

Cardiovascular disease, ABO locus and markers of platelet functionality

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Cardiovascular disease continues to be the most important global health challenge causing one third of mortality world-wide. A great proportion of cardiovascular deaths falls in the category of coronary artery disease (CAD) as a result of myocardial infarction. This catastrophic event in many cases occurs as the first sign of cardiovascular disease when it is too late for preventive strategies. It is thus particularly important to be able to understand mechanisms involved in cardiovascular disease and to predict an event preferably years before it occurs to allow time for risk modification.

The biological pathology underlying cardiovascular disease is atherosclerosis. In CAD, atherosclerosis occurs within the coronary arteries. The endothelial surface of the atherosclerotic plaque could lose integrity and rupture. Consequent coagulation cascade forms thrombus inside coronary artery and blocks it at which point myocardial infarction is inevitable. Coagulation factors and platelet functioning are pivotal in formation of thrombus. Currently aspirin is a commonly used as antiplatelet therapy [1] in patients with cardiovascular disease or those carrying high risk of cardiovascular disease. Aspirin has however side effects such as risk of bleeding which is a risk that is widely accepted since preventive impact of aspirin outweighs the risk of bleeding.

It is for long known that ABO blood group antigens are present at the surface of platelets [2] and for nearly half a century, a link between ABO blood group antigens and cardiovascular disease was known [3]. ABO blood group is associated with many traits in addition to cardiovascular disease including platelet function parameters among healthy adults and patients with CAD [4, 5].

Upon advent of agnostic statistical approaches such as genome-wide association studies (GWAS), new insight into mechanism of cardiovascular disease at molecular level started to emerge. In recent years, GWAS showed that ABO genetic locus that encodes for ABO blood group antigens has a highly pleiotropic nature and is strongly associated with many traits including coagulation factors, adhesion molecules and cardiovascular disease (**Figure 1**). Understanding biological interaction between the ABO locus and molecules involved in clot formation is fundamental. It provides insight that could potentially lead to production of new drugs to boost prevention of cardiovascular events.

In this issue of the journal, Christiansen and colleagues investigated the role of 45 CAD genetic variants on platelet activation and aggregation. They used a sample of 879

patients with CAD under aspirin therapy. Patients who used medication with potential effect on coagulation were excluded. However, most of the patients used aspirin and as the authors pointed out some could be under aspirin treatment long before entering the study. The results showed that except for the ABO CAD risk variants, none of the CAD variants were linked to platelet aggregation and activation. The study showed that measures of platelet aggregation (arachidonic acid, and collagen) were higher and sP-selectin levels was lower among carriers of ABO risk allele compared to non-carriers.

GWAS on general population indicate that the ABO locus is strongly associated with serum levels of adhesion molecules such as sP-selectin [6-10]. Additional to the findings of the GWAS, Christiansen and colleagues highlight differences in arachidonic acid, collagen, and sP-selectin depending on the ABO CAD genotypes among CAD patients who are under aspirin treatment.

As mentioned earlier, ABO locus is associated with CAD and several cardiovascular risk factors such as lipid levels and type1 diabetes. Thus, compared with non-carriers, carriers of ABO CAD risk allele are more likely to have had CAD risk factors prior to entering the study. Prescription of aspirin as a preventive method in CAD in many countries means that individuals at high risk of CAD (i.e. those with CAD risk factors) have a greater chance to receive aspirin. This means carriers of ABO CAD risk allele are more likely to have been under aspirin therapy well in advance of the time that measurement of platelet function was taken by Christiansen and colleagues. As a result of longer duration of aspirin therapy in carriers, their platelet functioning parameters decrease disproportional to the ones of non-carriers. Such effect might lead to underestimation of the finding with a magnitude that depends on the effect of long-term aspirin use on platelet function. This could be further complicated as aspirin response is not similar in all individuals. It is important for future research to ensure that aspirin response is independent of ABO locus which necessitates collecting data before and after aspirin use.

Christiansen and colleagues present interesting results, showing yet another evidence for the impact of ABO locus on platelet functioning parameters. It is however unclear how the finding would be different before and after aspirin therapy and if these findings are different from the results among healthy controls who use aspirin for reasons other than CAD or those who do not use aspirin at all. Follow-up research is essential to demonstrate

how the results observed here are linked to CAD and response to aspirin therapy in longitudinal studies.

It is yet too soon to believe that the findings of Christiansen and colleagues explain the greater chance of myocardial infarction among carriers of ABO CAD risk allele. Given the highly pleiotropic nature of ABO locus and presence of the ABO blood group antigens on many various cell types, it is more likely that ABO locus involves in multiple pathways leading to myocardial infarction.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Figure 1. Schematic illustration of pleiotropy in ABO locus.

