

9p21 Variation, CTSH, Diabetes, and Peripheral Artery Disease: Evidence for Risk, Disease Severity, and Limb Outcomes Across Populations

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Abstract

Peripheral artery disease (PAD) causes dangerous arterial narrowing in the legs, affecting over 200 million people worldwide [1]. Type 2 diabetes (T2D) accelerates PAD through chronic hyperglycemia and inflammation [1, 2]. This review synthesizes 20 peer-reviewed studies to examine how genetic variations within the 9p21 locus and the CTSH gene interact with diabetes to drive PAD progression and limb outcomes across global populations [1, 2]. Findings show that 9p21 risk variants combined with poor blood sugar control increase vascular risk nearly eightfold [3, 4]. Additionally, CTSH dysregulation weakens arterial plaques and impairs angiogenesis (new blood vessel growth), leading to severe tissue damage [4, 5]. Population differences in allele frequencies further explain global disparities in PAD severity. Understanding these gene-environment interactions supports earlier risk stratification and personalized therapies [5, 6].

Introduction

Peripheral artery disease (PAD) is caused by atherosclerosis, plaque buildup that restricts lower-limb blood flow. This leads to pain, slow-healing wounds, and amputations [1, 2]. Type 2 diabetes (T2D) multiplies PAD risk by 2x to 4x through chronic inflammation [2].

This literature review aims to answer the question: How do genetic variants at the 9p21 locus and CTSH gene interact with diabetic metabolic stress to drive PAD severity, plaque instability, and blood vessel repair across diverse populations [1-3]?

Beyond lifestyle choices, PAD is driven by genetics [3]. Single-nucleotide polymorphisms (SNPs) at the 9p21 locus and CTSH gene impair vessel wall structure and healing, which population specific genes contribute to global health disparities [3-6].

Methods

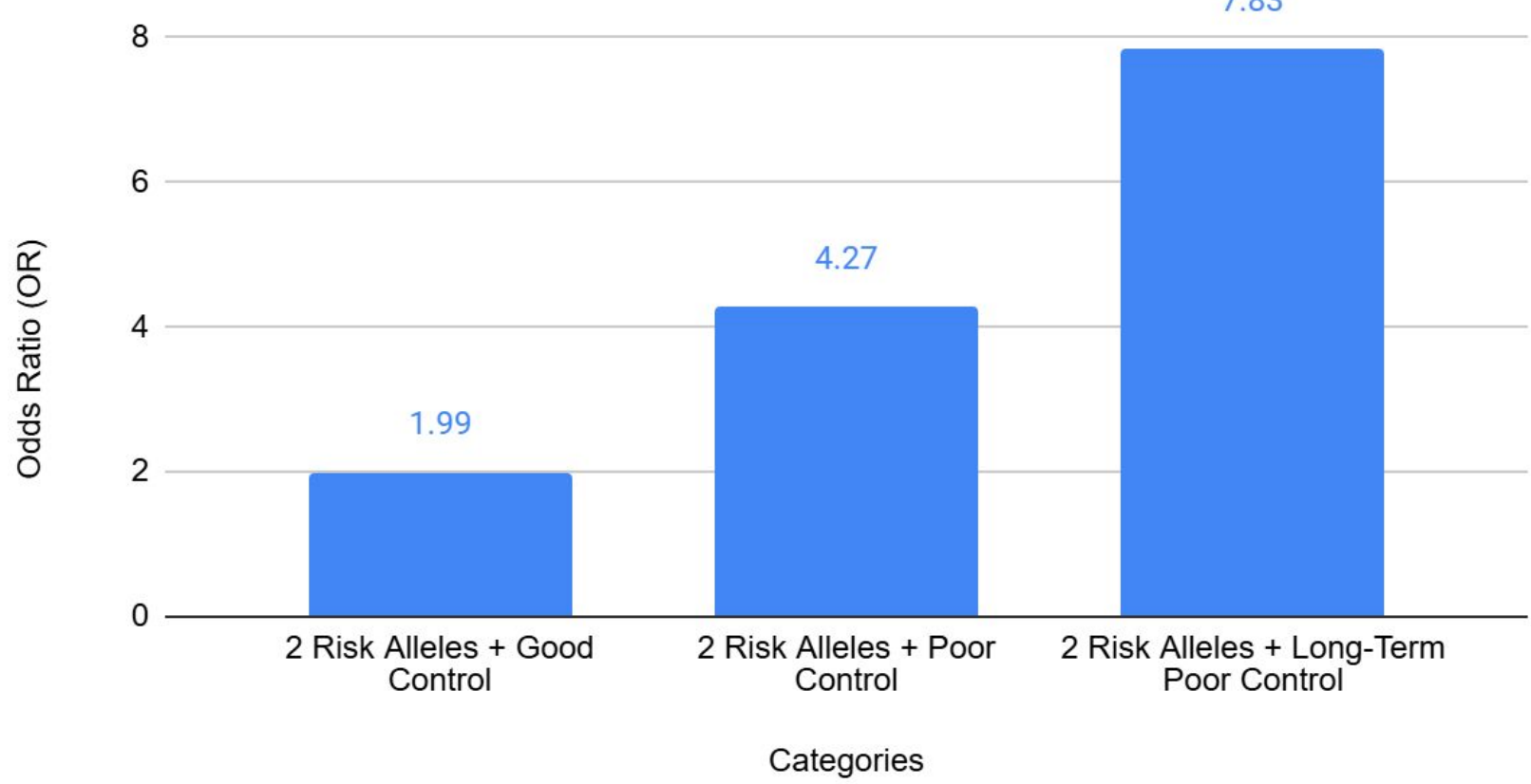
A systematic search of electronic literature was conducted by using the Google Scholar and PubMed/MEDLINE databases to identify peer-reviewed articles, genome-wide association studies (GWAS), systematic reviews, and clinical trials published between 1998 and 2024 [7]. The search included combinations of the following terms and keywords: “peripheral artery disease,” “type 2 diabetes,” “9p21 locus,” “rs1333049,” “rs10811661,” “CTSH gene,” “cathepsin H,” “glycemic control,” “angiogenesis,” and “racial disparities in amputation.”

Studies were excluded if they focused on non-human animal models, examined vascular conditions unrelated to peripheral limbs, or lacked peer-reviewed status.

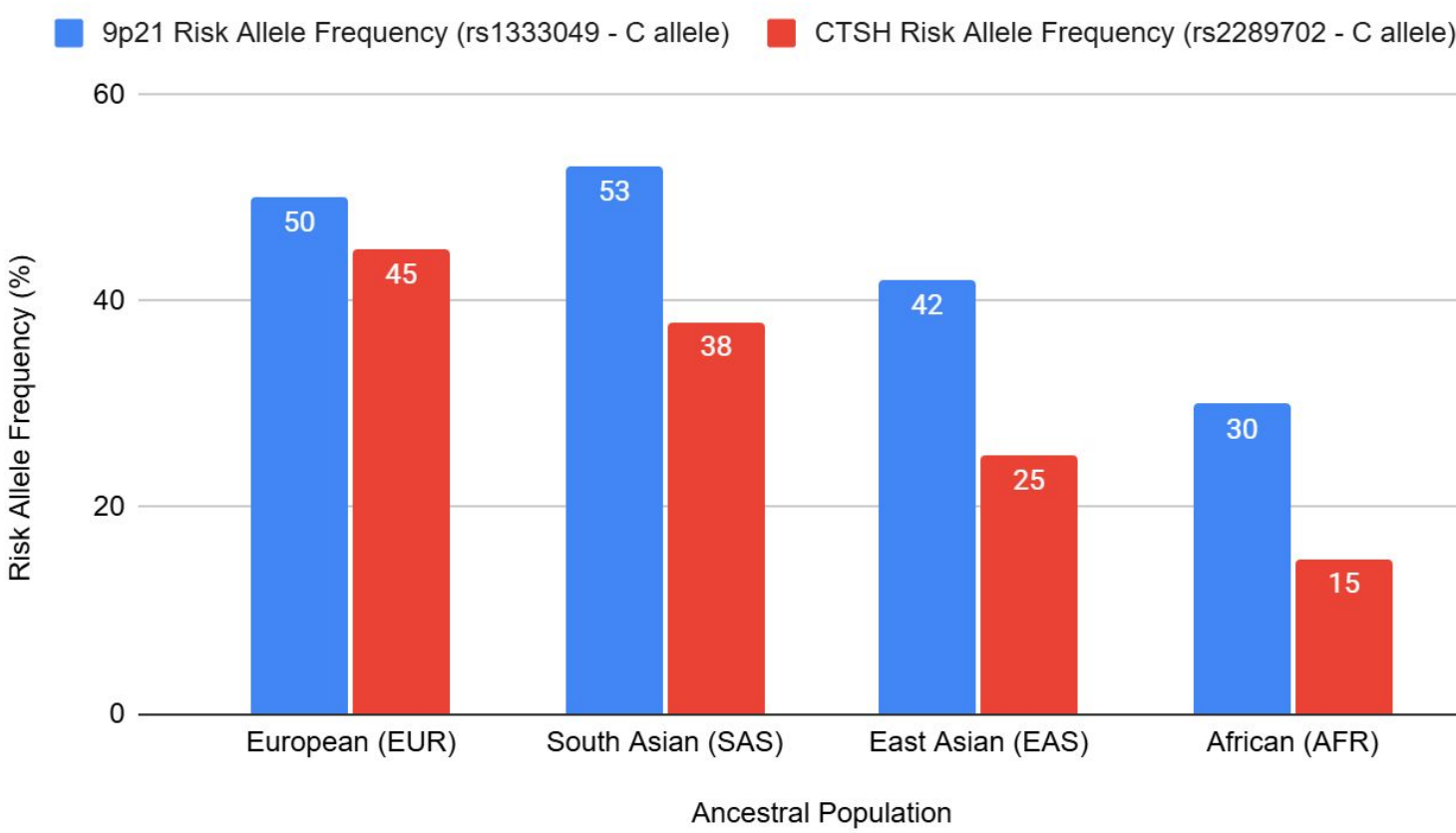
Results

The review revealed a gene-environment interaction between high blood sugar and variants in the 9p21 chromosomal region (SNPs rs1333049 and rs10811661) [3, 4]. These variants triggered vascular smooth muscle growth and arterial inflammation [3]. Carrying two 9p21 risk alleles paired with proper glycemic control doubles disease risk (OR = 1.99). However when combined with lacking glycemic control, the risk quadruples (OR = 4.27), and under long term poor blood sugar control, vascular risk multiplies nearly eightfold (OR = 7.83) [4]. This shows that chronic hyperglycemia coming from T2D directly amplifies the chance someone has of developing peripheral artery disease by pairing together with the underlying genetics [3, 4].

Effect of 9p21 Risk Alleles & Glycemic Control on Vascular Risk



Risk Allele Frequencies of 9p21 and CTSH Across Ancestral Groups



Discussion

These findings support the hypothesis that genetic factors and diabetic stress act together rather than independently. Aligning with foundational 9p21 GWAS literature, our analysis confirms that chronic hyperglycemia actively amplifies underlying genetic susceptibility [3, 4]. Furthermore, the evaluation of CTSH dysregulation reinforces molecular studies showing that cathepsin H imbalance drives plaque instability and impairs vessel repair (angiogenesis) [5]. Finally, distinct allele frequencies across ancestral groups agree with health equity research, confirming that European-centric genomic datasets obscure critical risk factors that are present in underrepresented populations that may face higher risks to this disease [6].

Conclusion

Genetic variants at the 9p21 locus and CTSH gene interact together with diabetic stresses to accelerate the progression of peripheral artery disease, plaque instability, and impaired vascular repair [3-5]. Crucially, the exponential risk jump shows that aggressive glycemic control directly subdues genetic susceptibility [4]. Moving forward, clinical management must integrate genetic risk profiles with early glycemic intervention, white research explores pathways for tissue repair [5]. Finally, expanding genomic research to include underrepresented, non-European populations is essential to achieve effective cardiovascular care that every person deserves [6].

References

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