A strategy to find gene combinations that identify children who progress rapidly to type 1 diabetes after islet autoantibody seroconversion.

We recently developed a novel approach capable of identifying gene combinations to obtain maximal disease risk stratification. Type 1 diabetes has a preclinical phase including seroconversion to autoimmunity and subsequent progression to diabetes. Here, we applied our gene combination approach to identify combinations that contribute either to islet autoimmunity or to the progression from islet autoantibodies to diabetes onset. We examined 12 type 1 diabetes susceptibility genes (INS, ERBB3, PTPN2, IFIH1, PTPN22, KIAA0350, CD25, CTLA4, SH2B3, IL2, IL18RAP, IL10) in a cohort of children of parents with type 1 diabetes and prospectively followed from birth. The most predictive combination was subsequently applied to a smaller validation cohort. The combinations of genes only marginally contributed to the risk of developing islet autoimmunity, but could substantially modify risk of progression to diabetes in islet autoantibody-positive children. The greatest discrimination was provided by risk allele scores of five genes, INS, IFIH1, IL18RAP, CD25, and IL2 genes, which could identify 80% of islet autoantibody-positive children who progressed to diabetes within 6 years of seroconversion and discriminate high risk (63% within 6 years; 95% CI 45-81%) and low risk (11% within 6 years; 95% CI 0.1-22%; \( p = 4 \times 10^{-5} \))
antibody-positive children. Risk stratification by these five genes was confirmed in a second cohort of islet autoantibody children. These findings highlight genes that may affect the rate of the beta-cell destruction process once autoimmunity has initiated and may help to identify islet autoantibody-positive subjects with rapid progression to diabetes.