The role of genetic factors in carpal tunnel syndrome etiology: A review

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Abstract

The direct causes of idiopathic carpal tunnel syndrome (CTS) still remain obscure. It has been suggested that the pathology of tendons and other connective tissue structures within the carpal tunnel may be involved in its etiology. The objective of this study was to review the literature about the potential role of genetic factors in the etiology of CTS. Three different mechanisms are suspected to be involved in genetic predisposition to CTS: collagen synthesis, collagen degradation and protection against oxidative stress effect in connective tissue. Several gene groups are involved in the regulation and modulation of these mechanisms, and the research reviewed in this study showed their possible effect on the development of CTS. Variants within the *COL1A1*, *COL5A1* and *COL11A1* genes – encoding the synthesis of minor collagen subtypes – may potentially be involved, as they alter the mechanical properties of tendons and other connective tissue structures within the carpal tunnel. The collagen within connective tissue structures is also remodeled by matrix metalloproteinases (MMPs), so variants of these genes have also been investigated for their possible role in the risk of CTS development. Next, the variants of genes encoding glutathione S-transferase (GST) synthesis were found to be involved in the etiology of CTS. The findings from the abovementioned studies provide reliable information on the potential role of genetic risk factors in the development of CTS.

Key words: genetic factors, collagen synthesis, gene variants, carpal tunnel syndrome etiology

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Introduction

Carpal tunnel syndrome (CTS) is the most common compression neuropathy in the upper limbs. Mechanical compression and local ischemia result in symptoms of paresthesia (numbness and tingling), pain, and sensory and motoric disturbance along the median nerve.¹ The pathogenesis of most cases of CTS has not been determined. In the “idiopathic” syndrome, the direct cause of the increased pressure in the carpal tunnel is unknown. Among numerous concepts on pathogenesis of CTS, the possible involvement of tendons and/or other connective tissue structures within the carpal tunnel structure has been proposed.^{2–4} Considering the proximity of the 9 flexor tendons and the thick flexor retinaculum to the median nerve within the limited space of the carpal tunnel, it is not unlikely that pathology of these tendons or the retinaculum may contribute to CTS pathology. This concerns possible genetic factors which may influence the characteristics and regulation of collagen fibrils, which are the basic ingredient of connective tissue structures such as tendons, ligaments and bones.

Collagen is not a homogenous substance. Several subtypes of collagen have been identified, but type I is the one most commonly found in all connective tissue structures. Although the collagen fibril consists predominantly of type I collagen, several other quantitatively minor collagens, including types V, XI and XII, have been identified. These types were suspected as playing a possible role in regulating the formation and maintaining the structural integrity of the collagen fibril and surrounding matrix.² It has also been postulated that collagen types V and XI interact to regulate fibrillogenesis (the size and assembly of fibrils) during tendon development.⁵ Characteristic features of collagen, such as elasticity and endurance, may be related to the proportions of the minor types of collagen composing the fibrils of tendons and filaments. Changes in these properties may translate into modulation of pressure in the carpal tunnel, followed by the development of compression of the median nerve. Previous studies showed a relationship between variants in genes encoding the production and degradation of collagen and some inflammatory/overuse diseases of the connective tissue and increased risk of traumatic damage to the tendons and ligaments.^{6–10} The results of these studies prompted investigators to search for a possible association between selected gene variants and the risk of developing CTS.

Another mechanism which may be involved in the etiology of CTS is the activity of matrix metalloproteinase (MMP) genes.¹¹ It has been shown that the products of these genes play an important role in connective tissue remodeling through collagen fibril degradation. Previous studies showed an association between variants of these genes and tendon and ligament diseases, as well as susceptibility to tendon and ligament injury.^{12–16}

Oxidative stress is another mechanism suspected to be involved in the etiology of CTS. It was found to play a role in the development of systemic inflammatory diseases, diabetes and some malignancies. Previous research showed that oxidative stress as a result of overproduction of reactive oxygen and hydroxyl free radicals in synovial connective tissue around the carpal tunnel may result in tissue damage, edema and subsequent development of compression of the median nerve.¹⁷ Glutathione S-transferases (GST) are a large family of isoenzymes involved in the defense mechanisms against reactive oxidative stress. Variants in genes encoding production of these proteins were investigated as playing a possible role in the development of CTS.¹⁸

The objective of this study was to review the literature on the potential role of genetic factors in the etiology of CTS.

Material and methods

This article presents a review of the published literature from PubMed and MEDLINE databases on the role of genetic factors in the etiology of CTS. A search for Cochrane Reviews was performed, but we were unable to identify any relevant reviews on this topic. The keywords used when searching for articles were as follows: carpal tunnel pathomechanism, genetics, collagen synthesis, polymorphism, molecular mechanisms, COL genes, MMP genes, and oxidative stress. We attempted to ascertain the role of selected factors – such as collagen, MMP and GST gene variants – as risk factors in the development of CTS.

Results

The role of collagen gene variants

Previous studies have found that variants within the genes encoding for synthesis of collagen types I, V, XI, and XII may be implicated in their potential role in various musculoskeletal soft tissue disorders. It was shown that a variant within *COL1A1*, which encodes for $\alpha 1$ chain of type I collagen of type I collagen, is the functional Sp1 binding site polymorphism (rs1800012, G/T). The TT genotype was associated with the mechanical properties of tendons and ligaments, specifically with greater endurance of the anterior cruciate ligament in the knee joint.⁸ Likewise, variants of the *COL5A1* (rs71746744) and *COL11A1* (rs3753841, T/C and rs1676486, C/T) genes – encoding for type V and XI collagen – are involved in modulating the risk of chronic Achilles tendinopathy.⁷ The results of these studies prompted investigators to search for potential associations between variants of genes encoding for synthesis of minor collagen types and the risk of CTS development.

The following associations were found:

1. The presence of the T allele of the *COL11A1* gene (rs1676486) has been reported to be associated with decreased $\alpha 1$ (XI) collagen chain production, and by implication type XI collagen synthesis might be involved in the etiology of CTS.^{7,10}

2. The presence of T-C (AGGG) variants (rs3753841, rs1676486 and rs1746744) of the *COL5A1* and *COL11A1* genes is associated with altered mRNA stability, which results in altered type V and XI collagen synthesis. Both types of collagen regulate collagen fibril assembly and diameter; thus, these variants could alter the mechanical properties of tendons and other connective tissue structures within the carpal tunnel, which may be implicated in the etiology of CTS.^{3,7}

3. A significant association has been found between the single-nucleotide polymorphism TT of *COL11A1* (rs3753841, T/C) and increased risk of CTS development. This variant, located in exon 52, results in a non-synonymous amino acid exchange of leucine to proline at position 1323 of the $\alpha 1$ (XI) chain, whereas the rs1676486 variant located in exon 62 results in amino acid substitution from proline to serine at position 1535. The combination of alleles from these variants could potentially cause conformational changes in type XI collagen with a potential effect on the structural and functional properties of new collagen fibrils. These changes, through their effect on tendons and other connective tissue structures in the carpal tunnel, may be further implicated in the etiology of CTS.¹⁰

4. The abovementioned minor T allele variant of *COL1A1* (rs1800012, G/T), which encodes for the $\alpha 1$ chain of type I collagen, was significantly associated with an increased risk of CTS among women. The substitution of a tyrosine with a guanine nucleotide within the Sp1 binding site of intron 1 of *COL1A1* has been suggested to result in an increased binding affinity for transcription factor Sp1. This results in *COL1A1* gene expression and the overproduction of type I collagen homotrimers consisting of 3 $\alpha 1$ chains. Increased amounts of type I collagen homotrimers in tendons and other connective tissue structures is believed to change their mechanical characteristics in terms of susceptibility to injury. These changes may also be implicated in the development of increased pressure in the carpal tunnel.^{3,6}

Dada et al. reported the results of their genetic studies performed on a self-reported Colored South African population. One hundred and three participants with a history of carpal tunnel release surgery and 150 matched control participants, without any reported history of CTS symptoms, were genotyped for *COL1A1* rs1800012 (G/T), *COL11A1* rs3753841 (T/C), *COL11A1* rs1676486 (C/T), *COL11A2* rs1799907 (T/A), and *COL12A1* rs970547 (A/G). It was shown that the TT variant of *COL11A1* rs3753841 was statistically significantly overrepresented among CTS patients in comparison with the control group (21.4% vs 7.9%; $p = 0.004$). A trend for the T minor allele

to be overrepresented in the CTS group ($p = 0.055$) was also observed with statistically significant differences ($p = 0.036$) when only women were considered in the analysis. The authors believe that constructed inferred variants, including the previously mentioned *COL5A1* gene variant rs71746744 (AGGG), suggest that gene–gene interactions between *COL5A1* and *COL11A1* modulate the risk of developing CTS.³

Findings from the abovementioned studies provide reliable information on the potential role of genetic risk factors and the possible role of variations of collagen fibril composition in the etiology of carpal tunnel syndrome. Genetic factors can potentially be included in models developed to identify individuals at risk of CTS.

The effect of variants of MMP genes on chromosome 11q22

In the previous paragraph, the association between some variants of genes encoding the synthesis of collagen and the risk of developing CTS was discussed. However, the final properties of collagen are also related to other factors. The collagen fibrils within connective tissue structures are remodeled by a family of endopeptidases called MMPs,¹¹ among other proteins. The following roles of MMPs in the modulation of collagen degradation have been identified^{12–15}:

- MMP3 and MMP10 are involved in the degradation of several collagens, including type V, proteoglycans and other extracellular matrix proteins.
- These MMPs also have the potential to activate several pro-MMPs.
- MMP1 is responsible for degrading the triple-helical region in most collagens.
- MMP12 is responsible for degrading elastin and other extracellular matrix proteins.

Several studies have reported a significant association of *MMP3* gene variants with chronic Achilles tendinopathy: AA *MMP3* rs679620 (A/G, E45 K), CC *MMP3* rs591058 (T/C) and AA *MMP3* rs650108 (G/A).¹³ An inferred haplotype constructed from MMP variants *MMP10* rs486055 (C/T, R5 3), *MMP1* rs1799750 (G/GG), *MMP3* rs679620 (A/G), and *MMP12* rs2276109 (A/G), which are clustered together on chromosome 11q22, was found to be associated with modulation of the risk of anterior cruciate ligament ruptures in the knee joint.^{14,16} Considering the potential effect of MMPs on homeostasis of soft tissue and their structures (tendons and ligaments), studies were commenced to investigate a possible association between various MMP variants and the risk of CTS development. The 4 variants of MMPs were particularly suspected because of previously reported associations with other musculoskeletal diseases and because of their potential functions – the ability to degrade various types of collagens. The *MMP1* rs1799750 (G/GG) variant consists of the presence (GG) or absence (G) of an extra guanine

nucleotide at position 1607 bp. The GG variant creates an Ets binding site that leads to increased transcription of the *MMP1* gene compared to the allele without an extra G nucleotide. The *MMP12* rs2276109 (A/G) variant modulates the binding of the transcription factor activator AP-1 protein, which regulates *MMP12* expression. Variants *MMP3* rs679620 and *MMP10* rs486055 result in a single-nucleotide substitution that causes an amino acid change in proteins – the products of these genes.^{11,15} The specific consequences of these amino acid substitutions are unknown, but previous studies have suggested potential associations with tendon and ligament diseases, susceptibility to tendon and ligament injuries, and the risk of CTS development.

Burger et al. reported the results of genetic studies on a self-reported Colored South African population: 97 women with clinically and electrophysiologically confirmed CTS and 131 healthy volunteers without any history of CTS symptoms were genotyped for 4 MMP gene variants: *MMP10* rs486055 (C/T), *MMP1* rs1799750 (G/GG), *MMP3* rs679620 (A/G), and *MMP12* rs2276109 (A/G). The results of this genotyping showed no independent association between these gene variants and CTS (negative outcome). Furthermore, no significant association was found between any of the inferred haplotypes constructed from these variants and CTS.¹² However, this finding does not exclude other variants within the same or other MMP genes within this locus from potentially being associated with the risk of CTS. Several other MMP genes, including *MMP7*, *MMP8*, *MMP13*, and *MMP20*, are located on the long arm of chromosome 11, close to the previously investigated genes. The *MMP3* 5A/6A variant has been associated with several multifactorial conditions and was found to be involved in the regulation of MMP gene expression.¹⁶ The authors suggest that these gene variants may be reasonable CTS candidates for future studies. Also, the use of next-generation sequencing technologies, i.e., targeted sequencing, in identifying additional potentially associated variants within the MMP cluster may yield positive results. It should be noted that the abovementioned study was based on a specific population and that the number of participants was relatively small. Therefore, further studies of other variants of the roles of MMP genes in modulating the risk of development of CTS, based on a European population and involving a greater cohort of patients, seems to be justified.

The role of GST variants

Another mechanism suspected to be involved in the development of idiopathic CTS is oxidative stress as a result of overproduction of free oxygen ($\cdot\text{O}$) and hydroxyl ($\cdot\text{OH}$) radicals in the sub-synovial soft tissue of tendons and ligaments.^{17,18} Increased synthesis or insufficient elimination of reactive oxygen species (ROS) may cause damage to soft tissue structures and may be an underlying mechanism in the development of systemic inflammatory

diseases and malignancies. There are several substances known as antioxidants or radical scavengers which exhibit properties that eliminate free radicals, including vitamins (C, D and E), amino acids (N-acetylcysteine), hormones (steroids), and mannitol. There are also several enzymes with this potential, such as peroxidase, catalase and GSTs (oddly enough, hydroxyl radicals do not have their own natural detoxifying mechanisms). The GSTs are a large family of isoenzymes involved in the defense mechanism against the cytotoxic activity of ROS by inactivating their secondary metabolites. The most investigated isoenzyme members of this family are GST-mu1 (GSTM1), GST-theta1 (GSTT1) and GST-pi1 (GSTP1). They are suspected of playing a protective role against oxidative stress-related development of systemic inflammatory diseases and malignancies.¹⁹ The most common GSTM1 and GSTT1 polymorphisms are deletions in these genes, resulting in a lack of enzyme function. Another frequent polymorphism in this group is *GSTP1* Ile105Val, of which the Ile105Val/Val (AG) and Ile105Val/Val (GG) variants result in reduced enzymatic activity in comparison with that of the Ile105Val/Val (AA) variant.²⁰ Several studies have demonstrated an association between some GST family isoenzyme variants and rheumatoid diseases, diabetes and malignancies in whose pathogenesis ROS are involved.¹⁹ The results of these studies prompted investigators to search for potential associations between variants of GST genes and the risk of developing CTS.

Eroğlu et al. reported the results of their study of the incidence of 3 GST variants – *GSTM1*, *GSTT1* and *GSTP1* Ile105Val – in a Turkish population of CTS patients and controls ($n = 140$ and $n = 97$, respectively). The incidence of *GSTT1* and *GSTM1* variants was determined using the polymerase chain reaction (PCR) method, whereas PCR-restriction fragment length polymorphism (PCR-RFLP) was used to detect the *GSTP1* Ile105Val variant. The researchers found a statistically significant ($p = 0.01$) higher incidence of the *GSTM1*-null variant in CTS patients compared to the healthy controls. Moreover, the *GSTM1*-null variant was associated with an approximately twofold increase in the risk of CTS. The combination of the *GSTM1*-null and *GSTT1* variants was also more prevalent in CTS patients, but it was of borderline statistical significance ($p = 0.045$) and did not increase the risk of CTS development. The authors also reported a statistically significant association between greater clinical severity of CTS (in terms of higher Levine questionnaire scores) in patients with the *GSTP1* Ile/Val and Val/Val variants compared to *GSTP1* Ile/Ile, which was more frequent in patients with clinically milder disease.¹⁸ The authors suggest that future studies investigating the potential role of GST variants in the development of CTS are justified.

Fernandez-de-Las-Penas et al. investigated the association of the Val158Met polymorphism with treatment outcomes in 120 female patients with CTS who received either surgery or manual therapy. The patients were randomly allocated to the treatment methods: 60 patients received

3 sessions of manual therapy and 60 underwent carpal tunnel release ($n = 60$). The rs4680 genotypes were determined after amplifying the Val158Met polymorphism with PCR. The subjects were classified according to their Val158Met polymorphism: Val/Val, Val/Met or Met/Met. Final outcomes were assessed 12 months after the intervention. No interaction was observed between the Val158Met genotype and any outcome: pain, symptom or function severity.²¹

Cevik et al. investigated the influence of interleukin 1 (IL-1) receptor antagonist (IL-1Ra) and angiotensin-converting enzyme (ACE) I/D polymorphisms on the susceptibility to CTS in 158 patients and 151 healthy controls. No statistically significant association was found between gene polymorphisms and the risk of developing CTS.²²

Discussion

Three different mechanisms are thought to be involved in genetic predisposition to CTS: collagen synthesis, collagen degradation and protection against the effects of oxidative stress in connective tissue. Several gene groups are involved in the regulation and modulation of these mechanisms and the studies presented herein demonstrated that they may be associated with the etiology of CTS. There are some interesting aspects of the disease which suggest the potential effect of genetic predispositions to its development^{23–25}:

- early onset of CTS in adolescents and young adults;
- familial occurrence – most of the members of the family have been affected;
- familial occurrence – higher incidence of the condition among relatives of some patients than in the general population;
- bilateral manifestation of CTS.

None of studies conducted to date have dealt with these specific aspects of the syndrome; therefore, additional investigations in this field seem to be promising. Another unexplored aspect of the genetic predisposition to CTS is that most studies have been based on non-European populations (South African, Turkish and Brazilian). It is known that the incidence of specific mutations may differ among races, so investigation into the abovementioned associations between selected gene variants and the risk of CTS in Caucasians seems to be justified.

Conclusions

The findings from the studies reviewed in this paper provide reliable information on the potential role of genetic risk factors in the development of CTS. None of the studies conducted to date have dealt with these specific aspects of the syndrome, thus additional studies in this field seem to be appropriate.

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