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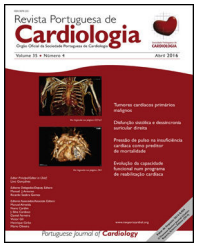

EDITORIAL COMMENT

The challenge of assessing variant pathogenicity in candidate Z-disc genes: The example of *TCAP* in hypertrophic cardiomyopathy

O desafio de avaliar a patogenicidade nos genes candidatos do disco Z: o exemplo de TCAP na miocardiopatia hipertrófica

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Hypertrophic cardiomyopathy (HCM) is primarily caused by mutations in genes encoding sarcomere proteins, inherited as an autosomal dominant phenotype and detected in 50% of the patients.[1] This incomplete yield of genetic testing is not ideal; establishing a genetic cause enables confirmation of the diagnosis in a proband/family and the planning of more informed screening and surveillance for relatives.

The remaining 50% of genotype-negative cases are likely to be explained by a mixture of novel genes. (one recent example is FHOD3)[2] rarer mutational mechanisms, such as copy number variation,[3] cryptic or deep-intronic variation, particularly relevant for *MYBPC3*,[4] and oligo/polygenic mechanisms, which defy classical Mendelian concepts and have been described for other inherited cardiac conditions, including channelopathies.[5]

Recent classification efforts, which take advantage of the growing availability of control genomes,[6] have repeatedly highlighted that the core group of initially described eight causal sarcomere genes (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *ACTC1*, *TPM1*) are still the most strongly associated with HCM.[7] The recently published genetic architecture of the large population recruited to the Portuguese Registry of HCM reflects this.[8] For other candidate genes, including the ones encoding Z-disc and cytoskeleton proteins, the level of evidence is weaker.[1,9] However, this field is always changing and co-segregation studies, sometimes in conjunction with functional research, have established causality for some of the candidate genes encoding non-contractile proteins, including junctophilin (*JPH*)[10] and alpha-actinin (*ACNT2*).[11]

Titin cap-telethonin, encoded by *TCAP*, mediates the assembly of the N-terminal domain of two adjacent titin molecules and interacts with other relevant Z-disc, ion channel and sarcomere-cytoskeleton components.[12] Due to this interaction, it has long been added to the list of possible candidate cardiomyopathy genes, and a small number of *TCAP* variants have been described in patients with HCM and dilated cardiomyopathy (DCM). However, while for DCM a significant excess of cases *vs* controls has been described, this does not seem to be the case for HCM. Additionally, co-segregation or functional data are

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nearly all absent.[7,9] It is therefore extremely challenging to attribute pathogenicity to a variant identified in this gene. Pathogenicity prediction for variants where familial linkage or convincing functional data are unavailable can be quite difficult, even for established causal genes. For candidate genes where evidence of causality is scarce, this task is even more difficult. Why a gene with such extensive interaction with major components of the sarcomere and related cardiomyocyte biology does not harbor more obvious causal variation is perhaps puzzling. A possible explanation could be its poor tolerance of variation (functional constraint)[13] but the constraint metrics available in the GnomAD browser (https://gnomad.broadinstitute.org/gene/ENSG00000173991?dataset=gnomad_r2_1)[6] appear to indicate otherwise.

In the case report by Toste et al., published in the current issue of the journal, the authors describe a small HCM family where the *TCAP* variant p.C57W was detected. No pathogenic variants in established causal genes were found. The authors describe this variant as likely pathogenic for HCM. The phenotype of the two affected members is not dissimilar to that commonly described in sarcomere HCM, including in the Portuguese population.[14] The variant is located in a region of the protein that interacts with muscle LIM protein and titin, it is well preserved across mammal species and causes a significant biochemical shift, which is reflected in the almost consensual in silico predictions of pathogenicity. Another feature supporting causality is the very low minor allele frequency in GnomAD v2.1.1[6] (four alleles, 0.0000166). In the reported family, the variant segregates with the phenotype, but a definitive co-segregation conclusion is limited by the small size (two affected and one non-affected siblings).

If applying strict American College of Medical Genetics criteria (PM2, PP3),[15] the variant would be classified as a variant of uncertain significance, but this would change in the presence of functional data, which would upgrade the variant to likely pathogenic. At its current status, it is advisable to be very careful; this variant should not be used for predictive testing, although further segregation efforts are certainly desirable.

Despite these challenges, interesting observations such as those made in the case reported by the authors should be shared. Other authors may encounter the same or neighboring variants in larger families or be interested in exploring functional data in collaboration. These joint curation efforts can potentially contribute to clarifying the role of candidate Z-disc genes, such as *TCAP*, in the genetic architecture of HCM and other cardiomyopathies, leading to an increase in the yield of genetic testing.

Conflicts of interest

The author has no conflicts of interest to declare.

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