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A genome-first approach to aggregating rare genetic variants in LMNA for association with electronic health record phenotypes.

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Abstract

PURPOSE: "Genome-first" approaches, in which genetic sequencing is agnostically linked to associated phenotypes, can enhance our understanding of rare variants' contributions to disease. Loss-of-function variants in LMNA cause a range of rare diseases, including cardiomyopathy.

METHODS: We leveraged exome sequencing from 11,451 unselected individuals in the Penn Medicine Biobank to associate rare variants in LMNA with diverse electronic health record (EHR)-derived phenotypes. We used Rare Exome Variant Ensemble Learner (REVEL) to annotate rare missense variants, clustered predicted deleterious and loss-of-function variants into a "gene burden" (N = 72 individuals), and performed a phenome-wide association study (PheWAS). Major findings were replicated in DiscovEHR.

RESULTS: The LMNA gene burden was significantly associated with primary cardiomyopathy (p = 1.78E-11) and cardiac conduction disorders (p = 5.27E-07). Most patients had not been clinically diagnosed with LMNA cardiomyopathy. We also noted an association with chronic kidney disease (p = 1.13E-06). Regression analyses on echocardiography and serum labs revealed that LMNA variant carriers had dilated cardiomyopathy and primary renal disease.

CONCLUSION: Pathogenic LMNA variants are an underdiagnosed cause of cardiomyopathy. We also find that LMNA loss of function may be a primary cause of renal disease. Finally, we show the value of aggregating rare, annotated variants into a gene burden and using PheWAS to identify novel ontologies for pleiotropic human genes.

KEYWORDS: LMNA; electronic health records (EHRs); genome-first; phenome-wide association studies (PheWAS); rare variants

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