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Neurogenetics: Precision Medicine-Based Approaches to Neurological Disorders with an Emphasis on Addressing Alzheimer's Disease and Schizophrenia

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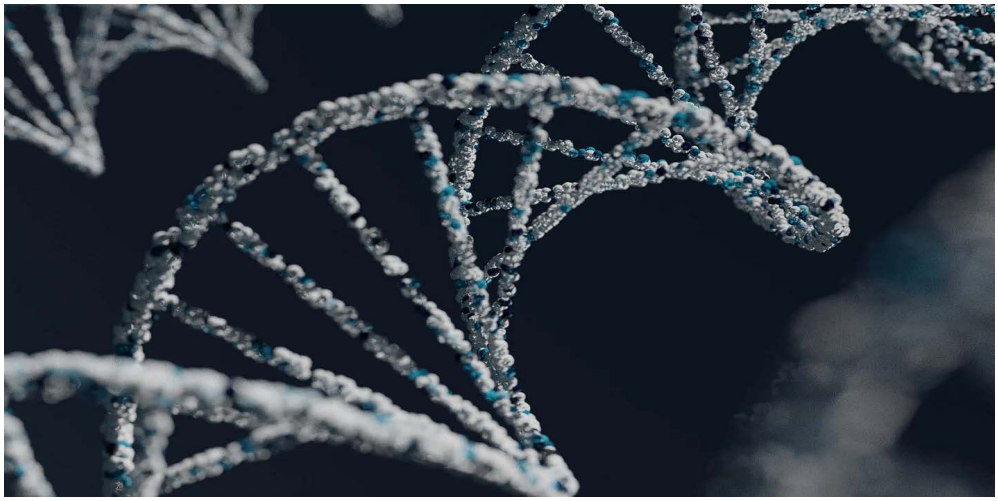

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Precision Medicine, Alzheimer's, Schizophrenia, iPSC, Pharmacogenomics, Genetic Profiling, Neurological Disease

Abstract

There exist over 600 neurological conditions, each characterized by unique pathologies tailored to individual patients. Over the past two decades, advances in biotechnology have propelled the field of neurogenetics forward. This progress has illuminated therapeutic targets and methodologies tailored to the specific needs of each patient. Current treatment options primarily encompass therapies and conventional medications like cholinesterase inhibitors for Alzheimer's disease and antipsychotics for schizophrenia. However, these treatments often address symptoms or general targets rather than the precise underlying causes. Precision medicine has emerged as a promising approach in both animal and human clinical trials. Examples include the identification of specific genetic variations linked to Alzheimer's risk and progression, as well as the application of multigenic pharmacogenomics-guided therapies for schizophrenia patients. This review paper delves into the role of precision medicine in neurogenetics, focusing on neural stem cells, induced pluripotent stem cells (iPSCs), genetic profiling, and pharmacogenetics within the contexts of Alzheimer's disease and schizophrenia. By evaluating current achievements alongside existing challenges, this paper underscores precision medicine as a pivotal strategy for effectively targeting neurological disorders.

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1. Introduction

As we delve into the secrets of the human mind, one thing becomes abundantly clear: our genes hold the key to understanding the most profound mysteries of consciousness. Neurogenetics is employing the evolving field of genomics–the study of our genes and genetic variations–to understand factors contributing to the structure and function of the nervous system.[1] Specifically, neurogenetics also seeks to understand how alterations in genes can lead to neurological diseases and conditions. As researchers continue to uncover various genetic factors for each disorder, precision medicine has started to address neurological diseases.

Precision medicine is an approach to therapeutics that uses an individual's genomic, environmental, and lifestyle information to form decisions about their treatment.[2] Often informally termed as personalized medicine, precision medicine can be used to create a more precise approach to diagnose, prevent, or treat a disease. The basis behind precision medicine is substantial because the human genome consists of about 3 billion base pairs of DNA, and no two humans are genetically identical, with genetic variation of about 0.1percent.[3] This means that about 6 million base pairs differ, making it necessary to understand genetic variation. Oftentimes, these variations occur as single-nucleotide polymorphisms, or single-base pair differences.[3] To target these various genetic risk factors, techniques of precision medicine such as drugs tailored to genomic or metabolomic targets and induced pluripotent stem cells (iPS) are promising methodologies.

While understanding the hallmark genes of neurological disorders through neurogenetics studies may help create therapeutics for these genes, many studies tend to exclude non-White individuals. Research involving diverse populations reveals varying prevalence rates of risk genes for Opioid Use Disorder (OUD) based on ethnicity, with specific genetic variations being linked to susceptibility in Caucasian individuals but not in African-American or Hispanic populations.[4] This evidence suggests that there are larger implications in other neurogenetic diseases such as Alzheimer's disease and Schizophrenia. There exist multiple polymorphisms in a diverse society, making neurogenetics a complicated field. We ought to

adopt precision medicine-based management through analyzing ancestry-based genetic information to provide the best precision-guided therapeutics. Variance in neurogenetics presumes the need for precision medicine to target genetic risk factors with tailored medicine specific to the patient with neurological diseases, such as Alzheimer's disease and schizophrenia. We present our evaluations by analyzing scientific literature on varied neurological disorders and diseases and their basis in neurogenetics, reviewing the scientific literature for recent advances in precision medicine, and examining clinical trials to understand the potency of precision medicine techniques in neurological conditions.

2. Variance in Neurogenetics

2.1 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive and irreversible neurological disorder that affects the brain, leading to a decline in memory, thinking, and ability to carry out simple tasks.[5] This decline in cognitive ability hasn't been attributed to a specific cause due to the complexity of the genetic and environmental causes of this disease.

2.1.1 Amyloid Beta (Aβ): Formation of Amyloid Plaques

β- amyloid proteins are known to be one of the main culprits of Alzheimer's Disease. They collect between neurons and inhibit neuronal function, and some molecular forms of these defunct proteins form plaques that are extremely detrimental to neuronal activity.[6]

2.1.2 Tau Protein: Formation of Neurofibrillary Tangles

Neurofibrillary tangles are clusters of abnormal proteins called tau which accumulate within nerve cells.[6] In healthy neurons, microtubules provide internal support for the function of transporting nutrients and molecules from the cell body to the axon and dendrites.[6] Tau usually binds to and stabilizes these microtubules; however, in AD, chemical changes cause tau to detach from microtubules and adhere to other tau molecules, forming threads.[6] These amalgamate to form tangles within neurons, disrupting the neuron's transport system and impairing synaptic communication.[6]

Evidence has shown that these plaques and tangles are associated with the occurrence of Alzheimer's disease, as represented in Figure 1, and that the occurrence of either plaques or tangles can cause the formation of the other.[6]

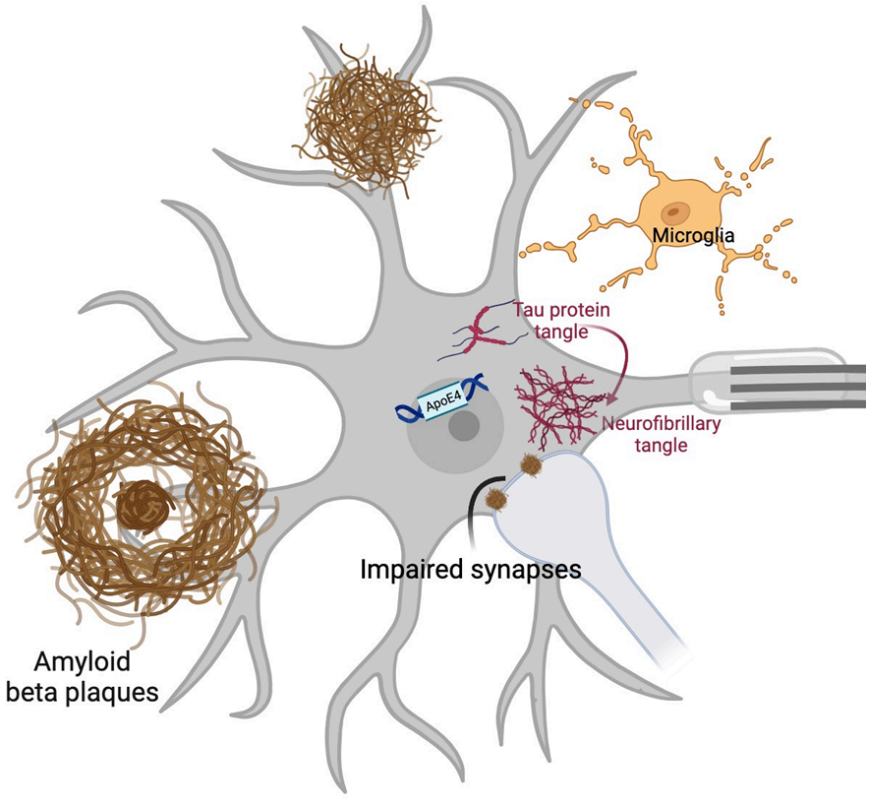

Figure 1. A visual representation of Alzheimer's disease manifests in patients because of genes that are prime targets for precision medicine techniques. The result of mutations or rare variants in certain genes, such as *ApoE4,* can have many harmful effects that manifest as Alzheimer's disease.[9]

2.1.3 Glial Cell interaction with Aβ

Microglia act as immune cells that monitor the brain for signs of damage, infection, or foreign substances.[7] When threats are detected, they activate and engulf via phagocytosis, cellular debris, aggregated proteins, etc.[7] Microglia have the ability to detect the presence of Aβ in the brain.[8] When encountered with Aβ plaques in healthy cells, they become reactive, indicating they are responding to abnormal protein accumulation.[8] Microglia in which Aβ has a direct interaction expresses a range of

structurally diverse molecules, including TREM2, CD33, CD35, etc.[8] These receptors are responsible for recognition and response to Aβ.[8]

2.1.4 Current target genes

APOE4: This gene variant is a risk factor for Alzheimer's disease. APOE expression produces a protein that helps move cholesterol in the bloodstream.[9] While the exact mechanism of APOE4 is not fully known, difficulties with a brain cell's ability to process fats may play an important role in Alzheimer's disease.

APP: This gene encodes amyloid precursor protein, the precursor for amyloid-B peptides.[10] The cleavage of APP forms amyloid beta plaques which aggregate in the brain in AD.

PSEN1 and PSEN2: These genes encode for a large component of the protein y-secretase, which is responsible for splicing and processing of APP to form amyloid B peptides.[11] The accumulation of amyloid beta plaques is prominently seen in those with AD.

TREM2: (Triggering Receptor Expressed on Myeloid cells 2): This gene provides instruction for a cell surface receptor found on microglia, immune cells in the brain. Variations in TREM2 have been associated with an increased risk of developing AD. TREM2 is responsible for various functions in microglia including cell survival, phagocytosis, etc.[12] Reports indicate that TREM2 deficiency results in the decreased presence of microglia around Aβ plaques.[12] Due to the plethora of mutations within the TREM2 gene resulting in the progression of AD, precision medicine can help target specific genetic subgroups. By catering to these specific TREM2 mutations, a more effective treatment plan can be constructed.

2.1.5 Current treatments for Alzheimer's Disease

The current treatments for Alzheimer's include cholinesterase inhibitors (Donepezil and Galantamine), antipsychotics (Brexpiprazole), and disease-modifying immunotherapies (Lecanemab and Aducanumab).[13] Besides the immunotherapies, these medications address the symptoms of Alzheimer's Disease rather than attacking the disease at its source. Meanwhile, the immunotherapies help remove amyloid plaques, but do not

stop the plaques from accumulating or the amyloids from forming. As revealed by extensive research, the pathophysiology of AD is incredibly nuanced with various factors. Current treatments are not a cure-all; more targeted treatments personalized to the root causes for each patient are necessary for prevention and mitigation.

2.2 Schizophrenia

Schizophrenia, unlike neurodegenerative diseases like Alzheimer's disease, is a neurological disorder commonly known as a mental illness impacting how a person acts, feels, and behaves, thus not only affecting themselves, but also the individual's relationships with those around them.[14] Coined by Eugen Bleuler in 1908, schizophrenia in more professional terms is a functional psychotic disorder characterized by the experience of delusional beliefs, hallucinations, and disturbances in thought, perception, and behavior.[15] Schizophrenia can be diagnosed through classification systems, of which the Diagnostic and Statistical Manual of Mental Disorders 4 (DSM-4) and International Classification of Diseases (ICD-10) are most commonly used. For the DSM-4:

> Two or more of the following symptoms must be present for a significant portion of time during a one-month period[16]:
>
> - Delusions
> - Hallucinations
> - Disorganized speech
> - Grossly disorganized or catatonic behavior
> - Negative symptoms.

There must also be social/occupational dysfunction. Continued negative symptoms and disturbances must last for at least six months, with at least 1 month of active-phase symptoms described above. On the other hand, the ICD-10 has sub-categories for schizophrenia based on presenting symptoms:

One of the following symptoms, for a period greater than or equal to a month:

- Thought insertion, echo, broadcast, or withdrawal
- Delusions of control, influence, or passivity
- Hallucinatory voices providing a running commentary of the patient
- Persistent delusions that are culturally inappropriate or implausible

Or, at least two of the following symptoms for a period greater than or equal to a month[16]:

- Persistent hallucinations in any modality when accompanied by fleeting delusions
- Breaks of interpolations in thought resulting in incoherence or neologisms
- Catatonic behavior
- Negative symptoms
- Significant and consistent transformation in the overall quality of behavior manifesting as anhedonia and social withdrawal

These detailed criteria allow for further characterizing schizophrenia into paranoid schizophrenia, hebephrenic schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, post-schizophrenic depression, residual schizophrenia, and simple schizophrenia.[16] Schizophrenic symptoms can be classified as positive symptoms, including hallucinations, delusions, and formal thought disorders, and negative symptoms such as anhedonia, poverty of speech, and lack of motivation.[15]

2.2.1 Pathophysiology

The neurochemical abnormality hypothesis credits imbalance in dopaminergic, serotonergic, and alpha-adrenergic hyperactivity or glutaminergic and GABA hypoactivity.[15] Another hypothesis includes the involvement of the four main dopaminergic pathways with the highs resulting from hyperactive D2 receptors via the mesolimbic pathway. This theory also attributes motor symptoms to low dopamine levels in the nigrostriatal pathway due to how the extrapyramidal system is affected.[15] Reduced mesocortical dopamine levels in the mesocortical pathway result in negative symptoms.[17] Research has demonstrated the exacerbation of positive and negative symptoms in schizophrenia from NMDA receptor antagonists, shining light on the potential role of glutamatergic hypoactivity.[18] Neuroanatomically, a ventricle enlargement and reduction of gray matter volume is typical in patients with schizophrenia.[17]

The genes neuregulin (NGR1) and dysbindin (DTNBP1), which are involved in glutamate signaling and glutamate release, have been implicated respectively, as well as a gene polymorphism that regulates dopamine function known as catecholamine O-methyltransferase (COMT).[15] Higher levels of the immune protein C4 are also linked to an increased risk of developing the condition.[19] Interestingly, other factors such as advanced paternal age and the association with auto-immune diseases have been recent epidemiological findings for increased risk of schizophrenia.[20]

2.2.2. Current treatments for Schizophrenia

Mainstream medications for schizophrenia include an oral second-generation antipsychotic (SGA) such as aripiprazole, olanzapine, risperidone, quetiapine, asenapine, lurasidone, sertindole, ziprasidone, brexpiprazole, molindone, iloperidone, etc.[14] Benzodiazepines such as diazepam, clonazepam, or lorazepam may also be prescribed to control behavioral disturbances and non-acute anxiety.[14] Apart from medication, cognitive behavioral therapy (CBT) can be used to address anxiety, depression, speech disabilities, and psychosis.[14] However, while these medications aim to target specific neurotransmitters or certain symptoms, they fail to target the root issues that may emerge in different ways for each patient. With multiple different factors, neurological conditions such as schizophrenia cannot be addressed with a blanket solution. Advances in

research uncovering schizophrenia pathophysiology reveal modulated receptors and neurotransmitters as possible targets for precision medicine through various methods, such as gene editing, pharmacogenomics, and iPSC models.

3. Precision Medicine

Precision medicine (PM)stands as a transformative paradigm, especially in neurology where diseases can exhibit dynamic and ever-changing characteristics. Neurogenetic disease, influenced by the diverse genetic, environmental, and stochastic factors, eventually leads to aberrant biological pathways that unfold at varying rates. This variability is further compounded by compensation mechanisms, resulting in subtle changes in physiological functions and behavioral performance. In the realm of neurology, PM has the potential to revolutionize healthcare by shifting the focus from diagnostic work-ups and therapeutic interventions after clinical manifestation to proactive prevention and health prolongation serving as a screener, changing expectations toward prevention, and prolonging health.[21]

It should be recognized that current applications have limitations in regard to diversity that exists within the human genome. Future integration of genome databases that reflect the global population could change how precision medicine is administered universally and remove some of the barriers that currently exist within the field.[21] Rather than intervening therapeutically only when diseases manifest clinically, PM enables time-sensitive detection and diagnosis. Treatment strategies can be tailored based on an individual's unique clinical, genetic, and biological characteristics, minimizing the risk and cost of unnecessary medical interventions, as demonstrated in Figure 2. Molecular changes, often the target of treatment, can be specifically addressed through PM, providing a more effective and efficient healthcare approach.

The proposed workflow for PM in neurology involves a comprehensive approach to data collection, integration, and clinical decision-making.[22] System biology and systems neurophysiology serve as major data sources, incorporating information from various modalities, including MRI, PET, genomics, cytomics, and proteomics. Digitally enabled data collection

systems and large-scale population genomic analyses, such as genome-wide association studies (GWAS), contribute to a holistic understanding of neurological diseases and are part of the model. Digital Data, GWAS, Systems Biology, and Systems Neurophysiology are then integrated using the three key steps–data generation, data integration, and clinical approach–that form the foundation of PM in neurology. AI plays a crucial role in facilitating time-dependent analysis, longitudinal tracking, and clinical decision-making, addressing the complexity and diversity of neurological diseases. By analyzing this data on a population scale, researchers can identify patterns, correlations, and genetic markers associated with neurological diseases. This comprehensive approach allows for a deeper understanding of the complex interplay between genetics, environment, and disease manifestation. Moreover, it enables researchers to uncover potential biomarkers, risk factors, and novel therapeutic targets, thus providing a more holistic view of neurological disorders beyond just their symptoms or genetic components.

The data system operates by collecting, storing, and analyzing vast amounts of genomic and clinical data from diverse populations. Through sophisticated algorithms and analytical techniques, researchers can identify genetic variants associated with neurological diseases, understand their underlying mechanisms, and predict disease risk in individuals. This knowledge can inform personalized treatment approaches tailored to a patient's genetic profile, lifestyle, and environmental factors, leading to more effective diagnoses and treatment plans for neurological conditions.

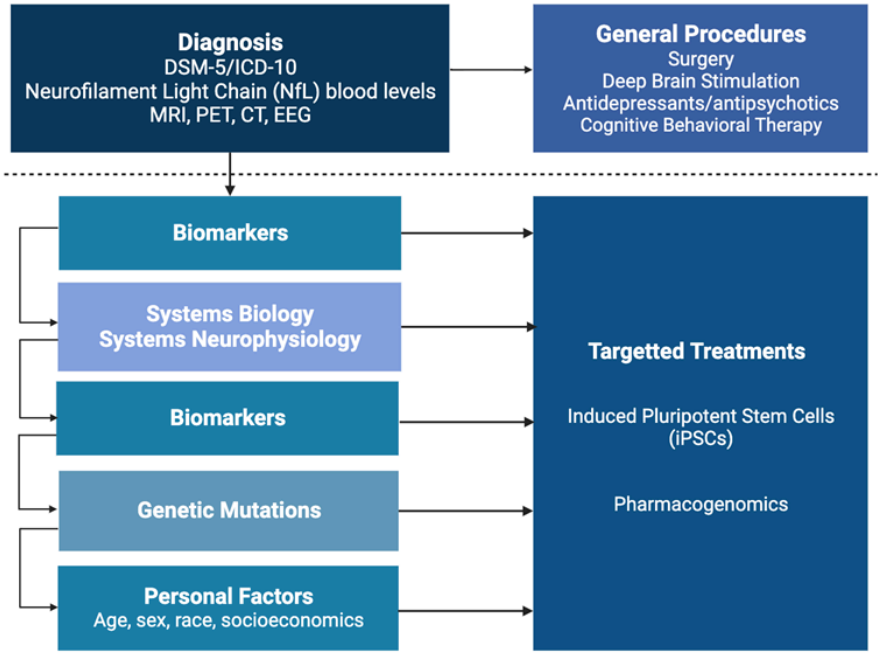

Figure 2. A diagram showing how precision medicine differs from traditional medicine by designing treatment plans that are individualized to target the specific patient. The use of general procedures versus targeted treatments is at the discretion of the physician and the availability of treatment plans for that particular patient, As the field advances, targeted treatment plans are expected to be more prevalent, providing a more holistic approach to addressing neurological disease.

4. Challenges and Limitations of Precision Medicine

Despite the promises of PM, there are notable challenges and limitations. "Black box" medicine refers to untransparent computational models in healthcare decision-making.[23] Traditional approaches rely on explicit understanding of biological mechanisms such as through clinical trials, whereas "black box" medicine utilizes large-scale datasets and sophisticated algorithms to uncover complex and often hidden relationships among multiple patient characteristics. Unlike traditional personalized medicine, which relies on explicit understanding of simple relationships, "black box" medicine delves into intricate networks of variables, such as observable factors like age and sex, as well as less obvious ones like genomic markers. "Black box" medicine represents a shift towards leveraging the power of big data and advanced algorithms to improve healthcare outcomes, but it requires careful navigation of technical, ethical, and regulatory complexities.

First, the "black box" issue in the underlying AI models raises immense concerns about the lack of transparency and understanding of model outputs.[23] Current AI approaches may reveal systems complexities without elucidating the underlying reasons, making interpretation and clinical decision-making difficult. Data standardization and curation challenges can also arise, particularly in large-scale, multimodal data collection and monitoring.

Addressing the complexities of algorithms in precision medicine necessitates a multifaceted approach. Transparency and interpretability are crucial for understanding algorithmic decisions, even in black-box systems. Rigorous validation and evaluation procedures ensure reliability and effectiveness, while ethical considerations guide fair and equitable outcomes. Regulatory oversight, continual monitoring, and interdisciplinary collaboration further enhance algorithmic development and deployment. By navigating these challenges thoughtfully, stakeholders can harness the potential of algorithms to advance precision medicine while safeguarding patient interests and promoting public health.[23]

Additionally, the transition from gene-gene association analyses to multi-omics analyses in systems biology poses difficulties that must be addressed for the effective implementation of PM in neurology.[23] Furthermore, the successful implementation of precision medicine encounters several other hurdles, encompassing ethical considerations, the impact of stigma, and potential issues related to cost-effectiveness. Ethical components crucial to the correct application of precision medicine involve confidentiality and privacy concerns, particularly regarding the analysis of massive datasets.[24] This requires the development of a robust ethical-legal framework to ensure secure data sharing. Both public and self-stigma could influence the acceptance of precision medicine, potentially affecting public health policies and patient participation.[24] The problem of cost-effectiveness in precision medicine lies at the intersection of evolving medical technologies and economic evaluations. While precision medicine holds the promise of tailoring treatments to individual patients, the economic viability of these interventions faces multifaceted challenges. Economic evaluations, typically assessing the cost per quality-adjusted life year (QALY) gained, encounter difficulties in capturing the true value of precision

medicine.[25] The scarcity of robust clinical and cost data, particularly in real-world settings, poses a significant hurdle. Additionally, the lack of standardized willingness-to-pay thresholds and the varying perspectives adopted in economic analyses contribute to the ambiguity surrounding the cost-effectiveness of precision medicine.[25] This all raises questions about the long-term sustainability of these approaches in public healthcare.

5. Specific strategies and methods

5.1 iPSC

With rapid and advanced-paced technology, new avenues have opened to treating neurogenetics disorders with stem cell treatment. For example, induced pluripotent stem cells (iPSC) are a type of stem cell derived from adult cells that have the potential to develop into different types of cells in the body.[26] These cells are created through a process called reprogramming which involves the introduction of specific genes into a specialized cell to reprogram it back to a state similar to that of an embryonic stem cell. Because these iPSCs are derived from the patients themselves, genetic information and characteristics unique to the individual can be transferred to the newly reprogrammed stem cell. By personalizing therapies, scientists can work toward creating treatments targeting specific underlying causes. An ongoing clinical trial derives iPSCs from somatic cells from individuals with neurological disease in hopes of creating a line of cells for modeling diseases and drug discovery.[27]

5.1.1 Alzheimer's Disease (AD)

Studies show iPSCs have enormous potential for treating neurological diseases such as Alzheimer's Disease and Schizophrenia.[28] In one study iPSCs derived from autologous, mouse skin fibroblasts injected into subiculum resulted in the decrease of alpha beta plaques deposition and beta/gamma secretase activity. These mouse models have immense impact in understanding the underlying mechanisms for AD; however, while mice are evolutionarily similar to humans, stark differences remain due to only 50% of microglial genes being identical between the two species.[29] Due to such limitations of modeling age-related neurodegenerative aspects of AD in dividing cells of mice, ongoing efforts focus on optimizing protocols for

the creation of induced pluripotent stem cells (iPSCs) tailored for human applications.

5.1.2 Schizophrenia

One study used human induced pluripotent stem cells (hiPSC) from individuals with high genetic risk for schizophrenia and those without, and found differences in how these cells behaved and functioned in people with schizophrenia. These differences in cell behavior matched some of the main symptoms seen in people with schizophrenia.[30] The identification of neurophysiological measures via hiPSC associated with the patient's personal clinical characteristics is significant for generating novel therapeutics.

5.2 Genetic Profiling

Genetic profiling involves studying an individual's DNA to identify specific variations (mutations or polymorphisms) in genes associated with neurological disorders.[31] Identifying specific genetic variations associated with the disease allows for personalized risk assessment.

5.2.1 Alzheimer's Disease

Specific genetic variations associated with Alzheimer's risk or progression can provide valuable information about a person's susceptibility to Alzheimer's and their risk of developing the disease, allowing for a personalized approach to treating the neurodegenerative disease. For example, certain variations in genes like APOE and mutations within the PS-1, PS-2, and APP genes are known to increase the risk of developing Alzheimer's in families with multiple individuals affected by AD. Studying these variations helps estimate an individual's likelihood of developing Alzheimer's based on their genetic makeup, allowing for implementation of proactive measures and lifestyle changes that may help reduce the risk or delay the onset of Alzheimer's. An example of this approach can be seen through genetic linkage analysis, where the researchers investigated the influence of the APOE, APP, PS1, and PS-2 genes on the increased risk of AD in families where multiple individuals were already diagnosed with the disease.[32]

5.2.2 Schizophrenia

Schizophrenia is believed to have a complex genetic component.[33] By studying an individual's genetic makeup, researchers aim to identify specific genetic markers or variations that may increase the risk of developing schizophrenia. This information can be used to provide personalized risk assessments, allowing for early preventative measures. One study used RNA sequencing (LCM-seq) on a specific area called the granule cell layer in the hippocampus, which is important for memory.[34] This area mainly has a type of brain cell called granule neurons, and they make up a small part of the whole hippocampus. Problems with these neurons have been linked to conditions like bipolar disorder and schizophrenia. The results posed a clear picture of which gene variants pose a risk for schizophrenia compared to more general methods.

5.3 Pharmacogenomics

Pharmacogenomics involves studying how an individual's genetic makeup influences their response to medications.[35] Genetic variations can affect how drugs are absorbed, metabolized, and utilized in the body. Tailoring drug choices maximizes effectiveness and minimizes side effects. This method helps identify drugs that may not be well-tolerated by a specific individual due to their unique genetic makeup.

5.3.1 Alzheimer's Disease

In the context of Alzheimer's, pharmacogenetics is crucial for optimizing medication selection and dosages. Studies have shown how an AD patient's biological response to drugs depends on specific gene clusters that influence how drugs are received in the body.[36] Pharmacogenetic research indicates that the effectiveness of drug therapies for Alzheimer's Disease (AD) varies depending on genetic makeup, which is closely linked to gene clusters associated with pharmacogenetic processes. In the course of the study, a significant proportion of AD cases exhibit an accumulation of 15 to 26 defective pharmagenes, affecting the metabolism of drugs through enzymes. Pharmacogenetics holds promise in enhancing drug development and maximizing the effectiveness of available therapeutic options for AD by optimizing patient care and therapeutic outcomes.[37]

Leveraging pharmacogenetics can enhance the efficiency of drug development and maximize the constrained therapeutic resources dedicated to Alzheimer's disease (AD). This approach enables the personalized utilization of anti-dementia medications, both independently and in combination with other drugs tailored to address concurrent disorders.

5.3.2 Schizophrenia

Schizophrenia can be treated through utilizing pharmacogenomics to analyze how genetic variations influence an individual's response to medications commonly used to treat the disease, such as antipsychotic drugs. This enables the selection of drugs and dosages that are most effective while minimizing potential side effects. While antipsychotics are the main treatment for Schizophrenia, many have adverse reactions towards these medications and the alternative is to use a trial and error method to find an effective treatment plan. The drawbacks to this are delays in treatment and overall worsening the disease condition. One study aimed to research the therapeutic efficacy of multigenic pharmacogenomics-guided treatment in patients with schizophrenia. The results displayed that patients treated with MPCT had greater symptom improvement than their counterpart, patients treated with the standard 6-week treatment. This highlights the effectiveness of pharmacogenomics as a potential treatment plan for those with schizophrenia.[38]

6. Conclusion/Future Directions

Precision medicine is the future to address neurological diseases due to addressing the genetic variance in patients that cause similar symptoms but require different treatment plans. Personalized care through a variety of treatment options that are based on the patient's genetic profile provides an opportunity to drastically improve their quality of life by treating the disease on a molecular level rather than only the symptoms. Currently, the accessibility and cost of precision medicine are limiting factors for it to be a realistic treatment plan for the masses. However, as the field continues to advance through continued research in pharmacogenomics, metabolomics, and novel treatments such as iPSCs, precision can become normalized as a

more effective strategy to cure neurological diseases, and costs will presumably be reduced as the technology becomes more widespread.

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