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RESEARCH ARTICLE

ALZHEIMER DISEASE & GENETICS: A MINI REVIEW

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ABSTRACT

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases AD is characterized by adult-onset progressive dementia, beginning with subtle memory failure that becomes more severe and is eventually incapacitating. The most common neuropathological feature of AD is the presence of neurofibrillary tangles and amyloid deposits that form plaques and cerebrovascular accumulations. AD is divided into familial and sporadic forms. AD is considered familial when more than one person in a family is affected, while sporadic refers to AD cases when no other cases have been seen in close family members. It has been over 100 years since the first cases of AD were described, and since then much has been discovered about the molecular nature of the disease. The genetic control of complex diseases is becoming more apparent as previously unidentified mutations in the human genome are described. As the genetic control of AD is uncovered, improved therapies may also be uncovered

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, and with a new case occurring every seven seconds globally, the disease itself is becoming a slow pandemic. One person for every 85 individuals can be expected to suffer from AD by the year 2050. AD also imposes tremendous emotional and financial burden to the patient's family and community through the provision of care and loss of wages (Anand *et al*., 2014). Scientists have identified rare changes (mutations) in three genes that virtually guarantee a person who inherits them will develop Alzheimer's. But these mutations account for less than 5 percent of Alzheimer's disease. Most genetic mechanisms of Alzheimer's among families remain largely unexplained. The strongest risk gene researchers have found so far is apolipoprotein e4 (APOE e4). Other risk genes have been identified but not conclusively confirmed. (Myoclinic website: accessed 14-11-2013). In this report, the author conducted a thorough literature search to identify the relationship of Alzheimer disease with genetic science. In addition to this "central core" it recognized the nature of Alzheimer disease, its risk factors, and mechanisms by which the disease may develop.

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Alzheimer disease (AD)

Definition of Alzheimer's disease

Alzheimer's disease (AD) is a fatal neurodegenerative disorder and is the leading cause of dementia in the elderly (Sherva *et al*., 2014; Murcia *et al*., 2013; AMA published sheet: accessed Nov., 2013). Alzheimer's disease is the most common type of dementia. "Dementia" is an umbrella term describing a variety of diseases and conditions that develop when nerve cells in the brain (called neurons) die or no longer function normally. The death or malfunction of neurons causes changes in one's memory, behavior and ability to think clearly. In Alzheimer's disease, these brain changes eventually impair an individual's ability to carry out such basic bodily functions as walking and swallowing. Alzheimer's disease is ultimately fatal (Alzheimer's Association Report, 2013).

Alzheimer's disease is the sixth leading cause of death in the United States, and of the 6, the only one lacking adequate treatment or prevention. AD is characterized by a progressive loss in cognitive function, and strikes memory early in the course. Neuropath logical changes include loss of neurons and synapses, extensive accumulation of amyloid plaques, and neurofibrillary tangles. AD has been identified as a proteopathic disease because of its extensive accumulation of amyloid plaques and neurofibrillary tangles (Murcia *et al*., 2013). The disease maybe classified based on the age of

onsetinto early-onset AD and late-onset AD. Early onset AD accounts for approximately 1%-6% of all cases and manifests roughly between30 and 60 years. Late onset form accounting for around 90% of cases has an age at onset later than 60 years (Anand *et al*., 2014). An estimated 5.2 million Americans of all ages have Alzheimer's disease in 2013. This includes an estimated 5 million people age 65 and older, and approximately 200,000 individuals under age65 who have younger-onset Alzheimer's (Alzheimer's Association Report, 2013).

Symptoms of Alzheimer's disease (AD)

AD is characterized by adult-onset progressive dementia, beginning with subtle memory failure that becomes more severe and is eventually incapacitating. Neurodegeneration is estimated to start 20-30 years before clinical symptoms become apparent. The most common neuropathological feature of AD is the presence of neurofibrillary tangles and amyloid deposits that form plaques and cerebro vascular accumulations (AMA published sheet, accessed Nov 2013).

Alzheimer's disease affects people in different ways. The most common symptom pattern begins with a gradually worsening ability to remember new information. This occurs because the first neurons to die and malfunction are usually neurons in brain regions involved in forming new memories. As neurons in other parts of the brain malfunction and die, individuals experience other difficulties (Alzheimer's Association Report, 2013).The Alzheimer's Association report showed in details the following are common symptoms of Alzheimer's:

- Memory loss that disrupts daily life.
- Challenges in planning or solving problems.
- Difficulty completing familiar tasks at home, at work or at leisure.
- Confusion with time or place.
- Trouble understanding visual images and spatial relationships.
- New problems with words in speaking or writing.
- Misplacing things and losing the ability to retrace steps.
- Decreased or poor judgment.
- Withdrawal from work or social activities.
- Changes in mood and personality.

Individuals progress from mild Alzheimer's disease to moderate and severe disease at different rates. As the disease progresses, the individual's cognitive and functional abilities decline. In advanced Alzheimer's, people need help with basic activities of daily living (ADLs), such as bathing, dressing, eating and using the bathroom. Those in the final stages of the disease lose their ability to communicate, fail to recognize loved ones and become bed-bound and reliant on around-the-clock care. When an individual has difficulty moving because of Alzheimer's disease, they are more vulnerable to infections, including pneumonia (infection of the lungs). Alzheimer's-related pneumonia is often a contributing factor to the death of people with Alzheimer's disease.

Risk factors for Alzheimer's disease (AD)

Many factors contribute to one's likelihood of developing Alzheimer's. The greatest risk factor for Alzheimer's disease is advancing age, but Alzheimer's is not a typical part of aging. Most people with Alzheimer's disease are diagnosed at age 65 or older. However, people younger than 65 can also develop the disease, although this is much more rare. Advancing age is not the only risk factor for Alzheimer's disease (Alzheimer's Association Report, 2013). The following sections describe other risk factors:

Family History

Individuals who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than those who do not have a first-degree relative with Alzheimer's. (21-23) Those who have more than one first-degree relative with Alzheimer's are at even higher risk of developing the disease. (24) When diseases run in families, heredity (genetics), shared environmental and lifestyle factors, or both, may play a role. The increased risk associated with having a family history of Alzheimer's is not entirely explained by whether the individual has inherited the apolipo protein E-ε4 risk gene.

Apolipoprotein E-ε4 (APOE-ε4) Gene

The APOE gene provides the blueprint for a protein that carries cholesterol in the bloodstream. Everyone in herits one form of the APOE gene — ε2, ε3 or ε4— from each parent. The ε3 form is the most common, with about 60 percent of the U.S. population inheriting ε3 from both parents. The ε2and ε4 forms are much less common. An estimated20 to 30 percent of individuals in the United States have one or two copies of the ε4 form; approximately 2 percent of the U.S. population has two copies of ε4. The remaining 10 to 20 percent have one or two copies of ε2.Having the ε3 form is believed to neither increase nor decrease one's risk of Alzheimer's, while having theε2 form may decrease one's risk. The ε4 form, however, increases the risk of developing Alzheimer's disease and of developing it at a younger age. Those who inherit two ε4 genes have an even higher risk.

Researchers estimate that between 40 and 65 percent of people diagnosed with Alzheimer's have one or two copies of the APOE-ε4 gene. Inheriting the APOE-ε4 gene does not guarantee that an individual will develop Alzheimer's. This is also true for several genes that appear to increase risk of Alzheimer's, but have a limited overall effect in the population because they are rare or only slightly increase risk. Many factors other than genetics are believed to contribute to the development of Alzheimer's disease.

Mild Cognitive Impairment (MCI)

MCI is a condition in which an individual has mild but measurable changes in thinking abilities that are noticeable to the person affected and to family members and friends, but that do not affect the individual's ability to carry out everyday activities. People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer's and other dementias than people without MCI. However, MCI does not always lead to dementia. For some individuals, MCI reverts to normal cognition on its own or remains stable. In other cases,

such as when amedication causes cognitive impairment, MCI is mistakenly diagnosed. Therefore, it's important that people experiencing cognitive impairment seek help as soon as possible for diagnosis and possible treatment.

Cardiovascular Disease Risk Factors: Growing evidence suggests that the health of the brainis closely linked to the overall health of the heart and blood vessels. The brain is nourished by one of the body's richest networks of blood vessels. A healthy heart helps ensure that enough blood is pumped through these blood vessels to the brain, and healthy blood vessels help ensure that the brain is supplied with the oxygen- and nutrient-rich blood it needs to function normally.

Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of developing Alzheimer's and other dementias. These factors include smoking, obesity (especially inmidlife), diabetes, high cholesterol in midlife and hypertension in midlife. A pattern that has emerged from these findings, taken together, is that dementia risk may increase with the presence of the "metabolic syndrome," a collection of conditions occurring together — specifically, three or more of the following: hypertension, high blood glucose, central obesity (obesity in which excess weight is predominantly carried at the waist) and abnormal blood cholesterol levels.

Conversely, factors that protect the heart may protect the brain and reduce the risk of developing Alzheimer's and other dementias. Physical activity appears to be one of these factors. In addition, emerging evidence suggests that consuming a diet that benefits the heart, such as one that is low in saturated fats and rich in vegetables and vegetable-based oils, may be associated with reduced Alzheimer's and dementia risk.

Education: People with fewer years of education are at higher risk for Alzheimer's and other dementias than those with more years of formal education. Some researchers believe that having more years of education builds a "cognitive reserve" that enables individuals to better compensate for changes in the brain that could result in symptoms of Alzheimer's or another dementia. According to the cognitive reserve hypothesis, having more years of education increases the connections between neurons in the brain and enables the brain to compensate for the early brain changes of Alzheimer's by using alternate routes of neuron-to-neuron communication to complete acognitive task. However, some scientists believe that the increased risk of dementia among those with lower educational attainment may be explained by other factors common to people in lower socioeconomic groups, such as increased risk for disease in general and less access to medical care.

Social and Cognitive Engagement: Additional studies suggest that other modifiable factors, such as remaining mentally and socially active, may support brain health and possibly reduce the risk of Alzheimer's and other dementias. Remaining socially and cognitively active may help build cognitive reserve (see Education, above), but the exact mechanism by which this may occur is unknown. Compared with cardiovascular disease risk factors, there are fewer studies of the association between social and cognitive engagement and the likelihood of developing Alzheimer's disease and other dementias.

Traumatic Brain Injury (TBI): Moderate and severe TBI increase the risk of developing Alzheimer's disease and other dementias. TBI is the disruption of normal brain function caused by a blow or jolt to the head or penetration of the skull by a foreign object. Not all blows or jolts to the head disrupt brain function. Moderate TBI is defined as a head injury resulting in loss of consciousness or post-traumatic amnesia that lasts more than 30 minutes. If loss of consciousness or post-traumatic amnesia lasts more than 24 hours, the injury is considered severe. Half of all moderate or severe TBIs are caused by motor vehicle accidents. Moderate TBI is associated with twice the risk of developing Alzheimer's and other dementias compared with no head injuries, and severe TBI is associated with 4.5 times the risk. These increased risks have not been studied for individuals experiencing occasional mild head injury or any number of common minor mishaps such as bumping one's head against a shelf or an open cabinet door.

Groups that experience repeated head injuries, such as boxers, football players and combat veterans, are at higher risk of dementia, cognitive impairment and neurodegenerative disease than individuals who experience no head injury. Emerging evidence suggests that even repeated mild TBI might promote neurodegenerative disease. Some of the seneurode generative diseases, such as chronic traumatic encephalopathy, can only be distinguished from Alzheimer's upon autopsy.

Mechanisms of developing Alzheimer's disease (AD)

The etiology is multifactorial, and pathophysiology of the disease is complex. The extensive insight into the molecular and cellular pathomechanism in AD over the past few decades has provided us significant progress in the understanding of the disease. A number of novel strategies that seek to modify the disease process have been developed (Anand *et al*., 2014).Recently, researchers have shown an increased interest in investigating the factors and mechanisms which may help us to understand the developmental process of AD. One of these trials was published by Anand *et al.* (2014). They explained the multiple mechanisms involved in the pathogenesis of AD in Fig.1. One of the most significant current literatures was written by Proitsi *et al.* (2014). By their review, the DNA variants can alter levels of transcription, RNA splicing, RNA stability, protein translation, post translational modification, RNA and protein localization, and/or protein function of genes located in their vicinity or elsewhere in the genome. Expression quantitative trait loci (eQTL) analysis is one approach that can reveal associations between variants at the DNA level and their influence on steady-state levels of RNA and thus influence the rate of transcription and/or RNA degradation. For many genes, levels of RNA are highly heritable. Cis-acting variants in promoters, non-coding regions such as those capable of binding micro RNAs and other regulatory proteins or coding regions can alter rates of transcription and/or RNA turnover. These in turn may have an impact on the levels of protein produced from a given gene, the generation of different protein isoforms, and ultimately protein functionality.

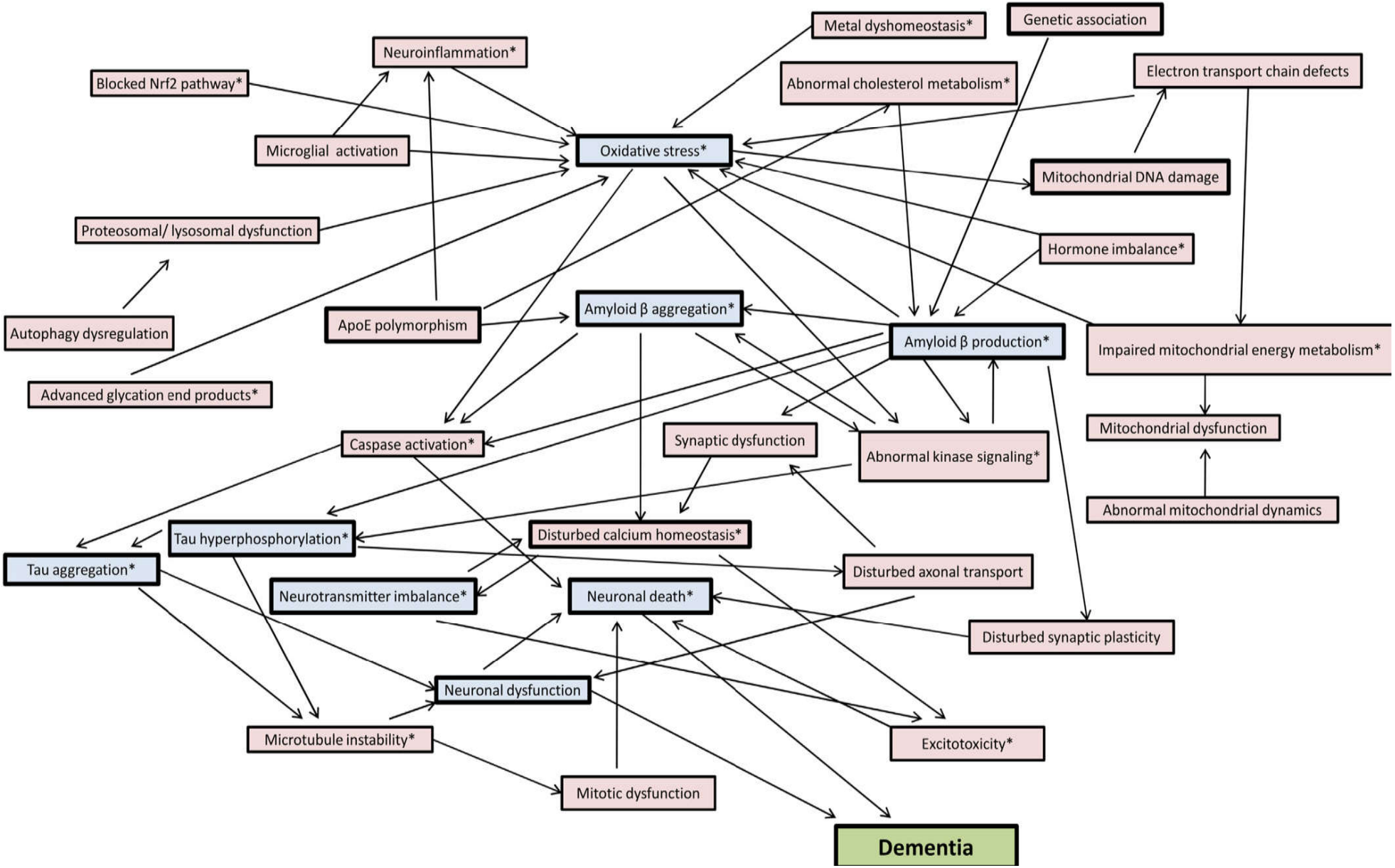

Fig.1. Multiple mechanisms involved in the pathogenesis of Alzheimer's disease (AD)

In reality, most genes have a very complex pattern of transcription, with different spatial and temporal patterns of expression involving multiple transcripts and regulated by both genetic and non-genetic factors.

Alzheimer's disease & genetics

In recent years, there has been an increasing amount of literature on Alzheimer's disease & genetics. American Medical Association publishedan article titled "genetics of Alzheimer disease". It shows that AD is divided into familial and sporadic forms. AD is considered familial when more than one person in a family is affected, while sporadic refers to AD cases when no other cases have been seen in close family members. Approximately 25% of AD is familial, with the rest sporadic. AD is further divided into early and late-onset forms; early-onset denotes onset of the disease before age 65 years, while late-onset denotes onset after age 65 years. Almost all cases of sporadic AD are late-onset, while approximately90% of familial AD is late-onset. Less than 10% of all AD cases are familial early-onset (AMA published sheet, accessed Nov 2013).

The Alzheimer's Association (is the leading voluntary health organization in Alzheimer care, support and research in the U.S.) reported about genetic testing and genetic risk factors of the disease. They identified that the researchers have observed that having a parent or sibling with Alzheimer's disease does increase one's risk somewhat above the general population's risk of developing the disease, but such a family history should not cause undue anxiety. Nonetheless, some people with such family histories, and some without such histories, wish to have a genetic test that will answer the question: Will I be next? (Alzheimer's Association sheet; accessed Nov 2013).

Genetic Mutations & Alzheimer's Disease

Several recent studies have succeeded in identifying the genetic basis of different disorders by using exome and genome sequencing. The most well-established link between AD and genetics is in familial early-onset AD. Three genes have been identified that account for a significant number of familial early-onset ADcases. The APP (amyloid precursor protein) gene encodes the Amyloid Precursor Protein, which isnormally cleaved to form amyloid β. Mutations in APP result in incorrect cleavage of the protein, producing a version of amyloid β that is more likely to form plaques. Mutations in APP account for 10%-15% of familial early-onset cases. The PSEN (presenilin) genes encode proteins that function in the cleavage of Amyloid Precursor Protein. Mutations in both PSEN1 and PSEN2 result in incorrect cleavage of APP, and are associated with development of familial early-onset AD. Mutations in PSEN1 are thought to account for 30%-70% of familial early-onset cases, while mutations in PSEN2 are thought to account for less than 5%. Familial early-onset AD is inherited in an autosomal dominant manner, meaning that inheritance of one mutant allele of APP, PSEN1, or PSEN2 almost always results in development of the disease. Children of an affected parent have a 50% chance of inheriting the mutation and developing the disease. It is important to note that mutations in APP, PSEN1 and PSEN2do not account for all cases of familial early-onset AD, so there are likely other genes not yet described that play an important role in familial early-onset AD (AMA sheet, accessed Nov., 2013).

On the other hand, Sporadic late-onset AD accounts for the majority of all AD cases, and this form can likely be caused by anumber of gene mutations, combined with aging and exposure to environmental agents. The most well-established genetic risk factor for development of sporadic late-onset AD is inheritance of the ε4 allele of the apolipoprotein E (APOE) gene. Although the function of APOE in coronary health is well-known, its mode of action in AD progression is unknown.1 The APOE ε4 allele appears to shift onset of AD toward an earlier age.3 Over 50% of people with AD carry at least one APOE ε4 allele.2 However, the APOE ε4mutation is incompletely penetrant, meaning that presence of the mutation does not always increase risk of developing the disease, and there are likely other mutations that contribute to the development of sporadic late-onset AD. Thus, a person carrying two APOE ε4 alleles has a 30% chance of developing sporadic late-onset AD (as opposed to a 100% chance if APOE ε4 were completely penetrant and the only mutation necessary).2 First degree relatives of a person with sporadic late-onset AD have an approximately 2.5 times greater risk of developing sporadic late-onset AD than those who are not first degree relatives (AMA sheet, accessed Nov., 2013).

Guerreiro *et al.* (2014) reported that mutations in 3 genes (APP, PSEN1, and PSEN2) are known to cause AD, but a large number of familial cases do not harbor mutations in these genesand several unidentified genes that contain disease-causing mutations are thought to exist. Hence, they performed whole exome sequencing in a Turkish patient clinically diagnosed with Alzheimer's disease from a consanguineous family with a complex history of neurological and immunological disorders and identified a mutation in NOTCH3 (p.R1231C), previously described as causing cerebral autosomal dominantarteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).Their results showed that complete screening of NOTCH3 in a cohort of 95 early onset AD cases and 95 controls did not reveal any additional pathogenic mutations. They demonstrate that exome sequencingis a valid, rapid, and cost-effective tool to identify genetic mutations in complex diseases. More specifically, this technology led us to a finding that was unexpected, given the clinical diagnosis, and reveals the power of this method in differential diagnosis.

Proitsi *et al.* (2014) mentioned in their article, that the development of late onset Alzheimer's disease (AD) has a high heritability. Some of this heritability can be explained by common variants with small effect in genes such as APOE or BIN1, CR1, PICALM, CLU, ABCA7, CD2AP, EPHA1, and the MS4A cluster, which have recently emerged as reliable risk-associated genes identified and replicated in large comprehensive studies. Sherva *et al.* (2014) performed the first genome-wide study to assess genetic variants associated with cognitive rate of decline in people with AD. They identified several single-nucleotide polymorphisms (SNPs) with statistical evidence in genes that have not been previously associated with AD risk, most notablyspondin 1 gene

(SPON1), which may contain variants of which minor alleles slow disease progression by lowering the amount of extracellularAb-40.

In their review about therapeutics of Alzheimer's disease, Anand *et al.* (2014) found that Population heterogeneity-wherein the genotype of the population determines the drug response E.g. Differential response of bapineuzumab in ApoE 34carriers/non-carriers. And they asked If the early epigenetic events affect the susceptibility of an individual to AD, how do we stop that ?. Murcia *et al.* (2013) genotyped R47H (rs75932628 (R47H) variant in TREM2 is an Alzheimer's disease risk factor) in a large, population-based sample, 2974samples (427 cases and 2540 control subjects) from the Cache County study using a custom TaqManassay. They concluded that, although the population-level effects of the R47Hvariant do not approach those of the APOE ε4 allele, TREM2 has aclear and replicable effect on AD risk. one of the machanisms is that the loss-of-function caused by the R47H variant contributes to the disruption of an immune response that triggers an inflammatory response leading to neuronal cell death and might contribute to the degeneration of phagocytic pathways that aid in the clearance of neuronal celldebris. However, Proitsi *et al.* (2014) reported that it is likely that other genes, TREM2 will be added to this list once greater sequencing depth on many more persons becomes available.

In their work, Proitsi *et al.* (2014) emphasized that an increased risk of developing Alzheimer's disease (AD) has previously been found to be associated with variants at the MS4A6A locus. They sought to identify which genes and transcripts in this region have altered expression in AD and mild cognitive impairment (MCI) and are influenced by the AD risk variant(s), as a first step to understanding the molecular basis of AD susceptibility at this locus. They found that persons with MCI may lower MS4A6A expression to minimize detrimental disease associated MS4A6A activity. However, those with the susceptibility allele appear unable to decrease expression sufficiently, which may explain their increased risk for developing AD. Inhibiting MS4A6A may therefore promote a more neuroprotective phenotype, although further work is needed to establish whether this is the case.

Genetic Testing

Alzheimer's disease is the object of intense genetic analysis. Researchers have identified four mutations, or variant forms, of genes associated with the disease. Three of those genes — located on chromosomes 21, 14, and 1 — are linked to the early-onset forms of Alzheimer's in which symptoms usually begin to appear between a person's early 40s and mid-50s. If someone has one of these gene mutations, he or she will at some point develop the disease. These incidents of Alzheimer's are very rare, possibly accounting for fewer than one percent of all cases (Alzheimer's Association sheet; accessed Nov 2013). It has been suggested that the fourth gene, APOE-e4 on chromosome 19, is linked to a greater risk of susceptibility for developing late-onset Alzheimer's, the more common form of the disease that is manifested after the age of 55 and generally associated with old age. APOE-e4 is a variant form of a gene that encodes the production of a protein called apolipoprotein E, which may play a role in repairing connections between brain cells. People with one copy of APOE-e4 have a greater risk of getting Alzheimer's than people with other forms of the gene, and people with two copies of APOE-e4 have an even greater risk (Alzheimer's Association sheet; accessed Nov 2013).

Genetic testing for the mutations associated with both familial and sporadic AD is available, although the circumstances under which testing is recommended vary. When familial early-onset AD is suspected, genetic testing to detect mutations in APP, PSEN1, and PSEN2 can be performed to identify the molecular lesion. For predictive testing of family members of a patient who has been diagnosed with familial early-onset AD, the disease causing mutation must be known. Although a large number of patients with sporadic late-onset AD have at least one allele APOE ε4, the association of the mutation with the development of the disease is not strong enough to recommend that APOE genotyping be used as a predictive test in asymptomatic individuals. Instead, APOE genotyping is most useful as an adjunct diagnostic test in individuals showing symptoms of progressive dementia (AMA sheet, accessed Nov., 2013).Biomarker signatures are being developed through the use of proteomics, metabolomics, and gene expression studies, with a demonstrated lack of reproducibility across cohorts (Snyder *et al*., 2014). Snyder *et al.* (2014) reported that AD may be associated with brain gene expression signatures correlating with similar signatures in blood. However, skepticism exists concerning whether changes in gene expression in blood white cells would show any relationship to gene expression in brain, in AD, or in any central nervous system disease. Nevertheless, several gene expression-based tests as clinical diagnostics are under development and maybe potential tools for an AD diagnostic workup.

One gene marker identified to be associated with AD is TOMM40 (translocase of outer mitochondrial membrane40 homolog), which is thought to play a role in transporting proteins into the mitochondria and has been shown in several genome-wide association study (GWAS) studies to be down regulated in AD. Studies of TOMM40 gene expression in blood suggest that a down regulation of the level of expression may serve not only as a marker for AD but may also correlate with disease severity or progression (Snyder *et al*., 2014).

According to Alzheimer's Association published sheet (accessed Nov 2013), genetic testing for APOE-e4 is controversial and should only be undertaken after discussing the benefits and risks with a physician or genetic counselor. APOE-e4 increases the risk of developing Alzheimer's, but it is neither necessary (people without APOE-e4 develop the disease) nor sufficient (not all people with APOE-e4 develop Alzheimer's). Although there is no way to change one's APOE-e4 status, lifestyle modifications may help reduce the potential effects of having APOE-e4. These lifestyle modifications include eating a heart-healthy diet, exercising and staying mentally active. The risks of APOE-e4 genetic testing include anxiety if the test results are positive. However, recent large scale studies showed that anxiety is manageable with appropriate genetic counseling.

Summary

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases AD is characterized by adult-onset progressive dementia, beginning with subtle memory failure that becomes more severe and is eventually incapacitating. The most common neuropathological feature of AD is the presence of neurofibrillary tangles and amyloid deposits that form plaques and cerebrovascular accumulations. AD is divided into familial and sporadic forms. AD is considered familial when more than one person in a family is affected, while sporadic refers to AD cases when no other cases have been seen in close family members. It has been over 100 years since the first cases of AD were described, and since then much has been discovered about the molecular nature of the disease. The genetic control of complex diseases is becoming more apparent as previously unidentified mutations in the human genome are described. As the genetic control of AD is uncovered, improved therapies may also be uncovered.

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