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GENETIC VARIATION AS A POSSIBLE EXPLANATION FOR THE HETEROGENEITY OF PAIN IN TENDINOPATHY: WHAT CAN WE LEARN FROM OTHER PAIN SYNDROMES?

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Abstract The mechanisms of pain in tendinopathy are unclear. Current theories implicate tendon structural changes, neovascularisation, inflammation or changes in central pain processing. As with other types of musculoskeletal pain, tendon pain has high interindividual variability, which could be attributed to genetic variation. Notably, the association between certain genetic polymorphisms and other pain syndromes is well established in the literature. Therefore, the investigation of the mechanisms of pain in tendinopathy could extend to include genetic variation as a possible explanation for the clinical features of tendon pain. This review summarises the current knowledge on genetic contributors to other pain syndromes and highlights findings that are relevant to chronic tendon pain. In particular, based on the current hypotheses on the possible sources of tendon pain, it focuses on findings that relate to genes that encode structural connective tissue components, inflammatory markers, ion channels and catecholamines and how they may relate to chronic tendon pain. In the absence of a definitive mechanism of tendon pain, an

a priori genetic approach that is guided by these current hypotheses may help elucidate the mechanisms of tendon pain which may allow a more rational approach to research and treatment.

Key words tendon pain, genetics, extracellular matrix genes, inflammation genes, COMT

Introduction

Tendinopathies are common in recreational and professional athletes (Lagas et al., 2020), and in certain occupations (Owens et al., 2013). The main presenting complaint in tendinopathy is pain of insidious onset (Silbernagel, Hanlon, Sprague, 2020), which is not proportionate to tissue damage (Docking, Ooi, Connell, 2015), is difficult to manage (Cook, Purdam, 2009) and persists even after resolution of other functional outcome measures (Van Ark et al., 2018). This is not surprising because its source and/or mechanisms are currently not fully understood. Consequently, several theories have been proposed explaining the potential sources of pain in tendinopathy, with no consensus on what the exact mechanisms of pain are in tendinopathy. Current theories implicate structural changes in the tendon (Bakkegaard, Johannsen, Højgaard, Langberg, 2015), neovascularisation (Mousavizadeh et al., 2014), inflammation (Abate et al., 2009; Battery, Maffulli, 2011; Dean et al., 2015), biochemical changes (Lian et al., 2006; Schizas et al., 2012), ion channel abnormalities (Rio et al., 2014), as well as alterations in central pain modulation (Plinsinga, Brink, Vicenzino, van Wilgen, 2015; Tompra, Van Dieen, Coppieters, 2016). The aetiology of chronic tendon pain remains poorly understood and most likely presents with its own unique clinical features. However, it is not implausible to assume that chronic tendon pain shares a proportion of its physiology (Caneiro et al., 2020) and burden (Mc Auliffe et al., 2017; Mkumbuzi et al., 2020) with other types of chronic painful musculoskeletal (MSK) conditions.

As with other chronic painful MSK conditions, tendon pain responses are characterised by robust inter-individual variability in sensitivity and susceptibility (Fillingim, Wallace, Herbstman, Ribeiro-Dasilva, Staud, 2008), and mounting evidence suggests that a significant portion of pain variability can be explained by genetics (Bjorland, Moen, Schistad, Gjerstad, Røe, 2016; Foulkes, Wood, 2008; Veluchamy, Hebert, Meng, Palmer, Smith, 2018). It is interesting that the estimated heritability of nociceptive and analgesic sensitivities is as much as 76% (Chidambaran, Gang, Pilipenko, Ashton, Ding 2019; Diatchenko et al., 2005; Peters et al., 2013; Ruau et al., 2012). Consequently, several genetic polymorphisms have been associated with specific pain syndromes (Foulkes, Wood, 2008), pain perception and analgesic use (Hooten, Hu, Cunningham, Iii, 2019; Olesen et al., 2018; Packiasabapathy, Horn, Sadhasivam, 2019; Wang, Wei, Xiao, Chang, Zhang, 2019), and response to physiotherapy treatment (Govil et al., 2020).

The aim of this narrative review was therefore, to summarise the current knowledge on genetic contributors to chronic pain in other pain syndromes, which could potentially also be considered for chronic tendon pain. Based on the current hypotheses on the possible sources of tendon pain, this narrative review therefore focused on findings that relate to genes that encode structural connective tissue components, inflammatory markers, ion channels and catecholamines. In the absence of a definitive source and/or mechanism of pain in tendinopathy, an *a priori* genetic approach guided by these current hypotheses may assist in identifying potential biological mechanisms to be considered for tendon pain which may also inform a more rational approach to its research and development of treatment paradigms.

The structural changes hypothesis: Extracellular matrix components and regulators

The *COL11A1* and *COL11A2* genes encode the a1 and a2 chains of the minor fibrillar type XI collagen. Individuals with knee osteoarthritis (OA) who had a *COL11A2* rs16868943 GG genotype had on average a higher heat pain tolerance (Ho et al., 2017). Additionally, an increased risk of developing OA was reported in the *COL11A2* knockout mouse model (Lapvetelainen et al., 2002). While *COL11A2* has not itself been associated with OA risk in humans, variations in the *COL11A1* gene have been implicated with risk (Raine, Dodd, Reynard, Loughlin, 2013). Additionally, mutations in the *COL11A2* gene have also been associated with osteochondroplasia (Avcin et al., 2008) and non- ocular Stickler's syndrome (Vuoristo, Pappas, Jansen, Ala-Kokko, 2004), both of which share clinical features with OA. It is tempting to speculate that *COL11A2* might not only be associated with risk of developing these conditions but potentially in the development of the associated pain.

Although the genotypes were not independently associated, the inferred T-C-T haplotype constructed from the *COL11A1* rs3753841 (T/C), *COL11A1* rs1676486 (C/T) and *COL11A2* rs1799907 (T/A) was previously associated with increased risk of Achilles tendinopathy in two independent populations (Hay et al., 2013). In addition, the *COL11A1* rs3753841 TT genotype and the inferred T-C haplotype constructed from *COL11A1* rs3753841 and rs1676486 was previously associated with carpal tunnel syndrome (CTS) (Dada, Burger, Massij, de Wet, Collins, 2016). *COL11A1* rs3753841 was also independently associated with elbow tendon pathology (Alakhdar Mohmara et al., 2020). Although these studies did not specifically investigate the association of the type XI collagen gene variants with tendon pain, this should be explored in future work. It would also be interesting to investigate the possible association of other collagen genes with tendon pain.

The matrix metalloproteinases (MMPs) are a family of enzymes that have been implicated in pain. Individuals with a *MMP1* rs1799750 GG genotype on average presented with higher temporomandibular joint pain scores (Planello et al., 2011). This finding was replicated in an independent cohort of low back pain patients where individuals with the GG genotype also presented with higher pain scores on the McGill Pain Questionnaire as well as more disability (Jacobsen et al., 2013). In addition, expression of *MMP10* mRNA was significantly increased in surgical patients with pain compared to pain free controls in a study by Richardson, Doyle, Minogue, Gnanalingham, Hoyland (2009). Furthermore, in animal models, *MMP2* expression was elevated in models of neuropathic pain (Miranpuri et al., 2016). Additionally, the roles of MMPs, in particular *MMP*-2 and *MMP*-9, in facilitating inflammatory pain have been demonstrated in various studies where these enzymes are required in the early and late stages of neuropathic pain development (Ji, Gereau, Malcangio, Strichartz, 2009). Interestingly, their inhibition led to pain relief (Li et al., 2016) and decreased mechanical allodynia in rodent models (Kular et al., 2012). Future studies should therefore also specifically investigate the possible association of variants within the family of *MMP* and tissue inhibitors of metalloproteinases (*TIMP)* genes, which have previously been associated with Achilles tendinopathy (Raleigh et al., 2009, El Khoury, Ribbans, Raleigh, 2013; Kang et al., 2019), with tendon pain.

The caspases (CASP), which are protease enzymes involved in apoptosis and inflammation (Berta, Lee, Park, 2017; Joseph, Levine, 2004), are another family of enzymes that are implicated in pain. CASP-6 regulates chronic pain via microglial inflammatory signalling, most likely through TNF-a secretion (Berta et al., 2017). Additionally, inhibition of CASPs-1, -2, -3, -8 and -9 attenuated pain related behaviour in HIV/AIDS and cancer neuropathy models (Joseph, Levine, 2004). This suggests that caspase signalling pathways contribute to pain. This is further demonstrated by an association between the -1263 *CASP-9* rs4645978 promoter variant with low back pain (Mu, Ge, Zuo, Chen, Huang, 2013). In this study, carriers of the minor G allele were overrepresented in the pain

group compared to their pain-free compatriots. Similarly, Guo et al. (Guo, Liu, Zhang, Guo, Wu, 2011) showed an association between the -1263 *CASP-9* rs4645978 GG genotype with discogenic low back pain. Since variants within *CASP8* have been associated with tendinopathy in some (Seale et al., 2020), but not all studies (Kang et al., 2019), future work should also consider it and other *CASP* genes as candidates for association with tendon pain.

Tendon pain as a channelopathy: Ion channels

Ion channels are very important in the pain pathway, where they manage the generation and processing of pain signals. Sodium, potassium and calcium channels are the main ion channels in neuronal transmission in nociceptors and have been firmly implicated in human pain disorders (Waxman et al., 2014). In particular, voltage-gated sodium channel 1.7 (Nav1.7) is expressed in nociceptors and amplifies subthreshold stimuli. Unsurprisingly, a number of clinical effects such as primary erythermelalgia, paroxysmal extreme pain disorder and congenital insensitivity to pain have been observed in individuals with gain of function and loss of function Nav1.7 mutations, respectively (Estacion et al., 2009; Reimann et al., 2010). In addition to these rare diseases that result from high impact mutations, variants in the gene encoding the a subunit of the sodium voltage gated channel 1.7 (*SCN9A)* were also associated with subtle effects in modulating risk and severity of pain in acquired pain conditions. For instance, the *SCN9A* rs6746030 variant results in an amino acid substitution of arginine to tryptophan at codon 1150 of the a subunit of Nav1.7, which enhances cell excitability of dorsal root ganglia (Estacion et al., 2009). Some studies have demonstrated that the minor rs6746030 A allele (tryptophan substitution) was associated with increased pain reports in individuals with OA, sciatica and phantom limb pain (Reimann et al., 2010) as well as postoperative pain (Duan et al., 2016) and small fibre neuropathy (Hoeijmakers, Merkies, Gerrits, Waxman, Faber, 2012). Additionally, functional characterisation of two rare non-synonymous mutations of *SCN9A,* methionine to threonine substitution (rs201561928) and threonine to isoleucine (rs200470541) at codons 1863 and 1607, respectively demonstrated gain of function changes consistent with an increase in neuronal excitability in a diabetic neuropathy cohort (Blesneac et al., 2018). Similarly, rare mutations in the *SCN10A* and *SCN11A* genes, encoding Nav1.8 and Nav1.9, respectively have also been shown to contribute to inflammatory and neuropathic pain (Huang et al., 2013) and familial episodic pain (Zhang et al., 2013), respectively (Table 1). However, other authors have not been able to replicate these results in independent cohorts (Holliday et al., 2012). The potential relevance of Nav to pain in tendinopathy was demonstrated by Gammaitoni et al. (2013) who reported success with topical lidocaine in managing patellar tendinopathy pain. As lidocaine provides pain relief by blocking Nav channels, their results suggest that peripheral Nav channels play a role in tendon pain; therefore, variants in sodium channels may well affect the pain profile in tendinopathy.

Variants in genes encoding other ion channels such as voltage gated potassium channels (Kv) and voltage gated calcium channels (Cav) have also been associated with chronic painful conditions. The rs734784 variant in potassium voltage-gated channel delayed rectifier subfamily S, member 1 (*KCNS1*) was associated with higher pain in healthy controls and in phantom limb pain, however, this variant did not associate with post mastectomy pain (Costigan et al., 2010). In addition, a number of variants in voltage gated, inward rectifying and two pore potassium channel genes were associated with risk and severity of persistent pain following surgery (Chidambaran, Gang, Pilipenko, Ashton, Ding, 2019) (Table 1). Voltage gated Ca^{2+} channels constitute the main pathway for depolarisation mediated Ca^{2+} influx into neurons. Genes that encode these Ca^{2+} channels have been implicated in painful conditions. For example, *Cacna2d3,* the gene that codes for the a253 subunit of the voltage dependent calcium-

Table 1. Genetic variants in extracellular components and regulators, ion channels, inflammatory mediators and cytokines; and in the catecholaminergic system that have been implicated in other pain syndromes

	Protein(s)	Gene	Polymorphism (s)	References
Extracellular Matrix Components and Regulators	Type XI Collagen	*COL11A1*	rs1676486 (C/T), rs3753841 (T/C)	Raine et al., 2013; Hay et al., 2013
		COL11A2	rs16868943(G/A)	Ho et al., 2017
	Matrix Metalloproteinases (MMPs)	*MMP1*	rs1799750 (G/-)	Planello et al., 2011
		CASP9	rs4645978 (A/G)	Mu et al., 2013
Ion Channels	Sodium Channels	*SCN9A*	rs6746030 (G/A)[1], rs201561928 (T/G)[2], rs200470541 (G/A)[3]	Estacion et al., 2009; Reimann et al., 2010; Duan et al., 2016; Hoeijmakers et al., 2012; Blesneac et al., 2018
		SCN10A	rs968515082 (T/G)[4]	Huang et al., 2013
		SCN11A	rs138607170 (C/T)[5], rs483352921 (C/G)[6]	Zhang et al., 2013
	Potassium Channels	*KCNS1*	rs734784 (A/G), rs13043825 (G/T)	Chidambaran et al., 2019; Costigan et al., 2010
	Calcium Channels	*CACNA2D3*	rs6777055 (A/C)	Neely et al., 2010
		CACNG2	rs4820242 (G/A), rs2284015 (C/G), rs2284017 (T/C)	Bortsov et al., 2019; Neely et al., 2010
	Acid Sensing Ion Channels	*ASIC*	Asic gene knockout model	Vick, Askwith, 2015
Inflammatory Mediators and Cytokines	COX-2	*PTGS2*	rs2383515 (G/T), rs5277 (G/C), rs5275 (T/C), rs2206593 (G/A)	Reyes-Gibby et al., 2009; pplebaum et al., 2015
	Tumour Necrosis Factor	*TNF-a*	rs1800629 (GA)	Reyes-Gibby et al., 2009
	Interleukins	*IL1A*	rs1800587 (G/A/C/T)[7]	Solovieva et al., 2004; Moen et al., 2014
		IL1B	rs16944 (G/A)[8] rs1143634 (G/A)[9]	Bessler et al., 2006 Slodovieva et al., 2004
		IL1R1	rs2110726 (G/A)	McCann et al., 2012
		IL1R2	rs11674595 (T/C)	Stephens et al., 2014
		IL1RN	rs2234677 (G/A)[10], rs2234679 (G/C)[11], rs9005 (G/A)[12]	Moen et al., 2014; Slodovieva et al., 2004
		IL6	rs2069840 (C/G) rs1800795 (C/G)	Białecka et al., 2016 Stephens et al., 2017
		CXCL8 (IL8)	rs4073 (A/C)	Stephens et al., 2014
		IL13	rs1295686 (T/A)	McCann et al., 2012
		IL10	rs3024505 (G/A), rs3024498 (T/C), rs3024496 (A/G), rs1878672 (G/A), rs1518111 (T/C), rs1518110 (A/C), rs3024491 (C/A)	Stephens et al., 2014
		IL16	rs4778889 (T/C)	Gan et al., 2010
Catecholaminergic System	Catechol-o- methyltransferase	*COMT*	rs6269 (A/G), rs4633 (C/T), rs6267 (G/T), rs4818 (C/G), rs4680 (G/A)[13], rs165774 (G/A), rs165774 (G/A)	Diatchenko et al., 2005; Li et al., 2017; 2014; Barbosa et al., 2012; Martinez-Jauand et al., 2013; Martire et al., 2016; Knisely et al., 2018

[1] Arg1150Trp; [2] Met1863Thr, Met1852T (www.ncbi.nlm.nih.gov/clinvar, Blesneac et al., 2018); [3] Thr1607Ile, Thr1596Ile (www.ncbi.nlm.nih.gov/clinvar; Blesneac et al., 2018); [4] Ile1706Val; [5] Arg225Cys; [6] Ala808Gly; [7] -889C/T polymorphism; [8] -511 G is allele 1 and -511 A is allele 2; [9] C+3954T (Phe105Phe); [10] G1812-A; [11] G1887-C; [12] T11100-C;[13] Val158Met.

channel complex, has been associated with thermal pain-related behaviour in animal studies (Neely et al., 2010). In healthy volunteers, the rare *CACNA2D3* rs6777055 C allele was also associated with reduced acute thermal pain while individuals with a CC genotype showed reduced risk for chronic back pain post discectomy (Neely et al., 2010). Additionally, *Cacng2* variants (*Cacng2* encodes for the y2 transmembrane AMPA receptor protein stargazin) affect susceptibility to chronic pain after nerve injury in mice (Neely et al., 2010). In humans, an association was observed between increased susceptibility to pain after mastectomy and the A-C-C haplotype constructed from the *CACNA2* rs4820242, rs2284015, and rs2284017 intronic variants (Bortsov et al., 2019).

Other ion channels whose expression may be modulated in tendinopathy are acid sensing ion channels (ASICs). The role of ASICs in pain has been demonstrated in rodent studies where *Asic* gene knockout mice were resistant to mechanical hyperalgesia (Vick, Askwith, 2015) as well as being linked to migraine in humans (Dussor, 2015). ASICs have also been associated with other painful conditions that, much like tendinopathy, involve acidosis, inflammation and ischaemia (Rio et al., 2014).

The inflammatory hypothesis: Inflammatory mediators and cytokines

A number of inflammatory mediators such as cytokines are also important in the pathology of painful tendinopathy. These cytokines include TNF-a, FGF, TGF-p and the interleukin family (Dakin, Dudhia, Smith, 2014). In particular, IL-1a, IL-ip and IL-33, with a signalling pathway through the activation of mitogen activated protein kinases (MAPKs), stimulate mediators of inflammation causing the onset of pain and extracellular matrix (ECM) breakdown (D'Addona, Maffulli, Formisano, Rosa, 2017). Research in other chronic painful conditions has shown some associations between cytokine gene variants and pain. For instance, a study on lung cancer patients showed that certain genotypes for *PTGS2,* which encodes Cyclooxygenase- 2 (COX-2), and Tumor Necrosis Factor alpha (*TNF-a)* polymorphisms are protective and permissive to pain, respectively (Reyes-Gibby et al., 2009) (Table 1). However, the *PTGS2* G-G-T-A haplotype constructed from rs2383515, rs5277, rs5275 and rs2206593 was associated with post-treatment pain following endodontic treatment (Applebaum, Nackley, BairMaixner, Khan, 2015). In a study of women with breast cancer, carriers of the minor A allele of *IL1R1* rs2110726 reported less breast pain while those with the minor A allele of *IL13* rs1295686 had higher pain scores (McCann et al., 2012). Stephens et al. (2014) also showed that *IL1R2* rs11674595 and the *IL10* haplotype A8 (Table 1) were associated with persistent postoperative pain following breast cancer surgery. In other work, Stephens and colleagues also showed that variants in *IL6, CXCL8 (IL8), and TNF* are associated with the development and maintenance of mild persistent breast pain after breast cancer surgery (Stephens et al., 2017) (Table 1).

A study from China on females diagnosed with endometriosis also showed an increased representation of the C allele of rs4778889 in the *IL16* gene compared to healthy controls and particularly in those with higher self-reported pain (Gan et al., 2010). These results were not replicated among women from a study in Iran (Azimzadeh, Khorram Khorshid, Akhondi, Shirazi, 2016). Individuals carrying at least one G allele of *IL6* rs1800795 also reported higher pain scores in the postoperative period following total hip replacement (Białecka et al., 2016). Additionally, simultaneous carriage of other interleukin-1 variants, *IL-1 RNA* and *IL-1a* has been shown to increase the pain intensity and duration in chronic low back pain (Solovieva et al., 2004) (Table 1). This suggests that *IL-1a and IL-1^* variants may promote or prolong low back pain. Furthermore, variants in *IL1A* rs1800587 affected pain scores and pressure pain threshold in a cohort of patients with lumbar radicular pain. In this cohort, the rs1800587 T allele was associated with an enhanced promoter activity resulting in increased gene expression which enhances the

release of IL-1a and hence the inflammatory response and pain report (Schistad, Jacobsen, Røe, Gjerstad, 2014). Furthermore, an association between the *IL1A* rs1800587 variant and pain intensity was observed in a cohort from Finland, of middle-aged men with low back pain (Solovieva et al., 2004). Similarly, Moen, Schistad, Rygh, Re, Gjerstad (2014) showed that in lumbar radicular pain, patients with the *IL1A* rs1800587 T allele in combination with the *IL1 RN* rs2234677 A allele had more pain and a slower recovery than other patients. Bessler et al. (2006) did not, however, show a relationship between postoperative pain or morphine use and *IL1B* variants in a cohort of women undergoing transabdominal hysterectomy (Table 1).

Although the association with pain was not investigated, several studies have investigated the association of interleukin gene variants with risk of tendinopathy. In one, the AA genotype of *IL6R* rs2228145 (C/A) was associated with reduced risk of developing CTS in a South African cohort (Burger, de Wet, Collins, 2015). In another, while variants within the *IL-1^*, *IL-6* and *IL-1RN* genes were not independently associated with Achilles tendinopathy risk, when found with the *COL5A1* rs12722 (C/T) variant, they were collectively implicated in modulating risk of Achilles tendinopathy (September et al., 2011). It is interesting to note that a study by Suijkerbuijk et al. (2020) implicated variable cytokine expression, specifically *ILip*, *IL6* and *IL-6* Receptor, in the context of a genetic dependent risk model using fibroblast cells. Taken collectively, the importance of the inflammatory pathway in tendinopathy is growing, it would be of interest to further explore the relationship between interleukin genes and tendon pain.

The central pain mechanisms hypothesis: COMT

Available evidence also suggests that tendon pain may be a result of defective central pain inhibition (Plinsinga et al., 2015; Tompra et al., 2016). The catecholaminergic system plays a crucial role in the facilitation or inhibition of nociceptive transmission (Millan, 1999). Abnormalities in catecholamine physiology are associated with decreased activity of catechol-o-methyltransferase (COMT), an enzyme which inactivates catecholamines. As a result, *COMT,* the gene that encodes the enzyme, is one of the most frequently studied of pain genes and has been associated with differential pain sensitivity under experimental and pathological conditions (Baumbauer et al., 2020) as well as with anxiety, depression, and other psychological traits that influence the perception of pain (Fernandez-De-Las-Penas et al., 2019).

Most commonly, various studies have demonstrated the association between Val/Met substitution at codon 158 in the *COMT* gene (rs4680) and numerous pain disorders (Tammimaki, Mannisto, 2012). Individuals homozygous for the Val variant have three to four times higher activity of the COMT enzyme and hence reduced pain sensitivity compared to homozygotes of the Met genotype (Diatchenko et al., 2005) whose variation leads to decreased COMT thermostability, activity and increased pain report in experimentally induced pain (Fernandez-De-Las-Penas et al., 2019) and in orofacial pain (Tchivileva et al., 2011). Furthermore, this variant has also been associated with Parkinson's disease related pain (Lin et al., 2017), fibromyalgia pain sensitivity (Barbosa et al., 2012; Martnez-Jauand et al., 2013), depression and experimental pain (Fernandez-De-Las-Penas et al., 2019), and variability in OA pain (Martire et al., 2016).

Other *COMT* variants such as rs6269, rs4633 and rs4818 were also associated with low back pain related disability in a mixed European cohort; the minor G, C and G alleles of these three polymorphisms were associated with lower baseline disability scores (Omair et al., 2015). Carriers of the rs4818 CC genotype were also over-represented in a cohort of fibromyalgia from Brazil (Barbosa et al., 2012) and the minor C, G and A alleles of rs4633, rs4818 and rs4680, respectively, were over-represented in other fibromyalgia cohorts though not associated with

pain (Brenton et al., 2017). *COMT* rs6267 has also been associated with Parkinson's disease pain wherein the minor T allele presented with higher pain scores (Li, Chen, Yin, Zhang, 2014). In addition, *COMT* rs165774 showed an association with heat pain; the wild type GG genotype with lower pain threshold (Mladenovic et al., 2018).

In addition, *COMT* variants have also been associated with chronic post-surgical pain (Lee, Delaney, Keogh, Sleeman, Shorten, 2011) in which individuals carrying the wild type *COMT* rs4818 CC genotype presented with lower pain scores than those with the CG and GG genotypes following molar extraction. While the high pain A-C-C-G haplotype constructed from rs4663, rs4680 and rs6269 and rs4818 was associated with severe pain after breast cancer surgery (Knisely et al., 2018). Additionally, *COMT* variants have been associated with post-operative analgesic response (Sadhasivam et al., 2014). In the latter study, minor G, C, G and A allele carriers of rs6269, rs4633, rs4818, and rs4680 were three times more likely to require analgesic intervention than homozygotes of the major alleles. *COMT* haplotypes have also been shown to affect response to analgesia in temporomandibular joint disease (Tchivileva et al., 2011). Some authors have however not replicated these findings (Kambur et al., 2013).

Wang et al. (2019) found no association between rs4680 and chronic post-surgical pain following caesarean section. Additionally, in other cohorts, there were no associations observed between *COMT* variants and chronic pain conditions such as Parkinson's disease related pain (Li et al., 2014), pain sensitivity in chronic widespread pain (Nicholl et al., 2010), chronic lower back pain (Omair et al., 2015), pain sensitivity in fibromyalgia (Park et al., 2016), vulvodynia (Patanwala et al., 2017) and chronic post-operative pain (Kolesnikov et al., 2013). The HUNT study was also unable to show any associations between *COMT* genotypes and twelve musculoskeletal conditions in a large Norwegian cohort (Hagen, Pettersen, Stovner, Skorpen, Zwart, 2006). Moreover, no associations were observed between recovery and pain intensity in a European cohort of whiplash injury (Rydman et al., 2017), migraine headache in a cohort from Japan (Takigawa, Kowa, Nakashima, 2017) or pancreatitis in an independent cohort (van Esch et al., 2011). These conflicting results among studies on the association between genetic and clinical variables may reflect the heterogeneity of pain conditions, related to potential subtypes of pain phenotypes, and the small sample sizes of some of the reported studies. It is important to note that three haplotypes of *COMT* (rs6269, rs4818 and rs4680) account for about 11% of the variability in pain perception and given the polygenic nature of pain perception, this is a substantial contribution (Diatchenko et al., 2005).This underscores the significant role that COMT likely plays in pain chronification.

Variants in *COMT* have also been associated with depression and other mood disorders (Femandez-De-Las-Penas et al., 2019). The potential role of the Val/Met variant in pain could be because individuals with the Met/Met genotype of the Val/Met substitution at codon 158 (rs4680) have greater activation of the limbic regions (anterior cingulate cortex-ACC) of the brain in response to emotionally challenging circumstances and negative stimuli such as pain (Smolka et al., 2005) and lower activation of the dorsolateral prefrontal cortex (Egan et al., 2001) when compared to Val/Val. The ACC is a key structure of cortical pain processing that is involved in the affective evaluation of pain as well as anti-nociception (Boadas-Vaello, Homs, Reina, Carrera, Verdu, 2017).

Additionally, Met/Met individuals also have higher pain sensitivity and dysfunctional p- opioid receptor mediated mechanisms in the parahippocampal regions when challenged with prolonged pain (Nascimento et al., 2019). The latter region has an integral role in episodic memory and emotional pain processing. In addition, *COMT* rs6267 GT genotype was associated with depression and Parkinson's disease pain (Lin et al., 2017). Another *COMT* variant that has been associated with cognition is rs4818, where the wild type CC genotype has also been shown to have lower efficiency at processing emotionally arousing stimuli (Roussos, Giakoumaki, Pavlakis, Bitsios, 2008).

This may predispose carriers to stress and dysfunctional responses in the face of disadvantageous situations such as chronic pain. The collective data is therefore suggesting that sequence variations within the *COMT* gene may reduce opioid mediated inhibitory control of pain, impact brain activity in cognitive domains and hence alter both the physiological and psychological domains of pain processing in a chronic pain condition. Chronic tendon pain affects mood and general affect in sufferers (Mkumbuzi et al., 2020), as well as being associated with altered conditioned pain modulation (Tompra et al., 2016) which is a proxy for the internal analgesic system. Since the internal analgesic system and mood are both reliant on COMT, any aberrations in COMT are relevant to the study of chronic tendon pain.

Conclusion

In conclusion, the causes of pain in tendinopathy are still unknown. As genetic variation is implicated in a variety of other pain conditions, a plausible extension of this work would be to explore the genetics of the main symptom in tendinopathy, pain, to further characterise its underlying mechanisms. Some of the genes that have previously been implicated in the pain associated with other conditions are also of interest in tendinopathy as they encode components of the tendon ECM, ion channels, inflammatory mediators and the internal analgesic system (Table 1). This review is by no means exhaustive; however, it does provide a theoretical framework on which to test the hypothesis that genetic variations previously associated with other pain conditions could, at least in part, modulate the variability observed in the pain syndrome of chronic tendinopathy. Using available and emerging technologies will allow us to identify the various genes that are implicated in tendon pain and this, in turn, allows us to explore the possible biological mechanisms underlying tendon pain. Hence, studying the genetic contribution of tendon pain may help identify the mechanisms involved in tendon pain as well as provide new therapeutic targets or strategies.

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