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IP – Final Project

Understanding and Personalizing Health Care for Alzheimer's Disease

Introduction

Alzheimer's Disease (AD) is a growing healthcare concern around the world and as medicine continues to advance and life expectancies rise around the world, the number of people affected by this disease is expected to grow substantially. In the United States alone, deaths from AD totaled over 121,000 in 2017, making it the sixth leading cause of death in the country. (Alzheimer's Association, 2019). As of 2019, an estimated 5.8 million Americans were living with AD, including 1 in 10 individuals aged 65 or older (5.6 million), and it is expected that this number will grow to 13.8 million by the year 2050 (Alzheimer's Association, 2019). Along with the growing number of cases also comes huge healthcare costs. Payments for health care and health services for patients with dementia, which AD accounts for 80% of cases, was estimated to be $290 billion in the U.S. in 2019 (Alzheimer's Association, 2019). In addition to paid services, unpaid caregivers and family members provided over 18.5 billion hours of care to dementia patients which was estimated to be a value of another $234 billion (Alzheimer's Association, 2019). Despite the ever-increasing number of AD patients, diagnosing and treating the disease still remains a major challenge. Current methods of diagnosis may involve examining biomarkers though cerebrospinal fluid (CSF) and positron emission tomography (PET) tests combined with certain clinical criteria including memory loss and persistent confusion, among other signs (Weller & Budson, 2018). As more research is done and we gain a better understanding of the biomarkers involved in this disease, this could lead to less invasive and improved diagnostic tests in the future.

While diagnosing and treating AD remain a challenge, the many factors underlying this disease are beginning to be uncovered. Genetics, the environment and epigenetics have all been implicated in the development of AD. Early Onset and Familial Alzheimer's point to the role of genetics in AD and genome-wide association studies have implicated variants in over 40 genes to be associated with an increased risk (Bellenguez et al., 2020). Additionally, environmental factors including regular exercise, a healthy diet, and socialization have all been shown to reduce the risk of developing AD, even when certain genetic risk factors are present (Weller & Budson, 2018). While there are current treatment options available to suppress symptoms and improve the quality of life for both the patient and caregivers, unfortunately these treatments have no effect at slowing the progression of the disease. A number of clinical trials are currently underway looking into potential drugs that target amyloid plaque formation and hyperphosphorylated tau proteins, and hopefully these drugs will prove efficacious. However, given the many factors that have been implicated in this disease, including environmental factors, genetics, epigenetics and even dysbiosis within the gut microbiome, it may be that the best treatment options for patients in the future are considerably more personalized and target multiple aspects of this devastating disease.

Genetics and Testing for Alzheimer's

While there are many factors involved in AD, an individual's genetics can certainly have a strong impact on this disease. The genes most commonly associated with AD include APOE (alleles ε2, ε3, and ε4), amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2). AD exists in two major forms, late-onset and early-onset, and these forms are typically distinguished by an individual's

genetic makeup. The majority of cases, between 95-99%, are classified as late-onset and have a complex etiology. Over 40 genes have been implicated in the development of this type of AD (most notably APOE), however having any one of the causative variants in one of these genes or even a combination does not guarantee that an individual will develop the disease. For early-onset AD, genetics plays a much more substantial role and variants in APP, PSEN1 or PSEN2 are almost always present. All of these genes are autosomal dominant and show nearly complete penetrance. For individuals who carry a disease-causing variant in one of these genes, the chance of developing Alzheimer's is 100% if they live long enough. In terms of genetic testing for AD, considering that the vast majority of cases involve the late-onset form, it does not make sense to perform preconception carrier testing unless there is a family history of the disease. Pregnancy or prenatal testing are also not appropriate for AD given the complex etiology, the fact that there is currently no cure for the disease and the fact that it is such a late developing condition. Ultimately, Alzheimer's is a multi-faceted disease with a complex risk profile and in the majority of cases, variants in any one gene will not accurately predict development of this disease which makes genetic testing unnecessary in the vast majority of instances. However, for the small percentage of cases (1%) that are inherited in an autosomal dominant fashion, testing for certain variants in APP, PSEN1 and PSEN2 may be warranted (Goldman & Van Deerlin, 2018).

Because of this, the American College of Medical Genetics guidelines for AD genetic testing currently only includes testing individuals with a family history of early-onset AD and those who have a relative who has tested positive for one of the autosomal dominant mutations (Johnson & Vega, 2011). Despite these recommendations and the low instances of early-onset AD, there are a number of tests available for this condition. According to the genetic testing registry, there are 114 clinical tests listed under Alzheimer's disease. These include commercially available tests such as the Alzheimer Dementia and Dementia Panel offered through Centrogene which looks at the entire coding regions of the APOE, APP, PRNP, PSEN1, PSEN2, SORL1 and TREM2 genes. Another commercially available test is the Alzheimer Disease Familial Panel offered through Prevention Genetics which looks at the APP, PSEN1 and PSEN2 genes. This test offers deletion/duplication analysis, targeted variant analysis and entire sequencing of the coding regions of these genes. Invitae also has a Hereditary Alzheimer's Disease Panel which includes deletion/duplication analysis as well as sequence analysis of the entire coding regions for the APP, PSEN1 and PSEN2 genes. Given that diagnosis of AD is sometimes difficult, some physicians may decide to perform testing for variants in the four common AD genes to help make a diagnosis between Alzheimer's and Frontotemporal Dementia, as many of the clinical signs between these two conditions may overlap initially.

Family Planning & Lifestyle Changes

Although genetic testing for AD is not recommended unless there is a family history of the disease, with the rise of direct-to-consumer testing services and an increased awareness towards this disease, it is likely that many will want to know their genetic risks of developing AD. If specific genetic variants are discovered through testing this may influence an individual to make certain lifestyle changes including exercising more regularly, eating healthier including consuming more omega-3 rich foods, socializing more and trying to develop more regular sleep patterns as these have all been shown to reduce the risk of AD. If certain variants associated with the autosomal dominant form are found such as those in APP, PSEN1 or PSEN2, more regular screenings may be done to identify amyloid plaque buildup and behavioral changes at an earlier stage to provide for quicker intervention. These results could also make patients eligible as candidates for any current or upcoming clinical trials. Due to the complexity of the disease, it is unlikely that most variants, if present, would impact any decisions on family planning. If,

however an individual is a carrier for one of the autosomal dominant variants, their offspring would have a 50-50 chance of developing the disease and this may impact family planning.

The Role of the Environment and Epigenetics in AD

Environmental factors play a significant role in the overall structure and function of the brain and many studies have shown that these factors can significantly impact the probability of AD development. Diet, exercise, sleep patterns and socialization have all been implicated in AD, however the exact mechanism by which some of these factors result in disease is not entirely understood and it is unclear how or if they affect an individual's epigenome (Bartolotti & Lazarov, 2016). Nutritional elements such as EGCG and curcumin have been shown to regulate neprilysin activity, an enzyme which is responsible for amyloid beta breakdown (Bartolotti & Lazarov, 2016). Other nutritional elements such as resveratrol may play a role in tau pathology by regulating the activity of the protein responsible for its hyperphosphorylation, GSK3-β (Bartolotti & Lazarov, 2016). Cognitive stimulation in rodents has also been shown to increase neprilysin activity and decrease GSK3-β activity, both of which can decrease the likelihood of AD development. Chemicals including some pesticides can increase APP and amyloid beta levels while metals such as copper have been found to decrease neprilysin levels leading to an accumulation of amyloid beta (Bartolotti & Lazarov, 2016). These many factors show that the environment can indeed have an effect at the genomic level in AD pathology. However, whether or not they are changing the epigenetic landscape in AD patients is still not completely understood.

A number of epigenetic mechanisms have been linked to AD from aberrant DNA methylation to non-coding RNA (ncRNAs) regulation to distinct histone modification patterns. In a recent study by Nativio et al., they used transcriptomics and epigenomic profiling to study histone modifications specific to AD. The study showed that histone acetyltransferases were upregulated in AD brains and there were increases in the histone H3 modifications H3K27ac and H3K9ac in genomic regions linked to the disease pathways associated with AD (Nativio et al., 2020). In addition to histone modification, aberrant DNA methylation in a number of genes important to the development of AD have also been implicated in disease development. Methylation of the microtubule-related protein tau (MAPT) can suppress its expression and alter tau protein levels and has been found in AD patients (Liu et al., 2018). Additionally, demethylation of the APP gene, which typically occurs with age, may lead to amyloid beta filament deposition in the brain (Liu et al., 2018). Finally, many ncRNAs have been found to be dysregulated in AD including a number of microRNAs. Members of the miR-29 family are decreased in patients with AD and this has been shown to result in high BACE1 gene expression levels (Liu et al., 2018). BACE1 encodes a transmembrane protease that is active in the formation of amyloid beta peptides. Other studies have shown increased levels of miRNA-7, miRNA-9, miRNA-23a, miRNA-27a, miRNA-34a, miRNA-125b, miRNA-146a, and miRNA-155, all of which play a role in amyloid development and clearance (Liu et al., 2018). Taken together, these alterations not only suggest that AD includes a reconfiguration of the epigenome, but also that these epigenetic alterations may be a driving force behind disease development. Understanding the role of epigenetics in AD and being able to identify which of these epigenetic alterations are present within individual patients may one day lead to the development of personalized epigenetic treatments for this devastating disease.

Transcriptomic, Proteomic and Metabolomic Alterations in AD

Determining which genes are differentially expressed is important in understanding the pathological mechanisms underlying any disease. In patients with AD, a number of transcriptomic changes have been found which may directly contribute to disease onset and/or progression. Single-cell expression studies have found a number of genes to be associated with neurofibrillary tangle pathology including upregulation of casein kinase 2, beta polypeptide (CSNK2B), apolipoprotein J (APOJ), and tissue inhibitor of metalloproteinase 3 (TIMP3) (Bagyinszky et al, 2020). More large-scale studies have also shown specific transcriptomic signatures present within AD patients including downregulation of pathways involved in ubiquitination and synaptic transmission along with upregulation of mitogen-activated protein kinase (MAPK) and JAK/STAT signaling pathways. Ultimately, knowing the impact of transcriptomic changes in AD may help to improve upon disease diagnosis methods and aid in the development of better, more personalized therapies going forward (Bagyinszky et al, 2020).

Proteins have long been known to be a driving force behind the pathological decline associated with AD. Specifically, aggregation of amyloid and tau proteins leads to the characteristic plaques and neurofibrillary tangles present in AD patients. Investigating the proteome of AD patients has shown increased levels of the acetyl-CoA acetyltransferase (ACAT2) and mitogen activated protein kinase 1(MAPK1) proteins, both of which are actively involved in the formation of tau proteins (McKetney et al., 2019). Other proteome changes, including increases in the levels of CNR1, NEC2, NPTX2, and SMS have also been found (Dayon et al., 2018). All four of these proteins have been associated with higher levels of beta-amyloid peptides in AD patients. There are currently promising treatments in clinical trials which specifically target amyloid and tau proteins.

As with transcriptomics and proteomics, changes within the metabolome are also associated with AD and these changes have been found in both the blood and through post-mortem brain tissue analysis. In a study looking at both blood and brain metabolite levels, it was found that higher serum levels of three acylcarnitines, including decanoylcarnitine, pimelylcarnitine, and tetradecadienylcarnitine, were associated with a significantly lower risk of developing AD (Huo et al., 2020). Besides predicting risk of developing AD, changes in ten glycerophospholipids and five acylcarnitines may also predict long-term changes in cognitive function among AD patients (Huo et al., 2020). This study also found 28 metabolites within post-mortem brain tissue to be associated with AD phenotypes, including metabolites belonging to the classes of acylcamitines, amino acids, biogenic amines, and glycerophospholipids (Huo et al., 2020). The levels of two potentially important metabolites, symmetric dimethylarginine (SDMA) and threonine, were shown to be positively associated with all AD phenotypes examined. While there are clearly metabolic disturbances at play with the AD, how these changes directly affect pathogenesis at the molecular level and which metabolites can be used as the best predictive biomarkers of this disease has yet to be determined. However, identifying specific metabolite levels within individuals may one day allow for more personalized preventative measure to be taken either through diet alterations or by other means.

The Relationship Between an Individual's Microbiome and AD

A healthy microbiome is a critical component in cognitive functioning and there have been many studies that have found alterations between the gut microbiome of normal, healthy individuals and patients with AD. One area in particular where intestinal bacteria can impact AD is in immunomodulation, specifically by influencing inflammation levels within patients. Inflammation is an

important aspect of AD pathogenesis because as this disease progresses, excessive inflammation caused by an overactive immune response can end up killing neurons. Lipopolysaccharides found within bacterial cell membranes have been shown to enter into the bloodstream and activate inflammatory processes which can contribute to the pathology of AD (Ellison, 2018). Besides influencing inflammation, the metabolites produced by intestinal bacteria can also play a role AD pathogenesis. Amyloid produced by intestinal bacteria can also enter into the bloodstream and eventually cross the blood-brain barrier leading to its accumulation within the brain (Ellison, 2018).

A large-scale study examining the microbiome composition of AD patients versus non-dementia patients, not only found differences between the species present, but also linked these differences to inflammatory mechanisms (Haran et al., 2019). This study found that AD patients had lower relative abundance levels of key butyrate producing bacterial species, such as members of the Butyrivibrio, Eubacterium, and Clostridium genera (Haran et al., 2019). Butyrate is believed to help in the maintenance of the gut barrier and has anti-inflammatory properties. Lack of butyrate may allow higher levels of amyloid and lipopolysaccharides to be released into the bloodstream, exacerbating AD symptoms. This study also found that AD patients had greater levels of specific bacterial species known to be associated in certain AD pathways including O. splanchnicus, K. pneumoniae, B. fragilis, and E. lenta (Haran et al., 2019). Considering the dysbiosis that exists with this disease and its impact on pathogenesis, it may be possible to administer personalized probiotic treatment that targets these imbalances with the goal of reducing inflammation, improving symptoms and perhaps slowing progression of the disease.

Pharmacogenomics in Current and Future Treatment Options

The field of pharmacogenomics has begun to shed light on how an individual's genetic makeup can significantly impact their response to certain drugs by affecting how quickly they clear and process different drugs. For patients with AD, pharmacogenomics is expected to become increasingly more relevant as we begin to understand the role that genetics may play in current and future treatments. Currently, there are only two FDA approved treatment options for Alzheimer's, the cholinesterase inhibitors and the N-methyl D-aspartate (NMDA) antagonist, memantine. Both of these treatments are used in patients with the mild to moderate form of the disease and neither is curative, but instead are used to help alleviate symptoms. Approved cholinesterase inhibitors include donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon), each of which may be impacted by an individual's genetics. Common side effects of these drugs include nausea, vomiting, diarrhea, muscle cramps, fatigue, and weight loss and as of now, the dosage of these drugs is typically adjusted based off each individual's response. However, screening for certain variants beforehand may help to avoid some of these potential side effects. For donepezil and galantamine, variants in both CYP2D6 and CYP3A4 can affect drug clearance and efficacy. Variants in CHRNA7, CHAT, BCHE and ACHE may influence a patient's response to the drug rivastigmine and variants in the NR112 gene may affect a patient's ability to clear memantine. As the associations between genetics and drug response continue to expand this may help to better tailor treatment decisions to each individual in the future. While currently approved treatments can only improve symptoms, there are a number of drugs that have shown promise in curing AD in clinical trials including anti-amyloid, anti-tau therapies and BPSD-relieving therapies. Anti-amyloid therapies in clinical trials now include *Aducanumab*, *Donanemab*, *Crenezumab*, *Gantenerumab*, and *Solanezumab* (Huang et al., 2020). Promising anti-tau therapies (*Zagotenemab* and AADvac1) and BPSD-

relieving therapies (AXS-05, *Lumaterperone* and *Apiprazole*) are also in clinical trials (Huang et al., 2020). When and if these therapies become approved, pharmacogenomics will likely become important in optimizing personalized treatment decisions and drug dosages.

Summary

Alzheimer's disease is a devastating condition affecting millions and is projected to become increasingly more prevalent due to longer life expectancies and aging populations around the world. While it is difficult to diagnose and there is currently no curative treatment, recent research Is beginning to shed light on the many factors influencing this condition including the roles that genetics, epigenetics, and the environment may play. The genetic component can involve variants in as many as 40 different genes, with the most common being those in the alleles ε2, ε3, and ε4 of the APOE gene along with the APP, PSEN1 and PSEN2 genes. Preconception carrier testing is available for individuals with a family history of early onset Alzheimer's and typically involves testing for variants in the APP, PSEN1 or PSEN2 genes, all of which are autosomal dominant and have nearly complete penetrance. For these individuals a positive result may impact lifestyle choices and family planning given the nearly 100% chance of disease development. However, given the overall complexity of the condition, in the majority of cases, testing, including pregnancy and prenatal testing, is typically not warranted nor is it recommended. Epigenetic alterations including histone modifications and specific DNA methylation patterns are known to be important in the formation and clearance of both amyloid and tau proteins and may even be a driving force behind disease development. Whether environmental factors specifically affect these epigenetic processes is not entirely clear, though the role of such factors as diet, exercise, sleep patterns and socialization have long been linked to the development of AD. Significant transcriptomic, proteomic and metabolomic changes have also all been associated with disease onset and progression and highlight the complexity of this condition. The role of the gut microbiome is also well-documented in impacting disease pathogenesis, particularly through immunomodulation and inflammatory processes. Cholinesterase inhibitors are currently the most common treatment option available for AD patients and variants in the cytochrome P450 genes, particularly CYP2D6, can affect both the efficacy of these drugs and how fast they are cleared. However, because drug dosages are typically adjusted based off patient response, pharmacogenomics is not particularly relevant in current prescribing practices, but with potential new treatments on the horizon such as anti-tau and anti-amyloid therapies, this may change in the future. Considering all of the factors involved, future treatment options are likely to become significantly more personalized as options become available to target any one of the many factors that may be impacting disease development and progression. As it currently stands, lifestyle changes which focus on increasing socialization and exercise, improving sleeping habits and consuming a more nutritional diet are the best options available for those who wish to decrease their chances of developing AD.

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