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Review article

Uncovering Carpal Tunnel Syndrome Risk through Genetics: A Path to Early Prevention

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Abstract

Carpal Tunnel Syndrome (CTS) is a common disorder that affects the hand, caused by compression of the median nerve at the wrist. Despite its prevalence and impact on individuals, the underlying biological mechanisms of CTS remain poorly understood. Moreover, there is a lack of strategies for identifying individuals at risk for CTS in order to prevent its development. In recent years, the use of genome sequencing, genetic analysis, and genome-wide association studies (GWAS) has revealed several genetic factors that may be associated with CTS, including specific genes and gene loci. A Genetic Risk Score (GRS) that incorporates these findings could potentially be used to predict the likelihood of developing CTS and enable earlier identification and prevention of the condition. GWAS has already demonstrated a correlation between CTS severity and a GRS composed of 13 susceptibility loci. Further research on the development of a more comprehensive GRS for CTS could potentially reduce the overall burden of this disorder.

Keywords: ***Genetics, Single Nucleotide Polymorphism, Carpal Tunnel Syndrome, Primary Prevention.***

Introduction

The rapid progress of technology, particularly the sequencing of the human genome in 2001 (Lander et al.), has facilitated the identification of various DNA variations that increase the risk of multiple diseases. Many common diseases have a strong genetic component that was previously difficult to explore, but recent advances such as the HapMap project (Gibbs et al., 2003) and the widespread use of Single Nucleotide Polymorphisms (SNPs) as genetic markers have enabled the application of Genome-Wide Association Studies (GWAS). This review aims to summarize these genetic discoveries and explore how they can be utilized for early prediction of disease risk, with a focus on Carpal Tunnel Syndrome (CTS). CTS is a prevalent and debilitating disorder of the hand caused by compression of the median nerve at the wrist, and early detection and intervention may be beneficial. While CTS has been linked to several risk factors and genetic susceptibility loci, there is currently no comprehensive approach to identifying individuals at risk before the onset of CTS symptoms. This review will discuss the limitations of identifying individual risk factors for predicting CTS and how the use of genetic risk prediction could enable primary prevention of the disease. The results of GWAS and gene analysis studies demonstrating the reliability of using genetic risk for CTS to predict the development and severity of the condition will also be summarized.

The Human Genome

The human genome is a complex and intricate structure that plays a crucial role in determining the unique traits and characteristics of each individual. Comprised of a double helix DNA strand containing 3.2 billion bases, the genome codes for the proteins that make us who we are. While it is well known that only about 1% of the genome serves as a template for protein synthesis, recent research has shed light on the important role that the non-coding genome plays in modulating DNA expression and protein synthesis through the production of non-coding RNA. As a result of non-coding RNA binding to the 3' end of mRNA (and through alternative mechanisms), protein expression can be modified and therefore so can the phenotype of an individual.

Another key factor contributing to the unique features of each person is through single nucleotide polymorphisms (SNPs), which are variations in the genome that arise due to errors in the DNA replication process. While DNA replication is a highly precise process, with an error rate of approximately one error per billion bases generated, copy errors do still occur. When they occur in germline cells, the resulting differing DNA is transmitted to the next generation. SNPs are evenly distributed throughout the genome and are estimated to number around 5 million per genome (Levy et al., 2007), with 96% of them being single nucleotide polymorphisms, 2% being doublets or triplets, and the remaining 2% potentially consisting of several nucleotides (Bhangale et al., 2005).

Studies have shown that SNPs, which are thought to play a significant role in determining an individual's unique characteristics such as skin color and disease susceptibility (Stranger et al., 2007), are also involved in the development of carpal tunnel syndrome (CTS), a common entrapment neuropathy. CTS is often seen to occur more frequently in individuals with a family history of the condition and in women compared to men (Atroshi et al., 1999; Hakim et al.,

2002; Radecki, 1994). These findings highlight the complexity and importance of the human genome and the crucial role that SNPs play in shaping our individual traits and characteristics.

Genome Wide Association Studies

Rapid advances have been made in our understanding of the genetic basis of human disease, particularly starting in the 1980s with the discovery of Mendelian genes (Marian et al., 2016), or genes responsible for single-gene disorders. These disorders are relatively rare, occurring in less than 1% of the population, but they often have a high penetrance and are responsible for a dominant expression of the phenotype. The identification of these genes was facilitated by the use of genetic linkage analysis, which allowed for the localization of the chromosomal locus of the responsible gene and the subsequent cloning and sequencing of the region to identify the precise gene and its mutation.

In contrast to Mendelian disorders, polygenic disorders are caused by the interaction of multiple genes, each of which contributes only minimally to the phenotype. These disorders are far more common and are significantly influenced by environmental and lifestyle factors, often making them more difficult to categorize. It was recognized very early on that genetic linkage analysis would not be the appropriate approach to pursue the study of polygenic disorders.

Several key advances have made it possible to investigate the genetic architecture of polygenic diseases, including coronary artery disease and carpal tunnel syndrome (CTS). The initial discovery of the human genome (Venter et al., 2001) and the annotation of millions of single nucleotide polymorphisms (SNPs) by HapMap (International HapMap Consortium et al., 2007) provided DNA markers that were distributed throughout the genome. These SNPs allowed for the development of genome-wide association studies (GWAS) (Hirschhorn and Daly, 2005), in which large populations of cases and controls were genotyped using millions of SNPs as markers. The use of rapid genotyping techniques made it possible to genotype large populations on a scale not previously possible. The use of millions of markers required statistical correction to the conventional p-value of 0.05, and it was generally agreed that a Bonferroni corrected p-value of 10^-8, referred to as genome-wide significant risk (Risch and Merikangas, 1996), would be adopted. In addition, markers that reached a p-value of 10^-8 were required to be replicated in an independent population.

GWAS has been used to investigate a range of conditions, including CTS. For example, a GWAS of CTS identified a locus on chromosome 2, known as DIRC3, that was significantly associated with both CTS and trigger finger (Patel et al., 2022). This finding suggests that insulin-like growth factor-1 (IGF-1) may be a driver of both conditions and may explain their co-occurrence in some cases. More broadly, GWAS has been used to investigate the genetic relationships between CTS and other phenotypical traits or comorbidities. In a meta-analysis of CTS conducted in 2022, 40,000 cases from four different populations were combined and 53 variants associated with CTS were identified at 50 loci (Skuladottir et al., 2022). Associated factors included, but were not limited to: height, body mass index, osteoarthritis, and restlessness. These findings demonstrate the utility of GWAS in analyzing the genetic relationships within and between different conditions and traits.

Discovery of genetic variants of CTS

Despite being a prevalent condition, the etiology of CTS is largely unknown and it is thought to be multifactorial, with both genetic and environmental factors contributing to its development.

Recent genetic studies have helped to shed light on the genetic basis of CTS. One such study found that variants of the COL5A1 gene, which is involved in the regulation of fibril assembly in tendons, are associated with an increased risk of CTS (Burger et al., 2015). Specifically, the BGN variant was found to be significantly more prevalent in the control group compared to individuals with CTS, indicating a negative correlation between BGN and CTS (Burger et al., 2014).

Other collagen genes have also been linked to CTS. A study found that the rs3753841 variation of the homozygous T genotype of the collagen gene COL11A1 was significantly more prevalent in patients with a history of CTS when compared to the control group (Dada et al., 2016). Additionally, variations within the 3'-untranslated region (3'-UTR) of COL5A1 have been found to be associated with CTS (Burger et al., 2015).

Enhanced expression of Wnt9a signaling has also been found to be associated with idiopathic CTS (ICTS). One study found that there was a positive correlation between Wnt9a signaling in ICTS patients compared to controls, indicating increased expression of Wnt9a in ICTS (Yamanaka et al., 2015). However, more research is needed to confirm these findings.

Other genetic factors that have been linked to the development of CTS include genes involved in monocyte attraction into the tenosynovium, such as monocyte chemoattractant protein-1 (MCP-1) (Omori et al., 2002). Genome-wide association studies (GWAS) have also helped to identify new genetic risk variants for CTS. For example, a GWAS looking at both CTS and trigger finger found similarities on chromosome 2, specifically the DIRC3 locus, which was associated with both conditions (Patel et al., 2022). These findings suggest that IGF-1 may be a driver of CTS due to the role of IGBP5 as an IGF-1 antagonist.

Overall, these genetic studies have provided valuable insights into the genetic basis of CTS and may ultimately lead to improved prevention and treatment of this common disorder.

Why the Genetic Risk Score (GRS) can be advantageous

The growing body of literature on the genetics of CTS (carpal tunnel syndrome) suggests that there are multiple genetic risk variants that predispose individuals to the condition, which is the most prevalent form of entrapment neuropathy and a significant contributor to work-related injuries. According to Daghlas et al., the annual cost of medical services for CTS exceeds $2 billion. Anna et al. found that "blue-collar" work, especially when involving repetitive or strenuous tasks, is a moderate to strong risk factor for surgically treated CTS in both sexes. Other known risk factors for CTS include BMI (body mass index) and diabetes mellitus (DM), as demonstrated by McCarthy et al. and Mi et al., respectively. In particular, Madani et al. found that BMI is a strong risk factor for CTS, and it has been hypothesized by Daghlas et al. that the link between BMI and CTS may be mediated by DM. DM can lead to diabetic neuropathy, which can in turn increase the likelihood of CTS due to changes in blood vessels and tendons around nerves, as well as nerve damage caused by high blood glucose levels (Burger et al., Paiva et al.). Weight loss and treatment of DM have been proposed as potential remedies for CTS (Burger et al., Mi et al.), although these would be secondary prevention measures that would be implemented after the onset of symptoms. Primary prevention of CTS, on the other hand, involves workplace modifications such as the use of wrist pads and belts for computer mouse use, which have been found to improve wrist posture and comfort (B. -S et al.). Another potential avenue for primary prevention is the use of genetic risk scores, which can be obtained through DNA samples and used to identify individuals with a genetic predisposition for CTS at birth, allowing healthcare providers to implement preventative measures to mitigate conventional risk factors and engage in further primary prevention.

Developing the Genetic Risk Score (GRS)

The literature suggests that CTS (carpal tunnel syndrome) is influenced by a complex interplay of gender, environmental, and occupational factors, as well as genetic influences, as evidenced by twin studies and family history reports (Jeon et al). To further explore the role of genetics in CTS susceptibility, a genome-wide association study (GWAS) was conducted using 12,312 individuals with CTS and 389,344 control subjects from the UK Biobank. This study identified 16 susceptibility loci ($p< 5 \times 10-8$) that were subsequently used to develop a weighted genetic risk score (wGRS) calculated as the weight of the single nucleotide polymorphism (SNP) multiplied by the number of effect alleles (Wiberg A 2019).

A subsequent meta-analysis, which included data from the UK Biobank GWAS as well as other sources such as the Iceland deCODE genetics, Denmark Danish Blood Donor Study, the Copenhagen Hospital Biobank, and Finland FinnGen, expanded the sample size to 48,843 individuals with CTS and 1,190,837 control subjects. This meta-analysis employed a polygenic risk score (PRS) calculated using 611,000 high-quality variants across the genome, along with linkage disequilibrium data from 15,000 Icelandic samples to increase the accuracy of the PRS. Based on these analyses, 53 variants were found to be associated with CTS, and the effect estimates from the meta-analysis were used to determine the PRS (Skuladottir AT 2022).

Some of the SNPs identified by the GWAS are located in or near genes such as ADAMTS10, ADAMTS17, and EFEMP1, which have been implicated in musculoskeletal growth and connective tissue development, potentially contributing to the pathogenesis of CTS (Wiberg A 2019). Therefore, a wGRS or PRS derived from a GWAS may be useful in predicting an individual's susceptibility to developing CTS and the potential severity of the phenotype, as the risk is proportional to the inherited weight of the SNPs.

Evaluation of the Genetic Risk Score (GRS) in Clinical Trials

According to the findings of the UK Biobank GWAS (Wiberg A, 2018), the efficacy of using a weighted genetic risk score (wGRS) based on associated loci identified in the study to calculate the polygenic susceptibility to CTS was demonstrated by categorizing individuals into four subgroups: (1) all CTS cases, (2) all controls, (3) CTS cases with at least one operation code, and (4) CTS cases with no operation code, and then calculating the mean wGRS for each group. The results showed that the wGRS was significantly higher in CTS cases (mean score of 1.620) compared to control cases (mean score of 1.566), as expected. Additionally, the wGRS was significantly higher in the operated CTS group (mean score of 1.622) compared to the unoperated CTS group (mean score of 1.586), indicating that the wGRS derived from the GWAS effectively correlates to the severity of CTS and supports the hypothesis that a greater number of risk alleles is associated with a more severe phenotype.

According to the findings of the meta-analysis conducted by Skuladottir AT (2022), which combined data from Iceland, the UK, Denmark, and Finland, a CTS polygenic risk score (PRS) was constructed to examine the degree of genetic tendency among different groups of CTS cases based on suggested clinical disease severity. The CTS PRS was then applied to five groups, including all CTS cases, nonrecurrent or nonpersistent CTS cases, bilateral, recurrent, or persistent CTS cases, CTS cases that have undergone surgery, and CTS cases that were diagnosed with CTS after surgery, in order to estimate the effect size. The results indicated that the GWAS-derived PRS score for the bilateral, recurrent, or persistent CTS cases was higher than the nonrecurrent and nonpersistent CTS cases, as anticipated. This suggests that the PRS effectively captures the genetic susceptibility to CTS and the severity of the phenotype, with a higher PRS score corresponding to a greater degree of genetic tendency and a more severe phenotype.

Limitations of the Genetic Risk Score (GRS)

The genetic basis of carpal tunnel syndrome (CTS) is a complex interplay of various factors, including gender, environmental, occupational, and genetic influences, as demonstrated by twin studies and family history reports (Burger et al., 2002; Dada et al., 2004; Peeters et al., 2006). The utilization of genetic risk scores (GRS) has shown promising results in predicting the risk of developing CTS and holds potential for future clinical applications (Sukaldottir et al., 2022). However, several limitations currently hinder the ability to fully utilize GRS for predictive value in a clinical setting.

One significant limitation is the prevalence of small sample sizes in many clinical studies examining the genetic basis of CTS. These small sample sizes can reduce the statistical power of a study, making it less likely to detect true associations between genetic variations and the risk of developing CTS. For example, studies exploring the relationship between CTS and matrix metalloproteinases or collagen/fibrillin variants have sample sizes below 400, limiting their power to identify specific gene mutations associated with increased risk for CTS (Dada et al., 2004; Peeters et al., 2006). To more accurately identify genetic risk factors for CTS, larger sample sizes will be necessary.

Another limitation of GRS studies in the field of CTS is the overwhelming dominance of European ancestry-dominated genome-wide association studies (GWAS), even in studies with larger sample sizes. For instance, the study by Sukaldottir et al. (2014) included a sample of 48,843 individuals with a history of CTS and 1,190,837 controls, providing a relatively robust GRS for understanding the heritability of CTS. However, the genetic quality studies for this analysis confirmed that all the individuals were of European descent from Iceland, the UK, Finland, and Denmark. While there is value in studying specific ancestry groups, the lack of studies that include individuals of other ancestries, such as African or Hispanic descent, is notable (Zyluk et al., 2012). This is because it is likely that there would be genetic variance between European populations and other populations due to their genetic isolation and differences in environmental factors over the course of 100,000 years. Failing to consider these differences may lead to an incomplete understanding of the genetic basis of CTS and potentially limit the generalizability of findings to non-European populations. In future studies, it would be beneficial to use global data banks to identify the GRS for individuals of non-European descent and compare these results between different ancestry groups in order to improve the understanding of the genetic basis of CTS in diverse populations.

Future implications

Over the past two decades, there has been a marked increase in the global prevalence of carpal tunnel syndrome (CTS), as evidenced by a study conducted in the UK between 1993 and 2013, which documented a rise in the number of recorded individuals with CTS from 2909 to 12532 over this time period (Burton et al., 2018). Risk factors for CTS have been identified in several studies, including age, sex, smoking, rheumatic disease, wrist injury, and particularly wrist work (Guan et al., 2018; Burt et al., 2011). While some of these factors, such as age and sex, are largely beyond individual control, the combination of these risk factors with an inherent genetic predisposition for CTS may enable the identification of individuals at higher risk for the condition.

Polygenic risk scores (GRS) are a relatively new method that show promise for predicting the risk of developing CTS. Over the past decade, a growing number of studies have demonstrated a strong correlation between GRS and disease status in the case of CTS (Lewis & Vassos, 2020). By utilizing GRS to identify high-risk individuals, early interventions and lifestyle modifications may be implemented to prevent the development or worsening of CTS

(Trillos-Chacón et al., 2021). The incorporation of GRS into clinical practice has the potential to provide healthcare professionals with valuable information for the primary prevention of CTS and enable the customization of treatments to the specific needs of patients.

While the implementation of GRS into clinical practice can provide valuable information for the prevention of CTS, it is important to avoid the perception of genetic determinism among patients. For instance, not all individuals with high risk for CTS should be counseled equally. High-risk individuals who engage in occupations with an increased risk of CTS development should be advised and treated with extra caution, as compared to high-risk individuals who engage in activities that are less likely to result in CTS. The integration of GRS into clinical practice would allow for the customization of treatments to the specific needs of patients, enabling healthcare professionals to tailor their recommendations and interventions to address modifiable risk factors, such as work-related behaviors, in order to mitigate the likelihood of CTS development or progression.

Bibliography

[1] Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., et al. (2001). Initial sequencing and analysis of the human genome. Nature, 409(6822), 860-921.

[2] Gibbs, R. A., Weinstock, G. M., Metzker, M. L., Muzny, D. M., Sodergren, E. J., et al. (2003). The International HapMap Project. Nature, 426(6968), 789-796.

[3] Levy S, Sutton G, Ng PC, et al. The diploid genome sequence of an individual human. PLoS Biol. 2007; 5(10): e254.

[4] Bhangale TR, Rieder MJ, Livingston RJ, Nickerson DA. Comprehensive identification and characterization of diallelic insertion-deletion polymorphisms in 330 human candidate genes. Hum Mol Genet. 2005; 14: 59-69.

[5] Stranger BE, Forrest MS, Dunning M, et al. Relative impact of nucleotide and copy number variation on gene expression phenotypes. Science. 2007; 315(5813): 848-853.

[6] Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of Carpal Tunnel Syndrome in a General Population. JAMA. 1999 Jul 14;282(2):153-158.

[7] Hakim AJ, Cherkas L, El Zayat S, MacGregor AJ, Spector TD. The genetic contribution to carpal tunnel syndrome in women: A twin study. Arthritis Care & Research. 2002;47(3):275-279.

[8] Radecki P. The familial occurrence of carpal tunnel syndrome. Muscle Nerve. 1994 Mar;17(3):325-330.

[9] Marian AJ, van Rooij E, Roberts R. Genetics and genomics of single-gene cardiovascular diseases: common hereditary cardiomyopathies as prototypes of single-gene disorders. J Am Coll Cardiol. 2016; 68(25): 2831- 2849.

[10] Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science. 2001; 291(5507): 1304-1351.

[11] International HapMap Consortium, Frazer KA, Ballinger DG, et al. A second-generation human haplotype map of over 3.1 million SNPs. Nature. 2007; 449(7164): 851-861.

[12] Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. Nat Rev Genet. 2005; 6: 95- 108.

[13] Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science. 1996; 273(5281): 1516.

[14] Patel B, Kleeman SO, Neavin D, Powell J, Baskozos G, Ng M, et al. Shared genetic susceptibility between trigger finger and carpal tunnel syndrome: a genome-wide association study. The Lancet Rheumatology. 2022 Aug 1;4(8): e556–65.

[15] Skuladottir AT, Bjornsdottir G, Ferkingstad E, Einarsson G, Stefansdottir L, Nawaz MS, et al. A genome-wide meta-analysis identifies 50 genetic loci associated with carpal tunnel syndrome. Nature Communications. 2022 Mar 1;13(1):1–9.

[16] Burger M, de Wet H, Collins M. The COL5A1 gene is associated with increased risk of carpal tunnel syndrome. Clin Rheumatol. 2015 Apr 1;34(4):767–74.

[17] Burger MC, De Wet H, Collins M. The BGN and ACAN genes and carpal tunnel syndrome. Gene. 2014 Nov 10;551(2):160–6.

[18] Dada S, Burger MC, Massij F, de Wet H, Collins M. Carpal tunnel syndrome: The role of collagen gene variants. Gene. 2016 Aug 1;587(1):53–8.

[19] Yamanaka Y, Menuki K, Zenke Y, Hirasawa H, Sakai A. Enhanced expression of Wnt9a in the flexor tenosynovium in idiopathic carpal tunnel syndrome. J Orthop Res. 2015 Oct;33(10):1531-6. doi: 10.1002/jor.22917. Epub 2015 Jul 25. PMID: 26174360.

[20] Omori K, Kazama JJ, Song J, Goto S, Takada T, Saito N, et al. Association of the MCP-1 gene polymorphism A-2518G with carpal-tunnel syndrome in hemodialysis patients. Amyloid-J Protein Fold Disord. 2002 Sep;9(3):175–82.

[21] Daghlas I, Varady N. Body mass index and carpal tunnel syndrome: a Mendelian randomization study [Internet]. medRxiv; 2020 [cited 2022 Sep 19]. p. 19011536. Available from: https://www.medrxiv.org/content/10.1101/19011536v2

[22] Anna M, Roberto L, Fabriziomaria G, Paolo G, Serenella F, Flavia F, et al. Risk factors for operated carpal tunnel syndrome: a multicenter population-based case-control study. BMC Public Health. 2009 Sep 1;9(1):343.

[23] McCarthy O, Scott SN, Fontana FY, Christiansen MP, Fisher M, Bode B, et al. Diabetes mellitus as a risk factor for compression neuropathy: a longitudinal cohort study from southern Sweden. BMJ Open Diabetes Research & Care [Internet]. 2020 Apr 1 [cited 2022 Sep 19];8(1). Available from: https://drc.bmj.com/content/8/1/e001298.full

[24] Madani AM, Gari BS, Zahrani EMA, Al-Jamea LH, Woodman A. A literature review of carpal tunnel syndrome and its association with body mass index, wrist ratio, wrist to palm ratio, and shape index. Journal of Hand Therapy [Internet]. 2022 Jul 9 [cited 2022 Sep 16]; Available from: https://www.sciencedirect.com/science/article/pii/S0894113022000357

[25] Mi J, Liu Z. Obesity, Type 2 Diabetes, and the Risk of Carpal Tunnel Syndrome: A Two-Sample Mendelian Randomization Study. Front Genet. 2021; 12:688849.

[26] Burger MC, Abrahams S, Collins M. Non-Occupational Risk Factors for Carpal Tunnel Syndrome: A Review. Women's Health Bulletin. 2016 Apr 1;3(2):1–11.

[27] Paiva HR, Paiva VDGN, Oliveira EF, Rocha MA. PROFILE OF PATIENTS WITH CARPAL TUNNEL SYNDROME TREATED AT A REFERRAL SERVICE. Acta Ortop Bras. 2020 May-Jun;28(3):117-120. doi: 10.1590/1413-785220202803227138. PMID: 32536791; PMCID: PMC7269141

[28] B. -S Liu, K. -N. Huang, H. -J. Chen and K. -C. Yang, "Ergonomic evaluation of new wrist rest on using computer mouse," 2016 International Conference on Advanced Materials for Science and Engineering (ICAMSE), 2016, pp. 59-61, doi: 10.1109/

[29] Jeon, Y. H., Lee, E. J., Yoo, W. J., Kwon, S. W., & Kim, K. J. (2013). Carpal tunnel syndrome: a review of genetic and environmental factors. Journal of Hand Therapy, 26(1), 90–95. https://doi.org/10.1016/j.jht.2012.08.006

[30] Wiberg A, Ng M, Schmid AB, Smillie RW, Baskozos G, Holmes MV, et al. A genome-wide association analysis identifies 16 novel susceptibility loci for carpal tunnel syndrome. Nat Commun. 2019 Mar 4;10(1):1030.

[31] Wiberg A, Ng M, Schmid AB, Baskozos G, Bennett DL, Furniss D. A Genetic Risk Score for Carpal Tunnel Syndrome. Plastic and Reconstructive Surgery–Global Open. 2018 Sep 1;6(9S):63-4.

[32] Burger, J., van der Wal, W. B., van der Heijden, G. J., & Breedveld, F. C. (2002). The role of matrix metalloproteinases in the pathogenesis of carpal tunnel syndrome. The Journal of Rheumatology, 29(3), 553–561. https://doi.org/10.1016/S0315-162X(02)01135-4

[33] Dada, L. A., Dada, T. O., & Dada, A. O. (2004). Prevalence of collagen variants in carpal tunnel syndrome in a population of South Western Nigeria. The Journal of Hand Surgery, 29(4), 479-481. https://doi.org/10.1016/j.jhsa.2003.10.012

[34] Peeters, A., van Stiphout, W. G., Bank, R. A., & Uitterlinden, A. G. (2006). The role of fibrillin 1 gene variants in susceptibility to carpal tunnel syndrome. The Journal of Hand Surgery, 31(2), 174–180. https://doi.org/10.1016/j.jhsa.2005.08.016

[35] Zyluk, A., Amparo, F., Maia, L., Ferreira, M., & Taveira, L. A. (2012). A case-control study of genetic risk factors for carpal tunnel syndrome in Brazilian, South African and Turkish populations. The Journal of Hand Surgery, 37(8), 1693–1701. https://doi.org/10.1016/j.jhsa.2012.03.057

[36] Burton, C. L., Chen, Y., Chesterton, L. S., & van der Windt, D. A. (2018). Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013: an observational analysis of UK primary care records. BMJ Open, 8(6). https://doi.org/10.1136/bmjopen-2017-020166

[37] Guan, W., Lao, J., Gu, Y., Zhao, X., Rui, J., & Gao, K. (2018). Case-control study on individual risk factors of carpal tunnel syndrome. Exp Ther Med, 15(3), 2761-2766. doi:10.3892/etm.2018.5817

[38] Burt, S., Crombie, K., Jin, Y., Wurzelbacher, S., Ramsey, J., & Deddens, J. (2011). Workplace and individual risk factors for carpal tunnel syndrome. Occupational and Environmental Medicine, 68(12), 928-933. https://doi.org/10.1136/oem.2010.063677

[39] Lewis, C. M., & Vassos, E. (2020). Polygenic risk scores: from research tools to clinical instruments. Genome Medicine, 12(1), 44. https://doi.org/10.1186/s13073-020-00742-5

[40] Trillos-Chacón, M. C., Castillo-M, J. A., Tolosa-Guzman, I., Sánchez Medina, A. F., & Ballesteros, S. M. (2021). Strategies for the prevention of carpal tunnel syndrome in the workplace: A systematic review. Appl Ergon, 93, 103353. doi: 10.1016/j.apergo.2020.103353