Whole genome and global expression profiling of Dupuytren's disease: systematic review of current findings and future perspectives

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ABSTRACT

Dupuytren's disease (DD) is a common fibroproliferative disorder affecting the palmar fascia, which may lead to permanent contracture of the affected digit. Profiling studies investigating DD at whole-genomic, transcriptomic and proteomic levels have been carried out, from which large numbers of candidate genes potentially involved in DD have been reported. This review focuses on identifying genes reported by multiple studies or validated by multiple experimental techniques, as well as signalling pathways suggested to contribute to DD. Meta-analysis was also carried out on three microarray datasets. Twenty-one genes were found to be reported as dysregulated in multiple gene expression microarrays, seven of which have been further validated by other experimental methods. Sixty-four genes determined to be dsyregulated by meta-analysis correlate to those reported by published microarray studies. In addition, several pathways have been proposed to be involved in DD by whole-genome or global expression profiling. Further investigation in these genes and pathways, and correlating them to genotypes or environmental factors for DD, may aid in further elucidation of mechanisms involved in DD pathogenesis.

Dupuytren's disease (DD) is one of the most common connective tissue disorders among Caucasians of northern European extraction.[1] DD is a fibroproliferative disease affecting the palmar fascia, and may lead to permanent flexion contracture of the digits.[1] In affected individuals, DD-like fibrosis can also be found over the knuckles (Garrod's pads), feet (Lederhose's disease) and penis (Peyronie's disease).[2 3] While surgical intervention is the mainstay of treatment for DD, there is a high recurrence rate post-surgery.[1 2] The aetiopathogenesis of DD remains unknown; however, a strong genetic component has been suggested. The evidence supporting this assertion includes increased family history, high Caucasian prevalence and reports of common occurrence in twins.[4] Several studies have attempted to identify the susceptibility genes to DD; however, to date no single gene has been confirmed to contribute to DD with a fully elucidated mechanism. Environmental factors, including trauma, alcohol, smoking and associated disease, have also been suggested to contribute to DD.[1]

The aim of this review is to summarise our current molecular understanding of DD, with a focus on findings from global gene expression studies by: (1) carrying out meta-analysis on microarray datasets available in public repositories; (2) comparing genes reported to be dysregulated by more than one global expression study or with more than one experimental technique; (3) comparing genes reported to be dysregulated and located within or adjacent to a genetic linkage in association with DD; and (4) signalling pathways suggested to be involved in DD by global expression profiling/meta-analysis.

CANDIDATE GENES IN META-ANALYSIS AND GLOBAL RNA EXPRESSION STUDIES

Eight global messenger RNA expression microarray studies[5–12] and one microRNA profiling[13] study were identified (see supplementary table S1, available online only). Four sets of microarray data on DD were identified at both the National Center for Biotechnology Information gene expression omnibus (GEO) and the European Bioinformatics Institute array express record ID for GEO: GSE4457, GSE2688, GSE21221 and GSE31356. Two of the datasets, GSE2688[12] and GSE4457,[6] were identical; therefore, the two datasets (and associated studies) were considered as one in the analysis of this review. GSE21221[10] involved the use of two experimental platforms on the same biological samples; the dataset from the CodeLink platform was selected for meta-analysis as the authors presented a higher number of significantly dysregulated genes with the CodeLink platform in their publication.[10] A total of 7072 unique UniGene ID was included in the meta-analysis (see supplementary text, available online only, and figure 1).

Twenty-one genes have been reported with consistent regulation by multiple gene expression profiling microarray studies (table 1 and figure 2). Nineteen of these 21 genes were assessed in the meta-analysis, 16 of which were also determined to show statistically significant dysregulation in DD with the same regulation (over/underexpression) (table 1). Eight of the genes reported by multiple microarray studies have also been validated by other gene-specific experimental methods (table 1), including *ADAM metallopeptidase domain 12* (*ADAM12*),[14] *collagen type I α 2* (*COL1A2*),[23] *matrix metallopeptidase* (*MMP*)*2*,[15 16] *periostin, osteoblast specific factor* (*POSTN*),[14] *proteoglycan 4* (*PRG4*)[10] and *tenascin C* (*TNC*) (table 1).[14]

There is only one array-based microRNA profiling study in DD. MicroRNA are post-transcriptional regulators that negatively regulate their mRNA targets.[17] Mosakhani *et al*[13] compared the microRNA profiles in their study with the mRNA expression profiles in the study by Forsman *et al*,[5] and showed concurrence on the downregulation of microRNA and upregulation of their target mRNA. The genes

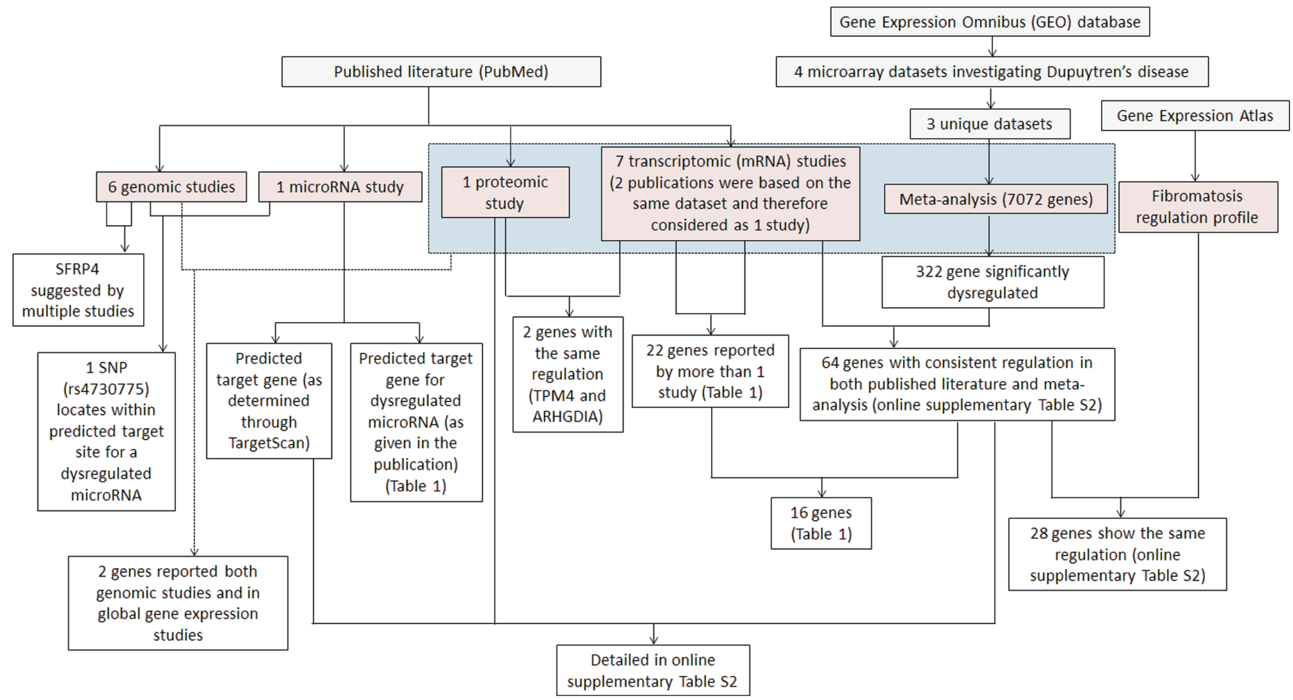

Figure 1 Flowchart of the analysis carried out in this review. The flowchart indicates results from the comparisons made in this study. Grey boxes indicate the origin of the data. Red boxes indicate raw data origin used in comparisons. The blue box indicates gene expression data that have been compared with whole-genome studies. Purple boxes indicate results, or the tables with the results, from comparisons. SNP, single nucleotide polymorphism.

highlighted by Mosakhani *et al*[13] include: *ADAM12, collagen, type V, alpha 2 (COL5A2), transforming growth factor* β *(TGFB)1, v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (MAFB) , POSTN, TNC, wingless-type MMTV integration site family, member (WNT)5A* and *Zic family member 1 (ZIC1)* (table 1). Other than *TGFB1*, all of these genes were found to be significantly upregulated in the meta-analysis (table 1).

A total of 322 genes (out of 7072 analysed) was determined to be significantly dysregulated in DD by the meta-analysis; 64 of the 322 genes demonstrated the same regulation as those reported by at least one gene expression microarray study (see supplementary table S2, available online only, and figure 1). Twenty-eight of these 64 genes share the same regulation as those seen in fibromatosis, based on the expression data available in the gene expression atlas[18] (see supplementary table S2, available online only, and figure 1).

COMPARING GLOBAL RNA EXPRESSION WITH PROTEIN EXPRESSION

Investigation of both mRNA and protein levels are necessary and complimentary for the identification of biomarkers in human disease.[19 20] Two whole-proteome studies have been carried out to identify differentially expressed proteins in DD.[21 22] While O'Gorman *et al*[22] identified three potential low molecular weight tissue protein markers that were positively associated with DD, the genes coding for these protein markers were not determined; therefore these findings were not included in this review. By comparing biopsies of DD with internal palmar fascia, Kraljevic Pavelic *et al*[21] have reported 44 genes showing five-fold upregulation in DD through two-dimensional gel electrophoresis. Of these genes, three were reported in mRNA expression profiling microarrays with consistent regulation; *ARHGDIA*,[8] *COL6A3* (meta-analysis) and *TPM4*.[11] *ARHGDIA* is also overexpressed in Peyronie's disease.[8]

Several genes determined to be dysregulated by multiple gene expression microarrays have been validated at the protein level by immunohistochemistry, western blotting, or zymography, and include *MMP2*,[15] *COL1A2*[23] and *POSTN*.[11] *POSTN* demonstrates the highest consistency in its altered expression in DD; found to be dysregulated in three mRNA microarray studies,[8 9 11] and the meta-analysis in this review (derived from data in Lee *et al*,[6] Satish *et al*[10] and Zhang *et al*),[12] which also showed upregulation of *POSTN*. *POSTN* is an extracellular membrane protein that is found in collagen-rich connective tissues,[24] and overexpression of *POSTN* may contribute to tumorigenesis by promotion of cancer cell survival, epithelial-mesenchymal transition, invasion and metastasis.[25] Application of exogenous *POSTN* to fibroblasts derived from DD and control fascia was found differentially to regulate apoptosis, proliferation, alpha-smooth muscle actin expression and fibroblast populated collagen lattice contraction.[11]

Protein staining for several extracellular matrix (ECM) proteins or growth factors in DD correlates to mRNA dysregulation reported in microarray studies.[9-12 26 27] Howard *et al*[27] demonstrated higher protein levels of fibronectin in DD, also supported by mRNA microarray studies.[6 12] ECM surrounding alpha smooth muscle actin-positive cells in proliferative nodules demonstrate staining of type IV collagen, laminin and tenascin.[28 29] Several immunohistological studies investigate specific ECM in DD.[27-30] Pathological collagen deposition has been associated with DD.[31] Collagens are triple helical proteins found in ECM, and there are more than 30 collagens and collagen-related proteins.[32] Early studies have noted an increase in the ratio of type III to type I collagen going from control palmar fascia through uninvolved, mildly involved cords to nodules of DD.[33] Murrell *et*

Table 1 Genes that have been reported by messenger RNA expression microarray studies

Gene symbol	Gene expression microarray studies	Upregulation or downregulation	Fold change	Meta-analysis (pfp*/regulation/ fold change)[6 10 12]	Dysregulated microRNA predicted to target the gene[13]†	Downstream confirmation
ADAM12	Multiple[6 9]	Up	4	<0.001 /Up/2.9	miR-1, miR-101, miR-130b, miR-204, miR-206, miR-29c, miR-30b	RT-qPCR[14]
ADH1B	Multiple[9 10]	Down	−3.4 to −4	<0.001 /Down/−4.1		
AKR1C2	Multiple[7 10]	Down	−2.3 to −11.8	0.003/Down/−1.9		
ALDH2	Multiple[7 10]	Down	−1.9 to −25.5	0.015/Down/−1.7		
ANGPTL7	Multiple[9 10]	Down	−2.6 to −4	<0.001/Down/−1.9		
APP	Multiple[7 8]	Up	1.7 to 5.8	Not significant		
ARL4C	Multiple[9 12]	Up	4	No assessed		
CDO1	Multiple[9–11]	Down	−2 to −4.8	<0.001/Down/−2.2		
CLU	Multiple[9 10]	Down	−4 to −4.8	<0.001/Down/−4.6		
COL1A1	Multiple[9 12]	Up	2 to 4.4	0.042/Up/1.9		
COL1A2	Multiple[9 12]	Up	2 to 2.3	Not significant		Western blot;[23] RT-qPCR[23 65]
COL4A2	Multiple[8 9]	Up	3 to 10.4	0.009/Up/2.4		
COL5A1	Multiple[6 9]	Up	2 to 4	<0.001/Up/2.7		
COL5A2	Multiple[6 9 12]	Up	2 to 4	<0.001/Up/2.9	miR-29c	
LAMB1	Multiple[9 12]	Up	2.9 to 3	Not significant		
LRRC17	Multiple[6 9 12]	Up	3 to 4	<0.001/Up/4.4		
MMP2	Multiple[8 9 12]	Up	3 to 29	0.012/Up/1.8		RT-qPCR;[97] zymography[15]
POSTN	Multiple[8 9 11]	Up	3 to 62.8	<0.001/Up/5.0	miR-140-5p	RT-qPCR;[11 14] western blot;[11] altered response;[11] immunohisto-chemistry;[11]
PRG4	Multiple[9 10]	Down	−3 to −137.5	Not assessed		RT-qPCR[10]
RGS3	Multiple[9 12]	Up	3	<0.001/Up/2.5		
TNC	Multiple[6 9 12]	Up	2 to 5.2	<0.001/Up/1.9	miR-1229, miR-1238, miR-494	RT-qPCR[14]
TGFB1	Single[9]	Up	n/a	Not significant	miR-130b, miR-29c, miR-296-5p, miR-301b, miR-654-5p	RT-qPCR[23]
MAFB	Single[6 12]	Up	n/a	0.022/Up/1.6	miR-130b, miR-29c, miR-301b	Immunohistochemistry[6]
WNT5A	None	n/a	n/a	0.047/Up/1.4	miR-22, miR-30b, miR-494	
ZIC1	None	n/a	n/a	0.003/Up/3.3	miR-101	

*pfp, estimated percentage of false positive predictions. This is an equivalent to the false discovery rate or adjusted p values.
RT-qPCR, reverse transcription quantitative PCR.
†MicroRNA that are both dysregulated in Dupuytren's disease and predicted (using TargetScan) to target the genes indicated in the first column are as given by Mosakhani *et al*.[13]
RT-qPCR, reverse transcription quantitative PCR.

al[34] suggested that this change in ratio is due to the inhibition of type I collagen expression at high fibroblast density. Conversely, type III collagen has not been suggested in global expression studies. Dysregulation in several collagen types has been suggested, including *COL1A1, COL1A2, COL4A1, COL4A2, COL4A5, COL5A1, COL5A2, COL6A1, COL6A3, COL7A1, COL8A1, COL9A3, COL14A1* and *COL15A1*. Of these collagens; types I, IV and V are most consistent in their dysregulation in DD (table 1). The fibrillar collagens; the major product synthesised by connective tissue cells, comprised five members, collagen types I, II and III, V and XI, with the former three types being the quantitatively major types.[35] Collagen V is assembled together within single fibrils with collagen I.[36] Fibroblasts isolated from individuals with *COL5A1* haplo-insufficiency suggest that the quantity of collagen fibrils deposited is highly sensitive to a reduction in type V collagen, despite being a minor collagen type.[37]

Higher levels of tenascin protein have been observed in more aggressive forms of DD,[30] which is in agreement with upregulation of tenascin C mRNA and downregulation of microRNA targeting *TNC*.[9 13 14] Similarly, *TGFB2* mRNA has been shown to be upregulated in DD,[12] and shows intense intracellular localisation within myofibroblasts in the proliferative and involutional stages of the disease.[26] Indeed, the addition of *TGFB2* had a significant effect on the development of myofibroblasts, a cell type thought to contribute to DD contracture.[26 38]

CORRELATING GENE EXPRESSION WITH LINKAGE AND GENOME-WIDE ASSOCIATION STUDIES

Several chromosomal regions have been associated with DD from genetic linkage and association studies, including comparative genomic hybridisation,[39–41] genome-wide family linkage,[42] and case–control whole genome association studies.[43 44] Genes within significantly associated loci were compared with the differentially expressed genes reported in the gene expression profiling studies. In this review, 2 genes, *MAFB* and *protein kinase X-linked (PRKX)*, were found to be highlighted by both types of studies (figure 2). *PRKX*, which contains a single nucleotide polymorphism (SNP; rs17335275) that showed a positive association with DD,[44] is upregulated in DD.[7] Interestingly, *PRKX* contributes to angiogenesis, as it stimulates endothelial cell proliferation, migration and vascular-like structure formation.[45] The potential involvement of angiogenesis in DD pathogenesis was suggested by Gonzalez *et al*.[46] *PRKX* locates to the x-chromosome, while the DD

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inheritance pattern has not been thought to be x-linked; a case with polyfibromatosis including keloid scars and DD was reported to be x-linked.[47]

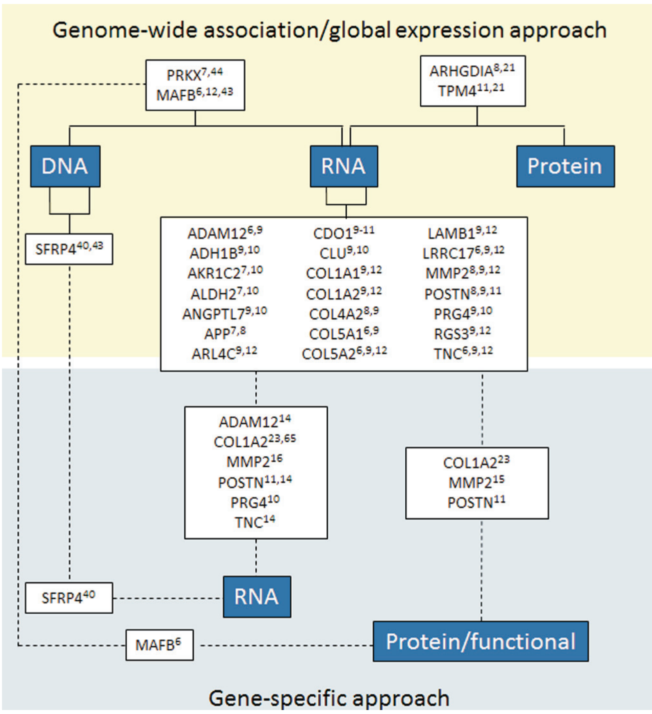

Figure 2 Summary of genes that have been implicated in Dupuytren's disease pathogenesis by multiple genome-wide association or global expression studies. The figure indicates genes that have been reported by multiple genome-wide association studies or global expression studies (yellow block); these include genes that have been reported in DNA and RNA studies, multiple DNA studies, multiple RNA studies and RNA and protein studies (joined by solid lines). Out of these genes, those that have also been confirmed by other gene-specific experimental approaches are indicated in the light blue box (joined by dotted lines).

The possible involvement of *MAFB*, a transcription factor that serves as a regulator of commitment and lineage determination of haematopoietic cells, has been extensively studied in DD.[6 13 48 49] *MAFB* is downstream of a SNP (rs8124695, showing a linkage)that has been shown to be positively associated with DD.[43] Both previous microarray studies and meta-analysis carried out in this review indicate upregulation of *MAFB* in DD at the mRNA level.[6 12] In addition, microRNA (miR-130b, miR-29c and miR-301b) predicted to target *MAFB* are downregulated in DD.[13] Furthermore, Lee *et al*[6] have observed that while all control fascia are negative for *MAFB*, half of the DD tissues showed positive immunohistochemical staining for *MAFB*. Upregulation of *MAFB* is also observed in fibromatosis (gene expression atlas).[18]

While no gene copy number variations were found in DD by Kaur *et al*,[39] increased DNA copy numbers at chromosomes 7p14.1 and 14q11.2 have been reported in DNA extracted from nodules, when compared with DNA from blood of the same patient or external controls.[40 41] *Secreted frizzled-related protein (SFRP)4* and *MMP14* are found within 450 kB of these copy number alterations, and significantly higher levels of *SFRP4* and *MMP14* expression were found in DD nodules.[40] In addition, SNP (rs16879765) that was shown in a genome-wide association study to be significantly associated with DD, is adjacent to *SFRP4*.[43] *SFRP4* is a *Wnt* antagonist and inhibitor of the *Wnt-β-catenin* pathway;[50] its expression is associated with reduced scar size after ischaemic injury[51] and restricted tumour growth.[52]

Genetic variations in the regulatory regions of genes can potentially result in altered protein levels.[53] Polymorphisms within microRNA binding sites in the 3′ untranslated region of candidate genes for colorectal cancer have been linked to colorectal cancer formation.[54] By comparing SNP reported to be significantly associated with DD and microRNA dysregulated in DD, a SNP (rs4730775)[43] is found to be located within a predicted target site for miR-299-3p,[53] a microRNA found to be exclusively detected in the majority of DD fascia (compared with the minority that shows an expression profile resembling the controls).[13] This SNP locates within the 3′ untranslated region

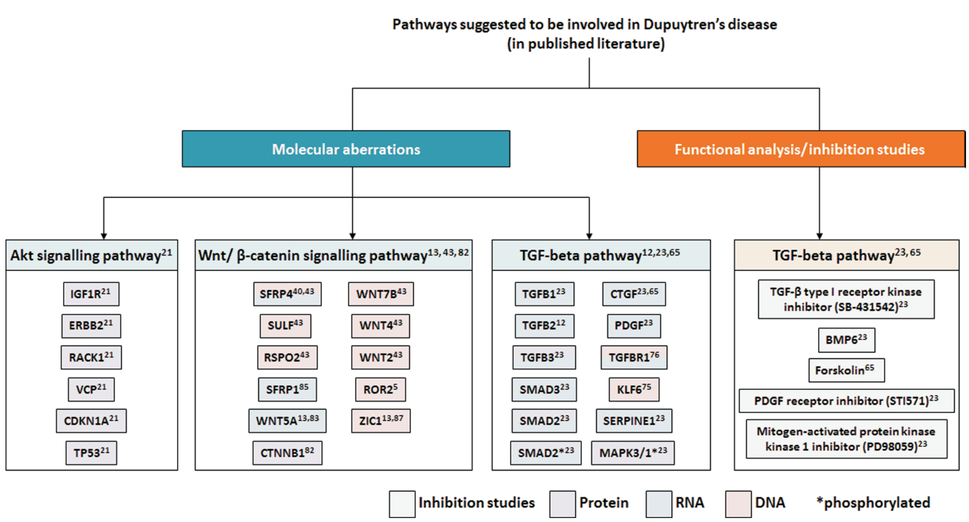

Figure 3 Studies carried out on the major signalling pathways that have been proposed to contribute to Dupuytren's disease (DD). From molecular aberrances observed in DD, three pathways have been suggested in the literature to be involved in DD pathogenesis, including the *Akt* signalling pathway, *Wnt/β-catenin* signalling pathway and *TGFB* pathways. In addition, functional analysis and inhibition studies have been carried out for genes within, or downstream of, the *TGFB* pathway. The study type (whether the observed aberrances are based on DNA, RNA, protein or inhibition/functional studies) is indicated by the colours, green, purple, blue and red. Molecules that have been studied by different methods (for example, *TGFBR1* has been proposed to be aberrant at both DNA and RNA levels) have been labelled by two colours.

Table 2 Pathway enrichment of genes reported by messenger RNA microarray, meta-analysis and whole proteome studies

Term name	Database	Term ID	No of genes dysregulated in DD	Background no of genes	Corrected p value	Genes
β1 Integrin cell surface interactions	PID curated	Integrin1_pathway	17	60	3.80E-05	CD14, CD81, COL1A1, COL1A2, COL5A1, COL5A2, COL6A1, COL7A1, COL18A1, FN1, LAMB3, LAMB1, PLAU, PLAUR, TGFBI, THBS2, TNC
Muscle contraction	Reactome	REACT:17044	11	49	0.000427365	TPM1, TPM2, NEB, TPM4, MYL12, MYL3, SORBS, MYL6, VIM, MYH8, AAT6
ECM receptor interaction	KEGG PATHWAY	hsa04512	16	85	0.000427365	CD36, COL1A1, COL1A2, COL4A1, COL4A2, COL4A5, COL5A1, COL5A2, COL6A1, COL6A3, FN1, LAMB1, LAMB3, THBS2, TNC, TNXB
Protein digestion and absorption	KEGG PATHWAY	hsa04974	15	81	0.000865334	COL14A1, COL15A1, COL18A1, COL1A1, COL1A2, COL4A1, COL4A2, COL4A5, COL5A1, COL5A2, COL6A1, COL6A3, COL9A3, CPA3, ELN
Developmental biology	Reactome	REACT:111045	32	392	0.001641686	ABLIM1, ADIPOQ, CD36, CDON, CNTN1, COL1A1, COL1A2, COL4A1, COL4A2, COL4A5, COL5A1 COL5A2, COL6A1, COL6A3, COL9A3, CTNNA1, DLG1, FABP4, KCNQ3, LAMB1, LPL, MYL12B, MYL6, NCAM1, PLIN1, PLXNC1, RHOA, SEMA6A, SLIT2, SPTBN1, STIP1, TCF4,
Phenylalanine degradation IV (mammalian, via side chain)	BioCyc	PWY-6318	4	5	0.015637937	ALDH2, ALDH3A2, MAOA, HPD
Amoebiasis	KEGG PATHWAY	hsa05146	15	108	0.01734527	CD14, COL1A1, COL1A2, COL4A1, COL4A2, COL4A5, COL5A1, COL5A2, FN1, GNAS, HSPB1, LAMB1, LAMB3, PRKX, TGFB2,
Glycogen breakdown (glycogenolysis)	PID reactome	500680	4	11	0.029934763	PYGM, PHKA2, GYG2, PHKG1
Integrin signalling pathway	PANTHER	P00034	18	157	0.029934763	ACTG1, ARF1, COL14A1, COL15A1, COL1A1, COL1A2, COL4A1, COL4A2, COL4A5, COL5A1, COL5A2, COL6A1, COL6A3, COL7A1, COL8A1, COL9A3, FN1, RHOA
β3 Integrin cell surface interactions	PID curated	integrin3_pathway	9	38	0.031254944	COL1A1, COL1A2, EDIL3, FN1, LAMB1, PLAU, PLAUR, TGFBI, THY1

DD, Dupuytren's disease; ECM, extracellular matrix; PID, Pathway Interaction Database

of *WNT2*; however, the expression of *WNT2* has not previously been reported to be abnormal. Further experiments investigating microRNA, associated SNP and protein expression for *WNT2* in the same group of patients would be required before determining a functional role.

Finally, a higher level of *iroquois homeoboxprotein 6 (IRX6)* mRNA has been observed in DD nodules and fat tissue adjacent to DD.[1 14] *IRX6* locates within a critical chromosomal region, where positive genetic linkage was previously reported in a Swedish family.[42]

PATHWAYS AND DD

Several signalling pathways have been suggested to be involved in DD in published global gene expression or genome-wide association studies, including *TGFB* signalling,[12] *Akt* signalling[21] and *Wnt* signalling[43] (see supplementary table S3, available online only, and figure 3). In addition, genes identified to demonstrate different regulation in this review (from published global gene expression studies and meta-analysis) have been used for pathway enrichment analysis using the KEGG orthology-based annotation system (KOBAs) 2.0, from which pathways associated with integrin from multiple databases were significant (table 2). These signalling pathways are not mutually exclusive from each other; activation of one pathway may induce another, or cross-talk between two pathways may occur (figure 4).[55–59]

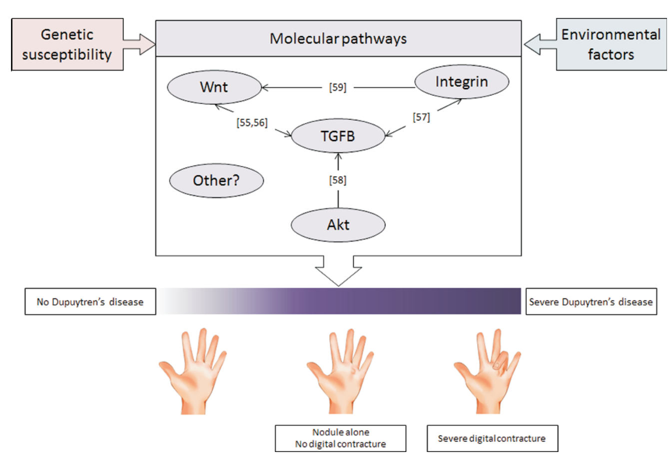

Figure 4 Potential molecular/environmental involvement inthe pathogenesis of Dupuytren's disease (DD). Both genetic and environmental factors have been proposed to contribute to DD development. Four signalling pathways have been suggested to be involved in DD, the *Akt*, *TGF-β*, integrin and *Wnt* signalling pathways. Interactions have been suggested to occur between these pathways (references as indicated on the arrows between the pathways). In addition, unknown signalling pathways can also be involved in DD pathogenesis. The different severity of DD may have resulted from different levels of contribution from environmental and genetics factors, thereby triggering different activated/suppressed signalling pathways.

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INTEGRIN SIGNALLING PATHWAY

Integrins constitute a family of transmembrane receptors that mediates attachment between the (intracellular) cytoskeleton and (extracellular) ECM, allowing transduction of signals from outside to inside of the cells, and vice versa.[57] Cross-talk between integrin and growth factors, such as *TGFB*[57] and *insulin-like growth factor 1 receptor (IGF1R)*[60] (these two growth factors have been implicated in DD and other signalling pathways), have been implicated in both normal physiological and pathological processes.[57 60] *Integrin* β*-1 (ITGB1)* has been suggested to modulate mechanical stress-induced *mitogen-activated protein (MAP) kinases*,[61] which have been suggested to be involved in the pathogenesis of frozen shoulder.[62] *ITGB1* has also been suggested to be upregulated in Peyronie's disease in the microarray data generated by Qian *et al*.[8]

Immunohistochemical studies in DD nodules have shown *α5 β1 integrin* expression in highly cellular areas, where fibronectin is expressed in ECM, of proliferative and involutional phases, but not in the hypocellular areas of the involutional phase or the fibrotic tissues of residual phases.[29 63] A higher level of *α2 integrin* ($p \leq 0.05$, against internal control fascia) and *α5 integrin* chains ($p \leq 0.07$, against external control fasica) has been observed in DD cord through fluorescence activated cell sorting.[64] *Fibronectin*, which is involved in the integrin signalling pathway, is elevated in DD, as shown by multiple studies at both mRNA and protein levels.[27 65–67] Isoforms of fibronectin, ED-A and ED-B, are found in the proliferative and involuational stage of DD.[67] Oncofetal glycosylated fibronectin is found to be exclusively localised in the active proliferative nodule, where it co-localises with *TGFB* and basic fibroblast growth factor.[68] Higher levels of plasminogen activator, which is involved in the integrin cell surface interactions, have been shown in DD nodules.[69]

AKT SIGNALLING PATHWAY

IGF1R and *v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (ERBB2)* are both involved in the activation of the *Akt* signalling pathway, and through an integrated proteomic approach were implicated as biomarkers involved in the regulation of cell proliferation in DD.[21] Furthermore, *POSTN*, a gene that has been characterised to be dysregulated in DD in several studies,[8 9 11 14] has been suggested to promote metastatic growth of colon cancer by inducing cell survival via the *Akt* pathway.[70] Kraljevic Pavelic *et al*[21] have also demonstrated upregulated levels of total *Akt* and phosphorylated *Akt* in disease fascia when compared with internal control fascia. Activated *Akt* is involved in the regulation of cell proliferation, survival and metabolism.[71] Upregulation of *RACK1*, a key mediator of *IGF1*-induced *Akt* activation,[72] has been observed in DD,[72] as well as overexpression of downstream targets of *Akt* signalling, including *valosin containing protein (VCP)*, *p21waf1/cip1* and *tumor protein p53* (figure 3).[21]

TGFB SIGNALLING PATHWAY

Involvement of *TGFB* in DD has been suggested by several earlier studies (figure 3).[26 68 73] Aberrant *TGFB* expression has been reported to contribute to the formation of excessive tissue fibrosis.[74] Dysregulated levels of *TGFBR*3 and *TGFB*2 mRNA have been reported in microarray studies.[9 12] A polymorphism (rs17731) in the *Zf9 transcription factor gene* (*KLF6*), a transcription factor that increases *TGFB*1 expression, has been positively associated with DD in a case–control association study.[75] A polymorphism in the promoter of *TGFB receptor 1* shows a significant difference in genotype frequency between DD cases and a control population if the disease model is assumed to be recessive.[76]

A recent study by Krause *et al*[23] indicated the involvement of the *TGFB* pathway in DD. Elevated expression and activation of the downstream molecules of *TGFB* have previously been reported, which include the *SMAD* pathway and the *extracellular signal-regulated kinase (ERK) MAP* pathway.[23] *TGFB* has been shown to induce bimodal proliferation in connective tissue cells through regulation of *platelet-derived growth factor (PDGF)*,[77] which has been implicated in DD.[23 78] Treatment with inhibitors of *TGFB*, the *PDGF* receptors and the *MAP kinase* pathway result in the decreased expression of fibrotic and proliferation markers.[23]

Different isoforms of *TGF-β* have been reported to have both profibrotic and antifibrotic effects. *TGFB*1 is thought to be profibrotic, while *TGFB*3 is antifibrotic. However, the profibrotic or antifibrotic effects of *TGFB*2 remain contradictory;[79] while diminished *TGFB*2 production has been observed to lead to increased expression of profibrotic procollagen α 2 type 1 messenger RNA in an animal model of systemic sclerosis,[80] the addition of *TGFB*2 antibodies reverses the increased contraction on the fibroblast populated collagen lattice by keloid fibroblasts treated with exogenous *TGFB*2.[81]

β-CATENIN AND WNT SIGNALLING PATHWAY

Aberrant levels of *β-catenin* have been noted in DD, which is also supported by microRNA profiling studies (figure 3). Varallo *et al*[82] showed high levels of *β-catenin* protein in the diseased fascia, whereas almost no expression is found in the control fascia. Neither genotypes nor DD recurrence could be associated with *β-catenin* overexpression.[82 83] Varallo *et al*[82] did not identify any mutations in the *β-catenin* in association with DD.

β-Catenin is a central component of the canonical *Wnt* signalling pathway, which influences cell survival and proliferation.[84] It has been suggested that the overexpression of *β-catenin* may be as a result of alterations in the *Wnt* signalling pathway. O'Gorman *et al*[85] investigated the gene expression of 13 *Wnt* molecules using microarray data and competitive reverse transcription PCR analysis and concluded that changes in *Wnt* expression were unlikely to be the cause of *β-catenin* dysregulation. However, O'Gorman *et al*[85] acknowledge that this does not rule out the potential involvement of altered *Wnt* signalling in DD pathogenesis; other genes involved in the *Wnt* pathway may be dysregulated, such as *SFRP1*, which demonstrated a consistently reduced level of expression in DD in their microarray data and in the meta-analysis carried out here. Downregulation of *SFRP1* in mammary epithelial cells results in increased sensitivity to *TGFB* signalling,[86] which would also tie in with the involvement of the *TGFB* pathway observed in DD (as discussed previously).

A recent genome-wide association study has revealed six different DD risk loci containing genes, which are involved in the *Wnt* signalling pathway, and include *WNT4* (rs7524102), *WNT2* (rs4730775), *R-spondin 2 (RSPO2)* (rs611744), *WNT7B* (rs6519955), *SFRP4* (rs16879765) and *sulfatase 1 (SULF1)* (rs2912522).[43] In addition, microRNA predicted to target *WNT5A* and *ZIC1* have been shown to be downregulated in DD cord,[13] which coincides with the overexpression of *WNT5A* and *ZIC1* mRNA observed in the meta-analysis in this review as well as analysis of mRNA microarray data of Forsman *et al*[5] (comparisons made by Mosakhani *et al*).[13] Higher levels of *WNT5A* have been observed in the β*-catenin*-accumulating involutional zones in comparison with proliferative and residual zones.[83] *ZIC1* and β*-catenin* co-expression have been described in DD myofibroblasts.[87] *Receptor tyrosine kinase-like orphan receptor 2 (ROR2)*, which was demonstrated to be upregulated in DD at both protein and mRNA levels, was shown to be involved in osteoclastogenesis,[5 88] and is considered a potential biomarker for leiomyosarcoma and gastrointestinal stromal tumours.[89] In addition, *WNT5A-ROR2* signalling has been suggested to be necessary for the expression of *MMP13* during the development of cartilaginous tissue; *MMP13* is also overexpressed in DD.[90 91] *Androgen receptors (AR)*, which interact with β-*catenin* and promote *Wnt* signalling at the chromatin level,[92] have been reported to be elevated and co-localise with α-*smooth muscle actin* in DD cultures and DD tissue.[93] Testosterone or dihydrotestosterone, which is converted from testosterone, activates *AR*; the involvement of AR may explain a male predominance that has been seen in DD.[93] *AR* mRNA levels, however, were reported to be significantly underexpressed by Satish *et al*[10] and the meta-analysis carried out here. While implication of the *Wnt* and β-*catenin* signalling pathways in the aetiology of DD has been reported by several studies through different techniques (figure 3), detailed analysis of the downstream components and targets of the *Wnt* pathway in vitro would be required to elucidate its involvement in DD.[94]

CONCLUSIONS AND FUTURE PERSPECTIVES

Whole genome association studies and global gene expression studies that have investigated polymorphisms, transcript or protein expression across the entire genome have provided data regarding genes that may be involved in DD, through altered gene expression or genotype associations. The initial analysis of these data created large lists of affected genes of potential interest, some with unknown biological function and relevance to DD. Interpreting these data continues to be a challenging task, but this effort has led to the identification of potential biomarkers involved in DD formation. However, these findings can also potentially lead to overinterpretations, whereby the observed molecular aberrances may not be truly aetiological.[95] Rehman *et al*[95] proposed a complex model for DD, involving simultaneous occurrences of aberrances in several networks, each consisting of internal factors, like genetic background and environmental factors, such as trauma and alcohol consumption (figure 4). A limited number of studies exist that have characterised the molecular differences that may arise from environmental factors, and compared differences between mild and severe forms of DD. Isometric tension on DD and control cells has been demonstrated to show a differential effect on β-*catenin* and *fibronectin* expression.[66] The *MMP* expression profile has also been associated with clinical outcome.[96] Further research on these areas may help elucidate the varying degrees of phenotypic severity observed in DD.

In conclusion, this review has described genes and pathways that have been identified to be involved in DD through whole genome and global gene expression studies, and highlighted genes that have been suggested to be involved in DD pathogenesis by detailed analysis of these previous studies. Further characterisation of functions and pathways in these genes, and investigation of the interaction between these pathways, may help in better understanding and elucidation of DD pathogenesis.

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Whole genome and global expression profiling of Dupuytren's disease: systematic review of current findings and future perspectives

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