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Letter to the Editor

The development of Brugada syndrome phenotype is multifactorial, combining genetic and environmental factors

Dear Editor,

Dear Editor, we read with great interest the article titled "*Putative role of Brugada syndrome genes in familial atrial fibrillation*" by Maltese et al[1]. The authors present an excellent study regarding the genetic basis of familial atrial fibrillation (FAF) and the association of Brugada genes with FAF[1]. However, the study has several methodological flaws[1]. The study involves only Russian families, but in conclusion the article suggests an association of FAF and Brugada genes in the general population[1]. It may not be possible to generalize the results to other populations.

The authors found several pathogenic genes in certain individuals[1]. None of the subjects, though, showed electrocardiographic patterns of Brugada syndrome (BrS), and the authors did not proceed to pharmacological challenge to unmask BrS according to current guidelines[1,2]. As a result, the conclusion that the study can identify subjects at risk of sudden death is not correct, because the screening for BrS was not complete.

The critical question is whether the novel variants cause BrS in these families[1,3]. The American College of Medical Genetics has recently published recommendations focused on classification of genetic variants to clarify their pathogenic roles[3]. Despite these guidelines, most of the BrS variants remain of unknown or ambiguous significance, and translation into clinical practice should be done with caution[3,4]. The proportion of pathogenic variants associated with BrS should be further analyzed to clarify the real percentage of BrS cases associated with each gene[3,4].

Family segregation and a comprehensive genotype-phenotype correlation help to interpret genetic variation[3]. However, incomplete penetrance and variable expressivity exacerbated by the unknown pathophysiological mechanism induced by each genetic variant clouds their definitive roles[3]. To provide insight into the functional effects of the genetic variants, a novel human cellular model using cardiomyocytes has been developed from human induced pluripotent stem cells. These patient-specific cardiomyocytes can incorporate phenotype features of single cells from a patient *in vitro*, and allow study of the electrophysiological properties of myocytes that lead to characteristic electrocardiographic alterations in BrS[3,5].

Conflict of interest

The Authors declare that they have no conflict of interests.

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