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Review Article

Next generation sequencing: A promising tool to explore the personalized medicine in understanding the neurodegenerative diseases

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ABSTRACT

Despite the various advances made in the diagnosis and treatments, the incidence of the neurodegenerative diseases has increased manifold during the last few decades. The inadequate early diagnosis appears to be the main reason behind the significant increase in the number of neurodegenerative diseases and their poor prognosis. Next generation sequencing has been discovered as an effective and indicative tool, especially for chronic and severe neurological illnesses, such as Parkinson and Alzheimer. As a clinical apparatus, next generation sequencing will help in creating explicit hereditary focuses for the treatment of neurodegenerative diseases and finding new diagnostic biomarkers. Next-generation sequencing has been demonstrated to be increasingly productive, practical and utilizes molecular determination, which determines biomarkers and different targets quicker and efficiently than the other established diagnostic methods. There is a desperate requirement to change the current treatment and medication regimes in order to make better prognosis for the patients. This can be accomplished by utilizing customized drug to treat neurodegenerative diseases and using next generation sequencing with personal medicine as the method for specialized treatment of the patients suffering from neurodegenerative disorders.

1. Introduction

Till date around 600 neurological disorders including the disorders of the brain, spinal cord and the nerves have been identified and out of that majority are genetic. The disorders included are like Huntington's disease, cerebral paralysis, spina bifida, and degenerative ailments like Alzheimer and Parkinson.[1] They are portrayed chiefly as dynamic dysfunctions of the nervous system mentioned as loss of neurons in the brain and spinal cord.[2] The essential unit of nervous system are neurons, so any harm to them is irreparable and can be fatal if not diagnosed or treated in time. Increase in the incidence of neurological ailments has hugely affected the quality of life and overall morbidity and mortality rates. Financial expenses on the medicines needed to treat these ailments make a huge monetary burden.[2] Patients with mental illness suffer with additional social stigma, which is the reason that they do not look for help.[3,4]

From the point of view of pervasiveness of neurological pathologies combined with aging populations the healthcare system in any nation throughout the globe is challenged and compromised. The advances made in biomedical researches such as the use of artificial intelligence in studying effects of genetics, epigenetics, aging, nutrition, drugs, microbiome etc., on the well-being or ailment of the human populations.[4] Genetics has prompted other

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ways to focus on many other prevalent diseases. Learning molecular insights of neurodegenerative diseases help in drug discovery, which may bring significant changes in the quality of life by improving the well-being or reducing mortality.[5] Now a days, the sequencing of the candidate genes in the patients with neurodegenerative pathologies is quicker, precise and pocket friendly with respect to the time of onset of neurodegeneration in healthy populations.[6]

1.1. Parkinsons disease

Parkinson's disease (PD) is chronic neurodegenerative disorder. This is the result of the loss of dopaminergic neurons in the Substantia Nigra pars Compacta (SNc), which also involves development of Lewy bodies made up of anomalously aggregated protein and is highly progressive. Over 10 million individuals around the world are suffering from Substantia Nigra pars Compacta involvement, with variables predominantly relying on the age, sex and geographic location.[4] This disease is chronic and dynamic in nature with an asymmetric onset. Motor and nonmotor deficits are trademark highlights of this ailment. It is somewhat unusual to take note of insufficient stress on this issue from neuropsychological viewpoint, since a wide range of cognitive dysfunctions are pervasive in PD. As the result, the treatment for this comorbidity has never been opiniated and satisfactorily developed.[7] The available practical treatment of PD is symptomatic which includes substituting dopamine or suppressing neuronal oscillations by means of deep brain stimulation.[8]

Since long time the methodologies which are practice-oriented and frequently pragmatic had been tried to improve the therapeutics in PD. The unpredictable connections between molecular, cell and clinical characteristics should be clarified to understand the basics.[8] Around 10% are sporadic familial cases which have mutated genes has been investigated and have shown the increased risk of early disease onset. Animal models which have been utilized to build two potential models for PD are neurotoxicity and hereditary models and unfortunately the greater part of them have been fruitless in recognizing the genuine reasons and types.[1] Mendelian autosomal dominant or recessive inheritance is displayed by PD in 5–10% of cases. Out of all regions on genes just six regions have the basic quality genes that cause normal monogenic types of PD. These have been distinguished as SNCA (α-synuclein) and LRRK2 for autosomal dominant PD and PINK1, PARK7 (DJ-1), ATPase type 13A2 (ATP13A2) and PARK2 (Parkin) for autosomal recessive PD.[8] The peculiarity is that the genome does not encode a protein but progress to a disease by influencing normal gene expression. The possibility of development of oligonucleotide anti sequencing of the exons as therapeutic options is widely known. The other possible modalities which will help in discovering the targets for diagnosis and treatments include introns/exons, repetitive RNA, micro RNAs and an enormous number of non-conforming RNA that can be contemplated with the assistance of genomic studies, including cutting edge next generation sequencing.[9]

1.2. Alzheimer's disease

Alzheimer disease is a neurodegenerative disease with polygenic inheritance and is characterized by the presence of amyloid plaques extracellularly and neurofibrillary tangles intracellularly. Numerous manifestations such as neuroinflammation, synaptic, synapse and neurotransmitter losses are some of the characteristic features of"
add before pathogenesis pathogenesis of AD.[10] In the recent years incredible advancements have been made in recognizing in vivo natural markers of AD. Neuropsychology has assumed a crucial role in describing the cognitive changes related to AD and dementing disorders. This has improved the capacity to precisely analyze AD and separate it from other dementing disorders. It distinguishes inconspicuous and subtle cognitive changes, happening in preclinical/prodromal period of ailment and following movement of disorder.[11] Despite underlying pathology, it recognizes the beginning and punctual cognitive decline affecting life and having option to foresee the course of psychological decrease, and to quantify the cognitive outcome of future medication.[12]

A precision medicine approach will enable numerous biomarkers to target particular pathologies, to show which pathologies are present, to investigate polygenic risk for different disorders, to evaluate neuropsychological assessment and to distinguish unmistaken examples of deficits mirroring differential effects of distinct pathologies on dementia disorder.[11] Hereditarily and genetically Alzheimer's is a very complex disorder. Early-onset familial AD is due to mutations in three important genes namely presenilin 1, amyloid antecedent protein, and presenilin 2.[13] A significant focal point of AD has been comprehended as the hereditary etiology of Alzheimer and its relationship to neuropathology. The key neuropathological highlights of AD are rich neurofibrillary tangles made of some tau protein and senile plaques made of units of β-amyloid (Aβ).[12] The accumulation of Aβ42 is a focal segment in the pathogenesis of this disorder, which has been related with three important autosomal dominant and deterministic genes. These 3 genes are engaged with early onset AD along with presenilin 1 (PSEN1) and presenilin 2 (PSEN2) and amyloid precursor protein (APP).[14] As of now, genes found till date with the assistance of cutting-edge next generation sequencing include genes on both on chromosome 9 and chromosome 10. On chromosome 9 it includes DAPK1 (demise related protein kinase 1) and Ubiquilin 1 (UBQLN1).[14]

2. Huntington's Disease

Huntington's disease (HD) is an autosomal predominant condition represented by movement disorders and cognitive decline. The motor defects incorporate chorea and loss of coordination. Psychiatric manifestations which are upsetting to the patients are depression, psychosis and obsessive compulsive disorder are basics in HD.[15] Huntington disease is described by general shrinkage of the cerebrum and degeneration of the striatum with specific loss of efferent medium spiny neurons. Despite that the striatum has all the earmarks of being the most influenced region of the brain, a regionally explicit diminishing of cortical ribbon was found in patients with HD. Mutations in HTT gene encoding mutant huntingtin, a universally expressed toxic protein is the frequently less examined than neurological signs which leads to HD.[16]

The quantity of CAG repeat and time of beginning of symptoms are inversely related : bigger CAG repeat developments are connected with earlier ages of onset.[17] Huntington has a few significant functions in the body; it helps embryonic improvement as a scaffolding protein. The major cause of lethality in HD is due to gaining the function by mutant protein. The deletion or inactivation of wild-type huntingtin prompts neurodegeneration. There is substitution of disposed toxic polyglutamine which results in lost function of the wild-type protein.[15] The two main characteristic features of Huntington's disease are the autosomal dominant nature and the familial nature which is predicted from the family history even before the beginning of any symptoms. As of now, no known disease-modifying drugs are accessible to treat HD or reduce its symptoms. Treatment has been symptomatic for the past few decades,[18] when standard drug treatment regimens were used even for the treatment of non-HD patients or patients having symptoms like Huntington disease. Atypical antipsychotics have been used to treat psychosis, and depression has been treated with SSRI, SNRI and antidepressants.[13] A better understanding of the fundamentals of HD still can't determine any alternate treatment plan. Movement disorders and cognitive decline are some important characteristics of Huntington Disease. For instance, psychological manifestations, discouragement, psychosis and over the top urgent issue are customary in HD, which are particularly upsetting for the patients.[15]

Ordinarily, the motor defects incorporate chorea along-with different levels of losing coordination. The depression, psychosis and obsessive–compulsive disorder are the common psychiatric symptoms in most of the patients.[15] The shrinkage of the brain and degeneration of the striatum are the major degenerative changes where there is severe loss of efferent medium spiny neurons. The striatum emits an impression of being the most influenced area of the brain and diminishing region of cortical ribbon was explicitly found in the patients affected with HD. Yet, generally less investigated than neurological symptoms, these additional signs might be a direct result of all-inclusive explanation of mutant huntingtin, which is a toxic protein, shown as the cause of Huntington disease in several studies.[16]

3. Bridging the Gap with Personalized Medicine

Inter-individual variability due to pharmacotherapy customizes therapeutic choices under personalized medicine.[19] The predominance of neurodegenerative pathologies together with quickly aging populations have been one of the fundamental difficulties for healthcare systems. In the field of biomedical research along with the field of informatics enormous advances have been made. Both for improving the information on how genes, epigenetic changes, age, nourishment, drugs and microbiome sway health and disease, these fields have been vital. Both hereditary and epigenetic diagnostic testing is required to understand the promise of personalized medicine.

The accessibility of high technology as well as computational facilities for huge scale examination empowered more profound examination of most neurodegenerative disorders, giving exhaustive overviews of disorders and disease, empowering advancement of precision medicine for the diagnosis and treatment as well as prevention of these pathologies.[4] Efforts needs to be done to move precision medicine from the bench to the bedside. There is the need for creating the collaborative networks among highly qualified specialists, research institutes and medical centers. The simple interventions like dietary and lifestyle interventions are useful instrumental tools for preventing or adjusting the course of these neurodegenerative diseases. The role of physical and mental exercises, nutrition and smoking in neurodegenerative disorders is very crucial. The effect of nutrition and smoking on brain health which impact reactions to specific foods and smoking-related compounds needs the profound exploration in connection to all these inter-individual variations in the genetic makeup

Even-though customized dietary and lifestyle approaches are being used for treating neurodegenerative pathologies, they can soon be received within the preventative and therapeutic programs within a few years.[20] Some of the highly recognized factors include epigenetics as well as genetics. Other ones include several environmental factors; all these then added to the diverse presentation of these disorders, which then added more to the factor and disease interaction module. In this manner, the most important need should be the management of variables in a single disease presentation or its outcome. This has necessitated the requirement of important factors like epigenetics, genetics and different environmental factors on disease progression to be conducive to the disease, felicitating a need to make a custom treatment plan unique to the needs of every

individual.[19] The clinical utility of any medicinal test is to treat the underlying ailment and is decided by the capacity of test results to alter and affect decisions of the physicians.

The diagnosis depends on the clinical presentation which is the characteristic of that particular disorder. The specific genetic testing or screening for disease-specific mutations in individuals can be the guide for prognosis, treatment and diagnosis of neurodegenerative disorders. The genomic studies helps to identify and recognize the numerous molecular biomarkers with gene mutations.[19] The results of these prognostic as well as diagnostic tests are utilized by health care professionals to analyze disorders and diseases. The appropriate dosage for individual is set up depending on metabolism and specific drug intervention for disease management in order to evaluate disease risk in a person. The personalized medicine is of use in a patient's personal genetic profile to foresee the disease and its prevention through medicinal interventions by settling on choices about lifestyle. Genetic screening is always significant for the personalization of prognosis as well as treatment for a patient.[19]

The genomic approaches like DNA sequence variations, transcriptomics, proteomics and metabolomics are helpful for precise prediction and management of the disease. These methodologies are valuable to bridge gaps between epigenetics and more importantly personalized medicine. The genomic data from an individual succession and communicated biomarkers are basic to accomplish customized and genomic treatments.[21] The inadequacy of traditional or regular treatments for a chronic disease, risk of which is mirrored in the patient's genomic foundation. The genomic applications can be utilized to customize personal health care of individuals at different pivotal checkpoints while observing a patient, slipping from a healthy state to an ailing situation. Epigenetic and drug management information of a diseased patient are helpful to successfully personalize medication.[21]

4. Parkinson's Disease: Pathogenic Roles PINK1, Parkin and Alpha-Synuclein gene

Several genes are responsible in the pathogenesis of Parkinson. In-depth genetic linkage analysis in an affected patient has yielded an unidentified gene, found located on the chromosome 6q25.2-27, which was responsible for autosomal recessive juvenile Parkinsonism. More researchers reported that early-onset Parkinsonism harbors another gene called as PARK2. Mutations in this gene leads to varying deletions or in certain cases point mutation causing losses of PARK2 protein functions.[22] The gene, PARK2 contains 12 exons that are specifically encoded with 465 amino acid proteins, named as Parkin.[23] Parkin is known to be an E3 ubiquitin ligase with its structure formation showing amino- and carboxyl-terminals with ubiquitin ligase like (Ubl) domain.[24]

Another crucial gene is found after in-depth genetic analysis which is identified at early onset of recessive Parkinson cases. The PARK6 gene contains 8 exon that encodes 581 amino acids, namely protein phosphatase. It also includes tensin homolog-induced kinase 1(PTEN), abbreviated as PINK1. The localization and confinement of PINK1 is to the mitochondria, where Parkin resides exclusively in the cytosol. In vitro analysis of various genetic epistasis models in Drosophila has revealed that both proteins work on the same pathway in order to maintain mitochondrial fidelity though originated at different location.[25] PINK1 is accumulated on dysfunctional mitochondria or damaged mitochondria and the kinase-like activity is required for translocation of protein Parkin to these damaged mitochondria and mitophagy. This is the important function of these autosomal recessive PARK gene product proteins and the same biochemical pathway is responsible in pathophysiology of Parkinson is involved.[25] The most crucial function of PINK1 along-with the protein Parkin is to contribute prevention of Parkinsonism in man while the mitochondrial dysfunction has a role in sporadic cases of Parkinson.[24] PINK1 accumulates precisely on damaged mitochondria, flagging them for elimination by natural processes of damaged cell apoptosis. This damage-sensing mechanism has been known to be due to the rapid and constitutive breakdown of PINK1 in healthy mitochondria within a cell.[26] When one mitochondrion becomes impaired, there is accumulation of PINK1 on the outer membrane of dysfunctional and damaged mitochondrion. PINK1 phosphorylates ubiquitin at Ser65 and phospho-ubiquitin activates Parkin E3 ligase activity. This whole process is somehow translated in the pathophysiology of Parkinson.[27] These genes are crucial targets for the treatment of sporadic as well as early onset Parkinson. Although more insight is needed in the development of target specific drugs against these genes depending their expressions.[14]

5. Role of Presenilin, Amyloid Precursor Protein, Ubiquilin and Sortilin-Related Receptor-1 in Alzheimer's Disease

The first gene causing Alzheimer was found to be because of the missense mutations in Presenilin.[29] These are found to be the catalytic components of the enzyme γ-secretases, as well as membrane-bound aspartyl protease complexes, which are responsible for generation of carboxyl terminus of amyloid β-protein (Aβ) from amyloid protein precursor (APP).[30] The role of presenilin's in amyloid protein precursor processing is depicted from the AD-causing mutations in PSEN1 and PSEN2 affecting generation of Aβ peptides. The another enzyme presenilin-dependent protease was responsible for both cleavages and blocking these enzymes which would cause major side effects in patients and affect treatment process. Studies in humans

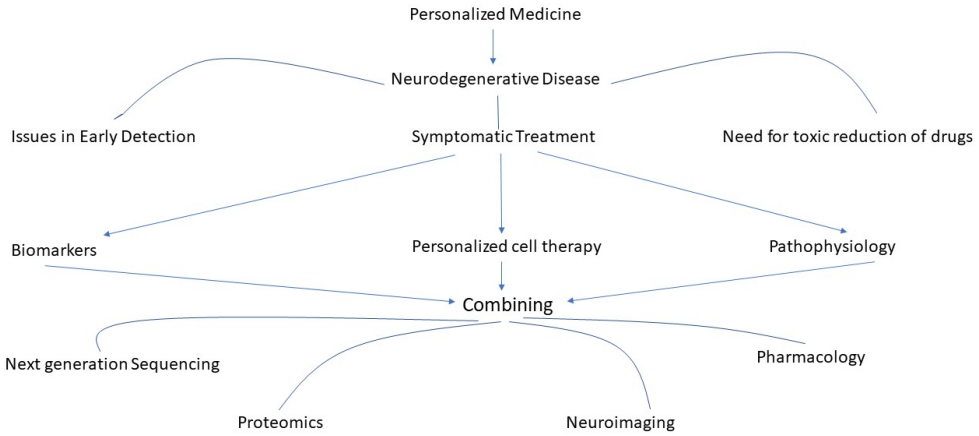

Fig. 1: Illustration of personalized medicine in neurodegenerative diseases

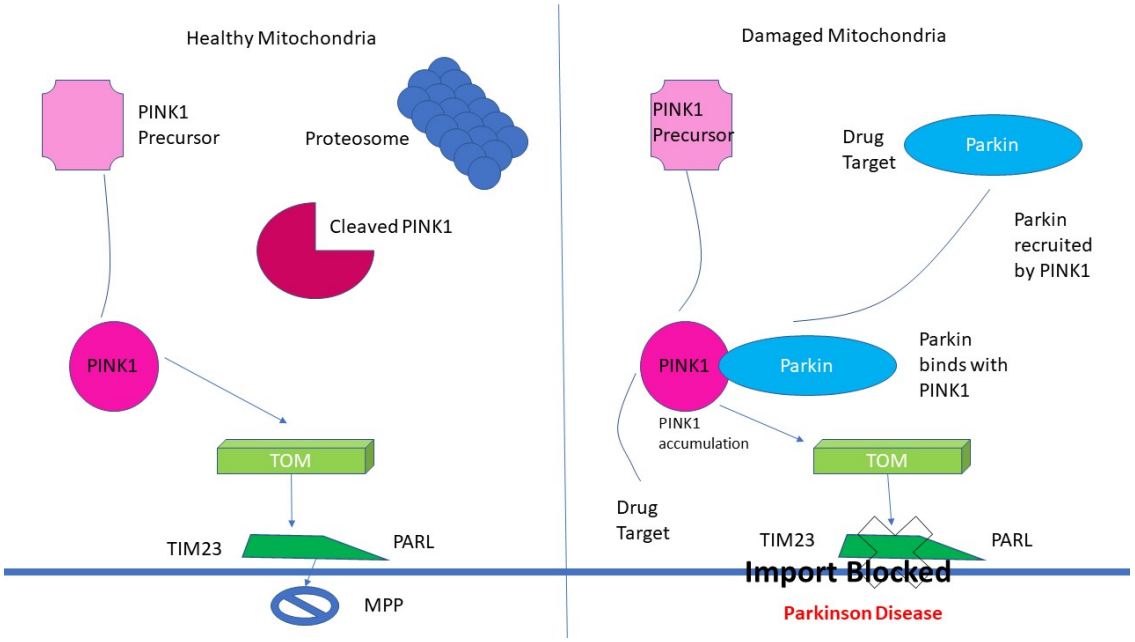

Fig. 2: Depiction of PINK1 and Parkin interaction in Parkinson Disease [PINK1-PTEN-induced kinase 1, PARL- Presenilin-associated rhomboid-like protein, TOM- Translocase of the outer membrane, TIM23-Translocase of the inner membrane, MPP- Mitochondrial processing peptidase][28]

showed that, PSEN1 and PSEN2, two homologous proteins exist, which are synthesized as precursor proteins of 50 kDa with nine TMDs and cleaved into a 30 kDa amino-terminal fragment and a 20 kDa carboxy-terminal fragment during the process of maturation.[31] The same gene has shown that other presenilin functions have been proposed in protein trafficking, in calcium homeostasis and in the positive and negative regulations of β-catenin signaling sometimes from within and sometimes outside of γ-secretase complex. In mammals, the Notch phenotypes are predominant in presenilin-deficient animals.[31] They also interfere with the Notch signaling pathway, which is important in the development of γ-secretase inhibitors in the treatment of Alzheimer patients.

Out of 160 mutations, mutations of presenilin's associated with AD are dominant. It is found that even single mutant allele is enough to cause carrier to develop AD in midlife.[30] One more gene was identified and named

as UBQLN1 gene. Few SNPs in UBQLN1 gene have been found to be associated by a positional candidate gene approach proving a family-based association with late-onset AD.[31] Changes in alternate splicing were known due to polymorphisms in UBQLN1 gene. A crucial molecule involved in trafficking checkpoint within the secretory pathway is Ubiquilin-1 that stops excessive amyloidogenic processing of APP by limiting access to secretase enzymes.[32] Over expression decreases Aβ42/40 ratio and prevents APP-induced toxicity in the cells, while reduction aggravates APP-induced toxicity. Ubiquilin-1 protein levels are also known to be related with Braak staging of disease, which is extremely crucial as therapeutic use. This suggests that drugs, which restore ubiquilin-1 expression in the brain may become a potential treatment for AD.[32] Another more important gene is SORL1. Amongst next generation sequencing processes, whole-exome sequencing has been used to identify potentially damaging SORL1 mutations in patients with both EOAD and LOAD.[33] SORL1 gene has been suggested to modify post-translational biology of APP at many intracellular regions. These includes ones during transporting out of the Golgi and during re-entry and recycling from the cell surface. Sorting of APP into secretory, endocytic, or recycling pathways is regulated by SORL1.[33]

Mutations in the gene SORL1 causes reduced trafficking of the mutated SORL1 protein from the endoplasmic reticulum as well as Golgi network to surface of the cell. This result more APP in wrong direction to the late endosome pathway, thus exposing APP to enzymatic cleavage of β-secretase and γ-secretase, which in turn causes an increase in Aβ production, specifically Aβ42 protein. A potential association between SORL1 alterations and a broader spectrum of Alzheimer has been postulated.[33]

6. Role of Huntingtin in Huntington Disease

Huntingtin is the first important and essential molecule discovered in pathophysiology of Huntington disease. The root genetic defect is expansion of CAG trinucleotide repeat in the first exon of HD gene that produces huntingtin (htt) protein with expanded polyglutamine.[35] Huntingtin is associated with a various organelles like nucleus, endoplasmic reticulum, Golgi complex, synaptic vesicles, and mitochondria. The onset of pathogenesis is first by the cleavage of huntingtin into huntingtin N-terminal fragments in cytoplasm followed by translocation of these into the nucleus of striatal neurons.[36] Enhancing nuclear localization of huntingtin N-terminal fragments more specifically within the medium spiny neurons of the striatum occurs concurrently which results in the onset of selective neurodegeneration. The huntingtin has been known to be a caspase substrate and all these truncated huntingtin fragments have shown a toxic effect in vitro. Thus, the inhibitors of caspase cleavage of huntingtin, which in turn may be of a huge potential therapeutic benefit in HD and relieve patients by giving them a better quality of life.[37]

7. Next Generation Sequencing in Neurodegenerative Disorders

The first and most established method that is next generation sequencing (NGS)was developed by Sanger et al.(1977), for sequencing an already known and determined fragment of deoxyribonucleic acid. A set of 500 bases may be sequenced with about 99% accuracy; the system may be tedious for large sequences e.g., recognizing NDs.[1] The genetics moving toward neurological diseases has regularly been dependent on the improvement and utilization of new advances. GWAS has been found as the valuable tool in finding new loci for the common forms of disease, where variations and comparisons were finished with a huge number of cases.[38] For these types of diseases, there is no predisposition of biological believability over the genome then the ideal outcomes. In this manner, identification of extremely uncommon causative mutations underlying Mendelian types of diseases through progression of innovation has been finished by linkage analysis. Through GWAS, the discovery of common variants specially which have low impacts and are for late-onset and sporadic disorders has been shown the great promising benefit.[6] However, limitation to these two approaches still remain, just like variations that do not impart an exceptionally solid impact on disease, tested by linkage analysis.[39] GWAS is appropriate for mutations that is generally most common in population.

The framework for NGS has been established with the help of Sanger sequencing. Neurodegenerative diseases are one of the least therapeutic in nature, when contrasted with others and the main actions taken at the very beginning stages, which are most difficult to diagnose and treat. NGS becomes an integral factor in this scenario.[39] NGS has extraordinarily accelerated the way toward distinguishing many such novel genes and has had a significant effect on numerous biomedical researches, which mainly include research on neurological disorders.[40] NGS, as called high-throughput sequencing, considers parallel sequencing of many deoxyribonucleic acid (DNA) molecules at the same time with the goal that several thousands to millions of nucleotide sequencing can be produced in a solitary instrument run on different stages.[37] A genome subset can be focused on the entire human genome, exons, noncoding RNAs or different locales of interest[41] Contingent upon the objectives of sequencing, a scope of uses have been created to fit various analytic and needs of the current research; including whole genome sequencing (WGS), whole exome sequencing (WES), targeted sequencing (TS) and RNA sequencing.[42]

The most broadly utilized NGS strategy is WES for genetic analysis, which catches all coding exons that

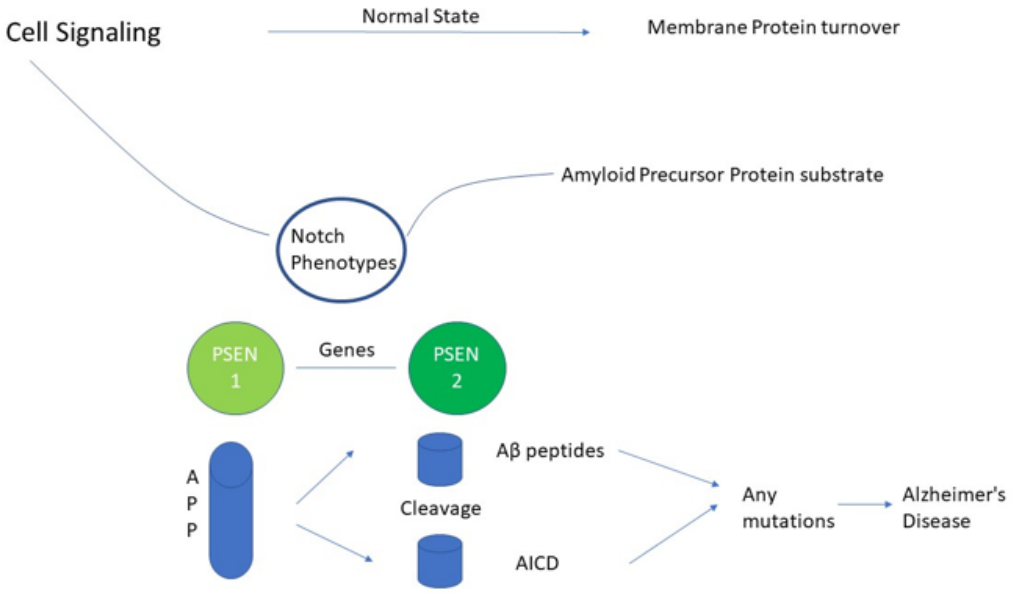

Fig. 3: Role of PSEN and APP in the pathogenesis of Alzheimer [PSEN- Presnelin, APP- Amyloid Precursor Protein, Aβ- Amyloid-b peptides, AICD- APP intracellular domain] [34]

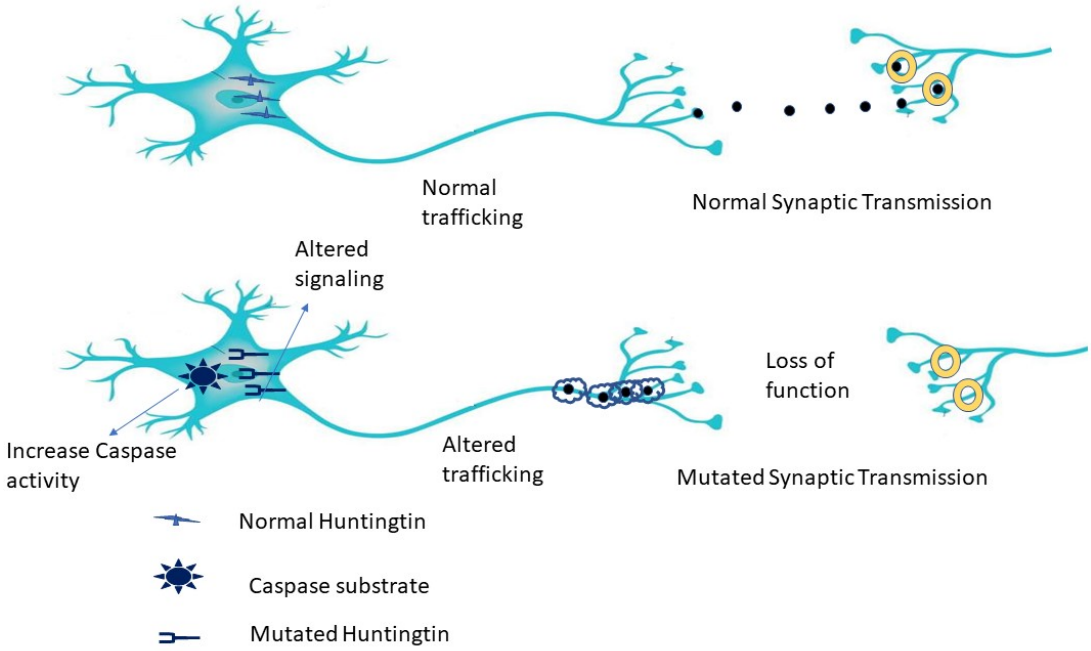

Fig. 4: Pathogenesis of Huntingtin protein in Huntington Disease. [35]

have been known so far and exon/intron limits in any genome. The exome is a piece of genome that include all encoding sites and regions and has around 200,000 exons from 21,000 genes. An exome is just over 1% of a genome and up to about 85% of all mutations that have been known to cause disease in Mendelian disorder. They are found inside encoding exons, as being the most mentioned and requested tool for diagnosis.[42] With NGS, the most important function of disease and gene identification challenge shifts from distinguishing proof to a very important interpretation phase. Many genomic variations are recognized per genome.

Variant's prioritization is vital to the disease-causing gene identification proof procedure. For serious Mendelian disorders prioritization assumes that mutation has a huge impact. These mutations are consequently exceptional in patients or possibly extremely uncommon in general community. They are situated inside the protein-coding locales of the genome and straightforwardly influence function of encoded protein by the mutated gene.[43] Another use of Next Generation Sequencing is CHIP-Seq analysis, which can be used for the examination of histones, protein changes and others. Chromatin immunoprecipitation pursued by deep sequencing (ChIP-Seq) and NGS application give exceptionally productive strategy for profiling of DNA-binding proteins, histone alterations, and nucleosomes on a genome-wide scale.[44]

The execution of new advancements has acquired new statures in the field of genetics. Presently, the variation and structure at genome-wide level gets simpler to be resolved and investigated its effect on phenotypes is unmatched. The variations causing impacts on Mendelian, just as on complex ailment, can be distinguished by Genome -wide association studies (GWAS), which sheds a light on common variability dependable to whole genome and exome sequencing. It turns out to be progressively inquisitive as how recreations of these advances are uncovering some unpredicted outcomes, when molecular information is entangled with clinical phenotypes and seen before biological procedures becoming focal key pathways in disease pathologically.[43] Now we can test such sort of variety by utilizing entire exome and other sequencing approaches.

Exome sequencing does not only allow quick recognizable proof of a few genes liable for different diseases but also uncovered new risk factors for chronic disorders.[44] The most commonly found causative genes have been distinguished in families with an alternate phenotypic isolation, either indicating a latent or predominant example of heredity. If there should arise an occurrence of recessive disorder, auto zygosity mapping guides exome sequencing results in case of dominant diseases, where genetic linkage analysis plays an important role.[40] The standardization of massively parallel sequencing and exome sequencing has allowed distinguished proof of different number of novel genetic defects prompting towards many disorders.[41] The analysis that mutations in similar genes is liable for influencing distinct clinical phenotypes has been wonderful and the concepts, which have been experienced in molecular genetics came from the first exome sequencing, which has continued towards the novel association between phenotypes that would help us for better comprehension of pathobiology behind various neurological illnesses.[41]

8. Conclusion

As of now there are no medicines available to conquer neurodegenerative diseases precisely. The pharmaceutical potential can simply lessen symptoms of diseases and help to upgrade patients' psychological state. For example, memantine and donepezil can at times moderately control development of dementia signs in individuals with Alzheimer's disorder and Levodopa can grow brain's dopamine level to help facilitate reduction in a few of the symptoms of Parkinson's disease. The rate of these illness is on prevalence, yet there is a lack of fruitful medicines to treat them. Research unifies around similarities in neurodegeneration that occur in all these three ailments. Through distinguishing these parallels, researchers might want to get a handle on instruments of disease with an ultimate objective to upgrade their chances of developing new medications and strategies that may benefit patients encountering any of the conditions. Because of the advances created in the last decade, we are currently in an extraordinary situation to examine hereditary fluctuation in Mendelian and complex ailments.

The future tasks incorporate investigations of huge information resulting due to available case reviews and combinations of these analyses with family and hereditary studies. NGS provides a hope for the development to target gene identified with the disease, which might be under or over communicated. Being amazingly monetarily cheap and effective NGS has changed the analysis of Genomics and Molecular Biology. Even though the instrument is low priced,the sequencing cost of single genome is high. The costs per base for sequencing are generally higher than standard instrument. The present advancement proposes characteristic challenges especially in dealing with colossal proportions of data. The massively parallel sequencing stages and progression in advancement have urged with a novel need to some degree. Starting now, better advancement is required to handle and translate material viably. This in turn will help in better targeting genes at an individual level rather than at generic level. More approaches towards the use of precision medicine must be brought as a mean of regular diagnosis tool than just a research tool. Precision medicine in combination with Next Generation Sequencing is the ultimate end goal for early

prognosis and diagnosis. This will also help in creating prompt and better treatment plans in future especially for the neurodegenerative diseases.

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10. Conflict of Interest

The authors declare no conflict of interest.

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