Archives of Medical Reports

1(3) (2024) 5-12

OPEN ACCESS

REVIEW ARTICLE

Genomic Insights into Pediatric Neurodevelopmental Disorders: Current Trends and Future Directions

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Articleinfo
Received: 7 April 2024
Accepted: 8 May 2024

Keywords: Neurodevelopmental disorders; Genomic technologies; Whole-genome sequencing; Functional genomics; Precision medicine.

How to cite this article: Diana Dovgy, Carolin Daniel. (2024). Genomic Insights into Pediatric Neurodevelopmental Disorders: Current Trends and Future Directions, 1(3), 5-12 Retrieved from https://archmedrep.com/index.php/amr/article/view/13

Abstract

Pediatric neurodevelopmental disorders (NDDs) such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability (ID), and epilepsy present complex challenges due to their diverse etiologies involving genetic, environmental, and epigenetic factors. Recent advancements in genomic technologies, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), have significantly enhanced our understanding of these disorders. This review provides a comprehensive overview of current trends and future directions in genomic research on NDDs. We explore the genetic basis of NDDs, highlighting single-gene disorders and polygenic contributions, as well as the role of copy number variations (CNVs). Functional genomics approaches, such as gene expression profiling and epigenetic studies, have elucidated key pathways and mechanisms underlying these disorders. Integrative approaches combining multi-omics data and systems biology have further advanced our knowledge, identifying novel genes and regulatory networks involved in NDDs. The translation of genomic findings into clinical practice is transforming the diagnosis and treatment of NDDs. Genetic testing, including WES, WGS, and targeted gene panels, has improved diagnostic accuracy, while therapeutic developments such as gene therapy and antisense oligonucleotides (ASOs) offer new avenues for treatment. Biomarker discovery is crucial for early diagnosis and monitoring treatment responses. Future perspectives include leveraging emerging technologies like single-cell genomics, long-read sequencing, and CRISPR-based functional genomics to deepen our understanding of NDDs. Addressing ethical and social considerations is essential for the responsible translation of genomic discoveries into clinical practice. This review underscores the potential of genomic research to revolutionize the understanding, diagnosis, and treatment of pediatric neurodevelopmental disorders.

1. Introduction

Pediatric neurodevelopmental disorders (NDDs) encompass a spectrum of conditions characterized by impairments in cognitive, motor, and social functions (Bednarz and Kana, 2018). These disorders, which include autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disabilities (ID), and epilepsy, are highly prevalent and pose significant challenges to affected individuals, their families, and society. The etiology of NDDs is complex, involving genetic, environmental, and epigenetic factors (De Felice et al., 2015). Recent advancements in genomic technologies have revolutionized our understanding of these disorders, revealing numerous genetic variants and pathways involved in their pathogenesis (Figure 1). This review aims to provide a comprehensive overview of current trends in genomic research on pediatric NDDs and explore future directions for improving diagnosis, treatment, and prevention.

2. Genetic Basis of Pediatric Neurodevelopmental Disorders

2.1. Single-Gene Disorders and Syndromic NDDs

Single-gene disorders, often syndromic, are characterized by mutations in a single gene that lead to distinct clinical phenotypes. Examples include Rett syndrome, caused by mutations in the MECP2 gene, and Fragile X syndrome,

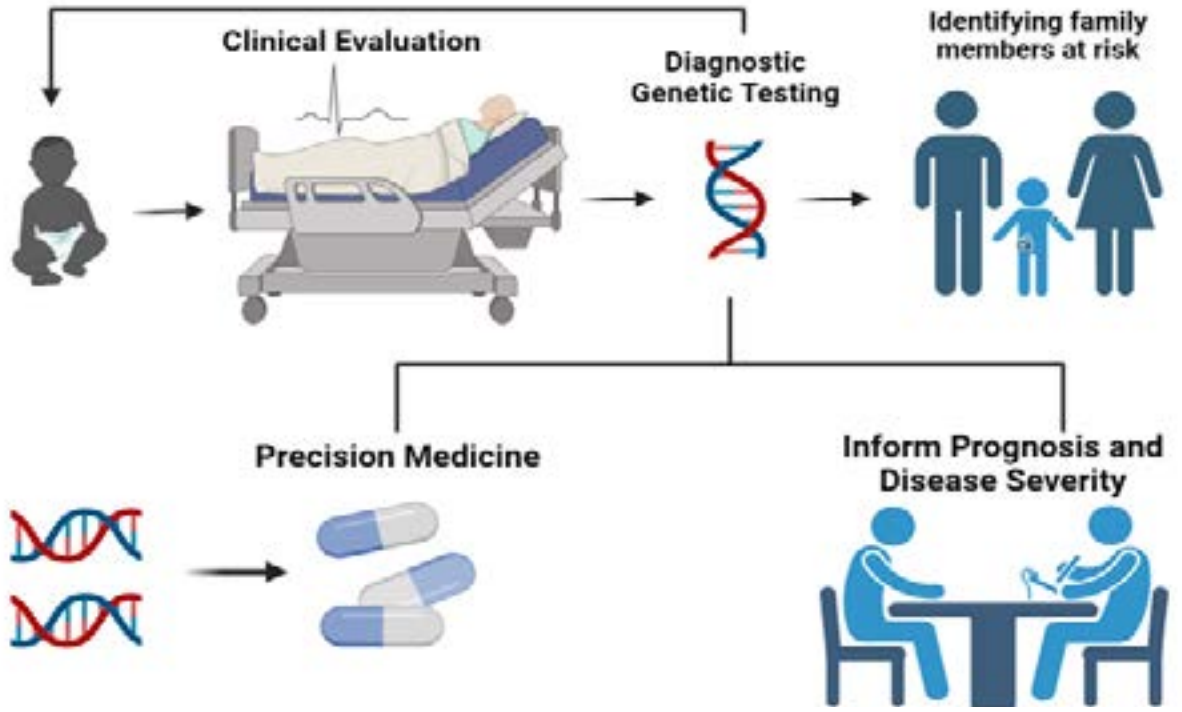

Figure 1: Genetic testing in patients with Neurodevelopmental disorder

resulting from expansions in the FMR1 gene (Bach et al., 2021). These disorders highlight the profound impact that a single genetic alteration can have on neurodevelopment (Table 1). Advances in sequencing technologies, particularly whole-exome sequencing (WES) and whole-genome sequencing (WGS), have enabled the identification of numerous genes associated with syndromic NDDs, leading to better diagnostic accuracy and understanding of disease mechanisms (Schwarze et al., 2018).

2.2. Polygenic and Multifactorial NDDs

Many NDDs, such as ASD and ADHD, exhibit a polygenic inheritance pattern, where multiple genetic variants contribute to the risk of developing the disorder (Clarke et al., 2016). Genome-wide association studies (GWAS) have identified numerous common variants associated with these conditions, though each variant individually confers a modest risk. The polygenic nature of these disorders underscores the complexity of their genetic architecture and the interplay between genetic and environmental factors (Smeland et al., 2020). Integrating GWAS findings with other omics data, such as transcriptomics and epigenomics, can provide a more comprehensive understanding of the molecular underpinnings of these disorders.

2.3. Copy Number Variations (CNVs)

CNVs, which involve the duplication or deletion of large DNA segments, have been implicated in various NDDs. CNVs can disrupt gene function and regulatory regions, leading to altered neurodevelopmental processes (Coe et al., 2019). For instance, deletions on chromosome 22q11.2 are associated with a high risk of schizophrenia and other neurodevelopmental phenotypes. High-resolution microarray technologies and WGS have facilitated the identification of pathogenic CNVs, enabling more precise genetic diagnoses and insights into the contribution of structural variations to NDDs (Qi et al., 2018).

3. Functional Genomics and Pathway Analysis

3.1. Gene Expression Profiling

Gene expression profiling through RNA sequencing (RNA-seq) has provided valuable insights into the transcriptional changes associated with NDDs. Studies have revealed dysregulated expression of genes involved in synaptic function, neuronal development, and immune responses (Babenko et al., 2016). Analyzing expression patterns in brain tissues, as well as peripheral tissues like blood, can uncover biomarkers for early diagnosis and potential therapeutic targets. Moreover, single-cell RNA-seq has enabled the dissection of cellular heterogeneity in the brain, revealing cell type-specific expression changes in NDDs (Cardona-Alberich et al., 2021).

3.2. Epigenetic Modifications

Epigenetic modifications, such as DNA methylation and histone modifications, play crucial roles in regulating gene expression and can be influenced by environmental factors. Aberrant epigenetic patterns have been observed in NDDs, suggesting that epigenetic dysregulation contributes to disease pathogenesis (Cacabelos et al., 2019). For example, altered DNA methylation profiles have been reported in individuals with ASD, affecting genes involved in neurodevelopment and synaptic function. Epigenome-wide association studies (EWAS) and chromatin immunoprecipitation sequencing (ChIP-seq) are powerful tools for elucidating the epigenetic landscapes of NDDs and identifying potential therapeutic targets (Rani and Mahadevan, 2019).

3.3. Functional Characterization of Genetic Variants

Functional genomics approaches, such as CRISPR-Cas9 gene editing and induced pluripotent stem cell (iPSC) models, have been instrumental in characterizing the functional impact of genetic variants associated with NDDs. CRISPR-Cas9 enables precise editing of specific genomic loci, allowing researchers to investigate the effects of mutations on cellular

Table 1: The different genetic mechanisms in pediatric neurodevelopmental disorders

Disorder	Genetic cause	Description
Rett Syndrome	MECP2 gene mutations	Causes severe cognitive and motor impairments, typically affecting females
Fragile X Syndrome	FMR1 gene expansions	Leads to intellectual disability, autism, and behavioral issues
Phenylketonuria	PAH gene mutations	Results in a metabolic disorder that can cause cognitive impairment if untreated
Down Syndrome	Extra copy of chromosome 21	Associated with developmental delays, intellectual disability, and characteristic physical features
Angelman Syndrome	UBE3A gene mutations or deletions on chromosome 15	Characterized by severe developmental delay, ataxia, and a happy demeanor
Prader-Willi Syndrome	Deletions or mutations on chromosome 15	Leads to intellectual disability, obesity, and behavioral issues
Autism Spectrum Disorder	Multiple genetic variants	Affects social communication and behavior, with both genetic and environmental factors contributing
Attention-Deficit/Hyperactivity Disorder	Multiple genetic risk factors	Influences attention, impulse control, and hyperactivity
22q11.2 Deletion Syndrome	Deletion on chromosome 22	Associated with congenital heart defects, immune deficiency, and developmental delays
Williams Syndrome	Deletion on chromosome 7	Characterized by cardiovascular issues, developmental delays, and a unique cognitive profile
7q11.23 Duplication Syndrome	Duplication on chromosome 7	Leads to intellectual disability and autism spectrum features

and organismal phenotypes (Klinkovskij et al., 2023). iPSCs, derived from patient cells, can be differentiated into neurons and other brain cell types, providing in vitro models to study disease mechanisms and test potential therapies (Penney et al., 2020). These technologies have advanced our understanding of how genetic variants disrupt neurodevelopmental processes and contribute to NDDs.

4. Integrative Approaches and Systems Biology

4.1. Multi-Omics Integration

Integrating data from multiple omics layers, including genomics, transcriptomics, proteomics, and metabolomics, can provide a holistic view of the molecular alterations in NDDs (La Cognata et al., 2021). Systems biology approaches leverage computational models to analyze these complex datasets, identify key regulatory networks, and predict disease mechanisms. For example, integrating GWAS data with gene expression and protein-protein interaction networks has uncovered novel genes and pathways involved in ASD (Chen et al., 2020). Multi-omics integration holds promise for identifying biomarkers, elucidating disease mechanisms, and discovering new therapeutic targets (Olivier et al., 2019).

4.2. Network-Based Approaches

Network-based approaches, such as gene co-expression networks and protein interaction networks, are powerful tools for understanding the functional relationships between genes and proteins in NDDs (Sriroopreddy et al., 2019). These approaches can identify modules of co-expressed genes or interacting proteins that are dysregulated in disease states. For instance, gene co-expression network analysis has revealed modules related to synaptic function and immune responses in ASD (Mahfouz et al., 2015). Network-based methods can also prioritize candidate genes for functional studies and drug targeting, facilitating the development of precision medicine approaches for NDDs.

5. Clinical Applications and Translational Research

5.1. Genetic Testing and Diagnosis

Advancements in genomic technologies have significantly improved the diagnostic yield for NDDs. Genetic testing, including WES, WGS, and targeted gene panels, can identify pathogenic variants in affected individuals, providing definitive diagnoses and informing clinical management (Lionel et al., 2018). Early genetic diagnosis is crucial for initiating appropriate interventions and genetic counseling for families. Moreover, identifying genetic subtypes of NDDs can facilitate stratification of patients for clinical trials and personalized treatment approaches (Chen and Geschwind, 2022).

5.2. Therapeutic Interventions

The identification of genetic variants and pathways involved in NDDs has opened new avenues for therapeutic interventions. Gene therapy, which involves delivering functional copies of defective genes, holds promise for monogenic NDDs such as Rett syndrome (Turner et al., 2021). Antisense oligonucleotides (ASOs) and small

molecules targeting specific genetic mutations or dysregulated pathways are being developed for various NDDs. For instance, ASOs targeting the mutated FMR1 gene in Fragile X syndrome have shown potential in preclinical studies (Winkelsas and Fischbeck, 2020). Additionally, understanding the role of epigenetic modifications in NDDs has spurred interest in developing epigenetic therapies to modulate gene expression.

5.3. Biomarker Discovery

Biomarkers are critical for early diagnosis, prognosis, and monitoring treatment responses in NDDs (Scassellati et al., 2020). Genomic and transcriptomic profiling of peripheral tissues, such as blood or saliva, can identify biomarkers reflective of neurodevelopmental changes. For example, altered gene expression profiles in blood have been associated with ASD and ADHD (McCaffrey et al., 2020). Proteomic and metabolomic studies can also uncover biomarkers related to neuroinflammation, oxidative stress, and metabolic dysregulation in NDDs (Maszka et al., 2023). Validating and implementing biomarkers in clinical practice can improve early detection and personalized treatment of NDDs.

6. Emerging Technologies in Genomic Research

6.1. Single-Cell Genomics

Single-cell genomics, including single-cell RNA sequencing (scRNA-seq) and single-cell ATAC sequencing (scATAC-seq), has emerged as a powerful approach to study cellular heterogeneity and gene regulation in the brain (Kim et al., 2024). These technologies enable the analysis of gene expression and chromatin accessibility at the resolution of individual cells, providing insights into cell type-specific changes in NDDs. Single-cell genomics can reveal how genetic mutations affect different cell populations in the brain and identify novel cell types involved in disease pathogenesis (Skene and Grant, 2016). Moreover, it can uncover rare cell populations that may play critical roles in NDDs but are undetectable in bulk tissue analyses.

6.2. Long-Read Sequencing

Long-read sequencing technologies, such as those developed by Pacific Biosciences and Oxford Nanopore, offer significant advantages over short-read sequencing for detecting structural variants, repetitive regions, and complex genomic regions. These technologies can resolve large insertions, deletions, and inversions that are often missed by short-read sequencing (Olivucci et al., 2024). Long-read sequencing can also improve the assembly of reference genomes and identify novel transcripts and isoforms that contribute to NDDs (Olivucci et al., 2024). By providing more comprehensive and accurate genomic information, long-read sequencing will enhance our understanding of the genetic basis of NDDs and facilitate the discovery of novel pathogenic variants.

6.3. CRISPR-Based Functional Genomics

CRISPR-based technologies have revolutionized functional genomics by enabling precise manipulation of the genome. CRISPR-Cas9 can be used to generate knockout and knock-in models to study the effects of genetic variants associated with NDDs (Rahman et al., 2022). Additionally, CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) can be employed to modulate gene expression and investigate the role of specific genes and pathways in neurodevelopment. CRISPR screens, which involve systematically targeting thousands of genes, can identify key regulators of neuronal development and function (Kampmann, 2020). These approaches provide powerful tools for functional characterization of genetic variants and the identification of potential therapeutic targets (Table 2).

7. Translating Genomic Findings to Clinical Practice

7.1. Personalized Medicine and Targeted Therapies

The integration of genomic data with clinical information and environmental exposures is paving the way for personalized medicine approaches in NDDs. Personalized medicine aims to tailor interventions based on an individual's genetic and molecular profile, improving treatment efficacy and reducing adverse effects Personalized medicine: motivation, challenges, and progress (Goetz and Schork, 2018). For example, pharmacogenomic studies can identify genetic variants that influence drug metabolism and response, guiding personalized medication choices. Personalized medicine approaches also encompass non-pharmacological interventions, such as behavioral therapies and educational strategies, tailored to an individual's unique needs and strengths (Sagud et al., 2021). By considering the genetic and molecular underpinnings of NDDs, personalized medicine holds promise for enhancing treatment outcomes and quality of life for affected individuals.

7.2. Development of Novel Therapeutics

The identification of genetic variants and pathways involved in NDDs has opened new avenues for therapeutic development. Gene therapy, which involves delivering functional copies of defective genes, holds promise for monogenic NDDs such as Rett syndrome and Fragile X syndrome (Turner et al., 2021). Antisense oligonucleotides (ASOs) and small molecules targeting specific genetic mutations or dysregulated pathways are being developed for various NDDs. For instance, ASOs targeting the mutated FMR1 gene in Fragile X syndrome have shown potential in preclinical studies (Protic and Hagerman, 2024). Understanding the role of epigenetic modifications in NDDs has spurred interest in developing epigenetic therapies to modulate gene expression. Additionally, targeted therapies that modulate specific signaling pathways or neurotransmitter systems implicated in NDDs are being explored. These approaches aim to correct the underlying molecular defects and improve neurodevelopmental outcomes.

7.3. Biomarker Validation and Implementation

Biomarkers are critical for early diagnosis, prognosis, and monitoring treatment responses in NDDs (Giampietri et al., 2022). Genomic and transcriptomic profiling of peripheral tissues, such as blood or saliva, can identify biomarkers reflective of neurodevelopmental changes. For example, altered gene expression profiles in blood have been associated with ASD and ADHD (McCaffrey et al., 2020). Proteomic and metabolomic studies can also uncover biomarkers related to neuroinflammation, oxidative stress,

Table 2: The technologies used in genomic research on pediatric neurodevelopmental disorders

Technology	Applications
Whole-Exome Sequencing	• Identifying mutations in coding regions associated with single-gene disorders • Enhancing diagnostic accuracy for syndromic NDDs
Whole-Genome Sequencing	• Comprehensive analysis of genetic variants, including SNVs and structural variations • Detection of large copy number variations (CNVs) and non-coding region mutations
Genome-Wide Association Studies	• Identifying common genetic variants associated with polygenic NDDs like ASD and ADHD • Mapping genetic risk loci to understand complex inheritance patterns
RNA Sequencing	• Gene expression profiling to identify dysregulated genes in NDDs • Single-cell RNA-seq to uncover cell type-specific expression changes
Epigenome-Wide Association Studies	• Mapping DNA methylation and histone modifications associated with NDDs • Understanding the impact of environmental factors on gene regulation
Chromatin Immunoprecipitation Sequencing	• Identifying binding sites of DNA-associated proteins and transcription factors • Investigating epigenetic modifications and their role in NDDs
Induced Pluripotent Stem Cells Models	• Modeling NDDs in vitro by differentiating patient-derived iPSCs into neurons • Studying the functional impact of genetic mutations on neurodevelopment
CRISPR-Cas9 Gene Editing	• Precise editing of specific genomic loci to study the effects of mutations • Generating knockout and knock-in models to investigate gene function in NDDs
Single-Cell Genomics	• Analyzing gene expression and chromatin accessibility at single-cell resolution • Revealing cellular heterogeneity and rare cell populations in the brain
Long-Read Sequencing	• Detecting structural variants and repetitive regions that are missed by short-read sequencing • Improving assembly of reference genomes and identifying novel transcripts and isoforms
Proteomics and Metabolomics	• Identifying protein and metabolite biomarkers for early diagnosis and treatment monitoring • Understanding metabolic dysregulation and neuroinflammation in NDDs
Network-Based Approaches	• Constructing gene co-expression and protein interaction networks to understand functional relationships • Prioritizing candidate genes and pathways for further study and therapeutic targeting
Multi-Omics Integration	• Combining genomics, transcriptomics, proteomics, and metabolomics data to gain a comprehensive understanding of NDDs • Using systems biology approaches to identify key regulatory networks and predict disease mechanisms.

and metabolic dysregulation in NDDs (Scarian et al., 2024). Validating and implementing biomarkers in clinical practice can improve early detection and personalized treatment of NDDs. Additionally, biomarkers can facilitate the stratification of patients for clinical trials, enabling the evaluation of targeted therapies in specific subgroups of patients (Catenacci, 2015). The integration of biomarkers into clinical workflows will enhance diagnostic accuracy, guide treatment decisions, and monitor therapeutic responses in NDDs.

8. Future Perspectives

8.1. Advances in Genomic Technologies

The continuous advancement of genomic technologies promises to further enhance our understanding of pediatric NDDs. Single-cell genomics, including single-cell RNA-seq and single-cell ATAC-seq, will provide unprecedented resolution of cellular heterogeneity and gene regulation in the brain. Long-read sequencing technologies, such as those developed by Pacific Biosciences and Oxford Nanopore, will improve the detection of structural variants and complex genomic regions that are challenging to analyze with short-read sequencing. These technologies will enable more comprehensive genetic and epigenetic analyses, leading to novel insights into NDDs. Furthermore, advances in bioinformatics and computational tools will facilitate the analysis and interpretation of large-scale genomic datasets, uncovering new genetic variants and pathways involved in NDDs.

8.2. Precision Medicine

The integration of genomic data with clinical information and environmental exposures will pave the way for precision medicine approaches in NDDs (Strianese et al., 2020). Tailoring interventions based on an individual's genetic and molecular profile can improve treatment efficacy and reduce adverse effects. For example, pharmacogenomic studies can identify genetic variants that influence drug metabolism and response, guiding personalized medication choices (Carr et al., 2021). Precision medicine approaches also encompass non-pharmacological interventions, such as behavioral therapies and educational strategies, tailored to an individual's unique needs and strengths (Kremers et al., 2022). By considering the genetic and molecular underpinnings of NDDs, precision medicine holds promise for enhancing treatment outcomes and quality of life for affected individuals.

8.3. Ethical and Social Considerations

The rapid progress in genomic research raises important ethical and social considerations. Genetic testing and the identification of genetic risk factors for NDDs can have significant implications for individuals and families, including psychological impacts and concerns about privacy and discrimination (Bi et al., 2022). Ensuring equitable access to genetic testing and personalized therapies is crucial, as disparities in healthcare can exacerbate existing inequalities. Engaging with patients, families, and communities in the research process and addressing ethical, legal, and social issues will be essential for the responsible translation of genomic discoveries into clinical practice. Furthermore, education and counseling are necessary to help individuals and families understand the implications of genetic findings and make informed decisions about their healthcare.

9. Conclusion

The genomic era has brought unprecedented insights into the etiology and pathogenesis of pediatric neurodevelopmental disorders. Advances in sequencing technologies, functional genomics, and integrative approaches have identified numerous genetic variants and pathways involved in these complex disorders. Translating these findings into clinical practice through genetic testing, biomarker discovery, and targeted therapies holds great promise for improving the diagnosis, treatment, and prognosis of NDDs. Future research efforts should focus on leveraging emerging genomic technologies, integrating multi-omics data, and addressing ethical and social considerations to advance precision medicine and ultimately improve outcomes for children with neurodevelopmental disorders.

Declarations

Ethics approval statement

No ethical approval was required for the current study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

Funding

Not Applicable

Acknowledgements

Not Applicable

Author contribution

D.D: Conceptualization, Writing and Reviewing draft. C.D: Investigation, Project administration, and Supervision

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