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Review Article

The mosaic genome: De novo variations driving neurodevelopment in autism spectrum disorder, intellectual disability, and epilepsy

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Abstract

Neurodevelopmental disorders (NDDs) such as Autism Spectrum Disorder (ASD), Intellectual Disability (ID), and Epilepsy (EP) are complex conditions caused by disruptions in brain development that are typically mediated by rare genetic mutations. Of these, de novo mutations (DNMs)—not inherited but spontaneous—have become the key drivers. These mutations, more likely to be pathogenic than inherited mutations, may arise from either gametogenesis or early embryonic development and in some cases result in mosaicism, where only some of the genes carry the mutations.

This is a review of the molecular etiology, mutation pattern, and pathogenicity of DNMs and mosaic variants in ASD, ID, and EP. With *denovo-db* curated databases and functional network analysis via the *STRING* database, the article addresses the type of DNMs (missense, frameshift, splice-site, etc.), where they occur on the chromosome, and the recurrent genes involved like CHD8, SCN2A, SYNGAP1, and GRIN2B. Interestingly, an unprecedentedly high proportion of these DNMs are CpG transition mutations, commonly linked to methylation instability and paternal age or environmental stress.

The paper also acknowledges the manner in which overlap between DNMs of such disorders generates shared molecular networks that include chromatin remodeling, synaptic function, and ion channel regulation. The findings are consistent with the hypothesis that shared genetic architecture explains differential NDD phenotypes, with DNMs as primary markers of early developmental derangements.

Through the translation of genomic data to functional gene assessment, the review presents a convergent summary of spontaneous and mosaic genetic variants' capacity to drive neurodevelopmental processes to the onset and comorbidity of ASD, ID, and EP. It emphasizes the importance of ongoing whole-exome and whole-genome sequencing research in the discovery of actionable mutations and the identification of future therapeutic targets.

Keywords: De novo mutations, Neurodevelopmental disorders, Autism spectrum disorder, Intellectual disability, Epilepsy, Whole exome sequencing, Whole genome sequencing, Gene ontology, Missense mutations, CpG transitions, Genetic overlap.

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1. Introduction

Neurodevelopmental disorders (NDDs) affect the development and functioning of the brain and neurological system evincing impairment in learning, behaviour, communication and cognition. NDDs are the consequence of heterogenous abnormal genetic conditions.[1]

Categorization of NDDs comprises of Intellectual Disability (ID), Specific Learning Disorder, Attention Deficit Hyperactivity Disorder (ADHD), autism spectrum disorder (ASD), Motor Disorders and Communication disorders, conforming to the 5th edition of Diagnostic and Statistical Manual of Mental Disorders, DSM-5.[2]

Excluding the domain of DSM-5, disorders like Epilepsy (EP) and Cerebral Palsy are also encompassed in NDDs.[1] The disorders overlap with each other as observed in multiple cases.[3] For example, 22% of children suffering for Epilepsy were diagnosed with ASD, and 33% with ADHD,[4] both Learning disorder and ADHD had great prevalence in 4% of the children in the United States. Likewise, Epilepsy is dynamically linked with Intellectual Disability and Autism Spectrum Disorders.[5]

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Multiple factors contribute to the genesis of NDDs that includes environmental conditions, such as effect of drug exposure to the foetus, contaminants in the environment, deprivation of oxygen in infants and genetic conditions incorporating chromosomal aberrations, monogenic conditions even extending to variation in single nucleotides.[1]

The genetic abnormalities contribute majorly in disorders such as ASD, ID and Epilepsy.[6] Techniques like Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES) have widely conferred the copious de novo mutations that are associated with NDDs. It has been acknowledged that these de novo mutations are the prime candidates responsible for the occurrence of the disorders.

1.1. De novo mutations (DNMs)

DNMs are rare genetic variants that are unique to the offspring and tend to be more pathogenic than variants that are inherited[7]. They originate either during gametogenesis or post the formation of zygote[8]. Multiple cell divisions during spermatogenesis increases the rate of mutation for substitution of nucleotide bases. We now acknowledge that DNMs majorly arise from paternal origin (75-80%) and at a higher paternal age.[9,10]

Large sex based cohort studies of offspring affected with NDDs and their parents identified enrichment of DNMs in sex based genes in females more than males, decoding that DNMs in females are likely to be more potential in the genesis of NDDs being the rarer class.[11] The intolerant genes carry fewer DNMs than tolerant genes. The development of NDDs are more likely to be influenced by intolerant genes.[12]

Additionally, batch studies of parents-offspring trio describe the distribution of DNMs throughout the genome and the context of their emergence with potential root mechanisms.

1.2. Causes of De novo mutations (DNMs)

DNMs arise when DNA polymerases make errors in the integration of nucleotides during the synthesis of DNA.[13] DNA polymerases δ and ε polymerize (in opposite strands) in an exceedingly selective process, with only one mismatch in 10^4-10^5 bp in average.[14] Their proofreading activity ensures the incorporation of the correct base.[13]

Mismatches that occur in the replicating DNA are reinstated by the Mismatch Repair Pathway (MMR). In efficiency, MMR pathway have a lower rate of base substitution errors in comparison with the error rate of polymerases. But, mutations arise when the speed of repair is comparatively lower than the base substitution frequency.[15] Furthermore, inefficient repair and incorporation of damaged bases also bring about mispairings.[16]

Mutagens such as UV radiation or Reactive Oxygen Species (ROS) can lead to spontaneous DNA lesions that are restored by base excision repair and nucleotide excision repair. Incomplete repair before replication can result in permanent lesions leading to germline DNMs. The rate of DNMs in germline depends on the rate of appearance of DNA damage before mutagenesis to the rate of DNA repair.[17]

Postzygotic DNMs that lead to mosaicism can be a factor contributing to NDDs.[18] It has been noticed that, the rates of postzygotic mutations in the early embryonic stages are imperceptibly higher than the rates of germline mutations. Studies on children affected with NDDs have perceived abundant occurrence of mosaic DNMs in the coding regions of the genome, 3-5% of which are responsible for causing the NDDs.[19]

DNA methylation majorly occurs at CpG sites. A methyl group is added at 5' C that makes it highly unstable and prone to deamination to T. This elevates the mutation rate even in the neighbouring sequences. Rate of mutation was also observed to be increased by deamination at TpC sites (C:G>{T:A, A:T, or G:C}).[20] Methylated DNA can be one of the prospective causes for the enrichment of DNMs.

1.3. Environmental factors causing DNMs

Research on the pathogenesis of NDDs was predominantly focused on the genetic factors.[21-23] But, it is evident that genetic deviations are not the only reason for the development of NDDs. Recent existing research gives us an overview of the complex interactions of the gene and environment that lead to NDDs. People diagnosed with Autism have low fertility, but the disorder manifests high heritability,[24,25] drawing our attention towards the high penetrance of DNMs. Through Twin studies of monozygotic twin pairs and dizygotic twin pairs, it was analysed that both genetic factors (38%) and environmental factors (58%) contribute in the etiology of Autism Spectrum Disorder.[26] Furthermore, analysis of 14,000 autistic children concluded that 50% of the disease is influenced by environmental factors.[27]

Studies on the epidemiology of Autism and other NDDs ascertained that intrauterine stresses and its exposure to environmental chemicals escalates the risk for the DNMs.[28] Exposure to mutagenic chemicals such as polychlorinated biphenyls, mercury, Nickel, Cadmium, Vinyl Chloride, Trichloroethylene and lead proved in deteriorating the developing nervous system, as they assert adverse effects on DNA.[23,29,30] These mutagens can trigger DNA repair inhibition, produce Reactive Oxygen Species inducing oxidative stress, transversions and gene deletions.[31-33] Foetal exposure to teratogens such as Bisphenol A that are found in plastics induces epigenetic variations by altered DNA methylation contributing in the formation of DNMs leading to onset of NDDs.[34] Not only chemicals but polluted air, including smoking, can play a major role in the development of DNMs. From various studies, authors inferred that ADHD is more likely to be diagnosed in children of smokers.[35] Additionally, prenatal exposure to alcohol leads to high

occurrence of brain malformations that leads to dysfunctional behaviours.[36] Maternal consumption of medicines constituting chemicals such as thalidomide and valproic acid have been also associated with children expressing traits that are related to Autism.[37] It can be hypothesized that DNMs originating from environmental factors contribute abundantly in the expression of NDDs.

The onset of NDDs have been observed due to maternal nutrition deficiency as well. Deficiency in iron, protein in the trimesters of pregnancy often leads to the child manifesting lower IQ, low memory power and lesser recognition.[38,39] Vitamin D is vital for controlling oxidative stress, as well as plays a role in the synthesis and repair of DNA, deficiency of which leads to DNMs in the offspring.[40-42] Research studies on Autism perceived prenatal deficiency of Vitamin D, typically at higher latitudes, interrupting the regular development of the brain.[43]

Paternal age is another prominent factor that elevates the risk for NDDs, particularly Autism. Sperm cells are produced enduring whole life, as a result of which there is a substantial increase in the frequency of DNMs in the later stages of life. Children who were conceived to fathers whose age were more than 40, were at higher risk to Autism Spectrum Disorders (ASD).[44,45]

1.4. DNMs in NDDs

Autism Spectrum Disorder (ASD) incorporates certain state of illness that are identified by impairment in social interactions and communication, confining interests and reiterative actions.[2] Recent analysis of large cohort study reports of monozygotic and dizygotic twins, and families manifests 83% of inheritance risking for ASD. SNPs are responsible for a considerable fraction of this inheritance out of which 7% are de novo variations.[46] DNMs are substantially responsible for the genesis of acute sporadic Intellectual Disability (ID).[47] ID is associated with children having deficits in functioning of intellect and adaptive behavioural conduct whose calculated frequency ranges between 1.5-2%.[48] Analysis of affected probands and their family studies concluded 45-55% of phenotypic expressions as a result of DNMs and small indels[47]. DNMs are highly responsible for the reduced fertility in ASD and ID as well.[49] Furthermore, Epilepsy (EP) in the early onset of development is co-occurring with NDDs such as ASD.[50,51] Epilepsy is marked with seizures without any direct provocation[52] which can pilot developmental regression in children.

2. Materials and Methods

2.1. Study design

This review is conducted systematically in accordance with PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The purpose was to collate existing data on de novo variants linked with ASD, ID, and Epilepsy, which focuses on the genetic framework, mutation landscape, and intersecting molecular pathways.

2.2. Information sources

Data were sourced from:

1. denovo-db (*https://denovo-db.gs.washington.edu*), an organized database of de novo variants across published human studies.
2. STRING database (*https://string-db.org*) for gene ontology enrichment analysis.
3. PubMed, Scopus, and Google Scholar, applying relevant keywords.

2.3. Search strategy

The literature search (2010–2024) was based on the integration of the following terms: *"de novo mutations"* AND *"autism spectrum disorder"* OR *"intellectual disability"* OR *"epilepsy"* OR *"neurodevelopmental disorders"* Extended filters included exome or genome sequencing derived from parent-offspring cohorts, the nature of variants, and peer-reviewed publications in English.

2.4. Inclusion criteria

1. Studies that have applied WGS or WES based on parent–offspring trios.
2. Published literature documenting DNMs in ASD, ID, or EP cohorts.
3. Publications presenting chromosomal locations, lists of genes, or types of variants.

2.5. Exclusion criteria

1. Case studies without any genomic data.
2. Studies without accessible variant-level data.

2.6. Data extraction and analysis

Data were sourced from denovo-db, where mutation types (missense, frameshift, splice-donor, stop-gained, etc.), chromosomal locations, and affected genes were integrated.

Tools for visualization and analysis included:

1. Microsoft Excel for data tabulation and frequency analysis.
2. R (ggplot2) and Python for graphical representation of mutational landscape and chromosomal distributions.
3. STRING (v12) for PPI network construction and Gene Ontology (GO) enrichment (FDR < 0.05).

PRISMA Flow Summary

Phase	Records	Description
Identification	134 studies retrieved	PubMed, Scopus, denovo-db
Screening	89 retained	Based on title/abstract

Eligibility	47 studies analysed in full	Containing trio-based DNM data
Inclusion	24 studies included	Meeting all inclusion criteria

3. Results

3.1. Nature of DNMs

It was ascertained that DNMs manifesting loss-of-function are predominantly single base substitutions.[53] Whole genome sequencing (WGS) and whole exome sequencing (WES) in diverse groups of parent-offspring trios and twins suffering from ASD, established numerous DNMs associated with the disorder. We combined data obtained from a database including only de novo mutations (https://denovo-db.gs.washington.edu), where fourteen studies based on WGS and WES[54-67] on ASD families were analysed. The analysis established that, predominantly, DNMs were missense mutations (frequency-0.257) or intronic (0.253) in nature. Intronic region does not code for genes, thus, DNMs have negligible impact. Most pathogenic DNMs were found to be missense in nature. Apart from these, nature of DNMs associated with ASD were found to be frame shift (0.05), stop-gained (0.04), splice-donor (0.01), non-coding exon (0.006), 3'UTR (0.01), 5'UTR (0.005). Additionally, DNMs were also figured out to be synonymous (0.06) in nature. Combining five studies on whole exome sequencing (WES) in families with ID,[47,67-70] we analysed and ascertained that more than 50% of the DNMs were missense mutations (0.54) in nature. Pathogenic DNMs are predominantly missense and stop-gained (0.98) in nature. Furthermore, nature of DNMs associated with ID were found to be frameshift (0.13), splice-donor (0.01), non-coding exon (0.04), 3'UTR (0.005), 5'UTR (0.002) and synonymous mutations (0.1). Correspondingly, we analysed DNMs from five studies concentrating on whole exome sequencing (WES) of families suffering from Epilepsy.[71-75] DNMs were largely missense (0.53) in nature. Moreover, nature of DNMs associated with Epilepsy were found to be frameshift (0.08), splice-donor (0.01), non-coding exon (0.04), 3'UTR (0.05), 5'UTR (0.01) and synonymous mutations (0.11). Since, we only considered studies based on WES, DNMs in the intronic region associated with ID and Epilepsy were not analysed. (**Figure 1**)

DNMs incorporated from the denovo-db database, drawn for studies on WGS and WES associated with ASD, ID and Epilepsy exhibit two types of DNA substitution, i.e., either transitions or transversions. We placed each of the substitution into four possible base pair transitions (C>T, G>A, A>G, T>C) and eight possible base pair transversions (G>C, C>A, C>G, G>T, T>G, A>T, A>C, T>A). Number of transitions (0.6) in ASD, ID and Epilepsy were much higher than the number of transversion (0.36) mutations. C>T (0.23) and G>A (0.21) base pair substitution was found to be dominant in all the three diseases. If we only acknowledge transversions, G>C (0.04) was found predominantly among ASD, ID and Epilepsy (**Figure 2**). Molecular incidents causing transitions are more prevalent than transversions. The elevated rate of C:G>T:A transition mutations is a consequence of cytosine deamination occurring at CpG dinucleotides.[20] Though CpG islands are rare in the genome, it accounts for 19% DNMs.[76] Methylation of 5' Cytosine manifests instability that leads to deamination of cytosine into Thymine.[77]

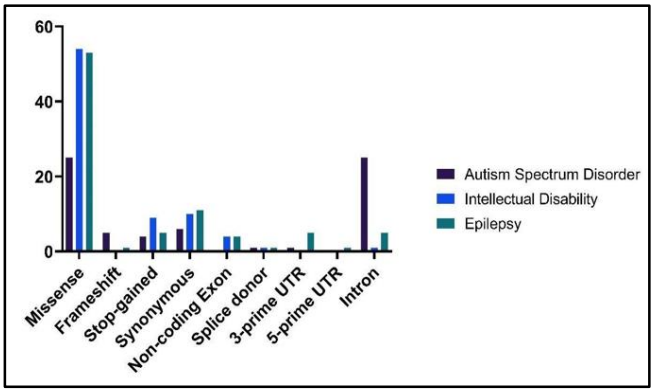

Figure 1: Nature of DNMs in autism spectrum disorder, intellectual disability and epilepsy.

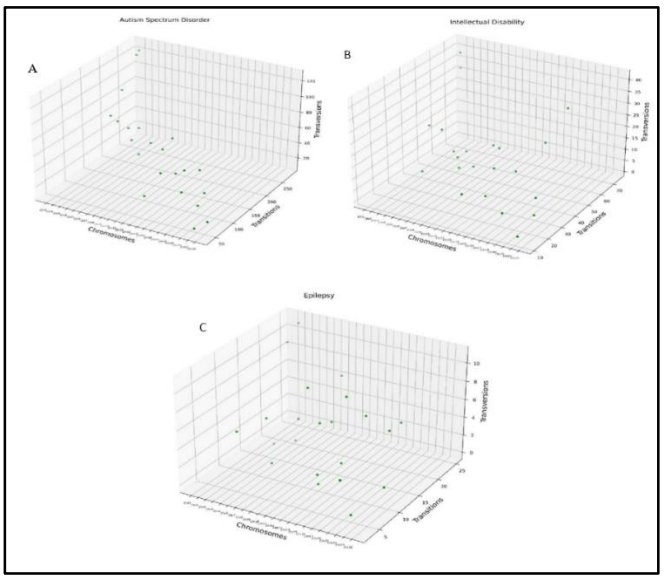

Figure 2: Transitions (C>T, G>A, A>G, T>C) and Transversions (G>C, C>A, C>G, G>T, T>G, A>T, A>C, T>A) in **A:** Autism Spectrum Disorder; **B:** Intellectual Disability, and **C:** Epilepsy

3.2. DNMs in ASD, ID and EP associated genes

It is widely believed that DNMs make a considerable fraction in NDDs. However, most of the aspects are still unknown. Besides coding regions, significant enrichment of DNMs were established in Conserved Non-coding Elements (CNEs) as well as enhancers that are conserved located in the active fetal brain and these being regulatory elements, enriched in DNMs (some pathogenic), acutely participate in the etiology of NDDs.[78] After analysing several studies that are majorly based on Caucasian population, we perceived DNMs

encompassed in genes that contribute substantially in the development of NDDs.

Parent-offspring cohort studies in 189 sporadic families impaired with Autism was carried out by sequencing the exome region of the genome. Recurring, protein-disruptive DNMs were remarked in two genes, *NTNG1 & CHD8*.[79] DNMs were also observed in *CHD3* and *CHD7* that popularly binds with *CHD8*.[80] By sequencing all the coding regions of the genome in 20 probands along with their families, 11 out of 21 DNMs were identified to be proteinaltering. DNMs potentially liable, were observed in *SCN1A*, *FOXP1*, *GRIN2B*, *CNTNAP2* and *LAMC3*.[81] Resequencing of large cohorts established multiple mutations in CHD8 (17 DNMs), out of which 6 are potentially deleterious.[52,62,63]

High sequencing projects on huge number of families confirmed 61 ASD-risk genes incorporating higher number of DNMs.[58] Furthermore, analysis by resequencing of exome and molecular inversion probes method of probands manifested significant genes carrying multiple de novo mutations including *CHD2, PTEN, TBR1, ADNP, GRIN2B, SYNGAP1, TRIP12, PAX5*, *SCN2A*, *POGZ*, and *KATNAL2, DYRK1*.[62-64] Barring Caucasian population, novel disruptive DNMs were found in Chinese ethnic group. Sequencing was carried out for 189 risk genes collected from large cohorts of Chinese parentsproband trios suffering from ASD. Novel DNMs recurred in *DOCK8, ZNF292, MYT1L, GIGYF2* and *CUL3*.[82]

In most of the cases, children impaired with ASD, also suffers from ID due to associated genes. Analysis of exome sequencing in parent-offspring trio of 41 children severely affected with ID identified genes encompassing potential deleterious DNMs (*CHD2, FOXG1, ARID1B, GATAD2B, GABRB3, GRIN2B, MED13L, TBR1, SETBP1, MBD5, WDR45, TCF4*).[83] Additionally, *SCN2A* and *ARID1B* has been observed to have higher mutations that increase the risk for ID with or without being associated to ASD.[68,69,88] Corresponding to different ethnic groups, de novo deletions and mutations were found in *CCNK* that plays a major role in controlling transcription. WES and Chromosome microarray analysis of three children from different Chinese families, found de novo deletions in *CCNK*, and missense DNM in *CCNK* in an African American girl, commonly suffering from ID along with facial dysmorphism.[84]

A common comorbidity of ASD and ID is Epileptic syndromes. Diagnostic exome sequencing analysis has been efficient in identifying DNMs in novel epileptic genes. Genes contributing in the genesis of Epilepsy (*STXBP1, MECP2, IQSEC2, KCNQ2, FOXG1, KMT2A*) were time and again influenced by DNMs.[72] Additionally, whole exome of 10 trios severely affected with Epilepsy was sequenced and more than one DNMs were manifested in significant genes including *SCN1A*, *ARHGEF1F* and *CDKL5*.[85] It is intriguing to note that analysed WES studies in infants impaired with early - onset epilepsy indicates presence of more DNMs that causes excitation anomalies and disrupt in the synaptic plasticity in the early brain development progress.[86] Studies conducted on people belonging to different ethnic groups in Europe and USA established DNMs in *KCNB1*.[87] These rare mutations develop seizures in infants and small children that are difficult to control using standardized drugs used for Epilepsy.[87-90]

We obtained huge number of DNMs associated with ASD, ID and Epilepsy from Denovo-db database (https://denovo-db.gs.washington.edu). We segregated each DNM based on its position in the genome (GRCh38). The number of DNMs in each chromosome was proportional with the length of the chromosome (**Figure 3-5**).

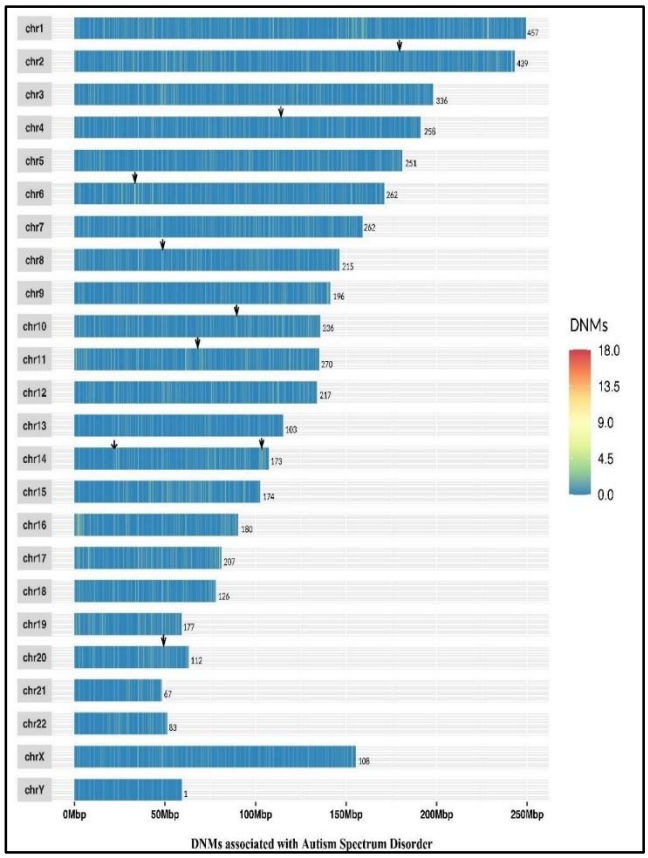

Figure 3: Enrichment of DNMs across the genome associated with Autism spectrum disorder.

3.3. Chromosomal distribution of DNMs

Chromosome 1 encompasses the majority of DNMs in ASD, ID and Epilepsy being the longest chromosome whereas, chromosome 21 being shortest in length, carries the least number of DNMs. Distinguished enrichment of DNMs in certain range of locations were observed throughout the genome.

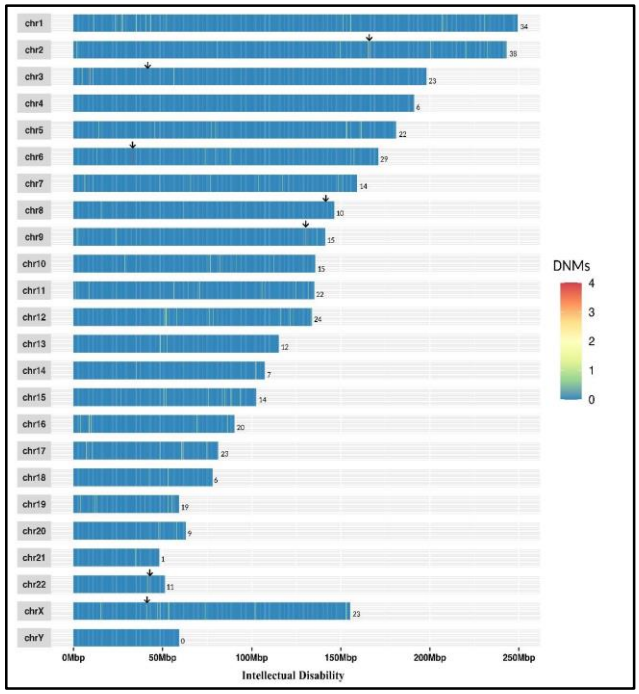

Figure 4: C – Enrichment of DNMs across the genome associated with Intellectual disability.

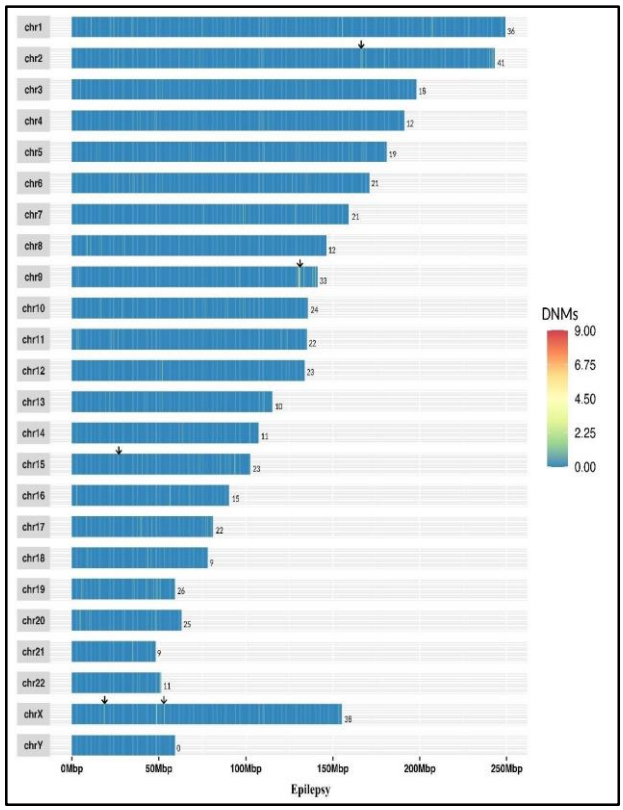

Figure 5: Enrichment of DNMs across the genome associated with Epilepsy.

We figured out genes accommodating ample number of DNMs leading to enrichment in those locations. In ASD, *CHD8* in Chromosome (Chr) 14 indicates excessive enrichment of DNMs, as the gene *CHD8* solitarily carries 17 DNMs. *CHD8* expresses chromatin remodelling functioning and is crucial for development of the fetal brain.[91] Enrichment of DNMs is also noticed in Chr1 (*POGZ*), Chr2 (*NRXN1*, *SCN2A*), Chr4 (*WDFY3*, *ANK2*), Chr6 (*SYNGAP1*, *ARID1B*), Chr8 (*CSMD1*) and Chr10 *(PTEN*). Similarly, Chr2 (*SCN2A*), Chr6 (*SYNGAP*, *ARID1B*), Chr17 (*DLG4*), Chr22 (*TCF20*) and ChrX (*DDX3X*) is substantially enriched in DNMs associated with ID. Additionally, in Epilepsy, we observed multiplicity of DNMs in Chr2 (*SCN2A, SCN1A*), Chr9 (*STXBP1*), Chr15 (*CHD2*, *GABRB3*), Chr20 (*KCNQ2*) and ChrX (*CDK15*, *IQSEC2*).

By analysing DNMs present in 623 genes (CADD score >=20) by STRING (https://string-db.org/) enrichment for gene ontology of ASD, the following significant genes were introduced forming the core network for the disease- *CHD8*, *KATNAL2*, *CACNA1C*, *ASXL3*, *POGZ*, *CACNA1H*, *ARID1B*, *ANK2*, *KDM5B*, *PTEN*, *SCN2A*, *TBR1*, *ASH1L*, *ADNP*, *DYRK1A*, *DSCAM*, *NRXN1*, *RELN*, *MECP2*, *MYT1L*, *SYNGAP1*, *SHANK2*, *GRIN2B*. These genes are highly influenced by de novo alterations disrupting multiple cellular processes including postsynaptic density organization (FDR- 1.30e-07), learning or memory (FDR- 1.30e-07), behaviour (FDR- 1.30e-07), system development (FDR- 2.33e-07), membrane potential regulation (FDR- 1.82e-06).

Similarly, 349 genes carry DNMs (CADD score >=20) contributing in the genesis of ID were assessed by gene ontology. The following genes, *KIAA2022*, *EEF1A2*, *EP300*, *DNMT3A*, *SMARCA2*, *SETBP1*, *GRIA4*, *ITPR1*, *USP9X*, *TLK2*, *CAMK2G*, *ARID1A*, *SMC1A*, *FOXG1*, *HUWE1*, *CTNNB1*, *ARID1B*, *KCNQ5*, *SCN8A*, *RAC1*, *DYNC1H1*, *KCNQ2*, *TCF20*, *SMC3*, *CHAMP1*, *GATAD2B*, *GRIN1*, *STXBP1*, *CDKL5*, *TRIP12*, *ADNP*, *IQSEC2*, *TCF4*, *DLG4*, *FBXO11*, *SETD5*, *TANC2*, *EFTUD2*, *SMARCA4*, *SATB2*, *SYNGAP1*, *TBL1XR1*, *SLC2A1*, *TUSC3*, *GRIN2B*, *FOXP1*, forming the core network impairing multiple cellular processes that are associated with abnormal neurodevelopment including development of the nervous system (FDR- 8.91e-08), organization of chromosomes (FDR- 8.76e-06), neuron generation (FDR- 2.26e-05), organization of chromatin (FDR- 2.33e-05), multicellular organismal processes (FDR- 4.91e-05).

Furthermore, gene ontology study of DNMs associated with 115 epileptic genes (CADD score >=20) manifested the following significant genes at the core of the network- *EEF1A2*, *CUX2*, *GNAO1*, *SLC1A2*, *SCN3A*, *GABRB1*, *SCN1A*, *YWHAG*, *GABRB3*, *MEF2C*, *SCN8A*, *KCNQ2*, *DHDDS*, *CACNA1A*, *MTOR*, *KCNT1*, *DNM1*, *STXBP1*, *SCN2A*, *CASK*, *CDKL5*, *KCNQ3*, *CHD2*, *ALG13*, *GABRA1*, *GRIN2B*. These genes are responsible for abnormal processes such as membrane potential regulation (FDR- 1.82e-09), inorganic ion transmembrane transport (FDR- 9.74e-09), chemical synaptic transmission (FDR- 1.20e-08), ion transport (FDR- 2.63e-08), ion transport regulation (FDR- 4.41e-08). It is intriguing that there is only a blurred line between these three NDDs.

3.4. Genetic overlap between ASD, ID and EP

The three neurodevelopmental disorders, ASD, ID and EP manifests intertwined phenotypes, for example, impairment in learning or memory, cognition and many more. On significant grounds, this is due to overlapping of genes that are common in either two of the diseases or all of them. We retrieved 123 genes encompassing DNMs (CADD score >=20) that are involved in the pathogenesis of ASD, ID and EP. These genes are overlapping in more than one of the diseases. Using STRING network analysis of all the 123 overlapping genes, we ascertained strong gene interaction networks. Gene ontology annotation of the network outlines substantial enrichment of DNMs in the development of the nervous system (FDR- 5.26e-10). Additionally, it considerably affects the development of the multicellular organism (FDR- 1.71e-09), cell signalling dysfunction (FDR- 6.19e-08), impaired system development (FDR- 6.19e-8) and abnormal regulation of the transcription process by RNA Polymerase II (FDR- 1.23e-07). In contrast, gene ontology of the cluster reports marginal damage in neuronal action potential (FDR- 0.0469), positive regulation of Wnt-signalling pathway (FDR- 0.0482), insulin secretion regulation (FDR- 0.0482), symbiotic process (FDR- 0.0482), and organic substance metabolic process (FDR- 0.0482).

Genes forming huge number of networks (ANK2, ARID1B, CACNA1A, CACNA1C, CHD2, CHD7, DNM1, DNMT3A, GABRG2, GRIN1, GRIN2A, GRIN2B, HDAC1, KCNQ2, KCNQ3, POGZ, SCN2A, SCN3A, SCN8A, SMARCA4, SPTBN2, STXBP1, SUPT6H, SYNGAP1, TRIP12, TRRAP) were all related to impaired neurodevelopment pathways (**Figure 6**).

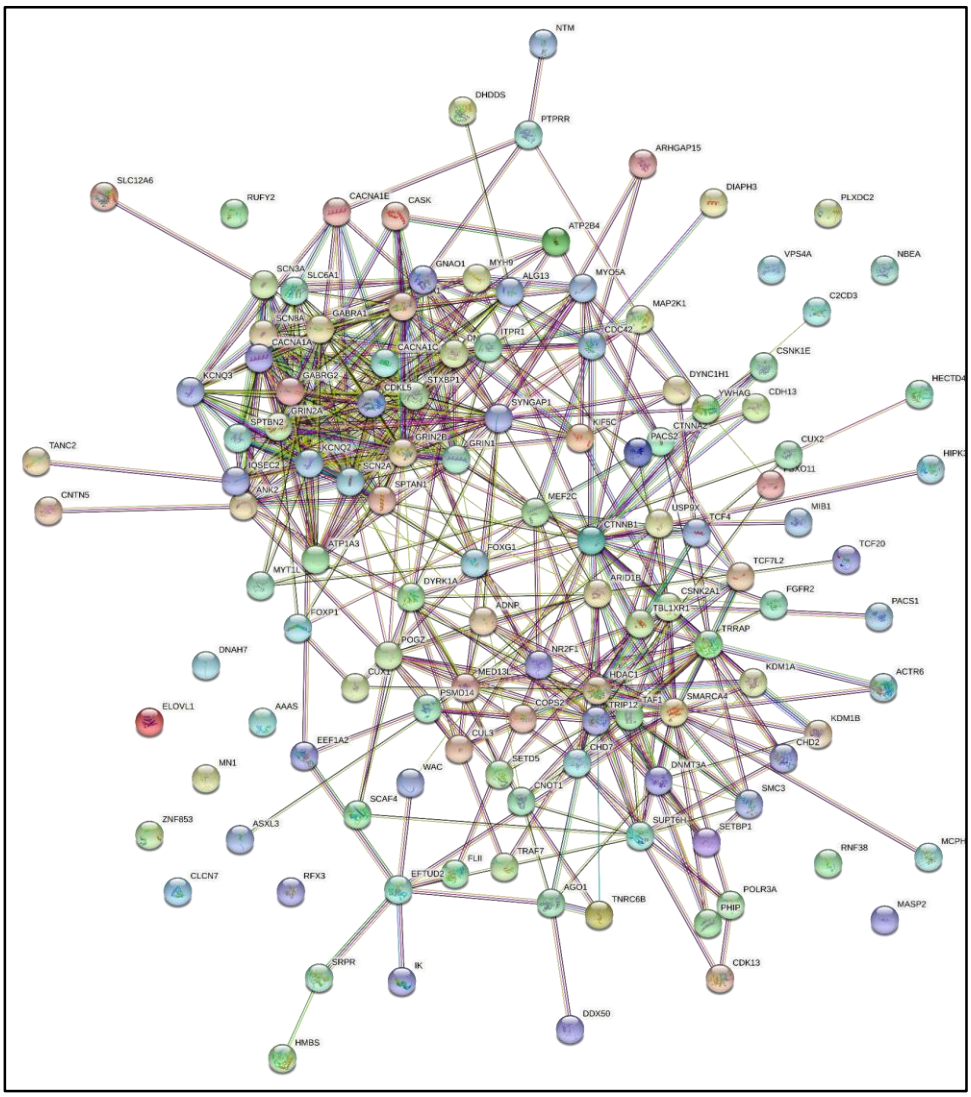

Figure 6: Overlapping genes associated with ASD, ID and Epilepsy (*ANK2*, *ARID1B*, *CACNA1A*, *CACNA1C*, *CHD2*, *CHD7*, *DNM1*, *DNMT3A*, *GABRG2*, *GRIN1*, *GRIN2A*, *GRIN2B*, *HDAC1*, *KCNQ2*, *KCNQ3*, *POGZ*, *SCN2A*, *SCN3A*, *SCN8A*, *SMARCA4*, *SPTBN2*, *STXBP1*, *SUPT6H*, *SYNGAP1*, *TRIP12*, *TRRAP*) forms a network. PPI enrichment p-value: < 1.0e-16. Gene ontology analyses were generated using the STRING database (https://string-db.org/)

In summation, all of the overlapping genes are associated with pathways contributing in the brain development and variations lead to seizures and several deficits including learning, memory, behaviour, cognition as observed in EP, ASD and ID patients.

4. Discussion

Progressing sequencing technologies brought a major breakthrough in finding most of the de novo mutations, present in our genome and those associated with neurodevelopmental disorders. Techniques like WGS and WES have facilitated advancements in research manifesting greater knowledge on the nature of DNMs and underlying mechanisms of their emergence. These DNMs that emerges spontaneously during gametogeneis or the development of the embryo have been observed to be missense in nature, frequently in all the three disorders, few being deleterious. It was also concluded that more than half of the DNMs were transition base substitutions occuring frequently in CpG dinucleotides. DNA methylation (*an epigenetic modification*) causes instability and deamination of 5'C to T at CpG dinucleotides increasing the mutation rate. It can be hypothesized that methylation of DNA can be responsible for the enrichment of DNMs.

Gene ontology of genes associated with all the three disorders show enrichment of DNMs in biological processes that are majorly involved in neurodevelopment. Epigenetic variables like CHD8, ARID1B, and DNMT3A are frequently involved, indicating the intersection of genetic and epigenetic disruptions in the development of neurodevelopmental disorders.

5. Conclusion

In summary, the rising genetic evidence has substantially enhanced our grasp of neurodevelopmental disorders, highlighting multifaceted de novo variants. Clinically, these findings accentuate more diagnostic tools that are precise, advanced risk profiling, and optimization of personalized therapies based on individual profiles. The review indicates our existing knowledge of gene-environment interactions to be limited, and the necessity of studying diverse and large-scale cohorts. Future research should emphasize investigating combined multi-omics data, computational models, and neuroimaging for translating these insights into precision medicine.

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None.

7. Conflict of Interest

None.

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