A Propitous Genetic Impact on Neurodevelopmental Disorders - A Flagstone for Personalized Medicine

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Abstract

There has been a precipitous advancement of unequivocal technological and methodological upgradings in genetics and genomics, thereby allowing to identify atypical mutations that are involved in complex neurodevelopmental conditions. Neoteric advancements in genomics such as whole – exome or whole genome sequencing have endorsed scientist to identify extensive mutations underlying NDDS. In this review we are recapitating the new-fangled developments in genomic analysis and deciphering it into clinical practice.

Key Words: *genetics, whole – exome sequencing, whole genome sequencing, genomics, neurodevelopmental conditions, NDD*

Introduction

One among the prominent health problems existing in paediatric health care is neurodevelopmental disorder (NDD).[1] About 3 percentage of the general population is to be posed by some form of NDDs.[2] Moreover, the spread of the disease is increasing significantly in people with poor socioeconomic status and health care, especially in the developing countries.[3] NDDs can be defined in a wide term for a multifarious group of conditions symbolized by disability in cognition, communication, behaviour and motor skills, because of abnormal brain development.[4,5] There are no curative pharmacological treatments for cognitive delay.[6] Thus, children with NDDs usually undergo treatment with a collage of rehabilitative therapies and early intervention strategies to optimize their developmental potential. NDDs could be categorized based on defects such as intellectual functioning, speech, language, and fine motor skills, and could coexist with a recognized syndrome. The existence of minor dysmorphism (facial and other superficial physical abnormalities) / multiple congenital anomalies (MCA) may coexist with symptoms of NDD in some instances. In patients with NDDs, the most common clinical features are intellectual disability (ID) or developmental delay (DD), voice delay (VD), linguistic delay (LD) and autism spectrum disorder (ASD). NDDs in children include attention-deficit/hyperactivity disorder (ADHD), autism, learning disabilities, intellectual disability (also called as mental retardation), conduct disorders, cerebral palsy and impairments in vision and hearing. The real dimension of the issue is mainly difficult to evaluate due to disorder definition, sampling processes, tool variations, cultural and environmental differences, training of information collectors and disorder awareness.[7,8] It has been proposed that 85% of children with neurodevelopmental illnesses live in low – and middle income nations, but little information is available to support this. The incidence of neurodevelopmental disorders in India, a study carried out by members of the International Clinical Epidemology Network (INCLEN) disclosed that 10 percent hilly area, 13 percent urban areas and 18 percent rural areas were found to have one or more NDDs in children aged 2 to 9 years. The tribal prevalence was 4.96%, possibly reflecting lower infant

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and child survival.[9] A significant interplay between environment and genes is also required to explain complicated NDD etiology associated by abnormality in brain morphology and/or functional activity, including those with a strong genetic element. maternal infection, chemical pollutants, dietary factors, medications, stress, deprivation are the various environmental irritants which may impede with typical brain development pathways, eventually augmenting the chance of either subclinical neuropsychological changes or clinical situations such as learning disabilities, autism spectrum disorders (ASD)[10] and attention deficit / hyperactivity disorder (ADHDs).

Pathology

Astrocyte dysfunction that affects neural circuit development is widely accepted pathomechanism of NDD.[11] Variations in exact timing of the neurogenic to glyogenic switch can lead to death or surplus of astrocytes, which leads to reduction of neuronal survival, synapse formation or limit the available number of neurons to contribute to specific circuits. Discharge of toxic factors or absence of survival or/and synaptogenic signals may precipitate pathogenesis of neural circuits.[12] MRI studies of autistic and normal patients showed brain abnormalities such as hyperplasia of cerebellar white matter, neocortical gray matter and cerebellar white matter in young age which slowed the growth further.

Role of Genetics in NDD

Inch - perfect technological and methodological breakthroughs in genomics have been rapidly evolving, enabling for the detection of mutations engaged in complicated neurodevelopmental disorder. A study exploring gene to phenotype connections for neurodevelopmental disorders classified genes centered on the particular disease were annotated and confirmed that genes connected with various diseases tend to be more multifunctional than specific (mentioned in Table 1). Also genes associated with Fetal Alcohol spectrum Disorder (FASD) were more multifunctional than Autism Spectrum Disorder (ASD) or Cerebral Palsy (CP).

Microarray based technologies for comparative genomic hybrization analysis has permitted the unmasking of submicroscopic microdeletions or microduplications also known by copy number variations (CNVs). Comparative genomic hybridization inquests suggest that rare copy number variations at numerous loci are muddled in the inducement of mental retardation, ASD and schizophrenia. These studies shows that the rearrangements were not disease specific, with possible oddment of maternally derived 15q13 duplication of gene TSPAN7, previously shown in MR and ASDs was spotted in case with schizophrenia.[15]

Animal Models of NDD

Animal models for NDD focus on a four tiered approach such as

i. Scoring for morphological changes in neural cells and in brain regions.

ii. Examination for alterations in brain activity and connectivity.

iii. Neurological behaviours such as sensory alteration, motor abnormalities and seizures.

iv. Higher order behaviour such as learning and memory or social behaviour changes etc.

Traditional models include environmental models such as neonatal brain infection using borna virus, [16] prenatal exposure of valproic acid in rodents, [17] prenatal influenza model, [18] LPS induced model[19] and thyroid models[20] for cerebellar dysfunction which causes NDD.

Genetic Models [21,22,23]

Various models for autism include staggerer mice (mutation of retinoic acid receptor related orphan receptor alpha gene), [24,25] SHANK3 (gene encodes for a post synaptic protein) existing shank3 models have not yet directly inspected on cerebellum, it is expressed in granule cells,[26,27] ENGRAILED2-En2 (involved in development of hind brain and cerebellum, it demonstrate decreased play, social behaviour, increase aggressive behaviour),[28,29] FMR1 (Gene encodes for fragile X mental retardation protein),[30,31,32] $FOXP_2$ (transcription factor, mutation causes excruciating speech and language disorder).[33,34] Tuberous Sclerosis Complex due mutation in TSC_2[35,36] and GABA receptors[37,38] are also studied in autism animal models. Genes studied in schizophrenia model involves G72/G30, [39, 40] Df (16) AKO, [41] DISC1.[42,43]

Although latest improvements in psychiatric genetics and epidemiological research have facilitated development of animal models, very few models have explicitily researched the impacts of mutation or environmental variables in cerebellum. More study

should be conducted in models to gradually regulate concentrations of expression of risk variables in purkinjee cells, as well as concurrent manipulation of genetic risk variables in the cerebellum and frontal cortex to decipher the function of separate brain linkages.[44]

Treatment For NDD

Conspicuous progress has been produced in defining the neurobiological processes of several diseases and the outcome of these diseases are being modified by targeted treatments.[45] A massive collaborative study from a various institutions, department, medical colleges, NGOs throughout India and USA, found the ubiquitousness of NDDs to be nearly 12% in Indian children of age group 2-9 years. Close to 1 in 8 chidren are suffering from not less than one of the NDDs. Recent advances suggest that through manipulations of environment or pharmacotherapy period - like plasticity can be reactivated in the adult brain. These scrutinies explore a tantilizing option that targeted pharmacological treatments in conjunction with training or rehabilitation schemes could relieve or reverse NDD symptoms even after critical department periods have ended. [46]

Personalised Therapeutic Approaches for NDDs:

Exposing various molecular pathways to evaluate novel therapeutic strategies became possible owing to the coalescence of genetics and functional analysis. Genomic sequencing guides the way from patient DNA to personalized medicine. DNA from patients with NDDs are used for sequencing, next generation sequencing which will be used to decipher the genetic code within exons (Whole Exom Sequencing) or entire genome (Whole Genome Sequencing). Mutations are identified in a series of genes with NDDs. The mutations are reinvigorated in various models in order to understand underlying mechanism which reveals targets that endorse the implementation of personalized medicine. Branched chain amino acids (BCAA) and antisense oligonucleotides (ASO) are two examples. The use of same drug for different diseases are used in drug repurposing due to novel mechanisms identified.[47] For example, Angelman syndrome which results from the functional mutations in the maternal allele of the imprinted UB3A gene or paternal allele is silenced by a lengthy noncoding RNA (UBE3A antisense transcript). In an AS mouse model study, reserachers have incorporated antisense oligonucleotides (ASOs) for unsilencing the maternal allele thereby normalizing the UB3A protein concentrations which resulted in the improvement of cognitive functions.[48] Replacing a defective gene may also be carried out by gene therapy using adeno – associated virus (AAV) vectors.[49] The application of antisense oligonucleotides and adeno – associated virus is challenging in clinical trial since safety and pharmacokinetic profile is not well established.[50]

Stem Cell Therapy in NDDS

A common motif among NDDs is a reduced capacity of affected Neural Stem Cells to proliferate, differentiate and migrate. Recent pluripotent methods have effectuated the possibility of modelling neurodevelopmental diseases integrated with genetic impairments. Patient fibroblasts were transformed into pluripotent stem cells to produce adequate neuronal progeny, specifically the cortical neurons which is responsible for higher cognitive skills in humans.[51] Induced pluripotent stem cells (ipsc) has provided new privileges for analysing brain development and the countrecoup of its dysfunctions in NDDs. Also it facilitated the analysis of neuronal phenotypes after the derivation of patients somatic cell into neurons, besides it is used in-vitro in case of syndromic and non-syndromic forms of ASD[52] and shankopathies(mutation of SHANK genes).[53] iPSCs are also used in reconstruction of brain circuitary using neural transplantation of human neurons into mouse brain.[54]

Main limitations of human iPSC cells in vitro: the cell reprogramming rate relies on cell types of the donor and culture conditions.[55] Various models are proposed to analyse the programming processes and transcription factors and epigenetic regulators and their role.[56] These techniques do not come across as sufficiently effective to reprogram human primary fibroblasts accurately.[57] A fresh, optimized technique combining mod mRNA with reprogramming variables and enhanced cell culture[58] environments is encouraging and appears to provide an alternative strategy to human fibroblast reprogramming for ASD and associated syndromes.[59] The low cell reprogramming efficiency observed to date has made it much harder to simultaneously derive separate isogenic cell kinds from the same human iPSC. In vitro systems do not permit the reproduction of globular cellular homeostasis and cell orientation and projections within the separate cortical layers. New movements which include three-dimensional culture systems[60] and brain organoids [61] have been developed for iPSC models. In addition, advances in genome editing technologies allow the genetic manipulations of iPSC in a site-specific way.

Conclusion

At current scenario, the treatments available for NDDs consists of both behavioural therapies and drugs for comorbidities such as irritability and anxiety, while in most cases the mainstay symptoms of NDDs are still unsolved. Numerous molecular pathways being identified in NDD which resulted from the combination of genetics and functional analysis. Genetic findings made personalizing the existing pharmacotherapy or behavioural interventions other than new targets for therapy. Because of the complexity of NDDs, versatile methods that combine genetics, functional genomics, robust biological models and objective reaction measures such as biomarkers,[62] as well as scientists and clinician's potential to work together will be crucial.

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Table1: Specific and multifunctional genes for various neurodevelopmental disorders. [13,14]

Disease category	No.of specific genes	Total No. of Genes	% of Specific Genes
ASD	189	321	69.8
FASD	27	106	25.5
CP	23	124	22.1

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