57th European Human Genetics Conference (ESHG Hybrid Conference), 01.-04. Juni 2024, Berlin, Deutschland

Comprehensive Blood Group Genomic Profiling: A Leap Forward with Adaptive Sampling

M. Gueuning (1), G.A. Thun (1), M.P. Mattle-Greminger (1), S. Meyer (2)
(1) Blood Transfusion Service Zurich (SRC), Department of Research and Development, Schlieren, Switzerland.
(2) Blood Transfusion Service Zurich (SRC), Department of Molecular Diagnostics and Cytometry, Schlieren, Switzerland.

Background: In transfusion medicine, genetic characterization of blood groups is of great importance, especially for patients regularly transfused like those with thalassemia or sickle cell disease. While SNV-based genotyping is generally effective for characterizing most of 45 known blood group systems, some systems involve paralogous genes prone to complex variation, which is challenging to resolve. Oxford Nanopore Technologies (ONT) has recently introduced a long-read sequencing enrichment method called 'adaptive sampling', which computationally eliminates off-target reads during real-time sequencing. As this approach does not pose restrictions on DNA fragment length, it is highly suitable to detect structural variants.

Methods: Our study aimed to evaluate adaptive sampling's effectiveness in the characterization of the entire blood group genome, particularly in cases where the genetic underpinnings for observed blood group phenotypes were unclear. We targeted ~8.6 Mb of the human genome, covering 51 blood group genes, along with 2 hematopoietic transcription factors and 7 human platelet antigen genes.

Results: Latest PromethION flow cells provided high mean read coverage across target regions (>45x), enabling accurate variant calling. Validation against genotype data for 17 blood group systems revealed 100% concordance with up to 73 pre-typed variants, including complex systems like RH and MNS. Notably, the sequencing data uncovered novel structural variants, such as a ~8.6-kb deletion in *RHCE*, providing explanations for previously unresolved blood group phenotypes.

Conclusion: In summary, adaptive sampling proved promising for complementing current tools in transfusion medicine, offering an accurate, user-friendly, and comprehensive approach to unravel the entire individual blood group genome.