Identification of Pathogenic Mutations for Dilated Cardiomyopathy Accompanied With Unicuspid Aortic Valve

To the Editor:
In the interest issue of the Journal, Higashi et al reported a case of unicuspid aortic valve. The patient in this case suffered from refractory heart failure with enlarged LV end-diastolic diameter of 65 mm and reduced LV ejection fraction of 33%. It would be natural for the authors to consider the co-existence of “idiopathic” dilated cardiomyopathy (DCM) in this case, because the aortic stenosis caused by the unicuspid aortic valve could not explain well this obvious LV dilatation. Consequently, the authors carried out genetic screening of the coding sequences of 172 genes, including 59 genes previously reported to be associated with DCM. Here, there are some concerns about this genetic screening.

First, there is no description of the family history. Before the genetic screening of a patient with idiopathic DCM is performed, family history should be obtained. Whether DCM in the present case was familial or sporadic, or even if the cardiac manifestations in family members were not identical to those in the proband, obtaining a family history is a mandatory step that should go ahead of genetic screening. In addition, family history is essential for appropriate verification of the pathogenicity of newly identified variants using segregation analysis.

Next, genetic screening would have supported the diagnosis if any variant previously reported as a causing mutation for DCM had been successfully identified. In practice, this patient was found to be heterozygous for 2 novel rare variants in ACTN2 and RYR2, but whether these 2 variants caused idiopathic DCM, or chanced to be there as non-functioning ones of no clinical significance, remains quite inconclusive. The pathogenicity of newly identified rare variants, even in the known causative genes, should be carefully assessed. In the present case, maybe because of the insufficient interpretation of genomic findings, genetic screening could not support the clinical diagnosis. Rather, the authors state that “this might explain the eccentric hypertrophy in the present case”, which seems misleading. The accumulation of descriptions of variants is necessary for the near-future realization of systematic genetic screening in the clinical setting (i.e., “clinical sequencing”). Notably, the extent to which each variant is certified as pathogenic should be carefully annotated. In the era of next-generation sequencing, the number of novel variants with inconclusive pathogenicity has been increasing.

In such a situation, we need to strive more to interpret and annotate the pathogenicity of novel variants identified in genetic screening.

In conclusion, we would appreciate if the authors would perform a more careful interpretation of genomic findings and provide additional descriptions for their readers.

Disclosure Statement
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Conflicts of Interest
None.

References
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