Letter to the editor regarding the article "A case of hypertrophic and dilated cardiomyopathic sudden cardiac death: *de novo* mutation in *TTN* and *SGCD* genes"

To the Editor,

We recently read the article entitled "A case of hypertrophic and dilated cardiomyopathic sudden cardiac death: de novo mutation in *TTN* and *SGCD* genes" by Baydar et al. (1) published in the Anatolia Journal of Cardiology in late 2016 with great interest. We commend the authors for their contribution to improving our understanding of sudden cardiac death mechanisms and suggesting potential reasons for occurrence of the condition of genetic origin. We do, however, have a number of thoughts about the study, which are outlined below.

The authors mentioned *de novo* mutation in the sarcoglycan (*SGCD*) and titin (*TTN*) genes. The article fails to mention, however, the parent-based variant approach to analysis. In human genetic diseases, the term "*de novo* mutation" by definition refers to an alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell of one of the parents or in the zygote itself. It is only by analyzing the parents that their true contribution to the disease burden can be proven (2).

Furthermore, in the discussion section, the authors mentioned population frequencies of 2 variants using Exome Aggregation Consortium (ExAC) browser data. If those variants are *de novo*, they should not be in genetic data browsers like ExAC (3). Moreover, variant TTN:c.21758T>C was previously identified by Pugh et al. (4). The team reported this variant with a different transcript (c.41249T>C, p.Ile13750Thr NM_133378.4), and it has been identified in 5 individuals with dilated cardiomyopathy (DCM) ranging in age from early infancy to mid 30s, with one individual in their 60s who has been diagnosed with hypertrophic cardiomyopathy (HCM) (4). Therefore, as these variants were already identified by other research groups, they are no longer novel, as maintained in the current report.

Since only a single SGCD:c.15G>C variant with unknown significance was identified, it is not very likely that the *SGCD* gene is implicated in the pathology of this case. According to general variant classification assertion criteria, homozygous mutant allele of rs549319429 is classified as "likely benign" variant [December 8, 2015; GeneDx Variant Classification (06012015)] (5).

Sequencing of *TTN* gene revealed heterozygote TTN:c.21758T>C. Pugh et al. (4) described effect of this variant on both DCM and HCM in 2014 (4). Therefore, though SGCD:c.15G>C variant may be benign, in combination with possible pathogenic variant, such as TTN:c.21758T>C, clinical phenotype might produce an exponential effect.

To understand the certain effects of these variants on gene products, parent testing and co-segregation analyses should have been conducted before mentioning pathogenicity of the variants. Unfortunately, in the current article, it appears as though the authors have not completed any of these experiments.

Once again we would like to thank the authors and acknowledge their great efforts in presenting their case study. *De novo* mutation or pathogenicity of the variant family studies and segregation analysis should be conducted. Until these studies are completed the pathogenic effect of variants should not and cannot be mentioned.

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References

1. Baydar CL, Özen M. A case of hypertrophic and dilated cardiomyopathic sudden cardiac death: *de novo* mutation in *TTN* and *SGGD* genes. Anatol J Cardiol 2016 Jul 31. Epub ahead of print.
2. Veltman JA, Brunner HG. *De novo* mutations in human genetic disease. Nat Rev Genet 2012; 13: 565-75.
3. http://exac.broadinstitute.org
4. Pugh TJ, Kelly MA, Gowrisankar S, Hynes E, Seidman MA, Baxter SM, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. Genet Med 2014; 6: 601-8.
5. General Variant Classification Assertion Criteria. GeneDx DNA Diagnostic Experts. http://www.genedx.com

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