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Next-Generation Sequencing in Medication Development has been identified in Clinical Trials

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Abstract

The technology of massively parallel or deep sequencing, known as next generation sequencing (NGS), has transformed genomic research. Next-generation sequencing, in comparison to first-generation sequencing, is characterised by high accuracy, rapid speed, and low cost. So far, there are a variety of NGS platforms that use various sequencing technologies. Despite significant differences in engineering, sequencing chemistry, output, accuracy, and cost, all NGS platforms execute parallel sequencing of millions of tiny pieces of DNA. Next-generation sequencing (NGS) is a high-throughput sequencing technique (HTS) that can be used for genome sequencing, re-sequencing, epigenome characterisation, DNA-protein interactions (ChIP-sequencing), and transcriptome profiling (RNA-seq). Next-generation sequencing has now proven to be a useful and efficient method for biosafety assessment. NGS is utilised for a variety of applications, including pathogen safety testing and genetic characterisation, because of its high accuracy and in-depth study of nucleic acid.

Keywords: NGS; Sequencing; GWAS

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Introduction

Genetic variables are known to cause or influence a significant range of human diseases, which might provide valuable insights into disease aetiology and lead to the development of new treatment techniques. For more than four decades, genetic linkage studies have been used to successfully identify causal genetic components in Mendelian illnesses. Despite these advances, many prevalent diseases do not have Mendelian inheritance and instead have complex multifactorial inheritance patterns, making genetic-linkage-based research less effective in capturing the allelic drivers of such disorders. Genome-wide association studies (GWAS) were frequently used to determine susceptibility loci linked with complex traits to overcome these constraints [1]. GWAS have been used in a number of human diseases and features since 2005, when the first one was published on individuals with age-related macular degeneration [2,3]. Among these findings are various examples of disease-associated genes that have been identified as effective therapeutic targets, such as HMGCR, which is linked to blood cholesterol levels and is a target of statins. GWAS can also aid in the discovery of molecular mechanisms that influence illness susceptibility. The confirmation of the interleukin (IL)-12/IL-23 pathways in inflammatory bowel diseases and the discovery of the autophagy pathway in inflammatory bowel diseases through the ATG16L1/IRGM associations are two early examples; indeed, it has now become clear that modulating autophagy has strong therapeutic implications for drug development. Pleiotropic SNPs have also been discovered in GWAS for a variety of disorders, sometimes with opposite effects. SNPs found in the IL23R locus, for example, have been linked to autoimmune diseases such ankylosing spondylitis, inflammatory bowel disease, and psoriasis. GWAS-discovered pleiotropic genes can be used for drug repurposing or basket trials that recruit patients with a variety of conditions. For the treatment of autoimmune illnesses, monoclonal antibodies targeting IL-23 and/or IL-12 are already in clinical studies. According to a recent study, the proportion of therapeutic mechanisms supported by direct genetic evidence across the drug development pipeline can increase at the preclinical stage for marketed medications in well-studied indications. As a result, human genetic research on well-phenotype populations can help guide the selection of the appropriate targets and indications, which can have a quantifiable impact on the success of novel drug development [4]. It has long been recognised that the vast amount of human genetic data may be used to find pharmacological targets, confirm therapeutic theories, and predict the probable safety of inhibitory drugs aimed at molecular targets.

NGS offers the potential to reveal a large number of mutations linked to genetic illnesses, as well as identify target genes for

future medication development. In comparison to GWAS, which relies on proxy markers for unknown causative variants or genes, NGS is gaining traction as a preferred method for identifying pharmacological targets. Sequencing well-phenotype populations in combination with longitudinal electronic health records (EHRs) as a test bed to uncover genes related with a variety of phenotypic qualities is a particular trend in the field for such objectives. The Discover research, a cooperation between Regeneron and Geiringer Health System, was one of the first to do whole-exome sequencing on a large number of participants with matched EHRs [5].

Conclusion

Next-generation sequencing (NGS) allows for the quick detection of both common and unusual genomic variations. For the application of customised pharmacotherapy, the discovery of variations that contribute to therapeutic medication response or side effects is critical. Despite predicted technological obstacles, short-read based NGS has already been demonstrated to be successful in pharmacogenes with high sequence homology, adjacent pseudogenes, and complicated structure. However, little is known about the efficacy of such panels in detecting copy number variation (CNV) in the highly polymorphic cytochrome P450 (CYP) 2D6 gene or identifying the UDP glucuronosyl transferase (UGT) 1A1*28 promoter (TA)7 TAA repeat polymorphism. PGxSeq, a targeted exome panel for pharmacogenes relevant to drug disposition and response, was created and validated.

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