

## Genetic determinants of glycosylated hemoglobin levels in the Greenlandic Inuit population

We previously showed that a common genetic variant leads to a remarkably increased risk of type 2 diabetes (T2D) in the small and historically isolated Greenlandic population. Motivated by this, we aimed at discovering novel genetic determinants for glycosylated hemoglobin (HbA1C) and at estimating the effect of known HbA1C-associated loci in the Greenlandic population. We analyzed genotype data from 4049 Greenlanders generated using the Illumina Cardio-MetaboChip. We performed the discovery association analysis by an additive linear mixed model. To estimate the effect of known HbA1C-associated loci, we modeled the effect in the European and Inuit ancestry proportions of the Greenlandic genome (EAPGG and IAPGG, respectively). After correcting for multiple testing, we found no novel significant associations. When we investigated loci known to associate with HbA1C levels, we found that the lead variant in the GCK locus associated significantly with HbA1C levels in the IAPGG ( $PIAPGG=4.8 \times 10^{-6}$ ,  $\beta_{IAPGG}=0.13SD$ ). Furthermore, for 10 of 15 known HbA1C loci, the effects in IAPGG were similar to the previously reported effects. Interestingly, the ANK1 locus showed a statistically significant ancestral population differential effect, with opposing directions of effect in the two ancestral populations. In conclusion, we found only 1 of the 15 known HbA1C loci to be significantly associated with HbA1C levels in the IAPGG and that two-thirds of the loci showed similar effects in Inuit as previously found in European and East Asian populations. Our results shed light on the genetic effects across ethnicities.

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## Loss-of-function variants in ADCY3 increase risk of obesity and type 2 diabetes

We have identified a variant in ADCY3 (encoding adenylate cyclase 3) associated with markedly increased risk of obesity and type 2 diabetes in the Greenlandic population. The variant disrupts a splice acceptor site, and carriers have decreased ADCY3 RNA expression. Additionally, we observe an enrichment of rare ADCY3 loss-of-function variants among individuals with type 2 diabetes in trans-ancestry cohorts. These findings provide new information on disease etiology relevant for future treatment strategies.

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## Awareness of diabetes in the population of Greenland

**Objective:** Type 2 diabetes (T2D) may develop slowly with few symptoms and may remain undetected for many years, leading to severe complications that potentially could have been prevented with timely diagnosis and treatment. Undiagnosed diabetes has been reported high in Greenland. However, awareness and knowledges about diabetes in the general population remains unexplored.

**Methods:** This study was performed as an observational cross sectional study based on telephone interview among a random sample of Greenlanders. The interview was performed in Greenlandic or Danish according to participant' preference and included information about age, gender, place of birth, place of residence, medical history of diabetes, awareness of the diabetes, risk factors, symptoms, complications, and local possibilities to

get tested for diabetes.

Results: In total, telephone contact was established with 196 adults. Of those, 161 participants completed the interview while 35 were unwilling to participate in the interview corresponding to a response rate of 82% (161/196). The majority of responders, 85.7%, were aware of diabetes and local testing possibilities. However, only around 65% were aware of risk factors of diabetes. Also, the knowledge about common symptoms of diabetes was quite low, around 50%, and in particular low, around 40%, among males and inhabitants in settlements.

Conclusions: The vast majority of the population was aware of diabetes. However, the present study revealed shortage of knowledge of common risk factors, symptoms, and complications to diabetes. This is challenging the effort to prevent diabetes and new alternative information strategies are needed. Furthermore, the shortage of knowledges of risk factors may not be isolated to diabetes and further studies on health literacy in Greenland are recommended.

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