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HAND & WRIST

Molecular genetics of Dupuytren's contracture

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- Dupuytren's contracture (DC) is a fibroproliferative disorder of the palmar fascia characterised by the digits' flexion contractures and is associated with abnormal build-up of type III collagen. The prevalence of the disease is reported to be highest among Northern European descendants. However, the disease is widespread globally with varying prevalence.
- DC is a multifactorial disease, having both genetic and environmental factors contributing to the causality of the disease.
- Over the years, various studies have been conducted to understand the molecular mechanism and genetic aspects of DC but there is a lack of reports on the variants found in the exonic regions. Most reports are backdated making it necessary to re-evaluate the variants to further understand the genetic aetiology of DC.
- In this review, we first highlight the genetic aspects and previous genetic studies on DC. The report is followed by a discussion on the molecular pathways suggested to be associated with DC and a summary of the genetic variants in the exonic regions found in DC and their connections with the molecular pathways.
- A total of nine variants were reported originating from six genes comprising three pathways. Most variants reported are involved in the Wnt signalling pathway. Moreover, all variants identified are in European/Caucasian subjects and the variants found in the exonic regions are missense variants.
- A comparison of these findings with variants from populations of other regions can be conducted to identify the variants with the most occurrence to act as biomarkers or therapeutic targets for DC.

Keywords: genetics; molecular pathways; variants; Dupuytren's contracture; Dupuytren's disease

Introduction

Dupuytren's contracture (DC) or Dupuytren's disease is a fibroproliferative disorder of the palmar fascia characterised by the digits' flexion contractures and is associated with an abnormal build-up of type III collagen (1). This results in thickening and shortening of the normal fibrous bands in the hand and fingers (2), which can affect hand mobility and grip strength (3). DC was first described by Guillaume Dupuytren in 1833 as a chronic fibrotic contracture occurring in the palmar fascia (4). Flatt (5) suggested that DC is a 'Viking disease' in which the disease originated from the Vikings and now can be found throughout Northern Europe and around the world.

The development of DC can be divided into three stages: proliferative stage, involution stage and residual

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stage. The proliferative stage is when the nodules are formed with increased fibrinolytic activity, followed by the transformation of fibroblasts into myofibroblasts. The involution stage occurs next when the fibroblasts shrink and become compacted. Lastly, the residual stage consists of the deposition of large amounts of extracellular type I, III and IV collagen deposits and a reduction in the number of fibroblasts (6).

DC is also associated with environmental factors such as excessive alcohol consumption, heavy smoking, hand injuries and traumas, and vigorous physical activities that involve using hands. Other diseases such as diabetes, hypertension, and hyperlipidaemia are shown to have a high association with DC (7). On the other hand, the relationship between DC and epilepsy remains unclear, although it has been reported that the rate of DC incidence among epileptic patients is 56% (8). Salari et al. (9) reported a DC prevalence of 34.1% in type 1 diabetic individuals and 24% in alcoholic patients.

Over the years, many studies have reported the prevalence of DC in European and Western countries to be the highest compared to other regions (10, 11, 12). In comparison, Asian countries tend to have a much lower incidence of DC (10, 13, 14, 15). This could be explained by the underreporting of DC or due to the disease being rare in these regions.

Despite previous reports on the low prevalence of DC in Asian populations, a recent meta-analysis of 85 studies has reported the prevalence rate of DC in Asian populations (India, Iran, Japan, China and South Korea) to be 15.3% (95% CI 7.5-28.5), which is higher than the occurrence among the European population (10.3%) and the American population (2.3%) (9). These differences can be due to the change in demographics in different countries globally.

Over time, researchers have aimed to elucidate the molecular mechanisms and genetic underpinnings of DC. However, there is a notable scarcity of reports concerning DC variants located in the exonic regions. Many of these reports are outdated, underscoring the need for a fresh assessment of these variants to gain deeper insights into the genetic basis of DC.

In this review, we addressed the genetic aspects and prior genetic investigations related to DC. Subsequently, we delve into a discussion of the molecular pathways that have been proposed to be associated with DC. Lastly, we provide a summary of the genetic variants located in exonic regions that have been identified in DC and explore their connections with these molecular pathways.

Genetics aspects of DC

Genetic variants associated with DC

DC is a multifactorial disease influenced by both genetic and environmental factors. Due to the complexity of DC, the genetic variants that predispose an individual to DC are still not well understood. Microarray analyses conducted on populations of European descent have found several genes to be differentially expressed in DC patients (16, 17, 18, 19). These candidate genes include collagen genes, extracellular matrix (ECM) genes and Wnt signalling genes. However, these studies only suggest genes that are differentially expressed in DC, and further analysis to understand the role of these variants in DC is required.

Genetic aberrations in DC

Cytogenetic abnormalities consist of any chromosomal structural or numerical aberrations that can be associated with a disease. Many genetic aberrations in DC have been reported but remain inconclusive due to their occurrence in single cases. Some patients exhibited trisomy 7 and trisomy 8 (20, 21), while male patients with DC had an absence of chromosome Y (22). The presence of trisomy cells in DC could be due to selection bias resulting in the trisomy cells having higher proliferation capability than cells with a normal karyotype (23). Moreover, a study conducted on 4866 Danish individuals suggested new susceptibility loci due to cytogenetic aberrations on chromosomes 5 and 11 for DC (24).

Familial and twin studies

Twin studies make a useful tool in identifying genetic influences in the heritability of a disease. In a comparative study of two pairs of twins, it was observed that only one twin was affected with DC, suggesting an environmental influence in the development of the disease (25). However, the sample size of this study was small, and data is underpowered. In a more recent light of findings, a study of 30 330 monozygotic and same-sex dizygotic twins in Denmark demonstrated heritability of DC to be approximately 80%, indicating a positive relationship between the disease and genetics (26).

Furthermore, a cohort study in England found that DC exhibited a sibling recurrence-risk ratio of 2.9, indicating a strong genetic basis for its causation. Among the 92 patients, 41% reported a positive family history, while other factors showed no statistical significance with the familial aggregation of DC (27). Similarly, Capstick *et al.* (28). reported a sibling recurrence-risk ratio of 4.5, with 47% of 100 siblings having DC, further quantifying the magnitude of genetic predisposition to the disease.

Gene copy number alterations

Gene copy number or copy number variants is defined as the number of copies of a particular gene found in the genotype of an individual. An array comparative genomic hybridisation was conducted to study copy number changes associated with DC. However, it

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was reported that no copy number changes were observed in the palmar samples (23). When genome-wide high-resolution screening was used, copy number variations were found in the 10q22, 16p12.1 and 17p12 locations. Nine other regions that may contain copy number polymorphisms were identified in DC (29). This could be due to the limitations of technology in the previous study which found no copy number variations associated with DC. The dissimilarity could also be due to differences in the sample sizes of the studies: 4 (29) and 18 (23).

Mode of transmission

The exact pattern of transmission of DC is not very well understood. In a Swedish family of five generations, DC was reported to be inherited in an autosomal dominant manner with variable penetrance (30). However, in many patients with DC, the etiology is likely to be multifactorial (1).

Molecular pathways

There are several signalling pathways associated with DC, such as the wingless/integrated (Wnt), fibroblast growth factor (FGF) signalling pathway, transforming growth factor beta (TGF-β), Akt signalling pathway and integrin signalling pathway (31) (Figure 1). The disruption of these pathways has been suggested to lead to the development of DC and other fibrotic disorders.

Wnt signalling pathway

Wnt proteins are a group of extracellular signalling glycoproteins that bind to lipoprotein receptor-related proteins, frizzled receptors or tyrosine kinase receptors (32). The Wnt signalling pathway can be divided into two arms, β-catenin dependent and β-catenin independent, and both are upregulated in DC (32, 33). Disruption in the normal function of β-catenin can result in diseases

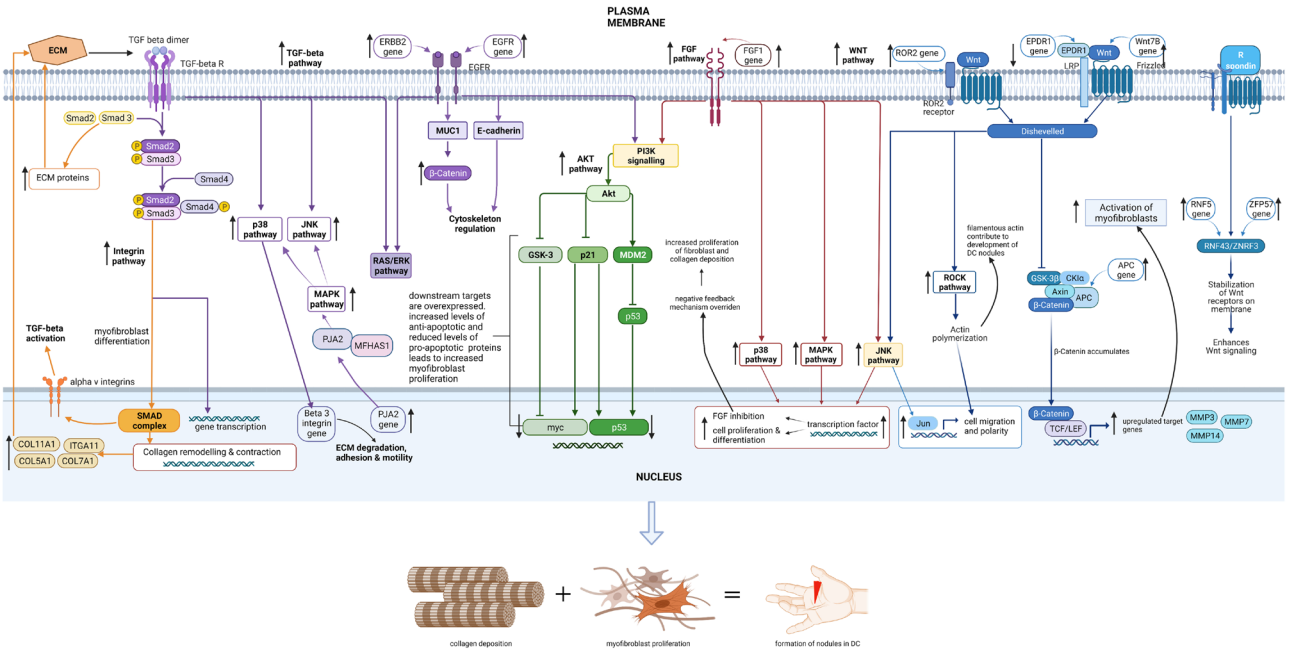

Figure 1

Summary of the pathways involved with DC and associated genes based on previous studies. Five pathways that play a role in DC are illustrated in the figure: Wnt signalling pathway (blue), TGF-β signalling pathway (purple), FGF signalling pathway (red), Akt signalling pathway (green) and Integrin pathway (orange). The pathways are interconnected through similar downstream proteins or pathways as highlighted (yellow). The upregulation of the pathways leads to increased deposition of collagen and uncontrolled proliferation of myofibroblasts. These mechanisms lead to the formation of nodules as well as the thickening of the cords observed in patients with DC. In the Wnt signalling pathway (blue), genes such as *WNT7B*, *APC*, *RNF5*, *ZFP57* and *ROR2* are upregulated, while the *EPDR1* gene is downregulated, leading to an upregulation of the downstream proteins. This, in turn, leads to an increased activation of myofibroblasts, contributing to the phenotypic expression of DC. On the other hand, in the FGF pathway (red), the *FGF1* gene is upregulated, causing the upregulation of the p38, MAPK and JNK pathways. This causes an increase in cell proliferation and differentiation as well as FGF inhibition. However, the fibroblasts gain sensitivity towards the negative feedback mechanism, leading to the increased proliferation of fibroblasts and collagen deposition. For the Akt pathway (green), the downstream targets are overexpressed; thus, the levels of anti-apoptotic proteins are increased while the levels of pro-apoptotic proteins are reduced, leading to an increased proliferation of myofibroblasts. Similarly, in the TGF-β pathway (purple), the genes *ERBB2* and *EGFR* are upregulated, causing the downstream pathways to be upregulated as well. Lastly, the upregulation of the TGF-β pathway leads to the upregulation of the integrin pathway (orange). This, in turn, results in elevated levels of collagen and ECM proteins, causing deposition of collagen as observed in DC patients. Created with BioRender.com, agreement no. HV23ISGD8W.

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and deregulated growth of cells. Therefore, increased levels of β-catenin may contribute to the proliferation of myofibroblasts observed in DC patients. In vitro cell cultures were observed to express increased levels of β-catenin (34), suggesting the overstimulation of the pathway in DC. The accumulated β-catenin translocates to the nucleus to induce the expression of Wnt target genes such as *MMP3, MMP7* and *MMP14* that play a role in collagen remodelling (35).

On a transcriptome level, several studies reported that DC tissues expressed higher levels of Wnt genes, including *WNT2, WNT4, WNT7B, WNT5B* and *WNT11* (36, 37, 38). Some of the microRNA identified in DC samples were found to be responsible for regulating important genes in the β-catenin pathway, such as *WNT5A, ZIC1* and *TGFB1* (39). Furthermore, SNPs related to the Wnt signalling pathway such as the *WNT7B* rs6519955 TT genotype and *RSPO2* rs611744 GG genotype, increase the probability of DC manifestation by 3.5 - and 2-fold, respectively (40). Elevated activity of Wnt and R-spondin genes can further stimulate Wnt signalling, reducing the degradation of β-catenin. In turn, this mechanism can trigger the proliferation of myofibroblasts and lead to the development of DC. The *EPDR* gene, also known as *SFRP4*, is responsible for the downregulation of the Wnt signalling pathway. When the protein encoded by this gene is downregulated, Wnt signalling is stimulated, and the degradation of intracellular β-catenin is reduced, resulting in the proliferation of fibroblasts (31).

FGF signalling pathway

Fibroblast growth factor (FGF) has been associated with DC through dysregulation of fibroblastic proliferation during the early stages of the disease. Through the production and secretion of FGF, the endothelial cells within blood vessels can cause the proliferation of fibroblasts (41). Normally, the endothelial cells within the blood vessels responsible for the rate of proliferation of fibroblasts are subjected to a negative feedback mechanism. This is to prevent FGF from being overproduced and leading to an elevated proliferation of fibroblasts. However, in DC, the high expression of FGF, TGF-β and their corresponding receptors disrupts the negative feedback mechanism (17). Therefore, the fibroblasts do not respond to the negative feedback mechanism and continue to proliferate and deposit collagen in surrounding tissues.

TGF-β signalling pathway

TGF-β pathway was studied due to its role in cellular differentiation, proliferation and as an important factor that contributes to fibrosis (42). TGF-β gives rise to the expression of alpha-SMA, which can enhance the contraction of myofibroblasts (33). Furthermore, the activation of TGF-β receptors can induce SMAD signalling cascades and non-SMAD signalling cascades such as mitogen-activated protein kinase (MAPK) (43). The TGF-β pathway was observed to work alongside the Wnt pathway, leading to the dysregulation of fibroblast proliferation in DC (44).

Moreover, a microarray analysis of DC cells showed that TGF-β induced the signalling of p38 MAPK, causing the expression of genes involved in cellular proliferation such as *THBS1, GADD45α* and *NUAK1* (16). It was also discovered that cell cultures of DC tissues resulted in an elevated concentration of myofibroblasts when TGF-β1 was added. An increase from 9.7% and 2.7% to 25.4% and 24.2% of myofibroblasts was seen in the nodule and cord cell cultures, respectively, upon addition of TGF-β1 (44). Furthermore, at a concentration of 12.5 ng/mL, TGF-β induced the myofibroblasts in DC from 12% to 23% (45).

Integrin signalling pathway

The integrin pathway controls the regulation of cell adhesion, spreading of cells and migration, proliferation, differentiation and ECM remodelling (46). The expression of integrin is regulated by TGF-β (a factor closely associated with the development of DC) and vice versa, creating a loop driven by cooperative signalling (47).

In the context of DC, cells isolated from the aponeuroses of DC patients were more capable of retracting the collagen gel, had stronger adhesion characteristics to collagen and fibronectin and expressed more integrin compared to the control (48). Similarly, Matsui *et al.* (49) demonstrated that, in comparison to normal fascia, the expression of αv and α8 RGD-recognising integrin was much higher in nodules of individuals with DC. These data imply that αv and α8 integrin are important regulators of DC pathogenesis. It was hypothesised that αv integrin, via controlling TGF-1 expression, could be a crucial intrinsic regulator of fibrous tissue formation in DC (49).

Akt signalling pathway

The Akt-signalling pathway is responsible for the regulation of cell survival, glucose metabolism, protein synthesis and cell motility (50). A proteomics study on DC found Akt levels to be upregulated in diseased tissues, with downstream targets of Akt signalling being overexpressed (51). Akt was found to increase the activity of anti-apoptotic proteins in DC (51). Furthermore, blood vessels associated with DC contained high levels of phosphorylated Akt along with the expression of bFGF, IGF-2 and CTGF (39). These factors, along with a favourable composition of the extracellular matrix, can sustain myofibroblast proliferation in the pathogenesis of DC.

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Table 1 Non-coding variants that have a significant contribution to development of DC phenotype through various signalling pathway and mechanisms.

Variants	Location	Gene/ nearest gene	Contribution to development of DC phenotype	Reference
rs16879765	chr7:g.37949493C>T	*EPDR1*	Decreases SFRP4 secretion, increase in WNT3A signaling, greater α-SMA expression and contraction of the DC cords, homozygous for the major allele showed downregulation of SFRP4, causes fibroblasts in the fascia of the hand to proliferate and form nodules	32, 58
rs17433710	chr1:g.162702221T>C	*DDR2*	Causes abnormal fibrotic cords due to abnormal ECM deposition*	58
rs6496519	chr15:g.88694953C>T	–		
rs977987	chr16:g.75472695G>A/C	*GHST6*		
rs1032466	chr14:g.50607743A>C/G	*ATL1*	Activated by both TNF and WNT3A, decreases expression of MAP4K5, inhibits GSK3β phosphorylation and subsequent β-catenin accumulation, integrating TNF and WNT signaling in DC fibrosis	
rs12677559	chr8:g.140946805T>C	*PTK2*	Regulates myofibroblast differentiation	
rs7524102	chr1:g.22371954A>G	–	Harbour genes that encode proteins in the Wnt signaling pathway. An imbalance of Wnt signaling in DC could cause fibroblasts in the fascia of the hand to proliferate and form nodules†	32
rs4730775	chr7:g.117277064C>G/T	*WNT2*		
rs2912522	chr8:g.69080145G>A/T	*LINC01592*		
rs2179367	chr6:g.149441401A>G	–		
rs201344092	chr6:g.30674641-30674642delCT	*DHX16*	Increase in gene expression of *ZFP57*	61
rs1042704	chr14:g.22843385G>A/C	*MMP14*	Abnormal and excessive ECM deposition causing abnormal fibrotic cords reduces collagen catabolism in tissue, which tips the balance of homeostasis of collagen in tissue, contributing to the fibrotic phenotype of DC	58, 62
rs6519955	chr22:g.46025962G>T	–	Habours genes that encode proteins in the Wnt-signaling pathway. An imbalance of Wnt signaling in DC could cause fibroblasts in the fascia of the hand to proliferate and form nodules, increasing the chances of developing DC by 3.5-fold	32, 38
rs611744	chr8:g.108215779A>G/T	*EIF3E*	Habours genes that encode proteins in the Wnt-signaling pathway. An imbalance of Wnt signaling in DC could cause fibroblasts in the fascia of the hand to proliferate and form nodules, decreasing the chances of developing DC by 2-fold	32, 38

*Pertains to rs17433710, rs6496510, rs977987; †Pertains to rs7524102, rs4730775, rs2912522 and rs2179367.
ECM, extracellular matrix.

DNA variants associated with DC

GWAS, WES and variant studies on DC

Genome-wide association studies (GWAS), whole exome sequencing (WES) and variant studies conducted on DC were compiled and reviewed (Supplementary Table 1, see section on supplementary materials given at the end of this article). These studies were all conducted on European populations. Two studies were conducted using data from a public database, with the comparison being performed using a previous GWAS study (32) which was conducted on Europeans. The search for previous studies was done using three databases (PubMed, Google Scholar and Science Direct) as well as the GWAS database. To our knowledge, few studies are reported for variants present in Asian populations with DC (10, 17, 19, 29, 32, 38, 43, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62). The previous studies (10, 17, 19, 29, 32, 38, 43, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62) also reported the variants to be associated with pathways such as the Wnt signalling pathway and other mechanisms such as extracellular matrix modification and inflammation. Most of the studies reported on the involvement of *WNT7B*, *RSPO2*, *SFRP4* and *EPDR1* genes in the development of DC.

Several reports (32, 38, 58, 61, 62) have shown that these variants still contribute to the development of the DC phenotype. Based on Table 1, most of the variants impact the Wnt signalling pathway and the mechanism of ECM regulation. The alleles rs7524102, rs4730775, rs2912522 and rs2179367 harbour genes that are involved in the Wnt signalling pathway. An imbalance in these pathways leads to the proliferation of fibroblasts,

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Table 2 Most commonly identified variants associated with Dupuytren's contracture.

Variants	MAF	*P* in studies (31)	*P* in studies (58)
rs7524102	0.23	2.8×1^{-9}	3.00×10^{-15}
rs16879765	0.13	5.6×10^{-39}	3.38×1^{-81}
rs2912522	0.33	2.0×10^{-13}	4.09×10^{-29}
rs611744	0.46	7.9×10^{-15}	1.15×10^{-32}
rs11672517	0.28	6.8×10^{-14}	1.99×10^{-17}

resulting in the formation of nodules as observed in DC patients (32).

Looking into the mechanism through ECM modulation, it is observed that the alleles rs17433710, rs6496519, rs977987 and rs1042704 may contribute to the formation of fibrotic cords in DC patients through abnormal and excessive ECM deposition. Variants such as rs6519955 and rs611744 were first identified in a GWAS study (32) and were further validated for their impacts (38). It was found that WNT7B rs6519955 genotype TT increased the likelihood of DC manifestation by 3.5 times, while RSPO2 rs611744 genotype GG reduced the likelihood of DC manifestation by nearly twofold (38).

Commonly identified variants

There were five commonly identified variants associated with DC based on previous studies (Table 2). All the variants were non-coding variants and studied in European populations. All the variants contribute to the phenotypic expression of DC through the Wnt signalling pathway. This further supports evidence that patients with DC have variants associated with the Wnt signalling pathway, suggesting this is a candidate pathway contributing to the disease. The most significant variant across both studies was rs16879765, which also has the lowest MAF (Table 2).

The variant that captured the most interest is the rs16879765 variant for its impacts on the development of DC (Figure 2). The variant increased the expression of *SFRP4*, resulting in the activation of the IL-6 amplifier in fibroblasts of diseased palmar aponeurosis (63). Patients with DC were found to have an increased incidence of these risk alleles (63).

The variant, rs16879765, was first discovered by Dolmans *et al.* (32) in a GWAS study ($P = 5.6 \times 10^{-39}$; odds ratio: 1.98). The variant lies in the intron (NM_017549.5:c.478+445C>T) between exon 5 and 6 of the *EPDR1* gene on chromosome 7. From a functional perspective, using myofibroblasts stimulated with recombinant WNT3A, SFRP4 and DKK1 proteins, this variant was observed to cause a slight imbalance of Wnt signalling which then contributes to the fibrotic phenotype (56). A fourfold difference in *SFRP4* mRNA expression between the two homozygous genotypes of the most associated single nucleotide polymorphism (SNP), rs16879765, was observed (56). Individuals homozygous for the high-risk genotype (TT) showed greater SFRP4 secretion, suggesting a slight increase in WNT3A signalling via the non-canonical pathway (56). The constant identification of this specific variant and analysis conducted in several studies (32, 56, 58) is promising as it could be used as a biomarker in either diagnostic or therapeutic approaches for DC.

Exonic variants

Over the years, many genome-wide association studies have been conducted on DC to identify the genetic loci involved in the disease. These studies reported on the main candidate genes and the loci that exhibited genetic susceptibility to DC. However, these findings consisted of many single nucleotide polymorphisms in the intron regions.

Exonic point mutations are typically categorised as missense, synonymous, silent, or nonsense mutations. Some point mutations result in aberrant precursor-mRNA (pre-mRNA) splicing, a crucial stage in gene expression, and this has been linked to the pathophysiology of several illnesses (64). A few studies (32, 58, 61) have reported variants that localise within exonic regions. Interestingly, all the variants reported in these studies were different but located in genes involved in similar pathways associated with DC. Some of the variants were observed to have genes nearby, that are often expressed as a group, suggesting they may be co-expressed in the molecular pathology of DC (65). In this report, we tabulated variants found in the exon region of previous studies (Table 3) and their possible involvement in DC. The genomic locations of these variants can be found in the Supplementary Index.

There are a total of nine variants within six genes from three pathways that have been included in Table 3. Of these nine variants, three were reported as missense variants, three as 2 kb upstream variants, two as non-coding exon variants and one as variant in the regulatory region. The variants were reported to be

Figure 2

Region of variant rs16879765 on chromosome 7 identified by the red line. The variant lies in the intron (NM_017549.5:c.478+445C>T) between exon 5 and 6 of the *EPDR1* gene on chromosome 7 (Source: UCSC Genome Browser on Human).

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Table 3 Exonic variants found to have association with DC and the molecular pathways involved from previous GWAS and WES studies.

Pathway/gene†	Variant	Type	AA change	dbSNP	Population size	Odds ratio	*P*	Origin	Reference
Integrin									
ITGA11 (15)	c.1297G>A	Missense	V433M	rs2306022	8557	1.286	7.59×10^{-6}	European	58
TGF-β									
PJA2 (5)	c.2113G>A	Missense	A705T	rs246105	8557	0.796	1.34×10^{-8}	European	58
WNT									
MIR6833, RNF5 (6)		2 kb UPV	N/A	rs2269423	Database	N/A	1.2×10^{-5}	N/A	61
	c.-10+71T>G								
	c.-10+71T>C								
	c.-10+71T>A								
MMP14 (14)	c.817G>A	Missense	D273N	rs1042704	8557	1.326	8.72×10^{-13}	European	58
*WNT7B** (22)	g.46421842G>T	Reg. region	N/A	rs6519955	3692	1.54	3.2×10^{-33}	European	32
WNT7B, LINC00899* (22)		NCT exon	N/A	rs8140558	3692	1.39	1.5×10^{-11}	European	32
	g.46044393A>G								
	g.46044393A>T								

*Variants found in the intron regions but are highly associated with the molecular pathways involved in DC; †Gene/nearby gene (chromosome).
AA, amino acid; N/A, not available; NCT, non-coding transcript; Reg., regulatory; UPV, upstream variant.

involved in three key pathways associated with DC: integrin signalling pathway, TGF-β signalling pathway and Wnt signalling pathway.

Genes such as *WNT7B* and *ROR2* reported here are involved in the Wnt signalling pathway (66). The SNP rs6519955 contains the *WNT7B* gene and is the most significant SNP (32). rs8140558 is also located in the *WNT7B* locus. Moreover, another gene involved in this pathway is *PJA2*. The ubiquitination of *MFHAS1* by *PJA2* will enhance the signalling of the MAPK pathway, in turn enhancing the p38 and JNK pathways (67). The FGF and TGF-β pathways cooperate to activate the Akt signalling pathway through the phosphorylation of PIP2 to PI3 (68). The variant rs246105 is within the *PJA2* gene. In the GWAS study consisting of a total of 4041 case subjects and 8,251 control subjects from the UK, the Netherlands and Germany, the frequency of the variant rs246105 was found to be 20.1% (58).

The *MMP14* gene variant found on chromosome 14 is also a strong candidate contributing to DC as it is known to interact with the extracellular matrix, suggesting it may play a role in the pathogenesis of DC (58). Expression of ECM component genes is reported to be upregulated in DC tissues (19). The allele rs1042704 at chromosome 14q11.2 may modulate the ECM through the *MMP14* gene (58). The ancestral allele at rs1042704 is G, which codes for Asp273 (D273) in the enzyme, while the alternate allele is A, which codes for Asn273 (N273), where the A allele is associated with DC. The strong relationship between rs1042704 and deficiencies in collagenolytic activity of its gene product, MT1-N273, suggests that the phenotype of the myofibroblasts may be linked to cord thickening during DC progression. It is also likely that collagen turnover in the cord tissue is significantly higher than in other regions of the body, which could explain why the MT1-N273's poor collagenolytic activity affects the cord tissue in the hand only (62).

ITGA11, a gene that encodes for integrin alpha 11 (58) is also reported in this article. Variant rs2306022 in chromosome 15q23 harbours the ITGA11 gene, thus modulating the ECM (58) and contributing to the progression of DC.

Conclusion and future perspectives

Technological advances in high-throughput genotyping and sequencing, as well as large-scale worldwide collaborative efforts, have helped researchers better understand the genetic architecture of DC. However, while SNP studies have quickly revealed causal molecular pathways disrupting DC formation, the functional coupling of GWAS results to molecular pathways has been limited. As a result, the most pressing task soon is to functionally validate SNP discoveries from GWAS to better understand their

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roles in disease causality. Only if SNPs can be connected to causative genes and pathways, can targeted therapeutic interventions be possible. Moreover, all the variants reviewed in this report are of European origin. However, recent trends show that the prevalence among other populations is on the rise (9). Yet the studies on disease-causing variants in these populations are still low. In the context of Southeast Asia, there are no studies on the genetic aspects of DC. A comparative study or a re-evaluation of the prevalence of DC in different countries through consortia and consolidating population cohorts with DC can be done to better understand DC from a global perspective, and this can facilitate better treatment and management for individuals with DC. This review has described the five pathways involved in the development of DC and the genetic aspects of DC. The genetic variants found in the exons based on previous publications were also highlighted, and further analyses of these variants may help us to understand the mechanism of DC better.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EOR-23-0056.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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