Blood Groups and Their Correlation with Hereditary Disease

Christoph Gassner^a Franz F. Wagner^{b, c}

^aInstitute of Translational Medicine, Private University in the Principality of Liechtenstein, Triesen, Liechtenstein;

^bGerman Red Cross Blood Service NSTOB, Springe, Germany; ^c MVZ am Clementinenkrankenhaus, Springe, Germany

When this edition of *TMH* dedicated to the relationship of blood groups and diseases was initially planned, the intention was to create a special issue on blood groups and their predisposition to hereditary diseases. Very quickly, a collection of proven and anecdotal evidence emerged as to which blood group systems and constellations were responsible for or protected against certain pathological situations. In addition to seemingly clear genetic heritability of certain disorders, numerous viruses (e.g., Noroviridae), microorganisms (different bacteria), and protozoan parasites (e.g., *Plasmodium*) interact with the products of our blood group genome and improve or worsen our health under certain conditions. The COVID-19 pandemic and the intensively discussed possible influence of the ABO blood type on it made such interactions a hot topic in transfusion medicine [1].

On closer inspection, the clear demarcation between “heritability” and “environmental influences” appeared difficult as exemplified by the long-known plasma-level variation of the von Willebrand factor (VWF), with high levels causative of higher risks for thrombosis in non-blood type O individuals and the level of expression linked to ABO phenotypes published elsewhere. It is estimated that approximately 65% of the VWF level variability is heritable, while the ABO blood group locus alone contributes approximately 25% [2, 3]. However, more recently in mice, hepatic VWF synthesis was also shown to be regulated by gut microbiota [4]. In the end, both “genes and environment make the organism” [5].

Notwithstanding the above considerations, for this issue we decided to focus on hereditary diseases that can be clearly deduced from certain blood group phenotypes. If

the term “hereditary disease” is used only for those disease states that impact life expectancy or quality of life, the list of known associations is surprisingly short.

A few blood group systems have been known to be associated with serious diseases for many years. Pertinent examples are the I (ISBT 027) blood group system in which the adult i phenotype may be accompanied by congenital cataract depending on the causative mutation [6]. Another example is represented by the XK (ISBT 019) blood group system, the underlying gene of which has been known to be associated with the McLeod syndrome for more than 25 years [7]. In this issue, Peikert et al. [8] report on the latest findings on the blood group system XK (ISBT 019) and the associated hereditary disease of McLeod syndrome. Observations of an interaction between Kx and the gene product of *VPS13A* published elsewhere finally promise to allow for an explanation of the neurological aspects of this disease [9, 10].

More recently, associations between new blood group systems and hereditary diseases have already been reported at the time of their discovery. The blood group system CD59 (ISBT 035) is one such example. CD59 was known as complement inhibitory protein, defects of which could cause inherited anemia long before the detection of anti-CD59 antibodies promoted it into a blood group protein [11]. In this context, Weinstock [12] reports on CD59 and inheritable paroxysmal nocturnal hemoglobinuria. Of note and in addition to CD59, the new blood group system EMM (ISBT 042), which has been described only recently, can also be observed in patients affected by paroxysmal nocturnal hemoglobinuria [13].

Latest reports on new blood group systems and their relationship to hereditary diseases also including individuals with the rare Ver-negative phenotype in the CTL2 (ISBT 039) blood group system show hearing loss for high frequencies, while PEL (ISBT 040)-negative individuals suffer from impaired platelet aggregation [14].

In this issue, Daniels [15] reports on another heritable condition related to the Augustine blood group system (ISBT 036). Augustine is encoded by the gene *ENT1* and is present in almost all human tissues. It facilitates the transfer of purine and pyrimidine nucleosides and is responsible for the majority of adenosine transport across plasma membranes. Adenosine transport appears to be an important factor in the regulation of bone metabolism. Affected individuals suffered frequent attacks of pseudogout, a form of arthritis, in various joints with multiple calcifications around their hand joints.

The three review articles on linkage between blood group phenotypes and hereditary diseases presented in this issue are a representative but not comprehensive collection of the current state of knowledge. We would have liked to see more contributions on this topic. Obviously,

the number of experts in the overlapping field of (new) blood group systems with concomitant relevance in hereditary diseases is limited. Thus, this area could offer a new field of activity for researchers. In any case, the articles – once again – prove that blood group antigens are located on functional proteins which, in addition to their importance for transfusion medicine, also fulfil important biochemical functions.

Conflict of Interest Statement

Christoph Gassner acts as a consultant to inno-train Diagnostik GmbH, Kronberg, Germany. Diagnostic procedures for the molecular detection of GYPB deletions of the 110- and 103-kb type have been submitted as a patent application (pending).

Franz Wagner declares no conflict of interest.

Funding Sources

There was no funding for this article.

References

- Gutiérrez-Valencia M, Leache L, Librero J, Jericó C, Enguita Germán M, García-Erce JA. ABO blood group and risk of COVID-19 infection and complications: A systematic review and meta-analysis. *Transfusion*. 2021 Nov;10.1111/trf.16748.
- Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr, Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. *Blood*. 1987 Jun;69(6):1691–5.
- Swystun LL, Lillicrap D. Genetic regulation of plasma von Willebrand factor levels in health and disease. *J Thromb Haemost*. 2018 Dec;16(12):2375–90.
- Jäckel S, Kiouptsi K, Lillich M, Hendriks T, Khandagale A, Kollar B, et al. Gut microbiota regulate hepatic von Willebrand factor synthesis and arterial thrombus formation via Toll-like receptor-2. *Blood*. 2017 Jul;130(4):542–53.
- Singh RS. Darwin's legacy II: why biology is not physics, or why it has taken a century to see the dependence of genes on the environment. *Genome*. 2015 Jan;58(1):55–62.
- Yu LC, Twu YC, Chou ML, Reid ME, Gray AR, Moulds JM, et al. The molecular genetics of the human I locus and molecular background explain the partial association of the adult i phenotype with congenital cataracts. *Blood*. 2003 Mar;101(6):2081–8.
- Ho M, Chelly J, Carter N, Danek A, Crocker P, Monaco AP. Isolation of the gene for McLeod syndrome that encodes a novel membrane transport protein. *Cell*. 1994 Jun;77(6):869–80.
- Peikert K, Hermann A, Danek A. XK-Associated McLeod Syndrome: Non-Hematologic Manifestations and Relation to VPS13A Disease. *Transfus Med Hemother*. 2022;49(1). <https://doi.org/10.1159/000521174>.
- Urata Y, Nakamura M, Sasaki N, Shiokawa N, Nishida Y, Arai K, et al. Novel pathogenic XK mutations in McLeod syndrome and interaction between XK protein and chorein. *Neurol Genet*. 2019 Apr;5(3):e328.
- Park JS, Neiman AM. XK is a partner for VPS13A: a molecular link between Chorea-Acanthocytosis and McLeod Syndrome. *Mol Biol Cell*. 2020 Oct;31(22):2425–36.
- Anliker M, von Zabern I, Höchsmann B, Kyrieleis H, Dohna-Schwake C, Flegel WA, et al. A new blood group antigen is defined by anti-CD59, detected in a CD59-deficient patient. *Transfusion*. 2014 Jul;54(7):1817–22.
- Weinstock C. Association of Blood Group Antigen CD59 with Disease. *Transfus Med Hemother*. 2022;49(1). <https://doi.org/10.1159/000521174>.
- Lane WJ, Aeschlimann J, Vege S, Lomas-Francis C, Burgos A, Mah HH, et al. PIGG defines the Emm blood group system. *Sci Rep*. 2021 Sep;11(1):18545.
- Azouzi S, Mikdar M, Hermand P, Gautier EF, Salnot V, Willemetz A, et al. Lack of the multidrug transporter MRP4/ABCC4 defines the PEL-negative blood group and impairs platelet aggregation. *Blood*. 2020 Feb;135(6):441–8.
- Daniels G. Augustine Blood Group System and Equilibrative Nucleoside Transporter 1. *Transfus Med Hemother*. 2022;49(1):1–5.