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GENETIC AND MOLECULAR MECHANISMS IN PEDIATRIC NEUROLOGICAL DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT
Pediatric neurological disorders represent a heterogeneous group of conditions characterized by early-onset impairment in cognitive, motor, and behavioral functions, with significant lifelong consequences. This systematic review aims to synthesize current evidence on the genetic and molecular mechanisms underlying these disorders. A comprehensive literature search was conducted across major databases following PRISMA 2020 guidelines, resulting in the inclusion of 15 high-quality studies. The findings highlight a predominantly de novo–driven genetic architecture, with key contributions from rare variants and copy number variations affecting neurodevelopmental pathways. At the molecular level, consistent disruptions were identified in synaptic signaling, ion channel regulation, and excitatory–inhibitory balance, indicating strong pathway-level convergence despite gene-level heterogeneity. These mechanisms were found to underlie major disorder categories, including autism spectrum disorder, epileptic encephalopathies, and intellectual disability. The review further emphasizes the importance of genotype–phenotype relationships, although variability in clinical expression remains a challenge. Advances in next-generation sequencing have significantly improved early diagnosis and facilitated the transition toward precision medicine approaches. However, gaps remain in translating molecular findings into targeted therapies due to limited functional validation and clinical trials. The study provides an integrated framework linking genetic variation to molecular dysfunction and clinical outcomes, offering valuable insights for future research and therapeutic development in pediatric neurology.

KEYWORDS: Pediatric neurology, genetic mechanisms, molecular pathways, neurodevelopmental disorders

1. INTRODUCTION
Pediatric neurological disorders (PNDs) is a heterogeneous group of disorders affecting the developing nervous system, including neurodevelopmental, neuromuscular, epileptic, and neurodegenerative disorders. These conditions are usually marked by the disabilities in cognition, motor, behavior, and sensory processing, which often manifest themselves at an early age and have long-term effects on individual development and quality of life (Lima et al., 2022). These disorders have a heavy burden, which leads to a significant contribution to childhood morbidity and long-term disability in the lifespan. In most instances, the development of critical developmental windows is disrupted by early-onset neurological dysfunction resulting in the development of long-term deficits that affect education, social participation, and overall well-being. This burden is especially acute in resource-limited environments, where access to diagnostic tools and specialized care is usually not sufficient, further contributing to health disparities (Birbeck et al., 2015). The chronicity of the conditions and the need to provide interventions that will help them achieve better functional outcomes instead of being cured completely (Bonouvrié et al., 2016). Also, the heterogeneity of pediatric neurological disorders is manifested by their different etiologies, including immune-mediated conditions, such as paraneoplastic neurological syndromes, and early onset neurodegenerative diseases and demyelinating disorders (Wells and Dalmau, 2011; Usta et al., 2023).
The recent developments in the field of genetic research have contributed greatly to the overall knowledge of the underlying cause of the genetic pediatric neurological disorders and have revealed a complex and multifactorial genetic architecture. These disorders could be a result of monogenic mutations whose effects sizes are large, or polygenic effects of the accrual effects of multiple variants (Loh et al., 2020). One of the most significant contributions has been the discoveries of de novo mutations and copy number variations (CNVs) which are often implicated in neurodevelopmental disorders and commonly occur without any family history (Coe et al., 2019). The introduction of next-generation sequencing technologies, such as whole-exome and whole-genome sequencing, has transformed the detection of these genetic changes, allowing them to comprehensively and at high-resolution analyze the human genome (Delanne et al., 2019). Not only have these technologies enabled the discovery of new disease-related genes, but also revealed a significant genetic overlap across a range of neurological conditions, suggesting shared biological pathways and mechanisms (Morgan et al., 2024; Gupta and Aman, 2025).

Pediatric neurological disorders at the molecular level are defined as the disturbance of the major biological processes that are central to normal brain development and functioning. They encompass the changes in synaptic signaling, ion channels, mitochondrial functions, and neuroinflammatory cascades, all which result in the dysfunction of neurons and the pathogenesis of the diseases (Lima et al., 2022). Interestingly, despite such variety of clinical manifestations, there is an increasing tendency to unify or at least approach the level of molecular pathways, in which case there are certain genetic mutations, which have disrupted common biological systems. This overlapping is an offer of a common language in interpreting the intricacies of these disorders and offers possible courses of action to be pursued by the therapeutic intervention. Nevertheless, even with these new advances the body of literature that was already present has been ripped apart with a multiplicity of studies in isolated genes or specific conditions without any synthesis of the findings in broader mechanisms. So, the acute dysconnectivity of the genetic variation with molecular dysfunction and clinical phenotype still exists. This gap should be filled out to proceed with the implementation of precision medicine strategies and to generalize molecular findings to clinically relevant findings.

Objectives

1. To identify key genetic mechanisms underlying pediatric neurological disorders
2. To analyze major molecular pathways involved in disease pathogenesis
3. To examine the link between genetic variations, molecular mechanisms, and clinical outcomes

2. RESEARCH METHODOLOGY

2.1 Study Design and Reporting Standards

To ensure that the systematic review is carried out in a way, which guarantees the methodological transparency, reproducibility, and rigor, this systematic review was carried out in accordance with the guidelines by Preferred Reporting Items to Systematic Reviews and Meta-Analyses (PRISMA) 2020. The review process was structured into a framework, which included study identification, screening, and eligibility assessment and inclusion. To minimize reporting bias and maximize the methodological credibility, the review protocol was prospectively registered in an international database (e.g., PROSPERO).

2.2 Data Sources and Search Strategy

A comprehensive literature search was performed across four major electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and Embase. These databases were selected due to their extensive coverage of biomedical, genetic, and neurological research. The search was limited to studies published between 2010 and 2025 to capture recent advances in genomic and molecular research. A Boolean search strategy was employed, integrating key concepts related to population, condition, and exposure. Specifically, terms associated with pediatric populations (e.g., “pediatric,” “childhood”), neurological disorders (e.g., “neurological disorders,” “neurodevelopmental disorders”), and genetic or molecular mechanisms (e.g., “genetic mutations,” “molecular pathways”) were combined using appropriate operators (AND, OR) to maximize retrieval sensitivity and specificity.

2.3 Eligibility Criteria

The selection of studies was done according to predefined inclusion and exclusion criteria. The inclusion criteria were the availability of pediatric populations that were 0-18 years of age and reported original research findings, specifically genomic, transcriptomic or proteomic studies. Besides, the studies to be used had to give clear data regarding the genetic variants, mutations, or molecular mechanisms involved in the pediatric neurological conditions. The studies were not included when they focused exclusively on adult populations, when they were non-primary studies (such as review articles, editorials, or commentaries), or when they lacked the sufficient mechanistic details that would be relevant to genetic or molecular pathways.

2.4 Study Selection Process

The process of study selection was performed in different phases to provide the methodological rigor. To begin with, all the retrieved records were curated by two reviewers acting independently, basing on title and abstract. The possibly relevant studies were then screened by the full-text examination to determine the eligibility of the studies against the preset criteria. Any difference between the reviewers was sorted out by discussion or consultation of a third reviewer to reach an agreement. The general selection procedure was recorded with the help of a PRISMA flow diagram, showing the number of studies identified, screened, excluded and included at each step.

2.5 Data Extraction Strategy

To ensure consistency and accuracy, the data extraction was done using a standardized and pre-piloted extraction form. The most important data that were obtained in each of the studies comprised bibliographic data (author, year of publication), study design and the population characteristics. Further, a systematic gathering of detailed data on reported clinical phenotypes, identified genes or mutations, associated molecular pathways or mechanisms, etc. was performed. This systematic methodology helped to compare and synthesize the themes across researches.

2.6 Quality Assessment and Risk of Bias

The quality of methodology and risk of bias of the included studies were assessed with the help of the established assessment tools. The quality of observational studies was evaluated using the Newcastle-Ottawa Scale that determines

the quality of research based on the domains of selection, comparability, and outcome. In research where it is applicable, Cochrane Risk of Bias tool was used to assess the possibility of bias in the study design and execution. The major areas that were evaluated were selection bias, measurement bias, and confounding factors. This assessment made sure that reliability and validity of the evidence included were critically reviewed.

2.7 Data Synthesis and Analytical Approach

The expected heterogeneity of study designs, populations, and reported outcomes, a narrative synthesis approach was embraced. The data obtained were mechanically tabulated and analyzed with the assistance of the thematic categorization to identify the common patterns and associations. In particular, the results were categorized into key areas, such as genetic processes and molecular pathways. Should such a possibility have existed, subgroup analyses were conducted and studies stratified in terms of type of disorder or specific types of mechanistic processes as a means to increase the interpretability and to provide a more subtle picture of the underlying biological processes.

3. RESULTS

3.1 Study Selection

The selection of studies was done according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and is summarized in Figure 1. The number of records obtained through database searching and other sources was 210, and 160 of them were found in electronic databases (PubMed, Scopus, Web of Science, Embase and Google Scholar). 50 records were identified through manual screening of references and other sources. Three hundred and forty-six unique studies were left after the deletion of 70 duplicate records and were to undergo title and abstract screening. In this stage, 55 records were filtered out because they were not relevant to the study goals. The entire text of the rest 85 articles was reviewed on the basis of eligibility criteria derived by predefined criteria on the basis of pediatric populations and investigation of genetic mutations and molecular mechanisms in neurological disorders. At the full-text review stage, 70 articles were excluded for the following reasons: non-neurological disease focus (n = 20), adult-only populations (n = 15), lack of genetic or molecular focus (n = 12), non-primary studies such as reviews or editorials (n = 10), insufficient mechanistic or clinical data (n = 8), and non-English publications (n = 5). Ultimately, 15 studies met all eligibility criteria and were included in the final qualitative synthesis, as illustrated in the PRISMA flow diagram (Figure 1).

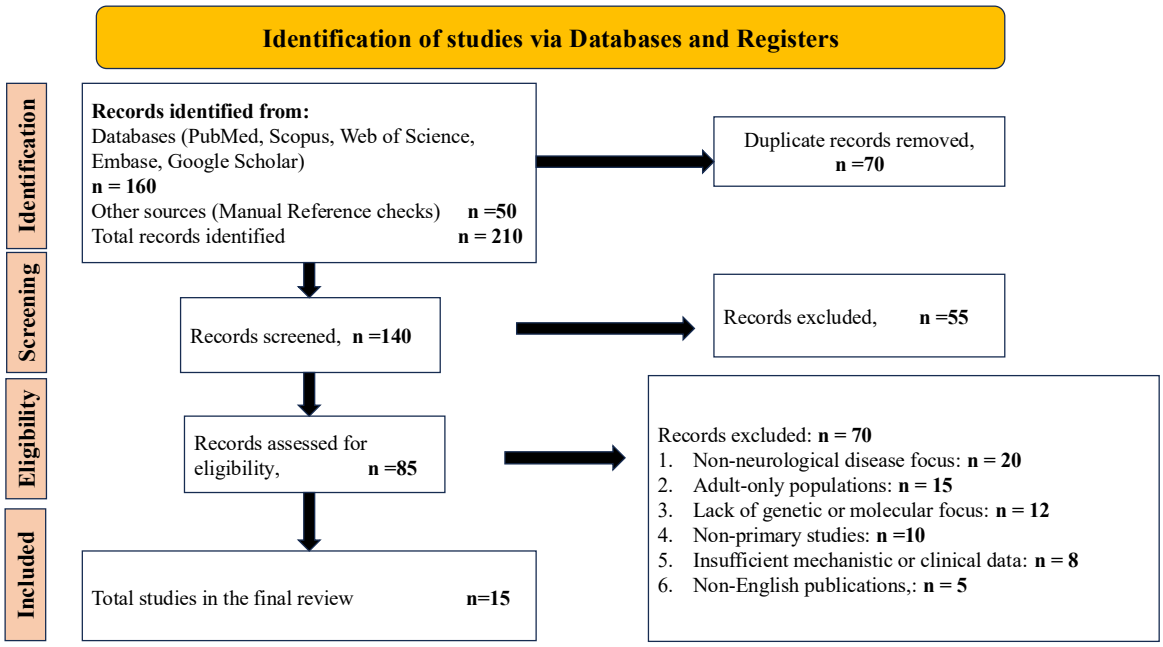

Figure 1: PRISMA Flow Diagram of Study Selection Process

This figure illustrates the systematic study selection process following PRISMA guidelines, detailing identification, screening, eligibility, and inclusion stages. It summarizes record counts, duplicate removal, exclusion criteria, and final inclusion of 15 studies for qualitative synthesis.

3.2 Characteristics of Included Studies

The studies included are mainly genomic and molecular studies and investigations of large scale on pediatric neurological and neurodevelopmental disorders. The majority of the studies used high-level methodologies like whole-exome sequencing, targeted resequencing, and mutation profiling to determine de novo variants and disrupted molecular pathways. The disorders studied are developmental disorders, autism spectrum disorder, epileptic encephalopathies, intellectual disability and early infantile neurological syndromes. The studies geographically represent multinational

collaborations and cohorts in Europe, North America and Asia. In the literature, there is a consensus on some important molecular mechanisms, such as synaptic dysfunction, ion channel disorders and disruption of neurodevelopmental signaling pathways, as well as shared and disorder-specific genetic architectures as illustrated in Table 1.

Table 1. Characteristics and Key Findings of Included Studies (n = 15)

Study (Author, Year)	Study Design	Population	Disorder Type	Key Genes	Molecular Mechanism
McRae et al., 2017	Cohort (Exome sequencing)	Pediatric	Developmental disorders	Multiple de novo variants	Genetic architecture, developmental pathways
DDD Study, 2015	Cohort (Genomic study)	Pediatric	Developmental disorders	Novel gene variants	Neurodevelopmental gene disruption
Satterstrom et al., 2020	Large-scale exome	Pediatric	Autism spectrum disorder	ASD-associated genes	Synaptic and neuronal signaling
Epi4K, 2013	Cohort (Genomic)	Pediatric	Epileptic encephalopathy	Multiple de novo mutations	Ion channel and synaptic dysfunction
Carvill et al., 2013	Targeted resequencing	Pediatric	Epileptic encephalopathy	CHD2, SYNGAP1	Synaptic regulation
Saitsu et al., 2012	Case-based genomic	Pediatric	Ohtahara syndrome	KCNQ2	Ion channelopathy
Saitsu et al., 2014	Cohort study	Pediatric	Epileptic encephalopathy	SCN8A	Sodium channel dysfunction
Syrbe et al., 2015	Genetic analysis	Pediatric	Epileptic encephalopathy	KCNA2	Potassium channel dysfunction
Johannesen et al., 2017	Cohort study	Pediatric	Epilepsy spectrum	GABRG2	GABAergic signaling
Rauch et al., 2012	Exome sequencing	Pediatric	Intellectual disability	Multiple genes	Neurodevelopmental disruption
Vissers et al., 2010	Genomic study	Pediatric	Intellectual disability	De novo variants	Genetic mutation paradigm
Hamdan et al., 2014	Cohort study	Pediatric	Intellectual disability	Multiple mutations	Molecular dysfunction
Sanders et al., 2012	Exome sequencing	Pediatric	Autism	De novo mutations	Synaptic pathways
Neale et al., 2012	Genomic analysis	Pediatric	Autism	Exonic mutations	Genetic variation patterns
Gaouzi et al., 2025	Exome sequencing	Pediatric	Mixed neurological disorders	Multiple variants	Multi-pathway disruption

3.3 Genetic Mechanisms Identified

The overall body of research covered by the studies included provides a description of a largely de novo-driven genetic architecture underlying the etiology of pediatric neurological disorders, especially among early-onset and severe phenotypes. Consistent large-scale trio-based exome sequencing studies consistently demonstrate that a significant proportion of pathogenic variants are due to de novo mutations (McRae et al., 2017; Deciphering Developmental Disorders Study, 2015). These mutations are overrepresented in genes with high mutational constraint and intolerance to functional variation, suggesting that there is strong selective pressure on these genes and that the genes play a critical role in neurodevelopmental processes.

Convergent evidence in independent exome sequencing studies has shown that in autism spectrum disorder (ASD), a significant burden of protein-disrupting and missense de novo variants in genes related to synaptic organization, transcriptional regulation, and chromatin remodeling is highly significant (Satterstrom et al., 2020; Sanders et al., 2012; Neale et al., 2012). Remarkably, these studies pinpoint dual genetic model, with rare high-impact variants that interact with polygenic background risk, leading to phenotypic heterogeneity. In the same vein, in intellectual disability, the genetic environment is extreme, with hundreds of genes implicated, many of which converge to common biological pathways despite the presence of many genetic origins (Rauch et al., 2012; Hamdan et al., 2014; Vissers et al., 2010).

In contrast, epileptic encephalopathies have a more mechanistically consistent genetic phenotype, in which the overwhelming majority of mutations are in genes encoding ion channel and neuronal excitability regulators. Pathogenic variants of SCN8A, KCNQ2 and KCNA2 have been repeatedly identified and have been found to cause early infantile epileptic syndromes that have a direct effect on membrane excitability and action potential dynamics (Saitsu et al., 2012; Saitsu et al., 2014; Syrbe et al., 2015). These results lend credence to the grouping of these disorders into developmental

channelopathies, in which the pathogenesis of the disease is a central role in disruption of electrophysiological homeostasis. Further, the involvement of gene mutations in CHD2 genes, SYNGAP1 genes and so on extend this framework by implicating the dysfunction of chromatin remodelling and synaptic signalling in the pathogenesis of epilepsy (Carvill et al., 2013).

In all of the included studies, one recurrent pattern can be identified of the genetic heterogeneity at the locus level converging to a limited number of central biological systems, including synaptic functioning, ion channel regulation, and neurodevelopmental signaling. This convergence underpins a network-based model of disease, in which a number of different genetic perturbations compromise interconnected molecular pathways, ultimately leading to overlapping clinical phenotypes. Recent whole-exome sequencing studies further support this idea by showing that even in clinically heterogeneous pediatric neurological cohort's pathogenic variants are often found to cluster within common functional modules (Gaouzi et al., 2025).

3.4 Molecular Mechanisms and Pathways

3.4.1 Synaptic Dysfunction

Synaptic dysfunction is a central and convergent pathogenesis underlying a wide range of pediatric neurological disorders, especially autism spectrum disorder (ASD) and intellectual disability. Various of the included studies show that the pathogenic variants are often active in the genes that are involved in the structure, plasticity, and intracellular signaling of neurons, resulting in disrupted neuronal communication and network formation. An example of this is mutations in SYNGAP1, a key regulator of synaptic Ras signaling and dendritic spine maturation (Carvill et al., 2013). Likewise, mutations in genes encoding synaptic scaffolding proteins and postsynaptic density components have been enriched in ASD cohorts on large scale exome sequencing studies (Satterstrom et al., 2020; Sanders et al., 2012). These results, along with other individual genes, are all indicative of neurodevelopmental dysfunction, which contributes to cognitive impairment and abnormal behaviour.

3.4.2 Ion Channelopathies

The dysfunction of ion channels is a predominant molecular pathogenesis in epileptic encephalopathies and in the early infantile neurological diseases. The articles included consistently report the mutation in the genes of voltage-gated ion channels, including SCN8A (sodium channel), KCNQ2 (potassium channel), and KCNA2 (potassium channel) as key factors in the establishment of neuronal hyperexcitability (Saitsu et al., 2012; Saitsu et al., 2014; Syrbe et al., 2015). These mutations cause gain- or loss-of-function effects, and disrupt the finely regulated balance between membrane depolarization and repolarization. Consequently, the neurons have abnormal firing patterns, are more excited and have low seizure threshold. Notably, the mechanistic consistency of these studies supports the categorization of such disorders as developmental channelopathies with the impairment of the functions at the level of ion conductance directly translating into such clinical phenotypes as refractory seizures and developmental delay. In addition, these findings can support the ion channels as the highly actionable therapeutic targets to support the translational relevance of this mechanistic classification.

3.4.3 Neurodevelopmental Signaling Pathways

It was common to find disruption of the neurodevelopmental signaling pathways across studies that examined developmental disorders and intellectual disability. Pathogenic variants of genes often play important roles in neuronal differentiation, migration, axonal guidance, and transcriptional regulation, which are critical during early brain development. A large number of these genes have been shown to be highly expressed by large cohort-based sequencing studies and are under strong evolutionary constraint, indicating their functional importance (McRae et al., 2017; Rauch et al., 2012). Moreover, the epigenetic dysregulation and altered gene expression programs are also the major factors in the pathogenesis of the disease due to mutations in chromatin-modifying and transcriptional regulatory genes. These impairments result in abnormal cortical development, impaired neuronal connectivity, and long-term impairments in cognitive and neurological functions. Remarkably, although there is a wide range of implicated genes, convergence at the level of shared developmental pathways is quite high, which supports the idea of pathway-level unity in neurodevelopmental disorders.

3.4.4 GABAergic and Excitatory–Inhibitory Imbalance

A disproportion between excitatory and inhibitory signaling is a pathophysiological critical feature in various pediatric neurological conditions, especially epilepsy. Gene mutations like those in GABRG2 gene, which encode one of the subunits of the GABA-A receptor, disrupt the inhibitory neurotransmission and cause a decrease in the synaptic inhibition (Johannesen et al., 2017). This impairment contributes to the transition to the excessive excitatory activity that prefers the instability of neuron network and the generation of seizures. The concept of excitatory/inhibitory (E/I) imbalance goes beyond the effect of single genes and represents a more global systems level perturbation in neural circuitry. Markedly, this imbalance does not only exist in epilepsy but also in ASD and other neurodevelopmental disorders, with the disturbed network dynamics playing a role in the cognitive and behavioral disorders. The synthesis of the outcome of studies points to the fact that the E/I disproportion is a unifying mechanistic model, between the molecular-level imbalance and the large-scale dysfunction of a network as shown in Table 2.

Table 2. Molecular Mechanisms and Associated Genetic Evidence

Molecular Mechanism	Key Genes	Functional Impact	Associated Disorders	Key References
Synaptic Dysfunction	SYNGAP1, CHD2	Impaired synaptic plasticity and neurotransmission	ASD, Intellectual Disability	Carvill et al., 2013; Satterstrom et al., 2020
Ion Channelopathies	SCN8A, KCNQ2, KCNA2	Altered neuronal excitability and action potential dynamics	Epileptic Encephalopathies	Saitsu et al., 2012; Saitsu et al., 2014; Syrbe et al., 2015
Neurodevelopmental Pathway Disruption	Multiple (de novo variants)	Impaired neuronal differentiation and development	Developmental Disorders, ID	McRae et al., 2017; Rauch et al., 2012
Excitatory–Inhibitory Imbalance	GABRG2	Reduced inhibitory signaling (GABAergic dysfunction)	Epilepsy, ASD	Johannesen et al., 2017
Multi-pathway Convergence	Multiple genes	Combined disruption of synaptic, signaling, and developmental pathways	Mixed Pediatric Neurological Disorders	Gaouzi et al., 2025

3.6 Genotype–Phenotype Correlations

The studies included indicate a complicated correlation between genetic variation and clinical presentation in pediatric neurological disorders, with indications of both mutation-specific effects and pathway-wide effects. The gene mutations in ion channels, including SCN8A, KCNQ2, and KCNA2, show rather strong genotype-phenotype relationships, with gain-or-loss-of-function variants directly affecting neuronal excitability and directly correlating with the early onset of seizures, and the severity of the disease (Saitsu et al., 2012; Saitsu et al., 2014; Syrbe et al., 2015). Likewise, GABRG2 mutation variants are linked to a range of epileptic phenotypes, some mild (febrile seizures), others severe (developmental and epileptic encephalopathy).

But in neurodevelopmental disorders, such as autism spectrum disorder and intellectual disability, there is less determinism in the relationships between genotype and phenotype, and a great deal of variation in genotype and phenotype expressivity and penetrance. Massive studies of exome sequencing show that mutations in genes associated with synaptic function and transcriptional control can have a wide spectrum of cognitive and behavioral phenotypes even among individuals with similar variants (Satterstrom et al., 2020; Sanders et al., 2012; Hamdan et al., 2014). Such variability is a result of the impact of other genetic modifiers, environmental conditions, and polygenic background risk as presented in Table 3. In addition, several research works emphasize phenotypic overlap between different genetic mutations, with different genes converging in common molecular pathways, resulting in similar clinical presentations such as developmental delay, epilepsy, and cognitive impairment (McRae et al., 2017; Rauch et al., 2012).

Table 3. Genotype–Phenotype Correlations in Pediatric Neurological Disorders

Gene Type	Molecular Function	Phenotypic Outcome	Correlation Pattern	Key References
SCN8A, KCNQ2, KCNA2	Ion channel regulation	Early-onset epilepsy, severe encephalopathy	Strong, mutation-specific	Saitsu et al., 2012; Saitsu et al., 2014; Syrbe et al., 2015
GABRG2	GABAergic signaling	Febrile seizures to severe epilepsy spectrum	Moderate, variant-dependent	Johannesen et al., 2017
SYNGAP1, CHD2	Synaptic function, transcription	ASD, intellectual disability	Variable expressivity	Satterstrom et al., 2020; Sanders et al., 2012
Multiple de novo variants	Neurodevelopmental regulation	Developmental delay, cognitive impairment	Heterogeneous, low specificity	McRae et al., 2017; Rauch et al., 2012
Polygenic effects	Multi-pathway influence	Broad neurodevelopmental phenotypes	Weak, influenced by modifiers	Hamdan et al., 2014

3.7 Therapeutic and Clinical Implications

The results of the studies included support the increased significance of the precision medicine methods in the treatment of the pediatric neurology disorders. The discovery of certain genetic defects, especially de novo variants of genes related to synaptic activity, ion channels, and neurodevelopmental pathways, allows a better classification and stratification of diseases. This genetic stratification enables the tailored clinical decision making and the tailored diagnostics and therapy based on underlying molecular etiology instead of only on clinical presentation (McRae et al., 2017; Satterstrom et al., 2020).

A significant translational impact of these genetic findings is the development and application of specific therapies, particularly those diseases the cause of which is well-defined and molecular in nature. The pharmacological regulation of

the activity of ion channels, such as SCN8A, KCNQ2, and KCNA2, is a logical approach to therapy in epileptic encephalopathy associated with mutations of ion channels (Saitsu et al., 2012; Syrbe et al., 2015). On the same note, insight into the breakages in the pathways of synaptic signaling has provided avenues of the interventions that can restore the balance of synaptic signaling and neuronal communication. The potential of mechanism-based therapy to help improve the outcome in conditions that are often refractory to standard care is indicated by a number of these approaches that are still in their infancy as far as clinical translation is concerned.

The introduction of genetic testing into clinical practice is critically sensitive to timing of therapeutic intervention, especially with children's populations where early neurodevelopmental trajectories are highly sensitive to timing of therapeutic intervention. Identification of pathogenic variants of the disease at early stages of the disease with the help of whole-exome sequencing and related genomic tools, it is possible to initiate specific management strategies and make informed genetic counseling. Early diagnosis will also assist in the prognostic assessment and will aid in enrolling in new gene-specific clinical research.

4. DISCUSSION

This systematic review provides a synthesis of the existing evidence regarding the genetic and molecular processes underlying pediatric neurological disorders and demonstrates a largely de novo-driven genetic architecture with a strong convergence at the pathway level. In the studies included, mutations of synaptic functioning, ion channels activity, and neurodevelopmental regulation were consistently revealed as the major pathogenesis agents of disease. Although the evidence of heterogeneity is extensive at the level of gene variation, the findings indicate that diverse genetic changes are converging on limited number of fundamental biological systems, and supports a network-based model, where the disruption of interlinked molecular pathways is converging on a small number of core biological systems. This trend is consistent with more general genetic principles according to which the expression of phenotypes is affected not only by individual mutations but also by dominance relationships, gene dosage, and interaction in complex biological systems (Veitia et al., 2018; Billiard et al., 2021).

One important observation of this review is how genetic variation is integrated with molecular dysfunction, whereby pathogenic variants can be translated into a disruption in cellular processes such as synaptic signaling, neuronal excitability and developmental regulation. Proteome-scale analyses have posited that there are strong genetic effects often explained by changes in protein stability and interaction networks, and dosage sensitivity, also in support of the importance of functional context in interpreting genetic variants (Badonyi and Marsh, 2024). Furthermore, the fact that the various mutations all assemble into common pathways is reminiscent of the findings of integrative genomics studies of other complex diseases in which multiple variants converge to disrupt common biology networks (Mäkinen et al., 2014). This overlap is perhaps best-defined in the systems that control synaptic plasticity and excitatory inhibitory balance and it is in these systems that it is most evident that these systems are prone to attacks.

The clinical implications of these results are quite significant, especially when it comes to genomic medicine and early diagnosis. The recent developments in genomic sequencing technologies have allowed their application as first-line diagnostic instruments, which will help to identify pathogenic variants in children at a very early stage (Chen et al., 2023). Genetic diagnosis is particularly important in neurological diseases, as early and correct diagnosis can make a significant impact on the developmental patterns and the ultimate outcomes. Simultaneously, the introduction of large-scale genomic screening programs should be carefully considered in terms of clinical utility, ethical concerns, and the preparedness of the healthcare system (Haddow and Palomaki, 2011; Alarcón Garavito et al., 2023). The application of genomic information into clinical practice processes is a symptom of a larger trend towards precision medicine, where diagnosis and treatment are increasingly directed by molecular etiology instead of being defined by symptom-based classification.

In the context of therapeutic use, defining certain molecular processes will serve as a basis in designing specific and individualized treatment approaches. Mechanism based interventions, especially those that involve the ion channel or synaptic pathways are promising avenues to enhancing outcomes in conditions, which are often difficult to treat with conventional therapies. The trend towards individualized treatment methods accentuates the need to tailor interventions according to the specific genetic profiles of people, which will increase treatment effectiveness and will reduce adverse effects (Cohen et al., 2021; Comai et al., 2025). Nonetheless, a major challenge is to translate genetic discoveries into a clinically effective treatment that will require further functional validation and clinical trials.

Although this review has strong points such as methodology being followed to a systematized approach, and focus on mechanistic synthesis having been made, there are several limitations that should be considered. The limited size of the sample of included studies as well as the heterogeneity of included studies in terms of their study design as well as in terms of their study populations lead to a less generalizable nature of the findings. Additionally, in the vast majority of studies, it is determined which of these variants is pathogenic, but the functional effect of these mutations is not always fully described, so it is necessary to conduct additional experimental verification. The findings could also be influenced by the possible publication bias and non-English literature. Among the most important areas of interest in the future research that can yield a more comprehensive picture of the disease pathogenesis and will be more useful in clinical translation is multi-omics integration, longitudinal cohort studies, and functional analyses. Overall, this review demonstrates the level of sophistication of diagnostic, treatment, and precision medicine within the framework of pediatric neurological conditions.

5. CONCLUSION

The systematic review provides an overview of the genetic and molecular pathways of the etiology of pediatric neurological disorders with a complex yet convergent biological environment. The findings indicate that among the

spectrum of genetic heterogeneity, a substantial proportion of these disorders are induced by de novo mutations and rare mutations that interfere with key pathways that are involved in the functioning of synapses, regulation of ion channels and neurodevelopmental mechanisms. The pathway level convergence enables the explanation of overlapping clinical phenotypes in the various disorders as well as the facilitation of a systems-based explanation of disease pathogenesis. The early diagnosis has been significantly enhanced with the implementation of genomic technologies and, to a larger extent, next-generation sequencing, which has resulted in the shift toward precision medicine in pediatric neurology. However, still there are problems with the transfer of these molecular understanding into effective clinical interventions, particularly due to the variability in genotype-phenotype relationships and the unavailability in the functional validation of identified variants. The review emphasizes the importance of integrating genetic, molecular and clinical data to facilitate the accuracy of the diagnosis and to apply special treatment techniques. Multi-omics approaches, longitudinal studies, and functional studies should be considered as future studies to address the current gaps and help fix the clinical translation. The study advocates the utmost significance of genetic and molecular information to enhance the outcome and further personalized care in pediatric neurological diseases.

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