Increased DNA methylation variability in type 1 diabetes across three immune effector cell types

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Abstract

The incidence of type 1 diabetes (T1D) has substantially increased over the past decade, suggesting a role for non-genetic factors such as epigenetic mechanisms in disease development. We performed an epigenome-wide association study across 406,365 CpGs in 52 monozygotic twin pairs discordant for T1D in three immune effector cell types: $CD4^+$ T cells, $CD19^+$ B cells, and $CD14^+CD16^-$ monocytes. We observed a substantial enrichment of differentially variable CpG positions (DVPs) in T1D twins compared to their healthy co-twins across all cell types. These T1D-associated DVPs were found to be reproducible and temporally stable, and to act independently of genetic variation. Evidence from cord blood of newborns who progressed to overt T1D suggests that the DVPs likely emerged after birth. Integration with cell type-specific gene regulatory circuits highlighted pathways involved in immune cell metabolism and cell cycle. Our findings, supported by 772 methylomes, implicate epigenetic changes in T1D that may contribute to disease pathogenesis.