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REVIEW

# Genetic Features of Lipid and Carbohydrate Metabolism in Arctic Peoples

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**Abstract**—Prolonged adaptation of ancestors of indigenous peoples of the Far North of Asia and America to extreme natural and climatic conditions of the Arctic has resulted in changes in genes controlling various metabolic processes. However, most genetic variability observed in the Eskimo and Paleoasians (the Chukchi and Koryaks) is related to adaptation to the traditional Arctic diet, which is rich in lipids and proteins but extremely poor in plant carbohydrates. The results of population genetic studies have demonstrated that specific polymorphic variants in genes related to lipid metabolism (*CPT1A*, *FADS1*, *FADS2*, and *CYB5R2*) and carbohydrate metabolism (*AMY1*, *AMY2A*, and *SI*) are prevalent in the Eskimo and Paleoasian peoples. When individuals deviate from their traditional dietary patterns, the aforementioned variants of genetic polymorphism can lead to the development of metabolic disorders. American Eskimo-specific variants in genes related to glucose metabolism (*TBC1D* and *ADCY*) significantly increase the risk of developing type 2 diabetes. These circumstances indicate the necessity for a large-scale genetic testing of indigenous population of the Far North and the need to study the biochemical and physiological consequences of genetically determined changes in the activity of enzymes of lipid and carbohydrate metabolism.

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## INTRODUCTION

Modern humans (*Homo sapiens*) had populated almost the entire planet in a relatively short period of time, approximately 70,000 years, travelling from Africa to all other continents and adapting to a variety of environmental conditions, including heat, cold, different altitudes, and multitude of pathogens they had encountered along the way. It is probable that the principal factor that had enabled our ancestors to outstrip earlier archaic human populations, including Neanderthals and Denisovans, was rapid growth in numbers and high level of genetic heterogeneity of modern humans. This is corroborated by the findings of paleogenomic studies conducted over the past 15 years [1]. The data obtained indicated that the genome has the capacity to adapt to specific challenges faced by humanity in the natural environment or climate. The accumulation of diverse genetic variants in large populations, including episodes of mixing with Neanderthals and Denisovans at the early stages of *H. sapiens* evolution, may have contributed to the increased resistance of these groups to climatic or environmental impacts, and may have paved the way for further expansion of human populations [1, 3].

One of the most significant natural experiments has led to the emergence of Arctic marine hunter cultures [4-7]. In addition to challenges of extreme conditions of the Far North, they had to adapt to very scarce food resources provided by the Arctic. It is thought that the traditional diet of marine hunters was based on the consumption of mainly meat and fat from marine mammals (seals, walruses, and whales) and fish rich in polyunsaturated fatty acids (PUFAs). Concurrently, indigenous populations of the Far North exhibited a notable deficiency in vegetable carbohydrates. Over time, however, the genetic makeup of the ancestors of sea hunters has undergone alterations due to their

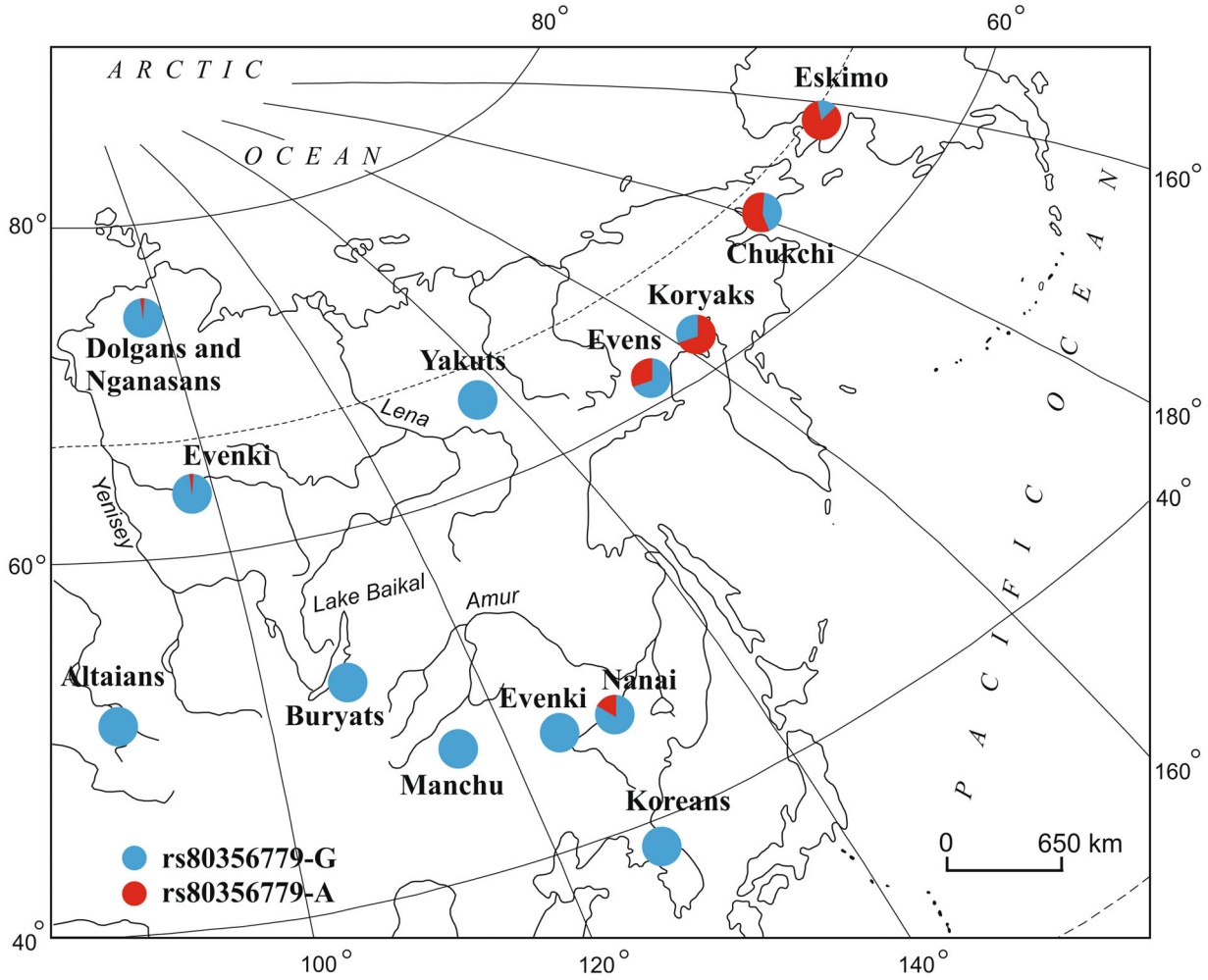


**Fig. 1.** Distribution of polymorphic variants of the *CPT1A* gene locus *rs80356779* in the populations of Eastern Siberia and Alaska (according to [11-13]).

adaptation to the exceedingly challenging conditions of the Arctic environment. Meanwhile, archaeologists propose that the Arctic zone has been developed by hunters and fishermen who had already adapted to the consumption of marine food [5]. It is postulated that these adaptations, as evidenced by the specificities of human lifestyle and economy, emerged approximately 9000 years ago in the climatically temperate and highly productive northeastern part of the Pacific Ocean. It is further hypothesized that these adaptations have spread northwards, first to the coasts and islands of the Sea of Okhotsk, Bering Sea, and Chukchi Sea, approximately 5000 years ago, and most intensively approximately 3500 years ago.

## ADAPTIVE CHANGES IN LIPID METABOLISM GENES IN ARCTIC POPULATIONS

One of the earliest identified genetic variants associated with the adaptation of the ancestors of marine hunters to the Arctic environments is the “Arctic” mutation in the *CPT1A* gene, which encodes the hepatic isoform of carnitine palmitoyltransferase type 1A. This enzyme catalyzes the acyl group transfer from acyl-CoA molecule to carnitine [8, 9]. Subsequently, acylcarnitines are transported across the inner mitochondrial membrane to facilitate β-oxidation. The “Arctic” mutation is caused by the nucleotide substitution G→A in the *rs80356779* locus of the *CPT1A* gene (amino acid substitution, Pro479Leu) [8]. This polymorphic variant is most common (50-70%) in populations of the Eskimo, Chukchi, Koryaks, and other peoples of the Sea of Okhotsk region, whose economic way of life is associated with the sea fur trade [10, 11]. The *rs80356779-A* variant has been identified at low frequencies (1-10%) in the Evenks of Yakutia, Dolgans, and Nganasans of the Taimyr Peninsula, and Nivkhs and Nanai, due to the migrations of sea hunters over the past 3000 years [12-14] (Fig. 1).

Paleogenomic studies conducted across a wide time range (from the Paleolithic to the Middle Ages)

**Table 1.** Hypotheses for the selective advantage of the "Arctic" mutation in the *CPT1A* gene (variant *rs80356779-A*)

| Hypothesis | Relevant factors | Source |
|---|---|---|
| Prevention of excessive ketone production | high PUFA intake, low carbohydrate intake | [9, 10] |
| Decreasing metabolic effects of a high-protein diet | low carbohydrate intake and high protein intake | [9] |
| Adaptation to cold due to changes in brown adipose tissue metabolism | cold, high PUFA intake | [10] |
| Glucose saving in low-carbohydrate diets | low carbohydrate intake, high protein intake, cold | [18] |

have demonstrated that the "Arctic" mutation in the *CPT1A* gene emerged in the Paleo-Eskimo of the Sakkak archaeological culture (Greenland) approximately 4000 years ago. A little later, this mutation appeared in the representatives of the Tokarev culture (Northern Priokhotye, approximately 3000 years ago) and ancient inhabitants of the Ekven settlement (Chukotka, approximately 2000 years ago) [4, 15]. At the same time, the *rs80356779-A* variant was also registered in the south of Priokhotye – in the bearers of the Late Jomon culture (Hokkaido, 3500-3800 years ago), who also actively hunted marine animals [16]. Phylogenetic analysis of ancestral haplotypes has revealed that the variant *rs80356779-A* emerged from a haplotype carrying the *rs3794020-T* substitution in the *CPT1A* gene [10]. This ancestral genetic variant is observed predominantly in East Asian populations, including Japanese (30%), Koreans (31%), and Vietnamese (37%). Therefore, the "Arctic" mutation originated from the East Asian haplotype, but it has only reached a high frequency in the northernmost populations. This is likely due to the advantages it gave to its carriers.

It is postulated that the maintenance of a high frequency of the *rs80356779-A* variant in the Eskimo populations over many generations has been favored by natural selection, most likely associated with the adaptation to both traditional Arctic diet rich in omega-3 PUFAs and cold [9, 10, 17, 18] (Table 1).

*In vitro* studies of the enzymatic activity of carnitine palmitoyltransferase 1A in cultured fibroblasts have demonstrated that the Pro479Leu amino acid substitution results in a reduction in the enzyme catalytic activity, which is a plausible consequence of omega-3 PUFA excess [8, 9]. It is postulated that individuals with the Pro479Leu mutation are more resilient to elevated levels of fatty acid oxidation and ketogenesis under conditions of chronic "ketogenic diets" [9, 10]. A more comprehensive examination of the results of biochemical, metabolic, and physiological studies has revealed that the selection of the 479Leu variant in the Eskimo ancestors may be associated with a greater number of metabolic adaptations [18]. Firstly, this refers to the possibility of saving glucose under conditions of a low-carbohydrate diet and its redirection to glycogen synthesis in the liver. Furthermore, it is probable that the Pro479Leu replacement increases production of acylcarnitines, which play a pivotal role in the metabolism of brown adipose tissue [19], and thereby reduces glucose uptake by the brown adipose tissue. It has been also observed that Eskimo individuals, who possess the Pro479Leu substitution, have a shorter stature. This adaptation is believed to contribute to the reduced heat loss and has been linked to the ability to cope with cold conditions [20]. These findings suggest that the formation of Arctic peoples has been accompanied by a series of adaptations to diet and extreme environmental factors. This strategy allowed development of the optimal thermoregulation and lipid metabolism mechanisms under harsh conditions of the Arctic and Subarctic.

From the medical and genetic perspective, the 479Leu variant is associated with the congenital deficiency of carnitine palmitoyltransferase type 1A, an autosomal recessive disease that is prevalent in the Eskimo children and is associated with an elevated risk of infant mortality, hypoketone hypoglycemia, more severe respiratory tract infections, and increased predisposition to obesity and type 2 diabetes [9, 21, 22]. This is of particular relevance in the context of transition of Arctic aborigines to the European high-carbohydrate diet [21]. Concurrently, there is evidence that the "Arctic" variant of the *CPT1A* gene may also have a protective effect in cardiovascular diseases. This is evidenced by the fact that in Greenland and Alaska Eskimo, the 479Leu variant is associated with higher levels of high-density cholesterol and apolipoprotein A1 [23, 24].

The results of studies of other genes in Arctic peoples also testify to the rearrangements in the functioning of fatty acid metabolism genes. For instance, an elevated mutation burden in carnitine acyltransferase genes was observed in Canadian Eskimo populations, which according to the study authors, is indicative of genetic adaptation to dietary and climatic

conditions [25]. Similarly, nonsynonymous substitutions leading to the carnitine acyltransferase deficiency (in addition to *rs80356779* of the *CPT1A* gene) at the loci *rs763273578* of the *CPT1C* gene encoding the brain isoform of carnitine palmitoyltransferase and *rs1588456303* of the *CRAT* gene encoding carnitine acetyltransferase have been identified in the Eskimo, Chukchi, and Koryak peoples of Northeastern Siberia [26]. Nonsynonymous substitutions (with high pathogenicity indices) in genes responsible for triglyceride cleavage – the *ABHD6* gene encoding monoacylglycerol lipase and the *GK2* gene encoding glycerol kinase 2 – have also been found in these northern peoples [26].

In a study of Alaskan Eskimo, the association of polymorphic variants in the *CPT1A*, *FADS1*, and *FADS2* genes with higher levels of fatty acid delta-5 desaturases in plasma and erythrocytes was first identified [27]. Genetic studies have shown that two major haplotypes are common in human populations. These haplotypes are defined by variants of polymorphisms in the *FADS1* and *FADS2* genes, which encode fatty acid desaturases catalyzing formation of double bonds in acyl chains [28]. The two major haplotypes exhibit significant differences in the expression levels and encode enzymes with decreased (haplotype A) and increased (haplotype D) desaturase activity. Population studies have demonstrated that haplotype A is most frequently found among indigenous populations of the Arctic and Siberia, as well as among Native Americans [29, 30]. Paleogenomic data indicate that the spread of haplotype A, which is less active in terms of fatty acid desaturation, commenced during the settlement of Eurasia and America by Upper Paleolithic humans who consumed food rich in lipids and proteins [31]. An increased frequency of the more active haplotype D in some regions of the world (Europe, South Asia) is presumed to be associated with the emergence and dissemination of agricultural technologies during the Neolithic period, which required the synthesis of PUFAs from plant lipids at a higher rate [32]. It has been demonstrated that the frequency of haplotype D in Europe has increased from less than 10% 10,000 years ago to 60-75% at present [29]. Furthermore, the frequency continues to grow at a rate of 0.009% per year, as evidenced by the analysis of UK Biobank data [33]. It can be reasonably assumed that the observed increase in the frequency of haplotype D in Europeans is a consequence of reproductive success associated with an increase in the fertility rate among carriers of this haplotype.

The high prevalence of the less active haplotype A of the *FADS* genes in Arctic populations (almost reaching fixation, as in Greenland Eskimo – 98%) is evidently also attributable to the excess of animal lipids in the aboriginal diet. Consequently, there is no requirement for additional synthesis of PUFAs [34]. A low frequency (5.6%) of 22-bp insertion in the *FADS2* gene (locus *rs66698963*), which increases the level of *FADS1* gene expression, was identified in the Koryaks of Northeastern Siberia [35]. For comparison, the frequency of this insertion is approximately one order of magnitude higher (45.3%) among the Buryats in Southeastern Siberia [35]. Similarly, significant differences were observed between the indigenous populations of the north-east (12.5%) and south (1.5%) of Siberia for the *rs115724324-G* variant of the *FFAR4* gene, which encodes a receptor for long-chain fatty acids [36]. This receptor plays a pivotal role in fatty acid binding and regulation of energy balance [37]. Furthermore, a distinctive allelic variant of polymorphism at the *rs1590886662* locus of the *CYB5R2* gene, which encodes NADH-cytochrome *b5* reductase, has been identified in the Koryak and Eskimo populations (with a frequency of approximately 10%) [35]. A stop codon at this locus results in the termination of the synthesis of the enzyme that provides electron transfer to desaturases encoded by the *FADS* genes. It is evident that the termination of synthesis of NADH-cytochrome *b5* reductase will inevitably result in the deficiency of this enzyme, which will in turn lead to further reduction in the activity of fatty acid desaturases in indigenous populations of the Far North.

## ADAPTIVE CHANGES IN CARBOHYDRATE METABOLISM GENES IN ARCTIC POPULATIONS

The Arctic diet had a profound impact on lipid metabolism, while also significantly influencing the allelic spectrum of carbohydrate metabolism enzymes in northern aboriginal peoples. This is believed to be associated with the deficit of plant carbohydrates in the Arctic environments. For instance, the maximum frequency (52%) of deletion of the whole gene of pancreatic amylase *AMY2A*, which is necessary for starch digestion, and the minimum number of copies of this gene in combination with a reduced copy number of the salivary amylase gene *AMY1* were found among other studied peoples of the world [38]. A study of northern indigenous peoples revealed that 30% of the population lacked the pancreatic amylase gene *AMY2A*, which leads to pancreatic insufficiency [38].

The high prevalence of the AG dinucleotide deletion in the *rs781470490* locus of the sucrase-isomaltase gene (*SI*) among Arctic indigenous populations can be attributed to the long-term adaptation to disaccharide deficiency. The *rs781470490*-delAG allele is registered with the highest frequencies in Greenlandic and Canadian Eskimo (17-20%) [39, 40], and somewhat less frequently in the populations of the Chukchi (14.3%),

Koryaks (7.3%), and Evens (3.5%) [41]. Analysis of populational genetic data, including results of paleogenomic studies, indicates that this variant of the *SI* gene polymorphism most likely emerged approximately 1200-2000 years ago among the ancestors of the Eskimo. This was attributed to the unique characteristics of their lifestyle and dietary habits. Furthermore, the distribution of the polymorphism has been associated with the expansion of the Neo-Eskimo Tule culture [42]. The dinucleotide deletion at locus *rs781470490* of the *SI* gene results in a shift in the reading frame of codon 92 (variant Gly92Leufs*8), which ultimately leads to the premature termination of sucrase-isomaltase synthesis [39]. As a consequence, the enzyme lacks two catalytic (sucrase and isomaltase) subunits; individuals with this genetic variant develop an autosomal recessive disease, congenital sucrase-isomaltase insufficiency (CSID) [43]. It was demonstrated that in individuals homozygous for the *rs781470490*-delAG variant, the encoded enzyme is functionally inactive. In individuals heterozygous for this variant, which is prevalent in Arctic populations, the enzymatic activity with respect to sucrose hydrolysis is reduced by 65% or more [44]. It is hypothesized that the truncated mutant variant has a negative effect on the enzymatic function. However, it is transport-competent, localizes on the cell surface, and actively interacts with wild-type sucrase-isomaltase. Therefore, heterozygous carriers of the *rs781470490*-delAG variant may also potentially manifest symptoms of CSID [44].

Nevertheless, the studies of Greenland Eskimo have demonstrated that adult homozygous carriers of the *rs781470490*-delAG variant exhibit a markedly healthier metabolic profile than the control group. This is evidenced by lower values of body mass index, adipose tissue content, fasting serum triglyceride levels, and residual cholesterol [40, 45]. The studies of homozygous Eskimo carriers have identified that these effects are due to an increase in circulating plasma acetate levels, rather than a decrease in the sucrose intake. These findings were validated by experiments in mice lacking the *SI* gene, which exhibited significantly elevated acetate content and reduced blood glucose levels in response to sucrose ingestion. It is hypothesized that this favorable metabolic effect is related to the enhancement of bacterial fermentation of undigested carbohydrates that have escaped cleavage in the small intestine due to the loss of enzymatic activity of sucrase-isomaltase [40]. In addition, an increased bacterial fermentation of carbohydrates may also result in a higher level of circulating acetate in individuals homozygous for the *rs781470490*-delAG variant [40, 45]. It is well established that acetate, as well as propionate, butyrate, and other short-chain fatty acids, are the most important metabolites of the gut microbiota. These metabolites have been shown to have the anti-inflammatory, immunoregulatory, antidiabetic, hepatoprotective, and neuroprotective effects [46].

A long-term deficiency of plant carbohydrates in the Arctic diet has led to the emergence of genetic polymorphisms associated with glucose homeostasis in populations of indigenous peoples inhabiting the northernmost regions of the globe. The most striking example thus far is the G→A nucleotide substitution in the *rs61736969* locus of the *TBC1D4* gene, which was found with a frequency of 13-17% in the Eskimo of Greenland, Canada, and Alaska [47, 48]. To date, this mutation has not been detected in the indigenous population of Siberia. The *TBC1D4* gene encodes the AS160 protein, which is necessary for the translocation of glucose transporter GLUT4 to the plasma membrane of cells [49]. The *rs61736969-A* substitution generates a stop codon in the *TBC1D4* gene, resulting in the synthesis of a truncated protein [47]. It has been demonstrated that individuals homozygous for this mutation exhibit significantly reduced levels of GLUT4 in muscle tissue, which is accompanied by a reduction in the insulin-stimulated glucose uptake in muscle. These factors contribute to postprandial hyperglycemia, impaired glucose tolerance, and a high risk of developing type 2 diabetes [47]. It is likely that the *rs61736969-A* variant of the *TBC1D4* gene has emerged among the Eskimo as a consequence of the weakening of natural selection due to the deficiency of carbohydrate substrates in the traditional Eskimo diet. However, in recent times, with the continued rise in carbohydrate consumption, individuals with the *rs61736969-A* variant have encountered challenges in maintaining optimal blood glucose levels. Such fluctuations in glucose concentrations inevitably affect their metabolic health.

A Greenland Eskimo-specific mutation was identified with a frequency of 3.1% in the acceptor splice site of the *ADCY3* gene (locus *rs1331776405*) encoding adenylate cyclase 3, which catalyzes the synthesis of cAMP from ATP and plays an important role in the regulation of adipogenesis and glucose homeostasis [50]. The C→T nucleotide substitution at this locus results in impaired splicing and decreased expression of the *ADCY3* gene. Individuals homozygous for the mutation exhibited alterations in body mass index and glucose metabolism, with nearly half of them developing type 2 diabetes. Furthermore, additional polymorphic variants (e.g., in the *ITGA1* [51] and *HNF1A* [52] genes) have been discovered in Greenland Eskimo diabetic patients. Although the biochemical processes caused by the decreased expression of the *ADCY3* gene in the Eskimo are poorly understood, the phenotypic manifestations of the mutation demonstrate that it represents one more example of genetic changes resulting from the adaptation of human populations to extreme environments, including a deficiency of plant carbohydrates in the diet.

## CONCLUSION

In general, it should be noted that the long exposure (at least 3500 years) of the ancestors of the Eskimo-Aleut and Paleoasian peoples to the extreme Arctic conditions resulted in numerous adaptive changes in their gene pools. A significant increase in the metabolic rate has been observed in indigenous populations of Siberia, particularly during the winter months. This increase is associated with changes in the functioning of the endocrine system and brown adipose tissue, as well as in lipid metabolism [53, 54]. The Eskimo and other indigenous peoples of Siberia have low levels of lipids in the blood, which is associated with the prevalence of specific polymorphism variants of lipid metabolism genes. These are not only *CPT1A*, *FADS1*, *FADS2*, and *CYB5R2* (as in the Arctic coast peoples), but also other genes, such as *PLA2G2A* (phospholipase A2), *PLIN1* (perilipin 1), and *ANGPTL8* (angiopoietin-like protein 8) that have been identified to have mutations in the peoples of Central Siberia (the Nganasans and Yakuts) [55]. In addition, the long-term deficiency of carbohydrates in the "Arctic" diet of the indigenous peoples of the Far North is likely to have contributed to the weakening of negative selection, which is responsible for the removal of mutations that could lead to abnormalities in the functioning of carbohydrate-metabolizing enzymes. As a result, mutations in genes encoding enzymes involved in the metabolism of starch and disaccharides (*AMY1*, *AMY2A*, *SI*), as well as polymorphisms in genes related to glucose metabolism (*TBC1D*, *ADCY*), began to spread among the ancestors of the Arctic peoples. The high prevalence of individuals unable to digest certain carbohydrates may be attributed to gene drift, the effects of which are more pronounced in small, isolated populations, such as Arctic indigenous peoples [10].

It appears that adaptive changes in the genes of lipid and carbohydrate metabolism have become a health concern for the indigenous populations of the circum-Arctic region only in modern times. This is associated with changes in their diet, which has shifted from the traditional Arctic diet to a Western diet rich in carbohydrates and poor in omega-3 PUFAs. It is therefore of great importance in the modern era to conduct extensive genetic testing of indigenous populations in the Far North and to study biochemical and physiological consequences of genetically determined changes in the activity of enzymes involved in lipid and carbohydrate metabolism.

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