Is there a Role for Genetics in Cardiac Calcification?

Urban Hellman1, Stellan Mörner1, Michael Henein1,2,3

1. Department of Public Health and Clinical Medicine, Umeå University, 90185, Umeå, Sweden.
2. Molecular & Clinical Sciences Research Institute, St. George University, London SW17 0RE, UK.
3. Brunel University, Middlesex, UK

Corresponding author:
Michael Henein
Professor of Cardiology
Department of Public Health and Clinical Medicine, Umeå University, Sweden
michael.henein@umu.se

Abstract
Calcific coronary artery disease (CCAD) may cause abnormal myocardial perfusion and hence generalized ischaemia. It is often accompanied by coronary atherosclerosis despite there being no fixed relation between the two. This potential discrepancy between the calcific expression pattern compared to the well-known atherosclerotic disease raises questions about the exact pathophysiology of coronary calcification and whether there is a genetic aetiology for it. In a pilot study we studied three candidate genes, ENPP1, ABCC6 and NTE5 that may predispose to coronary arterial or valvular calcification. We studied 65 patients with CCAD and 5 patients with calcific aortic valve disease (CAVD). Five DNA variants potentially affecting protein function were found in six patients. Our findings support the hypothesis that genetic variants might influence the development of CCAD and CAVD. However segregation in the families must first be performed to ascertain any damaging effect of these variants. The search for direct causative genetic variants in coronary artery and aortic valve calcification must be broadened with other genes.

Keywords: arterial calcification, coronary artery disease, gene

Introduction
Coronary artery calcification (CAC) is the most common cause of arterial stiffness and it develops with age. The extent of CAC usually correlates with the severity of arterial lumen stenosis in symptomatic patients [1, 2]. Low grade stenosis, however, may also be seen in a minority of patients with extensive calcification (calcific coronary artery disease, CCAD), in whom limiting symptoms can be explained on the basis of compromised coronary flow reserve causing abnormal myocardial perfusion and hence generalised ischaemia [3, 4]. Such a discrepancy in the expression pattern of coronary disease raises questions about the pathophysiology of coronary stiffness, caused by calcification, and whether it has a specific genetic predisposition.

The potential influence of molecular factors on the pathophysiology of arterial calcification is shown by the observation that genetic determinants of calcification seem partially independent of conventional risk factors of atherosclerosis, accounting for 40% of risk variability [5]. This is supported by the large difference in atherosclerosis burden in blacks, who have no coronary calcification, compared to whites in whom coronary calcification is a common finding, thus suggesting ethnic influences on calcification pathology. Two specific chromosomal loci harbouring genes have been found in patients with peripheral calcification, along with other polymorphisms including apolipoprotein E, E-selectin, matrix metalloproteinase 3, matrix GLA protein and CC Chemokine receptor 2, but the individual impact of each does not seem significant [5, 6]. This suggests that a genetic variant with a potentially stronger association with arterial calcification may yet be found. Mutations in the ENPP1 and ABCC6 genes have been described in generalised arterial calcification in infants and mutations in the NTE5 gene have been associated with peripheral arterial calcification [7]. In addition, polymorphisms causing the amino acid changes p.Thr376Ala (c.1126A>G, rs2229523) and p.Met379Thr (c.1136T>C, rs2229524) in the NT5E gene have been reported in aortic valve calcification [8].

In a pilot study, we attempted to identify the key genetic variants in candidate genes which may predispose to coronary arterial stiffness, mostly caused by calcification pathology and whether there is any impact of gender on this potential relationship [9].

We investigated three candidate genes, ENPP1, ABCC6 and NT5E involved in pyrophosphate (PPi) and inorganic phosphate...
(P) metabolism, which may predispose to coronary arterial or valvular calcification. 70 patients with calcific cardiac disease; 65 with CCAD (age 43-83 years) and 5 with calcific aortic valve disease – CAVD (age 76-82 years) were studied.

In six patients we identified both an already reported mutation associated with coronary artery disease and four previously unreported genetic variants possibly affecting protein function. We were also able to confirm a higher frequency of a polymorphism in Swedish patients, previously reported in Polish patients [8]. Our findings support that disturbances in the PPi and Pi metabolism might influence the development of CCAD and CAVD. However, segregation in the families must first be performed to ascertain any damaging effect of these variants we have found.

In most patients we failed to find any possible damaging variants and our results did not demonstrate a clear association between polymorphisms in the identified genes and coronary calcification as currently assessed by Multi Detector Computerised Tomography (MDCT) protocols. Also, it seems there is a gender impact particularly females of age 50-70 years who were shown to consistently have zero calcium score according to the conventional Agatston method. This potential association might be explained on the basis of coronary stiffness caused by a form of microcalcification which cannot be measured using conventional MDCT protocol and applying Agatston scoring system.

Thus, genetic investigation should embrace different phenotypic cardiac syndromes, segregation of genetic variants in families and factor for calcification severity.

Declarations of Interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [10].

References