Genetics of ACS and recurrent MI/cardiac death: are we getting to the heart of the (atherosclerotic) matter?

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This editorial refers to ‘A variant at chromosome 9p21 is associated with recurrent myocardial infarction and cardiac death after acute coronary syndrome: The GRACE Genetics Study’, by I. Buysschaert et al. on page 1132

Coronary artery disease (CAD) is still the most frequent cause of death in Western societies. It is now widely accepted that the classic environmental risk factors for atherosclerosis only partly explain the incidence of CAD and the development of acute coronary syndromes (ACS). Genetic factors that vary among human populations seem to be involved in the clinical manifestations of such patients.1,2

Substantial data already showed that genetic variation is likely to influence CAD both directly and through effects on known CAD risk factors, such as hypertension and diabetes. Despite extensive research efforts for more than a decade, the genetic basis of CAD remains largely unknown. Although there have been notable successes, linkage and candidate gene association studies have often failed to deliver definitive results.3,4

However, advances are now being made through the application of large-scale, systematic, genome-wide approaches. Due to the HapMap resource, which documents patterns of genome-wide variation and linkage disequilibrium (LD), association studies are being facilitated in terms of both the design and the analysis. Furthermore the availability of dense genotyping chips make it possible that genome-wide association studies are technically and financially possible. In this way genetics can serve as new risk targets and help to stratify patients at risk for CAD. Figure 1 shows the role of genetic testing. Moreover, recently it has been shown that genetic testing is not only useful in disease genetics, but nowadays studies also concentrate on the role of pharmacogenetics. Pharmacogenetics is the search for genetic polymorphisms that affect responses to drug therapy. Since the individual response to specific drugs is also to a large extent inherited, it can therefore have implications for individual drug therapy.5

Recent findings have particularly highlighted the link between CAD and inflammation and immunity. In particular, a common variant on chromosome 9p21 was recently identified as affecting the risk of myocardial infarction (MI). At least four genome-wide association studies identified chromosome 9p21 as a major locus for risk of CAD or MI.1,3,6,7

Still little is known about the function of this locus. This region contains the coding sequences of genes for two cyclin-dependent kinase inhibitors, CDKN2A (encoding p16INK4a) and CDKN2B (encoding p15INK4b). Both genes have multiple isoforms, have an important role in the regulation of the cell cycle and are widely expressed, with CDKN2B known to be expressed in the macrophages but not the smooth muscle cells of fibrofatty lesions. The expression of CDKN2B is induced by transforming growth factor-β (TGF-β). The only other known gene nearby is MTAP, which encodes methylthioadenosine phosphorylase, an enzyme that contributes to polyamine metabolism and is important for the salvage of both adenine and methionine.3 Further research to examine the exact function of this gene is already being performed.6 Besides its unknown function, it is also not known whether the 9p21 locus confers a risk for recurrent MI or cardiac death. Therefore, Buysschaert et al. investigated, in the Global Registry of Acute Coronary Events (GRACE) programme, which is a large, prospective multinational observational study of patients hospitalized with ACS, if this locus is also associated with the risk of ACS.

It is primarily a validation study and does not describe a novel discovery; nevertheless, it is a worthwhile and thorough study. It consists of a large population (3473 patients from eight participating centres in three countries). Patients with a clinical diagnosis of...
ACS were included. The follow-up was correctly performed and the endpoints were adequately chosen, thus allowing for meaningful results.

The locus of interest consists of two LD blocks. The rs133049 variant was selected as it was shown previously from haplotype screening to be the most representative single nucleotide polymorphism (SNP) in the first block. Furthermore, three tagging SNPs from the second block were selected. The lambda statistic was used to determine the most likely mode of inheritance. The authors used an additive model to show the association with ACS—previously studies also described this as the most likely inheritance model—and a dominant model to show the association between the SNP and recurrent MI. This difference in models is explained by the authors and could possibly be due to the fact that the primary population is already enriched for the SNP risk allele; therefore, there is a skewed distribution of genotypes.

The findings of this study are of interest for several reasons. First of all, in their study the authors confirm first that the C allele of rs133049 was associated with the full spectrum of ACS [ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), and unstable angina]. This result is not novel, since it has been established and replicated in different populations and publications; however, it does give a validation of the GRACE genetics study. Secondly they demonstrate that carriers of the at-risk C allele exhibited an increased risk of developing a recurrent MI or cardiac death within 6 months after the primary event. This association is an interesting finding, since it has not been demonstrated previously and certainly strengthens the case for rs133049 with regard to biological plausibility. One study by Horne et al. investigated if the 9p21 locus could predict MI among CAD patients; however, no significant association was found. The authors already mention in their discussion that the patient selection and outcome criteria were different from those from Horne et al. and could therefore explain the different outcome. Still the findings of this study do need confirmation, especially since the number of events in the observation period of 6 months is small (170 patients with recurrent MI and 205 patients with recurrent MI or cardiac death).

Thirdly, they speculate about the function of the 9p21 locus since this is not known yet. Due to the limited follow-up period they hypothesize not only that this locus promotes plaque formation, which a study by Ye et al. previously demonstrated, but that this locus could also play a role in plaque rupture. Although this is only a hypothesis and much more research is needed to understand the function of this locus, it does give a new interesting insight into how it could possible work.

Finally, and this is perhaps most important for clinical practice, the authors found that inclusion of rs133049 in the GRACE risk score nearly significantly improved risk classification for the prediction of recurrent MI (P = 0.073), but significantly improved risk classification of the combined endpoint or recurrent MI or cardiac death (P = 0.040). In this way they show a possible role for this locus in clinical practice, since it may help to improve risk stratification for patients at risk for a recurrent MI or cardiac death (see Figure 1).

What will be the implications of these findings? As already mentioned above, genetic studies indeed may help us in risk stratification and treatment even though we do not fully understand its mechanism. The high frequency of the risk allele suggests that genotyping for this locus could have clinical utility in risk prediction.

When these results are confirmed by other studies, does this mean patients should be tested after their first presentation of ACS? And if tested positive, what will be the consequences. These are appropriate questions, with, at the moment, no clear answers. So far, the study offers interesting insights. Whether the findings of Buysschaert et al. can be translated into better prevention or treatment of CAD will become clear only over time and with further research. Probably the results can be used as a framework for additional studies.

Thus this study regarding the genetics of ACS and recurrent MI/cardiac death does bring us closer, although only by a limited amount, to the heart of the matter—the vulnerable heart of the atherosclerotic plaque.

Conflict of interest: none declared.

References
3. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–678.
Cardiovascular magnetic resonance prior to surgical treatment of chronic thrombo-embolic pulmonary hypertension

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A 72-year-old lady was referred to our Pulmonary Hypertension Unit with WHO Class IV dyspnoea. Previous computed tomography pulmonary angiography had revealed chronic thrombo-embolism. The degree and distribution of disease was confirmed with gadolinium-enhanced cardiac magnetic resonance (CMR) pulmonary angiography (Panel A, see also Supplementary material online, Movie 1). The right ventricle was severely dilated with an ejection fraction of 32% by CMR. Functional testing demonstrated reduced 6 min walk distance (6MWD) of 225 m. The estimated right ventricular systolic pressure by echocardiography was 72 mmHg. Surgical pulmonary thrombo-endarterectomy (PTE) was performed. Eighteen months post-operation, both her right ventricular function and pulmonary pressures had returned to normal. The 6MWD had improved to 470 m ($P < 0.01$). Repeat CMR revealed normalization of right ventricular size with substantial improvements in pulmonary blood flow (Panel B, see also Supplementary material online, Movie 2).

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is an increasingly recognized condition, and is the only cause of severe pulmonary hypertension which is potentially curable without the need to resort to lung transplantation. Once considered a rare condition, it is now recognized that up to 4% of patients with acute pulmonary embolus may develop CTEPH. Pulmonary thrombo-endarterectomy is the treatment of choice when performed in major centres by experienced surgeons and offers a surgical remedy to this severely disabling and often fatal disease process. Long-term outcomes following PTE are generally excellent with most patients experiencing significant improvements in haemodynamics and functional capacity, as illustrated by this case. Cardiac MR imaging and MR angiography are emerging as key investigations in quantification of right ventricular function and the assessment of pulmonary vascular anatomy.

Panel A. Pre-operative magnetic resonance pulmonary angiogram demonstrating vascular obstruction, webs, and stenoses and poor tissue perfusion due to chronic pulmonary thrombo-embolism.

Panel B. Follow-up magnetic resonance pulmonary angiogram showing substantial improvement of the pulmonary vasculature. CMR also showed normalization of right ventricular volume and function (not shown).

Supplementary material is available at European Heart Journal online.

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