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The effect of genetical factors on the risk of carpal tunnel syndrome occurrence: a review

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ABSTRACT

Carpal tunnel syndrome (CTS) is the most common compression neuropathy in the upper limb. Mechanical compression and local ischemia of the median nerve result in paresthesia, pain, and sensory and motoric disturbances. There are some aspects of the disease that suggest the potential role of genetic predispositions. This article presents a review of the literature about the significance of genetic factors in the etiology of CTS. It discusses the effect of selected gene mutations on constitutional and anthropometric features which may predispose to CTS. These genes are involved in the organization of an extracellular matrix architecture, as well as in bone, cartilage, and tendons development pathways. Therefore they may be potentially responsible for the observed relationship between anthropometric/constitutional factors and CTS.

The findings from the studies provide reliable information on the association between genetic risk factors and the development of CTS.

Keywords: carpal tunnel syndrome etiology; carpal tunnel syndrome – genetic predispositions; collagen synthesis; *ADAMTS* genes; *COL* genes.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common compression neuropathy in the upper limb. Mechanical compression and local ischemia results in symptoms of paraesthesia (numbness, tingling), pain, and sensory and motoric disturbance along the median nerve [1]. The pathogenesis and molecular basis of most cases of CTS is not determined and the direct cause of an increase of pressure in the carpal tunnel is not known. Carpal tunnel syndrome is mostly sporadic (idiopathic), however familial occurrence is estimated at about 17–40%, suggesting a possible genetic predisposition [2, 3]. A heritability of 0.46 for CTS was shown in 1 study on twins, again suggesting an association between genetic factors and risk of CTS [4]. There are some interesting aspects of the disease, suggesting the potential effect of genetic predispositions to its development: early onset of CTS in adolescents and young adults; familial occurrence where most of the members of the family have been affected; familial occurrence in terms of higher incidence of the condition among relatives of some patients than in the general population; and bilateral manifestation of CTS [3]. Among numerous pathogenetic concepts of CTS, the possible involvement of tendons and/or other connective tissue structures within the carpal tunnel structure has been proposed. This concerns possible genetic factors which may influence the characteristic and regulation of collagen fibrils, which are the basic ingredient of connective tissue structures such as tendons, ligaments, and bones. A few non-syndromic CTS pedigrees with autosomal and dominant inheritance have been reported, but no causal genes or *loci* have been identified. Variants in some genes such as *ADAMTS*, *COL* family, *MMP*, and *COMP* are suspected as being associated with the risk of sporadic CTS [3].

The aim of this article was a review of the literature on the role of genetic factors in CTS etiology. Keywords used in searching articles were: carpal tunnel syndrome, anthropometric phenotypes, genetical predisposition, collagen synthesis, and *ADAMTS*, *EFEMP*, *MMP*, *COL*, and *COMP* genes.

THE RELATIONSHIP BETWEEN GENETIC FACTORS AND CTS-ASSOCIATED PHENOTYPES

The relationship between constitutional, anthropometric, and anatomical features and the risk of development of CTS is well established. The most known traits include short stature, increased body mass index (BMI), short hands, and 'squared' wrists. It has been demonstrated that women suffering from CTS are shorter, heavier, and have higher BMI than the general population [1]. It is also suggested that a specific anatomical configuration with short hands and 'squared' wrists predisposes the median nerve to greater compression. Results of the study of Wiberg et al. show that the expression of 3 genes: *ADAMTS17*, *ADAMTS10*, and *EFEMP1* may be associated with some anthropometric features, first of all with short stature, and this may contribute to CTS predisposition [5].

The ADAMTS proteins are a family of multidomain, secreted extracellular proteolytic enzymes related to matrix metalloproteinases (MMP) which are involved in extracellular matrix maintenance by splitting of procollagen and proteoglycans. These enzymes play a role in various cellular mechanisms, such as cell adhesion, migration, and death. They also are involved in the remodelling of the collagen fibrils within connective tissue structures [3, 6]. Several roles of MMP in the modulation of collagen degradation have been demonstrated. For instance, MMP3, MMP10,

and stromelysins are involved in degradation of several collagens, proteoglycans, and other extracellular matrix proteins. The MMP1 is responsible for degrading the triple-helical region in most collagens, and MMP12 is responsible for the degradation of elastin and other extracellular matrix proteins [7, 8, 9, 10]. Results from several studies show a significant association of MMP3 gene variants: *AA MMP3* rs679620, *CC MMP3* rs591058 (T/C), and *AA MMP3* rs650108 (G/A) with chronic Achilles tendinopathy [3].

With regard to the *ADAMTS* family, an overexpression of *ADAMTS17* and *ADAMTS10* genes has been demonstrated in connective tissue, muscles, and bones in patients with anthropometric phenotypes predisposing to CTS (high BMI and low height). A Mendelian randomization analysis showed that CTS patients were on average 2 cm shorter than controls [5]. Results of some studies revealed mutations in the *ADAMTS* genes family to be present in patients with some congenital syndromes characterized with short statute, brachydactylic, joint stiffness, and eye anomalies. Patients burdened with these syndromes frequently suffer from bilateral CTS [10].

Gene-based enrichment analysis has demonstrated the overexpression of *ADAMTS17, ADAMTS10*, and *EFEMP1* genes in the tenosynovial tissue excised from the carpal tunnel of CTS patients. This finding may suggest the role of these genes in stimulating excessive collagen synthesis that can lead to the thickening of tenosynovium of the tendons within the carpal tunnel. This, in consequence, can increase pressure in the carpal tunnel [11].

THE ROLE OF EXTRACELLULAR MATRIX COMPONENTS WITHIN THE MEDIAN NERVE

Gene-property analysis found that tibial nerve Schwann cells and transformed fibroblasts were the 2 tissues that showed high enrichment of *ADAMTS17* gene variants [12]. Schwann cells form a basement membrane composed of extracellular matrix which is essential for myelination. An upregulation of *ADAMTS17* was shown in the distal nerve stump after a nerve crush and this expression is related to expression of neuregulin-1, a growth-factor protein that is strongly involved in remyelination and nerve regeneration [11]. An increased expression of *ADAMTS17* has been shown in human cultured Schwann cells compared to human fibroblasts, which suggests that variation in the *ADAMTS17* gene may restrain the recovery of the median nerve after a carpal tunnel release [11].

THE ROLE OF *EFEMP1* IN THE DEVELOPMENT OF CARPAL TUNEL SYNDROME

EFEMP1 gene is involved in the creation of an extracellular matrix architecture, as well as in bone and cartilage development pathways. Therefore, it may be potentially responsible for the observed relationship between anthropometric/constitutional factors and CTS. It has been demonstrated in some studies that variations in the *EFEMP1* gene may be associated with adult height, inguinal hernia, and some neoplasms [13].

THE ROLE OF *COL* GENES FAMILY VARIANTS IN THE DEVELOPMENT OF CARPAL TUNEL SYNROME

Results of some studies show that variants within the genes encoding some subtypes of collagen synthesis (*COL* genes family) may predispose to various musculoskeletal soft tissue disorders. It has been proven that a variant within the *COL1A1* gene which encodes for α1chain of type I collagen, is the functional Sp1 binding site polymorphism (rs1800012, G/T). The TT genotype has been associated with the mechanical properties of tendons and ligaments, specifically with greater endurance of the anterior cruciate ligament in the knee joint. 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 the modulation of the risk of chronic Achilles tendinopathy [14]. The results of these studies prompted investigators to search for potential associations between variants of genes encoding synthesis of minor collagen subtypes and the risk of CTS development. The effects of variants of *COL* genes family on the synthesis of minor collagen subtypes were shown in Table 1.

TABLE 1. The effect of variants of *COL* genes on synthesis of minor collagen subtypes

Gene variant	Effect on the synthesis of minor collagen subtypes
Presence of T allele of *COL11A1* rs1676486 gene	decreased α1(XI) collagen chain production
Presence of T-C (AGGG) variants (rs3753841, rs1676486 and rs1746744) of *COL5A1* and *COL11A1* genes	altered mRNA stability which results in altered type V and XI collagen synthesis
Presence of SNP TT of *COL11A1* (rs3753841, T/C) gene localized in exon 52	non-synonymous amino acid change of leucine to proline at position 1323 of the α1(XI) chain
Presence of SNP TT of *COL11A1* (rs1676486) variant localized in exon 62	amino acid substitution from proline to serine at position 1535
Presence of T allele variant of *COL1A1* (rs1800012, G/T) gene	overproduction of type I collagen homotrimer consisting of 3 α1(I) chains
The substitution of tyrosine with a guanine nucleotide within the Sp1 binding site of intron 1 of *COL1A1* gene	increased binding affinity for the transcription factor Sp1

The presence of the T allele of *COL11A1* rs1676486 gene, T-C (AGGG) variants (rs3753841, rs1676486, and rs1746744) of *COL5A1* and *COL11A1* variants 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 CTS etiology [14, 16]. Presence of single nucleotide polymorphism TT of *COL11A1* (rs3753841, T/C). The combination of alleles from these variants may cause changes in type XI collagen with an effect on the structural and functional properties of arising collagen fibril. These changes, via their effect on tendons and other connective tissue structures in

the carpal tunnel, may be further implicated in CTS etiology [15]. The minor T allele variant of *COL1A1* (rs1800012, G/T) gene, which encodes for α1chain of type I collagen was significantly associated with an increased risk of CTS among women. The substitution of 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 the transcription factor Sp1. This results in *COL1A1* gene expression and the overproduction of type I collagen homotrimer consisting of 3 α1(I) chains. Increased amounts of type I collagen homotrimers in tendons and other connective tissue structures are believed to change their mechanical characteristics in term of susceptibility to injury. These changes may also be implicated in the development of increased pressure in the carpal tunnel [16, 17].

ASSOCIATION BETWEEN MUTATIONS IN CARTILAGE OLIGOMERIC MATRIX PROTEIN GENE AND RISK OF CARPAL TUNEL SYNDROME

Li et al. report 2 mutations in the cartilage oligomeric matrix protein (*COMP*) gene in 2 large families which were associated with CTS and multiple epiphyseal dysplasia. COMP is a non-collagenous extracellular matrix protein that plays a role in matrix assembly and organization through interactions with other extracellular matrix proteins, such as collagen I, III, and IX. Numerous mutations in *COMP* were identified in patients with multiple epiphyseal dysplasia and pseudochondroplasia. Both mutations discovered by Li et al. impair the secretion of COMP by tenocytes but the mutation associated with multiple epiphyseal dysplasia also disturbs protein secretion in chondrocytes. The *COMP* is expressed primarily in cartilage, tendons, and ligaments supporting the pathogenic role of mutant *COMP* in connective tissue disorders. Results of this study showed that cell-type specific regulation of mutant *COMP* secretion explains tissue-specific effects of *COMP* mutations affecting distinct domains. Mutant COMP complexes are poorly secreted by tendons and ligaments cells, whereas chondrocyte secretion remains unchanged. Mutant COMP is associated with abnormal activities in causing cell death and disrupting the extracellular matrix niche in tendons and ligaments which reduces their capacity to repair. Without sufficient repair activity and with continued inflammation, fibroblasts and other types of cells accumulate and the composition of extracellular matrix changes, resulting in the swelling and thickening of soft connective tissues. This subsequently causes the compression of neighboring structures, such as the median nerve in the carpal tunnel. The results of the study by Li et al. reveal a pathogenic mechanism leading to the development of CTS and emphasize the importance of genetic mutations in the extracellular matrix genes in this syndrome [18].

CONCLUSION

The findings from the studies analyzed in this review provide reliable information on the potential role of genetic risk factors in the development of CTS. It particularly concerns the relationship between the expression of some genes and anthropometric features, first of all, short height, because this may contribute to CTS predisposition. None of the studies conducted to date have dealt with these specific aspects of the syndrome and therefore additional investigations in this field seem to be promising.

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