European Journal of Human Genetics
https://doi.org/10.1038/s41431-018-0297-x

ARTICLE

A rare regulatory variant in the *MEF2D* gene affects gene regulation and splicing and is associated with a SLE sub-phenotype in Swedish cohorts

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Received: 28 April 2018 / Revised: 26 August 2018 / Accepted: 9 October 2018

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disorder with heterogeneous clinical presentation and complex etiology involving the interplay between genetic, epigenetic, environmental and hormonal factors. Many common SNPs identified by genome wide-association studies (GWAS) explain only a small part of the disease heritability suggesting the contribution from rare genetic variants, undetectable in GWAS, and complex epistatic interactions. Using targeted re-sequencing of coding and conserved regulatory regions within and around 215 candidate genes selected on the basis of their known role in autoimmunity and genes associated with canine immune-mediated diseases, we identified a rare regulatory variant rs200395694:G > T located in intron 4 of the *MEF2D* gene encoding the myocyte-specific enhancer factor 2D transcription factor and associated with SLE in Swedish cohorts (504 SLE patients and 839 healthy controls, $p = 0.014$, CI = 1.1–10). Fisher's exact test revealed an association between the genetic variant and a triad of disease manifestations including Raynaud, anti-U1-ribonucleoprotein (anti-RNP), and anti-Smith (anti-Sm) antibodies ($p = 0.00037$) among the patients. The DNA-binding activity of the allele was further studied by EMSA, reporter assays, and minigenes. The region has properties of an active cell-specific enhancer, differentially affected by the alleles of rs200395694:G > T. In addition, the risk allele exerts an inhibitory effect on the splicing of the alternative tissue-specific isoform, and thus may modify the target gene set regulated by this isoform. These findings emphasize the potential of dissecting traits of complex diseases and correlating them with rare risk alleles with strong biological effects.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that predominantly affects women of childbearing age [1]. A number of studies exploring the genetic basis of SLE in diverse populations identified over 40 risk loci [2], however it was estimated that these loci explain only about 30% of SLE heritability [3], indicating that disease pathogenesis results from a combined effect of different mechanisms and even a larger number of genes. The recently proposed omnigenic model of complex traits suggests that virtually any gene with regulatory variants active in relevant tissue may contribute to disease pathogenesis [4]. Genes are highly interconnected within the cell-specific gene networks, and thus any effect on one gene with regulatory function, that is not even

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Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41431-018-0297-x) contains supplementary material, which is available to authorized users.

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Published online: 20 November 2018