Complex Neurodevelopmental Disorders And Their Genetic Etiologies

Amna Batool, Mahira Arooj

Abstract: Complex Neurodevelopmental disorders (NDDs) exhibit complex etiological and genetic features, and the mutations have a fundamental role in this complexity, including common polymorphisms and rare variations in a single gene or cluster of genes. The analysis of complex NDDs have shown that the genetics has the major role in causation of such complex diseases. Interestingly both mutations and polymorphisms are involved, occurring in a single gene or clusters of genes. Likewise, a single gene variation may also be involved in multiple neurological disorders making the diagnosis of neurological diseases more difficult. Many candidate genes and chromosomal regions have been identified that are widely involved in neurological symptoms which necessitates the genotypic approach for describing the phenotype.

Index Terms: Complex Neurodevelopmental disorder (NDD); Intellectual disability (ID); Neurodegenerative diseases; Neurobehavioral traits; Autism spectrum disorders (ASD).

1 Introduction

Complex Neurodevelopmental disorders (NDD) encompasses a group of heterogeneous disorders in which the development and the function of the central nervous system (CNS) is altered which is apparent as neuropsychiatric problems, motor impairments, congenital anomalies, voluntary control, learning, language or non-verbal communication. NDD depicts a molecularly and phenotypically diverse classification comprising mental retardation, microcephaly, motor anomalies and neurobehavioral traits such as stereotypic movements (ASD) [1]. Whole exome sequencing (WES) has revealed and identified various candidate genes, susceptible chromosomal regions and mutations caused by them and it has been proposed that a mutation in single gene is linked with diverse range of neurodevelopmental and neurobehavioral traits [2], [3]. On these grounds, genotyping of the neurodevelopmental disorders is necessary to explain the associated phenotype. It has been shown that Complex Neurodevelopmental disorders are broadly categorized into four main groups: The Aneuploidy; Micro-deletion; Single Gene Defect and Multifactorial [4].

2 Aneuploidy

The cells in body contain 22 autosomal pair and a pair of sex chromosomes which is known as diploid. If a somatic cell deviates from the diploid number, it is termed aneuploid. Numerical changes resulting from the loss or gain of a whole chromosome represents aneuploidy.

- *Amna Batool is pursuing a degree program in biotechnology in Department of Bioinformatics and Biotechnology, International Islamic University Islamabad, Pakistan. amnabatoolQ@gmail.com*
- *Mahira Arooj is pursuing PhD degree program in biotechnology in School of Biomedical Sciences, CHIRI Biosciences, Curtin University, Perth, WA, 6012, Australia and also affiliated with Cancer Epigenetics group, The Harry Perkins Institute of Medical Research, Perth, WA, 6009, Australia. PH- +61 451260786. m.arooj@postgrad.curtin.edu.au*

However, structural rearrangements can also cause changes in whole chromosome number, which depends on the nature of the rearrangement. Breakage and repair events of chromosomes, such as the fusion of non-homologous chromosomes, can give rise to a different arrangement of chromosome in contrast with present before breakage. Some of the products of chromosomal fusion can be lost during cell division, depending on how the centromeric regions of chromosomes are separated, which interact with kinetochores. Both of these conditions can lead to syndromes such as Down syndrome (trisomy 21). Nonetheless, in Down syndrome numerical gain is predominantly more common [5].

2.1.1 Down's Syndrome

The major source of a Down syndrome (DS) is the presence of an extra copy of chromosome 21. The other causes of DS can be; Robertsonian translocation and isochromosomal or ring chromosome. Ischromosome is a condition which arises when two long arms of chromosome separate together the egg and sperm development. In Robertsonian translocation, chromosome q21 is attached to another chromosome (generally chromosome 14). Mosaicism deals with the error which occurs during cell division after fertilization [6]. There are many features conserved in all DS patients which include intellectual disabilities, deformities in the the head and facial bones, and low muscle tone [7], mental retardation, growth retardation and joint hyperlaxity. Variant phenotypes include atrioventricular canal defect (AVCD) in heart, leukemia, Alzheimer's diseases (AD) and Hirschprung disease (HD), hypertension and gastrointestinal problems. DS individual have characteristic physical appearance like a small chin, epicanthus, a saddle nose, a single transverse palmar crease and a protruding due to small mouth and large tongue [8], bigger toe, abnormal pattern of fingerprint and short fingers [9].

3 Micro-Deletion

Micro-deletion syndromes are defined as a set of clinically observable disorders characterized by a small (<5Mb) deletion of a chromosomal segment comprising multiple genes, each is furnishing to a characteristic phenotype [10]. FISH (Fluorescence in situ hybridization) is the standard diagnostic approach for known micro-deletions. The critical phenotype is the result of haploinsufficiency for specific

genes. Clinically well described syndromes, in it include 22q11 micro-deletion in Velocardiofacial syndrome, 7q11 micro-deletion in Williams's syndrome, 17q11 micro-deletion in Neurofibromatosis type 1, 17p micro-deletion in Smith-Magenis Syndrome and syndrome of 8p micro-deletion [11].

3.1 Prader-Willi Syndrome / Angelman Syndrome

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are two distinct neurodevelopmental disorders, related to few epigenetic and genetic mechanisms which involve the adjacent long arm of the chromosome 15 (15q). When the paternal copy of 15q11-q13 is lost it causes PWS and the loss of the maternal copy of UBE3A gene (gene present in 15q11-q13) causes AS [12]. Angelman syndrome patients have serious learning ailments, ataxia and suffer from epilepsy speech disorders, facial abnormalities, deep set eyes, microcephaly, delayed motor milestones and severe mental retardation [13]. They also have a characteristic hypopigmentation having fair hair and blue eyes. Prader-Willi syndrome is marked by decreased muscle tone by means of poor suck and poor development; hypogonadism which causes genital pubertal insufficiency and hypopalasia, hyperphagia, early-childhood obesity, mental retardation and neurobehavioral traits. Scoliosis and sleep disorders are common [14].

3.2 Smith-Magenis Syndrome

It is a complex neurological disorder which is evident by intellectual disability, verbal apraxia, behavioral and sleep abnormalities. Most often it occurs owing to a deletion in short arm of chromosome 17 (17p11.2) which includes the RAI1 gene. More genes typically involved in the phenotype include: PMP22, TNFRSF13B; which may cause impairments in immune system marked by IgA insufficiency, and MYO15A; causing loss of hearing [15], [16]. Behavioral disorders frequently include rage, hyperactivity, self-injury, nighttime agitation and excessiveness daytime sleep. Children with Smith-Magenis disorder (SMS) often have dull colored hair, protruding forehead, facial abnormalities (underdevelopment of medial part), saddle nose and an undersized jaw. Variant ENT phenotypes include infections of ear, hearing loss and voice hoarseness [17], [18]. Abnormal curvature of spine is commonly found [19]. Congenital heart disease, spleen malformations and defects in the renal and urinary system are also found [20]. Hypothyroidism and hypercholesterolemia may also appear [21], [22].

3.3 DiGeorge/Velo-Cardio-Facial Syndrome

The names DiGeorge sequence, conotruncal anomalies face syndrome, 22q11 deletion syndrome, CATCH 22, and Sedlacková syndrome are all connected to the same disorder. The syndrome is due to the micro-deletion of chromosome 22q at the 11.2 band. Despite most of the concerned individuals have 3 mega-base deletions, very few cases have smaller deletions; 1.5 or 2.0 mega-bases. The deletion of 3 mega-bases contains almost 40 genes [23]. The Velo-Cardio-facial syndrome is possibly an autosomal dominant syndrome. The most common features in effected individual include cleft palate, learning disabilities and typical faces. Less frequent finding includes mental retardation, microcephaly, delay in growth, thin hands and digits, and inguinal hernia [24].

3.4 William's-Beuren Syndrome

This is a rare genetic disease that is relatively easy to diagnose in early years of life. It is associated with defect in cardiac system, face dysmorphism and specific cognitive and behavioral profile. Effected children show hyperactivity and are sensitive to sounds. Blood pressure and kidneys are evaluated time to time. The adults do not have ability to self-care. Williams-Beuren syndrome is owed to a micro-deletion in chromosome 7q11.23. This micro-deletion eliminates several genes, notably the elastin gene [25].

4 Single-Gene Defect

These defects arise by the mutation in the DNA sequence of single gene. It can be Autosomal dominant; Neurofibromatosis, Autosomal recessive; Friedreich's ataxia, X-linked dominant fragile X syndrome; or X-linked recessive diseases; Fabry disease.

4.1 ATR-X Syndrome

X-linked alpha-thalassemia is an X-linked neurodevelopmental disorder. The gene for this disease is ATRX which is present at Xq13.3 [26]. It stretches about 300 kb in the genome and has 36 exons [27]. The protein is linked with SNF2 family of helicase/ATPases, which are involved in many cellular functions which include transcription regulation (SNF2, MOT1 and brahma), govern cell cycle (NPS1), repair of DNA (RAD16, RAD54 and ERCC6) and mitotic separation of chromosome (lodestar). Their function is to facilitate these processes by remodeling of chromatin. ATRX protein is also present at the N terminal of a zinc finger domain (called the ADD domain) [28]. Chiefly the mutations of the ATRX gene appear in the ADD domain and the Helicase domain marked by the decreased function of protein [29]. The individuals have learning issues linked with severe communication disorders and facial anomalies during early years of life. Genital deformities may also be present. The patients suffer from alpha thalassemia. Variant phenotypes include: skeletal dysplasia, microcephaly, delays in growth, seizures, cardiac breakdown and defects in urinary and renal systems [30].

4.2 Barth syndrome (X-linked cardioskeletal myopathy and neutropenia)

This disorder was reported as an unknown cause of fetus death (2010). It is generally regarded as a rare X-linked disorder. It is attributed by the mutations or deletions of the tafazzin (TAZ) gene, located at q28 of X chromosome; which brings about the cardiolipin remodeling. Clinical features encompasses: cardiovascular impairments, endocardial fibroelastosis (EFE), arrhythmia of ventricles, cardiac arrest, long QTC spell, motor anomalies, muscle weakness, restlessness, low levels of neutrophils, compensatory monocytosis, periodic bacterial infections, deficiency of glucose, elevated levels of lactic acid, delays in growth, problem in feeding, diarrhoea and facial anomalies [31].

4.3 FRAGILE-X SYNDROME

The Fragile X Syndrome (FXS) is due to a CGG trinucleotide extension in the 5'-untranslated region of fragile X mental retardation 1 gene (FMR1) [32] present at Xq27.3 [33] which causes an increase in methylation of promoter region, suppressing the gene involved in maturation and plasticity of synapse [34]. Effected patients have more than 200 CGG trinucleotide repeats. While permutation carriers having 55-200 CGG extensions do not bear typical phenotypes of FXS, but milder neurological phenotypes may appear [35]. Effected individuals are characterized by long face, big and prominent ears and large testes, anxiety, sensory hyper arousal, delay in language, intellectual disability, autism and hyperactivity. Males suffering from this disorder passes the permutation to their daughters. The females are carriers for this disorder and generally symptoms of mental retardation do not appear in them [36], [37], [38].

4.4 ICF SYNDROME

The immunodeficiency centromere instability facial anomalies (ICF) syndrome is a result of mutation in DNMT3B gene [39] on chromosome 20q11.2 are responsible for most of the ICF cases [40], [41], [42]. Complete failure of function of the DNMT3B is embryonic fatal in humans [43]. Therefore the difference among ICF patients depends upon functional level of DNMT3B. It a rare autosomal recessive disease marked by characteristic deficiency of immune system. Other characteristics of ICF syndrome includes; intellectual disability, bowel disorders, psychiatric and motor deterioration, facial abnormalities (orbital hypertelorism, saddle nose and unusual large tongue) and delays in development [44], [45]. ICF syndrome is attributable by the instability of pericentromeric heterochromatin which reveals that DNMT3B is restrained to mitotic chromosomes and interacts with constituents of the chromosome condensation [46], [47].

4.5 NEUROFIBROMATOSIS

Neurofibromatosis 1 is a dominant autosomal disorder which arises by the heterozygous mutations of the NF1 gene. It is outlined by multiple light brown pigments, axillary and inguinal mole, numerous skin neurofibromas, melanocytic hamartomas and learning disabilities. Less common but possibly more serious manifestations include benign tumour of peripheral nerves, optic nerve and a malignant tumour of the glial tissue of the nervous system, malignant tumours of peripheral nerve sheath, abnormal curvature of spine, Tibial bowing, and blood vessel disorders [48]. Neurofibromatosis type 2 (NF2) is marked by the presence of the tumor due to the mutations in the NF2 gene on chromosome 22. It is indicated by the progression of multiple neurolemoma and meningeal tissue tumour. The individuals foster schwannomas, genuinely affecting the vestibulocochlear nerve causing deafness accompanied by ear ringing. Vestibular schwannomas also causes dizziness or imbalance. Rare symptoms include Giddiness, vomiting, Nausea. The other prime tumors are schwannomas of spinal, peripheral and cranial nerves and tumor of the brain or spinal cord. Ocular manifestations include reduced vision clarity [49].

4.6 SMITH-LEMLI-OPITZ SYNDROME

The Smith-Lemli-Opitz syndrome (SLOS; also known as "RSH syndrome") is an autosomal recessive syndrome which is caused by an alteration in the biosynthesis of cholesterol. Effected patients have increased 7-dehydrocholesterol (7-DHC) level and particularly low amounts of cholesterol in serum. On these grounds of biochemical abnormality, it has been suggested that mutations in the human sterol Delta7-reductase (7-DHC reductase) gene encoded at chromosome 11q12-13 cause SLOS. Moreover, it can also be proposed that there is a mutation in a gene encoding a protein for the normal expression and functioning of 7-DHC reductase [50]. Frequent indication of SLOS includes poor feeding and postnatal growth failure. Classic craniofacial features include microcephaly, an upside nose, eyelid dropping and small jaw, cleft palate or cleft in uvula, small thumbs, proximal transverse palmar crease, polydactyly and syndactyly. Genital abnormalities in male patients are often observed. More adversely effected patients have defects in the brain (incomplete forebrain division, agenesis or impairments of the callosal commissure), heart (atrial and ventricular septal defects) and lungs. Moreover, the effected individuals exhibit definite behavioral symptoms. During childhood, they can be annoying, poor feeding and desire not to be controlled. Adults exhibit hyperactivity, self-harm, temperamental deregulation and sleep disturbances. Autistic characteristics are common and they reconcile with the criteria of autism diagnosis [51], [52], [53].

4.7 AU-KLINE SYNDROME

This syndrome is identified by the mutations in heterogeneous nuclear ribonucleoprotein K gene (HNRNPK gene). This gene encodes a protein which binds to the nucleic acid and play a distinct role in the modification of the chromatin architecture, cell regulation; transcription, translation, RNA splicing and stability, and regulation of cell signals [54], [55]. The effected individuals have characteristic facial features which includes flat head syndrome, Exophthalmos, malformed ears, prominent nasal root with a depression at the nasal tip, malformation of medial cleft, undescended testicle, coccygeal projection with a sacral dimple, low muscle tone, global developmental delay [56].

4.8 CORTICAL DYSPLASIA, COMPLEX, WITH OTHER BRAIN MALFORMATIONS (CDCBM)

Cerebral cortex development can be divided into three main stages: cell division, migration of neuronal cells and development after migration. The importance of these coordinated events is seen variable disease which includes microcephaly, incomplete development of outer region of the brain leading to smooth surface of brain and polymicrogyria [57], [58]. Individuals exhibit intellectual disability and intractable epilepsy. In addition to abnormal development of cortex, extra-cortical abnormalities of tubulin gene are associated with agenesis of the callosal commissure, dysmorphic basal ganglia and immature cerebellum [59], [60], [61]. Tubulins and microtubule polymers have a crucial role in development of mammalian cerebral cortex. Tubulin genes expressed neuronally are linked with cortical malformations which includes; TUBA1A [62], TUBB2B [63], TUBB3

[64], TUBA8 [65], TUBB [66], TUBB4A [67], and TUBG1 [68], [69].

5 MULTIFACTORIAL

Multifactorial diseases are not linked with a single causative agent. They result from combinations of risk factors (environmental influences) and genetic etiologies working together and interacting to cause wide array of symptoms.

5.1 SCHIZOPHRENIA

Schizophrenia is a neurological disorder which shows wide range of symptoms; including fluctuations in consciousness, thought and sense of self, loss of willingness, mental retardation, cognitive dysfunction and unsocial behavior [70]. Risk factors such as infection of viruses and fetal complications are being suggested. The gene PRODH, DAOA and G72, are commonly related with schizophrenia [71]. The expression level of gene ZDHHC8 or its splice variants is linked with schizophrenia exclusively in individuals with 22q11 deletions [72]. Moreover the polymorphisms in NRG1 gene have been shown to be linked with semantic disorders. Specifically verbal performance is directly associated with the number of harmful alleles of this gene [73]. Reduced amount of DISC1 gene in the nervous system affects the synthesis, migration, and development of adult neurons [74], [75]. The activation of an ion channel (KCNQ) modulated by phosphatidylinositol signaling, can reduce the basic activity of the dopamine [76], [77].

5.1.1 DYSLEXIA

Dyslexia or a reading disability is marked by severe difficulty in reading or interpreting words with accuracy and pace of word decoding. Spelling and text comprehensions also get affected. Numerous susceptible chromosomal regions are being identified for dyslexia. Chromosome 15q21 contain DYX1 (gene for dyslexia), the chromosome region 6p21–p22 (DYX2), DYX3 on chromosome 2p15–p16, DYX4 on chromosome 6q11–q12, the chromosome region 6q11–q12 contains DYX4, DYX5 on chromosome 3p12–q13, DYX6 on chromosome 18p1, DYX7 on chromosome 11p15, DYX8 on chromosome 1p34–1p36 and DYX9 on chromosome Xq26–q27 [78]. Dyslexia frequently shows comorbidity, such as with learning disability, hyperactivity, inattention, tourette and anxiety disorders [79], [80]. The dyslexic patients are highly variable so different individuals display different reading skills and their performance is linked with particular deterioration in cognition or in nervous system [81], [82], [83]. Both home literacy environment and child health predicted attention, behaviour and readiness. So it is likely that dyslexia represents gene-environment correlation [84].

5.2 EPILEPSY

Epilepsy encompasses wide range of disorders with abnormal and unusual electrical activity in brain. In childhood, Febrile seizures (FSs) is the root cause of epilepsy and is accompanied with high fever [85]. The analysis of genetic linkage has spotted various chromosomal regions for familial cases of FS, including chromosome loci 19p13.3, 2q23-q24, 5q14-q15 and 18p11.2. They contain the genes encoding casein kinase I gamma 2 isoform (CSNK1G2), sodium channel, voltage-gated, type I, alpha subunit (SCN1A), G protein-coupled receptor 98 (GPR98) and inositol(myo)-1(or 4)-monophosphatase 2 (IMPA2) respectively [86], [87]. Moreover, a number of other genes have also been identified, including the genes encoding cholinergic receptor nicotinic alpha 4 (CHRNA4), gamma-amino butyric acid A receptor gamma 2 (GABRG2) and beta 3 (GABRB3) interleukin 1 beta (IL1B) and interleukin 1 receptor antagonist (IL1RN) [88], [89], [90], [91], [92], [93].

5.3 ATTENTION-DEFICIT HYPERACTIVITY DISORDER

This disorder known as ADHD consists of the following symptoms: impulsivity, inattention, hyper activity restlessness and fidgety. Comorbidity includes brain dysfunction, hyperactive child syndrome, disruptive behavior, anxiety and mood disorders [94], [95]. Many gene variants are involved in ADHD: genes that code for the dopamine receptor D4 (DRD4) and dopamine transporter (DAT1 or SLC6A3) in the noradrenergic system (including norepinephrine), gene coding for the adrenergic alpha-2A receptor (ADRA2A), COMT gene; which codes for the enzyme catechol-O-methyltransferase and the gene for latrophilin 3 (LPHN3) [96]. A number of chromosomal regions are also being identified including chromosome (5p, 7p, 17p) and (6q, 11q, 12q) [97].

5.4 AUTISM

The neuroanotomy of Autism is difficult to distinguish because of several causes, comorbidity, heterogeneous phenotypes, and a complexity in the type and the extent of symptoms showed by different individuals known as (ASD) Autism spectrum disorders [98]. Around 70% of individuals with autism have mental retardation. The Asperger syndrome; Childhood disintegrative disorder; Rett syndrome; and PDD not otherwise specified (PDD-NOS) comprise of Autistic disorders which comes under the vast domain of Pervasive Developmental Disorders (PDD) [99]. Autism includes wide array of neurodevelopmental disorders which are marked by ailments in three neurological domains; social interactions; speech, communication, imaginative play; and restricted range of interests and activities [100]. Certain risk factors such as maternal metabolic syndrome, toxic exposures, prenatal infections and vitamin D and folic acid level in body may be linked with elevated risk of autism [101], [102]. Comorbid conditions are also associated with physical inactivity like obesity [103], [104]. Various genes are involved in causation of Autism. Cytogenetic anomalies at the 15q11-q13 locus are frequently found. Candidate genes include FOXP2; RAY1/ST7; IMMP2L; RELN at (7q22-q33) and UBE3A genes on (15q11-q13). Gene variants of the serotonin transporter gene on (17q11-q12) are often present in autism phenotypes [105]. The etiology of ASD has also been connected with the deformities in the functioning and development of nervous system including defects in plasticity of synapse [106], [107], [108], excitatory and inhibitory balance in a neural circuit, [109], [110], [111], neuron-glia interactions [112], altered axon guidance and dendritic branching [113], [114], which suggests that the ASD exhibits vast range of dysregulations in development [115], [116].

5.5 Asperger Syndrome

Asperger syndrome (AS) is indicated by impaired social interaction, absence of affinity, isolated interests and poor self-care, classified as Autism Spectrum Disorders (ASD). A genome-wide scan diagnosed nine chromosomal regions for Asperger susceptibility: chromosome 1q21-22 chromosome 3 (p14-24 and q25-27), chromosome 4 (p14 and q32), chromosome 6 (p25N and q16), chromosome 13 (q31-33) and chromosome 18 (p11) [117]. AS is also sometimes known as high functioning autism (HFA) [118], because according to the requirements of DSM-IV; Asperger Disorder in contrary to Autistic Disorder does not have delays in language development [119].

5.6 Childhood Disintegrative Disorder

Childhood Disintegrative Disorder CDD is also termed as Heller's syndrome or disintegrative psychosis. It is a rare autistic disorder with unknown etiology characterized by deterioration or loss of previously learned language and social skills after a time span of at least 2 years of regular growth [120]. CDD symptoms include normal mental and physical development marked by gradual regression of language skills, social relations, sympathy, adaptive capacities, peer play and interest in surrounding and peers deteriorate over a period years [121]. The CDD was found to be due to the deficiency of vitamin B12 and hyperhomocysteinemia [122]. The effected individuals display abnormal electroencephalogram (EEG) and seizures may appear sometimes [123], [124]. Recently it was found that a micro-deletion (22q13.3) in the SHANK3 gene usually in the first 17exons, is involved in causation of this disease [125].

5.7 Rett syndrome

Rett syndrome (RTT) include characteristics of autism, mental retardation, decreased muscle tone, difficulties in movement, loss of voluntary movements, hand wringing, abnormal spine curvature, seizures, and disturbances in autonomic nervous system [126], [127]. The patients also experience respiratory anomalies: excessive ventilation, holding of breath, sleep apnea as well as feeding problems and difficulties in food swallowing [128], [129], [130]. It is an X-linked dominant disorder attributed to mutations in MECP2. It is an X chromosomal gene, lethal in males, while girls foster the development of autism, intellectual disability, and sometimes epilepsy. These defects were supposed to be due to the absence of MECP2 function during neurodevelopment and were therefore expected to be irreversible by consequent restoration of MECP2 activity [131]. New genes have recently being discovered, the FOXG1 gene which codes specific transcriptional repressor of brain, [132], UBE1; human ubiquitin activating enzyme E1, UBE2I; ubiquitin conjugating enzyme E2I, GdX; ubiquitin-like protein, SOX3; SRY related HMG box gene 3, GABRA3; gamma-aminobutyric acid type A receptor alpha3 subunit and CDR2; cerebellar degeneration related autoantigen 2 [133].

6 Conclusion

The etiology of complex Neurodevelopmental Disorders (NDD) lies in the complex genetic networks and their interactions. A considerable research has been done to understand the genetics of the neurological disorders and interestingly in most of the cases mutations and polymorphisms are involved majorly. Many candidate genes and susceptible chromosomal regions have been discovered that are involved in the complex etiology of different disorders and various gene therapy approaches have been used based on the available genetic information for treating neurological disorders that offer many unique advantages. For example Lentiviral vectors are being used in gene therapy strategies that can effectively transport therapeutic molecules to neuronal cell types without causing immune rejection. More recent approach involves whole organ being synthesized using reprogrammed stem cells and also repair of damaged tissue using stem cells regenerative therapies which offers a great potential towards the therapy of these complex NDD's. Acquiring more advanced genetic information and applying it for treating complex disorders using advanced therapeutic techniques, would serve to have a better treatment for these diseases.

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