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An Analysis of Genetic Predisposition to Dementia: Genetic Variants, Prevention, and Gene Therapies

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ABSTRACT

This review aimed to understand how genetic factors play a role in a predisposition to dementia, which is a range of diseases that cause cognitive decline. Dementia rates are increasing globally due to a prolonged lifespan and it is becoming a more critical subject in the medical world. Through a secondary literature review, the focus of this article is to understand the various aspects of genetic risk in dementia. Other prominent causes for dementia such as cardiovascular disease, depression, and lifestyle choices are also outlined in the review. Genes such as chromosome 9 open reading frame 72 (C9orf72), APP, PSEN1, PSEN2, TREM2, and the apolipoprotein E (APOE) ε4 allele are associated with an increased risk of dementia. The genetic factors for Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, and Parkinson's disease are analyzed as well. Genetic testing and counseling can identify the source of a person's genetic predisposition. Studies are being conducted to elucidate the exact mechanisms of gene variants and to test new gene therapies, which are important for treating dementia. Lifestyle modifications and other actions may also be imperative in dementia prevention.

Introduction

Dementia comprises an array of diseases that can cause a decline in cognitive functioning and severely affect day-to-day activities. As life expectancy is increasing, so are rates of dementia. Various forms of dementia include Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal dementia (FTD). The accumulation of protein-tau, cerebrovascular dysfunction, and altered expression or mutations in certain genes can cause dementia. The difference between neurodegenerative disorders such as PD and dementia is that dementia refers to cognitive dysfunction rather than motor issues in PD.

In terms of geography, dementia prevalence has declined in high-income countries but increased in East Asia, consistent with worsening cardiovascular health in the region. Age arguably plays the greatest role in the onset of dementia and as the global population ages, cases of dementia are bound to increase. Dementia mortality has been steadily declining by as much as 30% in the past 14 years (Prince et al., 2016).

Many risk factors have been linked to dementia, including genetic factors. Some modifiable risk factors include smoking, lack of physical activity, high blood pressure, high cholesterol levels, and diabetes (Peters et al., 2019). Genetic factors for AD have been established as APP, PSEN1, and PSEN2. On the other hand, MAPT, GRN, and C9orf72 gene expression have been associated with an increased risk of FTD. For Huntington's disease (HD), the HTT gene is a risk factor and for Lewy body dementia (LBD), mutations in the GBA gene have been linked to the disease (Loy et al., 2014).

The impact of dementia goes deeper than just the cognitive effect; dementia undermines a person's ability to maintain relationships. Understanding genetic risk can help develop targeted interventions for those with a higher likelihood of dementia. These interventions could help those at higher risk significantly by reducing their chances of dementia. But also, a more holistic understanding of the genetic aspect of dementia risk

could help develop a vaccination or more effective treatment for the disease. Exploring the interplay between genetics and psychosocial factors, lifestyle choices, and health issues can provide a more comprehensive grasp of dementia etiology and allow for more effective prevention/intervention methods.

The primary objective of the review is to focus on the genetic risk factors associated with dementia. Genetic factors of AD, PD, FTD, and LBD will all be examined closely as they are some of the most prevalent forms of dementia with genetic associations. The review also discusses genetic testing and other modifiable risk factors of dementia.

Methodology

The primary objective of this research paper is to understand the role of genetic predisposition in dementia risk by analyzing genes, alleles, and genetic variants associated with various forms of dementia. The research conducted in this study was a secondary literature review based on several primary studies and informational research articles. The study utilized a qualitative method of study and many primary studies to understand the genetic susceptibility in dementia, including Alzheimer's disease, frontotemporal dementia, Parkinson's disease, dementia with Lewy bodies, and Huntington's disease. No physical tools or materials were implemented in the research, other than online resources. Research biases were accounted for by analyzing a variety of sources and research articles globally and by using articles from different journals to establish diverse perspectives.

Prominent Causes of Dementia

Several factors can play a role in a person's risk of having dementia. While genetics is a key aspect of understanding dementia and creating more targeted interventions, it is still crucial to comprehend the other elements of dementia susceptibility such as cardiovascular health, depression, other health conditions, and lifestyle choices.

An examination of 203,038 UK4 Biobank participants found a strong link between cardiometabolic multimorbidity, which refers to issues with both the heart and body processing of food and dementia occurrences. The study's participants with cardiometabolic multimorbidity tended to have lower amounts of gray matter and hippocampal volumes. The study also found that those with diabetes, myocardial infarction, and stroke had a significantly higher risk of dementia, almost five times greater. The association emphasized the need for initiatives to prevent cardiometabolic diseases (Tai et al., 2022). Another study with 1,211 patients had similar conclusions that cardiovascular health impacted dementia risk. Maintaining good cardiovascular health (CVH) could decrease dementia susceptibility by as much as 59% compared to those with worse cardiovascular health. Ideal CVH allows the brain to function optimally by preventing the risk of ischemia and lack of oxygen. Furthermore, proper CVH reduces the risk of hemorrhages forming in the brain and obstructing normal brain function. (Peloso et al., 2020).

Depression has also been found to affect vulnerability to dementia. Both depressive symptoms and recent depressive disorders can increase the risk of dementia. Depression can cause damage to the hippocampus, which is the center of memory and would therefore impact memory, a major part of dementia. However, for the study being discussed, late-life depression was the center of focus so, the subjects would not have had enough long-term damage to the hippocampus for that to be the cause of the increased dementia risk (Wang et al., 2021).

Total Lifestyle Index (TLI) that includes diet, sleep, and physical activity was found to be lower for those with dementia compared to those without cognitive decline. The TLI was computed by using linear regression models based on each factor and baseline cognitive performance. For each unit increase in TLI, the

study noted that the risk of dementia could go down by 0.2% each year, suggesting that a healthy lifestyle could reduce the risk of dementia. The same study also concluded that a healthier lifestyle is associated with improved cognitive function. Even before the onset of dementia, better lifestyle choices can improve cognitive function (Mamalaki et al., 2022).

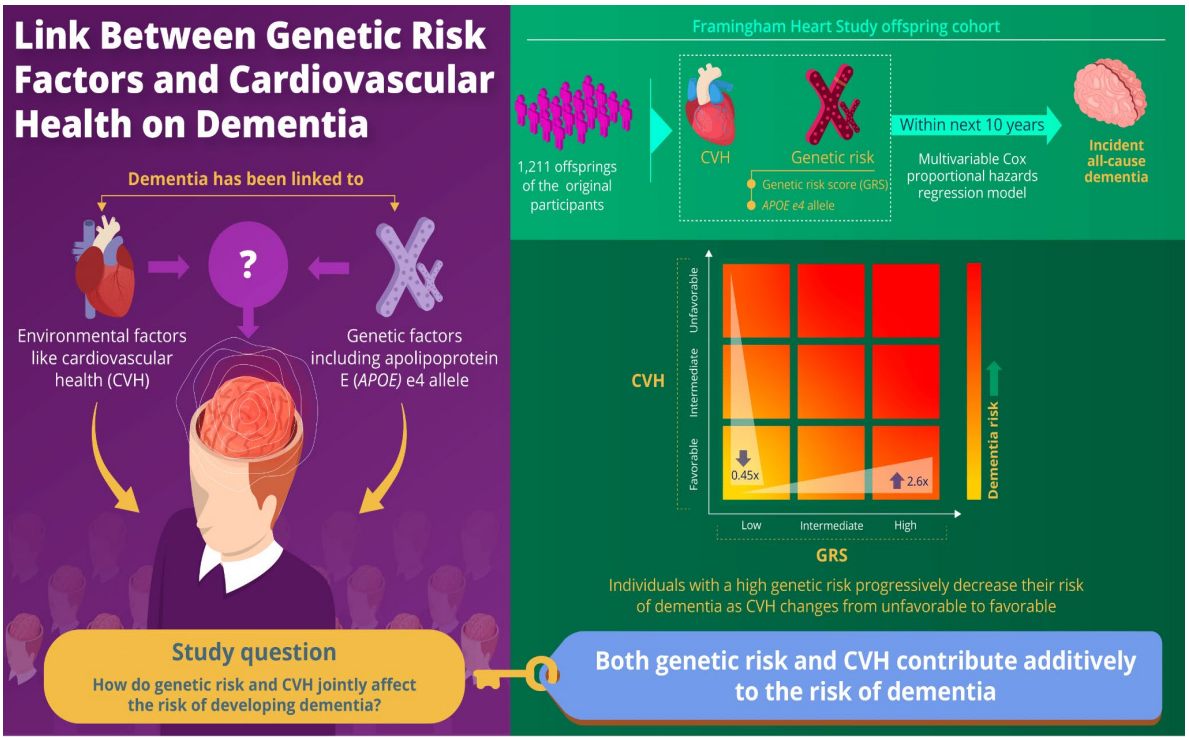

Figure 1. Impact of Cardiovascular Health on Dementia. Source: Peloso et al., 2020

Description: Genetic factors combined with cardiovascular health can increase the risk of dementia. Improved cardiovascular health can significantly reduce the risk of dementia, even if there is a high genetic predisposition. Environmental factors and genetic factors both impact risk of developing dementia and precautions can be taken to reduce the risk.

Mechanisms of Dementia

AD is characterized by the formation of plaques composed of Aβ peptides and interneuronal accumulation of neurofibrillary tangles (NFTs). These NFTs are composed of protein-taus (p-tau) which are responsible for microtubule binding. P-tau is considered a pathological marker for AD and is positively correlated with neurodegeneration and Aβ pathology. AD has also been recently associated with the alteration of blood vessels and decreased vascular density. Aβ has been considered a risk factor for cerebrovascular injury since it can be deposited in blood vessel walls (Raz et al., 2015).

The neuropathology of FTD is indicated by the atrophy of both the frontal and temporal lobes. FTD can be divided into three major categories: FTD-tauopathies, FTD-ubiquitin, and FTD-without-tau. In FTD-tauopathies, there are cellular p-tau inclusions while in FTD-without-tau, there is ubiquitin-positive inclusion. In FTD-ubiquitin, there are ubiquitin-positive tau-negative neuronal inclusions. While there is evidence indicating that vascular dysfunction may play a role in FTD, conclusions are difficult to make on the topic because of the diverse etiologies associated with FTD (Raz et al., 2015).

α-synuclein is a protein encoded by the SNCA gene, found on chromosome 4q21. The protein is thought to play a role in neurotransmitter release, synaptic function, and synaptic plasticity. In a normal condition, α-synuclein remains in the cytoplasm in a state of dynamic equilibrium between soluble monomers and oligomers. However, in LBD, lipid membranes may promote the aggregation of α-synuclein, which disrupts the membrane significantly. Mutations in the SNCA gene and unsaturated fatty acids can lead to disruptions in the membrane (Koga et al., 2021).

Genetic Basis for Major Forms of Dementia

Alzheimer's Disease (AD)

Globally, around 55 million people have AD and as improvements in socioeconomic conditions increase life expectancy, cases of AD are expected to rise even more. Almost 11% of the population in the U.S. have AD and about 60-80% of the risk for AD is due to genetic factors. Family-based transmission includes mutations in three genes: PSEN1, PSEN2, and AβPP. Another genetic factor for AD is the APOE gene; the ε4 allele is considered a risk factor for AD while the ε2 allele is a protective factor against AD (Reitz et al., 2023).

The Aβ precursor protein (AβPP) has been considered a potential risk factor for vascular dementia, a form of dementia triggered by damage or disruption in the cerebral blood vessels. Multiple abnormalities in the cardiovascular system can trigger vascular dementia such as hemorrhages and arteriosclerosis. Since AβPP plays a role in cerebral thrombosis and fibrinolysis and is involved in a condition known as cerebral amyloid angiopathy (CAA) where the walls of cerebral vessels have pathological Aβ deposition. Familial CAA can occur because of mutations within the AβPP gene. Cerebrovascular Aβ can result in reduced blood flow and ischemia to the nervous system, resulting in potential ischemic injury to the brain. Elevated AβPP can result in hemorrhaging while reduced AβPP can promote an ischemic environment in the brain. This negative influence on cerebral homeostasis can lead to AD or vascular dementia (Van Nostrand, 2016).

The APOE gene has been proven to play a role in AD risk. People with the APOE ε4 allele have been found to have a significantly accelerated cognitive decline. APOE ε4 carriers tend to have lower cognitive capabilities and earlier onset of AD. In fact, for every ε4 allele carried, the age of onset for AD decreases by 3-4 years. APOE ε4 increases the risk of transitioning from mild cognitive impairment (MCI) to AD almost twofold, suggesting that it both increases the susceptibility to AD and reduces the age of AD onset. The APOE ε4 allele negatively impacts brain functioning and the brain's internal environment. It tends to cause increased medial temporal lobe atrophy and decreased verbal memory while decreasing overall cognition and memory (Fan et al., 2019).

Mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) have all been linked with familial Alzheimer's disease (FAD). A study involving patients with early-onset AD showed that PSEN2 K115Efs*11 is possibly a pathogenic variant that could lead to AD. Furthermore, the variant can cause issues with substrate processing, protein folding, and subcellular localization. Alternative splicing of PSEN2 has been hypothesized to be a potential cause of AD (Braggin et al., 2019).

AD can be passed on in an autosomal dominant pattern due to variations between the alleles mentioned above and genes. A study was conducted to understand the difference between biomarkers in late-onset Alzheimer's disease (LOAD) and autosomal dominant Alzheimer's disease (ADAD). It was found that in ADAD, PSEN1 and PSEN2 variants were linked to variability in the amount of amyloid deposits and their distribution. These impacts might be the reason why ADAD can have a worse cognitive progression compared to LOAD. In ADAD, the hippocampal volume decreased more rapidly compared to LOAD but the levels of cerebrospinal fluid levels did not differ compared to LOAD (Schofield et al., 2021).

The Triggering Receptor Expressed in Myeloid Cells 2 (TREM2) gene has been linked to the onset of dementia. TREM2 is also considered one of the risk genes for LOAD. TREM2 is a myeloid cell surface receptor responsible for sending signals and regulating cellular processes such as phagocytosis and autophagy. Two major mutations, R47H and R62H, have been found to increase the risk of AD significantly. A study showed that R47H can cause TREM2 shedding where TREM2 is released more from the cell surface than normal, which could occur due to ADAM10, a shedasse (Hall-Roberts et al., 2020).

Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS)

In both FTD and ALS, one of the largest genetic factors is the chromosome 9 open reading frame 72 (C9orf72) repeat expansion mutation. The gene is mainly expressed in the brain, spinal cord, and myeloid cells and plays a part in immune regulation and axon growth. C9orf72 contributes to the cellular processes of endosomal transport and autophagy, as well. Mutations in the C9orf72 with an autosomal dominant pattern are the cause of 25% of familial FTD and 40% of familial ALS (Smeyers, Banshee, Latouche, 2021). Changes in the levels of autophagy and associated proteins can cause an increased accumulation of misfolded proteins, which could explain C9orf72's part in increased risk of dementia (Kragh et al., 2012). The mutation may also result in lower levels of endocytosis and disrupted lysosomal degradation, impacting certain motor neurons. Haploinsufficiency has been thought to impact the functioning of myeloid cells and systemic immunity in mice. Complete loss of C9orf72 could lead to a systemic proinflammatory state due to myeloid cells in the spleen and lymph nodes functioning differently (Ghasemi et al., 2021).

Parkinson's Disease

Commonly affecting the older population, PD is one of the most common neurodegenerative diseases. The G2019S mutation in the LRRK2 gene accounts for 10% of familial PD cases and 1% to 2% of all PD cases. LRRK2 interacts with several proteins such as CDC42 and RAC1, which might suggest that LRRK2 may have an impact on the actin cytoskeleton. LRRK2 also interacts with the protein product known as CORO1C and the protein product is likely the more functional interactor of LRRK2. Additionally, LRKK2 is linked to the protein product SSH1, responsible for maintaining actin filament, and SELPLG, associated with neuropsychiatric disorders (Lai et al., 2021).

Furthermore, variants in GBA, responsible for encoding the enzyme glucocerebrosidase (GCase), are associated with PD. Heterozygous GBA variants increase genetic susceptibility for both PD and LBD and are found in about 3% to 20% of patients with PD and LBD. It has been hypothesized that a decline in GCase activity can result in a reduced ability to degrade α-synuclein, which may result in misfolded α-synuclein protein deposits, a pathological hallmark of PD. GBA variants impact SNCA and CTSB, which have been implicated in the lysosomal autophagy pathway which plays a pivotal role in the onset of PD (Blauwendraat et al., 2019).

Dementia with Lewy Bodies

Another type of dementia that can be inherited is LBD, which accounts for up to 30.5% of dementia cases. The genetic risk of LBD has been linked to APOE, SNCA, and GBA. Because of the role of APOE ε4 in amyloid or tau pathologies and possibly synucleinopathy, it can increase susceptibility to LBD. Mutations in the GBA gene, that is responsible for encoding lysosomal glucosylceramidase beta (GCase) have been linked to LBD as well. Those with heterozygous mutations of GBA are 8 times more likely than those without to have LBD. Those with heterozygous mutations tend to have an earlier onset of the disease and worse cognitive and motor impairment. Furthermore, triplication of the SNCA gene, responsible for synaptic transmission, has been considered a risk factor for several types of dementia including LBD and PD (Combi et al., 2021).

Early Diagnosis and Prevention

With technological advances, knowledge of dementia and its genetic factors has grown. This increased comprehension of dementia provides an opportunity to improve prevention and intervention strategies for dementia. Taking into account the factors of dementia that may increase susceptibility to dementia, it is important to use this information to reduce the risk.

Genetic Testing and Counseling

Around 20% of ALS and FTD cases have a pathogenic variant that could be identified in diagnostic testing. Many argue that all individuals should be offered genetic testing regardless of whether or not they have a family history but despite these recommendations, genetic testing is not always offered. Genetic testing allows for a molecular diagnosis, and with emerging treatment trials that specifically target certain pathogenic variants, it is crucial to undergo diagnostic testing. If a pathogenic variant is identified, the information would also assist biological relatives in becoming aware of their dementia risk factors (Crook et al., 2022).

Genetic testing for PD is also growing more common as significant advances in genetic testing methods have been made. While no gene-targeted therapies exist for PD, trials are underway, making it even more important to understand whether or not a person has a high genetic susceptibility for PD. Genetic testing enhances subtyping due to correlations between a genotype and phenotype being identified (Pal et al., 2023).

Genetic testing can enhance the quality of diagnosis, provide crucial information to families, and give specific data about the disease. AD-associated genes are focused on in cases where there are many cases of AD in a family. On the other hand, if a tauopathy is reported, testing for MAPT mutations is the preferred choice and TDP-43 pathology would lead to targeted testing of GRN and C9orf72. Genetic counseling provides information about the causes and insight into the potential benefits and limitations of testing but also guides the family through the decisions they may face (Goldman & Van Deerlin, 2018).

Other Preventative Actions

Midlife hypertension has been linked to increased susceptibility to dementia later in life. A study has shown that those who have an optimal cardiovascular system have a lower 10-year risk of all-cause dementia, vascular dementia, and AD. Despite being free of cardiovascular disease, those who have a systolic blood pressure of 130 mm Hg or higher between the ages of 45 and 61 years, have a higher risk of dementia. In regard to mechanisms, hypertension is associated with decreased brain volumes and increased volumes of white matter (Livingston et al., 2020). Hence, it is important to maintain good cardiovascular health and address any existing concerns with cardiac health. Aspects include physical activity, proper diet, and maintaining healthy levels of cholesterol, blood pressure, and blood glucose.

Another modifiable risk factor of dementia is physical activity and exercise levels. Higher levels of physical activity have been associated with a reduction in dementia, based on a meta-analysis of multiple cohort studies. Aerobic exercise is linked to an upsurge in brain-derived neurotrophic factor (BDNF) which can sustain optimal status for neurons and stimulate neuronal cell growth. Furthermore, physical activity can lead to the production of neurotransmitters that lead to a decrease in oxidative stress and inflammation, aid in neurogenesis, and increase blood flow to the nervous system. Physical activity also assists in the management of factors such as diabetes, obesity, and hypertension, which can lead to cardiovascular diseases and as a result, poor cognitive performance (Dominguez et al., 2021).

More recommendations to reduce dementia risk include but are not limited to avoiding drinking alcohol in excess, preventing traumatic brain injuries and head trauma, maintaining physical activity, reducing obesity and diabetes through healthier diet choices and increasing movement, using hearing aids for hearing loss, and treating hypertension (Livingston et al., 2020).

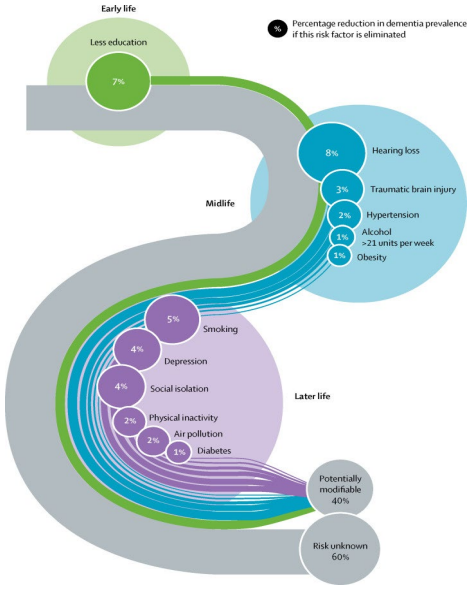

Figure 2. Dementia Prevention Tactics. Source: Livingston et al., 2020

Description: The diagram highlights the many ways to prevent dementia and reduce the risk of dementia. Taking these preventative steps can decrease the chances of experiencing the detrimental effects of dementia. By acting on modifiable risk factors, cognitive function can be enhanced and neuropathological damage can be lowered.

Gene Therapies for Dementia

Adeno-associated virus (AAV) gene therapies have been considered a potential treatment for disorders of the central nervous system (CNS). In PD, declining levels of the AADC enzyme, responsible for converting L-dopa to dopamine, worsen the progression of the disease. A gene therapy that delivers AADC using rAAV2 was developed to combat the reduction of AADC enzyme levels. As of 2023, 31 participants received rAAV2-hAADC to express the hAADC enzyme. Suggestions for the use of AADC in PD may include reducing off-target consequences and improving the expression of genes in target diseased cells (Ng et al., 2023).

RNA or DNA-based therapies (antisense oligonucleotides (AONs)) are another therapeutic strategy under evaluation as a potential therapy for AD and other neurodegenerative diseases. Preclinical trials where AONs mainly target APP mRNA to reduce the formation of Aβ plaques have been conducted. The trials found that the administration of AONs lowered the production of AB42, responsible for AB peptide formation, in the brain. Another clinical trial is evaluating the impact of delivering APOE2 to certain patients with AD using AAVrh10, another form of AAV therapy (Limia et al., 2022).

Antisense oligonucleotides (AONs) have also been implemented in the treatment of familial ALS. The drug nusinersen with the brand name Spinraza® is directed at survival motor neuron-2 (SMN2). The AON drug ensures the proper translation of a functional SMN protein. The drug significantly improves the motor functions of patients and reduces the need for permanent assisted ventilation. BIIB078 (Biogen) is an AON that targets

C9orf72 transcripts with expansions. Trials for the drug have been carried out on 90 adult participants but no interim results have been published yet (Cappella et al., 2021).

Other Research Approaches and Ongoing Clinical Trials

Currently, several critical trials and research are being done to understand the impact of genetic and environmental factors on dementia. N. E. McKean et al. have studied the impact of PSEN1 and APP mutations on dementia in sheep models. As mentioned, both of these mutations have been strongly associated with AD, and attempts to model them on rats do not fully capture the scope of the mutations. The model tests variations in the mutations such as homogenous compared to heterogeneous and notes frameshift mutations. It has been found that the Swedish lambs with the APP mutations tended to have high Aβ peptide levels. The experiment may provide further insights into the onset of AD (McKean et al., 2023).

Another experiment focused on the SNCA-gene coded aggregation of α-synuclein (α-SYN), which plays a major role in LBD. Stem cells from patients with an SNCA gene triplication were used to generate human cortical synucleinopathy models in cerebral organoids. Excitatory neurons were found to be impacted largely by elevated levels of α-SYN. The experiment also performed RNA sequencing analysis on the superior temporal cortex tissue derived from the brain of a patient with LBD. Four drugs directed at α-SYN aggregation were tested using a Real-Time Quaking-Induced Conversion (RT-QuIC) assay and showed a correlation between reduced symptoms and decreased a-SYN aggregation. They also reduced mitochondrial dysfunction in organoids impacted by the SNCA gene triplication (Jin et al., 2023).

Another study suggests that a novel E3 ubiquitin ligase IDOL is associated with increasing phagocytosis of Aβ plaques and increased expression of APOE ε4 and TREM2, genetic factors of AD. The long-term inhibition of IDOL was found to lead to decreased number and size of Aβ plaques. But also, the inhibition was found to lead to improved cognitive function and decreased plaque-associated neuritic dystrophy (Ailiya et al., 2023).

Researcher Name	Trial Number	Title	Description
Assistance Publique - Hôpitaux de Paris	NCT05304195	Exploration of Glucocerebrosidase Activity to Identify a Subpopulation Eligible for a Therapeutic Trial in Dementia With Lewy Bodies	The ongoing clinical trial strives to analyze the difference in Glucocerebrosidase (GCase) activity in patients without cognitive impairment as the control group and patients with LBD. Previous studies have shown that GBA gene mutations lead to decreased GCase activity in LBD. However, mutations of the GBA gene are also pathologic factors for Gaucher disease, which has a treatment. The objective of the trial was to understand if glucocerebrosidase activity is decreased in LBD. If the hypothesis is found to be true, then treatments for Gaucher disease may be experimented with as a therapeutic for LBD.

Baylor Research Institute	NCT03645993	Early Onset Alzheimer's Disease Genomic Study	This clinical trial aimed to understand the molecular changes that occur in early-onset Alzheimer's disease by studying the DNA and RNA of subjects. The two study groups of the trial were patients with early-onset Alzheimer's disease and a negative control, which was the family members of the patients with early-onset Alzheimer's disease. A one-time blood sample would be taken for each subject. Results from this critical trial could help doctors more efficiently diagnose, treat, and monitor those at risk of potentially developing early-onset AD in the future.
AviadoBio Ltd	NCT06064890	A Phase 1/2 Open-Label, Ascending Dose, Multicenter Study to Evaluate the Safety and Preliminary Efficacy of AVB-101 Administered by Bilateral Intrathalamic Infusion in Subjects With Frontotemporal Dementia With Progranulin Mutations (FTD-GRN)	This trial's goal is to learn more about an investigational gene therapy product known as AVB-101. The gene therapy is designed to treat FTD with progranulin (PRGN) mutations, caused by low levels of PGRN in the brain. The low levels of PRGN lead to the death of nerve cells and a decline in the brain's ability to function. The trial aims to give all participants a one-time treatment on AVB-101 and note whether it is safe, restores PRGN levels, and could stop the progression of FTD-GRN.

Discussion

Several genetic variants have been implicated in genetic predisposition to dementia. C9orf72 gene mutations can cause ALS and FTD due to increasing misfolded proteins and disrupting autophagy. APP, PSEN1, and PSEN2 are linked to familial AD since they cause protein folding and other issues with the processing of substrates. TREM2 gene expression can cause disruption in neurological signals, that leads to both Nasu-Hakola disease and AD. Mutations in the Aβ precursor protein gene cause vascular dementia by leading to hemorrhaging or an ischemic environment in the brain. The APOE ε4 allele has been linked to an increased risk of cognitive impairment, especially AD. Variants in SNCA and GBA cause an increase in misfolded α-synuclein protein deposits, that lead to both PD and LBD.

Genetic testing provides crucial information about the genetic variants causing dementia. This insight guides the family for future counseling and participation in clinical trials. But also, the information provided by genetic testing may allow for more specialized therapeutic use and treatment plans. Various gene therapies are being formed to combat the genetic variants associated with dementia. Both AON and AAV gene therapies have been discovered to treat AD, PD, and ALS. Ongoing clinical trials are being done to understand the impact of GCase activity in LBD, study the difference between those with early-onset AD and their family, and test potential treatments.

Conclusion

To summarize, several genes and alleles are involved in the mechanisms of dementia. Some genetic factors play a much larger role in certain diseases and are of greater prominence such as C9orf72 in ALS and FTD or the APOE ε4 allele in AD and LBD. Ongoing research about drugs and differences in AD cases is being conducted and may lead to further advances in understanding dementia's etiology.

Other physiologic factors can impact the risk of dementia such as cardiovascular health, lifestyle choices, and diabetes. Taking action to reduce the impact of these factors is critical to decreasing susceptibility to dementia. Genetic counseling and testing are important to understanding the various risks of dementia. Expanding the current knowledge about dementia etiology and its genetic component could lead to more comprehensive genetic testing and advances in precision medicine. Further investigation into the genetic components behind dementia is recommended. But also, more research on gene therapies and interventions against genetic components would be advisable.

Limitations

This research paper aimed to analyze the genetic factors associated with dementia ranging from specific alleles to genetic mutations. This study was a secondary literature review and covered a variety of sources that all suggested associations between certain genes and forms of dementia. However, it is possible that by focusing so extensively on particular genes, the study overlooked some less notable genetic factors. Furthermore, environmental factors such as cardiovascular health were discussed in the article but their impact may be understated.

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