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DUPUYTREN'S CONTRACTURE: EMERGING INSIGHT INTO A VIKING DISEASE

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ABSTRACT

Dupuytren's disease is a fibroproliferative condition of the palm, with a predilection for men, which has affected Northern Europeans since the Viking conquests. Although strongly heritable, clear evidence exists for environmental factors that modify the underlying genetic risk, such as diabetes, heavy drinking, and smoking. Evidence also exists for epilepsy (probably due to treatment with certain anti-epileptic drugs), and Human Immunodeficiency Virus infection. Recent large studies have shown no relationship with manual labour or vibrating tools. Two theories have emerged regarding the pathogenic mechanism: the first attributes the aberrant healing process that characterises Dupuytren's to free radicals, generated as a result of microangiopathy, whereas the second cites a genetic tendency toward apoptosis-resistant myofibroblasts. Despite only one study demonstrating linkage, emerging data from genome-wide association studies highlight a series of single nucleotide polymorphisms near members of the Wnt signalling pathway, and transcriptional profiling studies have consistently identified certain components of the extracellular matrix.

Keywords: Dupuytren's Contracture; Etiology; Genetics; Epidemiology.

INTRODUCTION

Dupuytren's disease (DD) is a progressive condition involving contractures of the fascia of the palm and fingers. The condition is named after an eminent French Surgeon, Baron Guillaume Dupuytren, despite being previously described a century before by a less well-known Swiss Physician, Felix Plater.[1] However, numerous references to the condition can be found in artistic creations dating back to the 16th century, and even earlier, in Viking and Scottish folklore.

CLINICAL PRESENTATION AND PATHOGENESIS

The earliest signs of DD usually appear in the distal palm, in the form of thickening and puckering of the skin, before palpable cords and nodules appear in the palmar fascia, which eventually impinge on finger movement. The ring finger is most commonly affected, followed by the little finger.[1] Bilateral disease is relatively common, and is often heralded by the formation of Garrod's nodes (raised regions of hard skin on the

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dorsum of the proximal interphalangeal joints, resembling calluses). The disease process tends to move in a proximal-to-distal fashion, with the metacarpophalangeal (MCP) joints becoming affected before the proximal interphalangeal (PIP) joints.

The pathological mechanism in DD involves the formation of nodules, which are composed of myofibroblasts (essentially fibroblasts that contain a similar contractile apparatus to smooth muscle cells). These nodules contract, forming cords of tight fascia that eventually restrict the movement of the fingers. Finally, the cellular component of these nodules is replaced by collagen matrix.[2] It has been known for some time that there is a relative abundance of type-III collagen and glycosaminoglycan in Dupuytren's fascia vs. normal fascia,[3,4] although later evidence has suggested that this is likely to be due to the down-regulation of a gene encoding the usually dominant type-I when fibroblasts are in dense populations.[5] The progression of a contracture can be divided up into three stages (Fig. 1)[6]; the first being uncontrolled proliferation of fibroblasts, followed by myofibroblast differentiation and contracture (stage 2), and finally, replacement of the cellular component of the nodule with collagen matrix (stage 3). However, the progression of the disease is not inevitable, with only 50% of those patients exhibiting nodules in one study going on to develop movement-limiting cords.[7]

The puckering of the skin of the palm has a similar pathological mechanism, involving the superficial Grapow fibres that tether the overlying skin to the palmar fascia. The contraction of these Grapow fibres leads to the formation of 'microcords', giving the skin the appearance of thickening and dimpling.[1] Flexion contractures of the fingers at the MCP joints generally result from cords affecting the pretendinous bands of the finger, which arise from the palmar aponeurosis and are variously named as they follow an indirect course through the structures of the finger (spiral band, lateral digital sheet), before terminating on the base of the middle phalanx. PIP joint involvement occurs when the central cord of the finger (also called the intertendinous band), which also arises from the palmar aponeurosis, becomes affected. The anatomical relations of these cords are depicted in Fig. 2.

Although the cause of nodule and cord formation in DD is not yet fully understood, the prevailing view is that it arises as a result of microvascular angiopathy,[1] a theory that is consistent with its association with increasing age, smoking, and diabetes. The microvascular angiopathy theory is further strengthened by the finding that the extent of DD in diabetic patients is related to the presence of retinopathy.[8] A further study from the 1980s has demonstrated the presence of short-chain fatty acids "not inconsistent" with a degree of ischaemia in the palms of patients with DD.[9] These authors further suggest that female gender may be protective in DD through the same mechanism that is protective in cardiovascular disease. A number of mechanisms for how ischaemia might give rise to DD have been put forward, including the idea that it may be mediated by free-radical release. In high concentrations, free radicals, which are defined as reactive atoms lacking the full complement of electrons required to achieve electrical neutrality, are toxic to all cell types; however, work by Murrell and colleagues[10] has
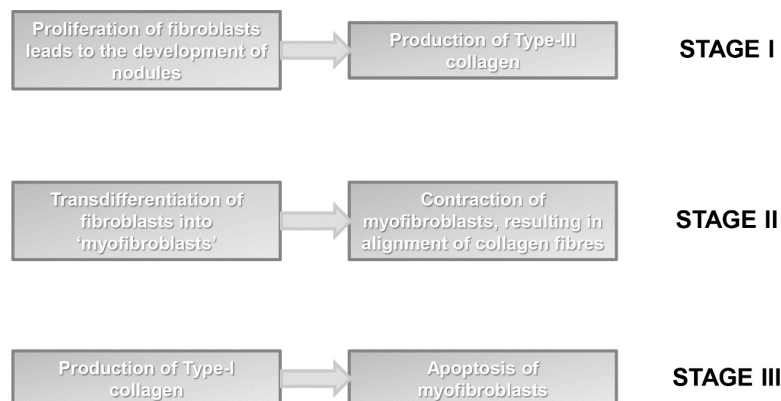

Fig. 1   Stages in the pathogenesis of Dupuytren's contracture, and the corresponding stage in Luck's classification system. Adapted from Lam WL, Rawlins JM, Karoo RO, Naylor I, Sharpe DT, Re-visiting Luck's classification: a histological analysis of Dupuytren's disease, *J Hand Surg Eur* **35**(4):312–317, 2010. Figure 7, Simplified flow-chart of pathological processes in Dupuytren's disease and the corresponding stages in Luck's classification system; pp. 316.

DUPUYTREN'S DISEASE
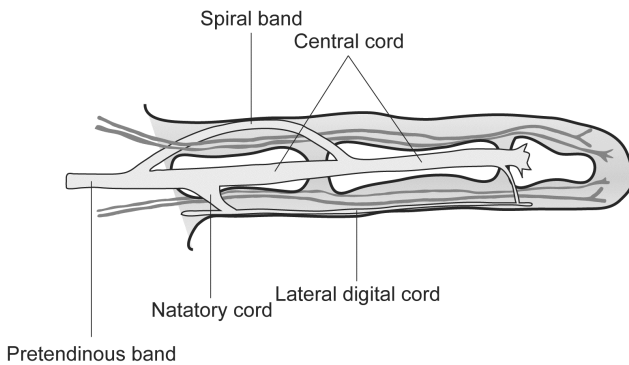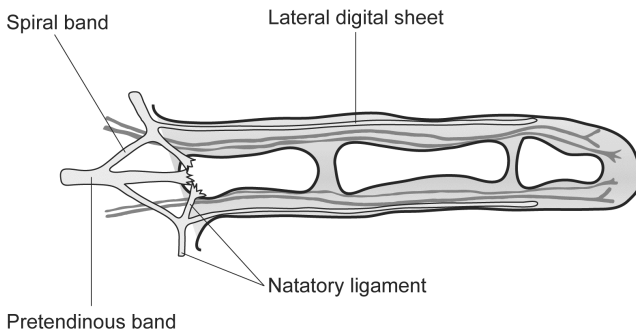

NORMAL FASCIAL ANATOMY

Fig. 2 The normal fascial anatomy of the ventral aspect of the finger, and the positions of the most common fascial components affected by Dupuytren's disease. Adapted from Wolfe SW, Pederson WC, Hotchkiss RN, Kozin SH, Cohen MS, *Green's Operative Hand Surgery*, 6th ed. New York: Churchill Livingstone; 2010. Figure 5.4, Normal fascial anatomy and pathoanatomy of the common cords of the distal palm, palmar digital junction area, and digit; p. 144.

shown that at low concentrations they provide a mitotic stimulus to cultured fibroblasts. Ischaemia in the tissues surrounding the palmar fascia may be the cause of the accumulation of hypoxanthine and xanthine (the precursors of free-radical release, see Fig. 3) detected by Murrell and colleagues. There is also evidence from other authors that platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β; specifically the TGF-β_1 isoform) are important in the proliferation of myofibroblasts, with the latter being expressed specifically in the myofibroblasts of those with active DD.[11,12] It is quite possible that both free radicals and the release of growth factors by fibroblasts in a pre-disease state may form part of the same pathogenic mechanism. An alternative theory to that of microvascular ischaemia is that repeated trauma from manual labour or vibrating tools,
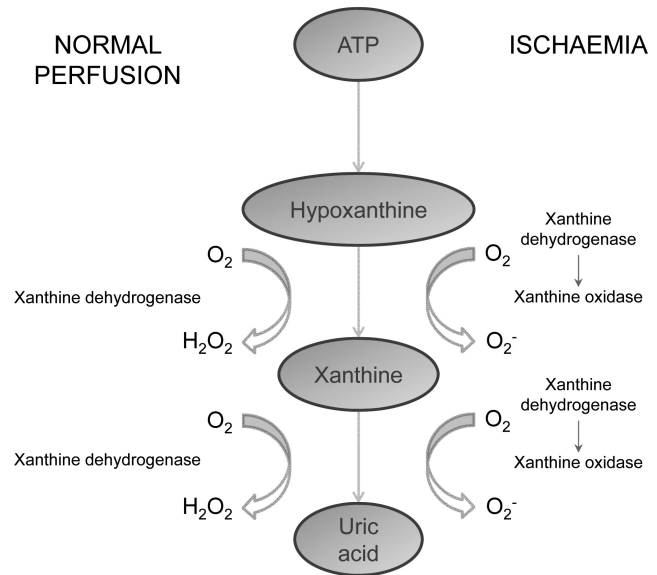

Fig. 3 Under ischaemic conditions, ATP is degraded to hypoxanthine, xanthine, and finally to uric acid. In hypoxic conditions, xanthine dehydrogenase, the enzyme responsible for reducing a number of compounds in this pathway, is converted to an oxidase, and generates dangerous free radicals. Adapted from Murrell GA, An insight into Dupuytren's contracture, *Ann R Coll Surg Engl* **74**(3):156–160, 1992. Figure 3, Schematic representation of the mechanism for ischaemia-induced free radical damage; pp. 158.

combined with abnormal healing of the palmar fascia, is to blame for contractures in DD, although recent evidence has cast doubt on this.[13,14] Another, more convincing hypothesis is that DD may share a pathogenic mechanism with other fibrotic diseases, such as pulmonary fibrosis, in which myofibroblasts resistant to apoptosis are thought to mediate the disease process.[15]

GENETICS

Dupuytren's contracture occurs in both hereditary and sporadic forms. Evidence for a considerable genetic component to its development, including the increased risk amongst siblings of affected individuals (three-fold),[16] has amassed over many years. The disease is most prevalent amongst Northern Europeans, and there is some evidence that the condition arose in Vikings or a precursor tribe,[17,18] and was thus spread throughout the surrounding regions. Having said this, DD does occur, with a lower prevalence, in all ethnic groups studied to date, including the Japanese[19] and Black Africans.[20] DD may also occur as part of a systemic disorder, in combination with penile fibrosis (known as Peyronie's disease).

◀ Dolmans SNPs

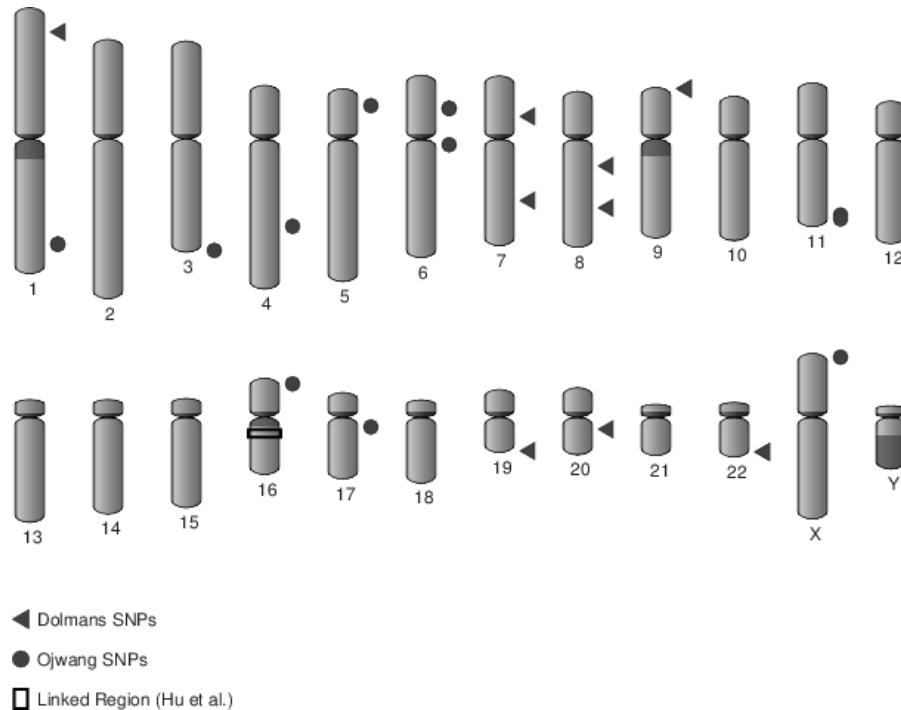● Ojwang SNPs

☐ Linked Region (Hu et al.)

Fig. 4   Locations of linked regions and associated SNPs.

An early cytogenetic study of Dupuytren's nodules[21] suggested that they contained chromosomally-aberrant fibroblasts, not seen in control fascia, and subsequent studies have reported the presence of clones of cells trisomic for either chromosome 7 or 8.[22–24] The presence of cells trisomic for chromosome 8 is particularly intriguing because this aberration is also seen in benign tumours of the gut[25] and some meningiomas.[26] However, Sergovich and colleagues' study[22] was very small (containing only eight patients), and Wurster-Hill's,[23] although larger, showed that numerical chromosomal abnormalities also occurred in control fascial cultures (with similar incidence), although they found that the most common in DD cultures were trisomy 7 or 8. Dal Cin and colleagues[24] found similar abnormalities. Chromosomally-abnormal cells (including those trisomic for chromosome 8) were found by Bonnici and colleagues[27] in the fascia of the flexor retinaculum from patients operated on for carpal tunnel syndrome, which may, as the authors suggest, support a common mechanism for these two disease processes or more likely, indicate that such chromosomal abnormalities are relatively common in rapidly-growing populations of fibroblasts. Other authors have found evidence of increased chromosomal instability in DD, but not clones of trisomic cells or any consistent patterns of chromosomal loss or

rearrangement.[28] A more recent 'high-throughput' approach to this question employing comparative genomic hybridisation, a technique in which long fragments of genomic deoxyribonucleic acid (DNA) from diseased and normal tissue are hybridised to an array, and compete for complementary probes, revealed no consistent cytogenetic abnormalities.[29] Taken together, these data seem to suggest that chromosomal instability is a consequence of the disease process, rather than one ubiquitous cytogenetic change being causative in the development or progression of a nodule. Alternatively, since the Kaur study[29] was performed using DNA extracted directly from nodules and found no cytogenetic abnormalities, as opposed to the fibroblasts expanded *in vitro* used in the preceding studies, these findings may merely represent an artefact of culture. However, more modern techniques have shown that localised changes in gene copy number (as opposed to gross cytogenetic changes) may indeed predispose to the development of DD (specifically at the 7p14.1 and 14q11.2 loci).[30]

Other authors have addressed the question of whether DD might arise from the inactivation of the tumour-suppressor gene, *BCL2*. *MYC* serves to induce programmed cell death (apoptosis) in cells, however, if *BCL2* is concomitantly upregulated, the apoptotic effects of *MYC* are masked and its

proliferative effects revealed. In the case of fibrosarcoma, for which DD nodules are occasionally mistaken, both *MYC* and *BCL2* are upregulated. However, although *MYC* expression was increased in certain types of DD tissue, *BCL2* levels remained low, contradicting this hypothesis.[31]

Surprisingly, only one study has identified linkage in DD to date, involving a Swedish family in which DD appeared to be inherited in an autosomal dominant fashion, leading to the identification of a region of chromosome 16 that co-segregated with the disease.[32] A subsequent genome-wide association study (GWAS) also identified chromosome 16,[33] although the linked single nucleotide polymorphisms (SNPs) were on the short arm, as opposed to the long arm (see Fig. 4). The authors also identified a variety of other chromosomes, including 1, 3 through 6, 11, 17, and 23. In addition to simple case-control analysis, they also employed publicly-available SNP databases of Northern and Southern European subjects and found a region of chromosome 6 that was enriched in Northern Europeans and within 10 kilobases of a significantly-associated SNP on this chromosome, which led them to regard this as one of their three strongest 'hits' (along with chromosomes 11 and 16). A larger GWAS published a year later, involving 960 DD sufferers (as opposed to the 40 in the original study), also identified a SNP in the vicinity of this region of chromosome 6, in addition to 10 other SNPs in a total of 9 loci.[34] The major finding of this study was that four of the implicated loci contained genes encoding proteins involved in the Wnt

signalling pathway, which is a prominent pathway in the pathogenesis of many cancers. This has led to an intriguing hypothesis about the way Dupuytren's nodules may arise that is analogous to polyp formation in polyposis coli. In the context of this condition, abnormal Wnt signalling causes intestinal crypt cells to proliferate for longer before migrating, leading to the formation of polyps, which eventually undergo malignant transformation. Abnormal Wnt signalling could thus explain the first histological stage of nodule formation in DD, in which fibroblasts proliferate excessively. Interestingly, a previous study showed an increased concentration of *β*-catenin, which accumulates when the canonical Wnt pathway is activated, in DD-affected fascia (see Fig. 5).[35] Further support for this hypothesis comes from the discovery that at least a proportion of DD sufferers may have reduced or absent expression of a number of micro ribonucleic acids (microRNAs) that restrain the Wnt pathway through negative regulation of genes such as *WNT5A*, *ZIC1*, and *TGFB1*.[36]

Pedigrees in which DD is inherited along the female line have also been described, and in one study, a mutation in a mitochondrial gene was identified in virtually all maternally-inherited cases of DD, and none of the controls.[37] In some ways mitochondria are attractive candidates for a role in DD, given their known tendency to 'leak' reactive oxygen species into the cytosol, and the fact that the enzymes responsible for 'mopping up' these free radicals become less efficient with age.[38] However, a pattern of maternal inheritance does not fit all families
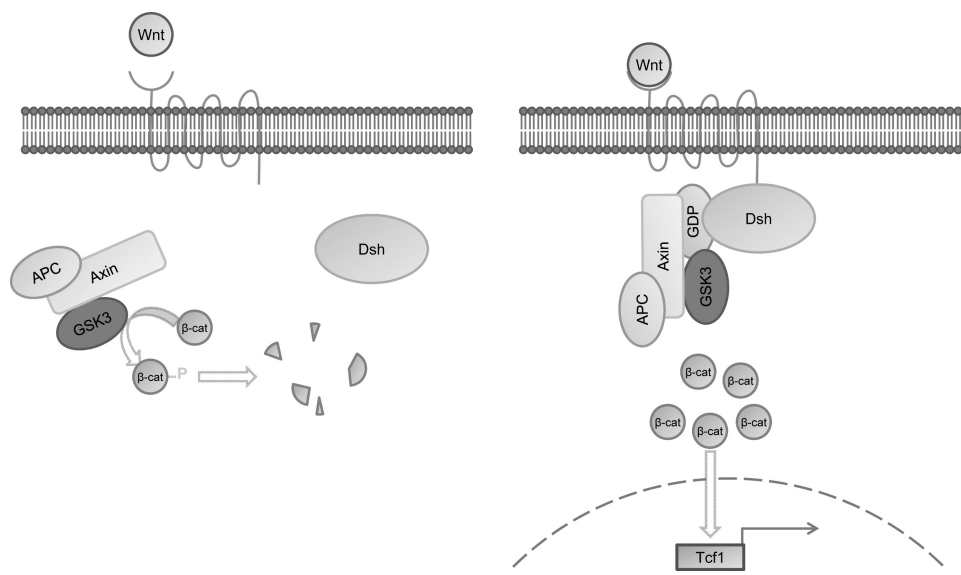

Fig. 5   Overview of the canonical Wnt pathway.

affected by DD, which is usually more suggestive of an autosomal dominant mode of inheritance.

Transcriptional profiling of Dupuytren's cords vs. normal fascia has contributed less than might have been hoped to our understanding of the pathogenesis of DD. All of these studies have identified components of the extracellular matrix such as collagens, collagenases, and metalloproteases, although intriguingly, bioinformatic analysis has revealed that other dysregulated genes fall into categories for lipid metabolism or cytoskeleton development.[39–42] However, as is often the case

Table 1   Summary of Transcriptional Profiling Studies.

Study	Design	Up-Regulated		Down-Regulated	
Lee *et al.*, 2006	DD-affected fascia vs. normal adjacent fascia, and vs. fascia from control subjects.	ADAM12 COL5A1 COL5A2 COL8A1 CNTN1 LRRC17 MAFB MXRA5 P37NB TNC TTYH3		*Not analysed*	
Rehman *et al.*, 2008	Pairwise comparison of DD nodule, DD cord, internal control fascia, external control fascia.	*DD nodules vs. controls:-* ACAN ADAM12 ARL4C COL1A1 COL5A1 COL5A2 CSRP2 LOXL2 LRRC17 NT5DC2 POSTN TNC	*DD cords vs. controls:-* CDH11 COL1A1 COL5A2 CSRP2 POSTN TNC	*DD nodules vs. controls:-* ADH1B ALDH1A1 CLU GPX1 MYOC PCOLCE2 TIMP1	*DD cords vs. controls:-* ADH1B ALDH1A1 CYP2C8 GPX3 HBA2 MMP3 MYOC PCOLCE2 PRG4 TNXB
Satish *et al.*, 2008	Diseased palmar fascia vs. fascia obtained from carpal tunnel-release surgery on two microarray platforms.	*No genes up-regulated on both platforms.*		*Four genes down-regulated on both platforms:-* ALDH3A1 COL5A1 FBLN1 PRG4	
Shih *et al.*, 2009	Bioinformatic refinement of a microarray list, informed by Hu *et al.* linkage analysis, and subsequently confirmed by RT-qPCR.	ADAM12 IRX† POSTN TNC		*None reached significance.*	

†This gene lies within the linked region of chromosome 16 identified by Hu *et al.*, 2005.

with transcriptional profiling experiments, the results are difficult to interpret owing to the large amount of data produced (summarised in Table 1), and leading to the identification of categories of gene function which are slightly vague. One study, for example, found that *ADAM12*, *POSTN*, and *TNC* were up-regulated in DD nodules vs. control fascia.[42] *ADAM12* and *POSTN* are up-regulated in certain cancers, whereas *TNC* has a known role in fibroblast migration. The other fundamental problem with transcriptional profiling in this context is that it is very difficult to tease out which dysregulated genes are an effect, rather than a potential cause of the disease. However, one transcriptional profiling study did identify a gene (*MAFB*) that has subsequently been corroborated by a GWAS hit.[34,39]

ENVIRONMENTAL RISK FACTORS

Aside from a genetic susceptibility to DD, there is evidence for modifiable, environmental risk factors such as smoking, heavy drinking, and exposure to vibrating tools (or more generally, manual labour). There are also non-modifiable risk factors such as age (incidence of DD is 4% below the age of 40, rising to 30% amongst the over 65s),[13] male gender (male-to-female ratio of DD is 5.9:1 in Europe),[43] and diabetes.[13,44] The reported prevalence of DD amongst diabetics has varied widely from 1.6% to 32%,[44] and this is thought to reflect the 'operator-dependence' of diagnosing very early signs of DD, of which even the patient themselves may be unaware. However, a recent study that examined nearly 100,000 miners in England applying for compensation for work-related injuries found an odds ratio of 1.52 for DD in diabetes, supporting a clinically significant effect.[13] The same study found an odds ratio of 1.31 amongst heavy smokers (≥ 20 cigarettes/day), which is consistent with previous work showing a higher incidence of cigarette smoking amongst patients undergoing surgery for DD.[45,46] Heavy drinking has also been associated with the development of the disease. Burge and colleagues[46] found that there was a higher incidence of an Alcohol Use Disorders Test score of > 7 amongst patients undergoing surgery for DD (compared to patients undergoing other orthopaedic operations), and Burke and colleagues[13] later confirmed this in their study, showing that heavy drinkers (> 22 units/week) were at an increased risk (odds ratio 1.59) of developing DD. This effect was preserved after correction for other potentially confounding factors, such as smoking.[13]

Previous authors have suggested that 'heavy work' may be responsible for the development of DD in at least a proportion of sufferers, and others have suggested that frequent use of vibrating tools may be the culprit. However, in their large study, Burke and colleagues[13] found no association with the use of vibrating tools (odds ratio 1.00, confidence interval 0.998–1.005). Recent work also appears to have debunked the belief that DD is associated with manual labour. Khan and colleagues[14] looked at the prevalence of DD within a large sample of individuals consulting their GP ($> 500,000$) and found no statistically significant associations between DD and different occupational social classes. Indeed, amongst those over the age of 65, it was found that the incidence of DD was actually higher amongst those who had been engaged in primarily non-manual work, although it has been suggested that this may be due to the under-utilisation of primary healthcare services by those in lower occupational social classes.

EPILEPSY

In addition to these risk factors, it has been known for some time that epileptics are at higher risk of developing Dupuytren's contracture. In the 1940s, Mögens Lund found that DD was four times more common among epileptics than controls, but found no association with any particular type of epilepsy.[47] Work by Scandinavian Neurologists suggested that DD was in fact a consequence of prolonged exposure to phenobarbitone (reviewed in Critchley *et al.*[48]), and more recent evidence has implicated other anti-epileptics, such as primidone and phenytoin.[48] An alternative explanation was put forward by James,[49] who felt that the association was more likely to be due to genetic linkage between a gene that causes idiopathic epilepsy and a gene that causes DD. However, previous and subsequent studies have shown that DD is not confined to patients with hereditary epilepsy, and that DD is seen even in those patients who have an apparent acquired cause for their epilepsy.[47,48] Critchley and colleagues[48] also alluded to studies of the hand in epileptics around the turn of the 20th century, which found only one case of DD in a large series, further supporting a causative role for an intervention introduced after this time (consistent with the emerging use of phenobarbitone). Dupuytren's contracture caused by anticonvulsant exposure is usually bilateral (although occasionally unilateral, favouring the left) and tends to be associated with dorsal pads (Garrod's nodes) and plantar nodules (Ledderhose's

disease).[17,48] It is important to note, however, that not all authors have come to the same conclusion regarding the relationship between phenobarbitone and DD, with one failing to demonstrate any relationship,[50] and another, more recent study, showing only a trend that was not statistically significant.[51] It has also been suggested that the association of prolonged anticonvulsant use and DD might be confounded by deranged liver function; however, Critchley and colleagues[48] found no statistically significant difference between liver function amongst those epileptics with DD, and those without.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Despite being a commonly-known association of DD, HIV infection appears to have a weak evidence base. Two studies have been performed on this topic, each involving 50 patients with AIDS. The first compared the prevalence of DD in serially-admitted patients with AIDS to a non-affected control group, and found a striking 36% prevalence in the AIDS group, compared with no cases in the control group.[52] The second addressed the prevalence of DD in AIDS patients presenting to a sexual health clinic, and found no greater prevalence than that seen in the general population (6%).[53] It may be that this discrepancy is due to the same 'operator dependence' that has dogged studies of other putative associations, or it may be attributable to the patient population under study: inpatients, who are likely to have been HIV-positive for longer, versus an outpatient population.

CONCLUSION

DD occurs as a result of aberrant development of myofibroblasts in the palmar and digital fascia causing nodule formation and contracture. The exact mechanism by which this occurs is unclear, but two main theories have been advanced; the first being that myofibroblast differentiation and proliferation are provoked by free radical release and the second implicating an increased tendency toward the development of apoptosis-resistant myofibroblasts in the condition. The increased prevalence of DD in siblings and in certain ethnic groups points toward a strong genetic component, and recent work has begun to identify genetic substrates for the condition. Linkage analysis has identified a region of the long arm of chromosome 16, whilst GWAS studies have highlighted

a number of significantly-associated SNPs and raised the tantalising possibility of a role for the Wnt pathway in the pathogenesis of the disease. Aside from a genetic propensity, environmental factors play a small, but significant role in the development of DD, of which diabetes, heavy drinking, and smoking are the most significant. There is a notable absence of evidence that vibrating tools or manual labour are implicated, and the evidence for an association with HIV is weak. Whilst the data for epilepsy is much more compelling, the exact cause of this effect remains open to debate. Further studies with higher statistical power may help to clarify these associations, but ultimately, a clearer understanding of the pathogenic mechanism of DD will be necessary to elucidate its true risk factors.

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