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Allele-specific methylation of type 1 diabetes susceptibility genes

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ABSTRACT

The susceptibility to autoimmune diseases is influenced by genes encoding major histocompatibility complex (MHC) proteins. By examining the epigenetic methylation maps of cord blood samples, we found marked differences in the methylation status of CpG sites within the MHC genes (*cis*-metQTLs) between carriers of the type 1 diabetes risk haplotypes HLA-DRB1*03-DQA1*0501-DQB1*0201 (DR3-DQ2) and HLA-DRB1*04-DQA1*0301-DQB1*0302 (DR4-DQ8). These differences were found in children and adults, and were accompanied by reduced HLA-DR protein expression in immune cells with the HLA-DR3-DQ2 haplotype. Extensive *cis*-metQTLs were identified in all 45 immune and non-immune type 1 diabetes susceptibility genes analyzed in this study. We observed and validated a novel association between the methylation status of CpG sites within the LDHC gene and the development of insulin autoantibodies in early childhood in children who are carriers of the highest type 1 diabetes risk genotype. Functionally relevant epigenetic changes in susceptibility genes may represent therapeutic targets for type 1 diabetes.

1. Introduction

Genetic susceptibility for autoimmunity is conferred by multiple genes encoding histocompatibility leukocyte antigens (HLA), proteins involved in T and/or B cell responses, and proteins relevant to the target tissue to which tolerance has been lost [1]. Type 1 diabetes, an autoimmune disease targeting insulin-producing pancreatic β cells, quintessentially follows this paradigm with strong susceptibility provided by the HLA-DRB*03-DQB1*0201 (DR3-DQ2) and the HLA-DRB1*04-DQB1*0302 (DR4-DQ8) haplotypes [2]. Susceptibility is also conferred by genes encoding T cell receptor and interleukin-2 signaling proteins, for example, and by polymorphisms in INS that affect insulin expression [3,4]. There is also substantial overlap with susceptibility for other autoimmune diseases. For example, the HLA-DR3-DQ2 haplotype is associated with increased susceptibility for type 1 diabetes [5], celiac disease [6], thyroid disease [7], rheumatoid arthritis [8], myasthenia gravis [9], systemic lupus erythematosus [10] and other autoimmune diseases [11]. The HLA-associated susceptibility to autoimmune

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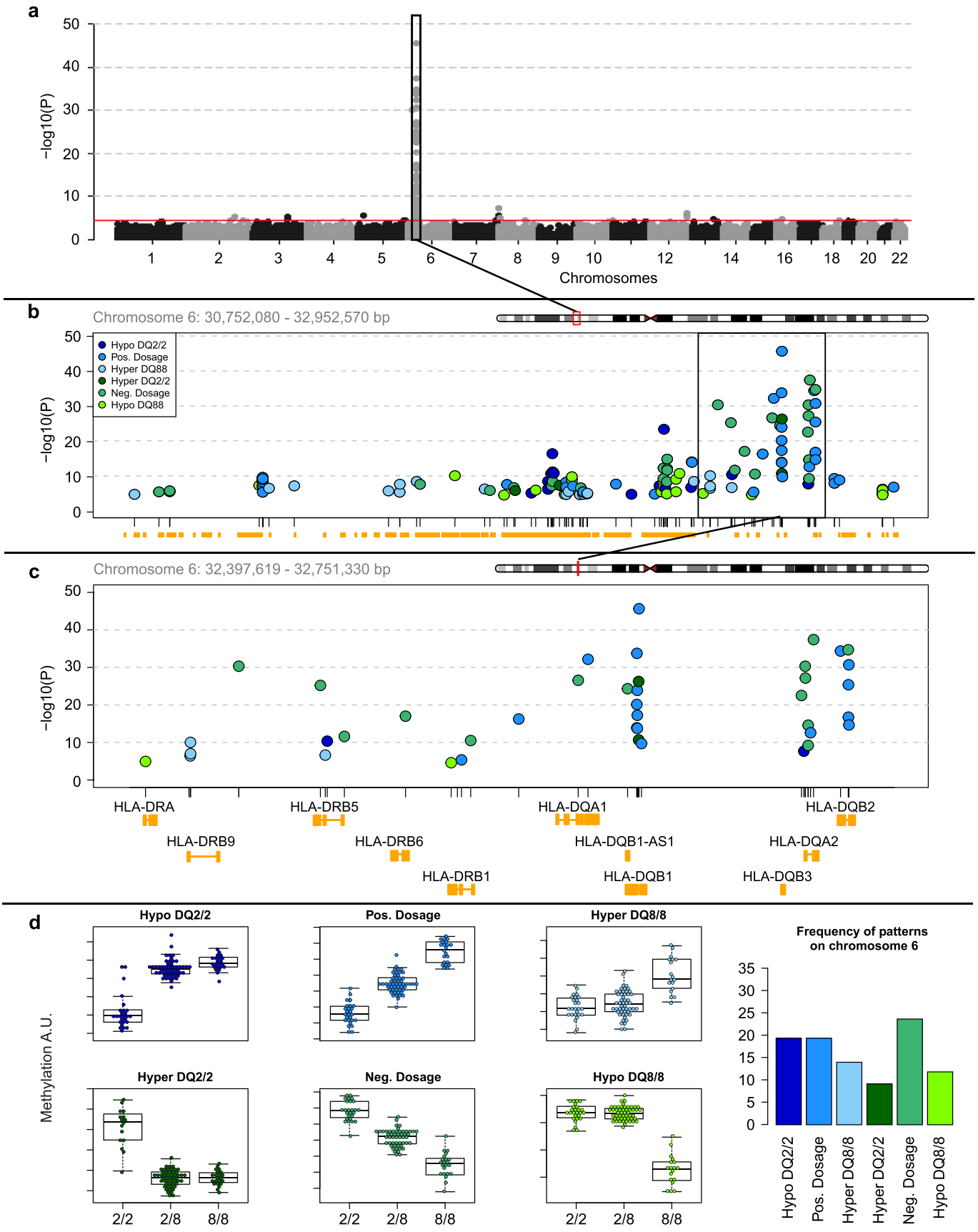

Fig. 1. Results of Illumina Infinium methylation array in neonates with HLA-DR-DQ genotypes associated with type 1 diabetes. (a) Manhattan plot of the differentially methylated CpG sites in neonates with HLA-DR3-DQ2/DR3-DQ2 (2/2; n = 26), DR3-DQ2/DR4-DQ8 (2/8; n = 52), and DR4-DQ8/DR4-DQ8 (8/8; n = 22) genotypes. This investigation was performed in the BABYDIET cohort using the Illumina Infinium methylation array. The maximum $-\log_{10}$ p-value was on chromosome 6. Significant signals were also detected

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