Elucidating the Pathogenesis of Congenital Heart Disease in the Era of Next-Generation Sequencing

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Keywords
Next-generation sequencing · Whole-exome sequencing · Variant · Mutation · Congenital heart disease

Over the last decade, genetic screening has become increasingly available for patients with congenital heart disease (CHD). Chromosomal microarray has proved to be promising, particularly in the diagnosis of syndromic CHDs, and is now considered first-tier cytogenetic testing [1]. Whole-exome sequencing (WES) is another approach for genetic screening aimed towards identifying single-gene mutations [2]. Trio- and pedigree-based WES facilitate the identification of de novo and compound heterozygous variants throughout the entire coding region. Filtering of variants based on allele frequency, in silico predictions and segregation status, effectively narrows down the putative mutation. Thus, application of next-generation sequencing (NGS) has the potential of enhancing gene discovery in CHD pathogenesis.

Despite all the progress, underlying causes for the vast majority of CHDs remain unknown. The present study revealed ~1 de novo coding variant per trio by WES of a heterotaxy cohort. In a familial case of CHD, WES identified compound heterozygous, loss-of-function variants cosegregating with the phenotype [3]. Now, the major challenge lies in interpreting so-called "private" mutations that are specific to each pedigree. Distinguishing a truly causal mutation from benign variants requires well-designed functional studies. Future investigations must focus on establishing vertebrate models that recapitulate human CHD pathogenesis, based on the accumulating mutational data on CHD patients.

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T. Nakanishi et al. (eds.), *Molecular Mechanism of Congenital Heart Disease and Pulmonary Hypertension*, https://doi.org/10.1007/978-981-15-1185-1_65

Acknowledgements All work was supported by JSPS KAKENHI Grant JP16K10059. Grateful acknowledgement is rendered to Professor Seishi Ogawa, Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, for support of NGS. The authors also acknowledge the Human Genome Center, Institute of Medical Science, The University of Tokyo, for providing computing resources (https://genomon-project.github.io/GenomonPagesR/).

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