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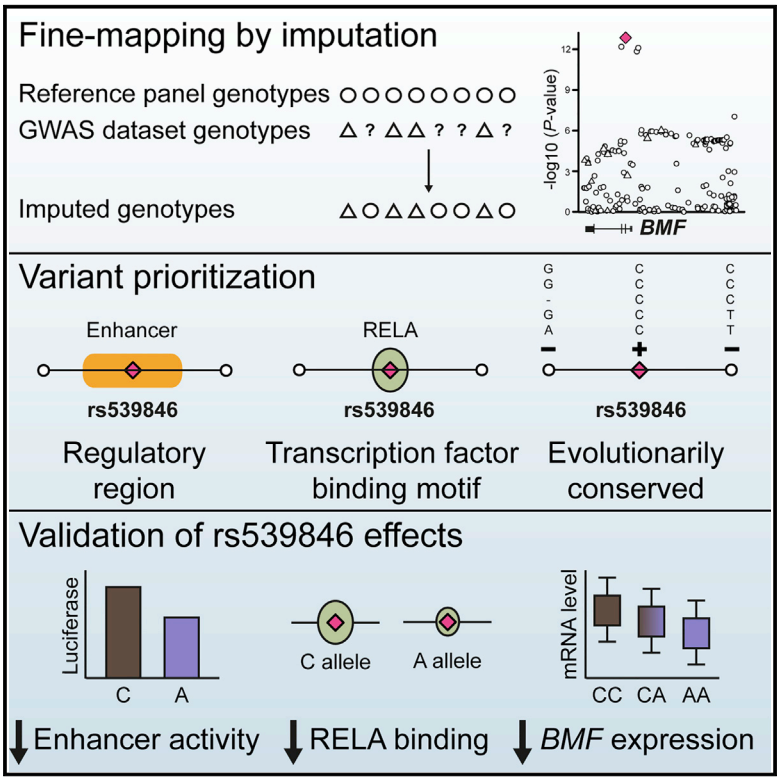
Report

Genetic Predisposition to Chronic Lymphocytic Leukemia Is Mediated by a *BMF* Super-Enhancer Polymorphism

Graphical Abstract



Highlights

- SNP rs539846 underlies 15q15.1 association with chronic lymphocytic leukemia
- rs539846 resides in a B cell super-enhancer, disrupting a conserved RELA-binding site
- The rs539846 risk allele (A) reduces enhancer activity and RELA binding in CLL
- rs539846-A confers lower *BMF* expression

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In Brief

Kandaswamy et al. find that SNP rs539846 underlies the 15q15.1 chronic lymphocytic leukemia risk locus. Follow-up data demonstrate that rs539846 resides within a transcriptional enhancer and alters RELA binding at a conserved site. The rs539846-A risk allele results in reduced RELA-mediated enhancer activity and lower expression of BCL-2-modifying factor.

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Genetic Predisposition to Chronic Lymphocytic Leukemia Is Mediated by a *BMF* Super-Enhancer Polymorphism

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SUMMARY

Chronic lymphocytic leukemia (CLL) is an adult B cell malignancy. Genome-wide association studies show that variation at 15q15.1 influences CLL risk. We deciphered the causal variant at 15q15.1 and the mechanism by which it influences tumorigenesis. We imputed all possible genotypes across the locus and then mapped highly associated SNPs to areas of chromatin accessibility, evolutionary conservation, and transcription factor binding. SNP rs539846 C>A, the most highly associated variant ($p = 1.42 \times 10^{-13}$, odds ratio = 1.35), localizes to a super-enhancer defined by extensive histone H3 lysine 27 acetylation in intron 3 of B cell lymphoma 2 (BCL2)-modifying factor (*BMF*). The rs539846-A risk allele alters a conserved RELA-binding motif, disrupts RELA binding, and is associated with decreased *BMF* expression in CLL. These findings are consistent with rs539846 influencing CLL susceptibility through differential RELA binding, with direct modulation of *BMF* expression impacting on anti-apoptotic BCL2, a hallmark of oncogenic dependency in CLL.

INTRODUCTION

Although genome-wide association studies (GWASs) frequently have identified statistically significant associations within non-coding regions of the genome, the underlying causal variant has been elucidated in only a few instances. GWASs of chronic lymphocytic leukemia (CLL) have identified 31 risk loci, with the signal annotating B cell lymphoma 2 (BCL2)-modifying factor (*BMF*) at 15q15.1 being highly robust (Berndt et al., 2013, 2016; Crowther-Swanepoel et al., 2010; Di Bernardo et al., 2008; Slager et al., 2011, 2012; Speedy et al., 2014).

Elevated expression of the anti-apoptotic protein BCL2 is a hallmark of CLL, driving the accumulation of mature leukemic lymphocytes (Hanada et al., 1993). BMF, a BH3-only pro-apoptotic member of the BCL2 protein family, neutralizes the anti-apoptotic activity of BCL2 through direct interaction (Puthalakath et al., 2001). Here we sought to identify the causal polymorphism(s) driving the 15q15.1 association with CLL susceptibility as a basis for understanding BCL2 addiction mechanisms in CLL.

RESULTS

Fine-Mapping of the 15q15.1 CLL Risk Locus

A previous GWAS reported an association between rs8024033 at 15q15.1 and CLL risk (Berndt et al., 2013). To refine the association signal, we performed fine-mapping of the 15q15.1 CLL risk locus by imputation of our European GWAS to 1000 Genomes Project (Abecasis et al., 2012) and UK10K (UK10K Consortium et al., 2015) reference panels. By this approach, we identified four risk SNPs with minor allele frequency >0.01 and association $p < 5.0 \times 10^{-7}$ (Figure 1A; Table S1). The lead SNP, rs539846 (odds ratio = 1.35, $p = 1.42 \times 10^{-13}$), mapped to the third intron of *BMF* and was in high linkage disequilibrium (LD, $r^2 = 0.91$) with the published SNP, rs8024033. We verified the fidelity of imputed rs539846 genotypes by Sanger sequencing in a subset of 176 CLL cases, demonstrating >95% concordance.

To rule out the existence of multiple statistical signals at the *BMF* locus, we repeated association testing conditional on

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