Clinical application of next-generation sequencing-based gene panel in patients with hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is most commonly caused by mutation in one of the genes known to encode different components of the sarcomere. To date, more than 30 genes are known to be associated with HCM and it is inherited in an autosomal dominant manner. It is known that mutation of one of the genes that encodes a component of the sarcomere are found in approximately 50%-60% of probands with a family history of HCM, and approximately 20%-30% of probands without a family history of HCM[1]. Genetic testing can be of benefit in confirmation of clinical diagnosis of HCM and in identification of at-risk family members. Testing other affected family members can also help interpreting the pathogenicity of the variants that are detected in the family. Still, there can be some limitations for the testing regarding the interpretation of the detected variants. Determining the pathogenicity of a variant can be challenging, and moreover, the interpretation may even change over time.

We have analyzed 32 genes related to HCM (*ACTC1, ACTN2, ANKRD1, BAG3, CAV3, CRYAB, CSRP3, GLA, JPH2, LAMP2, LDB3, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, NEXN, OBSCN, PLN, PRKAG2, RYR2, TCAP, TNNC1, TNNC2, TNNI3, TNNT2, TPM1, TTN, TTR,* and *VCL*) in 59 patients with left ventricular hypertrophy. Molecular genetic testing was performed by using a multigene panel and sequences were captured by TruSeq Custom Enrichment Kit (Illumina) and sequenced with MiSeq (Illumina). Among 59 patients, 11 patients were not found to carry any variants other than benign ones in the 32 genes that were analyzed in the study. In rest of the patients, 38 previously reported variants and 9 novel variants with high possibilities of pathogenicity were detected, allowing 36 patients to be genetically confirmed. Mutations in *MYBPC3* (20/47, 42.6%) were most commonly detected in this study, followed by *MYH7* (8/47, 17.0%) and *TNNI3* (4/47, 8.5%).

Multi-gene panels comprising genes known to be associated with HCM are becoming widely available. Genetic testing for HCM can provide confirmation of clinical diagnosis, especially in at-risk family members. Since the interpretation of a specific variant may be aided by the genetic testing of family members for cosegregation analysis, clinical evaluation in at-risk relatives can be of help in providing more comprehensive information.

Reference

1. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* Dec 13 2011;124(24):2761-2796.
2. Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews(R).* Seattle (WA)1993.