SHORT COMMUNICATION

From genetics to functional pathways, neurodevelopmental disorders

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Allen D, Green S. From genetics to functional pathways, neurodevelopmental disorders. Neurodev Disord Treat. 2022; 5(3):16-18.

ABSTRACT

NDDs are a group of illnesses that impact brain development and function and are defined by a wide range of hereditary and clinical characteristics. The numerous factors that determine the clinical presentation of NDDs are discussed in this review, with a focus on gene vulnerability, mutational load, and the two-hit model. Despite the complicated architecture of NDD mutational processes, the numerous proteins implicated tend to converge on common pathways such as synaptic plasticity/function, chromatin remodelers, and the Mammalian Target of Rapamycin (mTOR) pathway. The identification of candidates that could be targeted for therapeutic approaches would ideally result from a complete understanding of the mechanics behind these pathways.

Key word: *Neurodevelopmental disorders; Autism spectrum disorder; Mutations; Next-generation sequencing*

INTRODUCTION

The inability to meet cognitive, emotional or motor developmental milestones is a symptom of Neurodevelopmental Disorders (NDDs). NDDs are usually linked to a breakdown in the precisely synchronized events that contribute to brain development. NDDs are a severe public health issue in our culture, impacting more than 3% of children worldwide. They have a variety of causes and result in impairments in cognition, communication, adaptive behavior, and psychomotor skills. Autism Spectrum Disorder (ASD), Intellectual Impairment (ID), Attention Deficit Hyperactivity Disorder (ADHD), and epilepsy are all examples of NDDs.

Many investigations have shown that the many clinical symptoms that characterize NDDs are due to common molecular pathways [1]. As a result, comorbidity between two or more of these illnesses is common. Individual patients with ID, ASD, and epilepsy, for example, are frequently recorded. The discovery of shared pathogenic pathways among the many NDDs will aid in the explanation of the aforementioned comorbidity and, ultimately, lead to appropriate therapy.

Different forms of mutations, such as chromosomal rearrangements, copy number variations, minor indels, and point mutations, have been linked to NDDs in terms of genetics. As a result, molecular diagnostics, or the identification of a possible underlying mutational event, is a difficult undertaking that must overcome the heterogeneity of this vast array of genetic variations [2].

Starting with genetics and progressing to the functional level, this review focuses on the molecular etiology of NDDs. First, we'll go through how studying familial instances helped us better grasp the complex genetics of NDDs. Second, we evaluate genetic factors such as gene vulnerability, mutational burden, and various molecular diagnostics that influence and decide the phenotype. The importance of the two-hit model in understanding the genetics of NDDs is also highlighted. Finally, we discuss whether identifying frequently impacted cellular pathways might help to overcome the problem of NDDs' wide genetic diversity, as well as whether identifying such pathways can lead to new therapeutic options in the future [3].

The discovery of probable genetic origins of NDDs is critical for understanding the molecular mechanisms behind their start and for establishing a genotype-phenotype association that can be used to track the disorder's progression and predict future difficulties. Despite the discovery of multiple NDD-causing genes, many people with NDDs are still without a molecular diagnosis. Furthermore, phenotype-genotype correlation investigations have revealed that the quantity and intensity of clinical symptoms might differ significantly amongst patients with overlapping genetic etiologies. Thus, the lack

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Received: 04-Mar-2022, Manuscript No. pulndt-22-4425; Editor Assigned: 06-Mar-2022, PreQC No. pulndt-22-4425(PQ); Reviewed: 18-Mar-2022, QC No.pulndt-22 -4425(Q); Revised: 20-Mar-2022, Manuscript No. pulndt-22 -4425(R) Published: 25-Mar-2022, DOI: 10.37532/pulndt.22. 5(3).16-18.

of heritability and phenotypic heterogeneity suggest that NDDs are multifactorial and/or polygenic [1,3].

In the presence of a shared genetic background, familial NDDs provide a suitable model for dissecting the contribution of genetic and nongenetic variables to the etiology of these disorders [4]. As a result, numerous researches on monozygotic twins with discordant phenotypes or pedigrees with partial penetrance and phenotypical heterogeneity in multiple affected children have been done. This avenue of research offers enormous potential, not just in terms of identifying the disease's molecular causes, but also in terms of identifying risk and protective variables. It also offers the ability to create more precise genotype-phenotype relationships. The study of inherited NDDs has revealed that the phenotypical outcome is mostly determined by two factors: gene vulnerability and mutational burden.

Gene vulnerability is defined as a gene's ability to withstand disruptive variants: the lower the tolerance for mutations, the higher the vulnerability level. Some of the genes linked to NDDs are haploinsufficient genes with high dosage sensitivity. These genes are classified as highly susceptible genes, which mean that mutations affecting them are linked to a higher risk of disease [5]. DEPDC5, CACNA1A, and SCN8A, which are mentioned further in this section, are examples of extremely susceptible genes. In the absence of other causal events, disruption of one of these genes has a high probability of initiating the beginning of a disease phenotype, leading to monogenic variants of NDDs. As a result, mutations affecting these genes are typically subjected to a lot of negative selection. As a result, when compared to other genomic sites, population studies have discovered a lower proportion of disruptive mutations in susceptible genes. In other words, mutations in highly vulnerable genes are classified as rare variants with high penetrance and a high risk of disease.

Genes that are less vulnerable to disruptive mutations are at the other extreme of the vulnerability scale. Variants in these genes are not subject to negative selection and are regularly passed down across families. Indeed, the combined consequences of these mutational events may lead to a disease phenotype. The phenotypic outcome in these circumstances, however, is determined not only by the sum of the effects of the single mutations but also by the physical and/or functional connections between the afflicted genes. The idea of mutational burden, which claims that the number of disruptive events influences the penetrance and complexity of a disease manifestation, closely correlates with epistatic interactions and dose sensitivity.

A larger mutational burden may be determined by a mix of germline and somatic events in other situations, a mechanism known as the two-hit model. A constitutive hereditary mutation creates a vulnerable genetic background in the standard two-hit hypothesis [6]. The start of a disease phenotype or the amplification of already present clinical characteristics will be caused by a subsequent somatic hit later in development. Mutations in DEPDC5 are one example of a two-hit model. DEPDC5 loss-of-function mutations in the germline are a common cause of familial refractory focal epilepsies. In patients with a severe phenotype, a second somatic variation inducing biallelic inactivation of DEPDC5 was discovered to be responsible for the development of localized cortical dysplasia [6,7].

The use of next-generation sequencing (NGS) technologies in the diagnostic flowchart of NDDs has resulted in a significant increase in the number of patients receiving a molecular diagnosis. The discovery of the disease's genetic origin has significant implications for genetic counselling and patient care, as it allows for a more accurate evaluation of the risk of recurrence and the prediction of future medical consequences. The growth of functional genomic studies aiming at identifying the pathogenic pathways associated with the reported mutations has also been aided by breakthroughs in the study of genetics [8].

Most rare and common variations associated with NDDs impact genes that play a role in a few conserved pathways, according to functional analyses conducted over the last decade. The Psychiatric Cell Map Initiative was founded a few years ago with the goal of better understanding the molecular pathophysiology of NDDs and defining essential biological pathways across temporal and geographical axes [9]. Along similar lines, it was discovered that both common and unusual variations cause homeostatic homeostasis to be disrupted at various levels (i.e., at a cellular, circuit, or whole-brain level).

NDD-causing mutations, both rare and widespread, commonly disrupt the homeostatic balance of protein synthesis throughout neurodevelopment. The phosphatidylinositol 3-kinase (PI3K)-mTOR axis is a critical component of this equilibrium, and mutations in this axis have been linked to a variety of NDDs (also known as myopathies). mTOR is a widely expressed serine/threonine kinase found in all eukaryotic cells. Through the use of two distinct compounds (mTORC1 and mTORC2). mTOR is involved in several other important processes in the adult brain, including adult neurogenesis, learning, memory, circuit refinement, and synaptic plasticity. The growth factor pathway, which includes the PI3K-AKT-TSC complex, the energy-sensing arm, which response to low ATP concentrations via the AMPK-TSC complex, and the amino acid-sensing arm, which is the lesser-known regulator of the mTOR pathway and controls the activation of mTORC1 directly through Rag GTPases, are all inputs to mTOR. Multiple mutations affecting negative regulators of the growth factor and amino acid-sensing arms (such as TSC1, TSC2, and PTEN or DEPDC5, NPRL2, and NPRL3, respectively) have been discovered in people with NDDs and are known to cause hyper activation of mTORC1. Individuals with ASD, ID and epilepsy have been found to have mutations in TSC1, TSC2, and signaling proteins that function upstream of the TSC complex, such as AKT or PTEN. As a result, mutations in various mTOR-regulating signaling arms appear to be associated with various phenotypic consequences [3,6].

Loss-of-function mutations in the SET-domain containing 5 (SETD5) gene have been identified as one of the most common causes of ID and ASD in recent years. SETD5 is a crucial regulator of the transcription apparatus and the activity of chromatin-modifying transcriptional corepressor complexes. As a result, SETD5 appears to be critical for gene expression regulation during early development and learning [8,9].

The research of hereditary NDDs has contributed to a greater understanding of the role of many genetic variables in the etiology of these disorders. Despite NDDs' wide genetic diversity, the functional effects of many mutations appear to concentrate on the disruption of highly interconnected fundamental biochemical pathways. These signaling pathways are significant during various stages of neurodevelopment as well as in adulthood.

Despite these significant advances in our theoretical knowledge of NDDs, there is still a long way to go before we can treat them

effectively. Importantly, the functional convergence of genetic origins suggests that medications targeting these core networks may be able to reverse some of the clinical characteristics associated with NDDs [10]. A critical step toward this possibility is the development of accurate models to fully examine the molecular mechanisms of NDDs, identify promising targets, and eventually test new treatments.

CONCLUSION

Despite these important advancements in the theoretical understanding of NDDs, the road to successful treatment is still long. Importantly, the functional convergence of the genetic causes raises the possibility that drugs targeting these core networks could be used to reverse some clinical features associated with NDDs. The establishment of reliable models to fully dissect the molecular mechanisms of NDDs, identify potential targets and finally test new treatments represents a crucial step toward this possibility.

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