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Opinion Article

Exploring Complex Pharmacogenomic Regions with Long Working Sequencing

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DESCRIPTION

Pharmacogenomics (PGx) is essential for personalizing medicine dosages and enhancing the effectiveness of medicinal therapy. PGx is dependent on characteristics that are inferred from known pharmacogenetic variations. However, due to a number of reasons, conventional PGx genetic assays cannot completely account for genetic variation in drug response and enzyme activity. First of all, the genetic make-up of all the genes involved in drug response cannot be fully resolved by the genotyping assays used today. Second, it's not always clear how a medicine works or how its metabolic pathway works. To determine what percentage of variability is hereditary and what percentage can be attributed to other causes, it is critical to be able to explain all genetic components causing varying medication response. The majorities of pharmacogenes, however, are either partially or entirely located in complicated genomic regions or have polymorphisms such tandem repeats and pseudo gene hybrid conformations, which make this difficult. Short-read sequencing or SNV (Single Nucleotide Variant) microarrays are the two genotyping technologies now in use. Due to their inability to accurately and consistently resolve highly homologous regions and find PGx variations, both techniques are constrained in their ability to characterise these complex regions. Furthermore, haplotype phasing could reveal whether variations are found on the same allele or on distinct alleles, which might affect how phenotypes are assigned. PGx diplotypes are now phased according to genetic linkage. On a population level, this produces precise haplotypes, but it does not necessarily produce precise assumptions for a given person. These difficulties significantly influence clinical practise. Short-read sequencing, for instance, is unable to provide a complete picture of the complex gene *CYP2D6*, which is implicated in the metabolism of 20–30% of frequently prescribed medications.

The ability to characterise complicated pharmacogenomic areas has recently been demonstrated by long-read sequencing technologies from PacBio and Oxford Nano pore. Long, high-quality reads greatly increase the accuracy of variant calling for these regions and enable the resolution of completely phased diplotypes. Long-read sequencing has also been used recently to study the HLA genes in relation to PGx. Additionally, it has been applied to a variety of difficult clinical diagnostic research tasks, including resolving the *PKD1* gene to find mutations linked to polycystic kidney disease and the lengthy tandem repeat in the *FMR1* gene linked to Fragile X syndrome.

Finally, haplotype phasing is facilitated by long-read sequencing without the requirement for computational methods or pedigree information. This may be of utmost significance in helping PGx forecast phenotypes more precisely. Haplotype phasing and PGx complexity suggest that long-read sequencing has the potential to significantly enhance our capacity to accurately forecast drug metabolizer phenotypes. In this proof-of-concept article, we use the sequencing data of the well-characterized Genome in a Bottle (GIAB) reference sample HG002 to evaluate the potential of long-read PacBio sequencing to resolve complicated PGx regions. The polymorphic nature of pharmacogenes. Because it is very likely that one person would possess many variations of a single pharmacogenes, haplotype phasing is crucial. Additionally, compared to Gencode characteristics, the haploblocks for the pharmacogenes were substantially larger because to the high abundance of variants.

In terms of SNV detection, long read sequencing is comparable to short read sequencing, but it performs better when it comes to complicated SVs and haplotype phasing. An inferred intermediate metabolizer phenotype and a poor metabolizer phenotype may differ depending on haplotype phasing. Current PGx haplotyping methods include computational phasing, which often results in correct population-level phasing but not necessarily at the individual level. Accuracy in phasing for one person is essential because pharmacological changes are done on an individual basis. Here, we demonstrate that the majority of pharmacogenes may be fully phased into haploblocks without the use of computational phasing or lineage information thanks to long-read sequencing.

Additionally, due to the high precision and recall for SNVs, Indels, and SVs, long-read sequencing provides a thorough analysis of every variant in the chosen PGx loci, including

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structural and uncommon variants. For instance, the *CYP2D6* locus can be fully characterised, as well as any potential CNVs, because the median read length is about three times longer than the size of the locus. The use of long-read PacBio CCS data for the training of the Deep Variant caller can be used to explain the significant discrepancy between Deep Variant and GATK (Genome Analysis Toolkit) for Indels. Using over 100 times more substitutions than indels, GATK was created with the error mode of short read sequencing as its foundation. While PacBio HiFi training data contains a ratio of 30 times more indels than substitutions, Deep Variant has learned the error mode from this data. Long readings and Deep Variant specifically help identify Indels and tandem repeats much more accurately. This distinction underlines once more the superiority of long read sequencing over short read sequencing for the detection of complicated variations. With this restriction, we believe that it is adequate to act as a proof-of-concept study looking into the possibilities of long-read sequencing for PGx. People come to the conclusion that long-read sequencing data offers excellent opportunities to elucidate complex PGx loci and haplotype phasing while maintaining accurate variant calling in the chosen pharmacogenes based on these data regarding the variant calling accuracy and capacity to resolve complex pharmacogenes into phased haploblocks.