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Author's Reply

Reply to the Letter "The development of Brugada syndrome phenotype is multifactorial, combining genetic and environmental factors"

Dear Editor,

We are grateful to the authors of the Letter to the Editor entitled *"The development of Brugada syndrome phenotype is multifactorial, combining genetic and environmental factors"* for their interest in our article and their valuable comments.

We agree with them about the study's limits that we highlighted in the conclusions of the paper. Since the distribution of these variants varies in relation to ethnicity and our analysis was limited to the Russian population, the result of our study may not be translated to the general population[1].

Although the study did not aim to exclude cases of Brugada syndrome (BrS), it was a great limitation that the pharmacological challenge to unmask BrS was not performed. The screening of BrS genes in subjects with FAF and without a BrS-like electrocardiogram could be useful to identify subjects at risk who should be evaluated pharmacologically. Further studies are needed to validate this hypothesis.

In line with 2015 ACMG/AMP guidelines, we also agree that most of the BrS variants are of unknown significance (VUS). However, as suggested by other authors, those guidelines are not very effective for evaluating the variants involved in cardiomyopathies[2]. Indeed, a number of common variants, frequently classified as benign, have substantial epidemiologic and/or experimental evidence to suggest that they can mimic the effect of ultra-rare penetrant pathogenic variants under specific conditions[3]. Giudicessi et al[2] suggested adopting a new class of variants termed "functional risk alleles" to differentiate such variants from truly pathogenic/likely pathogenic variants and ambiguous VUS.

New methods, such as those using patient-specific human induced pluripotent stem cell cardiomyocytes will certainly help clarify the functional contribution of variants to the electrophysiological properties of patients' myocytes[4,5].

Conflict of interest

The authors declare that they have no conflict of interest.

References

1) Maltese PE, Aldanova E, Kriuchkova N, Averianov A, Manara E, Paolacci S, Bruson A, Miotto R, Sartori M, Guerri G, Zuntini M, Marceddu G, Tezzele S, Tadtaeva K, Chernova A, Aksyutina N, Nikulina S, Nodari S, Bertelli M. Putative role of Brugada syndrome genes in familial atrial fibrillation. Eur Rev Med Pharmacol Sci 2019; 23: 7582-7598.

2) Giudicessi JR, Wilde AAM, Ackerman MJ. The genetic architecture of long QT syndrome: A critical reappraisal. Trends Cardiovasc Med 2018; 28: 453-464.

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3) Giudicessi JR, Roden DM, Wilde AAM, Ackerman MJ. Classification and reporting of potentially proarrhythmic common genetic variation in long QT syndrome genetic testing. Circulation 2018; 137: 619-630.
4) Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Citation: present status of Brugada syndrome. J Am Coll Cardiol 2018; 72: 1046-1059.
5) Coppola G, Corrado E, Curnis A, Maglia G, Oriente D, Mignano A, Brugada P. Update on Brugada syndrome 2019. Curr Probl Cardiol 2019; 23: 100454.

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