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Heinig M, Petretto E, Wallace C, Bottolo L, Rotival M, Lu H, Li Y, Sarwar R, Langley SR, Bauerfeind A, Hummel O, Lee YA, Paskas S, Rintisch C, Saar K, Cooper J, Buchan R, Gray EE, Cyster JG; Cardiogenics Consortium, Erdmann J, Hengstenberg C, Maouche S, Ouwehand WH, Rice CM, Samani NJ, Schunkert H, Goodall AH, Schulz H, Roeder HG, Vingron M, Blankenberg S, Münzel T, Zeller T, Szymczak S, Ziegler A, Tiret L, Smyth DJ, Pravenec M, Aitman TJ, Cambien F, Clayton D, Todd JA, Hubner N, Cook SA

Abstract

Combined analyses of gene networks and DNA sequence variation can provide new insights into the aetiology of common diseases that may not be apparent from genome-wide association studies alone. Recent advances in rat genomics are facilitating systems-genetics approaches. Here we report the use of integrated genome-wide approaches across seven rat tissues to identify gene networks and the loci underlying their regulation. We defined an interferon regulatory factor 7 (IRF7)-driven inflammatory network (IDIN) enriched for viral response genes, which represents a molecular biomarker for macrophages and which was regulated in multiple tissues by a locus on rat chromosome 15q25. We show that Epstein-Barr virus induced gene 2 (Ebi2, also known as Gpr183), which lies at this locus and controls B lymphocyte migration, is expressed in macrophages and regulates the IDIN. The human orthologous locus on chromosome 13q32 controlled the human equivalent of the IDIN, which was conserved in monocytes. IDIN genes were more likely to associate with susceptibility to type 1 diabetes (T1D)-a macrophage-associated autoimmune disease-than randomly selected immune response genes ($P = 8.85 \times 10^{-6}$). The human locus controlling the IDIN was associated with the risk of T1D at single nucleotide polymorphism rs9585056 ($P = 7.0 \times 10^{-10}$); odds ratio, 1.15), which was one of five single nucleotide polymorphisms in this region associated with EBI2 (GPR183) expression. These data implicate IRF7 network genes and their regulatory locus in the pathogenesis of T1D.



