Unraveling a novel dual-function regulatory element showing epistatic interaction with a variant that escapes genome-wide association studies.

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Résumé

Regulation of gene expression has recently been complexified by the identification of Epromoters, a subset of promoters with enhancer function. Here, we uncovered the first dual cis-regulatory element, "ESpromoter," exhibiting both enhancer and silencer function, as a regulator of the nearby genes ATP2B4 and LAX1 in single human T cells. Through integrative approach, we pinpointed functional rs11240391, a severe malaria risk variant that escapes detection in genome-wide association studies, challenging conventional strategies for identifying causal variants. CRISPR-modified cells demonstrated the regulatory effect of ESpromoter and rs11240391 on LAX1 expression and T cell activation. Furthermore, our findings revealed an epistatic interaction between ESpromoter SNPs and rs11240391, impacting severe malaria susceptibility by further reducing LAX1 expression. This groundbreaking discovery challenges the conventional enhancer-silencer dichotomy. It highlights the sophistication of transcriptional regulation and argues for an integrated approach combining genetics, epigenetics, and genomics to identify new therapeutic targets for complex diseases.

Mots-Clés: Cis, regulatory elements, Enhancer, Silencer, Dual function, Epistatic interaction, Functional variants, Severe malaria

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