Fundació La Marató de TV3
21st SYMPOSIUM
Heart diseases

# GENETIC AND MOLECULAR BASES DE RIGHT-VENTRICLE ARRHYTHMOGENIC CARDIOMYOPATHY: TRANSFER TO CLINICAL PRACTICE

**Ramon Brugada Terradellas**
Centre de Genètica Cardiovascular - Institut d'Investigació Biomèdica de Girona

## 1. Summary

Arrhythmogenic right ventricular cardiomyopathy (ACM) is a hereditary disease characterized by the replacement of the myocardium by fibrofatty tissue. ACM can cause sudden cardiac death (SCD) in young people, especially athletes, in whom it is believed that disease progression is more rapidly due to tension in the right ventricle caused by exercise. Detection of structural changes is often poor using the clinical tools currently available, particularly in the early stages of the disease. Asymptomatic patients can remain undiagnosed, and therefore remain at risk. Genetics allows these diagnostic limitations to be overcome, given that ACM is a family disease mainly caused by pathogenic variations in genes that encode desmosome proteins. There are several scientific challenges in ACM, both clinical and molecular. Thus 50% of families with ACM do not yet have an identified genetic cause. Therefore, it remains to be defined whether there are other genes involved and what determines their severity, incomplete penetrance and variability in phenotypic expression. At the molecular level, it is not clear which are the pathophysiological mechanisms responsible for histological heterogeneity, such as focal adipogenesis and involvement of the left or biventricular ventricle. This project aimed to address some of these challenges. We propose to combine comprehensive genotype-phenotype correlations in the affected families, with in vitro and in vivo experiments in an animal model, to study the progression of the disease and the effect of the genetic variants on proteins of the intercalated discs. This proposal allows us to better understand the genetic and clinical expression of ACM, molecular mechanisms that trigger adipogenesis, electrical disturbances and the development of structural disease. Results from this work aim to improve the current diagnostic and prevention tools.

## 2. Results obtained

The results obtained from ACM research during this period are integrated into 3 main areas: genetic predisposition, progress in the knowledge of the molecular mechanisms underlying the pathology, and the environmental triggers.

Regarding genetic predisposition, results obtained clearly indicate that most cases have a genetic origin, specifically with the presence of a variant in the main desmosomal

genes. The identification of the variant, not only helps in the clinical diagnosis of the patient in question (in cases where the diagnosis is not definitive), but also allows early diagnosis in all those family members who have higher risk of suffering from ACM than general population; and therefore, they can undergo periodic controls with their cardiologist. This is especially important in ACM, since in many cases sudden death may be the first symptom. In this sense, the results obtained in 74 cases of sudden unexplained death are also of great clinical relevance since they have allowed the identification of a large number of asymptomatic carriers who otherwise would not have followed up until the onset of symptoms or in the worst case, sudden death. Regarding scientific knowledge, this proposal sought to deepen the current pathophysiological mechanism involved in the early onset, as well as in the rapid and aggressive progression of ACM. That is, to understand the genetics responsible for the ACM and the cellular pathways involved in the process of fibrofatty replacement of cardiac myocytes, as well as the resulting malignant electrical alterations that end up leading to a lethal cardiac arrhythmia, distinctive of the ACM. The results obtained so far indicate an important remodeling of the intercalated disks as a whole; in particular, deficiencies at the level of expression of important proteins of both desmosomes and GAP junctions as well as proteins calcium handling proteins have been observed. On the other hand, one of the important results is the decrease in the expression levels of Nav1.5. This is also confirmed in the results obtained in the animal model that presents a decrease without remodeling or histological phenotype, that is, it presents exclusively electric phenotype. This could have clinical relevance, since it indicates that electrical defects could be suffered without the presence of the classic structural defects described in the ACM. In this sense, after the results, future studies of the group could be directed to complete the molecular route that triggers the appearance of molecular defects that will result in structural and / or electrical defects to design possible new therapeutic targets.

Finally, the results obtained regarding the study of putative factors acting as triggers or aggravators of the pathology indicate that sport is clearly an important trigger. Studies show that continuous moderate training in individuals causes the appearance of structural defects that were masked in the case of untrained individuals. In vivo studies are focused on the progression of the disease in an animal model of ACM developed by our group. We intend to make a complete analysis of an environmental factor and we intend to translate this new knowledge into clinical diagnosis and risk stratification. As

mentioned above, early identification of people at risk helps clinicians to adopt personalized therapeutic measures to reduce the risk of malignant arrhythmogenic events.

## 3. Relevance and possible future implications

It is important to elucidate which are the common molecular pathways that trigger the characteristic cellular phenotype of the ACM, but also the specific pathways of the gene that can explain the variable expressivity ACM in the phenotype and its susceptibility to triggers. For this reason, future lines of research also focus on further progress in the clinical understanding of genetic causality and phenotype variability. It is essential to combine the clinical, genetic and functional research data to define the level of pathogenicity of the genetic variants, making a precise genetic interpretation before the transfer to the clinic. For this reason, the objective of translating research findings into clinical decision-making has been established. Specifically, functional studies will be carried out both in the HL-1 lines edited by PTC and with cardiomyocytes derived from patient-specific iPS, based on an accurate clinical evaluation of index and family cases previously characterized by our group (Campuzano, Alcalde et al. 2013, Mayor, Campuzano et al. 2014). The results obtained in our cellular model in combination with clinical parameters will provide conclusive genotype-phenotype correlations to make a proper interpretation helping to complete the clinical diagnosis and adopt personalized therapeutic measures. The future lines of research of the group include the first systematic study, both at the molecular level and at the cellular level, by premature termination codons (PTC) the desmosomal genes that are currently reported as a cause of ACM in an edited line of HL-1 cells and the corresponding exhaustive analysis of the expression and functional profile. Finally, we will explore a putative drug therapy based on the restitution of cellular phenotypes that combines a system of mediated disintegration of nonsense and a translational reading mechanism during translation. If the results are promising on this topic, we firmly believe that the next step would be to test this drug in the animal disease model and, if successful, propose clinical trials. However, at the clinical level, although there is a lack of information on what determines the progression of the disease, incomplete penetration and marked variability in the expression of the phenotype. Most studies have suggested that they could be related to a combination of genetic-environmental factors: the type of genetic

variation, the presence of genetic modifying variants and / or additional environmental interactions, such as exercise, which is one of the objectives of this proposal. Knowing the real impact of environmental factors on the emergence and progression of ACM will help risk stratification and be more exhaustive in limiting lifestyle.

## 4. Bibliography generated

During this period, the following scientific publications have been generated as a result of this research project.

Moncayo et al. a Hum Mol Genet. 2016
Moncayo et al. a Nat Rev Cardiol. 2017