By shaping the genomes of ancient populations, selection pressure allowed individuals to adapt to local environments and stressors. Well-known examples include thalassemia and sickle cell disease, which offered protection against malaria in Mediterranean and African populations, respectively. More recently, variations in the lactase gene have been identified among populations with a long history of cattle herding and milk consumption to maintain the ability to metabolize lactose into adulthood. Indeed, many of the ancient genetic variations shaped by selection pressure explain the phenotypic and physiological variation across geographically diverse populations that exist today. As is the case with sickle cell disease, however, the benefits of certain genetic variants can disappear, or worse, the variants can become detrimental in environments different from which they were derived.

See Article by Skotte et al

Whereas early investigations in molecular anthropology studied population genetics in relation to anthropometric or physiological characteristics, advances in ‘omics technology now allow the integration of genetic variation with additional molecular data to provide a more granular and mechanistic view of evolutionary adaptation. However, although this integrative molecular approach has been used within populations to characterize the genetic architecture of certain disease states, its application in unraveling the implications of genetic variation between populations has been limited. As populations become more and more admixed, discerning the contribution of unique ancestral traits to molecular phenotypic variation becomes more difficult. As such, the study of historically isolated, but recently admixed, populations provides a powerful approach to unravel the molecular networks of complex traits that vary from one population to another.

Inuit are a group of indigenous peoples that inhabit the Arctic regions of Greenland, Canada, and Alaska. Isolated for thousands of years, Inuit inhabited the harsh arctic climate subsisting on a mostly carnivorous and low-carbohydrate diet consisting of marine mammals and fish. Given these environmental pressures and dietary habits, it is not surprising that Inuit developed special metabolic adaptations over time. For instance, because of the traditional low-glucose diet, Inuit relied on fatty acids and ketone bodies as their main source of energy. Indeed, recent studies of Inuit have provided evidence for positive selection at a cluster of fatty acid desaturase genes and at CPT1 (carnitine palmitoyltransferase 1), a gene that regulates transport of fatty acids into the mitochondria. However, the impact of these genetic adaptations on fatty acid metabolism is incompletely characterized.

In this issue of Circulation: Cardiovascular Genetics, Skotte et al examine the genetic variation underlying metabolic and anthropometric differences in Inuit populations. They performed array-based genotyping using the Illumina OmniExpressExome chip in 1570 samples from individuals recruited from the Greenlandic population, enriched for individuals born in Greenland to parents also born in Greenland. Although there was still a relatively high degree of European admixture (sample average of 27% European ancestry), all participants had at least 20% Inuit ancestry. They then performed metabolic quantitative trait loci analysis using 232 serum metabolites obtained from a nuclear magnetic resonance-based metabolomics platform; the majority of these metabolites were lipid related. They focused on a ~10 Mb region on chromosome 11 that had significant associations with fatty acid metabolism, including degree of unsaturation and levels of polyunsaturated fatty acids. Using conditional analyses, they identified rs1017640 from the array, within the CPT1 gene, as the lead variant. Because of previous studies demonstrating the importance of the variant rs80356779 (not captured on their array), which encodes a missense mutation in CPT1 (p.Pro479Leu, L479), in indigenous arctic populations, they performed targeted sequencing for this variant as well. Through additional conditional analyses, they demonstrated that rs80356779 is likely the causal variant for the observed associations with lipid traits. Moreover, they show that the variant has evidence of positive selection in the indigenous populations and is additionally associated with anthropometric measures, namely height; each copy of the derived allele reduced height by an average of 2.1 cm. Remarkably, although the L479 allele occurred at frequency of 19.8% and 26.4% among the Greenlandic Inuit with no European ancestry, it was absent in most other populations they examined, including those of European and Chinese ancestry.

Although previous studies have noted the effect of rs80356779 on traits in Arctic populations, including anthropometric (body mass index) and lipid traits (high-density lipoprotein, apolipoprotein A-1), none have integrated
gene variation with comprehensive metabolomics. In doing so, Skotte et al uncover previously unappreciated associations in this CPT1A variant with distinct fatty acid metabolite signatures. These findings support another recently published study describing associations of rs80356779 with fatty acid composition of erythrocyte membranes in Greenlandic populations.\textsuperscript{13} On the basis of in vitro studies and structural modeling, it seems that the mutation exerts differential effects on CPT1A activity depending on the nutritional (fed versus fasting) state that, in sum, may enhance the ability to use fatty acids for energy even in non-fasting conditions.\textsuperscript{14} Additional mechanistic studies, including in vitro and animal models, are required to fully characterize the functional implications of the L479 mutation.

Although L479 likely helped Inuit adapt to their traditional diet, the impact of the variant in modern society remains to be explored. For instance, what is the metabolic response of individuals with L479 to the high-glycemic diets that now dominate typical Western diets? A study in Greenlandic individuals without diabetes mellitus recently demonstrated that a nonsense variant in the TBC1D4 gene confers increased diabetes mellitus risk.\textsuperscript{15} Does L479 have a similar effect? Although no statistically significant association was noted between L479 and hemoglobin A1c, prospective studies that perform detailed metabolic phenotyping of individuals with L479 would be informative.

In sum, the study of Skotte et al combines the power of studying recently admixed populations with the integration of multiple molecular data sets to provide insight into metabolic adaptations driven by selection pressure in Greenlandic Inuit. This approach highlights the potential of a multiomics approach to understand the functional implications of genetic variation among distinct populations.

Disclosures

None.

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