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Genome Driven Personalized Drug Therapy

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Abstract Genome driven personalized drug therapy is an important medical field, which can achieve precise medication and prediction of drug side effects by analyzing patient genomic information. This method utilizes the association between gene mutations and drug reactions to predict patients' responsiveness to specific drugs and the risk of side effects. Genome driven personalized drug therapy can also predict drug targets and mechanisms of action, providing guidance for personalized treatment plans. However, this field still faces challenges, including difficulties in analyzing and interpreting genomic data, the complexity of individual genomic variations, and the interactions between genes and the environment. This review explores genome-driven personalized drug therapy from the perspectives of genome analysis and screening, personalized drug therapy strategies, and application fields, in order to continuously develop and bring more hope and potential for disease treatment.

Keywords Genetic variation; Personalized healthcare; Drug reactions; Treatment strategies; Application area

The development in the field of medicine has been rapidly evolving, and in order to better understand and treat diseases, scientists are continuously seeking new methods. In the past few decades, genome-driven personalized drug therapy has emerged as a significant revolution in the medical field. This groundbreaking approach utilizes individual genomic information to guide the design of drugs and treatment plans, aiming to better meet the needs of patients, enhance treatment efficacy, and reduce unnecessary side effects.

Every individual's genome and biological characteristics are unique, leading to variations in disease risks, drug responses, and treatment efficacy. The goal of personalized medicine is to analyze the genetic and biological features of each individual and provide tailored medical solutions to maximize treatment effectiveness (Deng et al., 2021). Genome-driven personalized drug therapy is a treatment strategy that relies on individual genomic information to guide drug selection and usage. The principle involves analyzing individual genomic variations and biomarkers to determine an individual's response to drugs and drug metabolism capacity, thereby offering personalized drug treatment plans for patients. This approach is a personalized medical method that acknowledges the uniqueness of each patient, recognizing that their diseases and drug responses may differ. Traditional treatment methods are often 'one-size-fits-all,' applicable to a broad patient population, while overlooking individual differences. However, genome-driven treatment methods can more accurately identify specific gene variations in patients, enabling the selection of the most effective drugs and treatment plans (Admas and Banjaw, 2021).

With an increasingly profound understanding of the genome, the field of medicine is entering a new era. The genome serves as the blueprint of life, determining an individual's genetic characteristics, including susceptibility to diseases, drug metabolism capabilities, and treatment responses. Traditional treatment methods are often based on average population data and clinical trial results, while personalized medicine can create individualized treatment plans for each patient based on their genetic variations and biomarker information. This customized approach allows for more accurate targeting of the root causes of diseases, improving treatment effectiveness, and reducing adverse reactions in patients. Therefore, incorporating genomic information into clinical practice has become an innovative approach, providing doctors with more treatment options and helping patients receive better medical care. This review will delve into genome-driven personalized drug therapy from aspects such as genomic analysis and screening, personalized drug treatment strategies, and application areas, aiming to improve disease prevention, diagnosis, and treatment outcomes, thereby driving progress in medicine.

1 Genome Analysis and Screening

1.1 Development of genome sequencing technology

Genome sequencing technology has made tremendous progress in the past few decades, enabling a more comprehensive and efficient analysis of the structure and function of the genome. This development has brought revolutionary changes to fields such as basic biology research, medical diagnosis, and personalized treatment. With continuous technological development and innovation, genome sequencing is expected to be more widely applied in the future, further advancing progress in science and medicine (Figure 1).

Figure 1 Genome sequencing

The first-generation sequencing technology was primarily based on the Sanger sequencing method, which was invented by Frederick Sanger in 1977. It is a classic sequencing method that determines the sequence of bases on DNA one at a time through chain termination reactions during the DNA synthesis process. Although the first-generation sequencing technology is highly accurate, it is relatively slow and costly.

Next-Generation Sequencing (NGS) is a series of high-throughput sequencing technologies that emerged around 2005. These technologies involve the parallel processing of millions of DNA fragments, allowing for the efficient, rapid, and cost-effective acquisition of large-scale sequencing data. The advent of NGS technologies has significantly reduced sequencing costs, accelerated the pace of genome sequencing, and provided a robust foundation for large-scale genomic research and personalized medicine (Crovari et al., 2022).

Third-Generation Sequencing (TGS) technology is a new generation of sequencing technology that emerged after NGS. It has advantages such as real-time sequencing, long reads, low cost, and portability, which can better solve problems such as assembly and analysis of large genomes.

1.2 Analysis and interpretation of genomic data

The analysis and interpretation of genomic data involve the process of dissecting and understanding genomic information based on sequencing data. It is a complex and multi-step process, including data preprocessing, sequence alignment, variant detection, gene annotation, functional analysis, and result interpretation. The goal of these steps is to extract information about individual genetic variations and their relevance to diseases from genomic data, further promoting the development of personalized medicine and genomic research.

Genome sequencing data is typically vast raw data that requires preprocessing. This involves tasks such as removing read errors introduced during sequencing, improving the quality of base sequencing, discarding low-quality sequence fragments, and applying appropriate data filtering. The preprocessed sequencing data is then aligned with a reference genome to determine their positions on the genome and corresponding genomic regions (Zhou et al., 2022).

Variant detection is a crucial step in the analysis of genomic data. Identifying and annotating variations in sequencing data helps understand the genetic differences among individuals and populations, as well as genetic variations associated with diseases. Gene annotation is the process of functionally and meaningfully interpreting detected variations. This includes determining the position of the variation on the genome, potential impacts such as protein-coding regions, regulatory elements, or functional non-coding RNA regions, and how they might affect gene and protein functions.

In the interpretation of genomic data, functional analysis is a key step in linking genomic variations to biological functions and disease relevance. This can involve using bioinformatics tools and databases to predict and assess the impact of variations, such as predicting protein functions, identifying genetic pathways, and analyzing functional networks. Functional analysis aids in further understanding the influence of genomic variations on individual phenotypes and diseases.

Based on the results of the analysis, the interpretation and reporting of genomic data represent the final steps. This involves translating the analysis results into an understandable format, providing detailed interpretation reports to clinical professionals or researchers, explaining the significance of genomic variations, potential health risks, and possible treatment strategies.

1.3 Potential genomic biomarkers and drug response associations

Genomic biomarkers refer to specific genetic markers associated with individual genomic variations, used to predict an individual's response to drug treatment. The identification and application of genomic biomarkers can assist physicians in selecting appropriate drug treatment plans on an individualized basis, improving treatment efficacy, reducing adverse reactions, and providing guidance for the practice of personalized medicine. The following are some common examples of genomic biomarkers and their associations with drug responses.

Thioguanine is a medication used to treat leukemia and autoimmune diseases (Figure 2). The polymorphism of the TPMT (Thiopurine S-methyltransferase) gene is related to the metabolism of thioguanine. Individuals with TPMT variations that result in reduced enzyme activity may metabolize thioguanine more slowly, leading to potential drug toxicity. Therefore, before administering thioguanine treatment, testing the patient's TPMT gene status can help doctors determine the appropriate dosage, minimizing the risk of adverse reactions to the greatest extent possible.

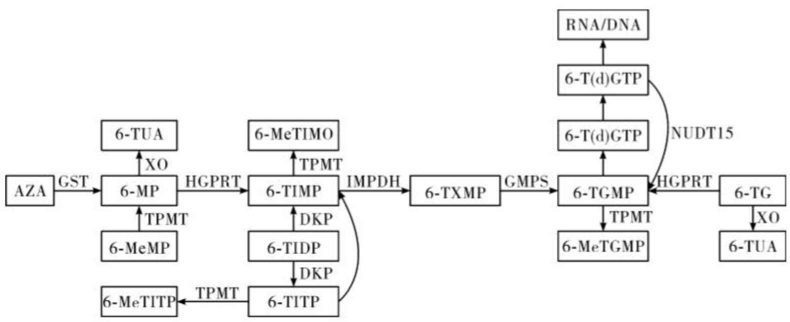

Figure 2 Metabolic process of Azathioprine in vivo

CYP2D6 is an enzyme encoded by the human *CYP2D6* gene, participating in the metabolism of various drugs. The polymorphism of the *CYP2D6* gene can result in differences in drug metabolism capabilities. For example, in patients being treated for hypertension with amlodipine, rapid metabolizers of CYP2D6 may require higher doses to achieve the desired therapeutic effect, while patients carrying *CYP2D6* variations may need lower doses to avoid adverse reactions.

2 Personalized Drug Treatment Strategies

2.1 Drug selection and customization

Drug selection and customization involve incorporating individual genetic, biological, and clinical characteristics into the process of making decisions about drug treatment. Through personalized drug selection and customization, treatment effectiveness can be improved, adverse reactions reduced, and better medical outcomes provided for patients.

Individual genomic variations can influence drug metabolism, efficacy, and side effects. By detecting the variation status of key genes, it is possible to determine an individual's metabolic capacity and the risk of drug reactions to specific medications. For example, variations in the drug-metabolizing enzyme gene *CYP2D6* can identify whether an individual is a rapid metabolizer, slow metabolizer, or ultra-slow metabolizer, allowing for adjustments in drug dosage and administration frequency. Understanding the relationship between individual genotypes and factors such as drug metabolism pathways and the affinity of drugs for their targets enables better predictions of drug efficacy and safety. Based on pharmacogenomic information, it is possible to select the most suitable drugs for individuals or adjust drug dosage and administration regimens (Alexandr et al., 2018).

Drug selection and customization also require a comprehensive consideration of individual biological characteristics, disease status, and clinical manifestations. This may include factors such as age, gender, body mass index, liver and kidney function, etc. By comprehensively assessing these features, it is possible to more accurately choose drugs and determine appropriate dosages and administration routes. Personalized treatment also necessitates regular monitoring of a patient's efficacy and drug safety. By monitoring drug concentrations, clinical indicators, and biomarkers, among other factors, it is possible to assess the effectiveness of drug treatment and make timely adjustments to the treatment plan. Regular monitoring and feedback contribute to optimizing individual treatment outcomes and reducing the risk of adverse drug reactions.

2.2 Genome-driven combination drug therapy

Genome-driven combination drug therapy is a personalized medical strategy that involves using multiple drugs simultaneously to target specific disease-driving genes or pathways based on a patient's genomic variations (Figure 3). This individualized treatment approach can more accurately select drugs suitable for the patient and has the potential to improve treatment responses and prognosis.

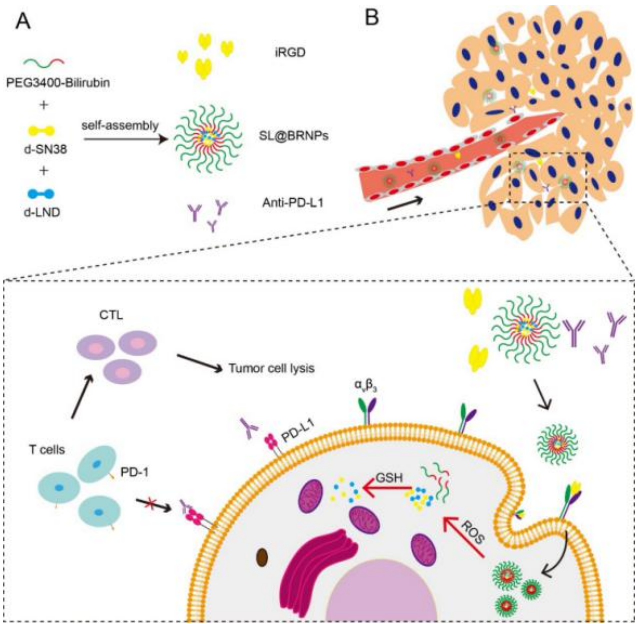

Figure 3 Combined delivery of multiple drugs for anti-tumor therapy

Conduct genomic analysis on patients, such as whole exome sequencing, gene chips, or other genomic technologies. This step can detect mutations, amplifications, deletions, or other variations in specific genes. Based on the results of genomic analysis, identify key genes or pathways driving tumor development. These driver genes are typically associated with processes such as tumor proliferation, angiogenesis, metastasis, anti-apoptosis, etc. Choose drugs that can target these driver genes or pathways. These drugs can be approved targeted therapies or experimental drugs in clinical trials (Schloss et al., 2022).

The selection of drugs is typically based on their sensitivity and inhibitory effects on specific gene mutations. Design drug combination therapy plans based on the characteristics of the target genes and drugs. This may involve the simultaneous or sequential use of multiple drugs to enhance efficacy, delay the development of resistance, or target multiple crucial pathways. After initiating treatment, regularly monitor the patient's response to treatment and drug tolerance. Based on monitoring results, adjust drug dosages, treatment plans, or introduce new drugs.

2.3 Assessment of drug safety and effectiveness

The assessment of drug safety and effectiveness is a comprehensive process involving multiple stages and various sources of data. These evaluations help ensure the safety and effectiveness of drugs in clinical practice, providing physicians and patients with reliable treatment options.

The early stages of drug development typically include preclinical studies, such as in vitro experiments and animal experiments. These studies are conducted to assess the drug's biological activity, toxicity, metabolic pathways, and drug interactions, among other factors. The goal of preclinical studies is to obtain the initial safety and potential therapeutic effects of drugs.

Clinical trials are a crucial step in assessing the safety and efficacy of drugs, divided into three phases: Phase I, Phase II, and Phase III. Phase I trials primarily assess the tolerability and pharmacokinetic properties of the drug in healthy volunteers. Phase II trials expand the sample size to evaluate the drug's efficacy and safety. Phase III trials are large-scale randomized controlled trials that assess the efficacy and safety of the drug in a large number of patients and compare it with existing treatments.

The safety assessment of a drug refers to the evaluation of adverse reactions and side effects during its use. This includes assessing the impact of the drug on the human organ systems, drug tolerability, potential for drug abuse, and safety in specific populations such as children, pregnant women, and the elderly. Data for safety assessment comes from clinical trials, epidemiological studies, drug monitoring, and adverse event reports, among other sources.

The assessment of drug effectiveness refers to evaluating the efficacy of a drug in treating the target disease or symptoms. Effectiveness assessment typically involves using clinical indicators, biomarkers, disease improvement, survival rates, etc., as measures. The assessment of drug effectiveness needs to be conducted in clinical trials, combining clinical experience and analysis of real-world clinical efficacy data.

After a drug is on the market, continuous post-market monitoring is conducted to assess its long-term safety and effectiveness. This includes monitoring adverse event reports for the drug, drug interactions with other medications, and usage patterns in specific populations, among other factors. Through post-market monitoring, rare adverse reactions or other safety issues can be promptly discovered and identified, leading to appropriate actions.

3 Applications of Genome-Driven Personalized Drug Therapy

3.1 Cancer treatment

Genome-driven personalized drug therapy plays a crucial role in cancer treatment. By analyzing the genomic information of a patient's tumor, key genes or pathways driving tumor development can be identified. Medications targeting these specific genetic abnormalities are then selected for treatment. Genome-driven personalized drug therapy provides cancer patients with more precise and targeted treatment strategies, improving treatment effectiveness while reducing unnecessary drug exposure and side effects.

By analyzing the tumor genome, activating mutations in driver genes such as EGFR, HER2, BRAF, etc., can be identified. The abnormal activation of these genes promotes tumor growth and spread. Based on these findings, approved targeted drugs such as EGFR inhibitors, HER2 inhibitors, BRAF inhibitors, etc., can be used to treat these driver genes. This personalized treatment strategy can improve response rates and significantly enhance patient survival and quality of life (Russo et al., 2019; Mao and Liu, 2019).

Immunotherapy is a treatment method that utilizes the patient's own immune system to attack cancer cells. Genome analysis can help identify the immune escape mechanisms of tumors and immune-related genetic variations, such as PD-L1. With this information, appropriate immune checkpoint inhibitors (such as PD-1 inhibitors, PD-L1 inhibitors) or other immunotherapeutic drugs (Figure 4) can be selected to enhance the patient's immune response and promote tumor suppression.

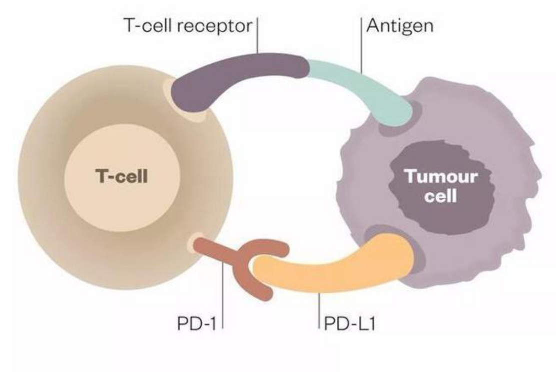

Figure 4 PD-1 inhibitors and PD-L1 inhibitors against cancer

Genome-driven personalized drug therapy can also employ a strategy of combination therapy. By analyzing the tumor genome, abnormal expression or mutations in multiple driver genes can be identified, and these genes may be involved in different signaling pathways. Therefore, using drugs that target different driver genes in combination can simultaneously inhibit multiple key pathways, increasing the effectiveness of treatment.

Genome-driven personalized drug therapy can also be used to monitor and adjust resistance in treatment plans. By regularly analyzing the evolution of the tumor genome, new mutations in driver genes or other mechanisms of drug resistance can be detected. Based on this information, drug selection, dosage, or the introduction of new drugs can be adjusted to overcome the development of resistance.

3.2 Treatment of genetic diseases

Genome-driven personalized drug therapy holds vast prospects and potential in the treatment of genetic diseases. Through the analysis of individual genomes, a better understanding of the pathogenic mechanisms of genetic diseases can be achieved, guiding the formulation of treatment strategies and providing more precise and effective treatment options for patients. The complexity of treating genetic diseases is high, with significant variations in genetic mutations and treatment responses among individuals. Therefore, more research and clinical practice are needed to refine personalized treatment strategies.

For some known genetic diseases, specific gene mutations have been identified as the primary causes of the diseases. Through the analysis of a patient's genome, the mutation types of these disease-related genes can be determined, and appropriate drugs can be selected for treatment. For instance, for specific gene mutations associated with Polycystic Kidney Disease, there are ongoing research and development efforts for treatment strategies.

In addition to known gene mutations, genetic variations among individuals can also impact the effectiveness of drug treatments. Through genomic analysis, genetic variations in genes related to drug-metabolizing enzymes, drug targets, or drug transport proteins in patients can be identified. Based on this information, drug dosages can be adjusted, medications with specific metabolic pathways can be selected, or the use of drugs sensitive to particular gene mutations can be avoided, thereby optimizing treatment effectiveness and reducing adverse drug reactions.

Some hereditary diseases occur due to impaired DNA repair mechanisms. For such diseases, genomic-driven treatment strategies can be employed to repair or enhance the patient's DNA repair mechanisms. For example, in the case of mutations in genes such as BRCA1 or BRCA2, PARP inhibitors can be used to interfere with the DNA repair capability of tumor cells, thereby achieving therapeutic effects.

Some hereditary diseases result from the functional abnormalities of specific genes. In such cases, gene knockout techniques can be employed to restore the normal function of the gene. For example, in the case of certain monogenic diseases, gene knockout or gene editing technologies can be used to repair or replace the patient's abnormal genes, thereby achieving therapeutic effects.

3.3 Precision medication and prediction of drug side effects

The goal of genome-driven personalized medication is to conduct precise treatment and assess the risk of side effects based on individual genomic information. Through genomic analysis and related predictive models, it is possible to better understand the patient's response to drugs and the risk of side effects, thereby optimizing treatment plans, improving treatment outcomes, and reducing unnecessary drug side effects.

By analyzing a patient's genome, gene variations related to drug metabolism, drug targets, or drug transport can be identified. These gene variations may impact the speed of drug metabolism, the affinity of drug targets, or the distribution of drugs in the body, thereby influencing both the efficacy and side effects of medications. Through associating these variations with clinical data, it is possible to predict a patient's responsiveness to specific drugs, thereby achieving precision medication (Xu et al., 2019).

Certain gene variations may impact the metabolic pathways of drugs, leading to changes in the clearance speed of medications. This could result in either excessively high or low concentrations of drugs in the body, thereby affecting both the efficacy and side effects of the medications. Through genomic analysis, gene variations related to drug metabolism can be identified, allowing for the adjustment of drug dosages to ensure that the concentration of the medication in the patient's body remains within the effective range.

Genome-driven personalized drug therapy can also leverage predictive models to forecast drug targets and mechanisms of action. By analyzing a patient's genomic data alongside drug databases, it becomes possible to predict the sensitivity of a patient's targets to specific medications. This aids in determining which drugs are more effective for the patient's condition and avoids the use of drugs insensitive to the patient's genomic characteristics.

Genomic information can also be used to predict a patient's sensitivity to drug side effects. Some genetic variations are associated with adverse reactions to specific drugs. By analyzing these variations, it's possible to predict whether a patient is prone to drug-related adverse reactions and make corresponding adjustments in the treatment plan. This helps reduce the risk of adverse drug reactions for patients and enhances the safety of the treatment.

4 Summary and Outlook

Genome-driven personalized drug therapy is an advanced and highly promising field that achieves precision medicine and predicts drug side effects by analyzing patients' genomic information. Through genomic analysis, associations between patients' genetic variations and drug responses can be identified, allowing the prediction of patient responsiveness and the risk of side effects to specific drugs. This brings significant breakthroughs to the medical field, enabling the optimization of treatment plans, improving efficacy, and reducing unnecessary drug side effects (Yan and Wang, 2022).

The development of genome-driven personalized drug therapy relies on technological advancements and continuous research deepening. The rapid progress and cost reduction of high-throughput sequencing technologies have made acquiring genomic data more convenient and economical, providing more opportunities for personalized treatment. At the same time, people's understanding of the relationship between genes and diseases is constantly deepening, and new gene markers and targeted therapy methods are emerging. However, genome-driven personalized drug therapy still faces challenges. The analysis and interpretation of genomic data require further research and the development of standardized methods to more accurately predict drug efficacy and side effects. The complexity and diversity of individual genomic variations, as well as the interaction between genes and the environment, make the formulation of personalized treatment strategies more intricate. Additionally, issues related to personal privacy and ethics need to be thoroughly considered to ensure the security and compliance of genomic data.

Genome-driven personalized drug therapy will continue to advance and find widespread application in the future. Further development of methods for analyzing and interpreting genomic data will enhance prediction accuracy and reliability. Strengthening research on the interaction between genes and the environment will provide insights into how environmental factors influence genome-driven treatments, enabling the formulation of more comprehensive personalized treatment strategies. The establishment of larger and more diverse genomic databases will strengthen the training and validation of prediction models. Additionally, there is a need to bolster clinical research on the application of genome-driven treatments, evaluating their effectiveness and cost-effectiveness across different diseases. With ongoing technological advancements and deeper research, more targeted treatment methods are expected to be discovered, accelerating drug development and clinical applications. Simultaneously, with the establishment and sharing of large-scale genomic databases, collective intelligence can be better utilized, expediting disease diagnosis and treatment. Genome-driven personalized drug therapy brings significant hope and potential to disease treatment. Through precise drug administration and the prediction of drug side effects, it can better meet individual patient needs, improve treatment efficacy, reduce unnecessary drug side effects, and contribute to the progress of the medical field and the well-being of patients.

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