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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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Microvascular complications in Nuuk, Greenland, among Greenlanders and non-Greenlanders diagnosed with type 2 diabetes

Aim: The objective of this study was to estimate and compare between Greenlanders and non-Greenlanders living in Nuuk the proportion of patients with type 2 diabetes with microvascular complications.

Methods: This study was performed as a cross-sectional register study based on information in the Electronic Medical Record (EMR). All patients diagnosed with type 2 diabetes and with permanent addresses in Nuuk were included. Patients born in Greenland were considered to be Greenlanders, while patients born outside Greenland were considered as non-Greenlanders. Proportions of patients with retinopathy, microalbuminuria, nephropathy and neuropathy were estimated based on information from the EMR.

Results: A total of 393 patients (295 Greenlanders and 98 non-Greenlanders) were included. In total 83.0% of all patients have been screened for retinopathy, while 66.4% were screened for microalbuminuria and 64.6% for neuropathy within a two year period. The most frequent microvascular complication was neuropathy, which was observed among half (49.6%) of all patients followed by microalbuminuria (28.4%), retinopathy (10.7%)

and nephropathy (7.3%). Retinopathy was observed among 21.4% of the non-Greenlanders compared to only 7.0% of the Greenlanders (p = .001). Microalbuminuria was also observed more frequently (p = .047) among non-Greenlanders (37.5%) than among Greenlanders (24.9%).

Conclusion: Greenlanders seem to be less prone to especially retinopathy than are non-Greenlanders.

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