Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(2): 43770
https://doi.org/10.31083/FBL43770

Review

Ion Channel Dysregulation in Neurodevelopmental Disorders: Mechanisms, Models, and Therapeutic Advances

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Academic Editor: Thomas Heinbockel
Submitted: 12 June 2025 Revised: 7 September 2025 Accepted: 17 September 2025 Published: 31 January 2026

Abstract

Ion channels are fundamental to neuronal excitability, synaptic transmission, and the coordinated development of brain circuits. Disruptions in their function—collectively termed ion channelopathies—have emerged as central mechanisms underlying a broad spectrum of neurodevelopmental disorders (NDDs), including epilepsy, autism spectrum disorder, and intellectual disability. This review synthesizes current knowledge on the physiological roles of voltage-gated and ligand-gated ion channels during brain development and elucidates how their genetic and functional dysregulation contributes to disease pathogenesis. We examine key channel families, such as sodium, potassium, calcium, and glutamate/(gamma-aminobutyric acid) GABA receptors, as well as mechanosensitive and polymodal channels including transient receptor potential and Piezo channels, highlighting the molecular mechanisms, pathogenic variants, and circuit-level consequences of their dysfunction. Emerging therapeutic strategies are discussed, spanning subtype-specific small molecule modulators, antisense oligonucleotides, CRISPR-based genome editing, and patient-derived organoid models for precision medicine and drug screening. We also address significant challenges in the field, including cellular heterogeneity, developmental timing, and translational model fidelity. Together, these advances underscore a rapidly evolving landscape in which precision neurogenetics and integrative platforms hold promise for transforming the diagnosis and treatment of ion channel-related neurodevelopmental disorders.

Keywords: ion channels; channelopathies; neurodevelopmental disorders; epigenesis; genetic; precision medicine

1. Introduction

Neurodevelopmental disorders (NDDs) are conditions in which atypical brain development leads to persistent impairments in cognition, behavior, motor, and sensory function. Major diagnostic categories include epilepsy, particularly developmental and epileptic encephalopathies (DEEs), autism spectrum disorder (ASD), intellectual disability (ID), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia. Across this spectrum, shared genetic architectures and overlapping circuit phenotypes are common, underscoring the need for mechanistic frameworks that cut across categorical diagnoses.

Ion channels are specialized membrane-spanning proteins that regulate the selective flow of ions across cellular membranes, thereby controlling membrane potential, action potential propagation, and synaptic communication. During prenatal and early postnatal brain development, these channels orchestrate a wide array of neurobiological processes—including neurogenesis, neuronal migration, axon guidance, synapse formation, and the establishment of excitation/inhibition balance—making them indispensable for proper brain architecture and function. Disruptions in ion channel expression, gating, or activity, or in subcellular localization, whether through genetic mutations, epigenetic modulation, or post-translational alterations, can derail these tightly regulated processes and contribute to the onset and progression of NDDs [1].

Many pathogenic variants alter channel function in opposite directions. Loss-of-function (LoF) refers to changes that decrease channel activity. For example, reduced current density or surface expression, right-shifted activation, faster inactivation, or impaired lipid/calmodulin coupling. Gain-of-function (GoF) denotes increased activity, such as larger or persistent currents, slowed inactivation, left-shifted activation, or an elevated opening probability. The field of channelopathies—disorders arising from dysfunctions in ion channel genes—has undergone substantial expansion over the past two decades, propelled by breakthroughs in high-throughput sequencing, electrophysiological profiling, and cellular modeling. Pathogenic variants in genes encoding voltage-gated sodium channels (Na_V; e.g., SCN1A, SCN2A), potassium channels (K_V; e.g., KCNQ2, KCNT1), calcium channels (Ca_V; e.g., CACNA1D, CACNA1H), and glutamatergic receptor subunits (e.g., GRIN1, GRIN2B) have been implicated across both monogenic and complex forms of NDDs. Beyond classical voltage-gated ion channels (VGICs), polymodal and mechanosensitive channels, including the transient receptor potential (TRP) family (e.g., TRPM3, TRPC6) and Piezo channels, also shape developmental programs by integrating ionic, trophic, inflammatory, and mechanical

cues. Notably, these mutations often exhibit functional diversity—manifesting as either GoF or LoF—which significantly influences both disease severity and therapeutic response [2,3].

Yet, despite major advances in our molecular understanding of ion channel dysfunction, effective therapeutic translation remains elusive. Current pharmacological treatments, such as broad-spectrum antiepileptic drugs and neuropsychiatric medications, typically offer limited efficacy and lack specificity, failing to address the underlying channel dysfunction in many cases. Furthermore, the spatial and temporal heterogeneity of ion channel expression across brain regions, cell types, and developmental stages complicates the development of targeted interventions [4,5].

In light of these challenges, novel therapeutic strategies have emerged, including subtype-selective small molecule modulators for Na_V/K_V/Ca_V/TRP targets, antisense oligonucleotides (ASOs) for transcript correction, gene editing technologies such as CRISPR/Cas9 and base editing, and human-induced pluripotent stem cell (iPSC)-derived organoids for disease modeling and personalized drug screening. These advances promise to reshape the landscape of therapeutic possibilities for NDDs caused by ion channelopathies.

This review aims to provide an integrated and up-to-date synthesis of ion channel dysregulation in neurodevelopmental disorders. We begin by outlining the fundamental roles of voltage-gated, ligand-gated, and mechanosensitive ion channels in brain development, and then examine the genetic, molecular, and circuit-level mechanisms linking ion channel dysfunction to clinical phenotypes. We further evaluate emerging ion channel-targeted therapeutic approaches and conclude with a discussion of the translational barriers and future research directions that will shape the next decade of ion channelopathy research. In addition, clinical and genetic studies emphasize the substantial overlap between epilepsy and other neurodevelopmental disorders, suggesting convergent pathogenic mechanisms across diagnostic categories [6]. Insights from epileptic channelopathies, therefore, provide an important framework for understanding shared ion channel dysfunction in broader NDDs. By bridging mechanistic insight with therapeutic innovation, we aim to chart a path toward precision medicine in the diagnosis and treatment of ion channel-mediated neurodevelopmental disorders.

2. Voltage-Gated and Ligand-Gated Ion Channels in Brain Development and Disease

Ion channels represent a diverse family of membrane-spanning proteins that are broadly classified into VGICs and ligand-gated ion channels (LGICs) based on their activation mechanisms. VGICs, including sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) channels, are activated by changes in membrane potential and are indispensable for initiating and propagating electrical signals. LGICs, such as GABA, glycine, and glutamate receptors, are activated by neurotransmitter binding and mediate rapid synaptic transmission, modulating the balance of excitatory and inhibitory inputs in neural networks. During brain development, ion channels fulfill more than their classical roles in membrane excitability. They actively shape key neurodevelopmental processes such as neural progenitor proliferation, neuronal migration, axon guidance, dendrite formation, synaptogenesis, and circuit pruning. The spatiotemporal precision of ion channel expression and function is thus crucial for normal brain maturation. Disruption—whether by pathogenic mutations, dysregulated expression, or impaired subunit assembly—can derail these processes, leading to maladaptive circuit formation, a common feature of many NDDs. Below, we provide an in-depth analysis of major ion channel families implicated in NDDs, beginning with voltage-gated channels and followed by ligand-gated channels, transient receptor potential channels, chloride channels, proton channels, and mechanosensitive ion channels (Table 1, Ref. [7–48]).

2.1 Voltage-Gated Channels

Voltage-Gated Sodium Channels (Na_V): Voltage-gated sodium channels initiate and propagate action potentials, with $Na_V1.2$ (encoded by SCN2A) playing a particularly critical role during early cortical development. SCN2A mutations have been strongly linked to ASD and epilepsy. Recent studies elucidate how SCN2A interacts with ANK2 (ankyrin-B), which anchors $Na_V1.2$ to dendritic membranes. Disruption of this interaction impairs dendritic excitability and synaptic plasticity, supporting a convergent mechanism in ASD pathophysiology [7]. Novel gating pore currents (I_gp) arising from S4-segment mutations in SCN2A variants introduce aberrant inward leak currents at resting membrane potentials, leading to cortical hyperexcitability—a newly recognized mechanism linking SCN2A dysfunction to ASD phenotypes [8]. A multicenter study of 69 SCN2A variants found that GoF mutations commonly present as early-onset epileptic encephalopathy, while LoF mutations are associated with ASD or later-onset seizures, highlighting the importance of functional classification for therapeutic precision [9]. Importantly, SCN2A exhibits developmentally regulated isoform switching, transitioning from fetal $Na_V1.2$ to adult $Na_V1.6$. Some pathogenic variants show isoform-specific effects, altering region-specific expression and drug responsiveness [10].

Voltage-Gated Potassium Channels (K_V): K_V channels shape action potential repolarization and modulate firing frequency. Among them, the K_V7 (KCNQ) family is a paradigmatic example where both LoF and GoF variants cause distinct neurodevelopmental outcomes. $K_V7.2$ and $K_V7.3$ subunits form the neuronal M-current that stabilizes subthreshold excitability. LoF in KCNQ2 or KCNQ3 reduces current density or shifts activation, leading to early-

Table 1. Ion Channels in NDDs.

Ion Channel	Subtypes	Functions	NDDs	Mechanisms	Ref
Voltage-Gated Sodium Channels	SCN2A, SCN1A	AP initiation; dendritic excitability	ASD, epilepsy, DEE	GoF/LoF mutations; isoform switching; gating pore currents	[7–10]
Voltage-Gated Potassium Channels	KCNQ2, KCNQ3, KCNQ5, KCND2, KCNH5, KCNA6, KCNB1	AP repolarization; firing control	ASD, epilepsy, ID, DEE	Altered gating, persistent excitability, gating pore currents	[11–14]
Voltage-Gated Calcium Channels	CACNA1C, CACNA1D, CACNA1G, CACNB1	Synaptic transmission; gene expression; plasticity	ASD, Timothy syndrome, ID, schizophrenia	Delayed inactivation, beta-subunit dysregulation, multisystem effects	[15–19]
GABA & Glycine Receptors	$GABA_A$ (ARHGEF9, GPHN), $GABA_B$	Inhibitory signaling; polarity switch; synaptogenesis	Epilepsy, ASD, ID	Scaffold protein mutations (collybistin, gephyrin), GABA polarity shift failure	[20–24]
Glutamate Receptors	GRIA3, GRIN2B, GRM7, GluD2	Excitatory transmission; pruning; adhesion signaling	ASD, ID, ADHD	GoF/LoF variants, CNVs affecting adhesion, impaired trafficking	[25–29]
Nicotinic Acetylcholine Receptors	$\alpha7$, $\alpha4\beta2$ nAChRs	Circuit assembly; interneuron maturation; neuroimmune modulation	ASD, epilepsy, schizophrenia	Disrupted lipid interaction, interneuron deletion, anti-inflammatory roles	[30–34]
TRP Channels	TRPM3, TRPV4, TRPC6	Calcium signaling; dendritic spine formation; synaptic plasticity	DEE, ASD, ID	GoF variants, inflammatory upregulation, BDNF signaling dysregulation	[35–38]
Chloride Channels	ClC-3 (CLCN3), VRACs (LRRC8), ASOR (TMEM206)	Vesicular trafficking; osmotic balance; progenitor migration	ID, epilepsy, GDD	Organellar acidification, glutamate release, acidotoxicity	[39–42]
Proton Channels	ASIC1a, HV1 (HVCN1)	pH regulation; microglial ROS response; plasticity	ASD, epilepsy	ERK signaling via ASIC1a, HV1-mediated ROS control	[43–45]
Mechanosensitive Channels	Piezo1, Piezo2	Mechanotransduction; neurogenesis; gliogenesis	ASD, sensory ataxia	Piezo1-dependent ATP signaling, ultrasound response, vascular integrity	[46–48]

AP, action potential; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; DEE, developmental and epileptic encephalopathy; ID, intellectual disability; GDD, global developmental delay; GoF, gain-of-function; LoF, loss-of-function; CNV, copy number variation; ROS, reactive oxygen species; SCN1A/SCN2A, sodium voltage-gated channel alpha subunits 1/2; KCNQ2/3/5, potassium voltage-gated channel subfamily Q members 2/3/5; KCND2, potassium voltage-gated channel subfamily D member 2; KCNH5, potassium voltage-gated channel subfamily H member 5; KCNA6, potassium voltage-gated channel subfamily A member 6; KCNB1, potassium voltage-gated channel subfamily B member 1; CACNA1C/D/G, calcium voltage-gated channel alpha1 subunits C/D/G; CACNB1, calcium channel auxiliary beta 1 subunit; $GABA_{A/B}$, γ-aminobutyric acid type A/B receptors; ARHGEF9, Rho guanine nucleotide exchange factor 9 (collybistin); GPHN, gephyrin; GRIA3, glutamate ionotropic AMPA receptor subunit 3; GRIN2B, glutamate ionotropic NMDA receptor subunit 2B; GRM7, metabotropic glutamate receptor 7; GluD2, glutamate receptor delta-2; nAChRs, nicotinic acetylcholine receptors ($\alpha7$, $\alpha4\beta2$); TRPM3, transient receptor potential melastatin 3; TRPV4, transient receptor potential vanilloid 4; TRPC6, transient receptor potential canonical 6; CLCN3 (ClC-3), chloride voltage-gated channel 3; VRACs, volume-regulated anion channels (LRRC8); ASOR, acid-sensitive outwardly rectifying anion channel (TMEM206); ASIC1a, acid-sensing ion channel 1a; HVCN1 (HV1), voltage-gated proton channel 1; Piezo1/2, mechanosensitive piezo channels 1 and 2; BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase.

onset DEEs. In contrast, recent work has identified GoF pore variants in KCNQ5 that increase opening probability, also resulting in DEE through abnormal network resonance and impaired spike-timing precision [49]. These findings suggest a unifying structure–function relationship: S4/S6 and pore-domain mutations primarily alter voltage sensing or open probability, while C-terminal calmodulin- and PIP_2-interacting domains affect stability, trafficking, and lipid-dependent gating [50]. Beyond K_V7, the KCNB1 ($K_V2.1$) channel has recently emerged as a dual-function molecule that integrates excitability with adhesion signaling. KCNB1 not only contributes to delayed rectifier currents in pyramidal neurons but also forms macromolecular complexes with $\beta1$ integrins. These integrin–KCNB1 complexes regulate cytoskeletal dynamics, neuronal migration, and cortical lamination, thereby linking ion flux with extracellular matrix cues [51]. Pathogenic KCNB1 variants can therefore produce combined conduction defects and disrupted integrin-mediated signaling, offering a mechanistic explanation for their association with DEEs and intellectual disability. Recent perspectives highlight that epileptic encephalopathy in KCNB1 channelopathies may arise not solely from altered repolarization but also from impaired integrin-dependent developmental programs, underscoring the broader role of ion channels as structural organizers in the developing cortex [52]. Mutations in KCNQ2, KCND2, KCNH5, and KCNA6 have been implicated in NDDs, including epilepsy, ASD, and intellectual disability. Variants in KCND2 ($K_V4.2$) are associated with ASD severity, possibly by altering dendritic integration of synaptic inputs [11]. KCNH5 mutations exhibit phenotypic variability, from benign familial seizures to severe encephalopathy, depending on mutation localization [12]. Rescue of function in patient-derived cells using acetazolamide supports a precision pharmacology approach [13]. Similarly, KCNA6 mutations disrupt channel deactivation, leading to persistent neuronal excitability and early-onset epilepsy [14]. Gating pore currents, long considered a hallmark of sodium channels, have now been observed in KCNQ2-related ASD mutations, reinforcing the cross-subtype relevance of aberrant ionic leak currents across VGIC families.

Voltage-Gated Calcium Channels (VGCCs): VGCCs mediate calcium influx required for neurotransmitter release, gene transcription, and synaptic plasticity. Mutations in CACNA1C ($Ca_V1.2$), CACNA1D ($Ca_V1.3$), and CACNA1G ($Ca_V3.1$) have been associated with a spectrum of NDDs. The p.A36V CACNA1C variant prolongs channel opening, leading to dysregulated Ca^{2+} signaling in ASD and schizophrenia [15]. Similarly, CACNA1D mutations (e.g., L271H) modeled in iPSCs recapitulate comorbid hyperinsulinemic hypoglycemia and ASD phenotypes [16]. Timothy syndrome (TS1), a multisystem disorder caused by CACNA1C mutations, exemplifies how L-type channel dysfunction can result in cardiac and neurodevelopmental phenotypes [17]. $Ca_V3.1$ mutations have been linked to cerebellar deficits and cognitive dysfunction [18]. Additionally, auxiliary β-subunit mutations (e.g., CACNB1 p.R296C) can influence multiple VGCC isoforms, adding a regulatory dimension to channelopathy-related NDDs [19]. Voltage-gated channels, through both canonical and non-canonical mechanisms, are essential regulators of neurodevelopmental programs. Functional dissection of disease-associated variants enables mechanistic understanding and informs tailored therapeutic strategies.

2.2 Ligand-Gated Ion Channels (LGICs)

LGICs mediate rapid synaptic transmission by opening in response to neurotransmitter binding, allowing selective ion flux across the postsynaptic membrane. These channels are essential for establishing and modulating excitatory-inhibitory (E/I) balance in developing neural circuits. Beyond their role in fast neurotransmission, LGICs orchestrate key neurodevelopmental events, including synaptogenesis, neuronal migration, and activity-dependent pruning. Dysregulation of LGICs—via genetic mutations, altered expression, or impaired synaptic localization—has been increasingly implicated in NDDs such as epilepsy, ASD, ID, and ADHD.

GABA and Glycine Receptors: GABA and glycine receptors, primarily permeable to chloride ions (Cl^-), are the principal mediators of inhibitory neurotransmission in the central nervous system. Notably, in early postnatal life, GABAergic transmission is depolarizing due to high intracellular Cl^- concentrations. The developmental upregulation of the potassium-chloride cotransporter KCC2 reverses this polarity, transitioning GABA signaling from excitatory to inhibitory—a crucial step in the maturation of cortical circuits.

Disruption of this developmental switch has been linked to multiple NDDs. Mutations in ARHGEF9, which encodes collybistin—a key scaffold for clustering $GABA_A$ and glycine receptors—impair inhibitory synapse formation. Variants such as p.I294T and p.R357I reduce synaptic density and result in epilepsy and developmental delays [20]. Similarly, biallelic mutations in GPHN, encoding gephyrin, compromise $GABA_A$ receptor anchoring and diminish inhibitory currents, causing early-onset encephalopathy [21].

Beyond $GABA_A$, $GABA_B$ receptor dysfunction also contributes to ASD. For example, abnormal visual contrast suppression in ASD—a proxy for impaired $GABA_B$ signaling—was normalized with arbaclofen, highlighting potential therapeutic applications [22]. Rodent studies further implicate $\alpha4\beta\delta$-containing $GABA_A$ receptors in cognitive deficits. Targeted modulation in the prelimbic cortex disrupts synaptic pruning and impairs temporal memory, mimicking features of ASD and schizophrenia [53]. In addition, structurally related non-canonical LGICs such as GluD receptors (e.g., GluD2) act as synaptic scaffolds rather than ion channels. Loss of GluD2 perturbs inhibitory

synaptic architecture without altering ion flux, emphasizing emerging roles for non-conducting LGIC homologs in circuit maturation [24].

Glutamate Receptors: Drivers of Excitatory Transmission and Plasticity: Ionotropic glutamate receptors (iGluRs), comprising AMPA, NMDA, and kainate receptors, mediate fast excitatory neurotransmission and underpin synaptic plasticity. Their developmental regulation and subunit composition are tightly linked to cognitive and behavioral outcomes. AMPA receptors (AMPARs), composed of GRIA1–4 subunits, exhibit functional heterogeneity in NDDs. A recent analysis revealed that >70% of GRIA3 variants manifest as gain-of-function mutations, leading to early-onset seizures and hypertonia, whereas loss-of-function mutations are associated with hypotonia and developmental delay, establishing a clear functional-genotype-phenotype correlation [25]. NMDA receptors (NMDARs), assembled from GRIN1, GRIN2, and GRIN3 subunits, are essential for calcium-mediated synaptic plasticity. NMDA receptor dysfunction is also critically implicated in schizophrenia. Converging evidence indicates that NMDA receptor hypofunction, particularly on GABAergic interneurons, disrupts cortical oscillations and impairs plasticity, producing the cognitive and behavioral phenotypes characteristic of schizophrenia [54]. The glycine modulatory site of the NMDA receptor has been a focus of translational work: co-agonists such as D-serine and glycine, or glycine transporter inhibitors, can partially restore receptor activity and have shown benefit in subsets of patients [55]. Recent studies also link persistent NMDA receptor dysfunction to treatment-resistant schizophrenia, highlighting receptor-level abnormalities as a mechanistic bottleneck for current therapies [56]. From a developmental perspective, schizophrenia is increasingly conceptualized as a disorder of early circuit vulnerability with symptom manifestation in adolescence or early adulthood. This view is supported by long-standing work proposing a neurodevelopmental hypothesis [57], further refined by contemporary perspectives framing schizophrenia as a developmental disorder with risk of non-specific but potentially avoidable decline [58]. Together, these findings position NMDA receptor signaling as a unifying mechanism linking classical neurodevelopmental disorders with psychiatric conditions that share a developmental origin. In iPSC-derived neurons from ASD patients, DSCAM deletion reduced NMDAR surface trafficking, impairing function. This phenotype was rescued by re-expression of wild-type DSCAM, demonstrating a synapse-specific pathogenic mechanism linking adhesion and glutamate receptor biology [26]. Metabotropic glutamate receptors (mGluRs), such as GRM7, modulate presynaptic neurotransmitter release. Biallelic GRM7 mutations result in developmental delay and disrupted axon extension [27]. Furthermore, copy number variants (CNVs) affecting mGluR-interacting genes—e.g., CNTN4, 22q11.2 locus—have been associated with ASD and ADHD [28], suggesting a convergence between glutamatergic signaling and synaptic adhesion.

Emerging studies also implicate adhesion G protein-coupled receptors (GPCRs) in excitatory modulation. For example, ADGRL1 (Latrophilin-1) haploinsufficiency in mice impairs glutamate release and calcium signaling, recapitulating ASD-like behaviors [29]. These data highlight novel regulatory axes linking adhesion, excitability, and neurodevelopmental pathology.

Nicotinic Acetylcholine Receptors (nAChRs): nAChRs are cation-permeable LGICs widely expressed during early brain development, particularly in hippocampal and cortical neurons. They contribute to neurogenesis, circuit assembly, and neurotransmitter release. Alterations in nAChR-cholesterol interactions, particularly under disrupted lipid metabolism observed in ASD, impair receptor conformation and function, compromising cholinergic signaling in cerebellar and cortical networks [30]. The $\alpha 7$ nAChR subtype, enriched in GABAergic interneurons, is critical for neuroprogenitor differentiation. Conditional deletion in mice leads to sex-specific deficits in social behavior and spatial learning [31]. In ASD models, dysfunctional $\alpha 4\beta 2$ nAChRs on dopaminergic axons impair striatal dopamine release, contributing to behavioral rigidity [59]. Additionally, $\alpha 7$ nAChRs expressed on microglia and astrocytes exert anti-inflammatory effects, linking cholinergic signaling to neuroimmune modulation in disorders such as epilepsy and schizophrenia [33]. Therapeutically, α-conotoxins—peptide inhibitors selective for specific nAChR subtypes—have emerged as powerful tools to dissect receptor function and develop targeted interventions [34]. The dysfunction of LGICs—whether through impaired gating, subunit misassembly, altered trafficking, or scaffold destabilization—plays a central role in the synaptic and circuit-level abnormalities underlying NDDs. Importantly, LGICs are not only passive conductors but also active regulators of neurodevelopmental trajectories. Their accessibility to pharmacological modulation and synapse-specific localization make them attractive candidates for precision therapeutic strategies.

2.3 Transient Receptor Potential (TRP) Channels

TRP channels constitute a large and evolutionarily conserved family of non-selective cation channels that are activated by a broad array of stimuli, including thermal, osmotic, mechanical, and chemical signals. These polymodal sensors are grouped into six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), and TRPP (polycystin) [60]. In the developing nervous system, TRP channels are broadly expressed in neurons, glia, and progenitor cells, where they participate in calcium signaling, cytoskeletal remodeling, synaptogenesis, and axon guidance. Dysregulation of TRP channel expression or function has been increasingly linked to the pathogenesis of NDDs, particularly DEEs, ASD, and ID.

TRPM3: Among the TRPM subfamily, TRPM3 has emerged as a well-characterized contributor to early-onset NDDs. TRPM3 encodes a calcium-permeable channel expressed in the brain and dorsal root ganglia. Pathogenic GoF variants—such as p.Val1002Met and p.Val837Met—have been identified in individuals with DEE, manifesting as early-onset seizures, axial hypotonia, global developmental delay, dysmorphic features, and cortical malformations [35,36]. A large multicenter cohort study of 43 individuals with TRPM3 mutations confirmed epilepsy in 72% of cases, frequently with spike-wave activation during sleep (DEE-SWAS). Functional studies revealed enhanced basal and heat-evoked TRPM3 currents in mutant channels, resulting in excessive calcium influx and neuronal hyperexcitability [37]. Notably, treatment with primidone—an approved TRPM3 antagonist—attenuated seizure burden and improved neurocognitive outcomes, supporting the translational relevance of TRPM3-targeted therapies. In addition, emerging variants such as p.S1202T have been associated with polymorphic seizures and intermediate phenotypes, further expanding the clinical and molecular spectrum of TRPM3-associated channelopathies [36].

TRPV4: TRPV4, a member of the vanilloid subfamily, functions as a calcium-permeable mechanosensor and osmotic stress responder. Recent studies implicate TRPV4 in neurodevelopmental vulnerability under inflammatory conditions. In a Shank3$^{+/-}$ mouse model—a validated ASD genetic model—neonatal immune activation via lipopolysaccharide exposure triggered social behavior deficits and nucleus accumbens circuit dysfunction. These phenotypes were accompanied by upregulation of TRPV4 in D1 receptor–expressing medium spiny neurons and were rescued by pharmacological TRPV4 inhibition [38]. This study illustrates a gene–environment interaction model in which TRPV4 acts as a molecular integrator of genetic susceptibility and inflammatory stress, contributing to synaptic instability and behavioral phenotypes relevant to ASD.

TRPC6: TRPC6 is a canonical TRP channel activated by diacylglycerol and neurotrophin signaling, enriched in developing hippocampal neurons. It plays a critical role in calcium-dependent cytoskeletal remodeling, dendritic spine development, and synaptic plasticity. In Trpc6-deficient mice, hippocampal neurons exhibit reduced dendritic spine density and impaired long-term potentiation, accompanied by ASD-like behaviors, including reduced social interaction and increased repetitive behavior. These phenotypes implicate TRPC6 in shaping synaptic architecture critical for behavioral outcomes. Human genetic data implicate TRPC6 in neurodevelopment, most robustly in ASD. De novo disruption and rare coding variants in TRPC6 have been reported in ASD cohorts [61], and patient-derived neurons show synaptic and dendritic spine deficits consistent with altered channel function and trafficking. In line with a plausible mechanism, human TRPC6 missense mutations alter channel conductance and downstream signaling, and post-translational modifications (e.g., N-glycosylation) regulate membrane trafficking [62,63]. For developmental delay and epilepsy, evidence is presently limited to isolated reports and to locus-level signals at 11q22—the chromosomal interval that encompasses TRPC6—so causal assignment to TRPC6 remains unresolved [64–67]. Large-scale genome-wide association studies (GWAS) also report common-variant signals for psychiatric and cognitive-language phenotypes within the 11q22 region near TRPC6 (e.g., ADHD linkage; schizophrenia association; ASD speech-delay ROH); however, effect sizes are modest and fine-mapping is required to pinpoint the responsible genes [68]. Taken together, the convergence of rare-variant evidence in ASD with locus-level GWAS signals supports the translational relevance of TRPC6, while underscoring the need for gene-specific validation across broader neurodevelopmental phenotypes. Mechanistically, TRPC6 likely acts via downstream Rho GTPase signaling, linking extracellular cues (e.g., BDNF, integrins) to intracellular cytoskeletal dynamics and synaptic maturation.

TRP channels are increasingly recognized as central mediators of neurodevelopmental signaling. TRPM3 represents a prime example of pathogenic gain-of-function channelopathy with defined therapeutic targets. TRPV4 exemplifies environmentally modulated channel dysfunction, highlighting its relevance in inflammation-associated ASD. TRPC6 integrates neurotrophin and adhesion signaling to regulate synaptic formation. Together, these channels expand the mechanistic and therapeutic landscape of ion channel dysfunction in NDDs, serving as both biomarkers and druggable targets in precision neurology.

2.4 Chloride Channels and Volume-Regulated Anion Channels

While chloride channels have been classically associated with inhibitory neurotransmission via GABA and glycine receptors, an expanding body of evidence highlights their broader roles in neurodevelopmental processes. These include the regulation of intracellular chloride concentration, vesicular acidification, cell volume homeostasis, and glial function. Non-synaptic chloride fluxes—mediated by chloride channel (CLC) family members and volume-regulated anion channels (VRACs)—are increasingly recognized as critical regulators of neural development, and their dysfunction has been implicated in a spectrum of NDDs including ID, global developmental delay (GDD), and epilepsy.

ClC-3 (CLCN3): CLCN3 encodes ClC-3, a Cl^-/H^+ antiporter predominantly localized to endosomal and lysosomal membranes. It plays a vital role in organellar acidification, vesicular trafficking, and maintenance of neuronal and glial architecture. Pathogenic variants in CLCN3 disrupt these functions, leading to altered neuronal signaling and structural brain anomalies. A recent multicenter study

identified nine disease-associated CLCN3 variants (both homozygous and heterozygous) in individuals presenting with a syndromic constellation of GDD, behavioral abnormalities, seizures, and midline brain malformations such as corpus callosum agenesis and pontine hypoplasia [39]. Electrophysiological characterization revealed both gain and loss-of-function effects. For example, the p.Ile607Thr variant exhibited increased current amplitude and reduced sensitivity to acidic luminal pH, implicating disrupted organelle homeostasis in disease pathogenesis. These findings underscore the dual pathogenic potential of CLCN3 mutations—either via excessive acidification or impaired vesicular function—both of which may contribute to neurodevelopmental impairments and aberrant synaptic maturation.

VRACs (LRRC8 Complex): VRACs, also referred to as volume-sensitive outwardly rectifying (VSOR) channels, are key effectors of regulatory volume decrease (RVD) in response to osmotic swelling. VRACs are heteromeric assemblies of LRRC8A and auxiliary subunits (LRRC8B–E), with subunit composition determining ion and solute permeability. In the developing brain, VRACs are expressed in both neural progenitors and glial cells, where they facilitate cell migration, proliferation, and extracellular matrix remodeling. Dysregulated VRAC activity has been implicated in pathologic glutamate and aspartate release under hypoxic-ischemic conditions, contributing to white matter injury in neonates and subsequent neurodevelopmental sequelae [40,41]. Recent structural and functional analyses have delineated critical domains within LRRC8 subunits responsible for gating and solute selectivity. Mutational disruptions in these regions compromise channel function and alter cellular responses to osmotic and metabolic stress, rendering the developing brain particularly vulnerable to excitotoxic injury.

ASOR/TMEM206: The acid-sensitive outwardly rectifying (ASOR) anion channel, formed by homotrimeric TMEM206 subunits, is activated by extracellular acidification. TMEM206 localizes to both plasma and endosomal membranes and becomes active under pathophysiological conditions such as ischemia, trauma, and inflammation [40]. In the immature brain, activation of ASOR leads to Cl^- influx, cellular swelling, and necrotic cell death—especially in regions exposed to hypoxia-induced acidosis. While ASOR activity is physiologically involved in endosomal maturation and macropinosome shrinkage, its dysregulation has been implicated in hypoxia-related neonatal brain injury, suggesting a role in modulating neurodevelopmental susceptibility to inflammatory and metabolic insults.

Advances in *in silico* screening and structural modeling have identified promising small-molecule modulators targeting chloride channels. For instance, virtual screening of LRRC8A revealed several high-affinity compounds, such as ZINC000018195627, with predicted efficacy in modulating VRAC function [42]. These pharmacological candidates hold potential for neuroprotection in settings of excitotoxic or osmotic stress. However, therapeutic targeting of chloride channels remains complex. Given their bidirectional roles in development and injury, channel modulation must account for developmental timing, cell-type specificity, and disease context. For example, inhibiting VRACs may be protective in ischemic injury but detrimental during progenitor migration or synaptogenesis.

Chloride channels such as ClC-3, VRACs, and ASOR extend far beyond synaptic inhibition, functioning as essential regulators of vesicular trafficking, volume control, and ionic balance during neurodevelopment. Their dysregulation contributes to a wide range of neurodevelopmental phenotypes, including structural brain defects, excitotoxic injury, and metabolic vulnerability. Future therapeutic strategies will require precise modulation of these channels, informed by patient-specific genetics, electrophysiological profiling, and developmental stage.

2.5 Proton and Other Specialized Ion Channels

Proton-permeable ion channels, though historically understudied compared to voltage- and ligand-gated channels, are now emerging as important regulators of neurodevelopmental physiology. Among these, acid-sensing ion channels (ASICs) and voltage-gated proton channels (HV1) contribute to cellular pH homeostasis, ion signaling, and neuroimmune interactions. Their dynamic regulation during early development and in response to injury or inflammation suggests that they may serve as critical modulators—and potential biomarkers—of neurodevelopmental disorder (NDD) risk.

ASIC1a: ASICs are voltage-insensitive, proton-gated cation channels primarily permeable to Na^+ and, to a lesser extent, Ca^{2+}. ASIC1a, the most widely expressed neuronal isoform, is activated by extracellular acidosis, as occurs in ischemia, inflammation, or metabolic stress. During development, transient changes in extracellular pH are common in regions of high metabolic activity or synaptic remodeling, positioning ASIC1a as a sensitive modulator of excitability and plasticity. Recent studies have expanded our understanding of ASIC1a's functional diversity. In addition to canonical activation by protons, ASIC1a can be modulated by non-proton ligands, such as tarantula toxin-derived peptides, which induce sustained ERK pathway activation. This prolonged intracellular signaling, distinct from transient proton-induced activity, may play a role in synaptic remodeling and memory formation [44]. Given ERK's essential role in neuroplasticity and cognition, aberrant ASIC1a signaling may contribute to maladaptive circuit changes in NDDs. Furthermore, ASIC1a-mediated Ca^{2+} entry has been linked to excitotoxic cell death in immature neurons under hypoxic conditions, suggesting a dual role in both normal circuit development and pathogenesis depending on activation context.

HV1 (HVCN1): The voltage-gated proton channel HV1 (encoded by HVCN1) is uniquely expressed in immune cells, including microglia and macrophages. It mediates proton extrusion during respiratory burst activation, contributing to intracellular pH regulation and the generation of reactive oxygen species (ROS). In the developing brain, microglial activation is a tightly regulated process necessary for synaptic pruning and immune surveillance. However, excessive or persistent activation is implicated in NDDs such as ASD and epilepsy. HV1 has been shown to regulate the inflammatory profile of microglia and macrophages in a pH- and ROS-dependent manner. Inhibition of HV1 impairs intracellular pH homeostasis and triggers ceramide-mediated apoptosis, particularly in pro-inflammatory M1-polarized macrophages [43]. These findings suggest HV1 plays a role in balancing microglial activation states during critical periods of brain maturation. Dysregulation could contribute to a pro-inflammatory environment, with downstream consequences for synapse integrity and neurodevelopmental outcomes. Additionally, recent structure-guided virtual screening has identified small-molecule inhibitors of HV1 with selective binding and anti-inflammatory properties. Several of these compounds also show anti-proliferative activity in cancer cells, highlighting HV1's broader pathophysiological relevance [45]. However, systemic inhibition of HV1 during early development could disrupt immune–neural homeostasis and warrants careful consideration.

Proton-permeable channels such as ASIC1a and HV1 are emerging as integral components of the neurodevelopmental landscape. ASIC1a modulates activity-dependent plasticity and is implicated in acidosis-related neurotoxicity, while HV1 governs neuroimmune tone through proton-dependent regulation of microglial activation. The precise spatiotemporal control of these specialized channels is essential for maintaining neurodevelopmental homeostasis, and their dysregulation may underlie or exacerbate NDD pathogenesis. Future studies combining structural biology, electrophysiology, and developmental neuroimmunology will be pivotal for unlocking their therapeutic potential.

2.6 Mechanosensitive Channels (Piezo1/2)

Mechanosensitive ion channels (MSCs) serve as fundamental biological transducers, converting mechanical stimuli—such as pressure, stretch, and shear stress—into electrochemical signals. Among these, Piezo1 and Piezo2 are large, non-selective cation channels that respond to membrane tension and mechanical deformation with rapid activation and inactivation kinetics. While Piezo2 is predominantly expressed in peripheral sensory neurons and mediates tactile and proprioceptive signaling, Piezo1 is more broadly distributed in neural progenitor cells, astrocytes, and the cerebral vasculature, implicating it in central nervous system (CNS) development. Recent evidence suggests that Piezo channels not only mediate mechanosensation but also influence diverse aspects of brain development, including neurogenesis, neural stem cell maintenance, gliogenesis, and neurovascular integrity. Their dysregulation may contribute to NDDs via disrupted mechanotransduction and impaired structural maturation of brain tissue.

Piezo1: Piezo1 is expressed in neural progenitor cells and astrocytes, where it mediates mechanosensitive Ca^{2+} influx in response to extracellular force or volumetric changes. In astrocytes, Piezo1 activation induces ATP release and calcium signaling that, in turn, modulate the behavior of neighboring neural stem cells (NSCs). Conditional deletion of Piezo1 in astrocytes leads to impaired hippocampal neurogenesis, reduced NSC proliferation, and spatial memory deficits. These deficits can be rescued by exogenous ATP administration, highlighting a critical astrocyte–NSC communication axis mediated by Piezo1-dependent mechanotransduction [46]. Moreover, Piezo1 has been implicated in regulating neurovascular development and blood-brain barrier stability. In pathological states, Piezo1 activation by aberrant mechanical stress may contribute to vascular remodeling or degeneration, linking mechanosensitive signaling to cerebrovascular components of neurodevelopmental disease [32]. Recent studies suggest Piezo1 may also mediate neural responses to ultrasonic stimulation—a technique increasingly investigated for non-invasive neuromodulation. In rodent cortical neurons, focused ultrasound elicits Piezo1-dependent calcium influx, which in turn recruits voltage-gated calcium channels to amplify intracellular signaling. These findings support a model in which Piezo1 acts as a primary mechanosensor in ultrasonic neuromodulation paradigms [48]. Such interactions may have translational implications for modulating neural activity in NDDs or treatment-resistant epilepsy.

Piezo2: Although primarily studied in peripheral mechanosensation, Piezo2 is increasingly recognized for its roles in CNS development. Piezo2 is expressed in a subset of dorsal root ganglion (DRG) neurons and spinal cord interneurons, where it contributes to proprioceptive input integration and motor coordination. Disruptions in Piezo2 function result in sensory ataxia and impaired motor development, and emerging data suggest Piezo2-mediated pathways may modulate brain–body feedback loops relevant to neurodevelopmental phenotypes.

Piezo1 and Piezo2 channels are key integrators of mechanical cues in neural tissues, regulating stem cell dynamics, astrocyte-neuron signaling, and sensorimotor circuit formation. Their mechanotransductive functions bridge the physical environment with intracellular developmental programs, positioning them as important contributors to the etiology and potential modulation of neurodevelopmental disorders. Ongoing studies into Piezo channel pharmacology and biophysical regulation may yield novel mechanotherapeutic strategies targeting CNS structural and functional maturation.

Table 2. Spatiotemporal roles of ion channels in neurodevelopment.

Stage	Process	Channel	Cell	Mechanism	Roles	Ref
Early neurogenesis	NPC calcium oscillations	CACNA1C ($Ca_V1.2$)	NPCs, cortex	Non-synaptic Ca^{2+} oscillations	Differentiation; ASD/TS	[49]
Migration	Neurovascular signaling	Endothelial NMDAR	Vasculature; interneurons	tPA–MMP-9 ECM remodeling	Interneuron migration	[54]
Synaptogenesis	Acid-sensing at growth cones	ASIC1a/2a	Growth cones	Acid response Ca^{2+} influx	Guidance; synaptic stabilization	[57]
Synaptic maturation	Hebbian plasticity	NMDAR	Hippocampus; PFC	Ca^{2+}-dependent LTP/LTD	Spatial memory	[59]
Region-specific	ASD trio WGS	SCN2A; GRIN2B	Cortex, hippocampus	Coding variants correlate with regional enrichment	Language delay; ASD	[67]
Regulation	Epigenetic control	TRPA1	Neurons/glia	Promoter methylation; histone acetylation; ncRNAs	Expression modulation	[69]

NPCs, neural progenitor cells; CaV1.2, L-type voltage-gated calcium channel alpha-1C; NMDAR, N-methyl-D-aspartate receptor; tPA, tissue plasminogen activator; MMP-9, matrix metalloproteinase-9; ECM, extracellular matrix; ASIC2a, acid-sensing ion channel 2a; LTP, long-term potentiation; LTD, long-term depression; PFC, prefrontal cortex; WGS, whole-genome sequencing; ncRNAs, non-coding RNAs; TRPA1, transient receptor potential ankyrin 1; TS, Timothy syndrome.

3. Spatiotemporal Roles of Ion Channels in Neurodevelopment

The development of the CNS is orchestrated through highly regulated spatial and temporal patterns of gene expression, electrical activity, and cell–cell communication. Ion channels, as central modulators of membrane potential, intracellular calcium dynamics, and neurotransmission, play indispensable roles across all stages of brain maturation. Their expression is dynamically regulated through transcriptional, post-transcriptional, and epigenetic mechanisms, allowing for precise control of function in region- and cell type–specific contexts. This section synthesizes evidence across key developmental stages—from early neurogenesis to postnatal circuit refinement—highlighting how ion channels act as both effectors and regulators of neurodevelopmental milestones, and how their dysregulation contributes to NDDs (Table 2, Ref. [49,54,57,59,67,69]).

3.1 Early Neurogenesis and Neuronal Differentiation

During embryonic brain development, neural progenitor cells (NPCs) undergo tightly controlled proliferation, fate specification, migration, and differentiation. Increasing evidence demonstrates that ion channels contribute to these early processes not solely through electrical activity, but also via non-conductive roles that regulate intracellular signaling, gene expression, and progenitor dynamics.

L-type calcium channels—particularly $Ca_V1.2$ (encoded by CACNA1C)—are among the earliest ion channels expressed during cortical neurogenesis. They mediate spontaneous, non-synaptic calcium oscillations in NPCs, which activate transcription factors such as cAMP Response Element-Binding protein (CREB) and NeuroD1, essential for neuronal survival and differentiation [70]. Splice variants of $Ca_V1.2$ are developmentally regulated, suggesting isoform-specific functions distinct from their later synaptic roles. Mutations in CACNA1C underlie syndromes such as Timothy syndrome and are implicated in ASD, reinforcing the channel's significance during early neuronal specification.

Beyond calcium entry, multiple voltage-gated potassium channels help set the resting membrane potential and shape repolarization kinetics of NPCs. These intrinsic properties gate Ca^{2+} influx and, by extension, regulate the timing of cell cycle exit and lineage commitment. For example, delayed rectifier and A-type K^+ currents influence neurogenic transitions, with sustained depolarization favoring differentiation over self-renewal. In parallel, early expression of sodium channels ($Na_V1.2$, $Na_V1.3$) and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels can generate spontaneous depolarizations that entrain Ca^{2+} oscillations, coupling electrical excitability to morphogenetic programs [71].

Early NPCs express high levels of NKCC1 and low levels of KCC2, resulting in elevated intracellular Cl^-. Consequently, activation of $GABA_A$ and glycine receptors produces depolarizing currents that open VGCCs and initiate Ca^{2+}-dependent transcriptional programs [69]. This excitatory action promotes proliferation, migration, and neuritogenesis and is a critical component of early cortical patterning.

Importantly, the timing of the developmental chloride switch (NKCC1 downregulation/KCC2 upregulation) is tightly coordinated with critical periods of neuronal migration and synaptogenesis. Disruption of this switch can prolong depolarizing GABA action, leading to aberrant network wiring and heightened vulnerability to seizures later in life. This underscores that ion channel regulation is not only a transient physiological state but also a determinant of long-term circuit stability [71].

Taurine, an amino acid of maternal origin, exerts developmental effects by modulating chloride homeostasis and GABAergic signaling. It tonically activates $GABA_A$

and glycine receptors and regulates NKCC1/KCC2 expression via the WNK1–SPAK/OSR1 pathway [69]. In radial glia, taurine functions as a migratory stop signal and contributes to laminar organization—highlighting the significance of maternal nutrient supply in neurodevelopment.

Diazepam binding inhibitor (DBI), a glial-expressed endogenous modulator of GABAA receptors, fine-tunes the excitatory effects of GABA during early development. DBI downregulates γ2-containing $GABA_A$ receptor activity, thereby adjusting the excitatory/inhibitory balance in NPCs. Disruption of DBI expression alters cortical excitability and impairs neuronal subtype allocation [72,73].

Embryonic stem cell (ESC)-derived glutamatergic neurons recapitulate key phases of early neurogenesis and have proven instrumental for dissecting ion channel function in development. These models reveal that ion channels regulate transcriptional programming, morphogenesis, and neuronal identity—providing a powerful platform for studying channelopathies and screening targeted interventions [74].

In summary, prenatal neurodevelopment depends on a finely tuned choreography of ion channel activity that integrates proliferative cues, migratory programs, and circuit assembly. Both conductive and non-conductive channel functions contribute to lineage specification, transcriptional control, and microenvironmental responsiveness in early neural development. Dysregulation at this vulnerable stage may constitute a convergent pathway underlying diverse neurodevelopmental phenotypes, as highlighted by recent integrative perspectives.

3.2 Neuronal Migration and Cortical Layering

Proper neuronal positioning is critical for cortical circuit formation. Excitatory pyramidal neurons migrate radially from the ventricular zone, while inhibitory interneurons follow tangential migratory routes. Ion channels regulate these processes by modulating membrane excitability, intracellular Ca^{2+} transients, and interactions with guidance cues.

Depolarizing GABA responses—facilitated by high intracellular Cl^- in immature neurons—generate calcium influx that modulates cytoskeletal remodeling essential for nucleokinesis and leading process dynamics. Tonic GABA signaling acts as a positional cue guiding both radial and tangential migration [69]. NMDA receptors expressed on developing endothelial cells respond to ambient glutamate during corticogenesis. Activation of these receptors triggers tPA–MMP-9–mediated extracellular matrix remodeling, facilitating the migration of GABAergic interneurons along vascular scaffolds [75]. This reveals a neurovascular intersection where ion channels guide migration through proteolytic signaling.

TRPC1 and TRPC6 mediate transient calcium signals in migrating neurons. These Ca^{2+} elevations regulate centrosome dynamics, integrin recycling, and actin cytoskeleton organization, thereby fine-tuning migration speed and trajectory. ASIC1a, dynamically localized to leading processes, responds to extracellular pH changes and contributes to polarity and motility through Ca^{2+} influx [76]. Similarly, Piezo channels transduce mechanical cues from the extracellular matrix into intracellular responses, influencing cytoskeletal tension and directional movement.

Microglia interact with migrating neurons, secreting guidance cues and reshaping the extracellular environment. Ion channels in microglia—including TRPs, ASICs, and Cl^- channels—modulate their morphology, motility, and chemokine release, indirectly shaping neuronal migratory paths [77]. In conclusion, ion channels operate as transducers of chemical, mechanical, and electrical signals that regulate neuronal migration. Perturbations in these processes may result in cortical malformations, aberrant layering, and ultimately cognitive and behavioral dysfunction.

3.3 Axonal Pathfinding and Synapse Formation

The formation of functional neural circuits during development hinges on the precise navigation of axons to their targets and the establishment of synaptic connections. Ion channels play pivotal roles in these processes, extending beyond their classical function in action potential generation. They orchestrate localized signaling at growth cones, modulate cytoskeletal dynamics, and regulate the responsiveness of developing axons to guidance cues, thereby directing pathfinding and initiating synaptogenesis.

Na_V, such as $Na_V1.2$ and $Na_V1.6$, are expressed early in developing axons and growth cones. These channels influence local excitability and, through depolarization, promote calcium influx via voltage-gated calcium channels (Ca_V). The resulting calcium transients in filopodia and lamellipodia regulate actin polymerization, adhesion complex turnover, and directional steering in response to attractant or repellent cues. Isoform-specific expression of Ca_V channels enables fine-tuned modulation of intracellular signaling cascades and cytoskeletal remodeling, allowing axons to differentially respond to spatially distributed guidance molecules.

ASICs, particularly ASIC1a and ASIC2a, are enriched at growth cones and presynaptic terminals. These channels respond to transient extracellular acidification—a microenvironmental feature common in actively remodeling brain regions—by permitting Ca^{2+} influx that supports axonal guidance and synaptic stabilization. Immunohistochemical studies reveal their co-localization with presynaptic markers, suggesting a dual role in axonal pathfinding and presynaptic development [78].

Ligand-gated ion channels also contribute to axon guidance and synapse formation. NMDARs, traditionally studied in postsynaptic compartments, are expressed in developing axons, where they influence filopodial dynamics and nitric oxide signaling. Activation of presynaptic NMDARs shapes axonal branching and synapse targeting

through calcium-dependent mechanisms. nAChRs, particularly $\alpha 7$ and $\alpha 4\beta 2$ subtypes, are involved in modulating early excitability, which, in turn, influences axon elongation and responsiveness to guidance cues.

The formation of functional synapses is shaped by early neural activity, which is partly mediated by the opening of ion channels in both pre- and postsynaptic compartments. Ion channel-driven calcium entry activates intracellular pathways that regulate synaptic protein expression and assembly. Notably, post-translational modifications, such as ubiquitination, dynamically regulate the surface expression and degradation of ion channels and synaptic scaffolding proteins. Ubiquitin ligases fine-tune synaptic strength by selectively targeting channels or receptors for endocytosis and proteasomal degradation, thus modulating synaptic specificity and plasticity [79]. The coordinated expression of ion channels ensures that structural development—axon branching, target innervation, and synaptic contact—is coupled with the emergence of functional excitability. For example, interactions between NMDAR activity and the cytoskeletal organizer synaptopodin enable the selective stabilization of mature dendritic spines and pruning of inappropriate contacts during early circuit formation.

In summary, ion channels act as transducers of extracellular signals into intracellular events that regulate growth cone behavior, axon guidance, and synaptic assembly. Their tightly regulated expression and localization confer spatial and temporal precision to these developmental processes. Disruption of these channel-mediated mechanisms can result in miswired neural circuits, contributing to the pathophysiology of neurodevelopmental disorders such as epilepsy, intellectual disability, and autism spectrum disorder.

3.4 Synaptic Maturation and Activity-Dependent Plasticity

Following the initial establishment of synaptic contacts, postnatal brain development is dominated by processes of synaptic refinement and plasticity. These include the stabilization of appropriate synapses, pruning of redundant or maladaptive connections, and the fine-tuning of excitatory and inhibitory balance. Ion channels are central to these processes, mediating both synaptic transmission and the intracellular signaling required for activity-dependent structural remodeling. Their regulation during critical periods is essential for the functional maturation of neural circuits, and their dysregulation contributes to cognitive and behavioral deficits characteristic of NDDs.

Ionotropic glutamate receptors, particularly NMDA and AMPA receptors, are the molecular mediators of classical Hebbian plasticity. NMDARs are calcium-permeable channels activated in a voltage- and ligand-dependent manner, and are crucial for long-term potentiation (LTP), long-term depression (LTD), and spike timing–dependent plasticity. Developmental studies have revealed sex-specific differences in NMDAR-dependent plasticity. In rodent models, juvenile males require NMDAR activation for spatial memory formation and LTP induction, while juvenile females show relative independence from this mechanism, suggesting divergent developmental trajectories in synaptic regulation [80]. AMPARs, particularly those composed of GluA1/GluA2 subunits, undergo dynamic trafficking during postnatal development. Their incorporation into synapses in response to activity strengthens excitatory transmission, whereas their removal underlies LTD. In NG2 glial cells, AMPARs undergo developmental tuning through auxiliary subunits such as TARPs and CNIH-2, altering calcium permeability and shaping neuron–glia interactions that contribute to hippocampal circuit refinement [81].

Beyond ionotropic receptors, group I mGluRs, particularly mGluR1, regulate synaptic structure via intracellular signaling cascades. mGluR1 activation promotes the stabilization of mature dendritic spines by retaining synaptopodin and preserving the spine apparatus, while enabling the pruning of immature spines. This selective stabilization is a mechanism for compartmentalized plasticity that supports both long-term memory storage and developmental circuit refinement [82].

Potassium channels also contribute to synaptic maturation by regulating neuronal excitability and homeostatic plasticity. Two-pore domain K^+ channels, such as TREK-1, influence resting membrane potential and action potential firing thresholds. In the prefrontal cortex, TREK-1 inhibition facilitates LTD, particularly in the context of early-life stress, suggesting that potassium channels integrate environmental experience with circuit remodeling during sensitive developmental periods [83].

A hallmark of synaptic maturation is the shift of GABAergic signaling from depolarizing to hyperpolarizing. This transition is driven by upregulation of the K^+-Cl^- cotransporter KCC2, which lowers intracellular chloride levels, thereby reversing the direction of chloride flow through $GABA_A$ receptors. The timing of this chloride switch is critical for establishing inhibitory control and preventing excessive excitation. Computational models suggest that concurrent glutamatergic input can modulate chloride flux through $GABA_A$ receptors in a developmentally stage-specific manner, illustrating complex crosstalk between excitatory and inhibitory systems during critical periods [84].

The coordinated regulation of ion channel expression and function enables the neural network to respond to sensory experience and learning. Activity-dependent calcium influx, mediated through NMDARs and voltage-gated channels, activates transcriptional programs involving CREB and other activity-regulated genes. These programs promote synapse stabilization, modulate intrinsic excitability, and enable homeostatic scaling to maintain network stability in the face of fluctuating input. Disruptions in these processes—whether due to mutations in

channel-coding genes, delayed maturation of chloride gradients, or aberrant activity patterns—can impair synaptic pruning, cause synaptic overgrowth or underconnectivity, and ultimately lead to neurodevelopmental phenotypes such as intellectual disability, autism spectrum disorder, and epilepsy.

Ion channels are indispensable for the maturation and refinement of synaptic connections. They serve as both executors and regulators of activity-dependent plasticity, enabling structural and functional optimization of neural circuits during postnatal development. Their developmental regulation—at the level of subunit composition, trafficking, and biophysical modulation—ensures a balance between plasticity and stability. Deviations from this tightly controlled process contribute to long-lasting impairments in cognition, behavior, and emotional regulation, underscoring ion channel dysfunction as a convergent mechanism in neurodevelopmental disorders.

3.5 Region-Specific Expression Patterns of Ion Channels in the Developing Brain

Neurodevelopment proceeds through a regionally specialized sequence of proliferation, migration, synaptogenesis, and circuit refinement. These processes are governed, in part, by the spatially and temporally restricted expression of ion channel genes. High-resolution transcriptomic and proteomic analyses have revealed that ion channel expression is not uniform across the brain but is tightly regulated in a region- and cell type–specific manner, reflecting the unique physiological requirements of developing neural circuits. Aberrations in the spatial patterning of ion channel expression can disrupt local excitatory-inhibitory balance, impair regional connectivity, and contribute to the heterogeneous clinical presentations of NDDs.

NMDAR subunits (e.g., NR1, NR2A, NR2B) display distinct regional and developmental expression profiles, conferring location-specific synaptic plasticity and learning properties. For instance, in rodent models of psychostimulant sensitization, both cocaine and ethanol exposure upregulate NR2A and NR2B in the prefrontal cortex (PFC), whereas ethanol alone induces similar changes in the dorsal striatum [85]. These findings support the idea that environmental stimuli selectively modulate NMDAR signaling in distinct brain regions, contributing to region-specific plasticity and vulnerability. Loss-of-function mutations in Grin2a (NR2A) result in widespread transcriptional reprogramming across multiple brain areas. In Grin2a knockout mice, prefrontal hypoactivity is observed alongside hyperactivity in the hippocampus and striatum, accompanied by alterations in dopamine signaling, astrocytic cholesterol metabolism, and regional glutamate receptor composition [86]. These spatially dissociable changes underscore the critical role of NR2A in maintaining the functional balance between limbic, associative, and executive circuits.

Whole-genome sequencing studies in Chinese ASD trios have identified both coding and regulatory variants in classical ion channel genes such as SCN2A and GRIN2B [87]. These genes exhibit enriched expression in cortical and hippocampal pyramidal neurons, particularly in layers II–IV of the neocortex and the CA1–CA3 regions of the hippocampus—regions heavily implicated in language, memory, and social cognition. The spatial enrichment of these variants correlates with the core clinical domains affected in ASD, including language delay, cognitive inflexibility, and sensory dysregulation. Moreover, several novel candidate ion channel genes identified in this cohort displayed spatial expression patterns overlapping with canonical ASD-associated loci. Integrative analysis of brain-region-specific transcriptomic disruption supports a model in which domain-specific cognitive impairments arise from disruptions in the expression of ion channels critical for the maturation of discrete neural circuits.

The timing of ion channel expression in different brain regions coincides with the critical periods of circuit development. For example, KCNQ2, a potassium channel gene implicated in neonatal epileptic encephalopathy, is highly expressed in early-developing motor cortex regions but later downregulated in favor of other K^+ channels during postnatal maturation. This transient expression pattern may explain why early-life seizures associated with KCNQ2 mutations often resolve over time but leave residual motor or cognitive deficits. Likewise, SCN2A (encoding $Na_V1.2$) is predominantly expressed in cortical pyramidal neurons during early postnatal development, with a gradual transition to SCN8A ($Na_V1.6$) in later stages. Mutations in SCN2A that disrupt this developmental switch contribute to a spectrum of phenotypes ranging from early-onset epilepsy to isolated autism, depending on the mutation's timing and impact on region-specific expression dynamics.

Ion channel gene expression is highly structured across both space and time in the developing brain. Region-specific transcriptional programs ensure that individual circuits acquire the electrophysiological properties necessary for their functional specialization. Disruption of these spatiotemporal patterns—whether by genetic mutations, epigenetic dysregulation, or environmental perturbation—can result in circuit-selective dysfunction and phenotypic heterogeneity in NDDs. Future research leveraging single-cell transcriptomics, spatial proteomics, and connectomics will be essential for mapping the precise topography of ion channel expression and for identifying region-targeted therapeutic strategies.

3.6 Regulatory Mechanisms of Ion Channel Expression

The precise expression and function of ion channels during neurodevelopment are orchestrated by multilayered regulatory mechanisms that operate at transcriptional, post-transcriptional, translational, and post-translational levels.

These mechanisms ensure that ion channels are expressed in the right cell types, at the right times, and in appropriate subcellular compartments to support processes ranging from neurogenesis to synaptogenesis. Dysregulation at any level of this regulatory hierarchy can disrupt neuronal excitability, impair synaptic plasticity, and predispose to NDDs. Understanding these control systems provides crucial insight into disease etiology and identifies novel points of therapeutic intervention.

Alternative splicing is a key mechanism generating ion channel isoform diversity with distinct biophysical properties and subcellular localization. For example, the developmental shift from SCN2A-encoded $Na_V1.2$ to SCN8A-encoded $Na_V1.6$ channels is tightly regulated at the RNA level and alters action potential initiation in maturing neurons. Dysregulation of this switch is associated with epilepsy and ASD. Epitranscriptomic modifications, particularly N6-methyladenosine (m6A), further fine-tune ion channel mRNA stability, localization, and translational efficiency. For instance, NMDA receptor subunit mRNAs undergo dynamic m6A methylation, which modulates their developmental expression and contributes to synaptic plasticity. These RNA-level controls are sensitive to environmental perturbations such as hypoxia and inflammation, linking external stressors to ion channel regulation [88].

Ion channels are also subject to rapid post-translational regulation. Phosphorylation alters gating kinetics, surface expression, and channel–protein interactions. For example, $K_V1.3$, a voltage-gated potassium channel expressed in both neurons and microglia, is modulated by multiple kinases (e.g., PKC, Src-family kinases). Phosphorylation patterns determine its functional integration into signaling microdomains through interactions with scaffold proteins and auxiliary subunits such as KCNE4 and $K_V\beta$. This regulation affects both excitability and immune responses, highlighting ion channels as convergence points between neuronal and immunological signaling pathways [89]. Ubiquitination also plays a critical role in channel turnover. Activity-dependent ubiquitination regulates the endocytosis and degradation of postsynaptic glutamate receptors, contributing to synaptic scaling and the homeostatic regulation of excitatory transmission.

In addition to plasma membrane-localized channels, ion channels within organelles (e.g., mitochondria, lysosomes, endoplasmic reticulum) are essential for subcellular calcium handling, pH regulation, and metabolic adaptation. Mitochondrial BKCa channels (mitoBKCa), encoded by KCNMA1 splice variants, are regulated by β1-subunits that alter voltage sensitivity and protect against oxidative stress. Notably, pathological agents such as amyloid-β impair mitoBKCa activity, linking mitochondrial ion channel dysfunction to both developmental abnormalities and neurodegenerative processes [90]. These findings highlight a continuum between early-life ion channel regulation and late-life neurological vulnerability.

Ion channel gene expression is also governed by epigenetic mechanisms, including DNA methylation, histone modifications, and regulation by non-coding RNAs. For example, the TRPA1 gene, which encodes a polymodal ion channel involved in nociceptive signaling, is epigenetically modulated in both inflammatory and neurodevelopmental contexts. Its expression is controlled by promoter methylation, histone acetylation, and interactions with microRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). These epigenetic mechanisms not only regulate baseline expression but may also establish developmental "memory" of early-life stressors [91]. Furthermore, emerging evidence suggests feedback loops between ion channel activity and chromatin state. For instance, ion fluxes can influence the expression or activity of chromatin-modifying enzymes, suggesting bidirectional coupling between electrical activity and epigenetic remodeling.

Neuronal activity itself constitutes a key regulatory input. Activity-dependent calcium influx, mediated by NMDA receptors and VGCCs, activates transcription factors such as CREB, MEF2, and NPAS4, which in turn regulate the expression of ion channels to maintain homeostatic balance. This feedback ensures that developing circuits adapt to changing input patterns without becoming hyper- or hypoexcitable. Impairment of these activity-dependent regulatory loops—due to genetic mutations or environmental insults—can lead to maladaptive stabilization of circuit dysfunction. Such dysregulation is increasingly implicated in disorders characterized by altered excitation/inhibition balance, including ASD, epilepsy, and schizophrenia.

Ion channel expression in the developing brain is controlled by a multilayered network of regulatory mechanisms, from RNA splicing and m6A modification to phosphorylation, epigenetic remodeling, and activity-dependent feedback. These mechanisms not only ensure functional precision during development but also offer adaptive flexibility to respond to environmental stimuli. Disruption at any of these regulatory nodes may initiate or exacerbate ion channel dysfunction, contributing to the pathophysiology of NDDs. Targeting these regulatory systems—rather than ion channels alone—may offer novel and more precise therapeutic avenues for correcting ion channel-related developmental abnormalities.

4. Genetic and Epigenetic Dysregulation of Ion Channels in Neurodevelopmental Disorders

Ion channels are evolutionarily conserved membrane proteins encoded by a diverse family of genes that regulate excitability, signaling, and synaptic function. Mutations or regulatory disturbances in these genes can disrupt neuronal development, contributing to a spectrum of NDDs, including epilepsy, ID, and ASD. Recent advances in sequencing technologies have revealed that both monogenic and polygenic variants affecting ion channels—or their regulatory

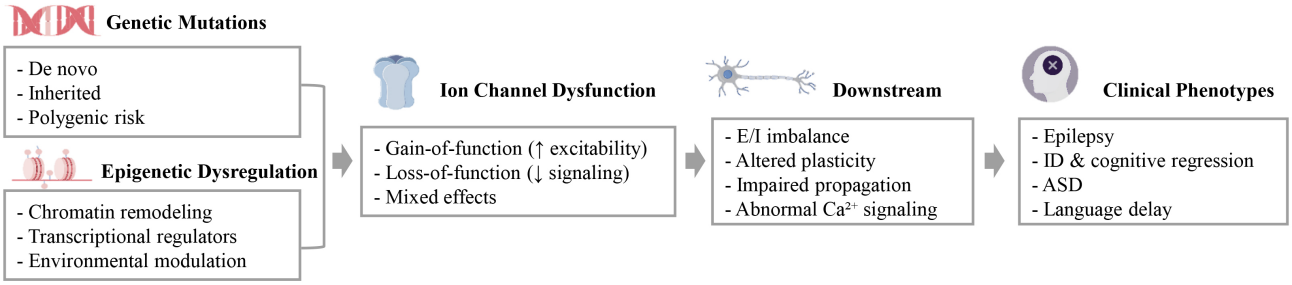

Fig. 1. Genetic and epigenetic dysregulation of ion channels in NDDs.

landscapes—are major contributors to NDD pathogenesis. This section provides an overview of the genetic architecture of ion channelopathies, emphasizing causal mutations, inheritance patterns, epigenetic modulation, and the complexities of genotype–phenotype correlation (Fig. 1).

4.1 Ion Channelopathies: Genetic Mutations Underlying NDDs

NDDs are increasingly recognized as developmental channelopathies—disorders resulting from pathogenic variants in genes encoding ion channels or their auxiliary subunits. These mutations often alter channel biophysics, subcellular localization, or expression, ultimately impairing neuronal excitability and circuit assembly. Among voltage-gated sodium channels, SCN1A mutations are canonical drivers of Dravet syndrome—a severe epileptic encephalopathy with comorbid cognitive decline and autistic features. SCN2A variants show broader phenotypic variability, from benign familial neonatal seizures to ASD and ID, with both gain- and loss-of-function effects documented. SCN8A mutations are linked to early infantile epileptic encephalopathies and profound developmental delay due to impaired action potential propagation and disrupted E/I balance.

Potassium channelopathies involving KCNQ2, KCNQ3, and KCNT1 contribute to early-onset epilepsy syndromes. Their dysfunction prolongs repolarization and perturbs rhythmic cortical oscillations, impairing thalamocortical synchrony. Notably, KCNT1 mutations cause autosomal dominant nocturnal frontal lobe epilepsy, often accompanied by cognitive regression.

Calcium channel mutations—particularly in CACNA1C (Timothy syndrome) and CACNA1H—are implicated in multisystem developmental disorders. Timothy syndrome is characterized by ASD, cardiac arrhythmias, and craniofacial dysmorphisms, driven by prolonged calcium entry and altered gene transcription. CACNA1H variants, though less penetrant, predispose to absence seizures via enhanced thalamic burst firing.

Ligand-gated channel mutations, especially in GRIN2A and GRIN2B (encoding NMDA receptor subunits), disrupt synaptic plasticity and contribute to epilepsy, ID, and ASD. GRIN2B variants alone account for ~1% of severe developmental delay cases, underscoring the clinical impact of glutamatergic channelopathies. Emerging data suggest that these mutations frequently interact with broader transcriptional networks. For instance, epigenetic dysregulation of autophagy and chromatin remodeling genes has been implicated in ASD and epilepsy, potentially exacerbating the effects of ion channel mutations via impaired synaptic pruning [92]. In a Turkish population cohort, 28.9% of genetically diagnosed NDD cases carried multilocus pathogenic variation (MPV), often within regions of homozygosity. This includes both known channelopathy genes and novel candidates, reinforcing the complex genetic architecture of NDDs [93].

Animal models carrying mutations in SCN1A, GRIN2B, or related genes have validated causality and offered therapeutic avenues. Adeno-associated virus (AAV)- and CRISPR-based interventions in these models demonstrate postnatal phenotypic reversibility, supporting the feasibility of targeted therapies beyond early developmental windows [94]. Mutations in Activity-Dependent Neuroprotective Protein (ADNP) and ADNP2, transcriptional regulators of synaptic and cytoskeletal genes, are also implicated in ASD and schizophrenia. Environmental exposures, such as endocrine-disrupting chemicals, have been shown to exacerbate ADNP-related behavioral phenotypes in zebrafish, illustrating gene–environment interactions in channelopathy models [95]. Further, the CAGI6 challenge identified de novo and inherited variants in MECP2, ANKRD11, and CHD8—genes with roles in chromatin remodeling and synaptic regulation—highlighting convergence on ion channel-linked pathways and the predominance of haploinsufficiency mechanisms [96].

In sum, ion channelopathies comprise a genetically heterogeneous group of disorders, often presenting as developmental encephalopathies with overlapping neuropsychiatric features. Their study provides a lens through which the molecular and functional convergence of NDD pathogenesis can be understood and therapeutically targeted.

4.2 De Novo vs Inherited Variants and Polygenic Contributions

The advent of large-scale genomic sequencing has transformed our understanding of the genetic landscape underlying NDDs, revealing that both de novo and inherited variants in ion channel genes contribute significantly to disease etiology. Trio-based whole exome and genome sequencing studies consistently demonstrate a significant enrichment of de novo mutations in individuals with ASD, ID, and developmental and DEE compared to unaffected controls. These variants frequently localize to functionally constrained regions within ion channel genes, underscoring their essential roles during early brain development. Notably, de novo missense mutations affecting the third transmembrane domain (M3) of NMDA receptor subunits—including GRIN1, GRIN2A, and GRIN2B—have been shown to alter gating kinetics and channel conductance. A functional study profiling 48 of these variants revealed that the majority (28/48) produced gain-of-function effects, resulting in excessive calcium influx and heightened excitability, which correlate with phenotypes such as epilepsy, cognitive impairment, and axial hypotonia [97]. These mechanistic insights support the therapeutic repurposing of Food and Drug Administration (FDA)-approved NMDA receptor antagonists in select patients with hyperactive receptor variants. Similarly, gain-of-function mutations in TRPM3, a neurosteroid-sensitive non-selective cation channel, have been implicated in a recently defined spectrum of DEEs. Functional analyses revealed increased basal channel activity and hypersensitivity to neurosteroids, resulting in intracellular calcium overload and cerebellar dysfunction. Notably, the antiseizure drug primidone effectively reduced hyperactive channel currents, demonstrating a pathophysiologically guided approach to drug repurposing in ion channelopathies [47].

De novo variants in GRIN2A have also been associated with combined phenotypes of epilepsy and ASD. While GRIN2A mutations are traditionally linked to epilepsy-aphasia syndromes and language delay, the presence of autistic features in some cases suggests involvement of modifier genes, epistatic interactions, or environmental influences. Structural studies of triheteromeric NMDA receptor assemblies involving mutant GluN2A subunits have illustrated how receptor stoichiometry can modulate phenotypic outcomes, underscoring the complexity of genotype–phenotype correlations [98]. A recently described DEE subtype was found to be caused by de novo missense mutations in KCNA3, which encodes the voltage-gated potassium channel $K_V1.3$. Affected individuals presented with developmental delay, ASD traits, speech impairment, and epilepsy. Electrophysiological analyses revealed a diverse spectrum of channel dysfunction, including loss-of-function and mixed gain/loss phenotypes. Interestingly, the antidepressant fluoxetine suppressed both wild-type and mutant channel activity, raising the potential for individualized pharmacological modulation based on biophysical profiling [99]. In contrast to de novo mutations, inherited variants in ion channel genes often exhibit incomplete penetrance and variable expressivity. A prototypical example is calcium release deficiency syndrome (CRDS), caused by loss-of-function mutations in RYR2, which typically remain subclinical under basal conditions but may produce overt phenotypes under physiological stress or specific triggers. Such findings underscore the importance of context-dependent phenotypic manifestation and highlight the diagnostic challenges associated with cryptic inherited channelopathies [100].

Beyond single-gene variants, accumulating evidence supports the contribution of common variants with small effect sizes in shaping susceptibility to NDDs. Polygenic risk scores (PRS) incorporating ion channel–related loci are associated with quantitative traits such as IQ, attention, and social behavior. Moreover, PRS analyses have revealed correlations between ion channel gene burdens and individual differences in response to antiepileptic drug therapy, suggesting a role for common variants in modulating treatment outcomes. Importantly, many ion channel genes—including SCN2A, GRIN2B, and CACNA1C—exhibit high intolerance to loss-of-function mutations, reflected in elevated pLI (probability of being loss-of-function intolerant) and missense Z-scores in population databases. These dosage-sensitive genes are particularly enriched in NDD cohorts, further emphasizing the vulnerability of ion channel pathways to both rare and common genetic variation.

In summary, de novo and inherited variants in ion channel genes exist along a continuum of risk, with their contributions shaped by molecular function, genetic background, and environmental context. Integrative frameworks that combine variant effect prediction, functional electrophysiology, and polygenic modeling are crucial for advancing precision diagnostics and therapeutics in ion channel-related NDDs.

4.3 Genotype–Phenotype Correlation and Variable Expressivity

A central challenge in understanding ion channelopathies in NDDs lies in decoding the complex and often unpredictable relationship between specific genetic variants and clinical phenotypes. While many pathogenic variants in ion channel genes exhibit high penetrance, considerable interindividual variability in severity, onset, and symptomatology persists—even among individuals harboring the same mutation. This phenotypic heterogeneity arises from a multifactorial interplay of mutation type and location, channel subunit composition, developmental context, epigenetic regulation, and modifier genes.

First, the functional consequence of a mutation—whether GoF, LoF, or mixed—strongly influences the clinical outcome. For example, GoF mutations in NMDA re-

ceptor subunits (GRIN1, GRIN2B) enhance synaptic excitation and calcium influx, often resulting in early-onset epileptic encephalopathies, ID, and hyperactivity. Conversely, LoF mutations reduce excitatory signaling and are more commonly associated with ASD and cognitive deficits [97,98]. Importantly, the incorporation of mutant subunits into triheteromeric NMDA receptor complexes can further modulate channel kinetics and downstream signaling in a region- and cell-type-specific manner. Second, ion channel variants often produce pleiotropic effects across different neurodevelopmental domains. TRPM3 GoF variants exemplify this pleiotropy: patients present with a constellation of symptoms including developmental delay, epilepsy, cerebellar atrophy, pain insensitivity, and motor dysfunction. These diverse manifestations may reflect differential TRPM3 expression across neuronal subtypes, coupled with the effects of secondary genetic or epigenetic modifiers [101]. Third, variants in KCNA3, encoding the voltage-gated potassium channel $K_V1.3$, demonstrate how divergent biophysical effects—ranging from complete LoF to mixed GoF/LoF—can result in overlapping phenotypes such as speech delay, seizures, and ASD features. This convergence suggests that disruption of critical thresholds for neuronal excitability, rather than specific channel behavior per se, may underlie common neurodevelopmental phenotypes [99]. Moreover, inherited ion channelopathies often display incomplete penetrance, suggesting the existence of compensatory pathways or latent pathogenicity unmasked by environmental or physiological stressors. In CRDS caused by RYR2 LoF mutations, for instance, affected individuals may appear phenotypically normal under baseline conditions but exhibit cognitive or motor dysfunction when exposed to heightened neuronal demand [100]. Such context-dependent penetrance complicates both diagnosis and prognosis, particularly in multiplex families and monozygotic twins with discordant clinical presentations.

Environmental factors, including endocrine disruptors and maternal immune activation, may further influence expressivity by altering ion channel gene expression or epigenetic status during critical periods of brain development. Recent studies in CRISPR-modified zebrafish models of ADNP mutation–associated ASD support this notion, demonstrating worsened behavioral phenotypes upon environmental stress exposure [95]. Finally, large-scale genotype–phenotype mapping efforts incorporating functional annotations, structural modeling, and constraint metrics (e.g., Combined Annotation-Dependent Depletion scores, regional missense constraint) have improved predictive accuracy. For instance, missense mutations in highly conserved transmembrane domains of voltage-gated sodium and potassium channels are more likely to produce severe developmental phenotypes and drug-resistant epilepsy, highlighting the utility of integrative bioinformatic tools in variant interpretation.

In conclusion, genotype–phenotype correlation in ion channelopathies is shaped by a dynamic and layered framework involving molecular function, circuit integration, and systemic modulation. Addressing this complexity requires a systems-level approach that combines electrophysiological profiling, multi-omics analysis, environmental modeling, and longitudinal clinical phenotyping. Such efforts are essential to advancing personalized medicine strategies for patients with ion channel–associated neurodevelopmental disorders.

5. Ion Channel-Targeted Therapies

The recognition of ion channel dysfunction as a central mechanism in NDDs has galvanized efforts to develop targeted therapeutic interventions. Beyond conventional antiseizure agents that non-selectively modulate excitability, emerging strategies are increasingly informed by molecular etiology, aiming to correct specific channelopathies or restore network-level balance. This section outlines recent advances in ion channel–targeted therapies, spanning small molecule modulators, ASOs, gene therapy, and next-generation *in vitro* platforms (Fig. 2).

5.1 Small Molecule Channel Modulators

Small molecule therapeutics remain foundational in the treatment of NDDs, particularly when directed at voltage-gated Na^+, K^+, Ca^{2+}, and glutamate receptors. Precision Targeting in SCN1A-Related Epilepsies: SCN1A GoF mutations produce aberrant persistent sodium currents, contributing to neonatal-onset epilepsies and movement disorders. In one study, 81% of patients with GoF variants showed clinical improvement with sodium channel blockers such as carbamazepine or phenytoin, emphasizing the value of mutation-specific pharmacotherapy [2]. Pharmacogenetic Modifiers of ASM Response: SCN1B polymorphisms have been linked to antiseizure medication resistance. The rs55742440-C allele conferred reduced responsiveness in Taiwanese patients, underscoring the utility of incorporating genetic screening into clinical decision-making [102].

Compounds such as GS967 and riluzole selectively inhibit late/persistent sodium currents, offering a rational therapeutic option for hyperexcitability-related disorders [103]. M-current enhancers like retigabine improve afferent excitability in vestibular systems. By restoring subcortical circuit stability, KCNQ2/3 modulators may alleviate sensory integration deficits common in ASD [104]. T-type Ca^{2+} channel blockade with TTA-A2 restores E/I balance in stress-altered mPFC circuits and reverses depressive phenotypes, suggesting relevance for mood comorbidities in NDDs [105]. Allosteric modulators and antagonists (e.g., memantine) can restore NMDA receptor function in GRIN-related channelopathies, partially correcting hypofunction and synaptic deficits [106–108]. Emerging modulators are also being developed for non-

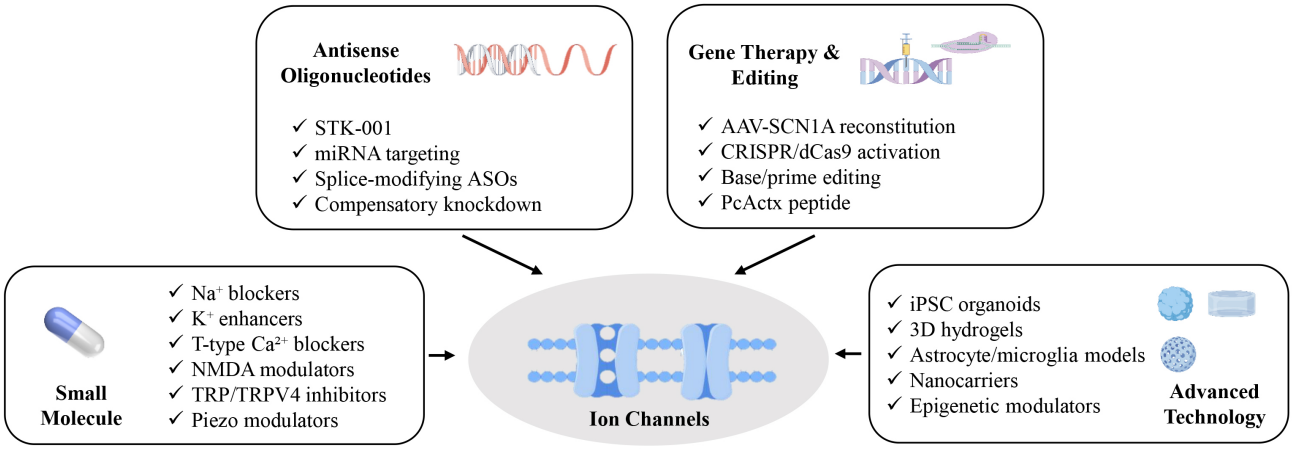

Fig. 2. Ion channel targeted therapies.

classical ion channels. For TRP channels, the TRPM3 antagonist primidone has been shown to reduce seizure burden and improve developmental/neurocognitive outcomes in individuals carrying TRPM3 gain-of-function variants, and it directly inhibits mutant TRPM3 channel activity—supporting a repurposing strategy using an already approved antiseizure drug [37,101,109]. TRPV4 inhibition rescues social and circuit-level deficits unmasked by inflammation in ASD-relevant Shank3 mouse models, providing a gene–environment interaction-targeted–targeted approach; the published rescue used the selective TRPV4 blocker HC-067047 (with GSK2193874 being another well-characterized, brain-penetrant TRPV4 inhibitor) [38,110]. For mechanosensitive channels, the peptide GsMTx4 suppresses Piezo-mediated stretch-activated currents, and small-molecule tools such as Dooku1 antagonize Yoda1-evoked Piezo1 activation, offering proof-of-concept that Piezo channels are chemically tractable [111,112]. While much of this work is still preclinical outside of the TRPM3/primidone case reports and series, these findings broaden the therapeutic landscape beyond traditional VGICs and underscore the potential of TRP and Piezo channels as druggable targets in NDDs. These findings demonstrate that targeted ion channel modulation, when guided by molecular diagnosis, offers a promising avenue for precision medicine in NDDs.

5.2 Antisense Oligonucleotides (ASOs)

ASOs provide a transcript-level intervention capable of correcting ion channel gene expression with high specificity. TANGO-Driven SCN1A Enhancement: ASOs designed using Targeted Augmentation of Nuclear Gene Output (TANGO) significantly improved $Na_V1.1$ expression and reduced seizure burden in DS mouse models. STK-001, an ASO targeting SCN1A, is undergoing clinical evaluation with favorable early outcomes [3,113].

ASOs targeting miR-335-5p derepress multiple sodium channels, enhancing excitability *in vitro* and *in vivo*. Intriguingly, both inhibition and overexpression of miR-335-5p yield opposing effects on seizure susceptibility, highlighting the delicacy of excitability modulation [114]. ASO knockdown of Scn8a in Kcnq2/Kcna1-deficient mice reduced seizures and improved survival, demonstrating a compensatory approach for balancing channel dysfunction [115]. Splice-modifying ASOs show potential in dominant-negative KCNQ2 mutations, offering a mechanism to restore channel functionality in early-onset epileptic encephalopathy [3]. ASOs can be tailored to various ion channel genes implicated in LGS and other DEEs, establishing them as a modular platform for genetically stratified therapy [116]. Nevertheless, despite their promise, ASOs carry potential limitations that warrant consideration. For example, although STK-001 and related constructs are designed to specifically upregulate SCN1A, partial sequence complementarity may inadvertently influence other sodium channel transcripts, with the risk of altering excitability outside the intended interneuron population. Additional concerns include variability in distribution and uptake across brain regions, long-term immunogenicity, and the challenge of balancing therapeutic efficacy against the possibility of off-target excitability changes. Ongoing clinical trials and preclinical studies are therefore crucial not only for efficacy but also for assessing durability, safety, and transcriptome-wide specificity. Overall, ASOs offer a flexible and scalable approach for NDD treatment, combining molecular precision with expanding clinical feasibility.

5.3 Gene Therapy and Genome Editing

Permanent correction or activation of ion channel genes has become feasible with the advent of advanced viral vectors and gene editing tools. A split-intein dual-AAV system enabled reconstitution of full-length SCN1A specifically in GABAergic interneurons, rescuing seizures and extending survival in DS mice. Pan-neuronal overexpression proved toxic, emphasizing the need for cell-

type-specific strategies [117]. Delivery of dCas9-VPR and promoter-targeting gRNAs upregulated SCN1A expression in parvalbumin interneurons, improving seizure thresholds. However, excessive activation in zebrafish models induced epileptiform activity, necessitating careful titration [4,118]. Base and prime editing platforms are expected to correct single-nucleotide channelopathies (e.g., GRIN2B, KCNQ2) with minimal genomic disruption, although clinical translation remains forthcoming. PcActx, a TRPV1 inhibitor peptide, suppressed seizures and modulated calcium/glutamate pathways in zebrafish, representing an innovative non-editing-based strategy for ion channel modulation [119]. Together, these techniques herald a shift toward curative interventions, contingent on delivery precision, developmental timing, and safety profiling.

5.4 Advanced In Vitro Modeling and Nanotechnology-Enabled Platforms

Translational success requires disease models and delivery systems that recapitulate the human neurodevelopmental context. iPSC-derived forebrain organoids from DS patients replicate $Na_V1.1$ deficits in interneurons, enabling personalized drug testing [5]. In SNCA-triplication organoids, α-synuclein aggregation and mitochondrial dysfunction were reversed by drug screening, demonstrating cross-utility for channelopathy modeling [120]. Culturing neurons in hydrogels supports synaptic maturation, upregulating markers like NCAM1 and GluR2. These systems facilitate screening for modulators of AMPA receptor function and other excitatory channels. iPSC-derived astrocytes and microglia reveal how Kir4.1 or VRAC dysfunction in glial cells affects neuronal development and E/I homeostasis, opening new therapeutic targets [121]. ESI1, an epigenetic rejuvenator, restored myelination and lipid metabolism in aged models. Given the role of membrane composition in channel function, such interventions may indirectly rebalance excitability [122]. These innovations not only deepen our understanding of channelopathies but also enhance preclinical screening and delivery efficacy, paving the way for personalized and mechanistically precise NDD therapies.

6. Challenges and Future Directions

Despite significant progress in elucidating the roles of ion channel dysfunction in NDDs and in developing targeted therapeutics, substantial scientific, technical, and translational challenges remain. These hurdles span from the biological complexity of NDDs to limitations in current modeling systems and the need for precision interventions.

NDDs such as epilepsy, autism spectrum disorder, and intellectual disability display profound clinical and genetic heterogeneity. Ion channel variants may exert either gain or loss-of-function effects, often within the same gene (e.g., SCN1A, KCNQ2, GRIN2B), complicating genotype–phenotype correlations. Additionally, non-genetic factors, including maternal perinatal depression and anxiety, have been associated with long-term impairments in offspring cognition, language, and socio-emotional development [1]. These findings highlight the need for integrative etiological models that capture both intrinsic genetic architecture and extrinsic environmental modulation of ion channel function.

Although advanced tools such as optogenetics and patch-clamp electrophysiology offer high-resolution dissection of synaptic properties (e.g., AMPA/NMDA current ratios, short-term plasticity), their application in human-relevant contexts remains limited. Optogenetic tools like channelrhodopsins and animal opsins face constraints in temporal precision, spectral overlap, and limited tissue penetration, reducing their translational potential [123,124]. Moreover, the specificity of transgenic models requires reappraisal. For instance, the widely used PV-Cre mouse line, assumed to target parvalbumin-positive interneurons, was shown to drive recombination in cerebellar granule cells due to transient Pvalb expression during development [125]. These observations underscore the necessity for temporally controllable and cell-type-restricted genetic tools to achieve accurate modeling of ion channelopathies.

Ion channel expression is finely tuned across neural circuits, developmental stages, and cell types. Non-selective or global modulation often results in unintended or paradoxical outcomes. For example, PV^+ interneuron activation in the thalamic reticular nucleus yields opposing effects on pain sensitivity depending on dorsoventral localization [126]. Similarly, manipulation of LHPP or TGR5 in glutamatergic versus GABAergic neurons produces divergent behavioral phenotypes in depression models [127]. These findings advocate for circuit-informed, cell-subtype-specific strategies in both preclinical modeling and therapeutic design. Human iPSC–derived neurons and brain organoids offer valuable platforms for modeling ion channel dysfunction in NDDs. However, limitations in maturation—such as incomplete synaptic development and immature ion channel profiles—impede the faithful recapitulation of disease phenotypes. Although 3D culture systems enhance expression of markers like GluR2 (AMPA subunit) and 4R tau, adult-like electrophysiological properties and long-range connectivity remain challenging to reproduce. Additionally, current models often lack fully integrated glial populations and immune signaling pathways, both of which play crucial roles in neurodevelopment and ion channel regulation.

To overcome these barriers, the following directions should guide future research: (1) Multi-omic, circuit-level integration: Merging single-cell transcriptomics, epigenomics, and functional imaging in patient-derived models will enable precise mapping of ion channel mutations onto network-level dysfunctions; (2) Spatiotemporally precise gene modulation: Development of inducible CRISPRa/i systems, light- or drug-sensitive transcriptional regulators,

and enhancer-specific delivery vectors will allow reversible and cell-specific control of ion channel gene expression; (3) AI-driven modeling and biomarker discovery: Machine learning algorithms that integrate electrophysiology, imaging, and transcriptomic data can aid in high-dimensional analysis, prediction of drug responses, and identification of mechanistic biomarkers; (4) Maternal intervention and preventive strategies: Given the influence of perinatal stress on offspring neurodevelopment and channel expression, targeted maternal mental health interventions during gestation may modulate epigenetic programming of ion channels and serve as upstream preventive measures [1].

Although therapeutic modulation of ion channels in NDDs is advancing rapidly, translating mechanistic insights into clinical success requires precision at the level of cell types, circuits, and developmental windows. By integrating cutting-edge genetic tools, patient-derived platforms, and AI-enabled analytics—alongside early-life risk intervention—future strategies can pave the way for personalized and durable therapies targeting the ionic basis of neurodevelopmental disorders.

7. Conclusion

Ion channels are essential gatekeepers of neuronal excitability, synaptic transmission, and neural circuit maturation. Their dysregulation—arising from genetic mutations, epigenetic alterations, or post-translational modifications—underlies a broad spectrum of NDDs, including epilepsy, ASD, and intellectual disability. Recent advances in high-throughput sequencing, stem cell–derived neural models, and *in vivo* circuit interrogation have deepened our mechanistic understanding of ion channelopathies and accelerated the development of targeted interventions. Therapeutic innovation is rapidly progressing across diverse platforms. Despite these advancements, critical challenges persist. The spatial and temporal heterogeneity of ion channel expression, coupled with complex developmental trajectories and incomplete model maturation, continues to limit translational fidelity. In sum, the convergence of molecular precision tools, circuit-level targeting strategies, and patient-relevant platforms marks a transformative era in the treatment of ion channel-related neurodevelopmental disorders. Finally, mechanistic work on epileptic channelopathies highlights how voltage-gated ion channel dysfunction can destabilize neuronal circuits and create overlapping phenotypes across epilepsy, ASD, and intellectual disability. Recent reviews underscore that understanding circuit-level dysfunctions and their pharmacological modulation provides both mechanistic clarity and therapeutic opportunities [128]. Integrating these epilepsy-derived insights into NDD research may accelerate the discovery of convergent targets and precision interventions. By leveraging these interdisciplinary innovations, personalized and durable therapeutic solutions are within reach for genetically and mechanistically diverse patient populations.

Author Contributions

ZS contributed to the acquisition of literature. SL and XJ contributed to the conception and design of the review. ZS, SL, and XJ wrote the paper and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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