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Systematic review

Genetic regulators of Achilles tendon pathogenesis and outcomes

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Achilles tendon conditions are common among the young owing to overuse injuries and the post middle aged due to misuse degenerative changes. Achilles-tendoninopathy does not occur in isolation (merely confined to morbidity, pain, restricted movement). Intertwined factors co-exist in form of psychological discomfort, time, productivity loss, adverse life-quality and care giving/financial issues. Since Achilles tendon conditions are common occurrence in orthopedic trauma and rehabilitation centers, this poses logistic burden on health care, insurance systems, work loss days. It has been observed that Achilles tendon conditions are not evenly distributed in the population. It aim to correlate demographic/geographic variations with genetic predispositions through comprehensively analyzing population based genome wide assays and gene mapping studies. This review aims to emphasize genetic aspects of Achilles tendinopathy and provide an evidence based understanding of factors determining vulnerability, progress, prognosis of tendonopathy at the molecular level. A literature search during (January to April 2018) using: NHS, TRIP database, Cochraine library, PubMed, MedLine, Embase, CINHALL, Global health, Web of Science, Scopus, PubMed, Clinical Queries using the following key words: (Ankle, Sports, Achilles tendon OR Tendo calcaneus OR Tendinopathy OR tendinitis OR tendonitis OR tendon rupture) and Genetic role in Achilles tendinopathy prevalence OR incidence OR epidemiology OR etiology. The search returned 1500 articles (reviews, meta-analysis, case control, prospective cohort, cross sectional studies, case studies), of which 121 were included based on best match of the pre-set inclusion criteria. Studies confirm that genes do play a definite role in the development, progress and prognosis of Achilles-tendinopathy. Race, ethnicity, geographic zones; all interplay in determining outcomes of this condition. Customized epigenetics do have a role in futuristic ankle and foot-health care clinics. It also welcomes an open questionin 21st century modern health care as to 'whether it is time to incorporate gene mapping' fortimely identifying and monitoring intervention for susceptible individuals.

Keywords: Achilles tendinopathy, Genetic regulators and Tendocalcaneus

INTRODUCTION

Achilles tendon, also known as 'tendocalcaneous' is one

of the strongest tendon in the human body and plays a pivotal role in lower limb movement. Achilles tendinopathy is a common problem facing the young as well as the old and is particularly common among maleathletes (Kujala et al., 2005). It often occurs during

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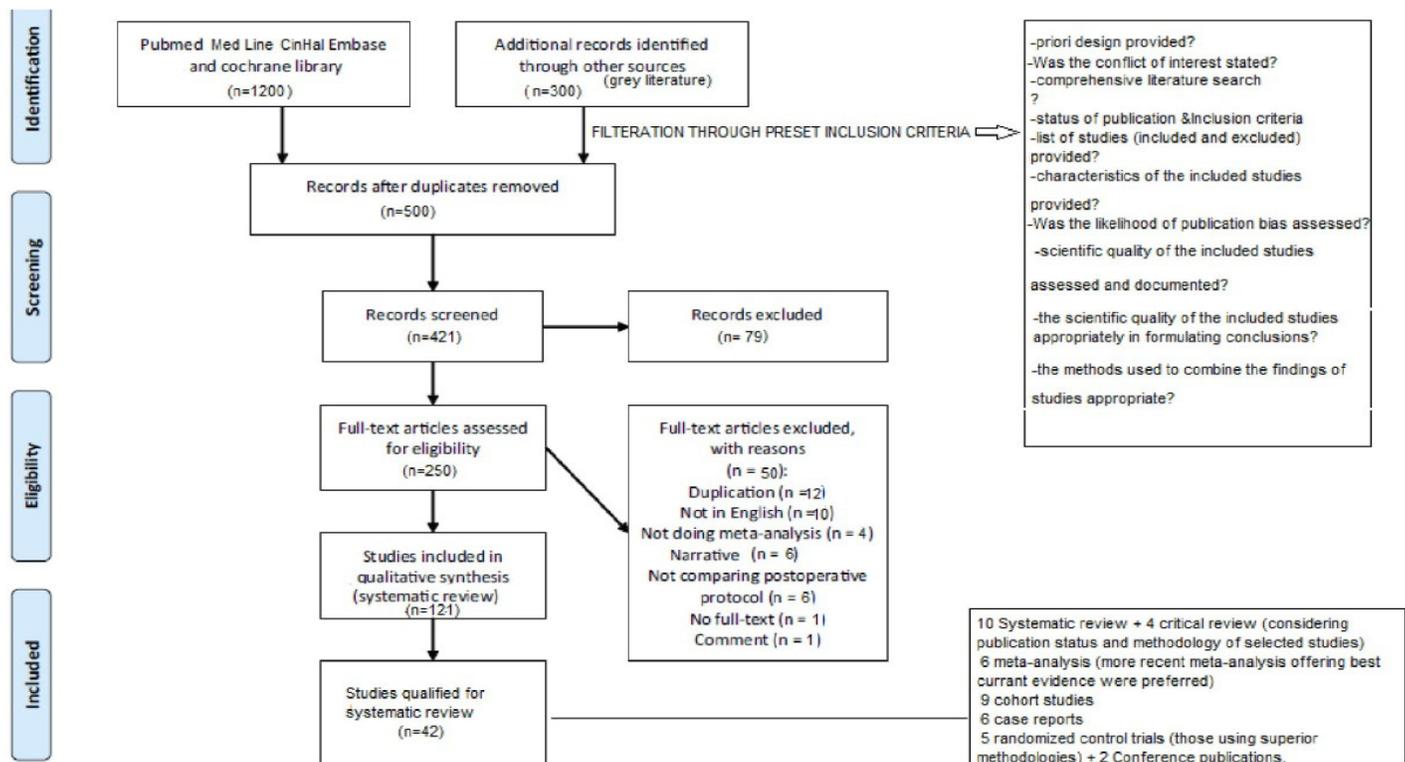


Figure 1. Flow Diagram summarizing the article selection process for the review employing various search database*

*CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, ExcerptaMedica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online; RCT, randomized controlled trial. "Cochrane Library Database" refers to any of the following: Cochrane database; Cochrane Musculoskeletal Injuries Group Specialized Register; Cochrane Bone, Joint, and Muscle Trauma Group Specialized Register; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials

the third or fourth decades of life and is frequent among those leading customarily sedentary lifestyles (Magnan et al., 2014).

Achilles tendon conditions take their toll in form of morbidity, pain, limited movement and adverse quality of life. Achilles tendon conditions do not occur in isolation. There are other intertwined factors like psychological discomfort, time and productivity loss, care giving and financial concerns (Furumatsu et al., 2015). Since Achilles tendon conditions are a common occurrence in orthopedic trauma and rehabilitation centers, there is definite logistic burden on health care (Hopkins, 2016), therapy and insurance systems, commercial work loss days, enforced early retirement set-backs and loss of sports personellelt has been observed that Achilles tendon conditions are not evenly distributed in the population (Longo et al., 2009). They show definite demographic and geographic variations that have been traced down to genetic predispositions (Kraemer et al., 2012; Wang et al., 2017).

This systematic review elucidates genetic aspects of Achilles tendinopathy. An evidence based understanding of the factors determining vulnerability traits progress and prognosis of Achilles tendinopathy at the molecular level might pave way towards gene mapping and customized epigenetics in futuristic ankle and foot health care.

METHODOLOGY OF REVIEW

A literature search was performed during the time period of January to April 2018 using various medical database: NHS, TRIP database, Cochrane library, PubMed, MedLine, Embase, CINAHL, Global health, Web of Science, Scopus, PubMed, Clinical Queries using the following key word search strategy: (Ankle, Sports, Achilles tendon OR Tendo calcaneus OR Tendinopathy OR tendinitis OR tendonitis OR tendon rupture) AND (Genetic role in Achilles tendinopathy prevalence OR incidence OR epidemiology OR etiology). Studies (reviews, meta-analysis, case control, prospective cohort, cross sectional studies, case studies) reporting on Achilles tendinopathy, tendinoses, etiology, epidemiology, incidence, prevalence and genetic aspects were included. Studies on upper limb orthopedic / muscular conditions: epicondylitis, rotator cuff tendinopathy and hip or knee joint conditions: patellar tendinopathy tenosynovitis, Non-english studies, reports on tennis or golfers elbow were excluded. Reviews older than 10 years, animal, and cadaveric studies were also excluded. The search returned 1500 articles, of which 121 were included based on best match of the pre-set inclusion criteria. The items of the inclusion criteria used to filter studies were:

- Was an a priori design provided?
- Was there duplicate study selection and data extraction?
- Was a comprehensive literature search performed?
- Was the status of publication (i.e., grey literature) used as an inclusion criterion?
- Was a list of studies (included and excluded) provided?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?
- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was the likelihood of publication bias assessed?
- Was the conflict of interest stated?
- The items of the inclusion criteria were:

Two researchers independently conducted the search according to the preset criteria and pooled in a repository of selected articles. The search was further refined according to the characteristics of the cohort (athletes, workers, general population, and patients with comorbidities), sample size, age group, duration and type of tendon condition and the reported prevalence and incidence data, management techniques used. The main body for information was derived from Cochrane Database of Systematic Reviews, Journals: Bone and Joint Surgery Am, Clinical Orthopedics and Related Research, Knee Surgery, Foot and Ankle surgery, Sports Traumatology, Arthroscopy, The American Journal of Sports Medicine, The British Journal of Sports Medicine, Orthopedic trauma and rehabilitation journal.

42 studies qualified for the present review article. 10 Systematic review, 4 critical review (considering publication status and methodology of selected studies), 6 meta-analysis (more recent meta-analysis offering best current evidence were preferred), 9 cohort studies, 6 case reports, 5 randomized control trials (those using superior methodologies), 2 Conference publications. reference-manager software -Ref Works and End Note were used to import citations and duplicates were removed. The reference-manager program Mendeley (Elsevier) was used during manuscript preparation.

DISCUSSION

Role of genes in Achilles tendon conditions

The genetic influence on susceptibility to Achilles tendon injury is not well understood and most published literature is limited to relatively homogenous populations (Maffulli et al., 2013; Vaughn et al., 2017). Limited works highlighting the role of genetic mutations in Achilles tendinopathy exist in literature (Vaughn et al., 2017; September et al., 2007). Some notable researches and their main findings have been summarized in (Table 1).

Posthumus and others notably (Posthumus et al., 2010; El Khoury et al., 2013) reported in a genome wide association assay in patients with Achilles tendon conditions that individuals who carry the TT genotype of the growth differentiation factor - GDF5 rs143383 variant face twice the risk of developing Achilles tendon pathology compared with non-carriers. The research done by Posthumus and his team represents one of the strongest genetic association studies on tendinopathies till date. Their case control cohort recruited Achilles tendinopathy patients from two geographically distinct populations of South Africa and Australia. An elevated frequency of rs143383 was observed in both populations as compared to controls. Such replication of finding in large cohorts from two distinct populations makes it questionable as spurious association. Furthermore, the effect size of TT genotype carrying GDF5 rs143383 was large. It twice increased the risk of developing Achilles tendinopathy, which further supports it "not" being a false-positive finding. The TT genotype of GDF5 rs143383 correlates with reduced expression of GDF5 in human soft tissues.

Mikic et al. (Mikic et al., 2011) observed that tendons from GDF5 knock-out mice models contain roughly 40% less collagen than normal. They display significantly impaired healing of tendons. Contrariwise, GDF5 transfection progresses tendon healing (Huang et al., 2018). However, clinical evidence of GDF5 efficacy in tendinopathy among human subjects is currently lacking (Longo et al., 2015). Fredberg et al. randomly selected 209 Danish Super League football players to receive eccentric training for Achilles and patellar tendons. Eccentric training resulted in higher incidence of tendinopathy (Fredberg et al., 2008; Collins and Raleigh, 2009). This welcomes an open question ground as to "whether patients with lower GDF-5 expression are less effective in adapting to mechanical loading, and more vulnerable to additional superimposed training harms"?

Bahr and Krosshaug (Bahr et al., 2010) developed an injury prevention scheme by further building up on the findings of Posthumus and his team. Bahr and Krosshaug emphasized that in overuse injuries; predisposing factors play a key role in the injury mechanism and GDF-5 SNP genes are a contributing factor for assimilation of injury mechanisms.

At the moment, in face of limited understanding of the genetic aspect of Achilles tendinopathy, the 'right preventive measures' face risk of being targeted at 'wrong persons'. Although it may presently appear too ambitious to incorporate GDF-5 SNP testing into routine clinical care, it clearly needs to be an agenda in the tendinopathy genetic research paradigm.

Achilles tendon's extracellular matrix consists of collagen fibrils, proteoglycans, glycoproteins and glycosaminoglycans. These structural and non-structural proteins and enzymes maintain homeostasis by constantly remodelling the extracellular matrix. The

Table 1. Genetic predisposition to multifactorial phenotypes is often population reliant, as has been observed in many population specific cohorts.

Genetic Factors in Achilles Tendon Injury						
Researchers	Year	Population studied	Number of patients	Number of control	Gene(s) studied *	Main findings**
Abrahams et al	2013	South African, Australian	160	342	COL5A1 30-UTR MIR608	COL5A1 30-UTR markers rs71746744, rs16399, and rs1134170 and MIR608 marker rs4919510 significantly associated with Achilles tendinopathy.
El Khoury et al.	2016	British	118	131	MMP3 TIMP2	TIMP2 rs4789932 and MMP3 rs679620 significantly associated with Achilles tendon injury
El Khoury et al.	2017	South African, Australian	173	248	ADAMTS ADAM12 TIMP2	Significant overrepresentation of CT genotype of TIMP2 rs4789932 in tendon injury patients; no significant genetic associations of ADAMTS or ADAM12
Hay et al	2015	South African, Australian	184	338	COL11A1 COL11A2 COL2A1	No significant associations identified Tendon rupture more common in patients with O blood type.
Jozsa et al	1989	Hungarian	797	1,200,000	ABO	Tendon rupture and tendinopathy more common in patients with O blood type
Kujala et al	2014	Finnish	291	5536	ABO, NOS3	No significant association of blood type and tendon rupture
Leppilahti et al	2012	Finnish	215	5000	ABO	No significant association of blood type and tendon rupture
Maffulli et al	2010	Scottish	78	24,501	ABO	Significant association of number of "GT" repeat polymorphisms with tendon injuries
Mokone et al	2014	South African	144	127	TNC	Significant association of BstUI rs12722 variant with chronic Achilles tendinopathy
Mokone et al	2015	South African	111	129	COL5A1	Significant associations of CASP8 rs1045485 and rs3834129 polymorphisms with tendon injury; no significant associations with NOS genes identified
Nell et al	2012	South African, Australian	166	358	CASP8	No significant association identified
Posthumus et al	2011	South African, Australian	171	238	NOS2	Significant association of GDF5 rs143383 variant with tendinopathy in Australian population; no significant associations with TGFB1 identified
Posthumus et al	2015	South African	126	125	TGFB1 GDF5	Significant associations of MMP3 rs679620, rs591058, and rs650108 polymorphisms with tendon injury
Raleigh et al	2012	South African	114	98	COL1A1	Significant association of BMP4 rs2761884 variant with tendinopathy; no association seen with FGFR1
Salles et al	2011	Brazilian	52	86	MMP3	No significant associations identified in genes studied
Saunders et al	2016	South African, Australian	178	340	BMP4	No significant independent associations identified in genes studied
Saunders et al	2012	South African, Australian	179	339	FGF3 FGF10 FGFR1	Significant association of BstUI rs12722 variant with chronic tendinopathy and rs3196378 in Australian patients
September et al	2015	South African, Australian	178	342	COMP THBS2	No significant independent associations identified in genes studied
September et al	2014	South African, Australian	175	369	COL27A1 TNC	No significant independent associations identified in genes studied
September et al	2014	South African	137	131	COL5A1 IL1B IL1RN IL6	Significant association of BMP4 rs2761884 variant with tendinopathy

Abbreviations

ADAM, A disintegrin and metalloproteinase; BMP, bone morphogenic protein; CASP, caspase; COL, collagen; COMP, cartilage oligomeric matrix protein; DEF, defensin; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GDF, growth differentiation factor; IL, interleukin; MIR, micro RNA; MMP, matrix metalloproteinase; NOS, nitric oxide synthase; TGF, transforming growth factor; THBS, thrombospondin; TIMP, tissue inhibitor of metalloproteinases; TNC, tenascin; UTR, untranslated region.

Table adapted from

Vaughn et al. The Orthopaedic Journal of Sports Medicine. 2017. Available: SAGE's website at <http://www.sagepub.com/journalsPermissions.nav>.)
And

Natalie H. Vaughn, Genetic Factors in Tendon Injury A Systematic Review of the Literature The Orthopaedic Journal of Sports Medicine, 2017;5(8):1-11. DOI: 10.1177/2325967117724416

Key Notes to Reflect

- The COL gene provides instructions for production of type V collagen, which is important in regulating the width of collagen.
- Multiple studies have attempted to explore the relationship between ABO blood type and tendon injury and their results are contradictory and inconclusive till date; some find significant correlation while others report vague to null correlation.
- The IL gene contains information necessary for production of interleukin-6, a cytokine that is primarily produced at sites of acute and chronic inflammation and has been linked to inflammation-induced diseases like Achilles tendinopathy.
- The CASP gene contains material required to generate cysteine-aspartic acid protease (caspase) 8, a proenzyme that plays a central role in executing cell apoptosis. CASP8 genotypes are significantly associated with Achilles tendinopathy.
- MMP gene encodes an enzyme that degrades fibronectin; laminin; collagens III, IV, IX, and X; and cartilage proteoglycans. There are suggested potential relationships between the MMP rs679620 allele and Achilles tendon injury.
- The TGFB gene is responsible for encoding the transforming growth factor beta-1 protein which is important in facilitating cell differentiation, motility, apoptosis and is abundant within extracellular matrix of tendons.
- The NOS genes encode nitric oxide synthases 2 and 3, respectively, which synthesize nitric oxide. Nitric oxide is a messenger molecule that encourages production of proinflammatory mediators such as IL6 and IL8.
- The ADAM genes encode disintegrin and metalloproteinase with thrombospondin motifs 2 and 14, respectively, enzymes that process procollagen molecules into collagen molecules.
- The TIMP gene provides instructions to produce TIMP metalloproteinase inhibitor 2, which appears to suppress the proliferative response of quiescent tissues to angiogenic factors and inhibits the activity of MMPs that degrade extracellular matrix.
- The MIR family of genes is responsible for producing microRNAs, that regulate gene expression by altering the stability and translation of mRNAs. Orthopaedically, this gene appears to regulate chondrocyte sonic hedgehog expression and is found to be overrepresented in the tendinopathy group.
- The COMP gene and THBS genes provide blueprints for creating cartilage oligomeric matrix protein (COMP) and thrombospondin 2, respectively. Both proteins are believed to be involved in cell-to-cell adhesion and communication.
- The FGF3 and FGF10 genes provide genetic information to synthesize fibroblast growth factors 3 and 10, respectively, that can bind to proteins, such as fibroblast growth factor receptor-1, a protein encoded by FGFR1. FGF proteins bind FGFRs, which span cell membranes and, when bound, trigger a cascade of intracellular events leading to cell maturation.
- The BMP4 gene encodes bone morphogenic protein 4, a cytokine important in the induction of bone and cartilage formation.
- DEF: Defensin b1 is a peptide encoded by DEFB1, produced by neutrophils, and believed to be important in resisting microbes from binding to epithelial surfaces.

metalloproteinases family (MMPs) plays an important role in controlling the integrity of the extracellular matrix by catalytically restructuring proteins like laminin, fibronectin, and different collagens.

MMP mRNA levels are constantly low in Achilles tendonopathy samples as compared to controls (Raleigh et al., 2009). Definite time-based alterations of metalloproteinases (MMPs) and Tissue inhibitors of metalloproteinases (TIMPs) occur in Human Achilles Tendons after acute Rupture (Minkwitz et al., 2017). Tissue inhibitors of metalloproteinases (TIMP) inhibit the activity of metalloproteinases by competing with MMP active sites. Thus, TIMP indirectly limits the activity of MMP.

Recent studies by El Khoury et al. have shown single nucleotide polymorphism (SNP) within the MMP gene like rs478992 SNP in TIMP gene as a potential risk factor for Achilles tendinopathy (Stepien-Slodkowska et al., 2017).

Till date, the most consistent data that supports a genetic association between tendon injury and COL5A1 has been provided by the Karren and Brown research of 2017 (Brown et al., 2017; Wang et al., 2017; Zhong et al., 2017). While contributing minimally to overall tendon composition, the molecule plays an important role in fibril formation by interacting with type I collagen to help regulate overall fibril size and matrix organization.

The risk of Achilles tendinopathy phenotypes, associated with loci, are modified by both gender and geographical location as suggested by a British Caucasians case-control cohort study (118 cases and 131 controls) during 2016 (ElKhoury et al., 2016).

All being said, it might be safely and unequivocally stated that a definite genetic predisposition to multifactorial phenotypes is population dependent, as has been observed in many population specific cohort studies with large sample sizes and along sound timelines that provide credibility to these findings. A summary of these studies has been represented in Table 1 above.

Is it time to incorporate gene testing into clinical care?

Despite excellent evidence based research supporting the utility of exercises for Achilles tendinopathy cases, many patients do not respond to rehabilitative treatment (Kozlovskaja et al., 2017; O'Neill et al., 2016). Obviously, prevention would be the best medicine for such cases. Identifying "at risk" individuals could alert clinicians in decide on those 'most in need' of preventive measures. The same loci (deletion or insertion) seem to modify the risk of Achilles tendon pathology or rupture in some ambiguous way.

This prompts another notion: As genetic testing becomes more affordable in the mid-21st century personalized medicine; recognition of specific genetic mutations may help identify vulnerable individuals; thereby prompting tailored preventive approaches, promoting awareness and behavioral / life style/ sport modifications.

Much of targeted gene therapy involving tendon ruptures is still in its juvenile stage and focuses on the reparative process (Rickert et al., 2005). Futuristic researches aiming on identification of predisposing phenotypes to tendon rupture and genetic tendencies might offer additional lineages to targeted intervention, perhaps even permitting structural alteration of tendon before injury occurs.

CONCLUSION

Achilles tendinopathy is not just a 'foot condition'; rather, it is a clinical syndrome characterized by a combination of morbid symptoms including lower limb pain, swelling, limited motion performance and impaired daily life activities. Etiology of Achilles tendinopathy is multifactorial and both extrinsic and intrinsic factors play intertwined roles. The tendon shows deteriorative changes at the cellular level; with high glycosaminoglycans concentration in ground matrix and an increased number of tenocytes. The mainstay of strength and endurance of any tendon in the human body is the strategic alignment of healthy collagen fibres. In Achilles tendinopathy; this very foundation is disturbed and there is disorganization and fragmentation of collagen fibrils, followed by compensatory neovascularization and neo innervation. However, these new blood vessels or nerves neither improve perfusion nor sensation. Conversely, they pave a derogatory path for further damage in the form of bleeding points, hematomas and sensory disturbances. The source of pain in Achilles tendinopathy is multifactorial and its pathophysiological mechanisms are complicated and difficult to understand. Management of Achilles tendinopathy is variable; depending on the condition of the patient and the best clinical judgement of the doctor based on 'risk versus benefit' evidence available from medical literature. Conservative treatment usually precedes surgical options for routine cases. However, there is yet no 'gold standard' treatment manifesto for Achilles tendinopathy because of contradictory clinical outcomes between various studies done on different cohorts. It still remains a point of debate as to 'whether' and 'to what extent' race, genes, age, occupation and gender play a role in incidence and clinical outcomes of Achilles tendinopathy. In future, more level I researches are needed to substantiate the effect of these interrelated factors on each other during the course and management

of the disease. Futuristic researches could focus on whether it is time to incorporate genes mapping in preventive and rehabilitative programs of Achilles tendinopathy.

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