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REVIEW ARTICLE

# Epigenetic Modification and their Significance in Neurodevelopmental Disorder

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## ABSTRACT

This study highlights the role of epigenetic processes as a key mechanism in the regulation and origin of neurodevelopmental disorders. Neurodevelopmental disorders encompass a different range of conditions that emerge while the developmental stage, marked by deficits in cognitive abilities or social interactions. Epigenetics plays a crucial role in gene regulation through chemical changes of DNA and histone proteins, which package the DNA. This regulation firstly involves DNA methylation and histone modifications, influencing chromatin structure and gene expression.

The failure of this mechanism can cause various congenital disorders, some of which are discussed in this review like autism spectrum disorder (ASD), Attention/Deficit-Hyperactivity Disorder (ADHD), Genomic imprinting disorder, Cerebral Palsy (CP) and Intellectual disability disorders (IDDs). Thus, it summarizes the current association between epigenetics and the given disorders. Epigenetic modification in the genome are highly susceptible to environmental influences, including malnutrition, exposure to chemicals, and psychological stress, particularly during early development. Additionally, endocrine-disrupting chemicals can alter epigenetic patterns and gene expression, potentially contributing to conditions like autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). This highlights the role of epigenetic mechanisms in neurodevelopment throughout life and their impact on both neurodevelopmental and neurodegenerative disorders. By focussing on these

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aspects, this study aims to bring attention towards the environmental cues, their influence on epigenetics and the variance occurrence of congenital disorders.

**KEYWORDS**

•Epigenetics • Neurodevelopmental disorders • DNA methylation • ASD • ADHD • Genomic imprinting • Environmental factors

## INTRODUCTION

Epigenetic dysfunctions play a crucial role in neurodevelopmental disorders (NDs) like ASD, ADHD, cerebral palsy, and intellectual disability[1], Cerebral Palsy, a group of motor impairment disorder[2] and Intellectual disability disorder, characterized by impairment in cognitive abilities[3]. Epigenetics regulates gene expression through DNA methylation and histone modifications without altering DNA sequences[4].

Environmental factors, including maternal toxicant exposure, hypoxia, endocrine disruptors, and malnutrition, contribute significantly to NDs by modifying the epigenome. Endocrine disrupting chemicals (EDCs) affect chromatin structure and histone modifying enzymes, leading to persistent epigenetic changes[10]. Exposure to low doses of BPA during prenatal development can cause persistent epigenetic alterations in the brain, while influencing DNA methylation and RNA levels of estrogen receptors (ERs) in the cortex[5] (*Figure 1*). These mechanisms highlight the complex interplay between genetics and environmental factors in shaping neurodevelopmental disorders[14].

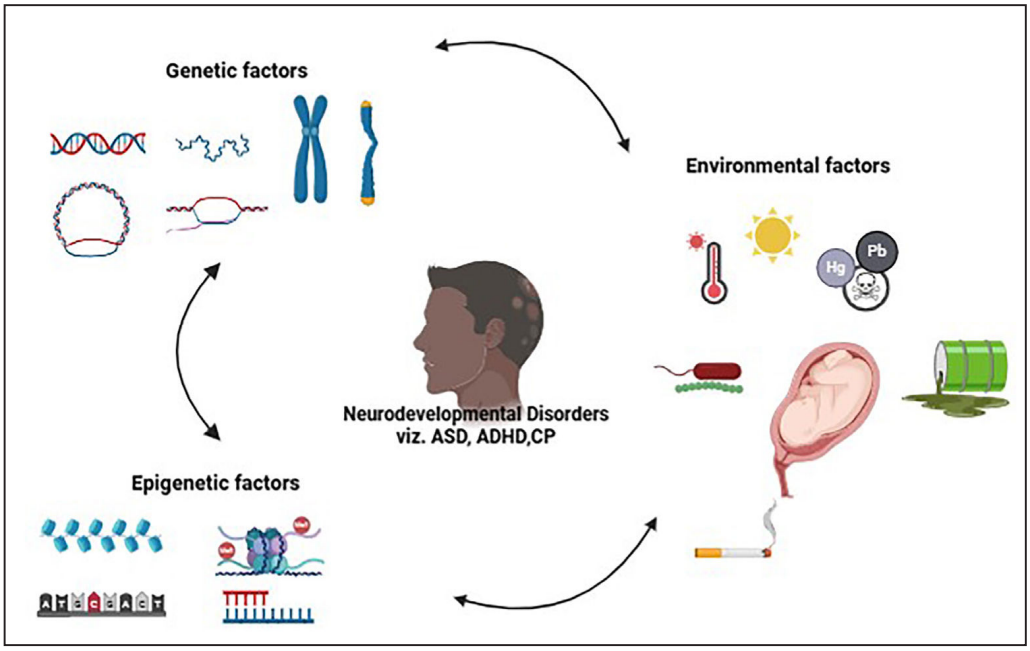



**Figure 1:** Depiction of potential roles served by various genetic, epigenetic and environmental factors in neurodevelopmental disorders

### Epigenetic Modifications

As per the current definition of epigenetics, it is the study of heritable changes in gene expression that occur without the alteration in the primary DNA sequences[5]. Chromatin is a genetic unit, composed of DNA and histone proteins, which gets modified during epigenetic processes such as DNA methylation, histone acetylation and methylation with the enzymes that brings changes in chromatin architecture[6]. Epigenetic mechanisms are crucial for regulating gene expression and are essential for proper development and cellular differentiation, including the formation of brain cells[7]. Epigenetic modifications are believed to be the key mechanisms through

which environmental factors are biologically encoded, serving as the intersection between genes and the environment[8].

### *Types Of Epigenetic Modifications*

#### (a) DNA Methylation

DNA methylation is one of the widely studied epigenetic modes of regulation that are involved in tissue differentiation during early development[2]. It adds a methyl group to the 5′ carbon of cytosine residue in dinucleotide CpG sequences, which are commonly known as CpG islands, and these sequences are mainly found in clusters and located in the promoter region of genes[1]. Depending on the extent of DNA methylation and methylation site, the methyl groups regulate gene expression by determining the activation or inhibition of activity[8].

This entire process gets initiated by the enzyme DNA methyltransferases (DNMTs) such as DNMT3a and b and maintained by DNMT1[1]. In addition to methylation at CpG sites, a substantial amount of methylation is reported to be positioned at non-CpG sites, particularly in neuronal cells[7].

Deficiency of DNA methylation leads to ICF syndrome which is a congenital disorder named after three major features, such as Immunodeficiency (e.g., IgG and IgA)[9], Centromere instability, characterized by the breakage of pericentric heterochromatic regions in chromosomes 1, 9, and 16 due to unusually low DNA methylation levels, along with facial anomalies[6].

#### (b) Histone Modifications

Nucleosomes consist of two copies each of four core histone proteins: H2A, H2B, H3, and H4, along with a linker histone, H1, which is positioned between them[10].

Histone modifications are post-translational changes that include various epigenetic alterations, such as lysine methylation and histone acetylation, which lead to chromatin remodelling and influence DNA expression[8]. These covalent modifications take place on specific residues located on the N- or C-terminal tail or the core of histones. They include acetylation, phosphorylation, methylation, ubiquitylation, and sumoylation, and are regulated by specialized enzymes such as histone acetyltransferases (HATs), histone deacetylases (HDACs), protein kinases, and histone methyltransferases (HMTs)[1].

Histone acetylation is generally linked to the activation of transcription, whereas the impact of histone methylation depends on the specific site of modification. For instance, methylation at histone 3 lysine 4 (H3K4) promotes gene activation, while methylation at histone 3 lysine 27 (H3K27) is associated with gene repression[8].

#### (c) Genome imprinting

Genomic imprinting, a form of intergenerational epigenetic inheritance which plays crucial role during human development, and alteration of these imprinted gene expression and function can lead to imprinting disorders. In humans, approximately 100 imprinted genes have been identified[11]. Many imprinted genes are organized into distinct clusters, approximately 1 Mb in size, and include genes that are expressed from both maternal and paternal alleles[12].

Disruption in imprinted inheritance can leads to several abnormalities that are known to occur in well-known developmental and neurobehavioral disorders such as Angelman, and Prader-Willi syndromes[13]. Both syndromes are neurodevelopmental disorders that share similar underlying mechanisms but exhibit distinct clinical features[1].

*Angelman syndrome*, this disorder is marked by profound intellectual disability, epilepsy that does not respond well to treatment, ataxic movements resembling a puppet-like gait, and frequent episodes of laughter. It arises from an abnormal epigenetic modification affecting the maternally inherited UBE3A allele on chromosome 15q12, which may be absent due to a maternal deletion or functionally inactive due to uniparental paternal disomy[6].

*Prader–Willi syndrome* is another epigenetic disorder caused by chromosomal deletion at 15q11-q13[6] and this condition is characterized by muscle hypotonia during infancy, undescended testes in males, short stature, small hands and feet, and the development of excessive hunger in childhood, which often results in obesity[9].

### *Role of Epigenetics in Neurodevelopmental Disorders*

Epigenetic modification is known to be one of the relevant factors in the occurrence of complex disorders[8]. It is defined as a stable

inherited phenotype resulting from alterations in a chromosome without any changes in the DNA sequences[5].

### (a) Autism Spectrum Disorder

Autism spectrum disorders are complex and pervasive neurodevelopmental conditions, which is marked by characteristics like disability in social interactions and communications, restricted interests or repetitive behaviour that typically emerged in early childhood[6]. Growing evidences from human and animal studies has suggested the significant role played by epigenetic modification in autism spectrum disorder (ASD). Early life environment such as prenatal and early postnatal periods, may also play a major role in influencing the development of ASD[4].

Several studies have suggested that ASD not arises due to the dysfunctioning of individual gene instead it resulted due to the disruption in specific genetic pathways which is an extension of an early "polygenic hypothesis" for the origins of such neurodevelopmental disorders[4]. This is conceptualized as a *spectrum* of disorders that shares the common features of previously defined different subtypes such as Asperger's Disorder, Autistic Disorder which could account for the variation in the given condition[8].

### (b) Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by excessive activity and functional impairment, arising from a mix of genetic and environmental influences[15], and characterized by impulsiveness, inattention and difficulties in organizational challenges. Affected individuals can exhibit a combination of hyperactivity and inattention or predominance of either symptom[14]. Epigenetic mechanisms, including DNA methylation, which control gene expression, have emerged as a promising molecular system for identifying biomarkers and understanding underlying processes to tackle this challenge[15].

Humans are widely exposed to methyl mercury (MeHg) through the consumption of contaminated seafood[16] oxidative stress, mitochondria toxicity and disruption of calcium homeostasis MeHg exposures at the environmental relevant level invoke the same mechanisms to alter neuronal functions. Recent research indicates that the toxic effects of environmental levels of MeHg are associated with epigenetic regulatory mechanisms[17]. Both neurodevelopmental disorders often continue into adulthood and frequently co-exist, with ADHD symptoms appearing in 30% to 50% of individuals with autism[8].

### (c) Cerebral Palsy

CP is the most prevalent motor disability found commonly in children with the prevalence rate of about 1 to over 3 per 1000 children. Principal epigenetic mechanisms that play fundamental physiologic roles connected with the CP include DNA methylation, histone modifications, and noncoding RNA[18]. It has multiple risk factors associated which includes intrauterine growth restriction or infection, placental abnormalities, inflammation, and signs of fetal distress[2].

Epigenetic modifications are considered a possible mechanism contributing to prenatal brain injury, which results in persistent motor, cognitive, and behavioural impairments. The therapeutic potential of targeting epigenetic pathways for cerebral palsy (CP) is gaining significant recognition. Research has shown altered methylation capacity and disruptions in folate one-carbon metabolism in children with severe CP[19]. Cerebral Palsy is a multifaceted and diverse disorder that can manifest in multiple ways that can vary in forms and degrees of motor impairment such as behavioural, sensory, and cognitive challenges[20].

### (d) Intellectual Disability Disorders

Intellectual Disability is not a single disorder rather a group of diverse and heterogenous collection of syndromic and non-syndromic conditions that have impaired intellectual abilities as a common hallmark. It is characterized by three major key criteria: (a) an intelligence quotient (IQ) below70; (b) limitations in at least two adaptive behaviours, such as communication, self-care, social skills, and (c) evidence that the mental manifestations began before the age of 18[21]. The causes of Intellectual and developmental disabilities are diverse and heterogeneous that encompasses environmental factors, chromosomal aberrations, and single gene mutations. Epigenetic modifications such as DNA methylation and post-translational modifications of histone proteins, including histone phosphorylation, acetylation, and

methylation, actively plays a role in the activity-dependent modulation of neuronal networks[3].

Recent studies have revealed that the mutations in several genes that encoding lysine methyl transferases (KMTs) of histone H3 causes ID in humans and represents a strong link between histone H3 methylation and cognitive capabilities[22]. Rett Syndrome (RTT) is a well-researched example of an X-linked dominant neurodevelopmental disorder (IDD) caused by mutations in a DNA methylation reader. Another IDD linked to mutations in key epigenetic regulators is Rubinstein-Taybi Syndrome (RTS)[23].

## Environmental Stress/Factors Affecting Epigentics in Neurodevelopmental Disorders

The epigenome is a potential molecular substrate through which environmental factors can alter gene expression patterns linked to normal neurodevelopment and has potential influence on brain structure and function[7]. Environmental factors such as smoking and stress may also influence epigenetic mechanism, both prenatally and throughout life[4] and maternal smoking during pregnancy is related to several adverse outcomes including congenital anomalies, reduced birth weight and sudden infant death[16]. Also, exposure to certain toxic metals, brain injury and early life stress are the identified potential factors for the diseases to occur[1].

Several environmental factors contribute to the development of neurodevelopmental disorders, including improper child-rearing practices such as neglect, malnutrition, and abuse by parents with mental health issues. Additionally, infections like rubella and cytomegalovirus can trigger immune responses in the brain, further influencing neurodevelopmental outcomes.The same study has highlighted several environmental chemicals which alters the epigenome structure. For example, a chemical named BPA (bisphenol A) known to cause reproductive toxicity that leads to immune dysregulation and growth alterations, it alters DNA methylation in fetal brain and mast cells[9] (*Figure 2*).

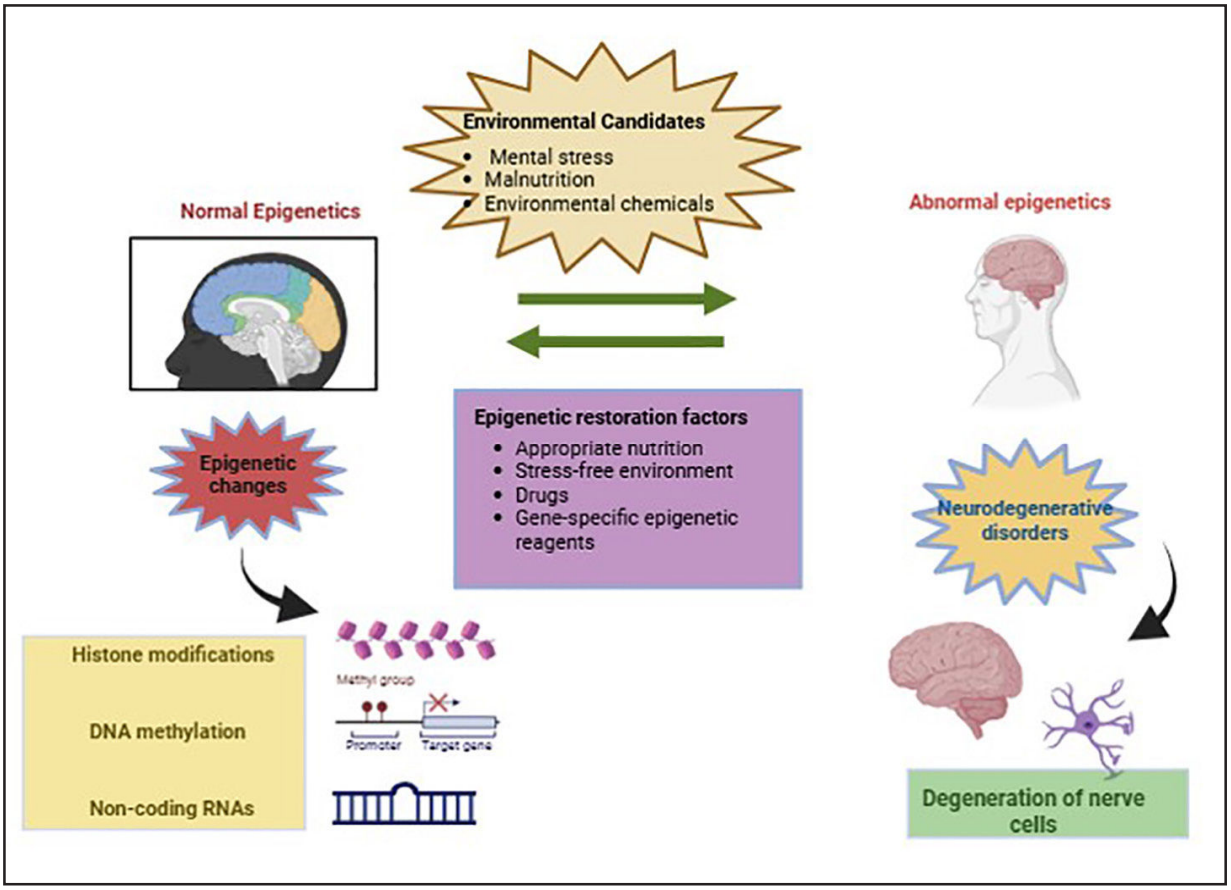



**Figure 2:** Schematic representation of normal and abnormal epigenetic candidates and restoration factors for their significant roles in NDDs

Certain environmental factors are also known to affect adult neurogenesis such as diet which can have positive or negative impact and such influence highlights a potential connection between diet and mental health[1]. These environmental factors that brings modification in a phenotypic trait do not only affect the directly exposed individual but also to the subsequent generations of offspring. Additionally, some other factors such as nutrition do not promote genetic mutations but instead play a significant part in promoting epigenetic changes[6].

## CONCLUSION

Epigenetic mechanisms are critical tool for the nervous system's development and their proper functioning as many aspects of epigenetic regulation are critical for normal in utero brain development[13]. DNA methylation and histone modifications are thought to play a significant and influential role in controlling gene expression and activity throughout the various stages of development, in adulthood[10]. Also, their active involvement in neuronal circuit and connected neurodegenerative diseases provides new insights into the underlying causes and mechanisms[12].

This article explores various disorders, including ASDs, ADHD, CP, and IDDs, that involve epigenetic abnormalities resulting from genetic mutations in key enzymes and proteins or chromosomal anomalies like Prader-Willi syndrome. Additionally, it examines epigenetic disruptions caused by environmental factors such as chemical exposure, nutrition, and psychological stress[17].

The transgenerational impact of environmental toxins necessitates alterations in the germline through either chromosomal changes or epigenetic modification pathways[10]. Thus, it became clear that environmental factors can influence the pathways of epigenetic reprogramming and contribute to the rise of imprinting disorders and the availability of factors needed for imprint may get affected by exposing to chemical pollutants[14]. The review also aims to bring insights into the inevitable role of maintaining imprinted genes, as it is vital for normal embryonic development, and misregulation of which leads to clinical diseases[15].

**Conflict of Interest:** Nil

## REFERENCES


1. Gapp K.;, Woldemichael B.T., Bohacek J., Mansuy I. Epigenetic regulation in neurodevelopment and neurodegenerative diseases Rights / license: Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International. doi:10.3929/ethz-b-000063022
2. Mohandas N., Bass-Stringer S., Maksimovic J., *et al*. Epigenome-wide analysis in newborn blood spots from monozygotic twins discordant for cerebral palsy reveals consistent regional differences in DNA methylation. *Clin Epigenetics*. 2018; 10(1). doi:10.1186/s13148-018-0457-4.
3. Iwase S., Bérubé N.G., Zhou Z., *et al*. Epigenetic etiology of intellectual disability. *Journal of Neuroscience*. 2017; 37(45): 10773-10782. doi:10.1523/JNEUROSCI.1840-17.2017
4. Loke Y.J., Hannan A.J., Craig J.M. The role of epigenetic change in autism spectrum disorders. *Front Neurol*. 2015;6(MAY). doi:10.3389/fneur.2015.00107
5. Kubota T., Takae H., Miyake K. Epigenetic mechanisms and therapeutic perspectives for neurodevelopmental disorders. *Pharmaceuticals*. 2012; 5(4): 369-383. doi:10.3390/ph5040369
6. Kubota T., Mochizuki K. Epigenetic effect of environmental factors on autism spectrum disorders. *Int J Environ Res Public Health*. 2016;13(5). doi:10.3390/ijerph13050504
7. Kundakovic M., Jaric I. The epigenetic link between prenatal adverse environments and neurodevelopmental disorders. *Genes (Basel)*. 2017; 8(3). doi:10.3390/genes8030104
8. Dall'Aglio L., Muka T., Cecil CAM, *et al*. The role of epigenetic modifications in neurodevelopmental disorders: A systematic review. *Neurosci Biobehav Rev*. 2018; 94: 17-30. doi:10.1016/j.neubiorev.2018.07.011
9. Kubota T. Epigenetic alterations induced by environmental stress associated with metabolic and neurodevelopmental disorders. *Environ Epigenet*. 2016; 2(3). doi:10.1093/eep/dvw017
10. Cristancho A.G., Marsh E.D. Epigenetics modifiers: potential hub for understanding and treating neurodevelopmental disorders from hypoxic injury. *J Neurodev Disord*. 2020; 12(1). doi:10.1186/s11689-020-09344-z
11. Monk D., Mackay DJG, Eggermann T., Maher E.R., Riccio A. *Genomic Imprinting Disorders: Les.sons on How Genome, Epigenome and Environment Interact*.

**12.** Kalish J.M., Jiang C., Bartolomei M.S. Epigenetics and imprinting in human disease. *International Journal of Developmental Biology*. 2014; 58(2-4): 291-298. doi:10.1387/ijdb.140077mb

**13.** *The Majority of Genes Are Inherited in 2 Copies*.

**14.** Dall'Aglio L., Muka T., Cecil CAM, *et al*. The role of epigenetic modifications in neurodevelopmental disorders: A systematic review. *Neurosci Biobehav Rev*. 2018; 94: 17-30. doi:10.1016/j.neubiorev.2018.07.011

**15.** Cecil CAM, Nigg J.T. Epigenetics and ADHD: Reflections on Current Knowledge, Research Priorities and Translational Potential. *Mol Diagn Ther*. 2022; 26(6): 581-606. doi:10.1007/s40291-022-00609-y

**16.** Tran NQV, Miyake K. Neurodevelopmental Disorders and Environmental Toxicants: Epigenetics as an Underlying Mechanism. *Int J Genomics*.2017;2017.doi:10.1155/2017/7526592

**17.** Ke T., Tinkov A.A., Skalny A.V., *et al*. Developmental exposure to methylmercury and ADHD, a literature review of epigenetic studies. *Environ Epigenet*. 2021;7(1). doi:10.1093/eep/dvab014

**18.** Romero B., Robinson K.G., Batish M., Akins R.E. An emerging role for epigenetics in cerebral palsy. *J Pers Med*. 2021;11(11). doi:10.3390/jpm11111187

**19.** Bahado-Singh R.O., Vishweswaraiah S., Aydas B., Mishra N.K., Guda C., Radhakrishna U. Deep learning/artificial intelligence and blood-based DNA epigenomic prediction of cerebral palsy. *Int J Mol Sci*. 2019; 20(9). doi:10.3390/ijms20092075

**20.** Salomon I. Neurobiological Insights Into Cerebral Palsy: A Review of the Mechanisms and Therapeutic Strategies. *Brain Behav*. 2024; 14(10): e70065. doi:10.1002/brb3.70065

**21.** Van Bokhoven H. Genetic and epigenetic networks in intellectual disabilities. *Annu Rev Genet*. 2011; 45: 81-104. doi:10.1146/annurev-genet-110410-132512

**22.** Parkel S., Lopez-Atalaya J.P., Barco A. Histone H3 lysine methylation in cognition and intellectual disability disorders. *Learning and Memory*. 2013; 20(10): 570-579. doi:10.1101/lm.029363.112

**23.** Toma I. De, Gil L.M., Ossowski S., Dierssen M. Where Environment Meets Cognition: A Focus on Two Developmental Intellectual Disability Disorders. *Neural Plast*. 2016; 2016. doi:10.1155/2016/4235898