Editorial



# Molecular genetics and genomics of blood group systems

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## Blood group genetics and genomics: a contemporary field of research

Description of the ABO antigens at the beginning of 20th Century by Dr. Karl Landsteiner is the founding event of modern transfusion medicine (1,2), the pioneering specialty of personalized medicine. After this report and the discovery of antigens belonging to many systems, it took nearly a century and the advent of molecular biology before the genetic basis of blood group antigen expression could be described for the first time. Indeed, in 1986, Siebert and Fukuda reported a nucleotide sequence encoding glycophorin A, the protein carrying the antithetical M and N antigens in the MNS system, defining the complementary DNA (cDNA) sequence of the *GYPA* gene (3). At that time, genetics started to revolutionize human medicine by the identification of many genes responsible for genetic disorders. Naturally, blood group genetics benefited from the successive advances in this field, and several blood group genes were soon characterized in the early 90s by the same approaches. This trend has definitely not ended since. After major progress in human genome mapping years ago, advances in functional genetics, molecular typing/sequencing and computational genomics have resulted, for the past years, in the identification of novel blood group genes and antigens, as well as the characterization of novel systems. In that context, this Special Series of *Annals of Blood* aims to present some of the major fundamental findings and recent technological developments in the field of blood group genetics and genomics by an international panel of leading experts.

The first three chapters aim to report the recent discoveries in the "historical" ABO blood group system, as well as in the complex Rh and MNS systems. First, Dr. Yamamoto, who dramatically contributed to the early description of the molecular genetics of ABO, provides a comprehensive review of the molecular determinants of ABO antigen expression and depicts how the variants alter the catalytic activity of the enzyme from a functional point of view leading to variant phenotypes (4). Then he reports on the evolution and phylogenetic analysis of the *ABO* gene in bacteria and eukaryotes. Finally, he discusses the physiological and pathophysiological conditions related to *ABO* gene polymorphisms resolved by genome-wide association studies and opens the debate regarding the relationship between ABO and COVID-19.

The Rh blood group system is the most complex and polymorphic system. Hundreds of *RH* alleles have been characterized in various populations and reported in the literature and databases since the identification of the genes 30 years ago. In the second chapter, Dr. Floch (I) presents a detailed review of both the *RHD* and *RHCE* variant alleles that have been proven to be associated with allo-antibody formation (excluding the null alleles) with exhaustive references; (II) lists the most common *RHD* variant alleles, for which no allo-antibody has been reported so far, but that request a cautious attitude; (III) describes the low-frequency antigens associated with those variant alleles that may be responsible for antibody production if exposed to recipients; and (IV) provides population-specific prevalence of *RH* variant alleles, which is critical for the management of patients (5). The author interestingly concludes that further reports of allo-antibody formation in the context of detailed serologic studies and in association with the molecular characterization of variant alleles will contribute to the better understanding of the clinical relevance of those antibodies, and ultimately to the optimization of guidelines for patient management.

In the third chapter, Dr. Lopez and collaborators review the molecular structure of the genes, as well as the

mutational mechanisms associated with the expression (or loss of expression) of the MNS blood group antigens (6). They detail the four antigens recently reported, i.e., SARA, KIPP, JENU, and SUMI (MNS47 to MNS50, respectively), and recapitulate the characteristics of the immunogenic Mi[a] antigen carriers at the serological, molecular and population levels. A specific attention is paid to the clinical consequences, in transfusion and obstetrics, of antibody production towards hybrid gene products and the development of dedicated genotyping approaches for identifying those hybrid gene carriers.

As suggested above, the field of molecular immunohematology has been extremely dynamic for the past decade. In the following chapter, Dr. Denomme explores some of the systems recently acknowledged officially by the International Society of Blood Transfusion (7). After a brief historical reminder in each group, the author reviews the current knowledge in the KANNO, SID, CTL2, PEL, and MAM blood group systems (ISBT 037 to 041, respectively). Interestingly, beyond the standard clinical and biological information characterizing probands of interest, this report illustrates the potency of combining various skills and complementary expertise—including *in vitro* biochemical assays, molecular and functional genetics, bioinformatics, etc.—towards an exhaustive and accurate description of a novel system.

Blood group genotyping has become standard practice in immunohematology to complement the gold-standard phenotyping procedure when inconclusive, or when no testing reagent is available for hemagglutination. In her narrative review, Prof. Castilho details how this strategy can be beneficial to patients exhibiting a variant phenotype, to transfusion-dependent patients suffering from hemoglobinopathies or myelodysplastic syndrome, but also to those with a suspected antibody or monoclonal antibody interference (8). In donors, genotyping has been used preferentially for the identification of rare phenotypes and antigen-deficient red blood cells (RBCs), and the preparation of RBC panels for antibody identification. Finally, non-invasive prenatal testing (NIPT) is another application that has been accessible in several countries by using cell-free fetal DNA in maternal plasma as a template. As a practical example, it is well established that fetal *RHD* status determined by NIPT typically guides Rh immunoprophylaxis to D-negative women for preventing the risk of alloimmunization.

The current molecular methods in blood group genotyping usually rely on the conventional polymerase-chain reaction (PCR) principle that can be carried out only in a limited number of samples at the same time. In the final chapter of this Special Series, Dr. Lane recapitulates comprehensively the history of the recent technological advances, which aim to increase drastically the scale of variations that may be identified in a single run, and suggests future trends in the field (9). Next-generation sequencing (NGS) has the potential to identify both known and unknown variations, including single-nucleotide variants (SNVs), but also structural variants (SVs), which are relatively frequent and potentially clinically-significant within the genes encoding the Rh and MNS blood group antigens. The throughput and coverage directly depend on the scale of targets that is determined by the project to be carried out, ranging from targeted sequencing for a selected number of genes/targets, up to whole-exome sequencing (WES) and even whole-genome sequencing (WGS), usually in the course of specific research projects. In parallel and by combining *trans*-disciplinary skills, the use of NGS in blood group typing has been accompanied by the development of automated softwares, which are mandatory for an optimal interpretation of the sequencing data. The flexible high-density DNA array is another potent strategy for large-scale studies, as the number of targets or samples can be easily increased, thereby contributing to reduce significantly the cost of analysis. Both approaches (and their respective developments) are undoubtedly to be critical for changing the practice in transfusion medicine in a near future.

As a Guest Editor, I am very grateful to the experts for their invaluable contribution and willingness to dispense and share their knowledge and expertise. I definitely hope this Special Series of *Annals of Blood* will be a source of references to the blood group and transfusion medicine community.

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