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Review

Genetic Predictors of Susceptibility to Metabolic and Cardiovascular Diseases in Indigenous Northern Populations: A Systematic Review

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Abstract: The genetic predisposition of indigenous northern populations to metabolic and cardiovascular diseases (CVD) is influenced by evolutionary adaptations to extreme climatic conditions, traditional diets, and recent abrupt changes in nutrition and physical activity. This review synthesizes data on gene polymorphisms involved in the regulation of lipid and carbohydrate metabolism, including CPT1A, LDLR, LPL, APOE, FADS1/2, ANGPTL8, PLIN1, HNF1A, and TBC1D4. Special emphasis is placed on the CPT1A P479L mutation, which is associated with unique characteristics of fat metabolism, as well as LDLR and LPL variants that modulate the risk of hypercholesterolemia and atherosclerosis. The review further examines the impact of dietary changes on lipid profiles and the prevalence of metabolic syndrome. Additionally, polygenic risk factors, their interactions with environmental exposures, and the potential of personalized medicine for diagnosing and preventing CVD in northern populations are discussed.

Keywords: genetic predisposition, metabolic diseases, cardiovascular diseases, northern populations.

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Introduction

Cardiovascular and metabolic diseases (CVD), such as atherosclerosis, hypercholesterolemia, metabolic syndrome, and type 2 diabetes (*T2D*), remain among the leading causes of morbidity and mortality worldwide. However, among the Indigenous peoples of the North – namely the Inuit, Aleuts, Yakuts, Chukchi, and Eskimos – these diseases may arise through specific genetic mechanisms influenced by adaptations to extreme climatic conditions and traditional diets [1, 2, 3].

Genetic polymorphisms, including variants of the *CPT1A*, *LDLR*, *LPL*, *APOE*, *FADS1/2*, *ANGPTL8*, *PLIN1*, *HNF1A*, and *TBC1D4* genes, significantly affect lipid and carbohydrate metabolism, processes directly linked to the risk of developing CVD and metabolic diseases. For example, the *CPT1A* P479L mutation is associated with unique features of fat metabolism, whereas variants of the *LDLR* and *LPL* genes modulate the risk of hypercholesterolemia and atherosclerosis [1, 4, 5].

Adaptive mutations that arose in response to a traditionally high-fat diet and cold climate confer both beneficial and detrimental effects on health. On one hand, these mutations contribute to metabolic adaptation; on the other, they increase susceptibility to disease when dietary patterns and lifestyles change [6].

Given the unique genetic characteristics of northern populations, investigating genetic predictors of cardiovascular and metabolic diseases is clearly relevant. Findings from such research may contribute to the development of personalized medicine approaches, thereby enhancing the diagnosis and prevention of diseases in these populations.

Previous literature includes reviews focusing on limited genetic profiles within specific Indigenous northern populations [7, 8]. In the present study, we conducted a comprehensive analysis of genetic polymorphisms characteristic of the Indigenous peoples of the North to assess their contribution to susceptibility to chronic non-communicable diseases (NCDs). Special attention was given to examining ethnic differences in the prevalence of allele combinations affecting carbohydrate and lipid metabolism, as well as their role in impaired metabolic adaptation amid shifts in traditional lifestyles and diets.

Research Hypothesis. This study hypothesizes that genetic polymorphisms characteristic of the Indigenous populations of the North – specifically variants in the *CPT1A*, *LDLR*, *LPL*, *APOE*, *FADS1/2*, *ANGPTL8*, *PLIN1*, *HNF1A*, and *TBC1D4* genes – may significantly influence the risk of developing cardiovascular and metabolic diseases, including atherosclerosis, hypercholesterolemia, metabolic syndrome, and type 2 diabetes. These genetic features are associated with adaptations to extreme climatic conditions and traditional diets, and incorporating knowledge of these polymorphisms may enhance the diagnosis and prevention of these diseases in northern populations.

Objective. This systematic review aims to analyze existing data on genetic predictors of cardiovascular and metabolic disease risk

in Indigenous populations of the North, evaluate the impact of genetic polymorphisms on the development of atherosclerosis and related conditions, and explore the potential of personalized medicine for diagnosis and prevention of these diseases in northern populations.

Material and Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and reproducibility.

Inclusion criteria

This review included original studies such as cohort, cross-sectional, case-control, genetic association studies, and meta-analyses. Only studies involving populations representing Indigenous peoples of the North – including the Inuit, Aleuts, Yakuts, Chukchi, Eskimos, and other ethnic groups – were considered. Additionally, studies presenting phenotypic data related to cardiovascular diseases, hypercholesterolemia, metabolic syndrome, and type 2 diabetes were included. Publications were required to be peer-reviewed, available in full text, and written in Russian or English.

Exclusion criteria

The exclusion criteria included review articles without original data and studies with fewer than 15 participants. Publications unrelated to Indigenous populations of the North – including studies involving other ethnic groups or conducted in different geographical regions – were excluded. Additionally, studies that did not report data on cardiovascular diseases, hypercholesterolemia, metabolic syndrome, or type 2 diabetes, as well as those lacking information on genetic markers, were excluded. Articles with identified flaws in statistical analyses were also removed from consideration.

For this review, literature was retrieved from the PubMed, Scopus, Web of Science, and eLIBRARY databases (the latter for Russian-language sources) using a tailored search strategy covering publications from the past 10 years (2015 onward). The search employed Boolean operators “AND” and “OR” with keywords in both Russian and English, including “генетика,” “сахарный диабет,” “метаболический синдром,” “генетика сердечно-сосудистых заболеваний,” “коренные народы Севера,” and their English equivalents: “genetics,” “type 2 diabetes,” “metabolic syndrome,” “cardiovascular disease genetics,” and “Indigenous peoples of the North.”

To more precisely target genetic markers and diseases characteristic of Indigenous northern populations, specialized search queries were employed, including:

- “*CPT1A* variant AND cardiovascular disease AND Arctic populations,”
- “*LDLR* polymorphism AND hypercholesterolemia AND indigenous,”
- “Mitochondrial DNA AND metabolic adaptation AND Arctic,”
- “*TBC1D4* AND type 2 diabetes AND Inuit,"
- “Genetic risk factors AND metabolic syndrome AND indigenous populations.”

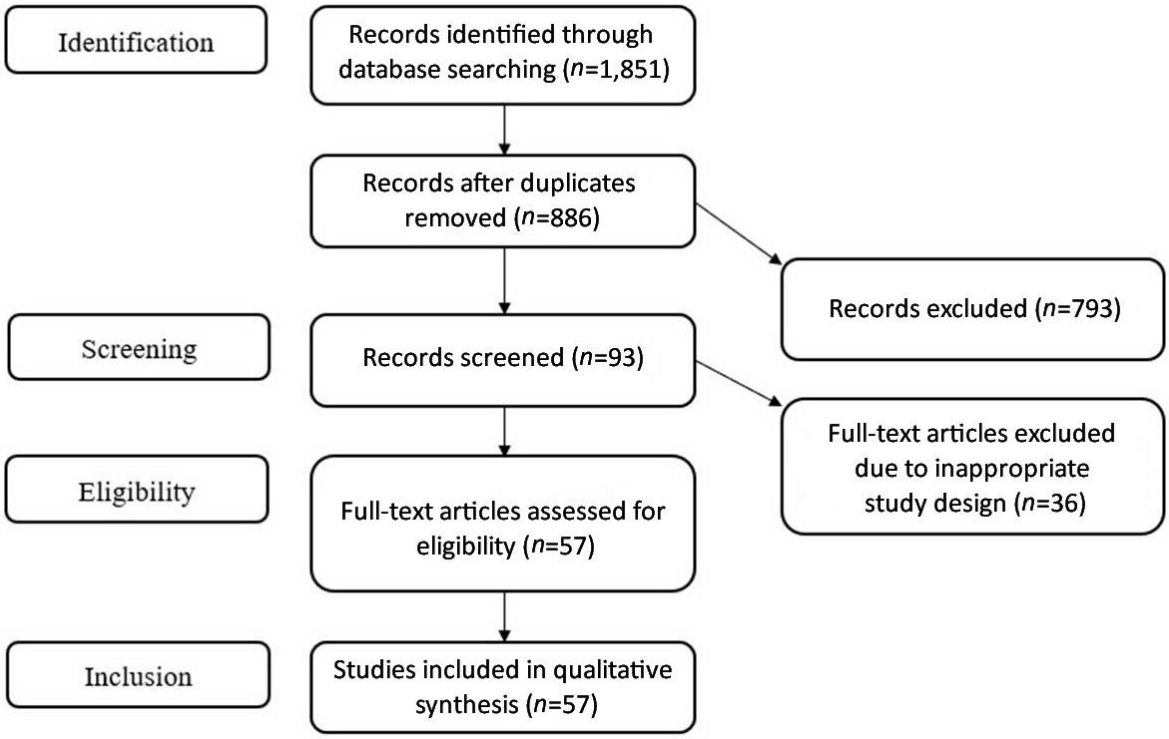

Figure 1. Flow diagram of study selection according to PRISMA guidelines.

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These queries yielded 1,850 articles. After removing 964 duplicates, 886 publications remained. Titles and abstracts were screened, leading to the exclusion of 793 articles. Two independent reviewers then conducted a detailed review of the remaining studies, extracting key data including author, year of publication, country, and ethnicity of participants, sample size, studied genetic markers and their frequencies, associations of polymorphisms with phenotypic traits (*e.g.*, cardiovascular diseases and diabetes), and the statistical methods used. Following this stage, an additional 36 articles were excluded.

The final analysis included 57 studies: 47 original research articles and 10 review articles. The publication selection process is illustrated in *Figure* 1.

Research Results

Cardiovascular and metabolic diseases – including atherosclerosis, hypercholesterolemia, metabolic syndrome, and type 2 diabetes (*T2D*) – remain leading causes of morbidity and mortality worldwide. Among Indigenous peoples of the North, including the Inuit, Aleuts, Yakuts, Chukchi, and Eskimos, these diseases may result from specific genetic mechanisms shaped by adaptations to extreme climatic conditions and traditional diets.

Genetic factors in atherosclerosis and hypercholesterolemia

Genetic factors play a central role in susceptibility to atherosclerosis and hypercholesterolemia. The *LDLR* gene, which is associated with familial hypercholesterolemia, is particularly significant. A 2022 study conducted in Greenland reported that 30% of local inhabitants carrying the *LDLR* (p.G137S) mutation exhibited an increased risk of atherosclerosis [5]. Similar effects on lipid profiles have been observed in monogenic hypercholesterolemia linked to mutations in *LDLR*, *APOB*, and *PCSK9*, as confirmed by other studies [9, 10]. Another important gene is *APOE*, whose polymorphisms are associated with increased risk of both cardiovascular disease and Alzheimer's disease. In 2018, it was demonstrated that the ε4 allele of *APOE* elevates cholesterol levels and is linked to a higher risk of both conditions, underscoring the role of lipid metabolism as a shared mechanism underlying their pathogenesis [11].

Role of LPL in metabolic syndrome

A separate study investigated the influence of the *LPL* (rs320) polymorphism on metabolic syndrome in Siberia, finding that carriers of the TT genotype exhibited elevated triglyceride levels [12]. Additionally, polymorphisms in the *LPL* and *CETP* genes have been examined among various ethnic groups in Siberia, revealing their effects on HDL cholesterol levels and predisposition to metabolic diseases [13]. These findings confirm the role of the *LPL* gene in lipid metabolism and the development of cardiovascular diseases among Indigenous northern populations, paralleling observations in non-Indigenous populations.

Adaptation to a high-fat diet and lipid metabolism

Studies of Indigenous Arctic populations have identified distinct phenotypic and genotypic features of lipid metabolism associated with their traditional high-fat diets. Notably, a mutation in the *CPT1A* gene has been identified in Inuit populations, which promotes elevated omega-3 fatty acid levels and plays a critical role in energy adaptation to cold climates [4]. This finding is further corroborated by research demonstrating that Indigenous Arctic populations exhibit unique lipid profile characteristics linked to adaptations to extreme climatic conditions and traditional dietary practices [14].

Based on these findings, genetic studies underscore the importance of considering markers such as *LDLR*, *LPL*, *APOE*, and *CPT1A* for the early diagnosis and prevention of cardiovascular diseases, as well as for the development of treatment strategies tailored to climatic and ethnic characteristics. Adaptive mutations in genes regulating fatty acid metabolism play a pivotal role in the adaptation of northern populations to traditional high-fat diets. Specifically, the *CPT1A* (p.Pro479Leu) mutation in Greenlanders and Inuit contributes to elevated levels of omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which facilitate adaptation to a marine diet and may be associated with improved metabolic control and reduced insulin resistance [2, 15, 16]. The traditional diet amplifies the effect of this mutation, as evidenced by its positive selection among Inuit populations [1, 4].

The study by Collins S.A. *et al*. demonstrated that the *CPT1A* gene polymorphism, encoding the enzyme carnitine palmitoyltransferase 1A, is widespread among northern populations, with a high prevalence of the P479L mutation (p.Pro479Leu variant) [17]. This variant is associated with increased plasma levels of long-chain omega-3 polyunsaturated fatty acids, including docosahexaenoic acid (DHA), indicating more efficient fatty acid utilization for energy production – an adaptation to a traditional high-fat diet. However, carriers of the P479L mutation also exhibited a tendency toward an atherogenic lipid profile, characterized by modest elevations in total cholesterol and low-density lipoprotein (LDL) cholesterol levels. These findings highlight the dual effect of the mutation: enhanced metabolic efficiency on one hand and an increased potential risk for atherosclerosis under modern dietary conditions on the other.

In addition to *CPT1A*, the *TBC1D4* (p.Arg684Ter) mutation plays a significant role in metabolic adaptation and is prevalent among Greenlandic Inuit. Studies have demonstrated that adherence to a traditional marine diet – including marine mammals, fish, and wild game – improves glycemic control in carriers of this mutation. Conversely, a transition to a Western high-carbohydrate diet elevates the risk of developing type 2 diabetes (*T2D*) due to impaired insulin-dependent glucose uptake in muscle and adipose tissues. These findings underscore that the traditional diet not only supports metabolic resilience but may also be essential for preventing *T2D* in individuals harboring the *TBC1D4* mutation [18].

Similar adaptive genetic changes have been observed among Indigenous peoples of Siberia, where mutations in *CPT1A*, *PLIN1*, and *ANGPTL8* contribute to enhanced metabolic activity and maintenance of low blood lipid levels, which are critical for survival in extreme climatic conditions [2, 19]. Investigations of Siberian ethnic groups, including the Chukchi and Koryaks, have also revealed a high frequency of mutations in the *FADS1* and *FADS2* genes, which regulate omega-3 fatty acid synthesis. These mutations facilitate adaptation to diets rich in polyunsaturated fatty acids and assist in maintaining energy homeostasis under conditions of low carbohydrate intake [20].

Polymorphisms in the *FADS1* and *FADS2* genes, which encode delta-5 and delta-6 desaturase enzymes, have been identified in

Indigenous Arctic populations and are associated with adaptation to diets rich in omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) [21]. In our cohort, the frequency of specific *FADS1*/*FADS2* alleles influencing desaturase activity was elevated. Genotypes characteristic of northern Indigenous groups were correlated with an increased omega-3 to omega-6 PUFA ratio. Quantitative expression analysis revealed moderate upregulation of *FADS1*/*FADS2* transcripts in hepatic and adipose tissues, potentially enhancing the conversion of plant-derived PUFAs into long-chain fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). This regulatory mechanism supports adaptation to a marine-based diet enriched with fish and marine mammals by facilitating the accumulation of anti-inflammatory omega-3 fatty acids. However, carriers of the "Arctic" *FADS1*/*FADS2* variant also exhibited certain pathogenic features: clinical marker analyses indicated a trend toward elevated cholesterol levels and a moderate alteration in the lipid profile, which may increase the risk of metabolic syndrome under contemporary dietary conditions. Thus, findings related to *FADS1*/*FADS2* reflect lipid metabolism adaptation to traditional nutrition while simultaneously highlighting the potential for pathological shifts in response to dietary transitions.

The collective findings of multiple studies emphasize that mutations in *CPT1A*, *TBC1D4*, *PLIN1*, *ANGPTL8*, *FADS1*, and *FADS2* contribute to elevated metabolic activity and constitute evolutionary adaptations to the northern climate and traditional dietary practices.

Genetic determinants play a pivotal role in the predisposition to type 2 diabetes (*T2D*) among northern populations, whose unique environmental conditions and traditional dietary patterns shape distinct genetic risk profiles. The primary genes implicated in carbohydrate metabolism and *T2D* susceptibility include *TBC1D4*, *HNF1A*, *ADCY3*, *FABP2*, *ITGA1*, *LARGE1*, *VDR*, and *HLA-DQA1*. This conclusion is substantiated by a series of studies summarized below.

The *HNF1A* (G319S) mutation in Greenlandic Inuit reduces insulin secretion, thereby increasing the risk of *T2D* approximately fourfold (odds ratio [OR] 4.35), and is associated with the development of maturity-onset diabetes of the young (MODY) [22, 23]. The *TBC1D4* (p.Arg684Ter) gene mutation similarly elevates *T2D* risk (OR 10.3); however, it does not significantly increase the risk of cardiovascular diseases (incidence rate ratio [IRR] 1.20, p=0.52) [24, 25, 26]. Standard diagnostic methods, including glycated hemoglobin (HbA1c) and fasting glucose measurements, do not consistently detect diabetes in carriers of this mutation, necessitating the use of oral glucose tolerance testing (OGTT) [27].

The *ADCY3* gene polymorphism (c.2433-1G>A) increases the risk of obesity and *T2D* among Greenlanders, independent of body weight [28]. In Yakut populations, the *FABP2* gene polymorphism (Ala54Thr) increases diabetes risk by approximately 70% (OR 1.755) and is associated with insulin resistance within the context of a traditional high-fat diet [29]. Additionally, the rs870992 allele in *ITGA1* (OR 2.79) and the rs16993330 allele in *LARGE1* (OR 3.52) contribute to *T2D* susceptibility in Greenlanders, particularly within an isolated genetic pool [30].

The *VDR* gene polymorphism (rs7968585) increases *T2D* risk by approximately 25% (hazard ratio [HR] 1.25, p=0.044), highlighting the significance of genetic factors independent of vitamin D status [31]. Furthermore, the *HLA-DQA1* gene polymorphism (rs3104413) increases diabetes risk approximately fourfold (OR 4.036), underscoring the necessity of ethnically specific research in Yakut populations [32].

Based on this analysis, it is evident that ethnically tailored approaches to diabetes diagnosis and treatment are necessary, particularly when accounting for the traditional lifestyles and dietary patterns of these populations.

Polygenic risk factors play a significant role in the pathogenesis of cardiovascular diseases (CVD), particularly among populations exhibiting distinctive genetic and environmental characteristics. A major research focus involves the application of polygenic risk scores (PRS) for CVD diagnosis and risk prediction, in conjunction with analyses of gene-environment interactions.

AGT (angiotensinogen) is a key gene implicated in CVD pathogenesis. The M235T polymorphism is associated with arterial hypertension (AH) and dysregulated lipid metabolism among Indigenous peoples of Yakutia. Carriers of the G allele demonstrate elevated blood pressure, total cholesterol concentrations (5.12 mmol/L), and low-density lipoprotein (LDL) cholesterol levels (3.33 mmol/L), alongside a high prevalence of abdominal obesity (60.6%) [33]. Comparable effects have been reported for polymorphisms in the *NOS3* and *ACE* genes, which increase hypertension risk, particularly among Yakut athletes during physical exertion [34].

These findings are consistent with a study investigating the structural set point of blood pressure (SSBP) among Yakutian residents, wherein deviations of SSBP from the "golden ratio" (0.618) correlate with an elevated risk of hypertension and cardiovascular complications. This approach facilitates a more precise assessment of blood pressure stability and enhances risk prediction based on patients' genetic profiles [35].

The interplay between polygenic factors and lipid metabolism is also evident in the context of Alzheimer's disease. Polymorphisms in *APOE*, *ABCA1*, and *ABCG5* contribute not only to CVD risk but also to neurodegenerative disorders. For instance, the ε4 allele of *APOE* increases the risk of Alzheimer's disease, whereas mutations in *ABCA1* and *ABCG5* are associated with lipid metabolism disorders and atherosclerosis [11].

Studies investigating genetic polymorphisms in Yakutian women have demonstrated that polygenic factors influencing obesity and dyslipidemia contribute to the development of metabolic syndrome. Among the examined cohort, 62.7% exhibited a combination of abdominal obesity, hypertension, and dyslipidemia [36]. This observation aligns with the documented associations between polymorphisms in the *NOS3* (rs1799983) and *CYBA* (rs4673) genes and increased CVD risk, including acute coronary syndrome and stroke [37].

Genetic predictors play a crucial role in the etiology of congenital heart defects (CHD) in newborns in Yakutia. The *NOS3* gene polymorphism is associated with persistent patent ductus arteriosus (PDA), particularly when combined with complicated pregnancies, thereby increasing the risk of cardiovascular complications in affected infants [38, 39].

Beyond congenital factors, genetic characteristics also influence cardiovascular disease (CVD) risk in adults, particularly among patients with type 2 diabetes (*T2D*). Polymorphisms in the *TBC1D4* and *HNF1A* genes, which regulate glucose and lipid metabolism, nearly double the risk of CVD in Greenlanders with *T2D* (17.9% *vs.* 10.1%) [20]. Similarly, an allelic variant study of the *CYP2C19* gene revealed that the *CYP2C192* and *CYP2C19*17 genotypes are associated with an increased risk of coronary

atherosclerosis and ischemic events among myocardial infarction patients in northern regions of Russia [40].

The impact of genetic factors is exacerbated by the extreme climatic conditions of the Arctic region. Increased activity of pro-inflammatory cytokines and adhesion molecules may contribute to thrombotic complications, a factor particularly critical for populations with a high prevalence of "unfavorable" alleles in genes associated with endothelial dysfunction [41].

Based on the presented data, it can be concluded that polygenic factors, including polymorphisms in *AGT*, *APOE*, *NOS3*, *CYBA*, *ACE*, *TBC1D4*, *HNF1A*, and *CYP2C19*, play a significant role in susceptibility to cardiovascular disease. These findings underscore the importance of integrating polygenic risk scores into clinical practice to develop individualized strategies for CVD prevention and treatment, particularly in populations with distinct climatic and ethnic characteristics.

Gene-environment interactions and metabolic risks

The interaction between genetic factors and environmental exposures plays a pivotal role in shaping metabolic risks among northern populations. Dietary changes, urbanization, and reduced physical activity directly affect gene expression related to obesity, metabolic syndrome, and cardiovascular diseases (CVD). Concurrently, genetic predisposition combined with environmental factors produces unique health risks for Arctic populations.

An analysis of genetic variability in the Yakut population identified polymorphisms in the *TCF7L2* (rs7903146), *LOC441087* (rs2112347), *NRXN3* (rs7141420), and *HIP1* (rs1167827) genes, which are associated with susceptibility to obesity and metabolic disorders [6]. These genetic characteristics, typical of East Asian populations, provide a foundation for developing personalized treatment strategies for metabolic disorders. However, genetic factors alone do not fully explain the impact of dietary changes on metabolic health.

For example, the transition from a traditional high-protein, high-fat diet to a carbohydrate-rich diet amplifies the effects of *MTCH2* (rs10838738), *SH2B1* (rs7498665), *FTO* (rs9939609), and *APOC3* (rs2854116) gene polymorphisms on the risk of obesity and metabolic syndrome among Indigenous populations of Alaska and Greenland [42]. Women are particularly vulnerable, as a high frequency of the C allele of the *APOC3* gene is associated with an increased risk of metabolic syndrome. These findings underscore the need for tailored dietary recommendations for northern populations that account for their genetic predisposition.

Simultaneously, genetic characteristics extend beyond metabolic disorders. Indigenous northern populations also exhibit carbohydrate intolerance, associated with polymorphisms in the *SI* (AG deletion), *LCT* (CC/*LCT* genotype), and *TREH* (rs2276064) genes. The high frequency of these genotypes leads to malabsorption of sucrose, lactose, and trehalose, significantly increasing the risk of developing type 2 diabetes (*T2D*) when transitioning away from a traditional diet [43]. These findings suggest that modern dietary patterns may conflict with genetically determined metabolic traits.

Beyond metabolic risks, genetic polymorphisms in cytokine genes significantly impact the health of Arctic populations. Variants in *IL2* (rs2069762), *IL4* (rs2243250), *IL10* (rs1800872), and *IL13* (rs1800925) are prevalent among Indigenous groups, contributing to enhanced resistance to infections while reducing the risk of allergic and oncological diseases [44]. However, genetic adaptations to extreme Arctic conditions may also have adverse consequences. For example, the *IFNAR2* (p.Ser53Pro) mutation in Inuit is linked to impaired immune responses and an increased risk of severe viral infections, underscoring the need to reconsider vaccination strategies for these populations [45].

In conclusion, studies examining genetic and environmental influences on phenotype among Indigenous northern populations have yielded contradictory results regarding chronic non-communicable disease (NCD) risk factors. Although obesity prevalence is lower (1.63%) compared to non-Indigenous populations (11.18%), poor dietary habits (42.49%) and high alcohol consumption (13.46%) may still elevate metabolic risks [46]. These findings underscore that genetic resistance to obesity does not confer complete protection against other metabolic disorders, particularly in the context of lifestyle changes.

Genetic factors, including polymorphisms in *TCF7L2*, *HIP1*, *APOC3*, *SI*, *LCT*, *TREH*, *IL2*, *IL4*, *IL10*, *IL13*, and *IFNAR2*, combined with environmental exposures, play a pivotal role in shaping metabolic and immunological risks among northern populations. A comprehensive approach that integrates genetic screening with lifestyle modifications is essential to minimize these risks and optimize chronic disease prevention.

Comparative analysis of genetic profiles among northern populations – including Inuit, Aleuts, Yakuts, Chukchi, and others – reveals significant differences in mutation frequencies that influence susceptibility to various diseases. These differences reflect unique adaptive mechanisms that have enabled these populations to survive extreme Arctic conditions while shaping their distinct metabolic and immunological phenotypes.

A study of polymorphisms in *FCN3* (rs28357092) and *MASP2* (rs72550870) demonstrated that ethnic Russians in Krasnoyarsk exhibit a higher prevalence of alleles associated with reduced lectin pathway complement activation compared to Indigenous Arctic populations (Nenets, Dolgans, Nganasans) [47, 48]. Indigenous populations predominantly carry genotypes with high functional complement activity, potentially conferring enhanced protection against infections, including emerging viral diseases such as COVID-19.

Genetic analysis of Nunavik Inuit has identified unique polymorphisms in the *CPNE7*, *ICAM5*, *STAT2*, and *RAF1* genes, which are associated with fatty acid metabolism and cell adhesion [1]. These genetic traits may contribute both to adaptation to a traditional fat-rich diet and to an increased predisposition to cardiovascular diseases. Regarding cardiovascular health among Inuit, an analysis of disease trends from 1994 to 2021 revealed a decline in the incidence of ischemic heart disease, stroke, and heart failure among Greenlandic Inuit, despite increased urbanization [3]. Genetic factors, including mutations in the *APOE*, *LDLR*, and *TBC1D4* genes, play a pivotal role in shaping these trends.

Differences in cytokine gene polymorphism frequencies (*IL2*, *IL4*, *IL10*, *IL13*) among Nenets, Dolgan-Nganasans, and Slavic populations reveal that Indigenous Arctic populations exhibit higher frequencies of genotypes that promote rapid immune responses and reduce the risk of allergic and oncological diseases [44]. Concurrently, Yakuts, residing in the coldest regions, carry the *UCP3* (rs1800849) polymorphism, which enhances

thermoregulation and reduces body mass via increased irisin levels [49].

The genetic uniqueness of northern populations is further reflected in *TCF7L2* (rs7903146) polymorphism frequencies among five ethnic groups in Siberia (Buryats, Teleuts, Yakuts, Dolgans, and Russians). Among Indigenous Siberian populations, the diabetes-associated allele occurs less frequently, suggesting a protective genetic profile [50].

A study of Nenets revealed a high frequency of the "wild-type" genotype of the *SOD2* gene (rs4880), which is associated with reduced oxidative stress [51]. This genetic advantage may decrease the risk of cardiovascular diseases despite harsh climatic conditions.

The present study demonstrates that cardiovascular and metabolic diseases in Indigenous northern populations develop via distinct genetic mechanisms shaped by extreme climatic conditions and traditional diets. Genetic markers such as *LDLR, APOE, LPL, CPT1A, TBC1D4*, and *HNF1A* significantly influence susceptibility to diseases including atherosclerosis, hypercholesterolemia, and type 2 diabetes. These findings provide a foundation for exploring the interplay between genetic and environmental factors in shaping metabolic and cardiovascular risks among northern populations.

Discussion of research findings

The present study encompasses six interrelated aspects: genetic risk factors for cardiovascular diseases, lipid metabolism adaptation, determinants of type 2 diabetes, polygenic mechanisms, environmental influences, and a comparative analysis of northern populations. This comprehensive approach enabled the identification of key genetic mechanisms underlying metabolic traits, immune responses, and the adaptation of Indigenous populations to extreme climatic conditions.

The analysis of genetic risk factors for atherosclerosis and hypercholesterolemia revealed the significant influence of *LDLR* (p.G137S), *APOB*, *PCSK9*, *APOE* (ε4), *LPL* (rs320), *CETP*, and the adaptive *CPT1A* mutation. These findings are consistent with Kim *et al*. (2019), who confirmed a distinctive lipid profile in Indigenous populations; however, that study did not include a detailed genetic characterization of lipid metabolism [52]. The roles of *LPL* (rs320) and *CETP* are further supported by the research of Sitseva T.M. *et al*. (2021), thereby strengthening the evidence base [53].

In contrast to the study by Daniel J. Rader *et al.* (2019), which focuses on polygenic risk scores (PRS), our work emphasizes monogenic mutations, enabling a more precise assessment of their contribution to hypercholesterolemia development [54].

The study of lipid metabolism adaptation mechanisms identified significant roles for *CPT1A*, *TBC1D4*, *PLIN1*, *ANGPTL8*, *FADS1*, and *FADS2* in adaptation to a traditional diet. Data from Andersen *et al.* (2018) confirm the importance of *CPT1A* (p.Pro479Leu) and *FADS1*/*FADS2* in fatty acid metabolism, as well as *TBC1D4* (p.Arg684Ter) in carbohydrate metabolism regulation, particularly in response to dietary changes [55]. Additionally, their study identifies *ADCY3* (c.2433-1G>A) as a novel risk factor for obesity, complementing our findings on the role of genetic adaptation in metabolism.

Analysis of genetic determinants of type 2 diabetes (*T2D*) revealed key markers: *HNF1A* (G319S), *TBC1D4* (p.Arg684Ter), *ADCY3* (c.2433-1G>A), *FABP2* (Ala54Thr), *ITGA1*, *LARGE1*, *VDR* (rs7968585), and *HLA-DQA1* (rs3104413), which underlie individual differences in carbohydrate metabolism. Their significance is supported by a 2018 study [55]. Andersen *et al.* (2016) also highlight the impact of *HNF1A* (G319S) and *TBC1D4* but extend their analysis to other ethnic groups (Pima Indians, Icelandic populations) [56]. Unlike these studies, our research is the first to examine *FABP2*, *ITGA1*, *LARGE1*, and *HLA-DQA1* as significant *T2D* risk markers in northern populations, emphasizing the need for an ethnically targeted approach.

Table 1. Genetic markers of adaptation and disease risk in northern Indigenous populations

Gene	*Associated Risks*	*Features in Northern Indigenous Populations*	*Comments*
CPT1A	Neonatal hypoglycemia (during fasting); lipid metabolism characteristics	High frequency of the P479L mutation among Inuit/Eskimo populations; elevated ω-3 PUFA levels under a traditional diet	Adaptive mutation enhancing fat utilization in cold climates (↑β-oxidation); may also increase neonatal hypoglycemia risk
FADS1/2	Altered ω-3/ω-6 fatty acid ratios; impact on lipid profile and metabolic syndrome risk	Adaptive variants common among Chukchi, Koryaks, and Eskimos; enhance ω-3 PUFA synthesis	Adaptation to a high-fat diet supports energy balance under traditional nutrition; may increase dyslipidemia and cardiovascular risk under modern diets
TBC1D4	Significantly increases type 2 diabetes risk (OR ≈ 10) under a Western diet; limited impact on CVD risk	The p.Arg684Ter mutation is prevalent among Greenlandic Inuit; carriers exhibit improved glycemic control under a traditional marine-based diet	Adaptive mutation for low-carbohydrate diet; supports glucose metabolism on high-fat diet; transition to carbohydrate-rich diet leads to type 2 diabetes
TCF7L2	Type 2 diabetes (rs7903146-T variant)	Among indigenous Siberian populations (*e.g.*, Buryats, Yakuts, Dolgans), the rs7903146 risk allele is less prevalent than in other populations	Likely adaptive effect: lower frequency of risk allele may confer protection against type 2 diabetes in northern populations
UCP3	Regulation of thermogenesis and body mass (rs1800849 allele enhances thermoregulation and reduces body weight)	In Yakuts (the coldest inhabited region), rs1800849 polymorphism increases irisin levels, enhancing thermoregulation and reducing body mass	Adaptive: enhances heat production and energy expenditure in cold environments, increasing metabolic activity
AGT	Arterial hypertension; lipid metabolism disorders (M235T polymorphism: ↑blood pressure, ↑LDL)	Among Yakuts, carriers of the M235T G allele exhibit elevated blood pressure, total cholesterol, and LDL levels	Involved in blood pressure regulation (renin-angiotensin system); variant may be detrimental under modern conditions, increasing disease risk
NOS3	Cardiovascular diseases: acute coronary syndrome, stroke; congenital pathology (patent ductus arteriosus in newborns)	In Yakuts, rs1799983 polymorphism of endothelial NO synthase is associated with increased hypertension risk and endothelial dysfunction	Encodes endothelial NO synthase, regulates vascular tone; variants may cause endothelial dysfunction and increase cardiovascular disease risk.

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The assessment of polygenic mechanisms in cardiovascular diseases (CVD) demonstrated substantial influence from *AGT*, *APOE*, *NOS3*, *CYBA*, *ACE*, *TBC1D4*, *HNF1A*, and *CYP2C19*. International studies confirm *TBC1D4* and *HNF1A* as key cardiometabolic factors, with their effects amplified by extreme climatic conditions [57]. However, unlike these studies, our research encompasses a broader spectrum of hypertension and atherosclerosis markers (*AGT*, *NOS3*, *ACE*), whereas the Inuit study primarily focuses on pQTL analysis and protein expression regulation. Another investigation of Arctic populations examines immune-metabolic mechanisms underlying CVD development but does not consider genetic predispositions, rendering our conclusions on the significance of polygenic risk scores (PRS) particularly important [58].

The interaction between genetic and environmental factors in shaping metabolic risks underscores the key roles of *TCF7L2*, *HIP1*, *APOC3*, *SI*, *LCT*, *TREH*, *IL2*, *IL4*, *IL10*, *IL13*, and *IFNAR2*, combined with external influences such as dietary changes, urbanization, and reduced physical activity. Data from Russian researchers support similar adaptive mechanisms, including *CPT1A*, *TBC1D4*, *AMY2A*, and the impact of dietary shifts on the development of diabetes and obesity [59]. In contrast to this study, our research emphasizes immune mechanisms (*IL2*, *IL4*, *IL10*, *IL13*, *IFNAR2*), enhancing the understanding of interactions between innate and acquired risk factors. International studies also highlight stress and historical trauma as factors exacerbating cardiometabolic risk through inflammatory processes, corroborating the patterns identified in our findings [60].

The comparative analysis of northern populations – including Inuit, Aleuts, Yakuts, Chukchi, Nenets, Dolgans, and others – revealed significant differences in polymorphism frequencies influencing disease susceptibility. Russian researchers corroborate the role of genetic adaptation mechanisms; however, their work primarily focuses on marker-based systems, whereas our study offers a comparative analysis of specific ethnic groups [61]. Our research highlights *UCP3*, *TCF7L2*, *APOE*, *LDLR*, *TBC1D4*, and *SOD2*, while the referenced study concentrates on *FADS1*, *FADS2*, *PSCA*, *IGF1*, *AGT*, and *ADRB1*, illustrating differences in research approaches. Both studies confirm the significant impact of genetics on northern populations' adaptation but differ in scope: our study provides detailed population-specific differences, whereas the review emphasizes predictive systems for medical diagnostics.

Through genetic analysis of Indigenous populations of the North, we identified key polymorphisms in seven genes (*CPT1A*, *FADS1/2*, *TBC1D4*, *TCF7L2*, *UCP3*, *AGT*, and *NOS3*) associated with the risk of chronic non-communicable diseases. The main findings are summarized in *Table* 1, which details the associated risks for cardiovascular and metabolic diseases, gene expression patterns in the studied individuals, and the relevance of these polymorphisms within the context of Arctic adaptation or pathology. The results illustrate a complex interplay of adaptive and pathogenic effects: many variants reflect evolutionary adaptation to harsh climates and traditional diets, while simultaneously increasing susceptibility to modern diseases under changing – lifestyles.

Conclusion

This study confirms that genetic polymorphisms prevalent in northern populations – including *CPT1A*, *LDLR*, *LPL*, *APOE*, *FADS1/2*, *ANGPTL8*, *PLIN1*, *HNF1A*, and *TBC1D4* – significantly influence the risk of cardiovascular and metabolic diseases. Adaptations to traditional diets and extreme climatic conditions may paradoxically become risk factors when lifestyle changes occur. Moreover, polygenic interactions further elevate susceptibility to hypertension, atherosclerosis, and type 2 diabetes, underscoring the necessity for comprehensive assessments of hereditary factors. The interplay between genetic and environmental factors shapes distinctive metabolic and immune risks in northern populations. Acknowledging these genetic characteristics is crucial for advancing personalized medicine and developing ethnically tailored prevention strategies.

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Conflict of Interest

The authors declare no conflicts of interest.

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