一般口演26（ II-OR26）
心血管発生・基礎研究

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Fri. Jun 28, 2019 4:30 PM - 5:20 PM 第6会場 (小ホール)

[II-OR26-03]iPS心筋を用いた QT延長症候群の表現型に基づく分類法

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Keywords:long QT syndrome, iPS, phenotype-based

Background: For long-QT syndrome (LQTS), recent progress in genome-sequencing technologies enabled the identification of rare genomic variants with diagnostic, prognostic, and therapeutic implications. However, pathogenic stratification of the identified variants remains challenging, especially in variants of uncertain significance.Objective: This study aimed to propose a phenotypic cell-based diagnostic assay for identifying LQTS to recognize pathogenic variants in a high-throughput manner suitable for screening.Methods: Disease-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) were differentiated from iPSCs generated from three LQTS patients (*KCNQ1* p.A344Aspl, *KCNH2* p.A422T, and *SCN5A* p.N406K, respectively). Response to specific current blockade was evaluated by using a multi-electrode array.Results: We first investigated the response of LQT type2 (LQT2)- iPSC-CMs following I_{Kr} blockade, finding that the response was significantly smaller in LQT2^{A422T}-iPSC-CMs than in Controls. Importantly, gene correction of the A422T mutation normalized the LQT2-CM phenotype. Furthermore, evaluation of this method for other LQTS types in response to I_{Ks} blockade using LQT1^{A344Aspl}-iPSC-CMs revealed a significantly smaller response relative to Controls. Moreover, response to I_{Na} blockade in LQT3^{N406K}-iPSC-CMs was greater than in LQT3^{corr}- iPSC-CMs. Conclusions: The methods presented in this study allowed classification of LQTS types 1, 2 and 3. This strategy potentially represents a breakthrough in compensating for the shortcomings of genetic testing of LQTS.