Review

UBE3A Dosage Imbalance as a Molecular Framework Linking Angelman Syndrome and Dup15q-Associated Autism Phenotypes

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Posted Date: 15 May 2026

doi: 10.20944/preprints202605.1078.v1

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 doi:10.20944/preprints202605.1078.v1

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UBE3A Dosage Imbalance as a Molecular Framework Linking Angelman Syndrome and Dup15q-Associated Autism Phenotypes

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Abstract

UBE3A is a dosage-sensitive HECT E3 ubiquitin ligase whose neuronal expression is shaped by genomic imprinting at the 15q11.2–q13 locus. Opposite directions of UBE3A dosage imbalance contribute to distinct neurodevelopmental phenotypes: loss of maternal UBE3A underlies Angelman syndrome, whereas maternally derived duplications involving UBE3A contribute to Dup15q-associated syndromic autism phenotypes. This review synthesizes evidence across molecular architecture, isoform biology, neuronal imprinting, synaptic regulation, circuit excitability, and therapeutic development. The central argument is that UBE3A should not be interpreted as a general explanation for autism, but as a mechanistically informative model for a defined subset of neurodevelopmental disorders in which parent-of-origin effects and copy-number state are central. In Angelman syndrome, UBE3A loss disrupts proteostasis, synaptic plasticity, inhibitory circuit function, and neuronal excitability through distributed rather than single-pathway mechanisms. In maternal Dup15q syndrome, increased UBE3A dosage is strongly implicated in neuronal and synaptic abnormalities, although interval-wide dosage effects also contribute. Therapeutically, the direction of dosage change creates opposite translational requirements: restoration or paternal reactivation in Angelman syndrome versus dosage normalization in Dup15q-associated gain-of-function states. A dosage-directionality framework may therefore clarify how UBE3A biology connects molecular mechanism, developmental timing, and precision therapeutic design.

Keywords: UBE3A; Angelman syndrome; Dup15q syndrome; autism phenotypes; genomic imprinting; synaptic plasticity; neurodevelopmental disorders

Introduction

UBE3A dosage imbalance helps explain why changes at the same imprinted locus can lead to different neurodevelopmental outcomes. Both Angelman syndrome and maternally derived Dup15q syndrome involve the 15q11.2-q13 region, but they differ in the direction of UBE3A dosage change. Loss of maternal UBE3A reduces neuronal UBE3A function, whereas maternal duplication of the same chromosomal interval can increase effective neuronal dosage and contribute to syndromic autism-associated phenotypes (Hogart et al., 2010; Bisba et al., 2024). This relationship is shaped by genomic imprinting, parent-of-origin effects and the broader architecture of the 15q11.2-q13 interval. It is also consistent with current clinical-genetic practice in Angelman syndrome, where deletion, UBE3A mutation, imprinting-defect and uniparental-disomy mechanisms are distinguished rather than treated as one uniform cause (Beygo et al., 2019). UBE3A should therefore not be presented as a general explanation for autism. A more precise conclusion is that UBE3A dosage dysregulation contributes to a defined subset of neurodevelopmental phenotypes in which imprinting and copy-number state are central.

The contrast between Angelman syndrome and maternal Dup15q provides a useful clinical-genetic starting point. Early family-based evidence showed that proximal 15q11-q13 duplication cosegregated with autism or atypical autism after maternal, but not paternal, transmission (Cook et

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al., 1997). Later cohort and postmortem cortical studies refined this picture. Maternally derived interstitial Dup15q is strongly associated with syndromic autism-spectrum phenotypes and increased UBE3A expression in human cortex, but the phenotype cannot be reduced to UBE3A alone because the duplicated interval also contains other dosage-sensitive transcripts and regulatory elements (Urraca et al., 2013; Scoles et al., 2011). These observations explain why UBE3A remains central, while also showing that Dup15q cannot be reduced to one gene. The main question is how a dosage-sensitive imprinted ubiquitin ligase can produce different outcomes depending on whether maternal expression is lost or increased. Recent reviews have taken this broader view by discussing UBE3A across molecular, cellular, developmental, circuit and clinical levels, rather than focusing on only one explanatory level (Biagioni et al., 2024). Figure 1 summarizes the central dosage relationship between maternal UBE3A loss, balanced neuronal dosage and maternally derived Dup15q-associated overdosage.

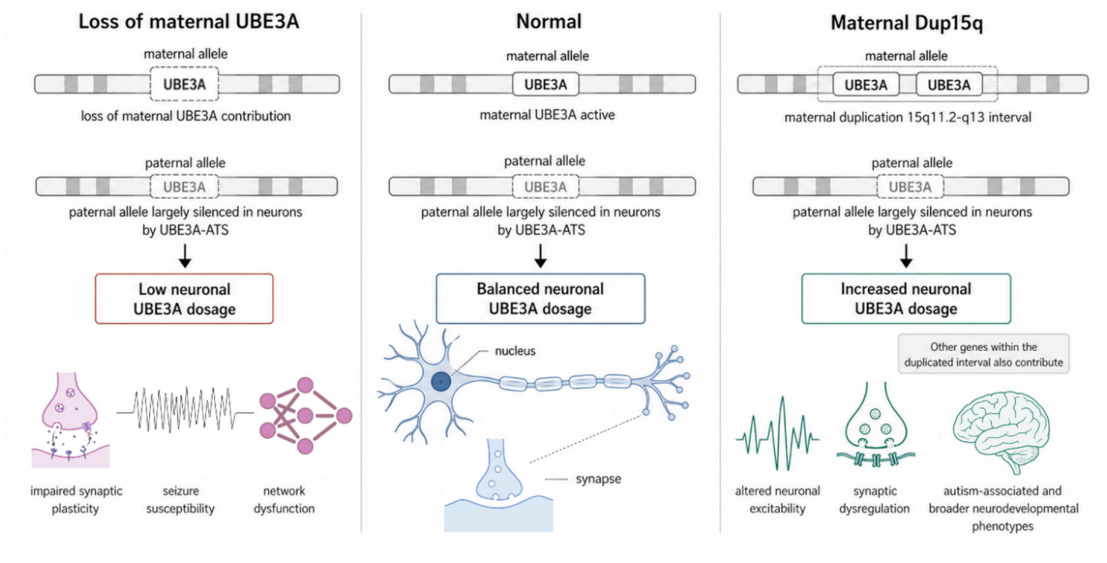

Figure 1. Central dosage imbalance model of UBE3A in Angelman syndrome and maternal Dup15q-associated neurodevelopmental phenotypes. In neurons, paternal UBE3A is largely silenced by UBE3A-ATS, making effective neuronal dosage strongly dependent on the maternal allele. Loss of maternal UBE3A reduces neuronal UBE3A dosage and is associated with impaired synaptic plasticity, seizure susceptibility and network dysfunction. In maternally derived Dup15q, duplication of the 15q11.2–q13 interval increases effective neuronal UBE3A dosage and may contribute to altered excitability, synaptic dysregulation and autism-associated neurodevelopmental phenotypes. The duplicated interval also contains additional genes and regulatory elements that may contribute to the full Dup15q phenotype.

Molecular Architecture, Isoforms and Imprinting Logic

UBE3A dosage matters because UBE3A/E6AP is not simply a constitutively active housekeeping enzyme. It is a regulated HECT E3 ubiquitin ligase whose catalytic behaviour depends on structural organisation, substrate engagement and cellular context. Biochemical and structural studies show that E6AP/UBE3A can engage E2~ubiquitin in more than one functionally relevant configuration, and that ligase activity is influenced by oligomeric state (Ronchi et al., 2013; Ronchi et al., 2014; Sailer et al., 2018). The N-terminal AZUL region also contributes to proteasome-related interactions, and Angelman-associated point mutations can disrupt this interface (Kühnle et al., 2018). These findings show that pathogenicity is not limited to loss of the terminal catalytic domain. Disruption of regulatory interfaces can also alter UBE3A function. Although much of this work comes from biochemical systems rather than structural studies in native neuronal systems, it supports the idea that both reduced and excessive UBE3A activity can disturb neuronal homeostasis.

 doi:10.20944/preprints202605.1078.v1

Isoform biology and subcellular localisation add another layer of control. Human UBE3A encodes multiple protein isoforms. Stem-cell-derived neuronal models suggest that isoform 1 accounts for most total UBE3A protein abundance, while endogenous UBE3A is found in both nuclear and cytoplasmic compartments (Sirois et al., 2020). Ultrastructural studies in mouse neurons and human cortex also support a mixed distribution across nuclear, somatodendritic and synaptic compartments (Burette et al., 2017; Burette et al., 2018). Comparative work suggests that broad subcellular organisation is conserved, but it is achieved through different isoform architectures and localisation mechanisms across species rather than through strict sequence identity alone (Zampeta et al., 2020). This matters functionally because missense variants that impair nuclear localisation or nuclear catalytic competence represent a major pathogenic mechanism in Angelman syndrome (Bossuyt et al., 2021). What appears to be conserved is spatially regulated function, not one identical protein architecture in every species.

This comparison is important because the UBE3A field depends heavily on mouse models, cellular systems and, increasingly, primate data. These models are informative, but they do not reproduce human biology in every detail. Differences in isoform architecture, developmental timing and regional organisation mean that conservation should be interpreted mainly at the level of function, not as evidence that every molecular feature is identical across species (Zampeta et al., 2020; Gonzalez Ramirez et al., 2024). A cautious structural interpretation is that catalytic logic and spatial regulation are broadly preserved, while the implementation of those functions has diverged in some respects. This strengthens rather than weakens the use of animal models, because it makes clear which inferences are likely to translate and which require human-specific validation.

Neuronal imprinting amplifies the effects of UBE3A dysregulation because paternal expression cannot fully compensate for maternal loss. In differentiated neurons, the paternal UBE3A allele is repressed by the long antisense transcript Ube3a-ATS, and experimental truncation of this transcript reactivates paternal Ube3a (Meng et al., 2012). Developmental mapping in mouse shows that paternal Ube3a expression is more evident in immature neurons and becomes increasingly restricted with maturation, which indicates that silencing is developmentally established rather than fixed from the earliest stage of neurogenesis (Judson et al., 2014). Human iPSC-derived neurons support the same broad model, although the timing depends on the system and appears to emerge during differentiation rather than being fully present in undifferentiated cells (Stanurova et al., 2016). Human postmortem, organoid and primate developmental studies are also consistent with later-stage silencing and a staged imprinting programme (Daily et al., 2012; Sen et al., 2020; Gonzalez Ramirez et al., 2024). Because paternal buffering is restricted in neurons, both maternal loss and maternal overdosage have unusually strong consequences. Maternal Ube3a is also required for experience-dependent cortical plasticity, which links imprinting directly to developmental timing (Sato et al., 2010).

The imprinting literature does not support a rigid view in which paternal UBE3A is silenced identically in all neuronal contexts. Available mapping studies support widespread neuronal silencing, but they also show variation by developmental stage, neuronal maturity and brain region (Judson et al., 2014). Human postmortem analysis supports persistent silencing as the dominant state, but does not exclude exceptions (Daily et al., 2012). A clear example comes from the adult suprachiasmatic nucleus in Angelman-model mice, where paternal UBE3A expression persists (Jones et al., 2016). Human cellular models point in a similar direction, with silencing emerging progressively during neuronal differentiation (Stanurova et al., 2016). Neuronal imprinting is a strong organising principle of UBE3A biology, but it should not be described as an absolutely uniform rule. Figure 2 summarizes the developmental restriction of paternal UBE3A contribution during neuronal maturation.

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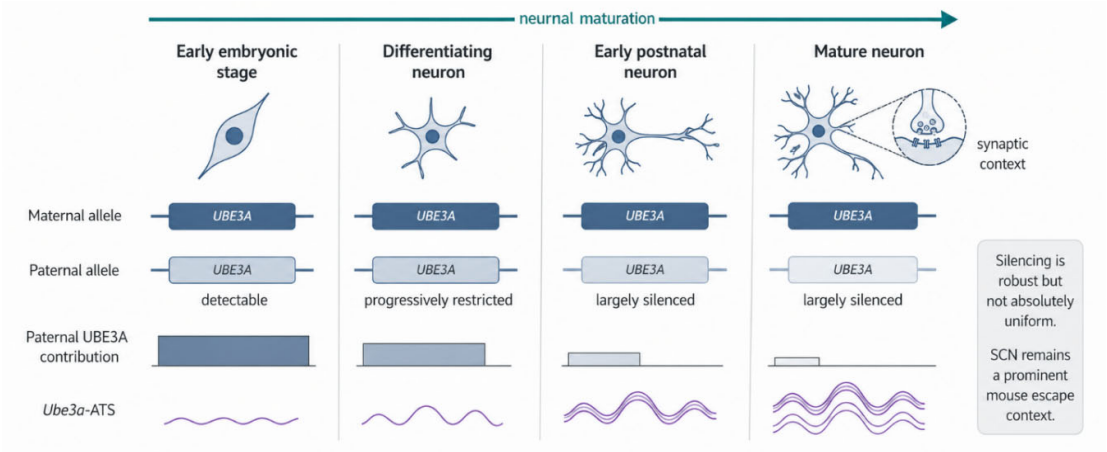

Figure 2. Developmental neuronal imprinting of UBE3A. Maternal UBE3A remains active across neuronal maturation, whereas paternal UBE3A contribution becomes progressively restricted as UBE3A-ATS-linked silencing emerges during neuronal differentiation and maturation. Although paternal silencing is a robust organizing feature of neuronal UBE3A biology, it is not absolutely uniform across all developmental stages, neuronal populations and brain regions. The suprachiasmatic nucleus remains a prominent mouse context in which paternal UBE3A expression can persist.

Angelman Syndrome: Beyond a Single Downstream Pathway

Loss of maternal UBE3A produces a multi-layered disturbance of neuronal homeostasis. It is not well explained by failure of one downstream pathway alone. Experimental work links UBE3A deficiency to altered proteostasis through the proteasomal shuttle Rpn10 (Lee et al., 2014), BK-channel-related hyperexcitability and synchronous network behaviour in human neuronal systems (Sun et al., 2019), and inhibitory-circuit pathology that is sufficient to generate EEG abnormalities and increased seizure susceptibility in conditional mouse models (Judson et al., 2016). Systems-level studies support the same general picture by implicating transcriptomic, signalling and mitochondrial abnormalities (Low et al., 2010; Lopez et al., 2019; Su et al., 2011; Panov et al., 2020). Angelman syndrome is better described as a convergent disorder of proteostasis, excitability, circuit regulation and metabolism than as a disorder with one dominant molecular lesion.

This broader view is important when interpreting the substrate literature. Substrate-specific mechanisms are clearly relevant, but the field still lacks a universally accepted catalogue of direct neuronal UBE3A substrates that explains pathology across all contexts. Arc illustrates the difficulty. The original direct-substrate model became highly influential, but later work did not support its simplest formulation under the tested in vivo-like conditions (Greer et al., 2010; Pastuzyn et al., 2017). Ephexin5 is supported more clearly at the phenotype level, because deletion of this substrate rescues selected hippocampal abnormalities in Angelman-model mice (Sell et al., 2021). Other candidate mechanisms, including SK2-associated trafficking pathways and broader neuronal ubiquitome findings, support a distributed substrate landscape rather than a single privileged target (Martinez et al., 2018; Sun et al., 2020; Sun et al., 2022; Krzeski et al., 2024).

This affects the mechanistic interpretation of Angelman syndrome, if no single direct substrate or signalling pathway explains the disorder across models, then the syndrome should be treated as a layered systems phenotype. Proteostasis, synaptic trafficking, excitability, inhibitory tone and developmental plasticity all contribute, but their relative importance probably differs by cell type, region, developmental stage and model system. This interpretation is stronger than searching for a single dominant pathological mechanism because it reflects the current evidence base and explains why therapeutic rescue can be selective. Correcting one downstream node may improve some physiological or behavioural readouts without normalising the entire syndrome.

 doi:10.20944/preprints202605.1078.v1

Dup15q and Autism-Associated Phenotypes

The same dosage relationship that helps explain maternal loss in Angelman syndrome also provides an entry point into the autism-associated branch of the UBE3A literature. However, the strongest human evidence comes from Dup15q syndrome rather than from broad idiopathic autism cohorts. Parent-of-origin effects in proximal 15q duplication were already visible in early family studies, where autism or atypical autism cosegregated with maternal but not paternal transmission (Cook et al., 1997). Later cohort analysis showed that maternally derived interstitial Dup15q is strongly associated with syndromic autism-spectrum phenotypes, while also emphasising that the duplicated region contains multiple dosage-sensitive genes and should not be collapsed into UBE3A alone (Urraca et al., 2013). More recent clinical reviews support this pattern (Bisba et al., 2024). The evidence therefore supports UBE3A overdosage most strongly in maternal Dup15q, not as a general explanation for autism as a whole.

Even within Dup15q, causal interpretation has to remain precise. Human isogenic neuronal work shows that normalising UBE3A in Dup15q neurons prevents many intrinsic excitability and synaptic phenotypes, which strongly supports a causal role for UBE3A overexpression in key neuronal deficits (Elamin et al., 2023). At the same time, UBE3A overdosage alone does not reproduce every aspect of the syndrome in every model. Earlier transgenic mouse studies reported autism-related behavioural and glutamatergic phenotypes after increased Ube3a dosage (Smith et al., 2011), but later work found limited behavioural and transcriptomic consequences of UBE3A overdosage in at least one mouse system (Punt et al., 2022). Additional evidence from hyperactivating variants, loss of phosphorylation-based restraint, isoform-specific overexpression, retinoic-acid pathway disruption and sex-biased connectomic effects supports the broader conclusion that excessive UBE3A activity can disturb neuronal programmes relevant to autism-associated phenotypes (Yi et al., 2015; Xu et al., 2018; Copping et al., 2017; Weston et al., 2021; Montani et al., 2024). A more cautious conclusion is that excess UBE3A is causally important for many Dup15q-relevant phenotypes, but it is not sufficient to explain the full syndrome in every experimental context.

Recent studies using human neuronal models, cortical organoids and postmortem tissue add molecular detail to the Dup15q literature. In human neuronal systems, Dup15q cells show increased intrinsic excitability and synaptic activity, and many abnormalities are strongly affected by UBE3A dosage normalisation (Elamin et al., 2023). Single-cell and single-nucleus profiling of cortical organoids and postmortem Dup15q cortex show cell-type-specific changes, with prominent dysregulation in excitatory neuronal populations and convergence with autism-relevant pathways (Perez et al., 2025). Mechanistic overexpression studies also support convergence on excitatory cortical dysfunction, including reduced AMPAR/GluA1 signalling through mRNA nuclear retention together with autism-relevant behavioural abnormalities (Tian et al., 2024). Together, these studies support a link between UBE3A-linked dosage imbalance, cortical excitability and synaptic regulation. The exact relationship between human syndrome biology and simplified overexpression models remains model-dependent.

The biomarker literature shows why Dup15q should not be treated as a direct readout of UBE3A alone. The beta-range EEG signature is the clearest example. Pharmacological and comparative EEG work suggests that this biomarker is more consistent with GABAergic network dysfunction than with isolated UBE3A overexpression, because a similar signature can be reproduced through GABAergic modulation and is also observed in paternal Dup15q cases (Frohlich et al., 2019). Clinical cohort data are compatible with this interpretation. Postmortem Dup15q cortex gives a broader explanation: interval genes such as GABRB3 and SNRPN do not behave as simple copy-number outputs, which suggests that syndrome-level biomarkers may arise from interval-wide regulatory disturbances rather than from one gene in isolation (Urraca et al., 2013; Scoles et al., 2011).

This interval-level complexity does not make UBE3A less important. It shows that UBE3A should be discussed as a central component of a broader dosage-sensitive region. UBE3A remains the most compelling dosage-sensitive candidate because of neuronal imprinting, strong human genetic context and direct normalisation data in human cellular models. At the same time, the

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duplicated interval includes other genes with plausible network and developmental relevance, and postmortem expression studies show that copy number does not translate into simple linear expression for every component of the region (Scoles et al., 2011). The most accurate synthesis is a hierarchical model: UBE3A is central, but it acts within a broader dosage-sensitive regulatory landscape.

Therapeutic Directionality and Translational Constraints

The therapeutic literature follows from the direction of the dosage change. In Angelman syndrome, the core molecular problem is loss of maternal UBE3A in neurons, so paternal reactivation or related restoration strategies are mechanistically logical. They aim to restore expression of the endogenous dosage-sensitive gene. In mouse models, reinstating Ube3a rescues multiple disease-relevant phenotypes, which provides strong proof of principle (Silva-Santos et al., 2015). The direction of correction is different in Dup15q-associated gain-of-function states, where improvement in human neuronal models follows UBE3A normalisation rather than further reactivation (Elamin et al., 2023). The Angelman therapeutic path developed stepwise: topoisomerase inhibition and direct manipulation of Ube3a-ATS first showed that the paternal allele was experimentally accessible, and antisense strategies then converted that principle into a therapeutic programme (Huang et al., 2011; Meng et al., 2013; Meng et al., 2015; Elgersma and Sonzogni, 2021).

Several paternal-reactivation platforms now show preclinical promise, but they should not be presented as one therapeutic class. Antisense oligonucleotides that target Ube3a-ATS can restore widespread brain UBE3A and rescue several phenotypes, although rescue is still selective and incomplete (Milazzo et al., 2021). Small-molecule unsilencing offers a different route, but remains at an earlier stage of platform development (Vihma et al., 2024). CRISPR/Cas9 editing of Ube3a-ATS, epigenetic editing of the imprinting-control region and transcriptional interference approaches all show that durable paternal unsilencing can be achieved through different mechanisms (Schmid et al., 2021; Liu et al., 2024; O'Geen et al., 2023; Wolter et al., 2025). The antisense branch has also moved beyond rodent proof of concept. Prenatal delivery improves brain-wide biodistribution in mice, and newer programmes such as rugonersen show prolonged target engagement in patient-derived neurons and non-human primates, although these findings do not yet establish human clinical efficacy (Clarke et al., 2024; Jagasia et al., 2025).

Gene replacement should be considered separately from paternal unsilencing. Secreted UBE3A constructs improve selected physiological and behavioural outcomes in rodent models, but they work by supplementing the system with exogenous gene product rather than reactivating the endogenous paternal allele (Nenninger et al., 2022). This distinction affects questions of dosage control, anatomical distribution, durability and off-target consequences. No platform has yet emerged as a clear therapeutic winner. Each approach occupies a different position in a translational design space defined by delivery, durability, specificity, reversibility and maturity.

Developmental timing remains one of the main constraints across all modalities. The unresolved issue is not simply whether UBE3A can be restored, but which phenotypes remain reversible after particular developmental windows. Conditional reinstatement studies show that rescue windows differ by endpoint. Some behavioural phenotypes require earlier intervention, while certain forms of synaptic plasticity remain recoverable later (Silva-Santos et al., 2015). Postnatal antisense treatment reinforces this point by demonstrating late rescue for selected outcomes such as epilepsy and hippocampal plasticity, but not broad normalisation of all neurobehavioural abnormalities (Milazzo et al., 2021). Adult reinstatement can improve selected prefrontal electrophysiological deficits even when global rescue is not achieved (Rotaru et al., 2018). Delayed-deletion experiments also support the idea that many Angelman phenotypes originate from embryonic or early postnatal UBE3A deficiency, although some later functions remain expression-dependent (Sonzogni et al., 2019). Reversibility is therefore phenotype-specific, modality-sensitive and developmentally constrained.

From a therapeutic engineering perspective, the challenge is not just to turn UBE3A back on. The harder problem is restoring the right dose, in the right cells, at the right developmental stage and

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for the right duration. Antisense oligonucleotides offer reversibility and dose adjustment, but may require repeated administration. Genome and epigenome editing offer durability, but raise more difficult questions about regional delivery, off-target effects and long-term control. Gene replacement provides a separate solution space, with its own constraints on biodistribution and physiological dosage matching. The field is moving from proof of biological feasibility toward the more demanding problem of precision control.

Conclusions

Current evidence supports UBE3A dosage imbalance as a strong organising model for linking Angelman syndrome and maternally derived Dup15q-associated autism phenotypes. The model is useful because it connects two apparently opposite clinical states through the same imprinted locus, while still preserving important mechanistic differences. Several conclusions are now well supported. UBE3A is a dosage-sensitive, spatially regulated HECT E3 ubiquitin ligase. Neuronal imprinting makes the system especially vulnerable to both maternal loss and maternal overdosage. Angelman syndrome reflects multi-layered disruption of neuronal homeostasis rather than one isolated downstream defect. Maternal Dup15q provides the strongest human autism-associated context for UBE3A overexpression, but the broader duplicated interval must also be considered.

Important questions remain unresolved. These include the identity and context-dependence of direct neuronal substrates, the extent to which UBE3A overdosage is sufficient within Dup15q, regional variability in paternal silencing, and the developmental timing of therapeutic rescue. These uncertainties do not weaken the value of UBE3A as a biological model. UBE3A links molecular architecture, neuronal function, comparative biology and therapeutic design in a single disease-relevant system. Its biology shows why dosage, imprinting, timing and delivery have to be considered together when moving from structural mechanism to translational strategy.

Funding: The author declares that no funds, grants or other support were received during the preparation of this manuscript.

Competing Interests: The author has no relevant financial or non-financial interests to disclose.

Author Contributions: Ruslan Kurmashev conceived the review topic, designed the conceptual framework, reviewed and interpreted the literature, prepared the figures, and wrote and revised the manuscript.

Ethics Approval: This article is a narrative review of previously published literature and does not involve new studies with human participants, animals, human data or biological material performed by the author. Therefore, ethics approval was not required.

Consent to Participate: Not applicable.

Consent to Publish: Not applicable.

Data Availability: Data sharing is not applicable to this article because no datasets were generated or analysed during the current study.

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