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GENETIC MAKEUP OF NEURODEGENERATION

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Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
AMPA	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid
ATP	Adenosine Triphosphate
AA	Aranchoidonic Acid
AP-1	Activator protein 1
ATF6	Activating Transcription Factor 6
ALAS2	Delta-Aminolevucinate Synthase 2
APP	Amyloid Precursoe Protein
APOE	Apolipoprotein E
AAV	Adeno-Associated Virus
Adv	Adenovirus
BACE1	Beta-site Amyloid Precursor Protein Cleaving Enzyme
BLVRB	Biliverdine Reductase B
BDNF	Brain Delivered Neurotrophic Factor
CNS	Central Nervous System
CREB	Camp Response Element Binding
DOPE	Dioleoylphosphatidyle thanolamine

DOTAP	1, 2-Dioleoyl-3-trimethylammonium propane
DODAP	18:1 DAP1, 2 dioleoyl-3-dimethylammonium -propane
DOTMA	N-[1-(2, 3-dioleyloxy) propyl]-N-N, N-tri-methyl ammonium chloride
DBD	DNA Binding Domain
ER	Endoplasmic Reticulum
ERAD	Endoplasmic Reticulum Associated Protein Degradation
ERK2	Mitogen-Activated Protein Kinase 2
FOXO	Freedom of Xpression Online
FECH	Ferrochelatase
GLU	Glutamate Uptake
GSK3	Glycogen synthase kinase 3
GDNF	Glial Derived Neurotrophic Factor
GPNMB	Glycoprotein NMB
GRN	Granulin Precursor
HD	Huntington's Disease
HSP	Heat Shock Protein
HIF-1α	Hypoxia-inducible-factor-1-alpha
HTT	Huntingtin gene
HSF1	Heat Shock Transription Factor 1
IP3	Inositol triphosphate
IL-17A	Interleukin-17A
IFN-y	Interferon gamma
JNK	Jun-N-terminal kinase
LPS	Lippopolysaccharide
LLRK2	Leucine –Rich Repeat Kinase2
LVs	Layout vs schematic
MGLUR	Metabotropic Glutamate Receptor
m-RNA	Messenger RNA
MEF2D	Myocyte –specific Enhancer Factor 2D
MCL1	Myeloid cell Leukemia 1
NO	Nitric Oxide
NF-Kβ	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated beta cells
NrF2	Nuclear Factor Erythroid-2-related factor-2

NMDA	N-Methyl D-aspartate
PD	Parkinson's Disease
PPARY	Peroxisome proliferator- activated receptor-Y
PITX3	Pitutary homeobox3
PSEN1	Presenilin-1
ROS	Reactive Oxygen Species
SOD	Superoxide dismutase
SNPs	Single Nucleotide Polymorphism
SNCA	Synuclein alpha
STAT3	Sigle transducer and activator of transcription 3
SP1	Specificity protein1
STX1B	Syntaxin1 B
TFs	Transcription factor
TNF	Tumor Necrosis Factor
TRAF2	TNF receptor associated factor
TFAM	mitochondria transcription factor A
TFEB	Transcription factor EB
UPS	Ubiquitin proteasome system
UPR	Unfolded protein response
UCHL1	Ubiquitin carboxy –terminal hydrolase-L1
VDCC	Voltage Dependent Calcium Channel

Abstract:

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are characterized by progressive loss of neurons and associated cognitive and motor dysfunctions. A growing body of research has revealed that genetic factors play a significant role in the pathogenesis of these conditions. Inherited mutations, genetic polymorphisms, and epigenetic modifications influence disease onset, progression, and susceptibility. Monogenic forms of disorders, such as HD caused by CAG trinucleotide repeats in the *HTT* gene, contrast with polygenic contributions seen in AD and PD, involving genes such as *APOE*, *SNCA*, *LRRK2*, and *MAPT*. Genome-wide association studies (GWAS) have identified multiple risk loci and novel candidate genes linked to neurodegeneration. Additionally, mitochondrial DNA mutations, somatic mosaicism, and gene-environment interactions further complicate the genetic landscape. Understanding the genetic makeup of neurodegenerative disorders is essential for early diagnosis, risk prediction, and the development of targeted therapies, potentially paving the way for personalized medicine approaches in neurodegeneration.

Introduction:

Neurodegeneration:

The term neurodegeneration can be broken down into two terms, neuron that relates to the nerve cells and nervous system and degeneration which is related to the progressive loss of normal functioning and concurrent damage and deterioration. Neurodegeneration is a central aspect of a large number of diseases that are broadly classified as Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) (Przedborski et al., 2003).These disorders can arise due to several conditions like hereditary and genetics, environmental factors and impaired mitochondrial function. Several factors like oxidative stress and protein misfolding have been found to play a vital role in the etiology of common neurological disorders. The aim of this review is to highlight the involvement of different genes pathways associated, various transcription factors, their target proteins involved in the neurodegenerative disorders.

Mechanisms of neurodegeneration:

Acute injury to cells causes them to undergo necrosis, recognised pathologically by cell swelling, vacuolisation and lysis, and associated with Ca2+ overload of the cells and membrane damage. Necrotic cells typically spill their contents into the surrounding tissue, evoking an inflammatory response. Chronic inflammation is a feature of most neurodegenerative disorders, and a possible target for therapeutic intervention. Cells can also die by apoptosis, a mechanism that is essential for many processes throughout life, including development, immune regulation and tissue remodelling. Apoptosis, as well as necrosis, occurs in both acute and chronic neurodegenerative disorders (Rang et al., 2016).

EXCITOTOXICITY: Calcium overload is the essential factor in excitotoxicity. The mechanisms by which this occurs and leads to cell death are discussed here.

Activation of AMPA receptors depolarises the cell, which removes the Mg2+ block of NMDA channels permitting Ca2+ entry. Depolarisation also opens voltage-dependent calcium channels (site 4). Metabotropic receptors cause the release of intracellular Ca2+ from the endoplasmic reticulum. Na+ entry further contributes to Ca2+ entry by stimulating Ca2+/Na+ exchange (site 5). Depolarisation inhibits or reverses glutamate uptake (site 6), thus increasing the extracellular glutamate concentration. The mechanisms that normally operate to counteract the rise in cytosolic free Ca2+ concentration, [Ca2+], include the Ca2+ efflux pump (site 7) and, indirectly, the Na+ pump (site 8). The mitochondria and endoplasmic reticulum act as capacious sinks for Ca2+ and normally keep [Ca2+] under control. Loading of the mitochondrial stores above a certain point, however, interrupts mitochondrial function, decreased ATP synthesis, thus decreasing the energy available for the membrane pumps and for Ca2+ accumulation by the endoplasmic reticulum. Formation of reactive oxygen species is also enhanced. This shows the danger point at which positive feed back emphasize the

process. Raised [Ca2+] affects many processes, the chief ones relevant to neurotoxicity being: increased glutamate release from nerve terminals activate of proteases (calpains) and lipases, causing membrane damage, activates nitric oxide synthase, which damage many important biomolecules, including membrane lipids, proteins and DNA. Excitotoxicity also increases arachidonic acid release, that increases free radical and inflammatory mediator production and also inhibits glutamate uptake (site 6) (Mattson, 2003).

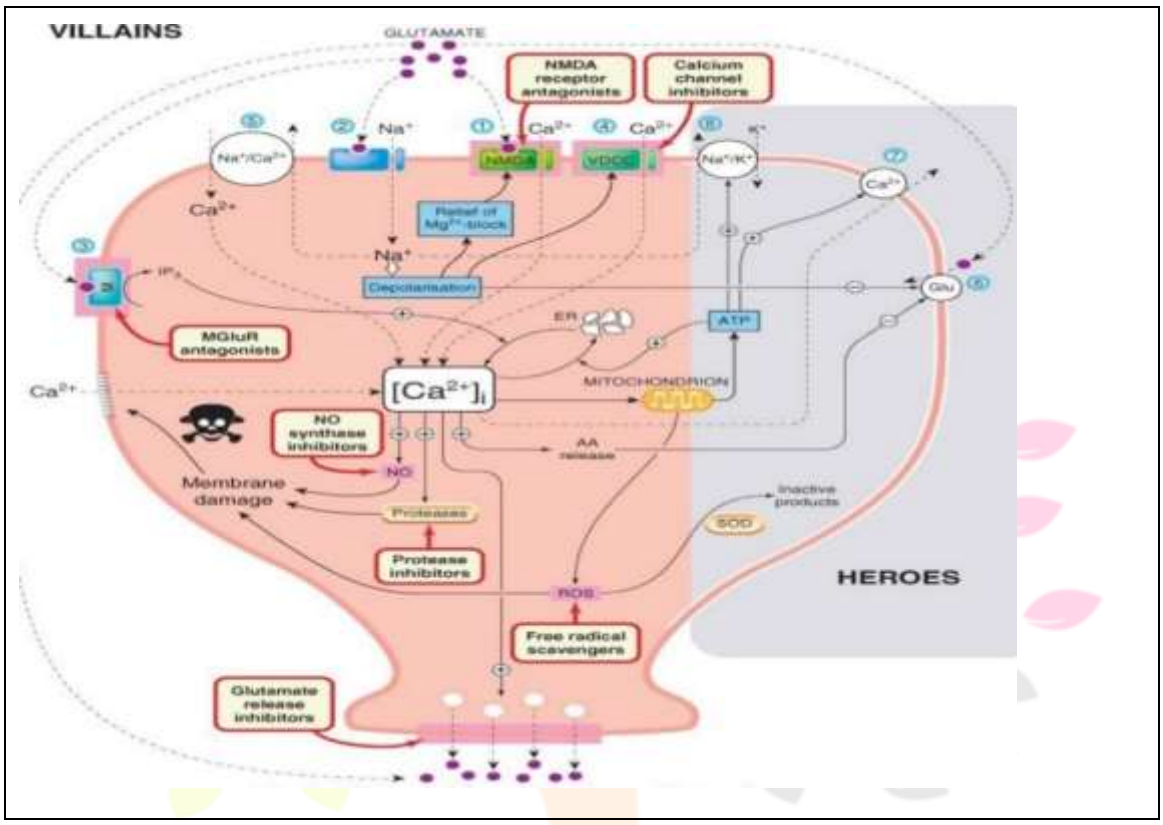

Diagram 1: Mechanisms of excitotoxicity: Membrane receptors, ion channels and transporters, identified by numbers 1–8, are discussed in the text. Possible sites of action of neuroprotective drugs are highlighted. Mechanisms on the left (villains) are those that favour cell death, while those on the right (heroes) are protective. (Rang et al., 2016).

APOPTOSIS: Many different signalling pathways can result in apoptosis, but in all cases the final pathway resulting in cell death is the activation of a family of proteases (caspases), which inactivate various intracellular proteins. Neural apoptosis is normally prevented by neuronal growth factors, including nerve growth factor and brain-derived neurotrophic factor, secreted proteins that are required for the survival of different populations of neurons in the CNS. These growth factors regulate the expression of the two gene products Bax and Bcl-2, Bax being pro-apoptotic and Bcl-2 being anti-apoptotic (Chi et al., 2018).

OXIDATIVE STRESS: The brain needs high energy, which are met almost entirely by mitochondrial oxidative phosphorylation, generating ATP at the same time reducing molecular oxygen to water. Under certain conditions, highly reactive oxygen species (ROS), for example oxygen and hydroxyl free radicals and H2O2, may be generated as side products. Oxidative stress as a result of excessive production of these reactive species. They can also be produces a by-product of other biochemical pathways, including nitric oxide synthesis and arachidonic acid metabolism as well as the P450 mono-oxygenase system. Defence mechanisms are provided, in the form of enzymes are superoxide dismutase (SOD) and catalase, as well as antioxidants such as ascorbic acid, glutathione and α-tocopherol (vitamin E), which normally keep these reactive species

in check. Some cytokines, especially tumour necrosis factor (TNF)-α, which is produced in brain ischaemia or inflammation condition, exert a protective effect, partly by increasing the expression of SOD. Mutations of the gene encoding SOD are associated with amyotrophic lateral sclerosis (ALS, also known as motor neuron disease), a fatal paralytic disease resulting from progressive degeneration of motor neurons. Accumulation of aggregates of misfolded mutated SOD may also contribute to neurodegeneration. Mitochondria play an essential role in energy metabolism, failure of which leads to oxidative stress. Mitochondrial integrity is vital for neuronal survival, and mitochondrial dysfunction is seen as a major factor in many neurodegenerative disorders. It is possible that accumulated or inherited mutations in enzymes such as those of the mitochondrial respiratory chain lead to a congenital or age-related increases susceptibility to oxidative stress, which is manifest in different kinds of inherited neurodegenerative disorders (such as Huntington's disease), and in age-related neurodegeneration. Oxidative stress is both a cause and consequence of inflammation, which is a general feature of neurodegenerative disease and is thought to contribute to neuronal damage (Rang et al.,2016).

Pathways of Neurodegeneration:

Common neuronal pathways: Many neurodegenerative disorders are characterized by the accumulation of protein misfolding or peptide fragmentation in the brain and spinal cord. Indeed, disease genes underlying strictly inherited forms of AD, PD, and ALS which give rise to disease-specific protein inclusions. The existence of identical inclusion bodies in patients with inherited and sporadic neurodegenerative diseases suggests overlapping disease mechanisms, the following neuronal pathways altered in various neurodegenerative disorders: protein folding and quality control, autophagy and lysosomal dysfunction, mitochondrial damage and homeostasis, protein seeding and propagation, stress granules, and synaptic toxicity (Diagram 2).

Inset I: molecular chaperones, including heat shock protein, regulate protein folding and ubiquitin–proteasome system (UPS)-mediated degradation, at the same time disaggregase could return misfolded proteins to their natively folded and functional state.

Inset II: dysfunction in the autophagy–lysosomal pathway could regulate the accumulation of pathogenic protein aggregates and damaged mitochondria.

Inset III: impairment of mitochondrial quality control because of mitophagy and mitochondrial dynamics results in reduced energy production and dysfunctional proteostasis network.

Inset IV: transcellular propagation and seeding of protein aggregates could control the disease progression.

Inset V: abnormal stress granule dynamics the one which favor aggregation and aberrant incorporation of misfolded proteins contributes to toxicity.

Inset VI: soluble forms of protein assemblies induce both pre-synaptic and postsynaptic defects, leading to network dysfunction. HSP; heat shock protein (Gan et al., 2018).

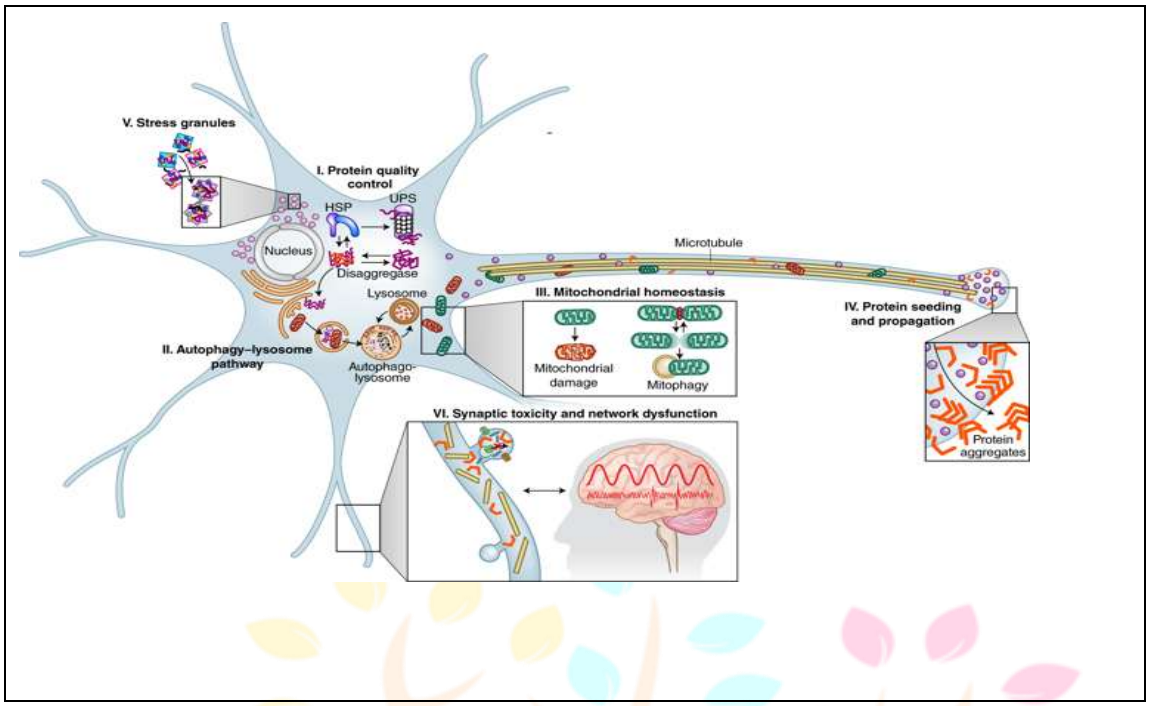

Diagram 2: Common neuronal pathways altered in multiple neurodegenerative diseases, including protein quality control, the autophagy–lysosome pathway, mitochondria homeostasis, protein seeding and propagation of stress granules, and synaptic toxicity and network dysfunction (Gan et al., 2018).

Innate Immune Pathway: The innate immune response protects the host by promptly detecting and removing pathogens through inflammatory processes. Innate

immune responses become maladaptive in the form of chronic inflammation, characterized by gliosis and elevated levels of pro -inflammatory cytokines in neurodegenerative diseases (Diagram3). Maladaptive innate immune responses were high considered to be caused by neurodegeneration. Amaladaptive innate immune response has emerged as a critical driving force in the pathogenesis of many neurodegenerative disorders. Single Nucleotide Polymorphism many disease-associate genes produce maladaptive innate immune responses that are also associated with aging and epigenetic changes. Microglia, the resident immune cells in the brain, involve in crosstalk with astroglia and are modulated by peripheral immune system. Neuronal circuits are damage by maladaptive microglia due to dysfunctioning their detection or response to homeostasis imbalance, resulting in accumulation of protein aggregates, in concert with astroglia and possibly the peripheral immune system. Microglia could also cause neuronal and network dysfunction by altering cytokine signaling and synaptic pruning, independently effects on protein aggregates (Gan et al., 2018).

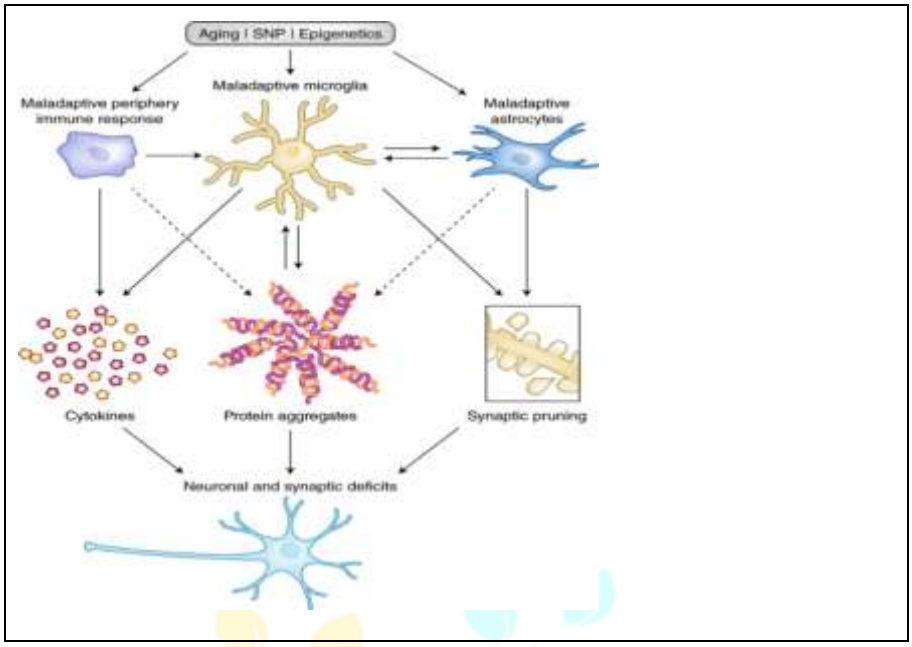

Diagram 3: Innate immune pathways in neurodegenerative diseases (Gan et al., 2018).

Transcription factors and their target protein:

Transcription factors (TFs) are protein molecules binding to the promoter region of genes, regulating the transcription from DNA to messenger RNA (mRNA). Transcription factors were characterized by at least one DNA-binding domain (DBD) and can be coordinated and work in groups, promoting or blocking the RNA polymerase. Transcription factors are potential targets of medicines, mutations in transcription factors are the cause of specific diseases which can be approached through the pharmaceutical design in targeting to them.

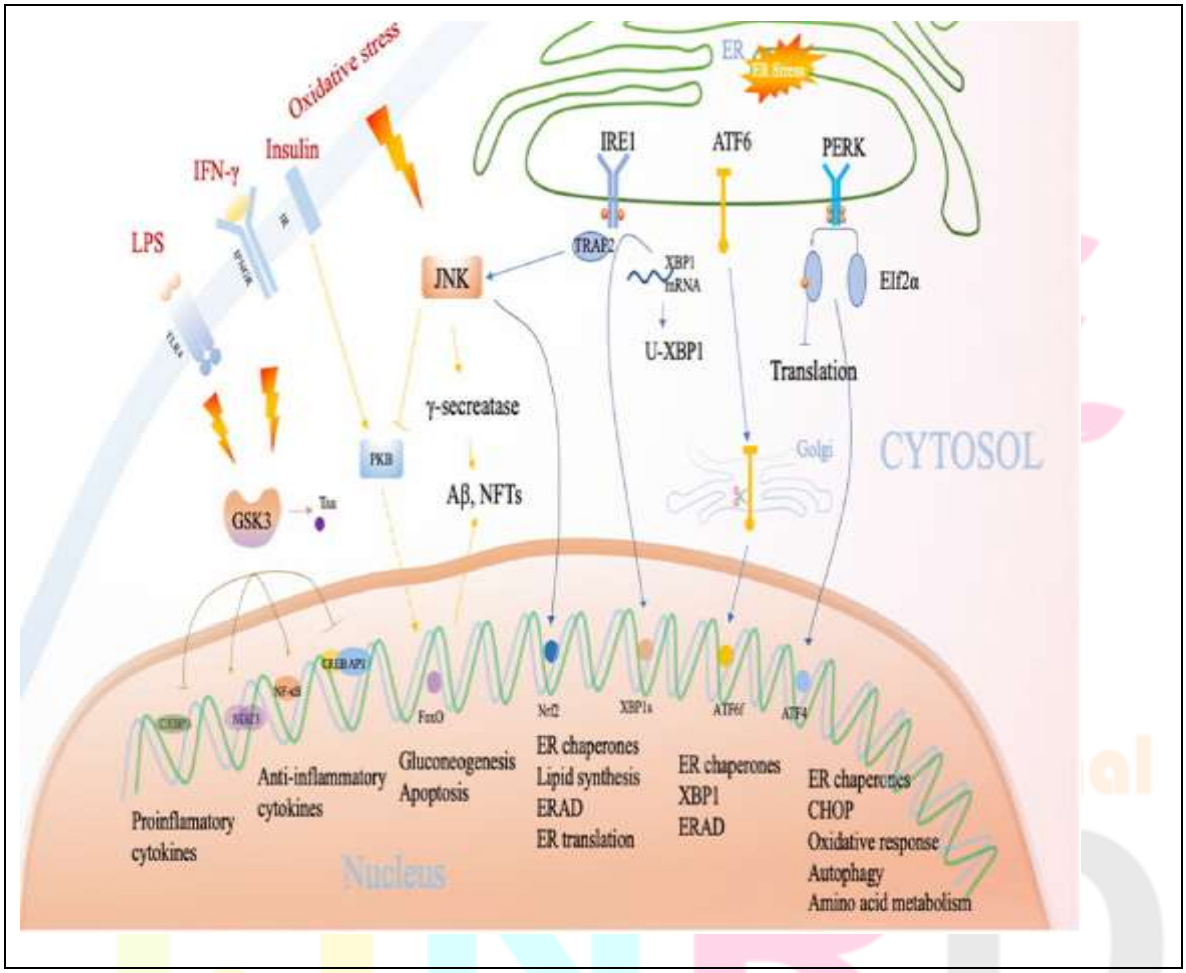

Diagram 4: An overview of transcription factors related to neuroinflammation, oxidative stress, and Proteinhomeostasis (Jin et al., 2019).

Transcription Factors in Alzheimer's Disease: Neurons in AD involves mitochondrial dysfunction and energy deficits that worsen the pathological processes of Aβ and Tau. Numerous studies show that autophagy and lysosomal pathways are also restricted in AD and results in the accumulation of dysfunctional mitochondria.

PPARγ: Peroxisome proliferator-activated receptor γ (PPARγ), is a transcription factor encoded by human *PPARG* gene. The aggregation of Aβ can lead to a series of dysfunctions, including NFTs, axonal injury inflammation and synapse loss. It is noted that PPARγ regulates adipogenesis, inflammation, lipid metabolism, and the maintenance of metabolic homeostasis. PPARγ binds to β-site Amyloid precursor protein Cleaving Enzyme 1(BACE1) gene's promoter region through its response element, suppressing BACE1 expression, therefore inhibiting Aβ production (Cao et al., 2016).

REST: REST gene encodes RE1-Silencing transcription factor (REST, or NRSF)in human as a transcription repressor to repress the expression of neuronal genes in non-neuronal cells. REST contains 8 C2H2 zinc fingers which is belonging to the Kruppel-type zinc finger transcription factor family. It is consideration to be the master negative regulator during neurogenesis. REST is down-regulated in AD patients. In the brain, regions that are sensitive to AD contain high levels of REST, suggesting a protective effect against dementia. REST has neuroprotective functions by repressing genes which promote cell death, inducing expressions of stress response genes, keeping oxidative stress and Aβ protein toxicity (Lu et al., 2014).

Sp1: Sp1 transcription factor which is also known as specificity protein1, encoded by *SP1* gene in human. Sp1 includes 785 amino acids and is a member of Sp/KLF family. Sp1binds to GC-rich motifs because of C2H2 zinc finger motif. Sp1 is relevant to multiple functions in cells which involves cell differentiation, growth, apoptosis, immune responses, DNA damage, and chromatin remodeling. Sp1is also in amount of posttranslational modifications, including phosphorylation. Sp1, together with c-Jun/AP-1, Nrf2, NF-κB, p53, is apro-inflammatory transcription factor which regulates the expression of leading genes in AD such as APP and BACE1, especially that in APP and APP induction by TGF-β, tau transcription, presenilin-2 upstream promoter transcription, and the regulation of BACE1. Moreover, genes that encourage neuronal survival can also be activated by Sp1. Sp1 expression level is increased in the brain of AD patients as well as the cortex and hippocampus of transgenic AD mice model (Christensen et al., 2004).

FOXO1: FOXO1 is a transcription factor also known as fork head in rhabdomyo sarcoma, which is encoded by the FOXO1 gene in human. It has been noted that FOXO1 has a strong link with oxidative stress response and pathophysiology of AD. FOXO1 is activated in response to the decreased level of AKT during the treatment of Aβ, AKT activity is inhibited by the increased levels of Trib3 due to the treatment. FOXO1 binds to the promoter of Trib3, which induces autophagy (Farmer, 2003).

HIF-1α: Hypoxia-inducible factor 1-alpha (HIF-1α), encoded by HIF1Agene, in addition to HIF-1β, is a subunit of the transcription factor HIF-1 that responds to cellular oxygen reduction. HIF-1α is degraded under normal physiological conditions due to its oxygen-dependent degradation domain, while below hypoxia, it is stable, and its levels are greatly increased (Maxwell and Salnikow, 2004).

Transcription Factors in Parkinson's Disease: Transcription factors promoting neuro inflammations in PD (NF-κB, STAT3, AP1) and Toll-like receptors are up-regulated, whereas neuro-protective pathways like mTOR, TGF-β, and YY1 are down-regulated. Symptoms of PD progress slowly. These include shaking, rigidity, slowness of movement, difficulties in talking and thinking, behavioral

problems, and even dementia, as the disease progresses. More than one third of the patients suffer from depression and anxiety. various transcription factors are discussed here (Jin et al., 2019).

GATA Transcription Factors: GATA transcription factors are a family of transcription factors, commonly bind to the DNA sequence "GATA". In both familial and sporadic cases, dosage of α-synuclein appears to play a major role in PD pathogenesis. It is recorded that GATA-1induces α-synuclein gene (SNCA) along with three other genes (ALAS2, FECH, and BLVRB) that SNCA naturally a bounds, and GATA-2 is highly expressed endogenously in substantia nigra in PD. The relationship between GATA transcription factors and SNCA transcription represent new ideas on PD pathology and therapeutic strategies to keep α-synuclein at a normal dosage (Scherzer et al., 2008).

PITX3: Pituitary homeo box 3 is encoded by PITX3 gene in human implicated in the formation of lens during eye development. During the development of neurons in mid brain, it is an important transcription factor for the dopaminergic neurons. In substantia nigra and midbrain's ventral tegmental area, PITX3 is highly expressed, and dopaminergic neurons are misplaced when its gene is disrupted. PITX3 can control critical neuro protectors, including glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), thus affecting dopaminergic neuronal growth and survival. In PD patients, PITX3 is inadequate in midbrain area, which results in a decreased microRNA expression. It is reported that polymorphism of PITX3 gene is related with sporadic and early-onset PD (Bergman et al., 2010).

TFAM: Mitochondrial transcription factor A (TFAM) is encoded by TFAM gene in humans. It is a key activator of mitochondrial transcription and mitochondrial genome replication. It has been found that TFAM interacts with some prominent proteins in PD, including PINK1 and parkin, which suggests that they are in the same physiological pathway (Jin et al., 2019).

MEF2D: Myocyte-specific enhancer factor 2D is encoded by MEF2D gene in humans. It has been noted that the selective degradation of MEF2D presents a basic mechanism to ensure an adequate neuronal response to injury. It has been recorded that MEF2D is found in decreased levels, in PD models, in response to the accumulation and aggregation of Asyn, thus implicated in PD pathogenesis. Moreover, after treating PD brains and animal models with PD-related toxins, MEF2D levels in mitochondria are decreased. MEF2D is directly oxidized by 6-hydroxydopamine (6-OHDA), PD brains have been found to have raised oxidized MEF2D levels. Furthermore, MEF2D in oxidized form increased the affinity of its binding ability to hsc70, and the up-regulation of lamp2A, resulted from the initiation of oxidative stress, will in turn increases MEF2D degradation. The expression of MEF2D is decreased by PD-related toxins, thus, suggesting the use of activators of MEF2D is a potential pharmacological strategy to lower the PD pathology in animal models. It has been recorded that MEF2D induction is beneficial in in-vitro model (Gao et al., 2014).

Transcription Factors in Huntington's Disease: HD is caused by an autosomal dominant mutation with multiple extension of CAG in either of the alleles of 5′- end exon1 in HD gene, which means a child has a 50% possibility of inheriting HD from his affected parent. The protein encoded by Huntington gene is known as Huntington (Htt protein). The alteration in Huntington gene results in the misfolding and aggregation of Htt protein, and mislocation of mutant Htt protein (mHtt) alters its original interactions with various transcription factors such as CBP and SP1 leading to a interruption of transcription process (Jin et al., 2019).

HSF1: HSF1 gene in human encodes Heat shock transcription factor 1, it is highly conserved in eukaryotes as a primary mediator results in proteotoxic stress that helps to prevent the misfolding, aggregation, and apoptosis of proteins. It helps gene expression which is associated to protein quality control, stress adaptation and cell survival. HSF1 is not active in normal conditions that exists in the form of a monomer suppressed by Hsp40 and so on. HSF1 is active as a multimer that binds to heat shock elements in target gene promoters under the condition that the body is going through raised temperature, oxidant invasion, and other incidents that can cause protein misfolding. Hormetic heat stress or overexpression of HSF-1 can cause autophagy, which is beneficial under stress, and decreases the accumulation of Poly Q expansion in Htt protein. Poly Q leads to Htt misfolding and cell death, causing HD (Akerfelt et al., 2010).

ATF5: ATF5 gene in human encodes Activating transcription factor 5 (ATF5), it is a stress-response transcription factor induced by different cell stressors and also part of the unfolded protein response (UPR), which is in line with transcription factors ATF4 and ATF6 in coping with ER stress. ATF5 induces transcription of anti-apoptotic target genes such as MCL1 during UPR. It has been noted that ATF5 levels are decreased in HD mouse model and human brain tissue. ATF5 is neuro protective due to its role in attenuating ER stress–induced apoptosis in neurons and ATF5 developing interventions might have therapeutic values for HD (Hernandez et al., 2017).

ATF6: Activating transcription factor 6, encoded by ATF6 gene in human, is a protein involved in UPR. UPR is a process started in ER that is by a series of ER stress. In HD patients, ATF6 processing is decreased. It is reported that derepression of ATF6 enhanced UPR functions in striatal neurons (Naranjo et al., 2016).

TFEB: TFEB is a protein encoded by TFEB gene in human. TFEB is a regulator of lysosomal hydrolases, membrane proteins and genes implicated in autophagy. In HD mouse brain and cultured cells, TFEB is significantly decreased. Overexpression of TFEB in cultured cells causes the biogenesis of lysosome and in turn increases the degeneration of proteins that causes HD (Jin et al., 2019).

Relationship of selected genes with different Neurodegenerative Disorders:

Alzheimer's Disease: The first causative gene identified for early onset AD was the amyloid precursor protein (APP) gene. The APP gene was identified because of linkage analysis in families segregating an autosomal dominant form of early onset AD. The APP gene, located at chromosome 21q21.22, encodes a transmembrane protein which is normally processed into amyloid fragments. In neurons, secretase cleave the

APP protein into smaller amyloid (Aβ) peptides. Secretase split APPinto A_40 and A_42 fragments. A_42 has proven to be the strongest factor in the pathogenesis of the disease. So far, 18 different mutations have been stated in the APP gene in 50 families. All 18 mutations cause amino acid changes in putative sites for the splitting of the APP protein. APP mutations are deeply penetrant (Garcia and Bustos, 2018). The number of carriers of the several mutations may differ across clinical populations. In the general population, not more than 0.5% of early onset AD patients carry an alteration in the APP gene. Mutations in two other genes have been found to lead to early onset autosomal prominent forms of AD. The presenilin-1 (PSEN1; 14q24.3) and presenilin-2 (PSEN2; 1q31.q42.3) genes were localized using linkage evaluation. These genes encode proteins that are implicated in the normal splitting of the APP protein, increasing the production of A_42. Actually, there is convincing evidence that PSEN1 encodes a _ secretase. A total of 142 mutations have been found in PSEN1in 281 families this makes it the gene with the highest number of pathogenic alteration in AD. For PSEN2, 10 mutations have been found in 16 families. In the general population, mutations in the presenilin genes justify about 7.5% of early onset AD (6.5% for PSEN1and 1% for PSEN2). The fourth gene related to AD is APOE (19q13.32), which was firstly identified using linkage analysis. The gene has three various alleles, APOE*2, APOE*3 and APOE*4. The APOE*4 allele is the variant related with AD and unlike the mutations found in APP, PSEN1and PSEN2, it is not a causal mutation for AD that also leads to disease in carriers. All of the genes identified for AD, appear to be implicated in the A_42 pathway (Pardo and Van-Dujin, 2005). Most of our insights into the pathogenesis of AD come from the relatively rare prominent mutations in the APP and presenilin genes, which essentially clarify this pathway. The role of the A_42 protein is limitless to carriers of the APP and presenilin genes. A_42 metabolism was found to be troubled in sporadic patients without dominant mutations or the APOE*4 allele. The identification of rare alteration, therefore, has not only led to new insights into the pathogenesis of familial forms of AD but also shed light on the pathways of sporadic forms of the disease. The genetics of AD is far from being resolve (Tanzi, 2012).

Parkinson's Disease: The first gene identified was SNCA (PARK-1; 4q21.q23), which encodes the -synuclein protein, one of the major component of Lewy body inclusions. Three missense mutations in SNCA have been identified in families segregating prominent forms of PD, including one recently reported in a Spanish family. Moreover, duplications and triplications of this gene leading to PD have been found (Garcia and Bustos, 2018). These alteration are rare in patients with sporadic and familial PD. Three other genes have been related with dominant forms of PD. NR4A2 (NURR1), which encodes a nuclear transcription-like protein, is involved in the production of dopaminergic neurons. The UCHL1 gene, which encodes an ubiquitin carboxy-terminal hydrolase L1, that is expressed in neurons and has been found in Lewy bodies. Although these genes are involved in physiological pathways of neuronal function, their actual role as causal genes for PD has not been confirmed (Pardo and Van-Duijin, 2005). The LRRK2 (PARK8; 12q12) gene has been related with familial and sporadic late onset PD. The gene encodes dardarin, a 2482 amino acid protein with various domains, including a tyrosine-kinase domain. Eight different mutations have been found in this gene. These mutations might explain up to 5–6% of familial PD and 1% of sporadic PD. The function of this gene in the

pathogenesis of PD remains to be investigated. The gene, placed at chromosome 6q25–q27, encodes an ubiquitineE-2 protein. More than 70 mutations have been identified in the parkin gene, containing point mutations and genomic rearrangements (Tanzi, 2012).

Epigenetic Biomarkers:

Epigenetic Biomarkers in Alzheimer's Disease: In Alzheimer's disease patients protein aggregates found in brain cells. Epigenetic modification play a major role in pathogenesis of AD. Three genes modified in AD include Presenilin-1, PSEN-1, PSEN2 and amyloid beta A4 protein (APP). Increased level of phosphorylated histone H3 has been recognized in hippocampal neuron in AD (Naseer, 2019). In AD temporal lobe histone acetylation found to be inadequate as compared to normal person. The miR-16 target the amyloid precursor protein and its expression is abnormally reduced in AD patients, which leads to accumulation of protein. In AD NEP (neprily-sin) enzyme which is efficient for amyloid-beta degradation suppressed. Amyloid beta may also suppress global hypo methylation (Portela and Esteller, 2010).

Epigenetic Biomarker in Parkinson's Disease: Alzheimer disease and Parkinson disease are heterogeneous disease as they are combination of genetic and environmental factors. In early 1800 James Parkinson named the PD known as "shaking palsy". Symptoms include, postural instability, muscle rigidity, tremor and bradykinesia. In PD loss of neurons in substantia nigra due to protein aggregation known as Lewy bodies. Methylation of synuclein-α gene leads to plaques accumulation in PD (Naseer, 2019). In PD alpha-synuclein reduces the level of acetylated histone H3 and inhibits histone acetyl transferase enzyme activity by binding to histone proteins. Methylation of SNCA intron 1 leads to decreased in SNCA transcription, which has been recognized in PD. Genes such as ARK16, GPNMB and STX1B are also show methylation in PD. Hyermethylation of GRN gene has been recognized in front temporal region of brain due to aberrant DNA methylation. Reduced expression of miR-133b, miR-10a has also been observed in PD (Portela and Esteller, 2010).

Gene Therapy: Several approaches to *in vivo* gene therapy for neurodegenerative diseases are currently being performed both in animal models and in early human clinical trials. Gene transfer and novel access to *in vivo* gene therapy for neurodegenerative disorders were focused on PD, HD, and AD. Genes can be delivered to the central nervous system (CNS) by means of viral and non-viral vectors. Many viral vectors have been form for this purpose, each with advantages and disadvantages. In general, viral vectors are delivered directly into the CNS through a craniotomy and are locally infused into specific neuroanatomical locations. Non-viral vectors such as liposomes may provide a means for delivering genes without the requirement for a craniotomy. The choice of vector and its mechanism of delivery will be determined by the specific disease and its Neurophysiology and the mechanism underlying the gene therapy. *In vivo* gene transfer therapy holds great potential for the treatment of neurodegenerative disorders. Recent accomplishment in human safety-tolerability trials will likely lead to an increasing number of human efficacy trials. Given the great number of potential neuroanatomical, neurophysiological, and genetic targets for interventions in

neurodegenerative disorders, the possibilities for gene therapy are extensive. These possibilities will likely be increased further as the techniques for viral and non-viral gene transfer to the CNS are improved. Many challenges occur for performing large scale strength trials including potentially risky genetic and neurosurgical interventions, including blinding and ethical considerations (Sheikh et al., 2013).

Viral and non-viral based gene therapy:

Viral Vectors: AAV based vectors have been applied almost solely in clinical trials of gene therapy for neurodegenerative diseases. AAV serotypes are the major determinant of various crucial characteristics of successful AAV-based gene therapy, including bio-distribution, tissue tropism, and susceptibility to neutralizing antibody generated *in vivo*. Inventing how the specific serotypes classify gene cargos to their intended tissues for vector delivery is vital for developing a reliable and predictable gene therapy strategy. More than one hundred AAV variants consisting of 13 serotypes (AAV1–13) have been found from humans and nonhuman primates. Because of its relative safety profile and its sustained expression in neurons, AAV2 has been used in numerous clinical trials and is now considered a satisfactory vector for gene therapy of neurodegenerative disorders. Specifically, researchers recommended that intra-cerebral administration of AAV2-NGF is well tolerated and shows evidences of therapeutic effect on cognitive decline in AD-related dementia. Interestingly, after administration near or into cerebral ventricles, AAV4 has a predilection to transfect ependymal cells, which represent the epithelial lining of neuro-blasts and the lateral ventricles. Because the BBB is an important barrier hindering delivery of most vectors to the CNS, the ability of AAV9 and AAVrh.10 to invade this obstacle is also consequential. Indeed cell-type specific screening of several AAV capsid libraries has identified increasing numbers of bioengineered AAV capsids with precise tropisms. Adenovirus (Adv) is an icosahedral capsid virus with size ranging from 70 to 100 nanometers. Adv cannot enter its gene into the host genome, which leads to relative transient transgene expression but an excellent safety profile. The innate immune responses against Adv inhibits Adv's therapeutic potential efficacy for CNS gene therapy (Chen et al., 2020).

Non-viral Vectors: Although nearly all clinical trials have used viral vectors such as AAVs, lentivirus, Adv, and retroviruses to carry therapeutic genes, these vectors have numerous drawbacks, including broad tropism, difficulty in vector production, limited loading capacity and host inflammatory responses. Gene therapies based on non-viral vectors have the potential to inhibit several of these drawbacks, especially those related to safety. Furthermore, although few of these strategies have been used in the clinic, it is extremely important to exploit novel kinds of vectors, particularly nanoparticles and liposomes. Based on the composition of the carriers' material, non-viral delivery vectors can be sorted into polymeric vectors and lipid-based vectors. The most widely applied non-viral gene carriers are lipid-based vectors. Neutral lipids like cholesterol, DOPE and DSPE, have served as the 'helper lipid' among liposomal components to enhance liposome stability and transfection capacity. The important features of cationic lipids, such as DOTAP, DODAP, DOTMA, and DC-cholesterol, which have been used for gene therapy, involve three major domains: hydrophobic tails, linking groups, and cationic cap groups (Yin et al., 2014). The main fault of cationic lipids are their unsatisfactory

pharmacokinetic bio-distribution due to nonspecific binding and rapid clearance, and their cytotoxicity. To overcome these drawbacks, optimized cationic lipids with suitable pKa values have been developed. Lipidoids (lipid-like materials), magnetic nanoparticles, and exosomes have also shown potential as gene delivery carriers for neurodegenerative disorders. Cationic polymers provide another kind of non-viral vector that is highly attractive for gene therapy due to their capacity for endosomal/lysosome escape, which is the result of their sponge-proton effect, fine spherical architecture, and tremendous chemical diversity. Additional insights into the relationship between structure and function of gene delivery material and fuller understanding of the critical factors that inhibit effective gene delivery are likely to progress the clinical treatment of neurodegenerative disorders (Chen et al., 2020).

Conclusion:

This project summarrized the involvement of genes in Neurodegeneration. There are several risk factors contributed to AD and PD including aging, genetic and environmental factor. Our understanding of the mechanisms involved remains rudimentary at best. Multiple pathways have been recognized to cause Neurodegenerative disorders. Large number of Transcription factors and their targeted protein are involve in pathogenesis of Neurodegenerative Disorders such as UPR pathways, Autophagy-lysosome pathways. Epegenetic Biomarkers in neurodegenerative disorders effect on numerous genes and different biological pathways, appear to be involved in diseases. Various therapeutic strategy to prevent neurodegenerative disorders such as gene therapy. A detailed understanding of genetics of neurodegeneration will be essential for design and development of effective early prediction and early prevention or treatment strategies, with the prospect of largely decreasing the incidence of these devastating disorders.

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