The genetic landscape of pediatric autoimmune diseases.

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Autoimmune diseases affect seven to ten percent of individuals living in the Western Hemisphere, and represent a significant cause of chronic morbidity and disability. High rates of comorbidity and familial clustering suggest that strong genetic predisposition underlies autoimmune disease susceptibility, and genome wide association studies (GWAS) have identified hundreds of susceptibility genes associated with autoimmune diseases with some shared across clinically-distinct disease groups. To investigate the genetic architecture of pediatric autoimmune diseases (pAIDs), we performed a heterogeneity-sensitive GWAS (hsGWAS) across 10 pAIDs in a nested case-control study including over 5,200 cases and 11,000 controls. We identified 86 independent pAID association loci reaching GWS ($P < 5 \times 10\text{-}8$), including lead SNPs mapping to candidate genes with established immunoregulatory functions (e.g., CD40LG; $P < 3.08 \times 10\text{-}11$ and NFATC3; $P < 1.18 \times 10\text{-}8$). Of the 147 lead GWS (86) and marginally significant (61) loci, 97% were supported by functional (n=30), regulatory (n=55), conservational (n=30) or literature-reported (n=40) data, which is enriched as compared to that observed at random across the genome ($p<0.021$), particularly for DNAse hypersensitivity sites ($p < 0.01$) as well as for genetic association annotations, eQTLs, and coding variants ($p<0.001$). In addition, we extensively characterized the expression profiles of the candidate genes mapped by the lead loci in human tissues and murine immune-specific cell typing, providing evidence to support a disease-specific gene expression signature across subsets of immune cell lineages. Integration of multiple in silico analytical approaches identified highly shared autoimmune signals (e.g., IL2-IL21 $P < 6.24 \times 10\text{-}12$) and converging roles for JAK-STAT, innate, and TH1-TH2/TH17 mediated T-cell signaling across pAIDs and as molecular pathways representing attractive pharmacological targets for pAIDs.

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