

## 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,  $p = 1.8 \times 10^{-8}$ ), and rs16993330 upstream of LARGE1 on chromosome 22 (OR 3.52,  $p = 1.3 \times 10^{-7}$ ). The LARGE1 variant did not reach the conventional threshold for genome-wide significance ( $p 5 \times 10^{-8}$ ) 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.

**Forfatter:** N Grarup ; I Moltke ; MK Andersen ; Peter Bjerregaard; CVL Larsen ; IK Dahl-Petersen ; E Jørsboe ; HK Tiwari ; SE Hopkins ; HW Wiener ; BB Boyer ; A Linneberg ; O Pedersen ; Marit Eika Jørgensen; A Albrechtsen ; T Hansen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Genetic association; Genome-wide association study; Greenlanders; Inuit; ITGA1; LARGE1; Recessive genetic model; Type 2 diabetes **Titel på tidsskrift:** Diabetologia **Volume på tidsskrift:** 61 **Nummer på tidsskrift:** 9 **Udgiver:** Springer **DOI nummer:** doi: 10.1007/s00125-018-4659-2.

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