Evolving concepts of left ventricular hypertrophy

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This editorial refers to ‘Characterization of the GNAQ promoter and association of increased Gq expression with cardiac hypertrophy in humans’† by U.H. Frey et al., on page 888

Adaptative left ventricular hypertrophy mainly derives from pressure or volume overload. Nevertheless, in the general population, about one-fifth of normotensives develop left ventricular hypertrophy despite a normal pressure load, while more than one-third of hypertensives do not develop it in response to pressure overload (Table 1). It is unclear why some subjects become hypertrophic while others do not. Hypoxic or ischaemic myocardial loss could account for a limited number of such cases. The natural history of left ventricular hypertrophy is also very different, with some subjects developing heart failure and premature death and others who seem to be free of these prognostic variables. Some subjects develop heart failure and others who seem to be free of these prognostic effects. One of the principal candidate signalling pathways for cardiac hypertrophy is stimulation of the G protein Gq through its G-protein-coupled receptors. The aim of the study by Frey et al. was to investigate in humans the Gq protein overexpression encoded by the GNAQ gene and to identify Gq promoter polymorphism and specific transcription factors that regulate gene expression, as already observed in animal models. In a recent study by Clerk et al., they first characterized the GNAQ promoter looking for a possible polymorphism suspected to play a prominent role in disease susceptibility. They then identified the transcription factors and their binding sites, and clarified whether the Gq promoter was inducible by circulating stimuli, and whether the novel single polymorphism was really able to increase Gq expression resulting in enhanced activation of the Gq pathway and in enhanced cell growth in a signal-dependent manner.

After identification of the promising GC(–695/–694)TT GNAQ promoter polymorphism and in vitro experiments highlighting its functional expression, they checked in a population survey for its possible association with left ventricular mass. Finally, applying multiple regression models in subjects from the general population, the authors concluded that the GC allele was more common in pathways that are under genetic control, not only to answer some unanswered questions about the pathophysiology of left ventricular hypertrophy but also from a prognostic and therapeutic viewpoint.

Cardiologists are in general sceptical about genetics. Cardiovascular disease is multifactorial, and responds to a mosaic of genes that interact in common pathways to yield a synergistic mechanism of action, adding further experimental uncertainty to the merely probabilistic value of classical risk factors. Furthermore, association studies based on the analysis of several polymorphisms have often been disappointing for cardiologists. However, it must be emphasized that the study of Frey et al. discussed here is not a mere study of association, but rather a wide spectrum of research going from genetics, to molecular characterization, to a large clinical study.

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After identification of the promising GC(–695/–694)TT GNAQ promoter polymorphism and in vitro experiments highlighting its functional expression, they checked in a population survey for its possible association with left ventricular mass. Finally, applying multiple regression models in subjects from the general population, the authors concluded that the GC allele was more common in
individuals with than without left ventricular hypertrophy, and—more importantly—that, in contrast, the above-mentioned polymorphism explained a significant part of the variance, really predicting left ventricular hypertrophy.

Every effort was made to demonstrate that this polymorphism was important and functional, by reproducing step by step the entire pathway from identification of a novel polymorphism to its phenotypic expression, ‘from genetics, to molecular characterization, to a large clinical study’. The in vitro study was carried out on fresh human atria, as there are no well-established continuous cell lines that can be used to study cardiomyocyte development and growth.13 The investigation showed that this single-nucleotide polymorphism had functional implications, with the GC allele increasing Gq expression (contrasting findings shown by others could be attributable to the different setting 14) and enhancing signal transduction via Gq-coupled receptors. In particular, in the GC allele carriers, Gq expression was found to be more inducible by stimulation with angiotensin II, which is of interest as there are higher circulating levels of this hormone in chronic disease, with increased workload leading to heart failure. The greatest merit of the study is to provide confirmation to the hypothesis that cardiomyocyte Gq signalling is both necessary for pressure overload hypertrophy3,4 and sufficient to produce overload-like hypertrophy even in the absence of haemodynamic stress,15 giving support to the pathological and physiological mass increase. In the population study, the effect of being GC allele carriers was more prominent (odds ratio 5.52) in women than in men, possibly explaining at the level of Gq mRNA expression why in population-based studies women have on average higher left ventricular mass and higher prevalence of left ventricular hypertrophy than men (Figure 2).

Although the study needs to be confirmed in further population cohorts respecting the criteria for internal validity of an association study, Frey et al.8 have opened a way through better knowledge of the onset and natural history of cardiac hypertrophy.

Conflict of interest: none declared.

References


