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High-Throughput Sequencing Technology: A New Chapter in Epigenetics and Disease Research

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Abstract This article outlines the applications of High-Throughput Sequencing (HTS) in identifying DNA methylation, histone modifications, non-coding RNA, and other aspects of epigenetics, as well as its role in understanding the genetic and epigenetic foundations of various diseases, especially cancer and hereditary diseases. It discusses in depth the significant role of HTS in disease diagnosis, treatment selection, and personalized medicine. Particularly in cancer treatment, HTS helps achieve more precise therapies by analyzing the genetic and epigenetic information of tumors. Despite challenges in data processing and analysis, advancements in technology and the development of new algorithms are continuously expanding its application scope. In summary, high-throughput sequencing technology is opening a new chapter in epigenetics and disease research, playing a key role in advancing our understanding of life sciences and driving medical innovation.

Keywords High-throughput sequencing; Epigenetics; Disease research; DNA methylation; Personalized medicine

Over the past few decades, High-Throughput Sequencing technology (HTS) has transformed from a basic research tool to a key driver of advances in modern biology and medicine. The origins of HTS technology can be traced back to 1977, when Sanger and Coulson first introduced the DNA sequencing method, which quickly became the cornerstone of genomics research due to its high efficiency and relatively low cost (Sanger et al., 1977). Subsequently, with the increase in computing power and continuous innovation in sequencing technology, the emergence of HTS technology marked the beginning of a new era, which was able to generate vast amounts of genetic information at unprecedented speed and scale in a very short period of time.

The core advantage of HTS technology is its ability to process thousands of DNA or RNA sequences in parallel, enabling rapid and cost-effective sequencing of entire genomes. This technology not only greatly accelerated the completion of Genome projects such as the Human Genome Project (International Human Genome Sequencing Consortium, 2001), It also opens up the possibility of large-scale analysis of individual genetic variation, thus deepening our understanding of genetics (Gibbs, 2020).

Epigenetics is the study of genetic phenotypic changes that do not involve DNA sequence variation, but regulate gene expression through mechanisms such as DNA methylation and histone modification. Epigenetics plays a crucial role in modern biology as it forms the bridge between the interaction of genetic information and environmental factors, affecting all levels from gene expression to cell function (Deichmann, 2016). With the application of HTS technology, researchers can now study epigenetic phenomena at the genome-wide level, revealing the complex role of epigenetics in development, cell differentiation, and disease occurrence.

The contribution of HTS technology to disease research is particularly significant. Through high-throughput analysis of genetic and epigenetic variations, scientists have identified multiple disease-related biomarkers, which are critical for early diagnosis and prognostic assessment of diseases (Orlov et al., 2022). Especially in the field of cancer research, HTS technology has revealed not only the genetic heterogeneity of cancer, but also the close link between tumor growth and epigenetic regulation. In addition, the application of HTS technology in the study of

genetic and rare diseases provides new insights into the molecular mechanisms of these diseases, opening up the possibility of developing new treatments.

Overall, the development of HTS technology has not only accelerated genomics and epigenetic research, but also provided a powerful tool for understanding the genetic and epigenetic basis of complex diseases and developing new diagnostic methods and treatment strategies. As these technologies are further refined and applied, we expect to see more significant advances in disease prevention, diagnosis and treatment in the future.

1 Application of HTS Technology in Epigenetic Research

1.1 DNA methylation analysis

High-throughput sequencing (HTS) technology has become a key tool in the field of epigenetics, particularly in identifying DNA methylation sites. HTS technology is able to identify methylation sites at high resolution across the whole genome, providing unprecedented depth and detail for understanding the regulatory mechanisms of genetic information. For example, by integrating HTS techniques and bioinformatics methods, researchers have been able to reveal the role of methylation in gene silencing, X chromosome inactivation, and embryonic development.

In 2023, Wei et al. found that PGC7 regulates genome-wide DNA methylation by regulating subcellular localization of DNMT1 mediated by ERK. This work reveals a new mechanism by which PGC7 regulates genome-wide DNA methylation by phosphorylating DNMT1 via ERK, which may provide new insights into the treatment of DNA-methylation-related diseases (Wei et al., 2023).

In 2023, Signoretti and Gupte found that G6PD regulates genome-wide DNA methylation and gene expression in rats with thalassemia G6PD variants. This suggests that G6PD plays a role as a regulator of DNA methylation in healthy vascular tissue, a finding that contributes to understanding the role of DNA methylation in non-disease states (Signoretti and Gupte, 2023).

By analyzing samples from different populations (including tobacco addicts, athletes, etc.), Chmielowiec et al. 2023 revealed methylation levels of multiple CpG islands of the DAT1 gene and found that these methylation levels differed significantly from control groups compared to tobacco addicts and athletes. This study provides new research directions to explore how DNA methylation regulates dopamine release (Chmielowiec et al., 2023).

By shedding light on these complex regulatory mechanisms, these studies not only increase our understanding of fundamental biological processes, but also provide possible future therapeutic targets for abnormalities that arise in these processes.

In the field of disease research, methylation is closely related to the occurrence and development of many diseases. In cancer research in particular, HTS techniques have revealed that methylation silencing of tumor suppressor genes is a common feature of many types of cancer. In breast cancer patients, for example, Azmi and Shahid's 2023 study found that hypermethylation of the BRCA1 gene is associated with silencing of gene expression, a major cause of breast cancer development. This study used sulfate sequencing technology to analyze DNA methylation status, demonstrating the importance of HTS technology in identifying and understanding the mechanisms by which tumor suppressor genes are silenced by methylation (Azmi and Shahid, 2023).

In addition, cardiovascular disease studies have also shown that changes in methylation of specific genes are associated with an increased risk of the disease. Ridha et al. 2023 used HTS technology, specifically multiple methylated DNA immunoprecipitation sequencing (Mx-MeDIP-Seq), to study changes in DNA methylation in low-volume DNA samples. This technique enables the analysis of methylation status in many DNA samples, revealing the critical role of methylation in the development of cardiovascular diseases, especially abnormal methylation outcomes in the regulation of gene expression, such as cancer, autoimmune diseases, atherosclerosis, and cardiovascular diseases (Ridha et al., 2023).

By gaining a deeper understanding of these methylation events, HTS technology can not only provide new insights into disease mechanisms, but also provide a basis for the development of new diagnostic approaches and treatment strategies.

1.2 Histone modification analysis

HTS technology also plays an important role in the study of histone modification. By precisely identifying the type and location of histone modifications, the researchers were able to explore how they affect gene expression and chromosome structure. Modification patterns such as acetylation and methylation of histones regulate gene activity by affecting chromatin tightness, which is particularly important in the process of cancer occurrence and cell differentiation.

For example, trimethylation at the K27 site of histone H3 (H3K27me3) is an important silent marker, and its abnormal increase in multiple cancers is strongly associated with dysregulation of gene expression and tumor development.

While the 2023 study by Zhao et al. focused on one invasive insect, However, Chromatin Immunoprecipitation with high-throughput sequencing (ChIP-seq) revealed that H3K4me3 was related to gene activation, while H3K27me3 was mainly related to transcriptional inhibition. This finding supports the role of H3K27me3 in gene silencing, providing a basis for understanding its role in cancer (Zhao et al., 2023).

The 2023 study by Zhou et al. used CUT&Tag technology to analyze histone modifications in early embryonic development in cattle and humans. It was found that H3K9me3 and H3K27me3 co-occupied the genome before embryo gene activation, suggesting a global transcriptional inhibition mechanism. This study reveals the primary role of H3K27me3 in limiting cell potential, providing insights into its function in cancer (Zhou et al., 2023)

This study from Yang et al. 2023 focuses on H3K4me3, but it mentions the effect of histone modifications on tumor cell proliferation, migration, and invasion, which echoes the role of H3K27me3, as both may co-participate in cancer development in some contexts (Yang et al. 2023).

These studies highlight the critical role of H3K27me3 in cell fate determination and cancer development, particularly in gene silencing and methylation silencing of tumor suppressor genes. By better understanding the role and mechanism of action of H3K27me3, we can provide new strategies and targets for cancer diagnosis and treatment.

1.3 Identification and functional study of epigenetic marks

HTS technology has not only made significant progress in identifying epigenetic marks, but has also advanced the understanding of the function of these marks. The latest research, using HTS technology, reveals a direct link between epigenetic marks and disease. For example, by analyzing genome-wide epigenetic maps in different disease states, researchers have been able to identify specific methylation and histone modification patterns that can serve as biomarkers for disease.

This study by Whelan et al. 2023 highlights the use of DNA methylation in animal welfare monitoring and, while focusing primarily on animal models, provides a methodological framework for understanding epigenetic markers in human disease. By analyzing animal DNA methylation patterns and techniques, the study demonstrates a key framework for complex DNA methylation biomarkers, DNA methylation clocks, and environment-specific DNA methylation signatures that can provide complex, context-dependent readings of health and disease in disease states (Whelan et al., 2023).

The 2023 study by Costa et al. focused on epigenetic reprogramming in cancer, particularly changes in DNA methylation, histone modification, and expression of non-coding RNA. These dynamic epigenetic changes are associated with tumor heterogeneity, infinite self-renewal capacity, and multiseries differentiation, and are a major challenge for treatment and drug resistance. Research has highlighted the ability to restore cancer epigenomes by

inhibiting epigenetic modifiers as a promising treatment strategy either as monotherapy or in combination with other anti-cancer therapies (Costa et al., 2023).

This study by Bunsick et al., 2023, focused on how cannabinoids transform the metabolic phenotype of cancer through epigenetic reprogramming. By analyzing the environmental influence of cannabinoid factors and their combined effects on epigenetic modification, the study reveals a novel mechanism by which cannabinoids regulate cancer metabolism and epigenetic reprogramming through a biased G protein-coupled receptor signaling platform (Bunsick et al., 2023).

These studies not only deepen our understanding of how the disease occurs, but also offer the possibility of developing new diagnostic methods and treatment strategies. For example, drugs developed to target specific epigenetic alterations have entered clinical trials, demonstrating the great potential of epigenetic research based on HTS technology (Jung et al., 2023; Liu et al., 2023; Lordo et al., 2023).

2 Application of HTS Technology in Disease Diagnosis and Treatment

2.1 Cancer research

High-throughput sequencing (HTS) technology has revolutionized our understanding of cancer diagnosis and treatment. Through in-depth methylation patterns and histone modification analysis of tumor samples, HTS technology can not only help diagnose cancer, but also provide prognostic assessment for patients.

2.1.1 Methylation pattern analysis

The HTS technique allows researchers to analyze the DNA methylation status of cancer cells on a genome-wide scale, revealing that methylation silencing of tumor suppressor genes is a feature common to many types of cancer. This discovery is crucial for early diagnosis and cancer typing.

Wu et al. (2023) examined the DNA methylation profiles of the regulatory sequences of 57 known DNA repair pathway genes through targeted methylation sequencing technology, and found that the methylation levels of 5 genes were significantly different between breast cancer cases and controls, suggesting that DNA methylation may be an epigenetic marker of breast cancer susceptibility in the blood.

Haber et al. (2023) mapped the partial methylation domains (PMDs) of circulating tumor cells (CTCs) in a patient's blood at the single-cell level and found that 40 "core PMDs" were shared within cancer cells and between different individuals, as well as in prostate cancer cell lines. These core PMDs are highly enriched in immune-related genes, which tend to be located within a single chromosomal locus that targets silencing caused by demethylation.

Luo et al. (2023) found that the LRRC3B (3B containing leucine-rich repeats) gene is a tumor suppressor gene that plays a role in the anti-tumor immune microenvironment. LRRC3B expression and the DNA methylation status of its promoter region can be useful markers for predicting response to anti-PD-1 therapy.

These studies further highlight the importance of HTS techniques for genome-wide analysis of DNA methylation status in cancer cells, revealing a common feature of methylation silencing of tumor suppressor genes in multiple cancers, and providing new opportunities and targets for early diagnosis and treatment of cancer.

2.1.2 Histone modification analysis

With the HTS technique, the researchers were able to study in detail the histone modification patterns in cancer cells, such as abnormal increases in H3K27me3, which are strongly associated with dysregulation of gene expression and tumor development. This information is valuable for understanding the pathogenesis of cancer and developing new therapeutic targets.

Vezzoli et al. (2023) showed that in human embryonic stem cells, the acetylation of H3K18ac and H3K27ac is only partially established by p300, which is the main mode of acetylation of these histone proteins in somatic cells.

The study reveals a more complex histone acetyltransferase (HAT) pattern in stem cells than previously thought, suggesting that H3K18ac and TFIIIC may play a role in regulating "stem-cell" genes, as well as genes associated with neural differentiation.

Zhao et al. (2023) through Chromatin Immunoprecipitation with high-throughput sequencing (ChIP-seq) technology, Two important histone modifications, H3K4me3 and H3K27me3, were screened in an invasive pest. The results showed that H3K4me3 was associated with gene activation, while H3K27me3 was mainly associated with transcriptional inhibition. This study provides a basis for understanding the role of histone modifications in cancer cells.

Lin et al. (2023) used CUT&Tag technology to map genome-wide H3K27me3 and H3K27ac placeholder maps in the neural tissue of a Benz [a] Pyrene (BaP) -induced neural tube defect (NTDs) mouse embryo model. Further RNA sequencing analysis revealed the regulatory effect of histone modification on gene expression. These findings provide important clues to understanding the role of histone modification in cancer cells.

These studies demonstrate the importance of HTS techniques in studying histone modification patterns in cancer cells, particularly the abnormal increase of H3K27me3 and its association with dysregulation of gene expression and the development of fistula. A deeper understanding of these epigenetic modifications could provide new strategies and targets for cancer diagnosis and treatment.

2.1.3 Epigenetic-based treatment strategies

With the application of HTS technology in cancer research, epigenetic-based treatment strategies are becoming a reality. For example, drugs developed to target specific epigenetic changes, such as DNA methylation and histone modification, have entered clinical trials, showing great potential to treat cancer (Jung et al., 2023; Shoaib et al., 2023; Zhang et al., 2023).

2.2 Hereditary and rare diseases

HTS technology also plays an important role in the diagnosis and treatment of genetic and rare diseases.

2.2.1 Reveal epigenetic mechanisms of inherited diseases

HTS technology allows researchers to understand epigenetic mechanisms of genetic diseases at the molecular level, such as methylation changes in specific genes that are associated with an increased risk of disease. This opens up the possibility of accurate diagnosis and early intervention.

A 2023 study by Noguer et al., using whole genome bisulfite sequencing (WGBS), found that 4,167 potential marker regions showed differential methylation signals in colorectal cancer (CRC), advanced adenoma (AA), and corresponding normal tissue (NAT) samples. Suggests that alterations in methylation in these regions are associated with an increased risk of disease (Noguer et al., 2023).

The study by Koowattanasuchat etc in 2023, developed a Methylscape sensing platform based on the methylation-dependent DNA dissolution principle to observe the dispersion of Cyst/AuNPs adsorbed on these DNA aggregates in a $MgCl_2$ solution. Methylation configurations of normal and cancer DNA can be distinguished, providing a new method for early detection of cancer (Koowattanasuchat et al., 2023).

A 2023 study by Visvanathan et al validated the clinical value of liquid biopsie-breast cancer methylation (LBx-BCM) prototype testing for early assessment of disease progression in metastatic breast cancer (MBC), showing the potential of methylation-based testing (Visvanathan et al., 2023).

These studies show that by analyzing methylation changes in specific genes, important biomarkers associated with increased disease risk can be revealed, providing new avenues for accurate diagnosis and early intervention in diseases such as cancer.

3 Challenges and Future Directions

3.1 Technical and research challenges

With the development of high-throughput sequencing (HTS) technology, researchers are able to generate large amounts of data in a short period of time. However, this also presents significant challenges for data processing and analysis, including data storage, increased demand for computing resources, and complex data analysis technical requirements (Lin and Ngiam, 2023).

Although the role of epigenetics in the development of disease has been widely recognized, how to directly derive the specific mechanism of disease from specific epigenetic changes remains a challenge. This is mainly because epigenetic alterations are often associated with multiple genes and biological pathways, and the interactions between these genes and pathways are very complex (Selcen et al., 2023; Li et al., 2023).

3.2 Future direction

The use of artificial intelligence (AI) and machine learning (ML) techniques in HTS data analysis is expected to increase significantly. These techniques can help automate the analysis process and identify patterns and associations in the data, thus solving the problem of large data volumes and high analysis complexity. In addition, the development of next-generation sequencing technologies will further increase sequencing speed and reduce costs, enabling more refined and comprehensive epigenetic studies (Lin and Ngiam, 2023).

The study of epigenetics can not only provide new insights into the mechanism of disease, but also provide new strategies for the early diagnosis and personalized treatment of disease. For example, by analyzing an individual's epigenetic characteristics, early biomarkers of disease can be found, enabling early diagnosis and prevention. In addition, the development of drugs and therapies that target specific epigenetic alterations is expected to provide new treatment options for many difficult-to-treat diseases (Lordo et al., 2023; Ren et al., 2023).

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