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Review

The Interplay of Genetic Predisposition, Immunological Mechanisms, and Environmental Factors in the Pathogenesis of Carpal Tunnel Syndrome: A Comprehensive Review

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Abstract: Carpal Tunnel Syndrome (CTS) is the most common entrapment neuropathy, yet its etiology remains multifactorial and incompletely understood. While often considered idiopathic, recent evidence points to a complex interplay of genetic predisposition, immunological factors, and environmental exposures. Objective: This narrative review aims to synthesize current evidence on the genetic, immunological, and environmental underpinnings of CTS to provide a holistic understanding of its pathogenesis. Furthermore, it seeks to highlight the novel integration of these three domains, discuss the practical applications for clinical practice, and acknowledge the limitations of the current evidence base. Methods: A narrative review of the literature was conducted, analyzing studies concerning genetic polymorphisms, immune system alterations, occupational risks, and histopathological changes in CTS. Results: Genetic studies highlight polymorphisms in genes encoding collagen types (COL1A1, COL5A1, COL11A1), matrix metalloproteinases (MMPs), and glutathione S-transferases (GSTs) as contributors to connective tissue susceptibility and oxidative stress response. Immunological findings indicate a role for adaptive immunity, with elevated levels of T-cells (particularly CD4+ and memory T-cells) and chemokines like CCL5 and VEGF in the synovial tissue and serum, suggesting a low-grade inflammatory or immune-mediated process. Environmental factors, particularly repetitive biomechanical stress, high job strain, and low social support, are significant modifiable risk factors. The core pathophysiology involves increased intracarpal pressure leading to ischemic and mechanical damage to the median nerve, exacerbated by individual susceptibility. Conclusion: CTS arises from a convergence of genetic susceptibility, dysregulated immune responses, and environmental triggers. A better understanding of these interactions is crucial for developing targeted prevention strategies, personalized risk assessment, and novel therapeutic interventions beyond mechanical decompression.

Keywords: Carpal Tunnel Syndrome, Genetics, Immunology, Occupational Medicine, Pathophysiology

1. Introduction

Carpal Tunnel Syndrome (CTS) is the most common entrapment neuropathy, clinically marked by pain, tingling, and sensory-motor deficits in the distribution of the median nerve [1]. The main pathophysiological mechanism consists of increased pressure in the inflexible carpal tunnel, resulting in ischemic and mechanical injury to the median nerve. Although both occupational and non-occupational biomechanical stressors are recognized risk factors, a significant portion of cases is deemed idiopathic, suggesting an inadequate comprehension of the fundamental causes.

This diagnostic gap has led to a shift in perspective towards a multifactorial model of pathogenesis. Growing evidence increasingly suggests a complicated interaction where genetic factors and immune processes notably influence personal vulnerability to environmental stimuli. This review seeks to integrate this evidence, asserting that "idiopathic" CTS often reflects a clinical indicator of hidden genetic and immunological susceptibilities, revealed by cumulative environmental factors, especially repetitive biomechanical strain.

This study advances beyond a solely compressive model by merging insights from genetic association studies, immunological profiling, and research on occupational health. It introduces an innovative integrative model a "triad of susceptibility" in which the interaction of genetic, immunological, and environmental elements determines disease emergence and advancement. This comprehensive viewpoint is essential for enhancing risk classification, creating tailored prevention plans, and investigating new treatment options beyond just mechanical decompression.

Increasingly, evidence suggests that CTS pathogenesis is multifactorial, involving an intricate interplay between genetic predisposition, immunological alterations, and environmental exposures. This review seeks to consolidate the current body of evidence regarding these three pillars of CTS etiology. By synthesizing findings from genetic association studies, immunological profiling, and occupational health research, this article aims to provide a comprehensive overview that moves beyond a purely biomechanical model and towards a more integrated pathophysiological understanding of CTS.

Figure 1 offers a visual summary of our unified pathophysiology model, demonstrating how three main susceptibility areas genetic influences (collagen/MMP/GST polymorphisms, diminished tissue compliance), immunological factors (elevated T-cells, chemokines, localized inflammation), and environmental/occupational pressures (repetitive motions, vibrations, work-related strain) combine to elevate intracarpal pressure. This increased pressure causes ischemia, mechanical distortion, and eventually demyelination/axonal damage of the median nerve, leading to the typical clinical signs of CTS

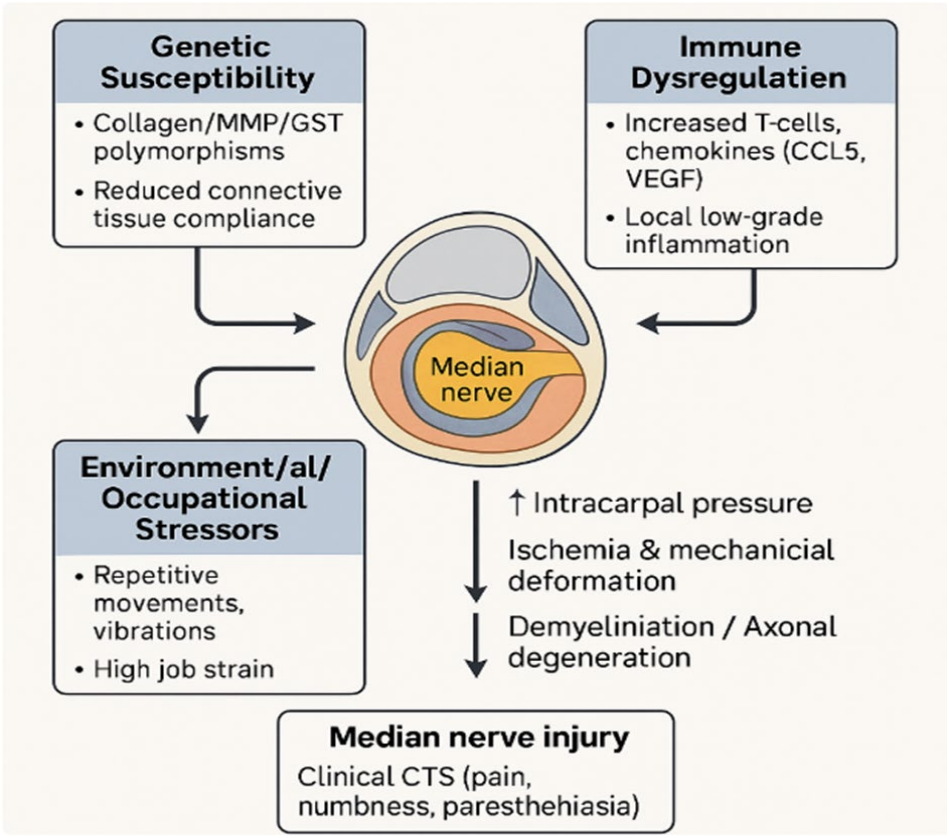

Figure 1. Integrated Pathophysiology of Carpal Tunnel Syndrome.

Objective, Aim, and Novelty of the Study

The primary **objective** of this comprehensive review is to critically appraise and synthesize the existing literature on the genetic, immunological, and environmental factors contributing to CTS.

The aim is to bridge the knowledge gaps between these traditionally separate domains of research, providing a unified model of CTS pathogenesis that can inform both clinical practice and future research directions.

The **element of novelty** in this review lies in its integrative approach. While many reviews focus on one specific aspect (e.g., occupational risks or surgical outcomes), this work deliberately connects findings from genomics, immunology, and environmental health to propose a more holistic "triad of susceptibility" model. This model posits that CTS manifests when environmental triggers act upon a genetically susceptible individual, potentially facilitated or exacerbated by a dysregulated immune response.

The **practical applications** of this synthesized knowledge are multifold. Firstly, it can lead to improved risk stratification, identifying individuals with high genetic or immunological susceptibility for targeted workplace interventions. Secondly, it opens the door for biomarker development (e.g., serum CCL5, T-cell profiles) to identify patients who might benefit from immunomodulatory therapies. Finally, it provides a scientific basis for personalized medicine in CTS management, moving away from a one-size-fits-all approach.

It is crucial to acknowledge **the limitations of this study**. As a narrative review, it is subject to potential selection bias, as it does not follow the systematic methodology of a systematic review or meta-analysis. The evidence presented is synthesized from heterogeneous studies with varying methodologies, which limits direct comparability. Furthermore, the field is rapidly evolving, particularly in genetics and immunology, and this review may not capture the very latest pre-print findings. Finally, the proposed

integrative model, while based on current evidence, requires validation through prospective, multi-omics studies designed specifically to test these interactions.

This assessment has constraints that need to be acknowledged. As a narrative synthesis, it does not include quantitative meta-analysis or a formal evaluation of the quality of the studies included. The evidence foundation is marked by diverse methodologies and inconsistent study quality. Special care is required in interpreting histopathological results, as earlier studies employing traditional staining methods might have overlooked immune participation identifiable through contemporary techniques. Crucially, the area is missing multi-omics strategies that could offer combined understanding across biological fields. Ultimately, although useful as a conceptual framework, our "triad of susceptibility" model needs future validation.

Materials and Methods

Process of Selecting Studies and Criteria for Eligibility

The selection process for the study consisted of a two-step screening of titles/abstracts and full texts, performed independently by two reviewers to reduce selection bias. Conflicts were settled through dialogue or by seeking input from a third reviewer.
Inclusion Criteria were established to obtain primary evidence regarding the causes of CTS. We incorporated:

• Original research articles: Observational studies (case-control, cohort, cross-sectional), genetic association studies (candidate-gene and GWAS), and immunohistochemistry studies.

• Research concerning human participants that concentrates on idiopathic or primary occupational CTS.

• Research articles published in English within peer-reviewed publications.

Exclusion Criteria were utilized to ensure a concentration on pathogenesis:

• Research that concentrates solely on surgical methods, outcomes after surgery, or the precision of diagnostic imaging without understanding the underlying causes.

• Research on CTS resulting from clearly defined systemic diseases (e.g., rheumatoid arthritis, diabetes mellitus, acromegaly), unless used as a comparison group to clarify mechanisms in idiopathic CTS.

• Editorials, case reports involving less than five patients, and abstracts from conferences.

• Publications and studies in languages other than English for which the complete text could not be accessed.

Screening Outcomes and Final Production

The initial search of the database uncovered 1,847 records. Following the elimination of duplicates, 1,215 distinct records were assessed according to title and abstract. This preliminary screening eliminated 1,023 records that failed to satisfy the inclusion criteria, mainly because they concentrated on surgery, diagnosis, or secondary CTS. The eligibility of the remaining 192 full-text articles was evaluated. Out of these, 124 were eliminated, with the primary reasons being irrelevant focus (n=68), secondary CTS lacking a relevant comparator (n=31), and absence of the complete text (n=12). A total of 68 studies were ultimately chosen for data extraction and synthesis in this review. The reference lists of important reviews were manually searched to find any other relevant studies.

Genetic Predisposition in CTS

Although CTS often presents sporadically, familial aggregation is observed in 17%–39% of cases, indicating a potential heritable component [11]. Research has focused on genes influencing the integrity and remodeling of the connective tissues within the carpal tunnel.

Genetic Susceptibility in CTS

While CTS typically occurs sporadically, familial clustering is noted in 17%–39% of instances, suggesting a possible genetic factor [11]. Studies have concentrated on genes that affect the maintenance and alteration of the connective tissues in the carpal tunnel, Table 1.

Collagen and the Structure of Connective Tissue

A prominent hypothesis suggests a genetic predisposition to tendinopathy. Genetic variants in minor collagen subtype genes—COL1A1, COL5A1, and COL11A1—might modify the mechanical characteristics of ligaments and tendons, possibly leading to a constricted carpal tunnel or diminishing its ability to adapt to pressure variations [1, 12].

Tissue Reconstruction: Matrix Metalloproteinases (MMPs)

The regulation of connective tissue collagen remodeling is controlled by MMPs. Variants in the MMP10, MMP1, MMP3, and MMP12 gene cluster located on chromosome 11q22 have been examined for their involvement in the breakdown of connective tissue. Nonetheless, research conducted by Burger et al. (2015) reported no meaningful link between particular MMP polymorphisms (MMP10 rs486055, MMP1 rs1799750, MMP3 rs679620, MMP12 rs2276109) and the risk of CTS, indicating that the genetic framework of tissue remodeling in CTS is intricate and necessitates additional clarification [2].

Response to Oxidative Stress

Oxidative stress in the subsynovial connective tissue can trigger edema and tissue injury, leading to nerve compression. Glutathione S-transferases (GSTs) play an essential role in protection against reactive oxygen species. Particular null polymorphisms in the GSTM1 and GSTT1 genes, resulting in reduced or absent enzymatic function, have been recognized as possible risk factors for CTS, suggesting a role of compromised oxidative stress regulation in its development [3].

Table 2. Key Genetic Polymorphisms Associated with Carpal Tunnel Syndrome

Gene Category	Specific Gene/ Polymorphism	Proposed Mechanism	Strength of Evidence	References
Collagen Structure	COL1A1, COL5A1, COL11A1 polymorphisms	Altered connective tissue compliance, reduced carpal tunnel capacity	Moderate (family studies, candidate gene)	[1, 12]
Matrix Remodeling	MMP1, MMP3, MMP10, MMP12 variants	Impaired connective tissue remodeling	Limited/Conflicting (no significant association in some studies)	[2]
Oxidative Stress Response	GSTM1 null genotype	Reduced detoxification of reactive oxygen species	Moderate (multiple case-control studies)	[3]
	GSTT1 null genotype	Impaired oxidative stress management	Moderate (replicated findings)	[3]
Genome-Wide Significant Loci	53 independent GWAS signals	Altered musculoskeletal morphology, tissue organization	Strong (genome-wide significance)	[13]

Immunological Alterations in CTS and Systemic Immune Profile

Systemic Immune Profile: Individuals with CTS display a unique systemic immune signature in comparison to healthy individuals. This is marked by notably higher serum concentrations of particular chemokines (CCL5, CXCL8, CXCL10) and vascular endothelial growth factor (VEGF), alongside a rise in circulating CD4+ and effector memory T-cells [4]. These findings usually come from single-center studies with small sample sizes, and the diagnostic specificity for CTS compared to other neuropathic conditions is yet to be thoroughly confirmed. CCL5 and VEGF serve as highly sensitive biomarkers for discrimination.

Initial analyses indicate that within these factors, CCL5 (a pro-nociceptive agent) and VEGF might be especially significant in distinguishing patients from controls. Certain research has indicated an inverse relationship between serum CCL5 concentrations and the severity of neuropathic pain, whereas memory T-cell quantities have demonstrated a positive association with irregular neurophysiological metrics [4, 14]. Nonetheless, these results need validation in more extensive, separate groups.

The clinical significance of this signature is highlighted by important correlations: serum CCL5 levels show an inverse correlation with neuropathic pain severity, whereas memory T-cell levels display a positive correlation with abnormal neurophysiological measures [4, 14]. Nonetheless, these correlations, despite being statistically significant, tend to be modest, suggesting that immune markers represent only a part of a complicated pathophysiology and are not yet suitable for use as independent clinical biomarkers.

Localized T-Cell Dominant Response: This systemic pattern is reflected locally within the carpal tunnel. In opposition to the conventional perspective of "non-inflammatory" synovium, immunohistochemical studies demonstrate a predominance of T-cell immune infiltration in the subsynovial connective tissue, characterized by a notable rise in CD3+ T-cells and a modified macrophage profile [5].

This is an intriguing discovery; however, it relies on a quite limited number of biopsy studies. There is considerable variability in the cellular makeup of synovial tissue across patients, implying the presence of different immunopathological subtypes of CTS that remain poorly characterized. The causative function of this T-cell infiltration whether it acts as a primary instigator of pathology or as a secondary reaction to nerve injury also continues to be an important question for forthcoming studies.

Histopathological and Pathophysiological Modifications

Histological analysis of tenosynovial tissue from CTS patients shows distinctive alterations. The most common observations are edema (85% of cases) and vascular sclerosis (98% of cases), with the latter being associated with patient age and the severity of edema [18]. It is essential to identify the kind of inflammation seen. The traditional "frank inflammation" mentioned in previous histopathological research (e.g., Fuchs et al., 1991) usually denotes significant neutrophilic infiltrates or extensive inflammatory exudates typical of acute, severe synovitis, observed in diseases such as rheumatoid arthritis. This obvious pathology is, in fact, uncommon in idiopathic CTS, found in merely around 10% of biopsies.

Nonetheless, this does not rule out a noteworthy, though more understated, immunopathological phenomenon. Contemporary immunohistochemical methods demonstrate a contrasting image: a notable rise in CD3+ T-cells and a change in T-cell and macrophage subsets in the subsynovial connective tissue [5]. This suggests a persistent, low-level, cell-mediated immune reaction that may not be apparent in standard histology but can be identified using specialized immunological staining techniques. Consequently, the results regarding T-cell infiltration and the infrequency of "overt inflammation" are not opposing but instead depict different aspects of the disease's pathology the former indicating a distinct adaptive immune engagement, and the latter affirming the overall lack of a vigorous innate inflammatory response. Additional frequent observations encompass synovial enlargement, reactive synovitis, and fibrohyalin nodules, which might add to the mass effect inside the canal [19].

CTS as an Adverse Immune Event

The association of CTS with autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus is well-known. Furthermore, case reports have identified CTS as an atypical manifestation of toxicity from Immune Checkpoint Inhibitors (ICIs), a class of cancer therapeutics [15]. The successful resolution of symptoms with corticosteroids, intravenous immunoglobulins, or methotrexate in these cases strongly supports an immune-mediated pathophysiology in a subset of patients.

Core Pathophysiology: Intracarpal Pressure and Nerve Damage

The final common pathway of CTS is elevated pressure within the carpal tunnel, leading to mechanical deformation and ischemic damage to the median nerve. In a neutral wrist position, pressure in patients with CTS averages 32 mmHg, rising dramatically to 94 mmHg with flexion and 110 mmHg with extension [8, 20]. This increased pressure compromises the blood-nerve barrier, leading to increased vascular permeability, endometrial edema, and impaired microcirculation [9, 21]. Chronic compression results in demyelination, fibrosis (e.g., Renaut bodies), and ultimately, axonal degeneration [22, 23]. Nocturnal exacerbation of symptoms is attributed to fluid redistribution, lack of muscular pumping action, and sustained wrist flexion during sleep [10].

Biomechanical and Psychosocial Stress

Repetitive hand/wrist movements and the use of vibrating tools are primary physical risk factors. Prospective cohort studies have shown that high job strain is associated with an increased risk of CTS (HR=1.86), while strong social support at work acts as a protective factor (HR=0.54) [6, 7]. The highest incidence of CTS is often observed within the first 3.5 years of employment, highlighting an interaction between novel biomechanical exposure and individual susceptibility [16].

Demographic Correlations

Epidemiological data consistently show that female gender, high body mass index (BMI), and increasing age are significant non-modifiable risk factors [17]. The interaction between these demographic factors and occupational exposures underscores the multifactorial nature of the disease.

Discussion and Results

This review synthesizes findings from genetic, immunological, and environmental studies of Carpal Tunnel Syndrome (CTS), highlighting the multifactorial and interconnected nature of its pathogenesis.

Genetic Insights:

Evidence from family aggregation studies and genome-wide association analyses suggests a heritable component in CTS, with polymorphisms in collagen (COL1A1, COL5A1, COL11A1), matrix metalloproteinases (MMPs), and glutathione S-transferases (GSTM1, GSTT1) influencing tissue compliance, remodeling, and oxidative stress responses [1–3, 13]. These findings support the notion that individuals with structural or biochemical vulnerabilities in connective tissue are predisposed to median nerve compression.

Immunological Findings:

The study selection process shows that, unlike the traditional perspective of CTS as solely a mechanical neuropathy, immunological profiling reveals a low-grade, chronic inflammatory state and particular immune dysregulation in certain patients. Elevated serum and tissue levels of T-cell subsets, chemokines (CCL5, CXCL8, CXCL10), and VEGF suggest that immune-mediated mechanisms may exacerbate or perpetuate nerve injury [4, 5, 14 Importantly, the correlation between specific immune signatures (e.g., T-cell subsets, chemokines) and neurophysiological abnormalities underscores their potential relevance as biomarkers for disease severity and progression.

Environmental and Occupational Factors:

Repetitive hand/wrist use, high job strain, and low social support significantly modulate CTS risk, demonstrating that genetic and immunological susceptibility interacts with external biomechanical stressors [6, 7, 16]. The early emergence of CTS within the first few years of occupational exposure reinforces the temporal relevance of environmental triggers in initiating median nerve injury.

Histopathological Range: From Non-Inflammatory to Immune-Related Types

The histopathology of idiopathic CTS varies along a spectrum, which has led to noticeable contradictions in the literature. Determining the kind of inflammatory response is crucial for finding a resolution.

Classical "Non-Inflammatory" Observations: Typical histological staining (e.g., H&E) of tenosynovial tissue usually shows non-inflammatory conditions. The primary results include edema (85% of instances) and vascular sclerosis (98% of instances), with the latter being associated with the age of the patient and the severity of edema [18]. Frank inflammation—marked by numerous neutrophils, significant fluid exudate, or extensive tissue necrosis, as observed in acute infections or rheumatoid arthritis is uncommon, occurring in only about 10% of idiopathic CTS biopsies [19]. This forms the foundation for the conventional characterization of CTS as "non-inflammatory."

Current "Immune-Mediated" Discoveries: Conversely, recent immunohistochemical methods uncover a distinct, more nuanced pathological mechanism. These techniques reveal a notable predominance of T-lymphocyte immune infiltration in the subsynovial connective tissue, particularly a substantial rise in CD3+ T-cells and changes in T-cell and macrophage subpopulations [5].

Conceptual Integration: These results are not opposing but rather supportive. They uncover two separate levels of disease:

- The lack of "classical acute inflammation" (neutrophils, exudate) in histological analysis.
- The existence of a "persistent, cell-mediated immune reaction" (T-cell infiltration) identifiable solely through immunohistochemistry.

Consequently, although idiopathic CTS usually isn't characterized as a condition of acute neutrophilic inflammation, a notable portion of cases features a mild, T-cell-mediated immunopathology. Persistent immune infiltration may lead to synovial thickening, fibrosis, and edema, which increases intracarpal pressure and causes nerve compression through a subtler mechanism than traditional inflammation.

This review compiles results from genetic, immunological, and environmental research on Carpal Tunnel Syndrome (CTS), emphasizing the complex and interrelated aspects of its pathogenesis. We suggest a "Triad of Susceptibility" framework to illustrate how these areas interact to trigger the disease, as shown in Figure 2.

This model suggests that clinical CTS arises at the intersection of three interrelated areas genetic vulnerability: establishes the basic inclination, influencing connective tissue flexibility, oxidative stress reaction, and anatomical design of the carpal tunnel.

Immunological Priming: Establishes a conducive setting via mild, T-cell-driven inflammation and unbalanced tissue remodeling, reducing the threshold for nerve damage. Environmental Factors: Serve as the immediate cause, mainly through biomechanical strain that raises intracarpal pressure.

The interaction is active: environmental factors (e.g., repetitive stress) influence a genetically prone person, and the ensuing micro-injuries can be intensified or sustained by a dysfunctional immune response, resulting in the ultimate common pathway of median nerve compression. This comprehensive perspective accounts for the diversity of clinical presentations, encompassing idiopathic cases, recurrent illnesses, and differing reactions to treatment.

Figure 2. The “Triad of Susceptibility” model for Carpal Tunnel Syndrome

, The model posits that CTS manifests when environmental triggers act upon a genetically susceptible individual, a process that is potentially facilitated or exacerbated by a dysregulated immune response. This integrative view explains the heterogeneity of

clinical presentations, including so called idiopathic cases, recurrent disease, and variable responses to conservative or surgical management, Table 2.

Table 2. Triad of Susceptibility in Carpal Tunnel Syndrome

DOMAIN	KEY FACTORS / FINDINGS	CLINICAL RELEVANCE	REFERENCES
GENETIC PREDISPOSITION	Collagen gene polymorphisms (COL1A1, COL5A1, COL11A1), MMP variants (MMP1, MMP3, MMP10, MMP12), GST polymorphisms (GSTM1, GSTT1), 53 GWAS-associated loci	Altered connective tissue resilience, decreased compliance of carpal tunnel, increased susceptibility to nerve compression	[1–3, 13]
IMMUNOLOGICAL FACTORS	Elevated T-cells (CD4+, memory), chemokines (CCL5, CXCL8, CXCL10), VEGF, local synovial infiltration, association with autoimmune conditions	Low-grade inflammation, immune-mediated nerve injury, correlation with neurophysiological abnormalities	[4, 5, 14, 15]
ENVIRONMENTAL / OCCUPATIONAL FACTORS	Repetitive hand/wrist use, vibrating tools, high job strain, low social support, female gender, increased BMI, aging	Modifiable risk factors, triggers for median nerve compression, interact with genetic and immune susceptibility	[6, 7, 16, 17]

Conclusion and Future Directions

This review shows that Carpal Tunnel Syndrome is a multifaceted condition resulting from a blend of genetic predisposition, immune system activation, and environmental influences. Our combined "triad of susceptibility" model offers a structure for comprehending how these areas interrelate to influence disease development. The findings indicate that genetic aspects affect connective tissue characteristics and reactions to oxidative stress, immune processes play a role in low-level inflammation and nerve sensitivity, while environmental factors serve as significant triggering elements.

This enhanced comprehension advances the discipline past a solely mechanical compression framework and paves the way for customized risk evaluation, focused prevention techniques, and possible immunomodulatory methods for particular patient groups. Future studies ought to focus on the integration of multi-omics and prospective validation of this combined model to move toward more accurate, mechanism-based management of CTS.

The combination of genetic, immunological, and environmental aspects into a cohesive "Triad of Susceptibility" framework has significant and relevant consequences for clinical practice. These insights allow a shift from a uniform approach to more individualized methods for prevention, diagnosis, and treatment.

Clinical Implications and Future Directions

The acknowledgment of significant genetic and immunological factors in CTS enables more advanced risk evaluation. High-Risk Occupational Screening: People in high-stress jobs may be screened for genetic susceptibility markers (e.g., COL5A1 polymorphisms, GSTM1 null genotype) to determine who would gain the most from rigorous ergonomic interventions, job rotation, or proactive workplace changes.

Proactive Counseling: Individuals with a significant family history of CTS or related autoimmune disorders may benefit from guidance on alterable risk factors, including weight control and steering clear of repetitive strain activities.

Enhanced Diagnostic and Prognostic Biomarkers

Present diagnosis largely depends on symptoms and electrodiagnostic tests, identifying nerve damage only after it has taken place. The immunological results present possibilities for earlier and more accurate diagnoses.

Inflammatory Subtyping: Serum biomarkers such as CCL5, VEGF, and particular T-cell profiles may assist in recognizing a unique "inflammatory CTS" subtype. This is especially significant for situations involving excessive pain or instances that return following surgery.

Prognostic Indicators: The relationship between memory T-cell levels and neurophysiological severity implies that these immune markers might aid in forecasting which cases are probable to advance, assisting in determining the timing of intervention.

New Treatment Paths Beyond Mechanical Decompression

For patients who do not adequately respond to conservative treatments or surgical interventions, the immunological discoveries present new therapeutic options:

Targeted Immunomodulation: Individuals showing substantial T-cell presence or increased pro-inflammatory chemokines may qualify for localized or overall immunomodulatory therapies. This method is backed by case studies demonstrating successful use of corticosteroids, methotrexate, or IVIG for CTS induced by immune checkpoint inhibitors.

Future research should focus on:

- Integrative Models: Conducting large-scale studies that simultaneously analyze genetic, immunological, and environmental data to identify high-risk patient profiles.
- Biomarker Development: Validating specific immune markers (e.g., CCL5, VEGF, T-cell subsets) as diagnostic or prognostic tools to distinguish inflammatory CTS subtypes.
- Targeted Therapies: Exploring immunomodulatory treatments for patients with evidence of immune dysregulation who respond poorly to standard therapy.
- Personalized Prevention: Using genetic and phenotypic risk assessment to tailor workplace ergonomic interventions for maximally susceptible individuals.

Moving beyond a purely mechanical understanding of CTS is essential for developing more effective, personalized prevention and treatment strategies in the future.

Take-Home Messages

1. CTS is multifactorial: Genetic, immunological, and environmental factors converge to determine individual susceptibility.
2. Genetic predisposition involves collagen, MMP, and GST polymorphisms that affect connective tissue resilience and oxidative stress handling.
3. Immune involvement may be subtle but significant, with systemic and local T-cell-mediated processes contributing to nerve damage.
4. Environmental factors such as repetitive movements, occupational stress, and wrist positioning are critical modifiable risks.
5. Pathophysiology is integrative: Elevated intracarpal pressure, ischemia, edema, and mechanical nerve deformation are influenced by underlying susceptibility.
6. Clinical implications: Understanding these three domains can improve risk stratification, guide personalized prevention strategies, and inform novel therapeutic approaches beyond surgical decompression.
7. Future directions: Large-scale, multi-omics studies are needed to validate integrative models and develop biomarkers for personalized CTS management.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, R.C. and A.C.; methodology, L.R.; software, R.P.; validation, T.C.S. and A.B.; formal analysis, C.E.B.; investigation, L.R.;A.B; resources, A.C.; data curation, G.D.S.; writing—

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