

Genome wide association studies in small and highly admixed populations.

In Greenland, population surveys among Inuits have shown a dramatic increase in prevalence of type 2 diabetes. However, Inuits seem to have a more advantageous metabolic risk profile for any given level of obesity as compared with a Danish population. While these ethnic differences may be due to diversity in environmental factors or body composition it is likely genetic factors contribute ethnic differences in metabolic risk.

Genetic association studies have traditionally been performed in large populations, such as Europeans, but there are several distinct advantages using smaller populations. In large populations, Darwinian selection tends to drive even slightly deleterious mutations to very low frequencies. In contrast, small populations tend to be more affected by genetic drift, which means that slightly deleterious mutations have a higher chance of reaching high frequency.

We perform a genome wide association study in Greenland for metabolic related quantitative traits. Although the individuals are highly admixed and closely related we can control the false positive rate using a mixed model. Both known and novel loci show an association with metabolic traits. However, one association is especially strong and using exome sequencing we identify a very likely causal variation. This variation has by far the largest effect, on both glucose levels and type 2 Diabetes, of any previous discovered common variation.

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