Advancing targeted haplotyping in pharmacogenomics using adaptive sampling

Deserranno Koen (1,2), Tilleman Laurentijn (1), Rubben Kaat (1), Deforce Dieter (1,2), Van Nieuwerburgh Filip (1,2)

(1) Laboratory of Pharmaceutical Biotechnology, Faculty of Pharmaceutical Sciences, Ghent University
(2) Cancer Research Institute Ghent (CRIG), Ghent, Belgium

INTRODUCTION

Pharmacogenomics (PGx) encompasses the personalisation of a patient's drug therapy based on its genomic blueprint. However, current microarrays and short-read sequencing genotyping techniques are limited in the information they provide as they are unsuccessful to identify complex structural variants. In addition, they fail to perform unambiguous haplotype assignment, critical for PGx star-allele classification. We applied adaptive sampling on PromethION to characterize a panel of 1056 relevant PGx genes extracted from the Pharmacogenomics Knowledge Base (PharmGKB). We characterized the Genome in a Bottle HG001, HG002 and HG005 samples, and assessed variant calling performance and phased structural variant identification.

METHODS

- ✓ Resulting .bed file targeting 5.68 % of the GRCh38 reference genome used as input for adaptive sampling
- ✓ Bioinformatics pipeline including guppy 6.4.2 SUP basecalling, minimap2 alignment, and Clair3 variant calling
- ✓ Structural variant identification and genotyping using CoLoRGen pipeline

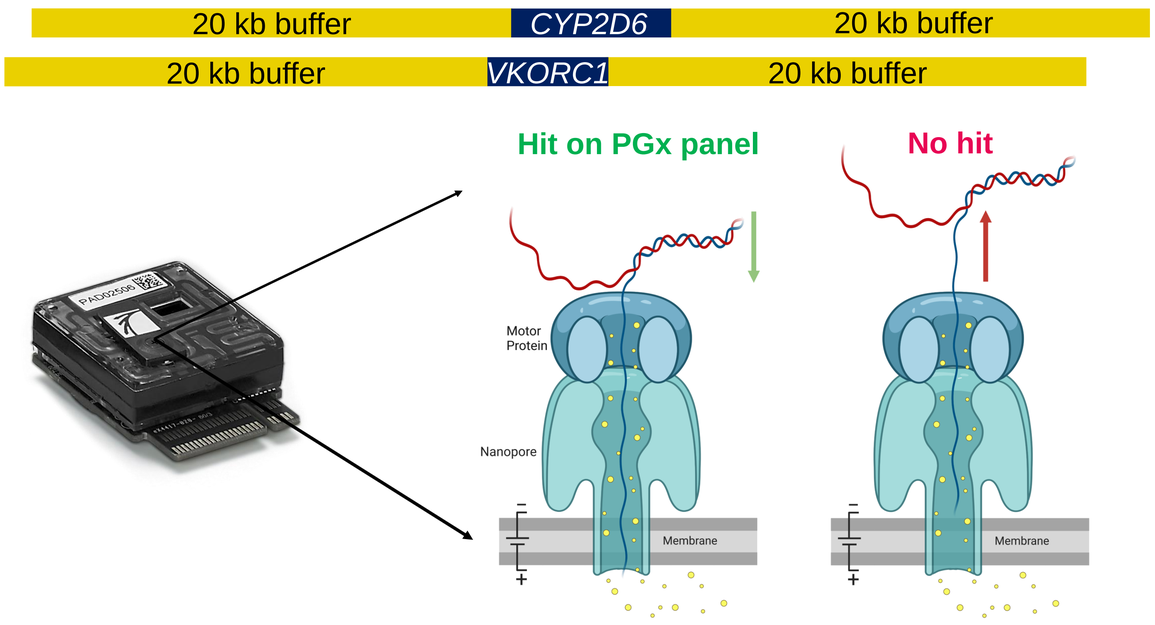

Figure 1: Graphical overview of our strategy. Based on initial alignment, a read was continued sequencing if matching to one of the PGx genes in the target .bed file.

CONCLUSION

- ✓ Our results show the potential of adaptive sampling and the latest nanopore sequencing chemistry to inform haplotype-guided pharmacological treatment.
- ✓ Structural variants can be detected and directly be used to call star alleles.
- ✓ Multiplexing of at least two samples is possible on a single R10.4.1 flow cell, thus increasing cost-effectiveness.

ACKNOWLEDGEMENTS

nxtgnt SEEquencing Genes
GHENT UNIVERSITY
FACULTY OF PHARMACEUTICAL SCIENCES

Krusche, Peter, et al. "Best practices for benchmarking germline small-variant calls in human genomes." *Nature biotechnology* 37.5 (2019): 555-560.
Nanoporetech website. https://nanoporetech.com/. Accessed on April 16th, 2023.

RESULTS

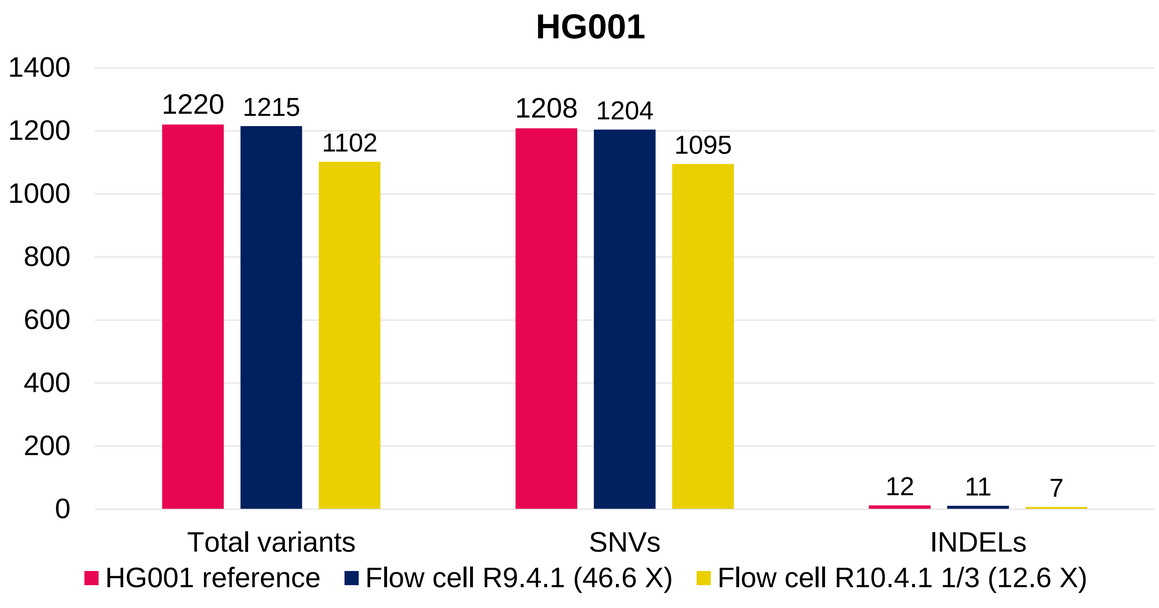

Figure 2: Benchmarking the number of small variants recovered compared to the HG001 Krusche et al. reference. For the R9.4.1 flow cell, a single sample was sequenced. For the R10.4.1 flow cell, three samples were multiplexed using the SQK-NBD114.24 kit. Overall recall was 99.59 % and 90.33 % for the R9.4.1 and R10.4.1 flow cell, respectively.

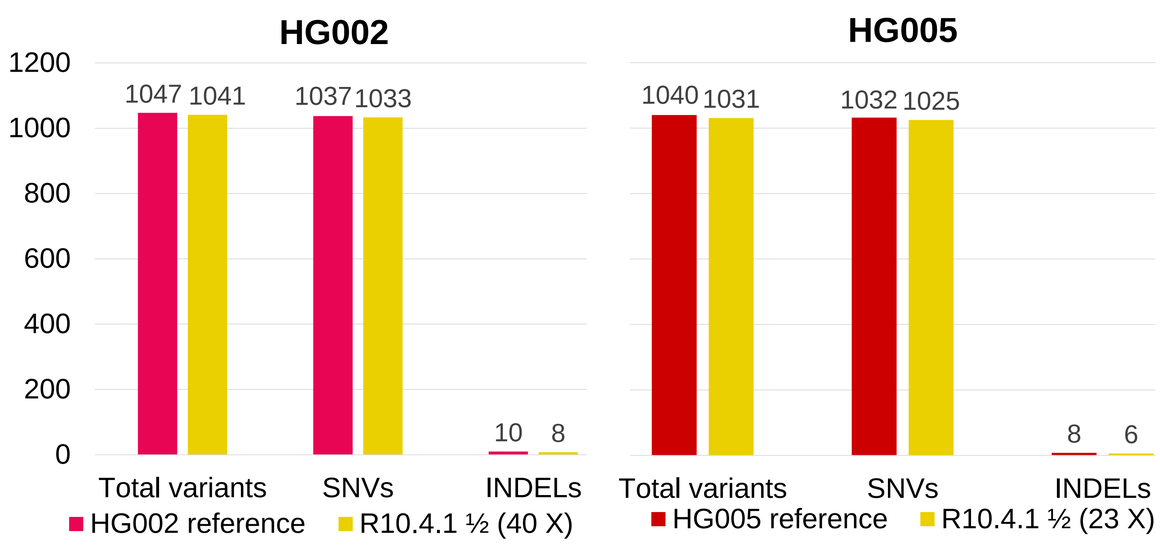

Figure 3: Benchmarking the number of small variants recovered compared to the HG002 and HG005 reference. Overall recall was 99.43 % and 99.13 %, respectively.

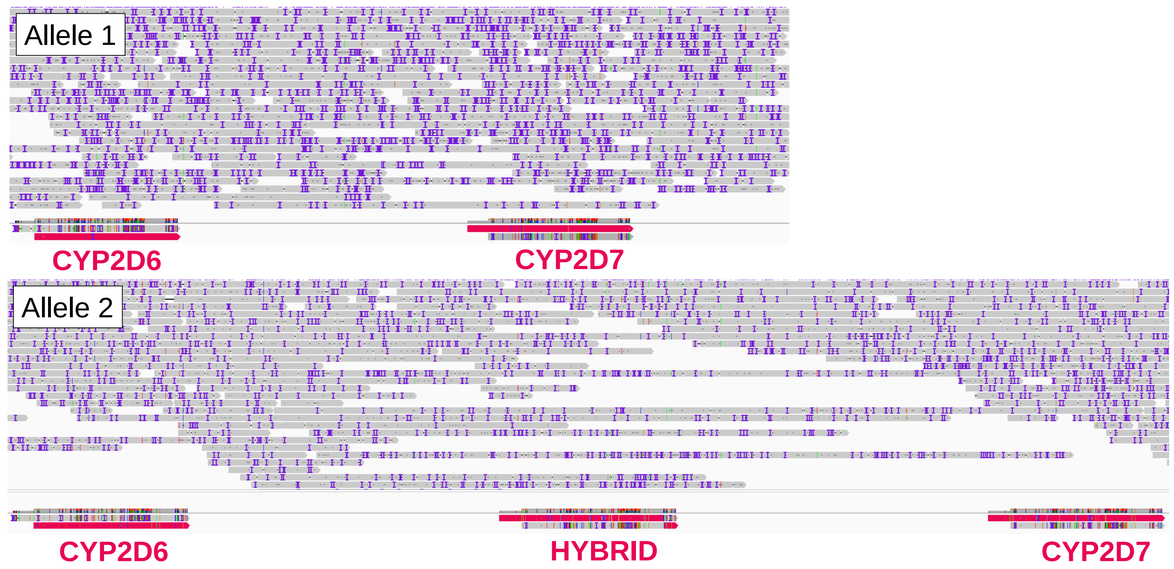

Figure 4: IGV-plots illustrating PGx structural variant identification. The GRCh38 *CYP2D7* and *CYP2D6* genes, and the raw reads were aligned to the CoLoRGen consensus sequence of allele 1 and 2. Red bars show the gene identified. The *3/*4+*68 diplotype was called correctly.

Contact:
✉ Koen.Deserranno@UGent.be
@KoenDeserranno