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Editorial

Genotype-phenotype correlations in ARVC: Toward a *precision medicine* approach

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Arrhythmogenic right ventricular cardiomyopathy is an unusual cardiomyopathy with prevalence estimated at 1/5000 overall but as high as 1/2000 in some countries such as Italy and Germany [1]. As the name implies it is classically characterized by arrhythmias that originate from the right ventricle, primarily the right ventricular outflow tract. Heart failure, particularly end stage heart failure, is a rare clinical manifestation of ARVC but an important one given the high degree of morbidity and mortality. As more patients with ARVC are identified and receive implantable cardiac defibrillators (ICD), more patients can be expected to live with ARVC long enough to see its progression to heart failure, and identifying those who are at higher risk to develop heart failure will become increasingly important. The pathophysiology of ARVC is due to mutations in desmosomal proteins that are typically inherited in an autosomal dominant pattern [1]. The ability to identify causative mutations and test for them in affected patients has rapidly evolved in recent years and it is now estimated that roughly 50% of patients with the clinical phenotype of ARVC will have an identifiable mutation raising the possibility that genetic mutation data could be used to predict disease severity [2]. The most commonly mutated ARVC gene is the *PKP2* gene, which encodes plakophillin 2, and accounts for up to 52% of ARVC patients in the Netherlands [3]. Previous work suggested that ARVC patients with different pathogenic gene mutations may have a different outcome. First, in a smaller series, desmosomal gene mutation carriers were found to have a higher mortality and risk of heart transplant compared with non-carriers [4]. Another study suggested that *DSP* gene mutation carriers appeared more likely to have left ventricular involvement compared with carriers of other disease genes, [5] Finally, having more than one mutation was reported to be a poor prognostic factor and to predict a more severe outcome [5,6].

The study by Vischer et al. [7] that appears in this issue of the International Journal of Cardiology adds important data on the role of ARVC mutations on the risk of end stage heart failure (defined as either death or heart transplant in their study) from ARVC. In this multicenter study collecting a cohort of 135 index subjects with ARVC, patients who met the heart failure endpoint were more than twice as likely (62%) to have a *PKP2* mutation that those who did not meet the endpoint (26%). Another way of looking at the data is that those with the *PKP2* mutations were more than four times as likely (12.8% vs 3.1%) to meet the primary study outcomes as compared with those without the mutation (OR 4.6). These data further our understanding of the relationship between genotype and phenotype in ARVC and set the stage for developing a *precision medicine* approach for ARVC.

One difficulty with any study that examines end stage heart failure in a rare disease like ARVC is that the infrequency of the condition makes it difficult to power studies appropriately: in the study of Vischer et al. [7], only 5.9% of patients met the endpoint. Interestingly, while the proportion of patients who met the primary endpoint of end stage heart failure with the *PKP2* mutation was statistically different from non *PKP2* carriers, the overall prevalence of the mutation was lower (28.8%) than in the work of Jacobs et al. presumably due to geographical differences [3]. Including relatives who were known carriers of the ARVC mutations would have increased the number of observations, although this would have been at the expense of the rigid inclusion criteria established for this paper and the better outcome that family members appear to have compared to probands. While important, these results will need to be validated by larger studies with more patients reaching the primary outcome. Further work could also include exploring the biological basis of why *PKP2* mutations associate with at higher risk for end stage heart failure.

Overall, we still have much to learn when it comes to the relationship between genotype and phenotypes in genetic cardiomyopathies, ARVC included. Studies such as the one in this IJC issue help to further advance our knowledge, although more data is needed before we will be able to incorporate this information into a *precision medicine* approach in clinical practice.

Conflict of interest

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

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