Editorial Commentary

Genetic blood typing by high throughput sequencing

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Accurate blood typing is an essential step to minimize alloimmunization caused by blood transfusion. For patients with chronic anemia, such as sickle cell disease and thalassemia, multiple transfusions are indispensable in the long run. However, the management of transfusion remains challenging in clinical practice (1). Limited accuracy of serological tests can cause mismatches and the resulting alloimmunization can be life-threatening (2). Weak or partial expression of antigen might also confuse the blood typing (3). Therefore, conventional blood typing using serology may not best suit the clinical demands on the rise and genetic blood group testing would be a better alternative to complement the current serological methods.

Conventional serological methods are based on the immunoreactions between transmembrane antigens of red blood cells and antibodies in the serum. Most of time, serological tests provide rapid and reliable results in an inexpensive fashion. However, there are cases where blood typing based on serology fails and leads to blood type mismatches. With the advancement of molecular techniques, commercial microarray- based platforms are clinically available for identifying single nucleotide polymorphisms (SNPs) in blood group antigen coding genes (4,5). The detection of SNPs can compensate for the less common variants which serological methods do not routinely cover. However, the current SNP typing method cannot fully identify the existing variations especially the unreported ones and is not applicable to detect rare chromosomal rearrangement events such as large insertion, deletion or hybridization (6). Therefore, more comprehensive database of blood group antigen coding genes are urgently warranted for precise blood typing.

As multiple next-generation sequencing (NGS) platforms have been commercialized since 2005, NGS has become a powerful tool for discovery of novel genetic variants in both clinical and scientific research. Stabentheiner and colleagues (7) applied NGS in blood group research first in RHD genotyping and provided a proof of concept in 2010. Then NGS was applied in whole blood group detection. In 2015, Giollo and colleagues (8) proposed a predictor, BOOGIE, for the inference of blood groups from SNV databases and achieved a 94% concordance for the Personal Genome Project database. The DNA data need to be analyzed in advance. Lane and colleagues (9) improved the accuracy of the whole genome sequencing typing algorithm, BloodTyper, by using iteratively learning method to compare the genotyping result with the traditional serological and SNP results. The initial concordance with the serological and SNP results was 99.5% across the 20 genomes from the MedSeq Project randomized controlled trial. The improvement of the following round, 99.8% concordant, of the remaining 90 MedSeq genomes was due to the discordances addressed. The final algorithm was 99.9% concordant for 200 genomes with low depth of coverage, 15×, from INTERVAL study after adjustment. Compared with BOOGIE, BloodTyper get full blood group profiles from genomic data automatically and obtain a higher concordance. However, a larger cohort of samples will be needed for further evaluation of the algorithm and more attention should be paid to rare blood groups, especially those with high homologous sequence, in future investigations.

The existing antibody-based serological tests do not cover

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all major blood groups that may pose an alloimmunization risk in blood transfusion (10). Besides that, serological method is usually labor-intensive and time-consuming. The abnormal antibodies caused by multiple pregnancies or previous blood transfusions may lead to the false conclusions of serological blood typing. The microarray-based SNP tests are established on the foundation of previous studies and therefore is not suitable for discovery of new variants. The major defect of this method lies in its inability to detect structural changes at chromosomal level. Targeted exome sequencing in blood group genotyping has been studied (11,12) due to its lower cost as compared to the whole genome sequencing. Despite the advantages of low cost, the method cannot detect splice variants and missing non-coding variants those are important for blood group genes (13,14). On the one hand, the blood group analysis using whole genome sequencing provides the complete profiles in one go and can be used for rare blood group discovery (15). NGS allows the detection of the unknown single nucleotide variations (SNVs) which is unavailable when using conventional serological tests or microarray-based platforms. On the other hand, NGS obtains a massive quantity of information all at once (16) and the abnormal antibodies that are misleading in serological test can be avoided in NGS analysis, too. However, the algorithm of the massive data processing remains the most challenging issue. The cost of sequencing, data storage and labor force need to be taken into consideration as well. From the perspective of NGS principles, the limitations of extensive use in blood group research include the short-read length and the high cost of experiment and data analysis (17,18). Along with the development of biological and computational sciences (19), we stay positive on the great expectation that the shortcomings of NGS will be overcome and that the accuracy can be improved in the foreseeable future. In Lane's research (9), only part of the known antigens was studied and the copy number analyses require further optimizations. In spite of the limitations, the study provides an exceptional idea of automatic analysis of whole genome sequencing for blood group typing and related medical applications.

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Footnote

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