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GENETICS OF DEMENTIA: THE CANDIDATE GENES AND AVAILABLE GENETIC TESTINGS

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ABSTRAK

Abstract:
When dementia is present, a person's memory, reasoning, behavior, and even their capacity to carry out day-to-day chores can all become distorted. This syndrome remains present and actually worsens as time passes. It's possible that synapse loss, death and dysfunction of brain cells, gliosis, and inflammation are all factors in the progression of dementia. The clinical syndrome, age, and a history of the ailment in the patient's family should dictate the choices made about counseling and testing. Dementia is known as a multifactorial condition, brought on by the combination of strong genetic factors and environmental factors. There are several candidate genes associated with Dementia; APP, PSEN1, and PSEN2 genes, in addition to the GRN and MAPT genes. This literatura review provide insight on the genetic of Dementia, particularly in the genetic causes and testings.

***Abstrak*:**
Demensia merupakan suatu kondisi multifaktorial yang dipengaruhi oleh berbagai faktor, di antaranya adalah faktor genetik. Dalam perkembangan penyakit, hilangnya sinaps, kematian dan disfungsi sel otak, gliosis, dan peradangan merupakan faktor-faktor yang mempengaruhi tingkat keparahan demensia. Sindrom klinis, usia, dan riwayat penyakit pada keluarga juga berperan dalam menentukan pilihan tatalaksana dan pemeriksaan lanjutan, antara lain pemeriksaan genetik. Beberapa kandidat gen yang diidentifikasi memiliki kaitan dengan kejadian demensia adalah gen APP, PSEN1, PSEN2, gen GRN dan gen MAPT. Tinjauan pustaka ini menyajikan informasi mengenai faktor genetik beserta pemeriksaan genetik yang dapat dilakukan pada kasus-kasus Demensia.

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INTRODUCTION

A person is said to have dementia when they have an received lack of cognition in lots of cognitive domain names to impede their ability to function socially or professionally [1] 5.8 million persons in the United States are living with Alzheimer's disease (AD). On the other hand, dementia is frequently connected to more than one neuropathology, most frequently Alzheimer's disease in conjunction with cerebrovascular pathology [2]. Diabetes mellitus, cerebrovascular disease, obesity, or cardiovascular disease history, using medications of anticholinergic, having genotype of apolipoproteins E4, and having a decrease staged of education are all risk factors for dementia [3] [4].

A history of cognitive decline and difficulty in day-to-day activities, as well as confirmation from a close friend or member of the family, are necessary for the diagnosis of dementia. In addition, a clinician needs to carry out a mental status assessment that is somewhat extensive in order to identify problems in the patient's memory, language, attention, visuospatial cognition (including spatial orientation), executive function, and mood. However, they all entail the steady buildup of aberrant forms of brain proteins, which is a process that can begin more than a decade before neuronal loss is visible in the brain. Some of these diseases are more prevalent than others, like Alzheimer's disease (AD), while others, including frontotemporal dementia (FTD) and prion diseases, are far less common or even extremely uncommon [5] [8].

However, the application of these tests in clinical practice is generally motivated by the onset of symptoms. At this point in childhood, molecular abnormalities are typically already prevalent throughout the brain. Even if imaging and biofluid indicators of these processes are already accessible, the application of these tests in clinical practice is still determined by the emergence of symptoms[9]. When disease-modifying medications are eventually found, the evidence from animal and clinical research shows that they will be more effective if administered earlier on in the disease's progression [10] [11].

On the other hand, the vast majority of clinical trials have been conducted on people with dementia who already have advanced pathologies, which may be a barrier to the development of medicines that can influence the course of the disease. It is imperative that individuals who participate in clinical trials of treatments for Mendelian dementias undergo genetic testing in order to be identified as carriers of disease-causing mutations.[7] Given that there are currently no medications that have been demonstrated to be beneficial in altering the course of a disease, the rationale behind conducting genetic testing in a clinical environment is not as obvious. As a result of developments in testing methods as well as shifts in general knowledge, several new areas of uncertainty have come to light. These aspects deal with the question of when testing should be made available and how it should be carried out in the most efficient manner [10].

Other research measured plasma total tau, A42, and A40. Mutant patients had amyloid and tau PET scans. Nine of 52 young-onset AD patients (17.3%) had mutations in APP, PSEN1, PSEN2, and TREM2. Two young-onset FTD patients (6.1%) had MAPT and LRRK2 mutations. 50% of the 6 patients with probable FTD and other neurodegenerative illnesses had APP, PSEN2, or MAPT mutations. PSEN1 mutations accelerated illness onset ($p = 0.02$). All dementia patients had higher plasma total tau and lower A42 and A40 levels than controls [11].

For clinical trials of treatments for Mendelian dementias, genetic testing to identify patients who carry disease-causing mutations is an absolute necessity. Given that there are currently no disease-modifying treatments that have been shown to be effective, the basis for genetic testing in a clinical setting is not as clear. Several areas of doubt have arisen as a result of advancements in testing technologies and changes in public knowledge. These areas

relate to when testing should be offered and how it should be done most effectively [3] [13].

DIMENTIA

Dementia is a syndrome that is marked by disorientation of memory and memory, thinking processes, behavior, and a decreased capacity to execute activities of daily living. This syndrome is both persistent and progressively worsening [1]. Due to its nature, dementia burdens not only those suffered from it but also the family and ultimately the society. Alzheimer's disease is the leading cause of dementia, accounting for the vast majority of cases. The elderly constitute the vast majority of those diagnosed with dementia. It is estimated that 55 million people around the world are living with dementia. The diagnosis of dementia was made based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) [5] [14].

Degenerative processes, such as Alzheimer's disease, vascular disorders, such as infarction, and psychiatric and neurological problems, such as hydrocephalus, all contribute to the etiology of dementia. In addition, neoplasms, metabolic and endocrine abnormalities, trauma, inflammation, and toxic chemicals are all potential contributors to the genesis of dementia. In addition to advanced age and circumstances related to one's way of life, researchers have found a number of disorders that have a role in the development of dementia [15].

Dementia's pathogenesis may be caused by molecular processes that produce synapse loss, brain cell death and malfunction, gliosis, and inflammation. Alzheimer's disease causes the brain to produce β-amyloid and tau proteins. Lewy bodies are also detected in Parkinson's disease and Creutzfeldt-Jakob disease. In Alzheimer's disease, acetylcholine levels drop and the N-methyl-D-aspartate (NMDA) receptor is overactive, according to one theory. entorhinal cortex, hippocampus, amygdala, frontal and parietal cortex have cholinergic and glutaminergic system disorders. Learning and memory are compromised. ROS trigger neuronal apoptosis. ROS buildup is caused by amyloid-, NMDA receptor activation, and aberrant neuronal mitochondrial metabolism. Intracellular calcium is involved in neuronal cell physiology. Alzheimer's causes neuronal malfunction and death due to calcium dysregulation. Unknown cause impairs calcium homeostasis [15] [16].

At the anamnesis stage, symptoms of cognitive deficits can be found in the form of complex attentional disorders, execution functions, learning abilities, memory/memory, language, motor perception, and social. The history is usually carried out by the family or caregiver. To assist in the diagnosis, standard neuropsychological tests can be used, namely mini mental state examination (MMSE), Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-Cog), and Mattis Dementia Rating Scale (MDRS) [5] [17].

GENETIC FEATURES INVOLVED

Numerous Mendelian inheritans causes of dementia were revealed; nevertheless, there's limited implementation of this knowledge in routine clinical practice. Before just a short while ago, there was only a small variety of tests that could be carried out in a clinical environment. In this study, we make an attempt to overcome this issue by giving information to help quality board analyze in dementia. This study was funded by the National Institute on Aging (NIA). To do this, we lead an investigation of a progression of patients that is enhanced for the individuals who are probably going to hold onto hurtful changes and is sufficiently large to impact clinical practice [10] [13].

Because of this, we are able to provide data that can be utilized to support the diagnostic use of gene panels in dementia. With the exception of older adults who lacked a negative family history and people who had dementia and motor symptoms that

may not have been caused by mutations in typical dementia genes, our study found that the detection of clinically significant variants was high in all groups. The rate at which clinically significant variations were discovered was lower in each of these groups. A study discovered a high frequency of previously undiscovered variants in genes, in addition to variants in genes that were already recognized [10].

Based on the clinical syndrome, an accomplished clinician most likely could not have chosen these genes for individual gene testing. As a result of our findings, it would be appropriate to conduct more extensive clinical testing than is typically done. As predictive factors that should be helpful in guiding counselling and decisions about referral for testing, we identified clinical syndrome, age, and the strength of the family history [10] [18]. Because of this, the likelihood of having homozygosity in susceptibility alleles like APOE4 is increased [14].

In contrast to the form of dementia that is produced by a single gene, known as hereditary dementia, the form of dementia known as multifactorial dementia is brought on by the interplay of a number of various genetic and environmental factors. It is more likely that an individual will have a hereditary type of dementia if there is a history of dementia in their family as well as an early onset of the disease. In addition, having an early onset of dementia increases the likelihood that an individual will have a hereditary form of dementia. There are three primary ways that dementia is passed down across generations: autosomal dominant inheritance, autosomal recessive inheritance, and X-linked inheritance. The dominant inheritance pattern is by far the most typical [19].

The clinical syndrome was a substantial predictor, although in very different ways, of the possibility of identifying a mutation and the gene. These differences were due to the fact that these two factors were analyzed separately. There was a connection found in 93.5% of FTD patients with DVs between three major genes and two additional genes associated with FTD symptoms (C9orf72, GRN, MAPT, SQSTM1, VCP) [20]. On the other hand, the DVs in genes associated to AD pathologies were found in just 63% of patients with clinically confirmed Alzheimer's disease (APP, PSEN1 or PSEN2). DVs were not very common in individuals who were diagnosed with dementia-motor syndrome, and the correlations between them and the dementia were quite variable [9].

Other NGS tests have a sensitivity and specificity that are both higher than 99% analytically. On the other hand, diagnostic sensitivity can be identified in 40–80% of cases in people who have early-onset familial Alzheimer's disease and a pathogenic variant in APP, PSEN1, or PSEN2. This is the case in people who have early-onset familial Alzheimer's disease and a pathogenic variant in APP, PSEN1, or PSEN2. This is how it is for people who have been diagnosed with the condition. One particular pathogenic variation is responsible for around 65 percent of all occurrences of frontotemporal dementia. A genetic predisposition can be identified as the cause of prion disease in roughly 10–15 percent of reported cases. The diagnostic specificity of Alzheimer's disease is roughly 70%, making it one of the most accurate diagnoses possible [19] [21].

The following are some of the consequences that these findings have for clinical practice: it would be fair to refer individuals who are suspected of having prion disease for testing of PRNP alone. When it comes to FTD and AD syndromes, the dementia gene panel approach seems to make the most sense because of the broad number of genes that are implicated as well as the clinical heterogeneity. Nevertheless, dementia-motor disorders are more challenging to diagnose; a low incidence of DV identification either shows that disease-relevant variations are not covered by our panel or signals that more testing is necessary [10].

GENETIC TESTING INTO DEMENTIA DISORDERS

There is a substantial amount of regional variance in its application, both between countries and even within individual nations. Currently, the use of genetic testing in clinical practice is fairly limited, and there are major differences in its application [9] [22]. Symptomatic hereditary testing is progressing from a specific method to a broadly involved clinical device as the accessibility of hereditary testing proceeds to develop and more is found out about the qualities and pathways that are engaged with dementia. This is due to the fact that more is being learned about the genes and pathways that are involved in dementia [22] [23].

The capacity to sequence numerous genes at the same time using a technique known as massively parallel sequencing is the most significant advancement in the technology for gene testing that falls under the umbrella of what is known as "nextgeneration sequencing" (NGS). The designated sequencing of genes with comparable related clinical phenotypes and frequently including testing for rare causes of disease is the most well-known use of NGS in diagnostic hereditary testing. This involves gene panels's application, which also frequently includes testing for rarer causes of disease [18] [23].

The majority of research facilities utilize focused gene panels, which can be produced in one of two ways: either by sequencing amplicon-selected regions of interest or by carrying out a combination of the two, whole-exome sequencing (WES) or whole-genome sequencing (WGS) and then restricting their analysis to genes that are chosen based on the referral diagnosis. There are a few distinct approaches one can take to accomplish this goal. A gene panel for dementia will typically comprise the vast majority of genes that have been connected to the trait in question. These genes include the Alzheimer's disease genes APP, PSEN1, and PSEN2, as well as the classical FTD genes GRN and MAPT. Other genes associated with the condition include APOE. On the other hand, the panel also includes genes that are related with familial dementia and leukoencephalopathy that have less common etiology [23] [24].

SELECTION OF TEST AND PATIENT

Over the past 20 years, our understanding of the genetic heterogeneity of dementia, the fact that the same or different mutations in the same gene can lead to a spectrum of phenotypes (a concept known as pleiotropy), and the clinical overlap that exists between the various dementia syndromes has greatly expanded[23]. Because of these factors, different kinds of genetic testing are necessary depending on the clinical phenotype, whether a genetic, clinical, or pathological diagnosis has been made in a relative, whether biomarkers of molecular pathology are available, as well as on the number of implicated genes and the type of mutation that is anticipated [10].

In addition, the kind of genetic testing that is essential differs from case to case based on whether or not a close family has the condition. This score provides a rough estimate of the likelihood of identifying a genetic factor that contributes to the development of the disease. It is essential to avoid falling into the trap of confusing a partial family history or a history that contains early deaths that are not related to the disease with a history that is negative. Although a negative family history does not always rule out the possibility of a genetic diagnosis, it is important to avoid falling into this trap. The discovery rate was 3.5% in Alzheimer's disease, 8.6% in frontotemporal dementia, and 10.7% in prion disease in a clinical diagnosis referral series of patients with a censored or negative family history but in whom the prior expectation of a pathogenic variant was high. Patients with prion disease had a higher prior expectation of a pathogenic variant. All of these patients went into the process with the assumption that they would have a variation that could potentially cause harm [18] [25].

Testing for specific point mutations, as well as for small insertions or deletions that

result in frameshifts or changes in the protein's in-frame context, is one way to achieve accurate results. Another method is to analyze the protein for changes in its in-frame context. However, testing only one gene in a diagnostic setting is really only appropriate for diseases with extremely distinct clinical presentations, such as HD and prion disease, because the odds of detecting a causal variant are otherwise low. This is because HD and prion disease both present symptoms that are extremely distinct from one another. This is the situation due to the fact that HD and prion illness both exhibit quite different symptoms and signs to their patients [8] [10] [25].

In addition, clinical overlap and pleiotropy show that a clinical diagnostic does not reliably correspond to the anticipated genetic explanation, and vice versa. This is due to the fact that a clinical diagnosis might be brought on by more than one genetic component at a time. Additionally, even if the testing of a single gene is successful in identifying a mutation that causes FTD, it is unable to detect concurrent mutations, which are discovered significantly more frequently in FTD than would be predicted by chance. This makes it impossible for the testing of a single gene to diagnose the condition. In addition, synergistic effects between novel variations and those that have not been definitively verified as deleterious variants can also lead to disease. Synergistic effects between novel variations and those that [8] [25].

Synergistic effects between new variations and those that have already been studied An method for computers has been developed in order to partly automate the assessment of such double variants; however, the therapeutic utility of such tools has not yet been established and is not yet known. Because of this, single-gene testing is not recommended in AD or FTD, with the exception of tests that are employed for the purpose of confirming a diagnosis.9 We suggest that conventional neurological, psychiatric, and geriatric therapy should include testing for dementia gene panels whenever it is conceivable that a genetic etiology is to blame for the problem being treated. This would apply to both younger and older patients. Routine testing will result in an increase in the number of patients who have a clear genetic diagnosis. This testing will also identify family members who are at risk and will make them eligible for targeted treatment as soon as it becomes available[10] [23].

A conclusive genetic diagnosis can cut down on the number of other diagnostic procedures that need to be performed and make it possible to provide care and therapy that is more effective. Alterations to the standard of care call for the development of new skills, have the potential to cause increased anxiety in patients and the relatives of those patients, as well as an increase in both direct expenditures and the requirement for counseling.26 It may be helpful to conduct a prospective review of various treatment approaches, such as a clinical trial comparing standard care with gene panel testing, in order to determine whether or not a change in treatment approach is beneficial or harmful [9] [27].

CONCLUSION

Genetic testing is distinct from other types of medical examinations since the results of the test can frequently have repercussions for the individual's family members. Incorporating genetic testing into the diagnostic process for certain patients suffering from dementia has the potential to cut down on the amount of time required to determine the cause of the patient's dementia. In spite of the fact that it is unquestionably advantageous to add genetic testing to the repository of diagnostic tools, it is essential to first weigh all of the potential benefits and drawbacks associated with this field. On another note, there is always two sides of the coin, where genetic testing does not only provide answers to the patients and the families, but its findings would give rise to ethical issues related to the consequences of identifying genetic causes that can be passed on in the family. Hence prior to the genetic

testing, it is imperative for patients and families to receive genetic counseling before they make informed choices regarding the situation.

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