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Targeted sequencing of the entire blood group genome by adaptive sampling

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In transfusion medicine, genetic characterization of blood groups is of great importance, particularly for patients who require regular transfusions, such as those with thalassemia or sickle cell disease. While SNV-based genotyping is often sufficient to characterize most of the 45 blood group systems, some systems consist of paralogous genes whose variation and haplotypes are notoriously difficult to elucidate, even with short-read sequencing. Adaptive sampling is a promising method because it allows to specifically target all relevant genes in one sequencing run and excels in resolving structural variants (SVs) and haplotypes thanks to the long reads.
Here, we aimed to assess the power of adaptive sampling for blood group identification, especially in cases where the observed blood group phenotypes had so far lacked a genetic explanation. Overall, we targeted ~8.6 Mb of the genome, encompassing 51 blood group genes, 2 transcription factors, 7 platelet, and 4 neutrophil antigen genes. For validation purposes, we compared variant calls obtained by clair3/sniffles2 with pre-typed genetic data for 17 blood group systems.
Sequencing cases on separate PromethION flowcells produced >45x read coverage across target regions, enabling accurate variant calling. Concordance was 100% with up to 73 pre-typed variants, half of which characterized the complex RH and MNS systems. Notably, the sequencing data also unveiled novel SVs (e.g. a ~8.6-kb deletion in *RHCE*) that explained hitherto unresolved blood group phenotypes. In summary, adaptive sampling showed great potential for improving transfusion medicine as an accurate, straightforward and comprehensive approach to unravel the entire individual blood group genome.