Interpreting Complex and Uncommon MNS Alleles from Whole Genomes

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Background
The MNS blood group system consists of three homologous genes: GYPA, GYPB, and GYPE. Many MNS alleles contain complex structural variations (SV) such as partial gene deletions and multi-step gene recombinations that form hybrid genes, which represent a challenge for the development of WGS genotyping algorithms. Here we performed WGS on nine established MNS samples exemplifying diverse types of MNS alleles: U+var and GYP hybrid series GYP(A-B), GYP(B-A), GYP(B-A-B), and GYP(B-E-B).

Methods
The MNS single nucleotide variations (SNV) and SV were identified using our bloodTyper software with SV being called using a combination of read depth, paired reads, and split read interpretations. Analysis of interpretive gaps from these nine known samples was used to update bloodTyper and then used to call the MNS alleles in all 3,202 high coverage whole genomes from the 1000 Genomes Project.

Results
U+var was shown to be expressed mostly as a hemizygous change trans to GYPB deletions, a finding confirmed in 25 known U+var samples. The analysis of the nine known samples also led to the description of unique breakpoints and characterization of three novel alleles: GYP*Hil.02, *JL.02, *JL.03, and confirmation of the recently described GYP*Bun.02. In addition, the GYP*JL.03 sample was identified to be compound heterozygous for the GYPA*01N allele, allowing for the first ever description of the exact breakpoint for this long established allele. Furthermore, the breakpoints for the GYP*Dantu(NE) were updated to include a region of GYPB exon 6 in a duplicated copy of GYPE. Analysis of the 1000 Genomes Project found GYP*Hil, *Sch (with three different breakpoints), *Dantu(NE) and several potentially novel alleles including two B-A hybrids, one E-A hybrid, and four complex SV likely representing several recombination events.

Conclusion
This work enhances characterization of WGS data within the MNS blood group system to include rare alleles, and further develops genomic analytical strategies and automated interpretation of blood group alleles.