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Editorial

Cardiac filaminopathies: lights and shadows in the phenotype associated with the *FLNC* gene

Filaminopatías cardiacas: luces y sombras en el fenotipo asociado con el gen *FLNC*

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Genetic analyses of inherited heart diseases constitute an essential piece of the diagnostic puzzle facing clinicians and help to more accurately explain the underlying cause of each condition. They are already a critical part of the diagnostic process, complementing other tests, not only for patients, but also—and above all—for their families, given that the incidence of these heart diseases is high due to the type of inheritance, largely autosomal dominant. In addition, it is increasingly evident that genetic analysis also helps to better determine the prognosis of our patients and even guide management, which is undoubtedly advancing toward personalized medicine.[1]

The problem currently facing clinicians lies in the interpretation of the huge number of genetic variants that are typically found, a consequence of the major advances in genetic diagnosis achieved with the latest next-generation sequencing techniques, and determination of their pathogenic significance. This represents a real challenge in modern medicine and requires considerable knowledge and specialization. Studies collecting data from high-volume centers offer a unique opportunity to share experience and advance understanding.[2]

A paradigm of the progress in recent years, in relation to the improved understanding of the genotype-phenotype relationship in cardiomyopathies, is the case of the *FLNC* gene, which encodes the protein filamin C and which is expressed in cardiac and skeletal muscle. Mutations in this gene have classically been associated with skeletal myopathies and, more recently, with cardiomyopathies and sudden cardiac death.[3]

Filamin C comprises an actin-binding domain, 2 hinge regions, and a domain containing 24 immunoglobulin-like repeats. It is mainly expressed in cardiac and skeletal muscle and functions in the Z discs and subsarcolemmal regions. In the Z discs, filamin C interacts with various proteins associated with cardiomyopathies, such as calsarcins (linked to hypertrophic cardiomyopathy [HCM]), myopalladin (linked to restrictive cardiomyopathy [RCM]), Cypher (linked to noncompaction cardiomyopathy [NCCM]), and actin (linked to dilated cardiomyopathy [DCM]). In addition, filamin C binds to sarcolemma via β1 integrin and δ-sarcoglycan (part of the dystrophin complex in muscle). The *FLNC* gene, which encodes filamin C, comprises 48 exons and is located at chromosome 7q32-35. Mutations in *FLNC* cause the formation of intracellular protein aggregates and disorganized sarcomeres. Most of the pathogenic variants in *FLNC* that lead to cardiomyopathy are localized to the actin-binding domains ROD1 and ROD2, which are considered hotspots.[4]

The literature contains a considerable amount of evidence concerning the genotype-phenotype correlation between truncating mutations in *FLNC* and overlapping aggressive phenotypes of arrhythmogenic cardiomyopathy (ACM), DCM, or RCM, without skeletal myopathy. However, the presence of missense mutations has also been linked to a HCM phenotype, although this aspect is a source of some uncertainty, given that the evidence is more limited. Indeed, it is unfortunate that some missense mutations previously classified as pathogenic are actually variants of uncertain significance following the American College of Medical Genetics (ACMG) criteria.[5] Moreover, those studies failed to clearly show cosegregation of the variants with the phenotype. In addition to the variable phenotype, variability has also been found in the types and locations of the *FLNC* variants. Thus, more clinical and functional studies are required to better characterize these variants and their possibly pathogenicity. In addition, there are few histopathological studies of endomyocardial biopsies, which would also be useful.

We must first highlight the work by Ortiz-Genga et al.,[6] who analyzed the *FLNC* gene in more than 2800 patients with distinct inherited heart diseases. These authors identified 23 truncating variants in 28 families. The mutations clearly cosegregated with an overlapping phenotype of DCM/ACM in the left ventricle, with a penetrance > 97% in carriers older than 40 years, and all had left ventricular dilatation, systolic dysfunction, myocardial fibrosis, a high burden of ventricular arrhythmias, and a family history of sudden cardiac death. A notable finding of this series is the lack of skeletal myopathy, which is traditionally associated with mutations in *FLNC*. In addition, there was a striking and unexpected absence of filamin aggregates in the histopathological studies. The phenotype ultimately described would comprise an overlap between DCM and ACM, with major similarities to laminopathies and desminopathies.

More recently, Gigli et al.[7] reported a cohort of 85 patients with truncated *FLNC* and DCM or ACM phenotype (mostly left-sided). These patients had a poor prognosis, with a very high incidence

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during follow-up of malignant ventricular arrhythmias, sudden cardiac death, and heart transplant.

Regarding the previous studies linking missense variants in *FLNC* to HCM, these mutations are mainly associated with HCM with a prevalence ranging from 1.3% to 8.7% in various cohorts.[8–11] Nonetheless, 2 studies failed to detect any missense variants in *FLNC* in patients with HCM, which calls into question the importance of this type of variant in this gene.[9,12] If just publications with functional studies and/or demonstrated cosegregation are considered, only 13 of the 54 missense mutations described would probably be pathogenic[8–11]; the others (according to current ACMG criteria) would be classified individually as variants of uncertain significance. In addition, we must highlight the high concentration of missense mutations in the ROD2 domain of *FLNC*, which is a vital region for cell signaling. This suggests that, collectively, missense mutations in the ROD2 domain have a higher probability of being pathogenic for HCM.

In contrast to the histological findings in other cardiomyopathies associated with *FLNC* truncations (DCM/ACM), Valdés-Mas et al.[11] did find large aggregates of mutated filamin C protein (in vivo in patients and in vitro in cells expressing mutated *FLNC*), as well as myofibrillar disarray and fibrosis but without clear skeletal myopathy. Strikingly, people with HCM and missense mutations in *FLNC* also appeared to be more susceptible to ventricular arrhythmias and sudden cardiac death. It is hypothesized that, in contrast to truncating mutations, missense mutations would lead to loss of function phenotypes in HCM, although the exact consequences of these mutations in *FLNC* remain unclear. In contrast, in another study, Gómez et al.[10] determined that most *FLNC* variants found were associated with mild forms of HCM and exhibited reduced penetrance. Indeed, both in that study and in that by Cui et al.,[9] the clinical characteristics of the patients with HCM with mutations in *FLNC* were not significantly different from those of other patients with HCM, in contrast to the results of Valdés-Mas et al.[11] Regardless, although much remains to be elucidated, it can be said that, first, patients with truncating mutations have a higher risk of sudden cardiac death than carriers of missense mutations and that, second, various carriers have been described with missense mutations in *FLNC* with overlapping phenotypes, even cases of arrhythmias without detectable structural abnormalities, congenital heart diseases, mitral valve prolapse, RCM, and NCCM. Accordingly, the range of phenotypes that can be linked to mutations in this gene is very wide, and they warrant better understanding. An overlap among phenotypes is often the norm.[13–16]

Currently, *FLNC* and the gene encoding titin (*TTN*) are the 2 individual genes associated with all types of cardiomyopathies, including DCM, ACM, HCM, RCM, and NCCM. This association with different myocardial phenotypes highlights the range of intracellular functions of filamin C related to the complex structure of the protein and the presence of diverse functional domains affected by mutations.

There are several lines of basic research into this pathology, such as the role of filamin C protein in the stabilization of the Z disc, the discrepancy between its highly mobile nature and its role in maintaining sarcomere structure, the role of filamin C aggregation during pathogenesis, and the differences in the target organs (skeletal and/or cardiac muscle) among the *FLNC* variants. Understanding of these mechanisms will lead to the judicious development of new treatments for these diseases, which may include gene editing, such as the CRISPR/Cas9 system, and ultimately, personalized treatments.[17]

In the excellent article by Bermúdez-Jiménez et al.,[18] published recently in *Revista Española de Cardiología*, the authors delve into and clarify aspects related to the genotype-phenotype correlation for missense mutations in *FLNC* and the development of MCH. As previously mentioned, until now little light has been shed on this poorly understood matter. The work comprises a multicenter retrospective study (involving 7 centers, most Spanish) in 21 families with HCM or RCM with particular myocardial features and with missense mutations in the ROD2 domain of *FLNC*. In total, 9 variants in this region of the gene were analyzed. In addition, the authors provide histological data on 3 explanted hearts; although this is a small number, the results are nonetheless valuable and they were supplemented by the transfection of cells with plasmids containing missense mutations in *FLNC* for confocal analysis. The authors describe a highly characteristic phenotype in this cohort, which was found in 20 individuals in 11 families (52% of the cohort) and which comprises HCM/RCM and left ventricular hypertrabeculation with characteristic sawtooth imaging findings. This phenotype could clearly be a variant of NCCM (although the authors state that it does not meet the diagnostic criteria) or, more likely, an overlap among HCM/RCM/NCCM, all of which are associated with a poor prognosis due to a high frequency of heart failure, need for heart transplant, and death. This distinguishes this entity from classic HCM, or is, at least, similar to HCM caused by mutations in *NNT2* or *TNNI3*, which share this aggressive early-onset phenotype. Many of these variants (a total of 5) were de novo, which not only indicates the pathogenicity of these mutations according to the ACMG,[5] but also limits the study of segregation in this work to just 6 families, in whom it was additionally milder, and the authors could not definitely conclude if the mutation and phenotype strongly cosegregated. Of the 9 variants described in this study, the researchers only managed to establish the pathogenicity of 4, classifying the others as variants of uncertain significance. In this work,[18] as in previous work,[11] no protein aggregates of filamin C were seen in the cells analyzed.

In conclusion, although the work by Bermúdez-Jiménez et al.[18] improves our understanding, multiple questions about this topic are posed, which require in-depth investigation in future studies. For example, it remains unknown why the different variants in *FLNC* can produce such highly variable phenotypes. Nonetheless, the use of appropriate cell culture models in combination with animal studies would help us to better understand the pathogenic mechanisms of the different filaminopathies. The article by Bermúdez-Jiménez et al.[18] adds to the previous work linking HCM and *FLNC* and provides highly pertinent functional data supporting the conclusion that some missense mutations in *FLNC* cause HCM. All of this will help to further the development of a personalized medicine model whose ultimate objective will be new specific therapies.

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CONFLICTS OF INTEREST

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