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" Role Of Pharmacogenomics In Personalized Medicine Qualification : Study Of Individual's Genetic Makeup Provides Effective Drug Treatment"

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Role Of Pharmacogenomics In Personalized Medicine
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ABSTRACT :

Pharmacogenomics (PGx) is the highly emerging field of science. It is based on unique genetic characteristics of an individual. Personalized medicine is an approach of treatment of disease by the used of patient genetics information and study of lifestyle.

The wide range of pharmacological response, toxicity is depend on drug used in clinical setting. The concept of personalized medicine is occurred when disease can be predictable and preventable. It involves understanding of disease at molecular level. Inter individual different to drug response, genetic testing, complexity of genetic interaction are the challenges faces in implementation of personalized medicine.

Key words : Pharmacogenomics, Personalized medicine, Genetics, Patient, Drug response

Introduction

The history of personalized medicine is not about development of the concept of personalization. It was first introduced by Hippocrates (ca.460 BCE – ca. 370 BCE) around 2400 years ago but about the evolution and increasing a precision of diagnosis and treatment. (1).
The roots for personalized medicine can be traced all the way back to Hippocrates, he famously said it's far important to know what person the disease has than what disease the person has this introducing the patient centric concept .(2)
The personalized medicine use the concept of genetic information which has played major role in certain aspects of personalized medicine (Eg. Pharmacogenomics) ,and the term was first coined in the context of genetics though it has since broadened to encompass all sorts of personalization majors including the use of proteomics, imaging analysis.(3)

In 2011, the National Cancer Institutes of the Health,USA, give the defination of "personized medicine" as a form of healthcare that considers information about a person's genes, proteins and environment to prevent diagnos and treat disease. Genome -guided clinical care mostly focuses on the individual patient's genomic markers. It help ascertain whether that a person respond to given therapy or not and avoid toxic side effects from the drug as well as adjusted the dosage of medication to optimize their efficacy and safety. The person variation to drug response is 20% and 95% based on genetic variability.(4)

Scopes of pharmacogenomics:

1.Genomic and proteomics profiling
2.Genetics and drug metabolism
3.Genetic variability in drug toxicity and efficacy
4.Genetic based vaccine development
5.optimizing drug selection and dosage based on patient's genetic profile (5)

Basics of Pharmacogenomics

Pharmacogenomics "a word formed by combining the terms pharmacology and genomics."

The pharmacogenomics adequately describe the scope and covers the potential of using human genetics variation to personalized medicine. According to the U.S. National institute of health defines the term pharmacogenomics as the study of how genetic variation affects the response to the drug .(6)

History

Friederich Vogel coined the term "pharmacogenomics" in 1959 (Vogel , 1959) to define a new science aimed to study the influence of inherited factors on drug response variability genetic and pharmacological knowledge and method.

Evidence for genetic basis associated with administration of drugs emerged in early 50's when the antimalarial drug (primaquine) were shown to induced haemolytic anaemia in patient having deficiency of glucose -6-phospate dehydrogenase enzyme.In that same period further studies revealed that adverse drug reactions like isoniazode-induced peripheral neuropathy and succinylcholine induced apnea were associated to inherited deficiency of enzyme N-acetyl- transferase and succinylcholine esterase was found.

The discovery of the relation of pharmacogenetics deficiency at the molecular level first found in 1980's when Gonzales et al. Cloned CYP2D6 gene and characterized genetic polymorphism responsible for the decreasing in expression of CYP2D6 enzyme.

At the end of the 1990's the term "pharmacogenomics" was introduced in medical literature.(7)

The study of influence of the genetics information of the person is directly related to the response of drug to a person from different ethnic backgrounds was followed by a number of reports in characteristics population. Example, enzymuria of liver isoenzyme UDP-glucoronyl transferase appears in men drinking alcohol,and methemoglobinemia after intake of nitrate – contaminated water. At the same period of time the pharmacogenetics discovery were being made and it was found that in humans the antinuclear antibodies level in plasma differs and it occurs with greater frequency of certain drugs.(6)

Genetic variability and drug response

The wide range of pharmacological response, toxicity, phenotypic variation is depend on drug used in clinical settings. Less than 70% of patient receive a satisfactory response with advanced drugs available today in market and their significant portion causes adverse effects. Understanding variability reqires the need of understanding the two factors – pharmacokinetics and pharmacodynamics. A complex phenotype known as clinical dug response results from the interaction of several factors including genetic, clinical, environmental, demographic once. Through genotype – informed prescription and monitoring guidelines pharmacogenomics – the research and practical use of genetic information to drug response variation – aims to maximize therapeutic effectiveness and decrease adverse drug responses. A number of approved cardiovascular medications such as simvastatin , warfarin, clopidogrel have documented pharmacogenomics relationship.(8)

Genetic variability and drug response are important factors for patient care, there is a potential to explore persons genetic constitution. These constitution serve as markers for identifying the individual's sensitivity to a specific drug or adverse reaction. These information is significant in order to adjust drug therapy for special patients group. Variability associated with a single nucleotide polymorphism in a group of person can help predict the development of disease.(6)

Human genetics variability the result of millions of years of evolution, plays a pivotal role in drug metabolism and response. Understanding genetic blueprint of drug response requires details study of genetic variation.

One of the most important aspects of pharmacogenomics is the study of genetic polymorphism. Polymorphism in genes encoding enzymes CYP450 family. These enzymes responsible for metabolism of many drugs. Genetic difference in these enzymes can potentially cause variation in metabolism rates of drug which in turn influence on the drugs efficacy and safety. (9)

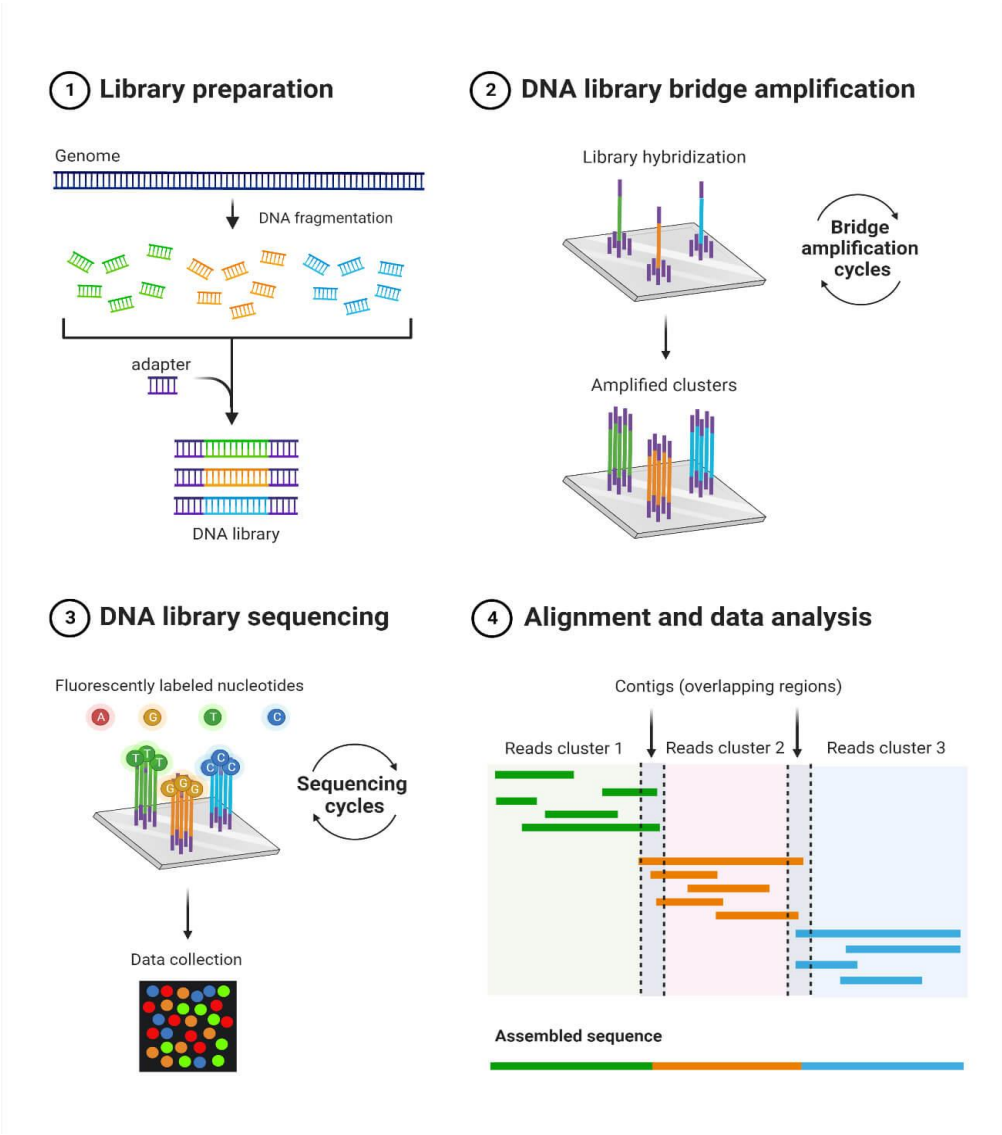
Techniques used in pharmacogenomics

1.Next Generation Sequencing
2.Gemone wide associated studies

Next Generation Sequencing

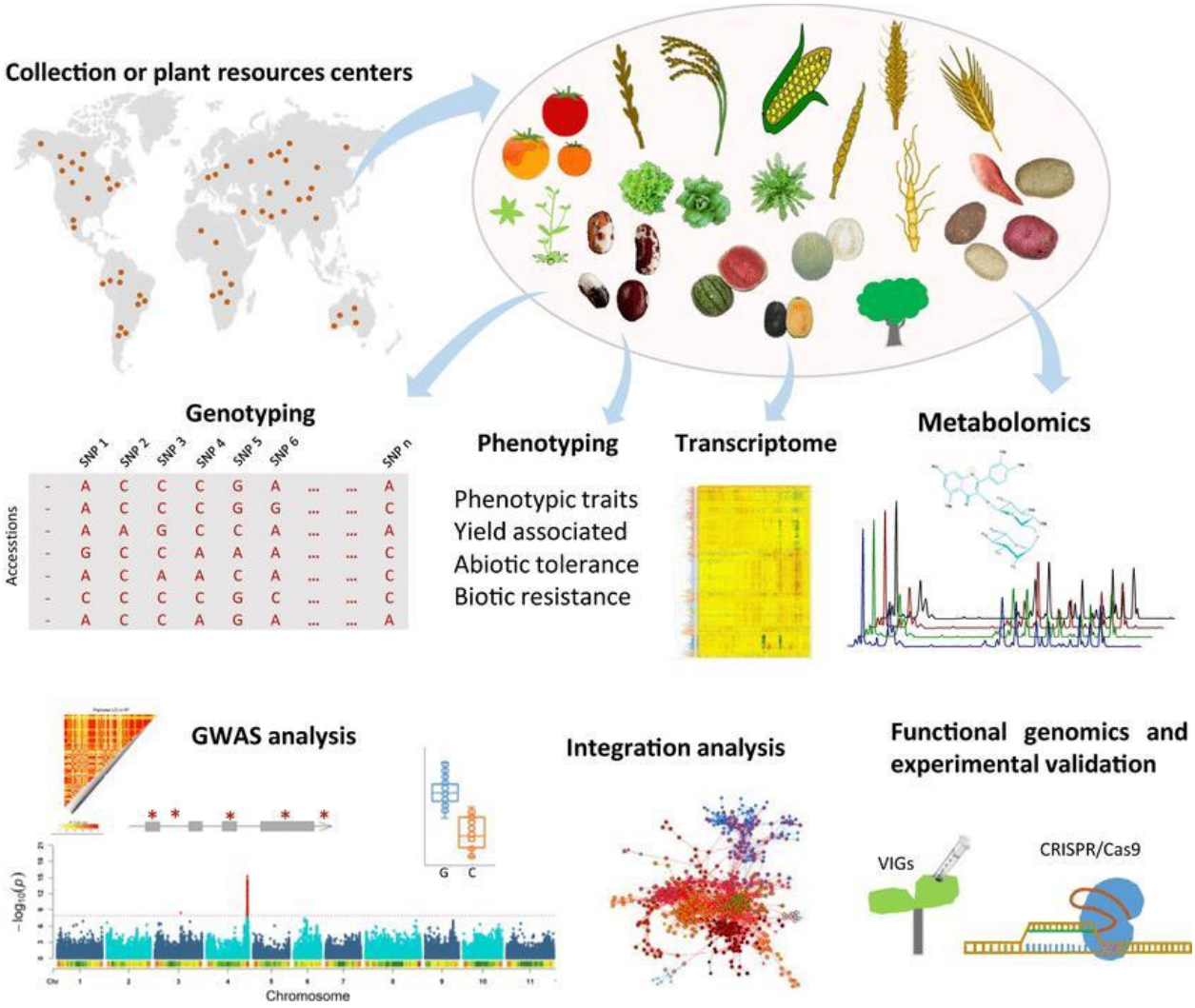
Next Generation Sequencing also called massively parallel sequencing or second generation sequencing. Some of these technique emerged between 1993 and 1998 and have been commercially available since 2005 . It approaches to DNA sequencing.
It is a high throughput technology that sequences millions of DNA fragments simultaneously , allowing for rapid and cost effective analysis of entire genome for targeted region. (10)
Using next Generation Sequencing and entire human genome can be sequenced within a single day in contrast Sanger sequencing technologies which is used to decipher human genome required a decade to deliver the final draft.(11)
Genetic diseases is the condition which result due to changes in individual genetic makeup (DNA) . DNA carries the genetic information that makes each persons phenotype variation such as color of hair and chances of having health condition. Mutation is occur in single gene or multiple gene .NGS include whole genome sequencing, whole exome sequencing .
NGS reduces time as well as cost as compared to other traditional method such as Sanger sequencing .(12)

Genome wide association studies



The widely available genotype data linked with information about drug response has enabled genome wide association studies.
GWAS discovered interrelation of genetic variation and both drug efficacy and adverse drug reactions despite these success the design of GWAS in pharmacogenomics faces many challenges.
The study of role genetics plays in drug response broadly known as pharmacogenomics (PGx).(13)
GWAS have matured into efficient and effective tools for mapping genes underlying human phenotype. The recent studies shown that uses of GWAS approach for examining PGx traits including drug metabolism, efficacy, toxicity.

Personalized Medicine : Concept and Development



The concept of personalized medicine is happened when the disease becomes predictable and preventable based on specific genotype. In case of disease genetic diagnosis and availability of prospectively validated molecular targeted agent result in more effective and safer treatment . (6)

Personalized medicine refers to any clinical approach that emphasizes the systematic use preventive, diagnostic, therapeutic interventions based on genomic and family history data to enhance health. The personalized medicine have several health strategies that depends on identification of genetic markers including molecular diagnosis, prognosis.(14)

Role Of Proteomics, Genomics and Metabolomics

Genomics

Next generation sequencing (NGS) is most important to generating the bulk amount of DNA data for whole genome sequencing (WGS) and whole exome sequencing (WES) project . Because exome comprises 1.5 % (40 Mb) of our genome (2) Genomics is an interdisciplinary field of molecular biology which focuses on structure, function, evaluation, mapping of genomes.(15)

Personalized Genomics is the human genetics study that analyzed an interpreted individualized genetic information by genome sequencing an identify genetic variation compared to the known sequencing (16)

Proteomics

The term “proteomics” indicates PROTEINS expressed by genome and is the systematic analysis of proteins profile of tissues.(17) Studying the proteom by mass spectroscopy method is important. Firstly because not all mRNA is translated into protein, sometimes because miRNA bind to the 3’ UTI of their target genes thus blocking translation.(2)

Proteomics technology plays vital role in molecular diagnostic, which is basis of personalized medicine. Proteodiagnostic, have advantages over nucleic acid diagnostic and complement the latter . (17)

Metabolomics

Metabolomics is the study of various chemical processes involving metabolites, small molecular substrates , intermediates and products of cell metabolism .Metabolomics is the “systematic study of the unique chemical fingerprint that particular cellular processes leave behind” (18)

The personalized medicine is rapidly emerging approach to the medicine guided by genetic makeup. Metabolomics is an approach that quantify small molecules in a given bio fluid majors snapshot of health.(19)

Relationship of Genomics and Personalized Medicine

There has long been interest in the field of personalized medicine involved information by understanding diseases at molecular level. It is a form of medicine that uses person's genes, proteins, environment, to prevent, diagnose, mitigation, treatment of disease. Thus, a physician can deliver personalized care in the absence of DNA profile.(20) Understanding the role of genetics and human diseases coupled with advancing sequencing technology.(21).

Pharmacogenomics include various tools like health risk assessment , family history and clinical decision for complex risk and predictive information. Genomic medicine which uses information from genome of the person and their derivatives like proteins, RNA , metabolites is a key component in development of personalized medicine which rapidly advancement in health care field.(22)

Integration of Pharmacogenomics in clinical practice

Various groups have already developed the guidelines on the use of pharmacogenomics tests. Prompted by the fact that CYP2D6 genotype is already beginning to influence clinical practice. The patient with genotype CYP2D6 and CYP2C19 if are the candidates of treatment with imipramine, tricyclic antidepressants, antipsychotic. Among these according to guidelines recommended that levomepromazian, haloperidol, other low therapeutic index antipsychotic agent should not given to the patient identified as CYP2D6 or CYP2C19. (6)

Challenges in clinical implementation

1. The most important challenges is that diverse genetic and acquired factors plays role in inter – individual differences in treatment response. There are also many barrier for implementing personalized medicine strategies. Some of these include medical inertia, acceptance of evidence based genetic study . (6)
2. Cost of genetic testing for pharmacogenomics is relatively high particularly in low and middle income countries.
3. Ethical and privacy concern : The use of individual information in clinical practices rises significant question related to privacy and data security.
4. Complexity of genetic interaction: Certain variation in generics established links in drug metabolism and response full complexity of genetic interaction remains poorly understand. Pharmacogenomics responses can influence by multiple genes interaction. (23)
5. Lack of education as well as understanding by physicians regarding available pharmacogenomics test.
6. Lack of guidelines on interpretation and uses of genotype result.(24)
7. Validated markers needed administrative approval.
8. Access for assays through GLP or regulated laboratories . (25)

Global landscape and Regulatory Framework

Personalized medicine global market overview:

The global personalized medicine market size in the world was estimated to be 567.10 billion USD in 2024 and there is a chances of projected to reach USD 1, 1996.18 billion by year 2033, growing at a CAGR of 8.80% from 2025 to 2033 . This growing demand causes significant expansion of personalized medicine globally. (26)

Regulatory framework:

The regulatory landscape for pharmacogenomics is continue to evolve world wide. Regulatory agencies are working on the subject of use of genetic information in plant treatment of disease. Understanding these regulation needed for healthcare provider, researchers, pharmacist working in the field of personalized medicine (9)

Future perspective

1. Pharmacogenomics knowledge include genetic testing into routine medical care and ensuring equitable testing in wide variety of population.
2. Expanding genetic database reflect diversity in the world population ensuring benefits to all . (23)
3. Pharmacogenomics has thus far made the most important in cancer and cardiovascular disease but there are significant opportunities to explore its potential in areas such as autoimmune disorders, neurology and infectious diseases.
4. Pharmacogenomics holds potential to transform personalized medicine by increasing drug efficacy, minimizing adverse drug reactions and optimizing dosing strategies.(6)
5. Next generation sequencing (NGS) technologies have transformed our ability to rapidly sequence entire genomes. These technologies enable pervasive pharma profiling, allowing for the simultaneous analysis of various genes and varients.
6. Patient may have the chance to accommodate their genetic data to research initiatives. (9)
7. Pharmacogenomics will decrease the number of failures and guarantee the safety of the clinical investigations.
8. Pharmacogenomics is useful technique for understanding inter individual heterogeneity in drug response and toxicity. (8)

Conclusion

Pharmacogenomics Play an important role in advancing personalized medicine by enabling to modify the drug therapy based on an individual's genetic data . By understanding genetic variation that affect to the drug response, clinicians can select the most effective medication, reduce adverse drug reactions and optimize dosing strategies. Despite current challenges such as limited clinical implementation, including inter individual variability due to complex genetic and environmental factors, high costs of genetic testing especially in low and middle income countries.

Future efforts should focus on expanding genetic data , increasing clinical education and develop cost effective methods to fully realize the potential of pharmacogenomics in delivering safer and more effective personalized medicine.

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