitin ligases. Ubiquitination can result in proteasomal degradation, altered subcellular localization, or modulation of protein activity. Green indicates substrate modifications or modifying enzymes. Yellow denotes ubiquitin or ubiquitin ligases. Red represents deubiquitinases. M, modification. Ubi, ubiquitin.

In this context, we propose that differential ubiquitination of critical neuronal substrates may represent an important molecular mechanism contributing to phenotypic heterogeneity in NDDs. Rather than focusing broadly on the ubiquitin system, this review highlights representative examples in which multiple regulatory layers converge on specific substrates relevant to NDDs. We discuss β-catenin, a central signaling molecule in Wnt pathways, methyl-CpG binding protein 2 (MeCP2), a transcriptional regulator implicated in Rett syndrome, and SH3 and multiple ankyrin repeat domains 3 (SHANK3), a synaptic scaffold protein strongly associated with autism spectrum disorders. Through these examples, we illustrate how the convergence of ubiquitin ligases, DUBs, and priming post-translational modifications at the level of individual substrates may generate differential ubiquitination states, potentially contributing to the phenotypic diversity observed in patients with NDDs.

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## 2. Ubiquitination of β-Catenin

β-Catenin is a central component of the Wnt signaling pathway, which plays essential roles in neural development, including the regulation of neural progenitor proliferation, neuronal differentiation, and synapse formation [20–22]. Consistent with these functions, dysregulation of β-catenin signaling has been implicated in NDDs, and mutations in the gene encoding β-catenin, *CTNNB1*, have been identified in patients with intellectual disability, autism spectrum disorder, and other developmental abnormalities [23,24]. A notable feature of *CTNNB1*-associated disorders is the considerable variability in clinical manifestations among affected individuals [25,26], suggesting that regulatory mechanisms controlling β-catenin activity may modulate disease phenotypes.

The abundance and activity of β-catenin are tightly regulated by ubiquitin-mediated proteolysis [27]. In the absence of Wnt signaling, β-catenin is incorporated into a multiprotein destruction complex composed of Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK3), and casein kinase 1 (CK1). Within this complex, β-catenin undergoes sequential phosphorylation by CK1 and GSK3 at specific N-terminal residues. These phosphorylation events generate a phosphodegron that is recognized by the $SCF^{\beta\text{-}TrCP}$ ubiquitin ligase complex, which catalyzes the polyubiquitination of β-catenin and targets it for degradation by the 26S proteasome. Through this mechanism, phosphorylation acts as a priming modification that enables ubiquitin-mediated turnover of β-catenin. Binding of Wnt ligands to their receptors leads to inhibition of the destruction complex, resulting in the stabilization and accumulation of β-catenin. Stabilized β-catenin interacts with TCF/LEF transcription factors to activate gene expression programs that control cell proliferation and differentiation. The ubiquitination status of β-catenin therefore acts as a molecular switch that determines the activity of Wnt signaling.

In addition to ubiquitin ligases, DUBs contribute to the dynamic regulation of β-catenin stability. Four DUBs (i.e., USP2a, USP4, USP6NL, and USP47) have been reported to remove ubiquitin chains from β-catenin, thereby promoting its stabilization and enhancing Wnt signaling activity [28–31]. Although pathogenic mutations in the genes encoding these DUBs have not yet been identified, all four DUBs are expressed in the brain [32–35]. Notably, *Usp2* gene knockout mice exhibit an anxiety-like behavior [34], a phenotype frequently observed in patients with NDDs. Combined with the report demonstrating that excessive expression of β-catenin in the brain induces autism-like behaviors in mice [36], these observations suggest that the activity or abundance of these DUBs may influence NDD pathogenesis through β-catenin regulation.

Taken together, β-catenin provides a well-characterized example in which multi-layered regulation of substrate ubiquitination determines signaling output (Figure 2). Variations in kinase activity, expression levels of ubiquitin ligases or DUBs, or cellular signaling contexts may shift the threshold at which β-catenin is degraded or stabilized, and such differences could lead to divergent transcriptional responses during neurodevelopment, even in individuals carrying similar genetic variants affecting β-catenin signaling. Given the central role of Wnt signaling in brain development, differential ubiquitination of β-catenin may represent a plausible mechanism contributing to the phenotypic heterogeneity observed in NDDs.

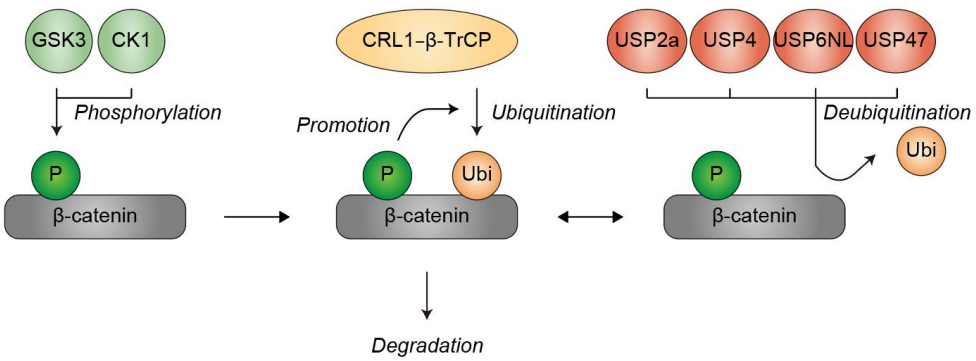

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**Figure 2.** Regulation of β-catenin ubiquitination by substrate phosphorylation, ubiquitin ligase, and deubiquitinases. GSK3 and CK1 phosphorylate β-catenin, thereby promoting its susceptibility to subsequent ubiquitination catalyzed by the CRL1 ubiquitin ligase complex containing β-TrCP as the substrate receptor (CRL1–β-TrCP). USP2a, USP4, USP6NL, and USP47 remove ubiquitin from β-catenin, thereby antagonizing ubiquitin-mediated degradation. Green indicates phosphate group or kinases. Yellow denotes ubiquitin or the CRL1–β-TrCP ubiquitin ligase complex. Red represents deubiquitinases. CRL1, Cullin-ring ubiquitin ligase 1. P, phosphate group. Ubi, ubiquitin.

## 3. Ubiquitination of MeCP2

MeCP2 is a transcriptional regulator that plays a crucial role in neuronal maturation [37]. It binds methylated CpG dinucleotides in DNA and modulates gene expression through interactions with chromatin remodeling complexes and other transcriptional regulators [38,39]. The importance of MeCP2 in neurodevelopment is underscored by the fact that mutations in the *MeCP2* gene cause Rett syndrome, a severe NDD characterized by intellectual disability, motor impairment, and autistic features [40,41]. Notably, both loss-of-function and increased dosage of MeCP2 can result in neurological abnormalities, highlighting the requirement for precise regulation of MeCP2 abundance and activity [42,43].

Consistently, emerging evidence indicates that MeCP2 is subject to multiple post-translational modifications that may regulate its stability [44]. Phosphorylation at S92 by HIPK2 and S413 by unknown kinase is positioned within PEST degrons and has therefore been postulated to promote MeCP2 degradation [44,45], although this mechanism has not yet been experimentally validated. Several ubiquitin ligases (i.e., RNF4, NEDD4, HERC2, and CRL4–DCAF13) ubiquitinate MeCP2 and promote its proteasomal degradation, thereby contributing to the turnover of this transcriptional regulator [46–49]. In contrast, the deubiquitinase USP15 counteracts this ubiquitin-mediated degradation by removing ubiquitin moieties from MeCP2 [50]. Interestingly, mutations in genes encoding CUL4B, a core scaffold component of the CRL4 complex, and USP15 have been identified in patients with NDDs. Determining whether these patients exhibit altered MeCP2 abundance will be of important in the future studies. If confirmed, these findings would suggest that differential ubiquitination of MeCP2 contributes to NDD pathogenesis in these individuals.

Given that both excessive and reduced levels of MeCP2 can lead to NDDs, variability in the regulatory mechanisms controlling MeCP2 ubiquitination may contribute to the broad phenotypic spectrum observed in disorders associated with MeCP2 dysfunction (Figure 3). In this regard, extracellular cues such as synaptic activity and neuromodulatory signals have been shown to converge on nuclear MeCP2 through $Ca^{2+}$-dependent and cAMP/PKA-dependent kinase pathways, inducing site-specific phosphorylation that modulates MeCP2 chromatin binding and its interactions with transcriptional cofactors [51,52]. In parallel, MeCP2 ubiquitination in neurons is also likely governed by intracellular signaling cascades downstream of these extracellular stimuli. However, key mechanistic aspects, including the specific E3 ubiquitin ligases involved, the lysine residues targeted for ubiquitination, and the stimulus–response kinetics, remain poorly defined in the neuronal literature. Taken together, differential ubiquitination of MeCP2 provides an illustrative example of how multilayered regulation of transcriptional regulators may contribute to phenotypic heterogeneity in NDDs.

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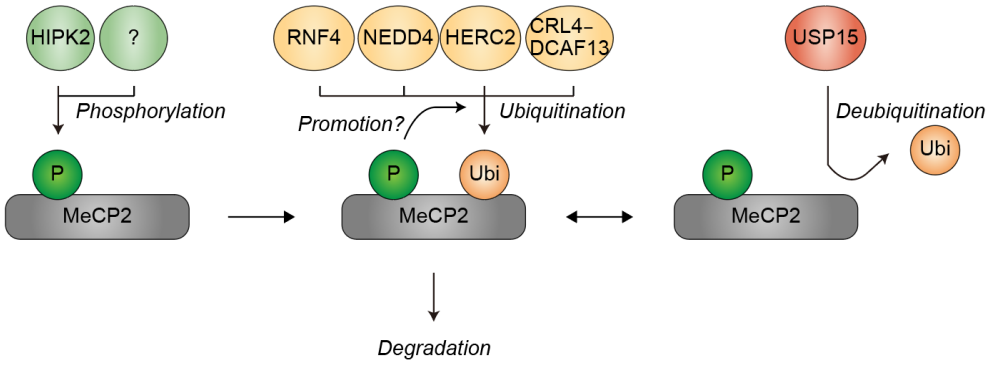


**Figure 3.** Regulation of MeCP2 ubiquitination by substrate phosphorylation, ubiquitin ligases, and a deubiquitinase. HIPK2 and an unidentified kinase phosphorylate MeCP2 within PEST degrons, likely enhancing its susceptibility to subsequent ubiquitination catalyzed by RNF4, NEDD4, HERC2, and the CRL4 ubiquitin ligase complex containing DCAF13 as the substrate receptor (CRL4–DCAF13). USP15 removes ubiquitin from MeCP2, thereby antagonizing ubiquitin-mediated degradation. Green indicates phosphorylation events or kinases. Yellow denotes ubiquitin or the ubiquitin ligases. Red represents a deubiquitinase USP15. CRL4, Cullin–RING ubiquitin ligase 4. P, phosphate group; Ubi, ubiquitin.

## 4. Ubiquitination of SHANK3

Ubiquitination of synaptic proteins is widely recognized as a dynamic regulatory mechanism that shapes synapse formation, stability, and multiple forms of synaptic plasticity [53,54]. Among these substrates, SHANK3 is a prominent core component of the postsynaptic density (PSD), where it orchestrates the assembly of multiprotein complexes linking neurotransmitter receptors, signaling molecules, and cytoskeletal elements [55,56]. Genetic studies have established that mutations or deletions of the SHANK3 gene are strongly associated with autism spectrum disorders and Phelan–McDermid syndrome, underscoring the importance of SHANK3 in normal brain development and synaptic function [57,58]. Notably, individuals carrying similar SHANK3 variants often display considerable variability in clinical severity [59,60], suggesting that regulatory mechanisms affecting SHANK3 stability may influence phenotypic outcomes.

The abundance of SHANK3 at synapses is tightly controlled by protein turnover mechanisms. ERK2 phosphorylates SHANK3 at three serine residues (S1134, S1163, and S1253), resulting in enhanced ubiquitination and subsequent degradation of SHANK3 [61]. Although the ubiquitin ligases responsible for SHANK3 ubiquitination remain to be characterized, USP8 has been identified as a deubiquitinase that removes ubiquitin chains from SHANK3, thereby promoting its stabilization [62].

Given the central role of SHANK3 in organizing synaptic architecture, alterations in its stability or turnover may exert profound effects on synaptic development and plasticity. Variability in the regulatory pathways controlling SHANK3 ubiquitination could therefore influence synaptic protein homeostasis, potentially contributing to the diverse phenotypic manifestations observed among individuals carrying SHANK3 mutations (Figure 4). As with MeCP2, extracellular events such as synaptic activity and ischemic stress have been shown to regulate SHANK3 protein levels through ubiquitin-dependent proteasomal degradation in neurons [62,63], indicating that environmental conditions can modulate the ubiquitination and degradation of SHANK3. In this manner, SHANK3 exemplifies how differential ubiquitination of synaptic proteins may constitute a molecular mechanism underlying phenotypic heterogeneity in NDDs.

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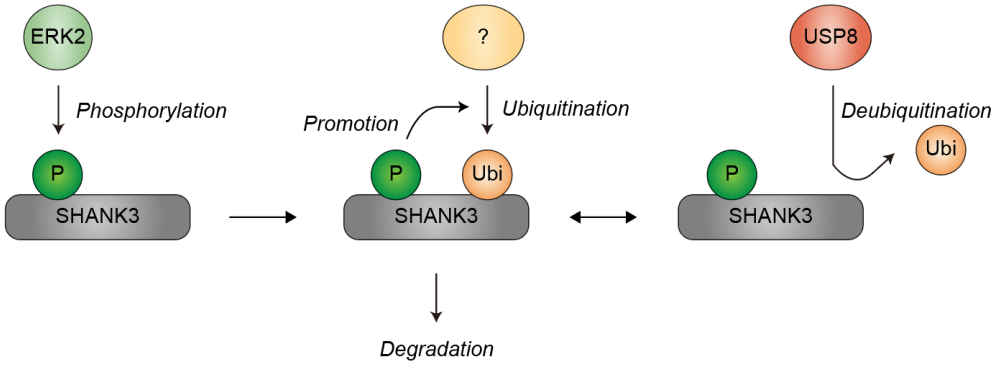


**Figure 4.** Regulation of SHANK3 ubiquitination by substrate phosphorylation, ubiquitin ligase(s), and a deubiquitinase. ERK2 phosphorylates SHANK3, thereby enhancing its susceptibility to subsequent ubiquitination catalyzed by currently unidentified ubiquitin ligase(s). USP8 removes ubiquitin from SHANK3, thereby antagonizing ubiquitin-mediated degradation. Green indicates phosphorylation events or kinases. Yellow denotes ubiquitin or ubiquitin ligases. Red represents the deubiquitinase USP8. P, phosphate group; Ubi, ubiquitin.

## 5. Conclusions

Advances in neurogenetics and neurogenomics have markedly expanded the repertoire of genes associated with NDDs. Nevertheless, a central challenge that remains unresolved is the striking phenotypic heterogeneity observed among patients carrying identical or closely related genetic variants. The molecular mechanisms that translate genetic variation into diverse cellular and clinical outcomes are therefore an important subject of investigation.

In this review, we have highlighted ubiquitination of key neuronal substrates as a potential mechanism contributing to such phenotypic variability. Ubiquitination is regulated through multiple interconnected layers, including substrate accessibility, ubiquitin ligases, DUBs, and priming post-translational modifications. Through the integration of these regulatory processes, the ubiquitination status of a given substrate can vary substantially depending on cellular context. As illustrated by the examples of β-catenin, MeCP2, and SHANK3, such multilayered regulation converges at the level of individual proteins that control signaling pathways, transcriptional programs, and synaptic organization, respectively. Variability in these regulatory mechanisms may therefore influence the stability or activity of these substrates and ultimately shape neurodevelopmental outcomes.

Importantly, recent neurogenetic and neurogenomic studies increasingly reveal that many NDD-associated genes encode proteins involved in ubiquitin signaling or its regulatory networks. Integrating these genetic insights with molecular studies of ubiquitination dynamics may provide a valuable framework for understanding how genetic variants are translated into heterogeneous phenotypes. In particular, multi-omics approaches that combine genomic, transcriptomic, and proteomic analyses at multiple time points in different cell types may help uncover context-dependent ubiquitination states of disease-relevant substrates across different neuronal cell types and developmental stages.

Although many questions remain regarding the precise mechanisms by which ubiquitin signaling contributes to NDD pathogenesis, a substrate-centered perspective may provide a useful conceptual framework. By focusing on how multiple regulatory layers converge on key neuronal proteins, it becomes possible to consider how subtle variations in ubiquitination dynamics might amplify or buffer the effects of genetic mutations. Further investigation into these regulatory networks may therefore not only improve our understanding of phenotypic heterogeneity in NDDs but also provide new opportunities for therapeutic strategies aimed at modulating ubiquitin-dependent pathways in an individual patient-specific manner.

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