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Using Two-Sample Mendelian Randomization to Identify Potential Drug Targets: The Case of Desmoplakin

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BACKGROUND

Two-sample Mendelian randomization (2SMR) is a powerful tool for causal hypothesis testing. However, the simplicity of the statistical techniques combined with lack of causal inference reasoning has prompted an explosion of 2SMR studies, flooding scientific literature with findings that are often irrelevant or implausible. Here, we present a molecular biology application where we used 2SMR to advance understanding on the etiological mechanisms of familial arrhythmogenic cardiomyopathy (fACM). fACM is mostly caused by mutations in one of the five genes (DSP, JUP, PKP2, DSG2, and DSC2) that encode proteins constituting the cardiac desmosome, a cell junction responsible for cardiomyocytes mechanical coupling [1].

OBJECTIVES

Because Mendelian traits can be considered as extreme manifestations of common complex traits and share with them genetic architecture [2], the objective of our investigation was to test whether common genetic variants at desmosomal genes would also be associated with the normal variability of cardiac conduction traits in the general population. We show how a 2SMR analysis based on careful design and instrumental variable (IV) selection can help prioritize laboratory experiments, which are ultimately necessary to demonstrate causality.

METHODS

We analysed data of 4342 Cooperative Health Research in South Tyrol (CHRIS) study participants [3], fitting linear mixed models to assess the association between 2742 imputed genotype variants, covering all five genes, and four electrocardiographic traits: the P-wave, PR, QRS, and QT intervals. Replication was assessed in three independent studies from the same (MICROS [4], N=636) or different (SHIP-START and SHIP-TREND [5], N=3779) geographical region. We interrogated the GTEx-v8 database [6] to assess associations with transcriptomic levels in the cardiac left ventricle (N=386). Causality was assessed via Wald-ratio-based 2SMR, followed by in vitro experiments on human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs).

RESULTS

The QRS interval was significantly associated with a genetic variant located in a genomic region shared between DSP and the promoter of DSP-AS1, a long non-coding RNA of unknown function. The association was replicated in the MICROS but not in the SHIP studies. The variant resulted associated with DSP-AS1 but not DSP expression. Supported by evidence of statistical colocalization, 2SMR highlighted a significant causal effect of DSP-AS1 on DSP expression and QRS interval. In vitro experiments in hiPSC-CMs, showed that downregulating DSP-AS1 expression resulted in the upregulation of DSP expression and protein levels.

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CONCLUSIONS

The evidence that DSP can be regulated by intervening on DSP-AS1 makes the latter a potential target for pharmacological development for DSP-related diseases such as fACM. Coupling population-based genetic association studies with 2SMR enabled efficient laboratory experiment prioritization to assess the causal molecular connections. Experimental validation also resolved statistical uncertainties related to partial replication and the problem of overlapping samples in 2SMR.

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