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Advancing Neurodegenerative Disorder Treatment Through Pharmacogenetics: A Personalized Medicine Approach

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ABSTRACT

The discipline of pharmacogenetics examines how a medicinal intervention affects our genetic makeup. Nowadays, pharmacogenetics is generally heralded as having the potential to completely transform medicine. This quickly expanding discipline seeks to explain the genetic underpinnings of individual variations in drug response and to utilize that genetic data to forecast the safety, toxicity, and effectiveness of medications in either a single patient or a group of patients. It is also crucial for researching how several genes affect a drug's pharmacological function. In this we find and study about numerous components of the genes that affect the therapeutic of the drug. The majority of medications don't work as intended in the later phases. This could be because to an unforeseen side effect of the medication, which could be caused by different gene components. There are several phases of drug development where pharmacogenetic studies can be applied. Pharmacogenetics can be used in clinical research to stratify patients according to their genotype, which is correlated with their ability to metabolize. This promotes improved clinical trial results and the avoidance of numerous adverse medication reactions. In the global context, the advancement of pharmacogenetics and pharmacogenomics in Western Europe is extremely significant. Many research groups made up of basic and clinical researchers have been actively working in this subject for decades despite the typically minimal institutional backing. Their work had a global influence and cleared the path for additional research and pharmacy. In neurodegenerative illnesses, the use of genetic background as a predictor of therapeutic response is a relatively new and unexplored area.Even though sporadic degenerative illnesses have a complex etiopathogenesis, current understanding indicates that genetics is primarily responsible for directing the pathological events and even significantly altering the disease phenotype from patient to patient. Genes can function as regulatory factors that alter the strength and severity of pathogenic processes or the response to medication treatment, or they can work as susceptibility factors that raise the likelihood of disease development. Applying this knowledge to develop more targeted and efficient treatments and to customize therapy for each patient based on their genetic profile is the aim of pharmacogenomics.

INDEX TERMS: Pharmacogenetics, DNA, Pharmacogenetic test, metabolism, personalised medications, neurodegenerative disorder, dementia, Alzheimer's disease, Parkinson's disease, clinical studies

INTRODUCTION

PHARMACOGENETICS

Pharmacogenetics, also referred to as pharmacogenomics, is the branch of medicine that studies how an individual's genetic composition may impact how their body reacts to particular drugs. Genetic testing is used to check for alterations in particular genes. The field of pharmacogenomics has rapid growth. This is a customized course of treatment based on your lifestyle, surroundings, and genes. Pharmacogenetics can assist your doctor in prescribing a drug that may be more effective for you or that has few adverse effects.

Pharmacogenomics is currently used by providers for a small number of drugs and medical conditions. several drugs for HIV, several types of cancer, depression, and heart disease are a few examples. However, this area of medicine is developing and changing quickly. Pharmacogenomics is soon expected to soon assist clinicians in selecting more effective drugs to treat a wide range of common illness, according to researchers [1].

Pharmacogenetics, a rapidly expanding field in molecular biology and clinical medicine, describes the variation in human responses to medication interventions. The foundation of this field of study is the knowledge of Mendel's Laws of Inheritance and how gene mutations impact how humans metabolize medications. With the advent of genetic testing, pharmacogenetics—a concept that gained popularity in the 1930s—has now been rediscovered. Numerous genetic and non-genetic factors influence how we react to treatments. Pharmacogenetics has become an important area with the advent of personalized treatment. The term "personalize medicine" describes the branch of medicine where therapeutic decisions are made using all of the patient's information, including their individuality [2].

Gene: A gene is the basic physical and functional unit of inheritance. Genes are made up of DNA. Some genes act as instructions to make molecules called proteins, which are needed for the body to function. However, many genes do not code for proteins, instead they help control other genes.

Typically, people have two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1 percent of the total) are slightly different between people. Forms of the same gene with small differences in their sequence of DNA bases are called alleles. These small differences contribute to each person's unique physical features.

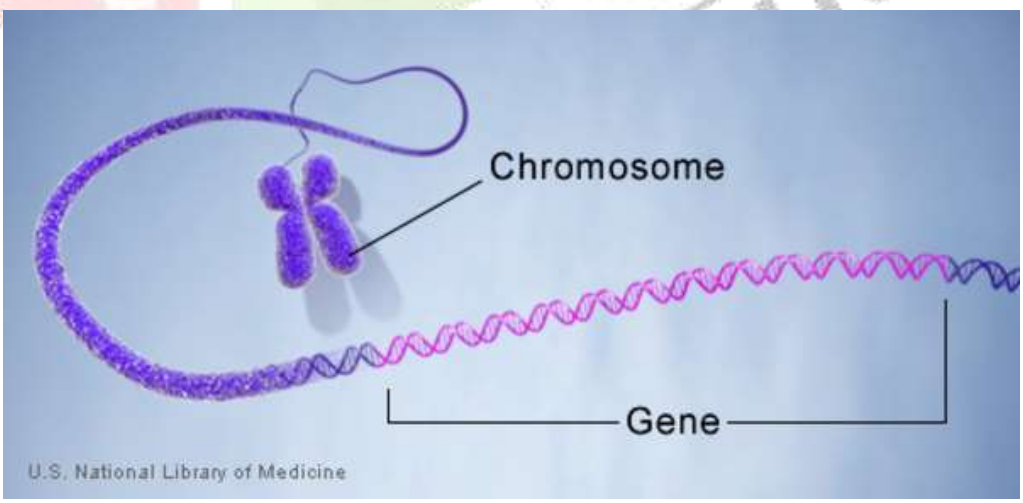

Fig-1: Structure of Gene and Chromosome

Effect of gene on working of medication:

The cells in your body receive instructions from your genes. Genes aid in the synthesis of enzymes, which are protein molecules. Among the many other things that enzymes perform is break down (metabolize) drugs. Genetic variations that alter the amount of enzyme produced or its functionality may be the cause of people who don't react to drugs as prescribed. A standard dosage of a drug won't function

as intended if your body breaks it down too rapidly, too slowly, or not at all. The drug may have little or no impact on addressing the ailment at hand, or it may cause serious side effects [3].

Pharmacogenomics & DNA

The idea that DNA may predict and explain an individual's response to a particular medicine is the foundation of pharmacogenetic testing. Medication DNA testing looks at drug receptors, absorption, and degradation in the body, providing information about possible adverse effects and precise dosages.

DNA plays a role in pharmacogenomics in the following ways:

• **Drug receptors:** For medications to work, they must bind to cell receptors, and DNA regulates the type and quantity of accessible receptors. Higher dosages of a drug are required to produce effects in those with fewer receptors.

• **Drug uptake:** This refers to how quickly and effectively drugs are absorbed by the body. For instance, if uptake is too low, a medicine will not build up in the body and deliver the desired benefits, increasing the likelihood of negative side effects.

• **Drug breakdown:** The term "drug breakdown" describes how a substance is processed by the body. While low breakdown rates may suggest lower dosages, high breakdown rates necessitate more medication[3].

Pharmacogenomic test:

A pharmacogenomic test is a type of genetic test that looks for particular modifications that affect how well a medicine breaks down in one or more genes. Prescription and medicine use are made less uncertain by pharmacogenomics. Pharmacogenomics testing allows clinicians to tailor prescriptions to each patient by using individual genetic variables to predict the likelihood of medicinal success. For pharmacogenomic testing, providers usually use a buccal swab or blood sample. Your sample is sent to a lab by your provider, where a technician looks for particular alterations in your DNA. The test your provider has ordered, the diseases they are attempting to address, and the treatments they are contemplating will all influence the gene or genes they check[4].

Results of a Pharmacogenetic Test:

For those who want to change their pharmaceutical regimen, pharmacogenetic test results might not offer a clear route forward. They can, however, demonstrate how rapidly and efficiently a person will process a drug. This information will have a big impact on many people's pharmaceutical choices.

Additionally, tests reveal if a patient is a fast or slow metabolizer and whether a certain drug may have negative side effects. This allows clinicians to quickly choose better alternatives at more effective dosages because they know what to rule out from their possibilities.

When combined with previous knowledge from drug trials, new data can greatly guide the course of treatment. In other cases, the results might not provide much more information, so the treatment team will continue to make some educated guesses about the medicines[4].

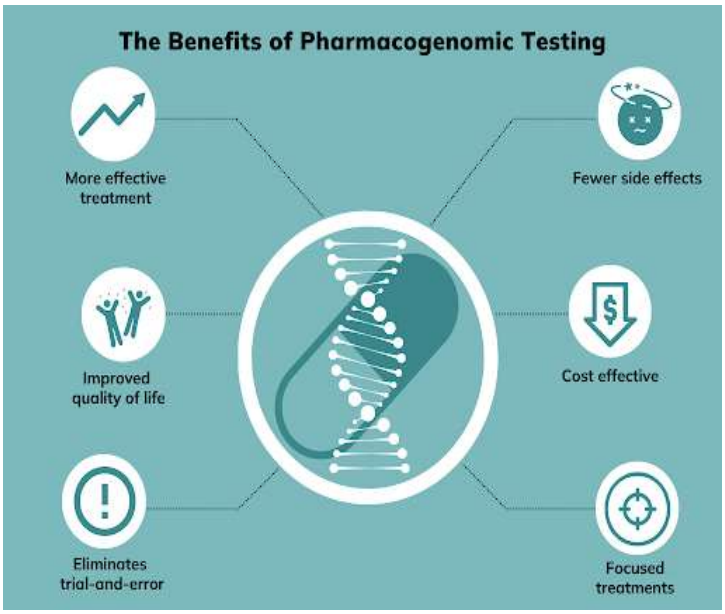

Fig-2: Benefits of pharmacogenetic testing

Limitations of Pharmacogenetic Testing:

With time, pharmacogenetic testing should provide more useful and comprehensive data. But for the time being, the restrictions are substantial. To discuss the possible dangers and advantages of the procedure, anyone interested in testing possibilities should speak candidly and openly with their treatment team.

The appropriate course of treatment for each individual cannot be determined by current tests due to the novelty of pharmacogenomics. Thankfully, the main danger arises when a person or a prescriber depends too much on the outcomes. Pharmacogenetic testing offers few answers despite its potential.

The applicability of pharmacogenetic testing to children and adolescents is another drawback. Since the majority of researchers in this field work with adult populations, knowledge regarding pharmacogenetics does not apply to younger people. Therefore, while choosing medications for children, physicians and families shouldn't go for pharmacogenomic testing.

"Pharmacogenetic tests aren't useful for answering other commonly asked questions about family history or likelihood of developing a certain disease because they look at very specific genes related to treatment," the doctors explain. They are more inclined to explain to someone how their enzymes function and how they can react to drugs [5].

Pharmacogenetic testing in the future

The availability of genetic testing as a component of medication therapy selection will be influenced by two factors: test validity and testing technologies. As demonstrated above, there are currently a number of approaches available to meet pharmacogenetics demands. These pharmacogenetic testing techniques are capable of highly multiplexed analysis and can easily identify single base mutations, intricate rearrangements, and variations in gene expression. Automation needs to be improved, particularly in the areas of cost, speed, and sample preparation. However, the increased application of pharmacogenetics is not much constrained by test technology. Establishing suitable test validation is the bigger challenge in creating pharmacogenetic assays for clinical usage. To accurately identify sequences of interest in patient samples, an analytical test needs to be sufficiently accurate, reproducible, and repeatable. All of the assay techniques covered here can produce findings that are analytically sound. A test must also accurately anticipate the relationship between the test result and a clinical outcome in order to be considered clinically valid [5]. Given the inherent high analytical validity of genetic tests, the clinical validity of genetic tests mostly depends on how a gene and its sequence variants relate to an anticipated result.

It may be challenging to establish this relationship; for instance, some genes may contribute independently to a given drug-related response, resulting in a low positive predictive value for any one of

these; additionally, for any gene, multiple alleles may give rise to the illness, most or all of which must be detected; and finally, in genes with low penetrance, the presence of the sequence will correlate to the condition in only a small percentage of cases. Only thorough clinical studies can demonstrate that a test has clinical validity and can produce a useful result[4].

History of pharmacogenetics

When Pythagoras observed that eating fava beans caused a potentially lethal reaction in some but not all people around 510 B.C., the field of pharmacogenetics began to take shape. Two years after Arno authored his groundbreaking study on how drug reactions may be regarded as relevant models for demonstrating the interaction of heredity and environment in the pathophysiology of disease, Friedrich Vogel, a German pharmacologist, came up with the term "pharmacogenetics" in 1959. Marshall coined the term "pharmacogenomics" in 1997. Although the phrases are interchangeable, the later term, pharmacogenomics, indicates that we have the capacity and expertise to assess the entire genome and can examine several genes in relation to medication response instead of focusing on just one gene at a time.

The Papyrus of Ebers, which dates back to 1500 BC, demonstrates the ancient Egyptians' knowledge of medicine and their enjoyment of "healing substances," albeit with some magical undertones. With their "pangenesis" idea in genetics, the ancient Greeks also contributed to the advancement of scientific knowledge. The fact that both normal and diseased features must be passed on to offspring through a “information carrier" gave rise to this early developmental theory of inheritance[5].

Analysing Motulsky's writings reveals that he highlighted the connection between drug response and heredity long before mainstream medicine did, and crucially before contemporary genotyping was accessible to reveal the underlying biochemical pathways. Karl Singer, Motulsky's mentor during his haematology fellowship, had constantly urged him to consider the potential molecular processes behind illnesses like sickle cell anaemia. Motulsky had grown to appreciate the "beautiful story" that genes and diseases tell under this direction, and he was also aware that patients would benefit from a deeper grasp of their link. The 1957 JAMA article "Drug Reactions, Enzymes, and Biochemical Genetics" summarizes two of his seminal discoveries. The first details the observation he made while researching blood problems at the Army Medical Centre in Washington, D.C., during the Korean War (1950–1953). Parallel to Pythagoras's findings with favism intolerance, Motulsky observed that while most men would tolerate an average dosage of the antimalarial medicine primaquine very well, some men would experience haemolytic anaemia.

Professor Friedrich Vogel, born in 1925 in Berlin, Germany, was a second significant figure in the subject of pharmacogenetics. He was drafted into the army at the age of 19, but he was captured by the Soviet Union shortly after. After nearly passing away from malnutrition and poor health, he was freed in the fall of 1945 and was able to go back to Germany to continue his scientific studies. As evidence of how young the subject was at the time, Vogel chose to follow the "road less travelled" and enter the field of human genetics after receiving his medical degree in 1953 at the age of 28. The geneticist was especially interested in expanding our understanding of adverse medication reactions that are monogenetically controlled[6].

Werner Kalow, a German-Canadian professor who was born in Cottbus, Germany, in 1917, was the third significant figure who helped establish pharmacogenetics as a respectable scientific discipline in the postwar period. Kalow discovered that different animals had significantly different pharmacological reactions to the toxin phenyl ethanolamine, and that humans and horses had different enzyme-substrate affinities, when researching various genetic variations and their associated enzymatic functions. He thus postulated that there would be variation on a smaller scale, within the same species, as well, since it was clear that interspecies variation was the cause of the detectable differences in enzyme activity. He added an evolutionary explanation for the differences to his reasoning, claiming that distinct enzymes have evolved to handle various environmental pollutants and, as a result, respond to medications in different ways.

Current progress in pharmacogenetics

Despite decades of progress in pharmacogenetics, few tests (phenotype or genotype) have reached clinical practice, according to the majority of academics and pundits. This is a concern even if the idea of "lost in translation" has been explained for many scientific domains, therefore it is not specific to pharmacogenetics. The lack of translation into clinical practice can be attributed to a variety of factors, all of which require further investigation.

Future prospects of pharmacogenetics

I definitely don't want to forecast the future of pharmacogenomics, especially in light of the Danish physicist Niels Bohr's (1885–1962) famous statement, "Prediction is very difficult, especially about the future." Instead, I would want to discuss some broad themes based on my own observations on the opportunities and difficulties that I believe this field's researchers will face in the future.

Most pharmaceutical companies now routinely acquire DNA samples from clinical trial participants, particularly in early phase clinical trials. Implementing PGx research, however, can provide a number of difficulties for businesses, ranging from a changing worldwide legal environment to growing worries about patient privacy and data access. At the same time, new and developing options for PGx research have been made possible by the quick scientific advancements in the field of genetics. In recent years, high-throughput sequencing and genotyping have become much more affordable, and businesses are now regularly carrying out thorough genomic analysis of clinical trial participants. Big databases that connect genomic and patient health information have developed into effective tools for medication development. Both the deeper characterisation of preexisting targets and the discovery of new targets can be accomplished with the help of these databases.

Pharmaceutical corporations will keep making significant investments in databases, PGx investigations, and genomic technology in the future. From early target discovery to the latter phases of clinical development, genomics has become a crucial component of drug development. Pharmaceutical companies will continue to confront the considerable hurdles described in this perspective as they expand their use of precision medicine methodologies in medication development. The most difficult obstacle to overcome may be the ever-changing legal and regulatory landscape for undertaking international research. Overly restrictive policies will hinder the growth of PGx discoveries, which will ultimately hinder breakthroughs in precision medicine more widely for populations around the world, even though worries about patient privacy and the misuse of patient data are legitimate concerns. On the plus side, genomic technologies are developing quickly, and pharmaceutical firms are taking advantage of this. In the upcoming years, clinical trial PGx investigations will probably benefit from the integration of patient level sequencing, polygenic risk scores, and information from sizable EHR/genomic databases [7].

Challenges in clinical research

Everybody involved in clinical translation has high hopes and expectations for PGx: patients who want effective treatment free from side effects; doctors who need help choosing the best medication and dosage for their patients; healthcare providers who need to figure out how to improve medical care while cutting costs; regulatory bodies that require proof of concept before issuing guidelines and laws; and drug developers who are afraid of losing their expensive drug candidates because of unexpected toxicity in the later stages of development. Pharmacogenetic information is found on more than 200 drug labels in the United States, which accounts for around 10% of FDA-approved medications.

The development of more sophisticated algorithms that can account for additional genetic predictors and confounding factors and produce quantitative test-data that can be better compared between studies and with other commonly used clinical tests (which are frequently not better regarding their test parameters compared to PGx tests) could aid in demonstrating clinical utility in addition to carefully planned and sufficiently large prospective studies. In addition to these practical examples, a major challenge in clinical research will be to continue to fill the PGx pipeline with additional successful clinical significance demonstrations. This will help to maintain the development of tests that are both affordable

and reliable enough for the industry to use on a regular basis. It will also continue to encourage other industry, health care, and regulatory players to join (or remain) in the pursuit of clinical translation. Furthermore, it is frequently challenging to validate reports that have therapeutic significance. To prove clinical value in these situations, it could be necessary to improve the characterization of clinical phenotypes and endpoints and create guidelines for clinical PGx research that take power, confounding factors, and test statistics into account[7].

Challenges for PGx analysis during clinical development

Throughout the clinical development life cycle, genetic studies based on clinical trial data can serve as a crucial foundation for well-informed decision-making. They may also open up significant clinical and business opportunities for therapeutic value propositions and patient classification. However, doing genetic analysis during clinical development has a number of limits and obstacles, including as small sample sizes, limited worldwide representation, and challenges validating results. First and foremost, a genetic or PGx hypothesis is not the main goal of the majority of clinical investigations. Instead, PGx or genetic aims are either a tertiary or exploratory goal, and trials are powered to identify differences in safety and efficacy, primarily with a therapeutic premise. Unless data from several studies are combined, phase I studies are typically underpowered for even candidate variant analysis. Even phase II and phase III studies are frequently underpowered when performing genome-wide association studies, despite their higher size [13].

The absence of population variety in clinical trials is another difficulty. According to the FDA (2017), most clinical trial participants are of European heritage. This imbalance is a well-known drawback of the existing corpus of genetics research more generally and is undoubtedly not specific to genetic analysis carried out in clinical trials. However, missed signals that could be crucial in clinical practice can arise from PGx studies' inability to sufficiently capture global genetic variation. In fact, non-European groups have significantly greater frequencies of several known clinically significant PGx indicators. For instance, some East Asian and South Asian people are more likely to have HLA-B*15:02, which is linked to cutaneous adverse responses to carbamazepine or oxcarbazepine.

For instance, Asian populations have significantly greater rates of the CYP2C19 poor metabolizer phenotype, which is linked to either increased or decreased chances of side events or efficacy for a variety of medications. Such connections might not be seen if various populations are not included. Furthermore, when there are few subjects available for analysis, it might be difficult to assess the generalizability of results from a genetic association study of medication response carried out in a dataset with a largely European ancestry to other (non-European) populations. Last but not least, the data generated from early clinical development programs for new chemical entities or drugs with novel mechanisms are probably the first and only 1168 Human Genetics data available, making it challenging to confirm or deny novel genetic findings until more clinical studies have been carried out. However, the interpretation of PGx results from follow-up clinical studies may also be difficult because to variations in clinical trial design, demographic heterogeneity, and a lack of statistical power for replication. Because the risk of an uninterpretable, unconfirmable exploratory discovery may outweigh any possible benefits, the lack of clarity surrounding the therapeutic utility of genetic analysis during drug development generally discourages the start of exploratory investigations [7].

Challenges in PGx ADME studies

Many known PGx connections are caused by genetic variations that change the action of drug transporters and enzymes that metabolize drugs. Variants in enzyme or transporter activity can cause inter-individual exposure variability, which may affect drug safety or efficacy if exposure variability surpasses the therapeutic window for small compounds. In addition to the previously mentioned problems with small clinical trial sizes, PGx research in early phase trials presents a number of particular difficulties. These include the ongoing appearance of variations with therapeutic significance and the possible uncertainty in identifying metabolic pathways for novel drugs in early clinical development. In order to increase the likelihood of success when performing analyses in extremely limited trial datasets, PGx analyses in early phase studies should ideally be carried out in a targeted manner, giving priority to

gene variants that have been demonstrated through preclinical work to be significant for the compound's disposition. However, phase II or even pivotal studies are frequently initiated before preclinical in vitro studies of the major and minor metabolic pathways are finished. To increase statistical power to evaluate a larger selection of ADME genes, it is frequently crucial to combine as many early phase clinical studies with pharmacokinetic (PK) data as feasible [13]. Furthermore, in order to evaluate the possible influence of variations in ADME genes, estimations of PK parameters can be obtained by population PK modelling in bigger phase II/III investigations. Nevertheless, there may not be enough statistical power to identify genetic connections in these data sets. Specifically, the ability to identify uncommon variations that can affect safety exposure is nearly always restricted, particularly for patients who might have multiple functional mutations in a group of metabolizing enzymes. Over the past few decades, rational drug design has largely discarded medications that are primarily metabolized by highly polymorphic CYPs, like CYP2D6, in favour of distributing the proportion metabolized across multiple CYPs or, when feasible, other enzyme families. That doesn't completely rule out the possibility that a patient will have a poor metabolizer profile in two of those enzymes, which could result in exposure variability that has clinical significance. Additionally, it has become apparent that additional metabolic clearance pathways, like glucuronidation and the function of membrane transporters, may be pertinent to PGx research.

PGx investigations will probably be necessary to comprehend their possible influence on PK and pharmacodynamics, even if there is typically less solid prior clinical evidence to support the functional impact of genetic variations in these other types of metabolic enzymes or in membrane transporters. Therefore, it is advised to perform ADME gene genotyping in early and late phase clinical trials and to thoroughly evaluate the metabolism pathways of all prospective clinical candidates. Studying the possible impact during the development of the novel chemical entity is probably warranted if a medicine is metabolized by pathways with known polymorphism variation, for which there is good evidence suggesting clinically important effects for previous approved treatments. Furthermore, in situations when unexpected PK variability is present and cannot be explained by conventional PGx genotyping, the EMA has published PGx guidelines that suggest the possible use of broader, whole-exome or whole-genome sequencing to evaluate possible new variations. Regulatory bodies may seek phenotypic proof of new variations, which is one of the extra problems associated with broader genome-scale sequencing [8].

The goal of pharmacogenomics: It is to comprehend how a person's genetic composition affects the effectiveness of a medication and the likelihood of adverse effects. Knowing this makes it easier to customize medications for a group of people or for that individual (personal medicine). Advantages of PGX are as follows:

- More potent medications
- Safer medications the first time
- Better vaccines
- More accurate techniques of establishing dosages

Ethical-societal aspects of pharmacogenetics

Without taking into account the ethical, societal, and legal implications of genetic/genomic approaches to healthcare, no consideration of their use can be considered comprehensive. Contrary to "genetic" testing for primary disease risk assessment, it has been argued that genotype determinations for pharmacogenetic characterization are less likely to raise sensitive issues related to patient confidentiality, the misuse of genotyping data or other information derived from nucleic acids, and the potential for stigmatization. While this is undoubtedly the case when pharmacogenetic testing is contrasted with predictive genotyping for highly penetrant Mendelian disorders, it is unclear why problems involving primary disease risk predictors in common complex disorders would be any more or less sensitive than those involving treatment success/failure predictors.

In fact, two lines of reasoning would suggest that pharmacogenetic data may raise more ethical concerns and complicated conflicts between the different stakeholders. First, pharmacogenetic data's very nature necessitates a somewhat more liberal stance regarding its use; if it is to fulfil its intended purpose,

namely increasing the patient's chances of successful treatment, it must be shared among at least a slightly wider circle of participants in the health care process. This is in contrast to genotyping and other nucleic acid-derived data related to disease susceptibility, which can have strictly limited access [9].

Therefore, a prescription for a medication that is restricted to a subset of patients with a specific genotype will unavoidably reveal the patient's genotype to any of the numerous people involved in the patient's care at the administrative and medical levels. The patient would have to forgo the advantages of the recommended treatment in order to protect data confidentiality, which would be the only way to restrict this quasi-public exposure of the patient's genetic information.

Second, from the perspective of, say, insurance risk, patients who are profiled as having a high probability of developing the disease and a high likelihood of responding to treatment may be seen as being fairly comparable to those who have the opposite profile, that is, a low risk of developing the disease but a high likelihood of not responding to medical treatment, should the disease actually occur. Therefore, patients who are less likely to respond to treatment would be viewed as a more unfavourable insurance risk for any given disease risk, especially if non-responder status is linked to chronic, expensive illness rather than early mortality, the latter of which has far more significant economic ramifications.

The final set of principles should affirm such appropriate use of medical information as long as we believe that societal agreement is reflected in our political decision-making processes and that this consensus respects the values of equality and justice. In fact, the WHO's "Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services" include two fundamental requirements: autonomy, beneficence, no maleficence, and justice. These requirements encompass data protection as well as patient/subject protection. To sum up, pharmacogenetics will be a significant new approach to comprehending disease biology and drug action in the various contexts covered by this word. It will also present new chances for patient stratification to attain the best possible treatment outcomes. Therefore, rather of being a revolution, it is a logical, subsequent step in the history of medicine. It will not be equally applicable to all diseases and treatments, and its adoption will take time. Significant advancements in healthcare will be accomplished if society can approve the appropriate use of this data, enabling and safeguarding its unrestricted usage for the benefit of the patient [9].

APPLICATIONS OF PHARMACOGENETICS IN DRUG DEVELOPMENT

The use of pharmacogenetic and Pharmacogenomics principle in the drug development process has reduced the drug dose, increase the rate of absorption and drug targeting is increased remarkably.

1.Target identification:

At present, the drugs that are present in the market act at less than 450 out of 1000 target in the human proteome. By using the technique of Pharmacogenomics and pharmacogenetic the number of targets for the drug therapy have been increased remarkably through:

- Detection of new protein that is involved in disease process.
- Targeting the disease-causing process.

2. Pre- clinical drug development:

Pharmacogenomics has a significant influence on this stage of medication development. Only the discovery of a molecular defect—which varies from person to person—allows for in-vitro screening. For instance: The cytochrome P450 enzyme, which breaks down drugs, has been used to make progress. These are the most significant biological catalysts that control how various medications are metabolized. As a result, the drug's interaction with the P450 enzyme was evaluated.

3. Phase I-III studies:

Regulatory approval to introduce a medication to the market is granted at these stages of clinical trials. Phase I clinical trials usually cost around $7 million, whereas phase III clinical trials can cost up to $43 million. Pharmacogenomics principles, which emphasize individual genotype through preclinical testing, are used to refine the phase I trial. Early detection of the drug's flaw during phase I may result in the compound drooping early on, which helps to save time and money on development. Phase III trials may see a decrease in sample size as a result, which could lead to faster and more effective medication development as well as a net cost savings.

4. Phase IV studies:

This phase, which is sometimes referred to as post-marketing surveillance or pharmacovigilance, is the time frame during which licenses are issued to introduce medications onto the market. The phase encompasses a range of research activities, including pharmacoepidemiologic studies, hypothesis testing, reporting, and hypothesis generation. Pharmacogenomics can help improve marketing monitoring with less effort than creating a single market and harmonizing the marketing authorization process. Since many patients are exposed to the medications during this phase, it is possible to detect any negative effects.

The risk-benefit ratio was improved by pharmacogenetic testing and the identification of genetic predisposing factors made possible by the storage of various DNA samples from patients receiving medication treatment. The abacavir hypersensitivity study, which identified a strong genetic predisposing factor in the MHC locus, provides the best explanation for this. A high number of patients and a more structured phase IV investigation are required to discover unusual and long-term harm if the total number of patients in the phase III study is reduced. In phase IV, prospective DNA sample collection is feasible but costly [10].

Table-1: APPLICATION OF PHARMACOGENETIC METHOD IN VARIOUS STAGE OF DRUG DEVELOPMENT

STAGE	APPLICATION OF PHARMACOGENETICS
Drug target identification	Identification and characterisation of the gene coding for drug targeting and to assess the variability
Phase I clinical trail	Patient selection
Phase II clinical trail	Dose modification Dose range selection
Phase III clinical trail	Interpretation of trail results based on pharmacogenetic test results
Phase IV clinical trail	Analysis of report adverse event with PGX data during development of FDA
Regulatory issues	Requirement for submission of pharmacogenetic data during development by FDA
Patient therapeutics	Personalisation of drug therapy Pharmacogenetic data in drug labelling Identification of responders and non-responders Identification of high-risk group of adverse events

APPLICATION OF PHARMACOGENETICS IN NEURO-DEGERATIVE DISORDERS:

Neurodegenerative Diseases

Chronic illnesses known as neurodegenerative disorders gradually harm and kill off components of your nervous system, particularly your brain. Despite being permanent and incurable, many of these illnesses can now be treated because of in medicine. Conditions known as neurodegenerative illnesses cause your nervous system, particularly sections of your brain, to progressively deteriorate and die. The signs and symptoms of these illnesses typically manifest later in life and typically grow gradually.

Since they are essential for communication, neurons are essential to the proper operation of the human brain. The majority of neurons start in the brain. On the other hand, neurons are found throughout the body. The bulk of neurons are produced by neural stem cells throughout childhood, and as people age, their numbers drastically decline. Despite the fact that neurons are not eternal, neurodegeneration—the progressive loss of neurons, their structure, and their functions is a major health concern and a key factor in the pathogenesis of a number of brain illnesses [11].

FUNDAMENTALS OF NEURODEGENERATIVE DISEASES:

Progressive malfunction and neuronal loss are hallmarks of neurodegenerative disorders. Functional system involvement varies among illnesses and is linked to a broad range of clinical manifestations. The deposition of proteins with changed physicochemical characteristics—also referred to as misfolded proteins—is a significant characteristic. According to the theory of conformational disorders, a physiologic protein's structural shape might change, leading to a change in function or perhaps harmful intracellular or extracellular buildup. Protein deposits are a feature of the majority of neurodegenerative diseases, although not all of them. For instance, current techniques do not detect specific protein inclusions in hereditary spastic paraplegia or certain types of spinocerebellar ataxia. Familial disorders are caused by mutations in the genes that code for these proteins. According to the protopathic hypothesis, research focused on the function of the unfolded protein response and protein elimination pathways, including the autophagy-lysosome route, the ubiquitin-proteasome system, chaperones, and stress response proteins. Crucial elements of the pathogenesis also include metabolic alterations, adaptability, dysregulation of energy and ion balance, and interaction with molecular damage. The proteins linked to neurodegenerative illnesses may spread throughout the neural system, according to a novel theory known as spine-like spreading. There may be overlap with the pathophysiology of prion diseases due to template-directed protein misfolding, parallels in pathogenic proteins' cell-to-cell dissemination, and the deposition of proteins that appear to follow anatomic pathways [11].

Epidemiology degenerative brain diseases

Although rare, degenerative brain illnesses occur frequently enough to be widely recognized. According to researchers, they impact about 50 million individuals globally. Although some disorders, such as Huntington's disease and ALS, frequently manifest earlier, the majority of these conditions are closely linked to age and are far more likely to occur in those over 65. The number of persons over 65 is expected to at least double over the next 30 years, according to World Health Organization (WHO) projections. Accordingly, the population suffering from neurodegenerative diseases will likewise increase at a comparable pace [12].

Symptoms of neurodegenerative diseases

The symptoms of neurodegenerative diseases vary widely. Some may have obvious connections to a degenerative brain disease. Other symptoms might seem completely unconnected without specific medical testing.

In general, the different types of conditions cause the following symptoms:

- **Dementia-type diseases**: These cause confusion, memory loss, trouble thinking or concentrating, and behaviour changes.

- **Demyelinating diseases**: Common symptoms include tingling or numbness, pain, muscle spasms, weakness and paralysis, coordination issues and fatigue.
- **Parkinsonism-type diseases**: These often involve slowed movements, shaking and tremors, balance problems, shuffling steps and hunched posture.
- **Motor neuron diseases**: These affect parts of your brain and nervous system responsible for muscle control. As the neurons in those areas die, you lose muscle control. That causes weakness and eventually paralysis.

Variations in the symptoms:

The symptoms of neurodegenerative diseases can vary widely, even among people with the same condition. There are a few reasons for this:

- **Each person's brain is unique**: No two brains form or work in exactly the same way. That means the same condition can still affect two people differently.
- **Neurodegenerative diseases happen for many different reasons**: The possible causes can vary widely for these conditions, even among conditions of the same type.
- **The symptoms depend on what's affected**: The parts of your brain or nervous system affected determine the symptoms of these conditions.

Causes neurodegenerative diseases: Some neurodegenerative diseases have a single cause that healthcare providers can identify. But in many cases, there isn't a single cause. Instead, research shows multiple factors probably contribute to neurodegenerative diseases. And there are times when providers might not be able to find a cause which can be frustrating for someone with one of these conditions or their loved ones.So far, experts have identified dozens of possible causes or risk factors. These tend to fall into a few specific categories, including:

- **Age**: This is generally the most important factor in developing neurodegenerative diseases. These conditions have strong ties to age. The older you are, the greater your chances of developing one. Some degenerative brain diseases can start earlier in life, but this is less common.
- **Genetics**: Many neurodegenerative diseases have strong ties to family history. That's often because of specific mutations you can inherit that increase your risk. Spontaneous mutations can also happen, and sometimes a combination of genes plays a role.
- **Environment**: Your environment can be a major factor in developing these conditions. Exposure to pollution, chemicals and toxins, certain types of infections and even where you live may all play a role (for example, lower vitamin D levels, which are more common the farther you live from the Earth's equator, have links to dementia-type diseases).
- **Medical history**: Your medical history and past health events can all play a role in developing neurodegenerative diseases. Some neurodegenerative conditions can either happen because of specific medical events or can get worse because of them. Some examples include cancer, certain types of infections, if you've had head injuries and more.
- **Habits, routine and choices**: Examples include what you eat, how active you are, whether or not you use tobacco products, how much alcohol you consume and many more[12].

Complications of the neurodegenerative diseases:

Complications are common with neurodegenerative diseases because these diseases damage parts of your brain and nervous system. As the damage worsens, you lose the abilities that the damaged areas once controlled. Some examples of this include:

- Movement disorders affect your strength, flexibility, agility and reflexes. When those decrease, your risk of falls and fractures increases.
- Motor neuron disorders cause gradual paralysis. When this affects muscles that control breathing, it increases the risk of pneumonia and other respiratory conditions.
- Dementia-type diseases affect memory, judgment and thinking. As these worsen, people typically can't live independently anymore because of risks to their health and safety.

Types of this condition

Some of the main types of degenerative brain diseases include (but aren't limited to):

- **Dementia-type diseases**: These cause progressive damage to various areas of your brain, causing neurons in several areas of your brain, to die. That can then cause a wide range of symptoms depending on brain areas affected. These include many conditions, such as Alzheimer's disease, frontal temporal dementia, chronic traumatic encephalopathy (CTE). Lewy body dementia and limbic predominant age related TDP-43 encephalopathy (LATE)
- **Demyelinating diseases**: These involve myelin damage or loss, which affects sending and relaying of nerve signals. Examples include multiple sclerosis (MS) and neuromyelitis optical spectrum disorder (NMOSD).
- **Parkinsonism-type diseases**: These happen because of damage to specific neurons in your brain that help manage coordination and precise control of muscle movements. This includes Parkinson's disease and other forms of parkinsonism (the general term for conditions that look similar to Parkinson's).
- **Motor neuron diseases**: These happen when neurons that control movement die off. Examples include amyotrophic lateral sclerosis(ALS, often known as "Lou Gehrig's disease") and progressive supranuclear palsy (PSP).
- **Prion diseases:**These are a type of protein misfolding disease that cause serious brain damage in a relatively short time (most people don't survive more than a year). Creutzfeldt-Jakob disease is the most common, and most cases happen for unknown reasons. It can also be genetic (survival time for these cases is between one and 10 years)[12].

IMPLEMENTATION OF PHARMACOGENETICS IN TREATMENT OF NEURODEGENERATIVE DISORDERS

Developmental steps in pharmacogenomics applied to CNS disorders include the following:

1) mapping of genes for specific diseases.

2) identification of genetic polymorphisms responsible for drug metabolism and disposition.

3) identification of genetic polymorph isms associated with drug transporters.

4) identification of genetic polymorphisms linked to drug targets.

5) characterization of polymorphic variations in population clusters to be treated for a specific disease.

6) primary screening of novel and/or conventional drugs in biochips for specific targets.

7) preclinical assessment of drugs for a given disorder, acting on specific targets, by using biochips and/or DNA microarraytechnology.

8) clinical trials with poly genic evaluation for efficacy and safety.

9) development of new technologies in functional genomics, proteomics, high-throughput screening methods, DNA microarrays, and biochips for drug evaluation.

10) development of powerful databases and bioinformatic tools to speed up clinical trials, improve patient stratification based on polygenic genotyping, reduce costs and potential side-effects, and optimize therapeutic outcomes[13].

Pharmacogenomics of Alzheimer's disease

For many years the heterogeneity of AD has been well known and how apparently identical phenotypes assessed with international clinical criteria don't always respond to the same drugs. In fact, the therapeutic response of AD patients to conventional cholinesterase inhibitors is partially effective in only 10±20% of cases, with side-effects, intolerance and non-compliance in more than 60% of the patients due to different reasons (e.g., efficacy, safety). Therefore, the individualization of therapy or pharmacological tailoring in AD and other CNS disorders is just a step towards the standard goal of molecular

pharmacogenomics taking advantage of the information and procedures provided by the sequencing of the entire genomes of free-living organisms.

Several studies have indicated that the presence of the APOE-4 allele differentially affects the quality and size of drug responsiveness in AD patients treated with cholinergic enhancers (tacrine, donepezil). For example, APOE-4 carriers show a less significant therapeutic response to tacrine (60%) than patients with no APOE-4. An APOE-related differential response has also been observed in patients treated with other compounds devoid of acetylcholinesterase inhibiting activity (CDP-choline, anapsos), suggesting that APOE-associated factors may influence drug activity in the brain either directly acting on neural mechanisms (choline acetyl transferase activity, nicotinic-receptor binding, neurotransmission modulation, amyloid deposition, tau degradation or phosphorylation) or indirectly influencing diverse metabolic pathways (cholesterol internalization, apoE/LDL receptor regulation, neuronal membrane phospholipid homeostasis) [14]. Since APOE, PS1 and PS2 genes participate in AD etiopathogenesis regulating neuronal function and brain amyloid genesis, in an attempt to envision the potential influence of major AD-associated genes on the therapeutic response in AD patients, we have performed the first pharmacogenomic study in AD using a genetic matrix model to identify the response of a multifactorial therapy in different AD genotypes combining allelic associations of APOE + PS1 + PS2 genes. AD patients received for 2 years three different drugs in combination:

1) CDP-choline (1000 mg/day, p.o.), an androgenous nucleotide.

2) piracetam (2400 mg/day, p.o.), a nootropic agent.

3) anapsos/calagualine (360 mg/day, p.o.), a neuro immune-trophic agent.

These three compounds have been previously tested as useful neuroprotectants and cognition enhancers in individual trials for AD, and they are currently used in memory disorders and dementia in several countries.

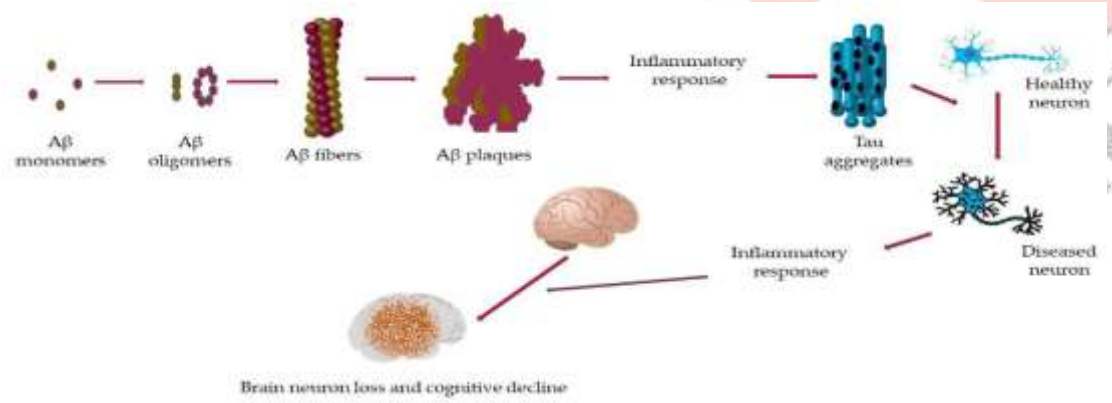

FIG-3: Schematic representation of cognitive decline in Alzheimer's disease

Furthermore, this multifactorial therapeutic strategy has been successfully proven in previous studies in AD, vascular dementia, and as a preventive strategy in people at risk with genetically confirmed family history of dementia. Mental performance in APOE-2/3 patients improved from baseline (MMSE score: 19.71 + 8.20) to 23.6 + 2.52 (6 months) and decreased thereafter to 8.5 + 3.6 (24 months) (r = ¡0.62). APOE-2/4 patients also improved during the first 12 months (from 19.85+9.37 to 20.66 + 8.5) and then deteriorated progressively (r = ¡0.75). APOE-3/3 patients improved from base line (21.41 + 7.57) up to 6 months (22.3+5.77, P<0.003) and were stable until the 15th month (20.03+5.48) to decline thereafter (r=-0.93) APOE-3/4 were the best responders, showing a progressive improvement during the first 18 months and a positive regression line along the study (r=+0.013). In contrast, APOE-4/4 patients were the most responders (r=-0.93), although a clear improvement was observed from baseline (21.93+7.35) to the 3rd month (26.17+1.54). patients with different PS1 genotypes showed a very similar therapeutic response.

Since genetic alterations and/or genetic variability in major AD genes seem to play a differential role in AD pathology, associated with or independent of abnormal APP metabolism and βAP accumulation, it is highly recommended that novel therapeutics for AD be tested on an independent basis for each gene involved at the preclinical level, and also on a polygenic substrate to assess the influence of a particular drug on the genetic interactions potentially involved in AD neuropathology.

At the clinical level, the pharmacogenomics of AD is much more complex due to several reasons:

1) AD patients older than 70±75 years usually show an important vascular component aggravating AD

2) more than 60% of dementia patients are taking many drugs simultaneously to treat concomitant pathologies

3) nutritional factors in the elderly can interfere with drug metabolism,

4) CYP genes family-dependent drug metabolism has not been well studied in elderly demented people

5) the direct influence of mutational genetics and susceptibility genetics and their interactions to elicit AD pathology is not yet clear

6) the involvement of epigenetic phenomena and environmental factors in AD is practically unknown.

In consequence, the preliminary approach to the pharmacogenomics of AD is very limited, but substantially informative when both susceptibility factors (SNPs) and mutational factors are integrated in a polygenic screening applied to evaluate conventional therapeutic outcomes (e.g., cognitive improvement, biological parameters) in AD clinical trials. However, many issues surrounding the technical, regulatory, legal, and ethical framework of pharmacogenomics remain unanswered, and educational programmes for the public and healthcare professionals are needed before this new discipline can be widely accepted[15].

Impact of Genetic Factors in Randomized Clinical Trials on Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative dis ease with a significant public health burden. It is characterized by the gradual degeneration of dopa mine neurons in the central nervous system. Although symptomatic pharmacological management remains the primary therapeutic method for PD,

Most pharmacological approaches to the treatment of PD are symptomatic and target the nigrostriatal dopaminergic pathway. Loss of dopamine, once considered the cause of PD, is now questioned as the initial event in PD pathogenesis and is certainly not the only viable path way. Responses to L -DOPA and other dopamine agonists, as well as side effects, consistently vary among individuals, and this is largely determined by genetic background. The pharmacogenetics of PD consists of association studies with genes whose products directly interact with L -DOPA, dopamine, or dopamine agonists. It is nearly impossible to determine whether and which dopamine-related polymorphisms are important for dose determination, avoiding side effects, or predicting a positive response. There are several reasons for this, which include disparity in study designs, small sample sizes, and lack of replication.

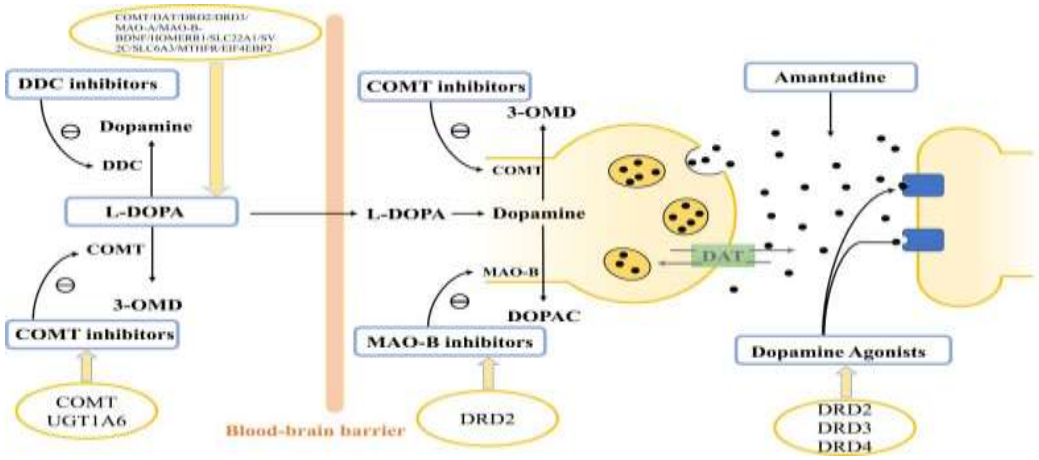

FIG-4: Parkinson's disease drugs and their associated gene polymorphism

In order to create personalised precision treatments for PD, it is important to conduct large, homogenous, multi centre, prospective, randomized controlled clinical studies of PD pharmacogenomics encompassing common therapeutic anti-PD medicines. Additionally, to better apply the research results of pharmacogenomics to guide the clinical diagnosis and treatment of PD, we need to incorporate the probable genetic variations of all patients with suspected PD into the diagnostic chain for better drug selection. The identification of a genetic variant associated with drug response in PD is a significant step preceding its use in clinical practice. Therefore, the biological functional effect of identified genetic variants and their interactions with other genetic or environmental factors should be explored further. Finally, cost-effectiveness analyses should be conducted to assess the translation of research evidence into clinical practice [16].

Impact of Genetic Factors in Randomized Clinical Trials on Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

FTD is a neurodegenerative disorder usually presenting with either behavioural or language impairment, although it has significant overlap with motor neuron disease and the atypical parkinsonian disorders. The clinical evidence of overlap between FTD and motor neuron disease has recently gained support after the C9orf72 mutation was found to be the most common genetic abnormality in familial and sporadic forms of both FTD and ALS, particularly frequent in patients and families with both conditions. At present, there are no treatments that can delay the onset or prevent the progression of genetic FTD. Evidence from other neurodegenerative diseases, as seen above for AD, shows that there are changes in a number of biomarkers many years before symptom onset, suggesting that the ideal time for treating these disorders is likely to be prior to clinical presentation. The identification of robust bio markers in genetic FTD that are indicative of dis ease onset and progression are therefore prerequisites for any disease-modifying treatment. Ideally, therapies should have been instituted when the minimum of irreversible neuronal loss has occurred, making RCT design challenging and increasing the importance of biomarkers in selecting suitable subjects and in monitoring progression [17].

Unfortunately, there are still no biomarkers of genetic FTD that can confidently predict when a disease-modifying treatment should be initiated or how the response to it should be monitored. The only robust and clinically accepted biomarker is decreased plasma levels of progranulin in GRN mutation carriers. Decreased plasma progranulin concentrations are found in symptomatic patients with GRN mutations, but similarly low levels have also been found in presymptomatic mutation carriers who are in their 20s and 30s, and therefore many years prior to disease onset. For GRN mutations, a uniform disease mechanism of loss of progranulin function operates in all mutation carriers, and drugs such as chloroquine, nimodipine, and vorinostat have been shown to increase progranulin concentration, suggesting their possible use in future preventive RCTs. Based upon these models, the Genetic Frontotemporal Dementia Initiative (GENFI) was set up in 2011 to bring together research centres across Europe and Canada with an interest in clinical studies of presymptomatic genetic FTD.

In ALS, there are only a few RCTs that have adopted a priori or a posteriori stratification of patients according to the presence of mutations in one of the known genes, even though they often influence the phenotype. This is understandable for SOD1, TAR DNA-binding protein, fused in sarcoma, or other genes with low frequency, especially in sporadic cases. It is less understandable for C9orf72 G 4 C 2 expansion, which has a frequency of up to 50% in familial cases and up to 10% in sporadic ones, and which strongly influences phenotype in terms of prognosis directly or through the association with frontotemporal cognitive decline. Before one can translate these findings into new causal or modifying therapies, better insights into the exact pathogenic mechanisms are essential, which should result in the development of a completely new class of therapeutic strategies. However, emerging technologies in antisense oligonucleotides and RNA silencing are promising as novel therapeutic strategies targeting specific genes in familial ALS, such as SOD1 and C9orf72. Their therapeutic potential was recently demonstrated by the phase I trial of the intrathecal delivery of antisense oligonucleotide ISIS 333611 in SOD1 patients with familial ALS. A major problem in translating preclinical findings into new treatments for ALS patients is the lack of reproducibility of the preclinical studies. Recently, the ALS Therapy Development Institute (TDI) retested different compounds with a reported beneficial effect in the mutant SOD1 mouse model. Unfortunately, TDI was unable to obtain any beneficial effect in humans [18].

Conclusions

Pharmacogenetics is founded on long-standing traditions in clinical practice, where therapies are selected based on history and physical findings in order to maximize benefit and minimize risks. Genetic tools allow increased sophistication in patient profiling and treatment optimization. Pharmaceutical companies are aware of the value of collecting genetic data during their randomised control trails.

***Pharmacogenetic research is bidirectional with Randomised control trails*:** efficacy data are correlated with genetic polymorphisms, which in turn define subjects for treatment stratification. The role of pharmacogenetics in RCTs for neurodegenerative diseases is still a young, unexplored, and promising field. A better understanding of the role of genetics in drug response to stratify patients in genetic homogeneous groups will have a great impact on RCT design, improving statistical power and al lowing the identification of group-specific treatments. This will increase the success of phase III RCTs for therapeutic interventions in neurodegenerative diseases and will delineate the basis for future personalized medicine.

If it is true that RCTs must evaluate the efficacy of a given drug on a series of patients, it is also true that the role of genetics in influencing this response has been underestimated. It is clear that the great majority of neurodegenerative diseases are complex diseases in which genetic factors interact with nongenetic factors to produce clinical phenotypes. However, idiopathic PD, as well as AD, ALS, and other neurodegenerative diseases, have a strong genetic component and RCTs ignore the role of genetics, which in turn leads to the failure of almost all RCTs in neurodegenerative diseases. In recent years, the complete characterization of the most important drug-metabolizing system has provided us with the knowledge to aim RCTs towards a second generation in which interindividual differences in drug metabolism do not bias the study, but instead become the basis to construct the trials, with the advantage of a cross-sectional role across diseases and drugs.

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