Supplementary Table 1

List of previous GWAS, WES and variants studies on DC.

Title	Year	Population	Sample size	P-value	Main findings	Reference
Genetic susceptibility to Dupuytren's disease: transforming growth factor beta receptor (TGFβR) gene polymorphisms and Dupuytren's disease	2003	Caucasians	184 patients, 181 controls	0.048	The substantial discovery in C/C vs. A/C and A/A alleles indicates that this cohort of DC cases has a recessive influence. The presence of the C allele compared to the A allele is linked to a higher chance of developing DC.	1
Genetic susceptibility to Dupuytren disease: association of Zf9 transcription factor gene	2003	Caucasians	138 patients, 255 controls	0.0025	The presence of the G allele versus the A allele is linked to a higher risk of DC.	2
Positive association of HLA-DRB1*15 with Dupuytren's Disease in Caucasians	2008	Caucasians	67 patients, 537 controls	0.029	The HLA-DRB1*15 phenotypic frequency of DC positive Caucasoid was greater (37.3 %) compared to control (20.9 %).	3
Genome-wide high-resolution screening in Dupuytren's disease reveals common regions of DNA copy number alterations	2010	European	4 patients, 10 controls	<0.05	Three novel CNVs, situated at 10q22, 16p12.1, and 17p12.1, were discovered in three DC cases previously unreported in the phenotypically normal population. Using the strategic selection criteria, nine polymorphic CNVRs likely linked with DC were identified on chromosomes 1q31, 6p21, 7p14, 8p11, 12p13, 14q11, 17q21, and 20p13. More than three of the DC patients evaluated had a CNVR in a short region on 6p21 and four CNVRs inside the human leukocyte antigen (HLA) genes on 6p21–22.	4
Wnt Signaling and Dupuytren's Disease	2011	European	960 patients, 3117 controls	$<1 \times 10^{-4}$	Eight SNPs at three loci were found to have a substantial genome wide correlation with DC. Replication tests and a combined analysis of all data revealed a link between 11 SNPs from nine distinct loci. *WNT4* (rs7524102), *SFRP4* (rs16879765), *WNT2* (rs4730775), *RSPO2* (rs611744), *SULF1* (rs2912522), and *WNT7B* are among the genes known to be involved in the Wnt signalling pathway (rs6519955).	5

DNA Copy Number Variations at Chromosome 7p14.1 and Chromosome 14q11.2 Are Associated with Dupuytren's Disease	2012	European	4 patients, 10 controls	<0.05	Array-based comparative genomic hybridization detected five frequent copy number changes on chromosomes 17q12, 1p31.1, 20p13, 7p14.1, and 14q11.2. In quantitative polymerase chain reaction validation, significantly higher copy numbers of copy number variants at chromosomes 7p14.1 and 14q11.2 were confirmed in DC. In nodules, matrix metalloproteinase-14 and secreted frizzled-related protein 4 (located near a polymorphism linked to DC) were highly up-regulated.	6
Genome-Wide Analysis Using Exon Arrays Demonstrates an Important Role for Expression of Extra-Cellular Matrix, Fibrotic Control and Tissue Remodelling Genes in Dupuytren's Disease	2013	European	5 patients, 6 controls	<0.01	In DC patient samples, three matrix metallopeptidases (*MMP1*, *MMP3*, *MMP16*), follistatin, and *STAT1* expression levels were dramatically reduced, while fibroblast growth factors (*FGF9, FGF11*), a number of collagen genes, and other ECM genes were significantly enhanced. Many of these gene products have been linked to fibrosis, tumour development, and normal tissue remodelling processes.	7
SNPs Previously Associated with Dupuytren's Disease Replicated in a North American Cohort	2014	European	296 patients, 919 controls	<0.004	Five of the 12 SNPs previously linked to DC illness were replicated. The findings imply that the Wnt signalling pathway plays a role in the development of DC, and that additional research into this system could lead to early detection and non-surgical treatments for the condition.	8
Dissecting the Development of Dupuytren Disease Through Human Genetics	2016	European	7934 patients, 12861 controls	$<5 \times 10^{-8}$	A total of 24 DC-associated areas were discovered in the GWAS meta-analysis, in which 15 were novel. The two homozygous genotypes of the most related single-nucleotide polymorphism rs1687975 had a 4-fold differential in SFRP4 mRNA expression. Surprisingly, extracellular SFRP4 protein secretion was found to have an inverse relationship. SFRP4 inhibits WNT3A-induced connective tissue growth factor (CTGF) production by 20% in Wnt signalling pathway stimulation experiments. *SFRP4* had no effect on the expression of alpha-smooth muscle actin, *COL1A1*, or *COL3A1* mRNA.	9

Dupuytren's disease susceptibility gene, *EPDR1*, is involved in myofibroblast contractility	2016	European	4 patients, 4 controls	0.03	Minor allele carriers (A/G) had higher *EPDR1* expression than those who solely have the main allele (G/G),. Furthermore, in this dataset, rs16879765 is not linked to a change in gene expression of the nearby gene SPFR4.	10
Meta-Analysis of Genome-Wide Association Studies and Network Analysis-Based Integration with Gene Expression Data Identify New Suggestive Loci and Unravel a Wnt-Centric Network Associated with Dupuytren's Disease	2016	European	1580 patients, 4480 controls	$<1 \times 10^{-5}$	The meta-analysis found 910 SNPs in 23 chromosomal locations that showed a possible link to DC. 371 SNPs were found to have genome-wide relevance. SNPs on chromosomes 7p14.1, 8q13.2, 8q23.1, 9p24.3, 19q13.43, and 22q13.31 have been discovered. In the meta-analysis, the imputed SNP rs17171229 had a little greater signal than the previous GWAS top SNP, rs16879765. Close linkage disequilibrium exists between SNPs rs17171229 and rs16879765.	11
A Genome-wide Association Study of Dupuytren Disease Reveals 17 Additional Variants Implicated in Fibrosis	2017	European	8557	$<5 \times 10^{-8}$	The study found 17 new variations while validating connection at all nine previously known signals. In surgical specimen-derived DC myofibroblasts, the link of the high-risk genotype at the statistically most highly related variant with lower production of the soluble Wnt-antagonist SFRP4 was proven as a proof of principle. Wnt signalling, extracellular matrix modification, and inflammation are all essential processes in the aetiology of fibrosis, according to these findings.	12
Dupuytren's and Ledderhose Diseases in a Family with LMNA-Related Cardiomyopathy and a Novel Variant in the *ASTE1* Gene	2017	European	7	-	Exome sequencing and family studies of five family members revealed an unique heterozygous missense mutation (c.230T>C, p.Val77Ala) in the Asteroid Homolog 1 (ASTE1) gene as a possible risk factor for fibrotic illness. ASTE1 may play a role in epidermal growth factor receptor signalling, which could explain why patients with Lamin A/C haploinsufficiency are more likely to develop palmar/plantar fibromatosis.	13
Ethnic differences in prevalence of Dupuytren disease can partly be explained by known genetic risk variants	2019	Public database	-	<0.05	The correlation between documented DC prevalence in the literature and mean unweighted GRS derived from the 26 known DC SNPs was significant (0.60), implying that these 26 SNPs account for 36% of the variance in DC prevalence. Only three of 10,000 correlations between	14

					DC prevalence and the mean of GRSs made up of sets of 26 random SNPs were higher than the observed correlation, indicating that the GRS made up of DC SNPs has a considerable impact on DC prevalence.	
Integrative analysis of Dupuytren's disease identifies novel risk locus and reveals a shared genetic etiology with BMI	2019	European	3871 patients, 4686 controls	<0.01	A total of 36 of the 43 important tissue-specific gene models were within 0.5 Mb of any of the 24 risk areas previously identified. It was discovered that 13 regions only had significant GWAS SNP(s), 1 region only had significant TWAS model(s), and 11 regions had both significant GWAS SNP(s) and TWAS model(s).	15
Integrative genomic and transcriptomic analysis of genetic markers in Dupuytren's disease	2019	Public database	-	$< 1.2 \times 10^{-5}$	MHC class II genes and *ZFP57* were found to be linked to ER stress and the UPR, suggesting that these genetic markers could be used to treat DC.	16
A common SNP risk variant MT1-MMP causative for Dupuytren's disease has a specific defect in collagenolytic activity	2021	European	-	<0.0001	rs1042704 lowers collagen catabolism in tissue, tipping the collagen homeostasis balance in tissue and contributing to the fibrotic phenotype of DC.	17
Evaluation of WNT Signaling Pathway Gene Variants WNT7B rs6519955, SF RP4 rs17171229 and RSPO2 rs611744 in Patients with Dupuytren's Contracture	2021	European	133 patients, 103 controls	<0.05	WNT7B rs6519955 and RSPO2 rs611744 single-nucleotide polymorphisms are linked to the development of DC. *WNT7B* rs6519955 genotype TT raises the odds by 3.5-fold, whereas *RSPO2* rs611744 genotype GG appears to reduce the possibility of DC manifestation by nearly twofold. The results of genotype distributions among DC patients and controls reveal that *SFRP4* rs17171229 is not significantly linked to disease development.	18

References

1. Bayat A, Stanley JK, Watson JS, Ferguson MWJ, Ollier WER. Genetic susceptibility to Dupuytren's disease: Transforming growth factor beta receptor (TGFβR) gene polymorphisms and Dupuytren's disease. *Br J Plast Surg*. 2003;56(4):328–33.
2. Bayat A, Watson JS, Stanley JK, Ferguson MWJ, Ollier WER. Genetic susceptibility to Dupuytren disease: Association of Zf9 transcription factor gene. Plast Reconstr Surg. 2003;111(7):2133–9.
3. Brown JJ, Ollier W, Thomson W, Bayat A. Positive association of HLA-DRB1*15 with Dupuytren's disease in Caucasians. Tissue Antigens 2008 Aug;72(2):166–70.
4. Shih BB, Tassabehji M, Watson JS, McGrouther AD, Bayat A. Genome-Wide High-Resolution Screening in Dupuytren's Disease Reveals Common Regions of DNA Copy Number Alterations. *J Hand Surg Am*. 201;35(7):1172-1183.e7.
5. Dolmans GH, Werker PM, Hennies HC, Furniss D, Festen EA, Franke L, et al. Wnt Signaling and Dupuytren's Disease. *N Engl J Med*. 2011;365(4):307–17.
6. Shih B, Tassabehji M, Watson JS, Bayat A. DNA copy number variations at chromosome 7p14.1 and chromosome 14q11.2 are associated with Dupuytren's disease: Potential role for MMP and Wnt signaling pathway. Plast Reconstr Surg. 2012;129(4):921–32.
7. Forrester HB, Temple-Smith P, Ham S, de Kretser D, Southwick G, Sprung CN. Genome-wide analysis using exon arrays demonstrates an important role for expression of extra-cellular matrix, fibrotic control and tissue remodelling genes in Dupuytren's disease. PLoS One 2013;8(3).
8. Anderson ER, Ye Z, Caldwell MD, Burmester JK. SNPs previously associated with Dupuytren's disease replicated in a North American cohort. Clin Med Res. 2014;12(3–4):133–7.
9. Ng M, Zeggini E, Hennies HC, Werker PM, Furniss D. Dissecting the development of Dupuytren disease through human genetics. HAND. 2016;11(1_suppl).
10. Staats KA, Wu T, Gan BS, O'Gorman DB, Ophoff RA. Dupuytren's disease susceptibility gene, EPDR1, is involved in myofibroblast contractility. J Dermatol Sci. 2016;83(2):131–7.
11. Becker K, Siegert S, Toliat MR, Du J, Casper R, Dolmans GH, et al. Meta-analysis of genome-wide association studies and network analysis-based integration with gene expression data identify new suggestive loci and unravel a Wnt-centric network associated with Dupuytren's disease. *PLoS One*. 2016 Jul 1;11(7).

12. Ng M, Thakkar D, Southam L, Werker P, Ophoff R, Becker K, et al. A Genome-wide Association Study of Dupuytren Disease Reveals 17 Additional Variants Implicated in Fibrosis. Am J Hum Genet. 2017;101(3):417–27.
13. Zaragoza M V., Nguyen CHH, Widyastuti HP, McCarthy LA, Grosberg A. Dupuytren's and Ledderhose Diseases in a Family with LMNA-Related Cardiomyopathy and a Novel Variant in the ASTE1 Gene. Cells 2017;6(4).
14. Riesmeijer SA, Werker PMN, Nolte IM. Ethnic differences in prevalence of Dupuytren disease can partly be explained by known genetic risk variants. *Eur J Hum Genet* 2019;27(12):1876–84.
15. Major M, Freund MK, Burch KS, Mancuso N, Ng M, Furniss D, et al. Integrative analysis of Dupuytren's disease identifies novel risk locus and reveals a shared genetic etiology with BMI. Genet Epidemiol 2019;43(6):629–45.
16. Jung J, Kim GW, Lee B, Joo JWJ, Jang W. Integrative genomic and transcriptomic analysis of genetic markers in Dupuytren's disease. BMC Med Genomics 2019;12(Suppl 5).
17. Itoh Y, Ng M, Wiberg A, Inoue K, Hirata N, Paiva KBS, et al. A common SNP risk variant MT1-MMP causative for Dupuytren's disease has a specific defect in collagenolytic activity. Matrix Biol. 2021;97:20–39.
18. Samulėnas G, Smalinskienė A, Rimdeika R, Braziulis K, Fomkinas M, Paškevičius R. Evaluation of WNT Signaling Pathway Gene Variants WNT7B rs6519955, SFRP4 rs17171229 and RSPO2 rs611744 in Patients with Dupuytren's Contracture. *Genes (Basel)* 2021;12(9).