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Identification of novel high-impact recessively inherited type 2 diabetes risk variants in the Greenlandic population

Aims/hypothesis: In a recent study using a standard additive genetic model, we identified a TBC1D4 loss-of-function variant with a large recessive impact on risk of type 2 diabetes in Greenlanders. The aim of the current study was to identify additional genetic variation underlying type 2 diabetes using a recessive genetic model, thereby increasing the power to detect variants with recessive effects.

Methods: We investigated three cohorts of Greenlanders (B99, n = 1401; IHIT, n = 3115; and BBH, n = 547), which were genotyped using Illumina MetaboChip. Of the 4674 genotyped individuals passing quality control, 4648 had phenotype data available, and type 2 diabetes association analyses were performed for 317 individuals with type 2 diabetes and 2631 participants with normal glucose tolerance. Statistical association analyses were performed using a linear mixed model.

Results: Using a recessive genetic model, we identified two novel loci associated with type 2 diabetes in Greenlanders, namely rs870992 in ITGA1 on chromosome 5 (OR 2.79, p = 1.8 × 10−8), and rs16993330 upstream of LARGE1 on chromosome 22 (OR 3.52, p = 1.3 × 10−7). The LARGE1 variant did not reach the conventional threshold for genome-wide significance (p 5 × 10−8) but did withstand a study-wide Bonferroni-corrected significance threshold. Both variants were common in Greenlanders, with minor allele frequencies of 23% and 16%, respectively, and were estimated to have large recessive effects on risk of type 2 diabetes in Greenlanders, compared with additively inherited variants previously observed in European populations.

Conclusions/interpretation: We demonstrate the value of using a recessive genetic model in a historically small and isolated population to identify genetic risk variants. Our findings give new insights into the genetic architecture of type 2 diabetes, and further support the existence of high-effect genetic risk factors of potential clinical relevance, particularly in isolated populations.

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