Joint Bone Spine xxx (2011) xxx–xxx

Available online at ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

Genetics of Dupuytren's disease

Laëtitia Michou[a,*], Jean-Luc Lermusiaux[b], Jean-Pierre Teyssedou[b], Thomas Bardin[b], Johann Beaudreuil[b], Elisabeth Petit-Teixeira[c]

[a] Service de rhumatologie du CHUQ-CHUL, centre de recherche du CHUQ-CHUL, département de médecine, université Laval, 2705 boulevard Laurier, G1V4G2 Québec, Canada
[b] U.R.A.M, centre Viggo-Petersen, hôpital Lariboisière, AP–HP, Paris, France
[c] GenHotel-EA3886, université d'Evry-Val-d'Essonne, Evry-Genopole, France

ARTICLE INFO

Article history:
Accepted 23 May 2011
Available online xxx

Keywords:
Dupuytren's disease
Heritability
Gene expression
β catenin
TGFβ

ABSTRACT

Dupuytren's disease (DD) is a progressive fibrosis of the palmar fascia characterized by the formation of a nodule, which evolves into a cord. DD is the most common hereditary disease of the connective tissue preferentially affecting Caucasoids originating from Northern Europe. Some environmental factors are associated with DD, namely alcohol consumption, tobacco exposure and, possibly, manual activities. Diabetes and epilepsy are the most frequently reported DD-associated diseases. The genetic mode of inheritance is not well understood, but seems to be heterogeneous: most frequently, autosomal dominant with variable penetrance, and rarely recessive autosomal or maternal (matrilinear), suggesting a mitochondrial heredity. Initially, a suggestion of linkage with the *DUPC1* locus at *16q* was proposed. Then, among the genomic variations observed in DD, alterations in the copy number of genes in chromosomal regions *10q22*, *16p12.1* and *17p12*, associations with the *HLA-DRB1*15* allele and a mutation in the *rRNA 16s* identified in forms with a matrilinear heredity, were reported. Finally, a genome-wide study has shown a genetic association of DD with 6, 11 and 16 chromosomes. Pathophysiology of DD involves mainly myofibroblasts and the extracellular matrix of collagen. Gene and protein expression studies have confirmed the central role of the β catenin of the TGFβ pathways in the pathogenesis of DD.

1. Introduction

Dupuytren's disease (DD) is a fibrosing disorder of the palmar fascia, which may lead to an irreducible and disabling progressive flexion of the fingers. Clinically, a palmar nodule is observed, often followed by the formation of a cord. The skin of the palmar region is also modified with the occurrence of umbilications and fibrosis in the subcutaneous tissue adhering to the underlying lesions [1]. The ring finger is the most frequently affected finger, followed by the little finger, the thumb, the middle finger and the index finger. The fibrosis usually starts in the palm then extends to fingers. The evolution, classified in different stages (Fig. 1), is progressive and irreversible, and there is a high risk of relapses after surgical excision. Extrapalmar lesions of DD are more frequently observed as knuckle pads, which are fibrosing lesions of the dorsal digital fascia at the level of proximal interphalangeal joints, as fibrosis of the plantar fascia or Ledderhose's disease and/or as fibrosis of the tunica albuginea and corpus cavernosum penis or Peyronie's disease (Fig. 2). The notion of "diathesis", classically used in DD, may be defined as the occurrence of diversely localized affections (hand, foot, penis), simultaneously or sequentially occurring, of the same nature and from the same origin in a single individual [2], thus manifesting in a phenotypic spectrum. Clinical studies have shown that some elements of the Dupuytren diathesis, including ethnic origin, family history, bilateral Dupuytren affection, and extrapalmar localizations were associated with a more severe disease, allowing for the prediction of the recurrence and the continuance of the disease after surgical treatment [2]. In 2006, the factors of the Dupuytren diathesis were revisited. Two factors were added (male sex and age of onset before 50 years) and two factors were modified: the family history, now specifying the affection of at least one first-degree relative and ectopic localizations were further clarified (knuckle pads only). The presence of all these factors of the Dupuytren diathesis in a patient would increase the risk of postoperative relapse by 71%, compared with a base risk of 23% in patients non-carrier of these criteria [3].

2. Some epidemiological data

2.1. Descriptive epidemiology

DD is considered to be one of the most common hereditary disorders of the connective tissue, preferentially affecting Caucasoid individuals from Northern Europe [4]. After 60 years of age, its

* Corresponding author. Tel.: +1 418 654 2178; fax: +1 418 654 21 42.
E-mail address: laetitia.michou@crchul.ulaval.ca (L. Michou).

1297-319X/$ – see front matter © 2011 Société française de rhumatologie. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.jbspin.2011.05.027

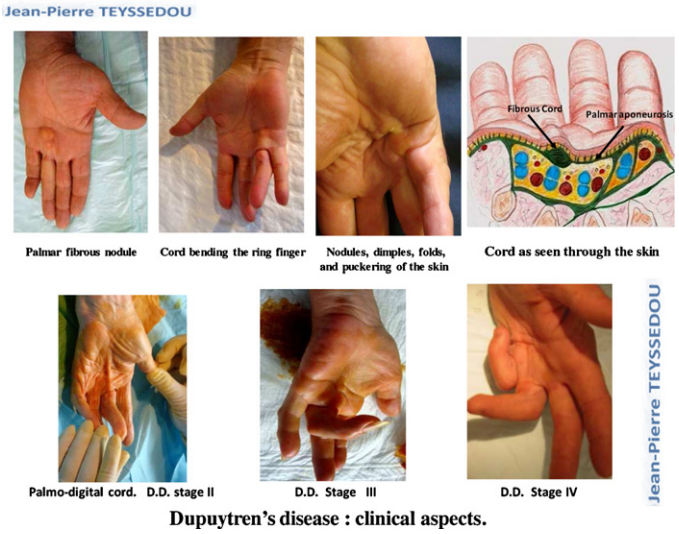

Fig. 1. Clinical presentation of palmar region Dupuytren's disease.

prevalence is high in Norway (46%), Scotland (39%), Iceland (33%) and Australia (28%) [5]. However, DD prevalence figures vary considerably depending on the studies and diagnostic criteria used by the authors. Currently, DD prevalence is estimated to be more than 4% for men in England, with a prevalence of 25% in the Caucasoid population over 60 years of age. The European countries which currently exhibit a high DD prevalence are the same as those of the Viking invasion areas of the 10th century [6]. Prevalence of DD is non-negligible in several Asian countries and an association with classical DD risk factors and a positive family history is also found in less than 10% of cases [7]. However, current objective scientific data do not allow confirmation of the migratory or Nordic theory of DD. The presence of DD in most countries may suggest an origin and spread of DD at a earlier time than initially believed [5]. Men are afflicted with DD approximately three to five times more frequently than women. Women with DD have a higher risk of post-surgical relapse, higher familial aggregation, more frequent bilateral disease and more frequent association with Ledderhose's disease [8].

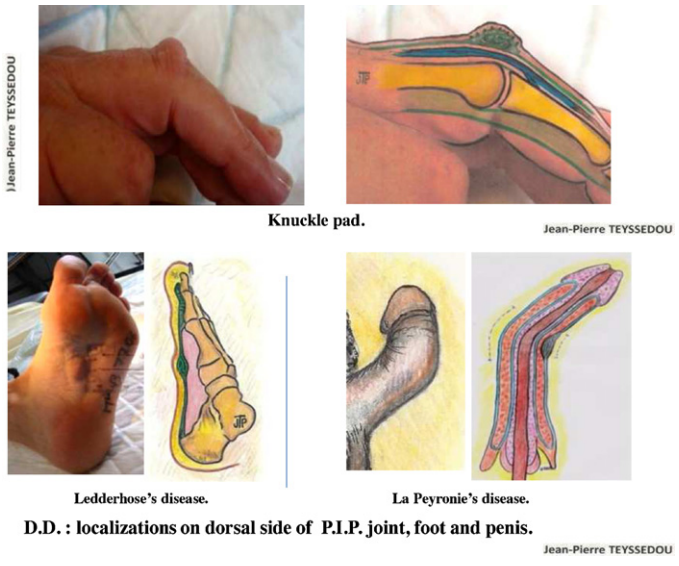

Fig. 2. Ectopic localizations of Dupuytren's disease.

2.2. Environmental and lifestyle-related risk factors

Several environmental factors are known to be associated with DD, including alcohol intake (relative risk = 1.6 [1.5–1.7] for more than 22 drinks per week) and tobacco exposure (relative risk = 1.3 [1.2–1.5] for more than 20 cigarettes per day), which may be two independent DD risk factors [9]. Palmar fascia repeated injuries during sport, such as rock climbing, may also contribute to the development or the severity of DD [10]. However, the facilitating role of professional exposure to repeated microtraumas is more controversial [9].

2.3. Pathological associations

Classically reported DD pathological associations, besides ectopic localizations previously described, concern retractile capsulitis, epilepsy, diabetes, HIV and dyslipidemia, whereas rheumatoid arthritis and/or its treatment may have a protective effect [5]. A British study has shown an increased DD risk in the presence of diabetes (adjusted relative risk = 1.8 [1.2–2.6]), especially in the case of insulin treatment (adjusted relative risk = 4.4 [2.1–9.1]), whereas no significant association was observed with epilepsy or antiepileptic drugs [11].

3. Familial aggregation and genetic transmission modes

3.1. Familial aggregation studies

The first familial aggregation studies, performed in the 1940s, have shown that about 40% of DD patients had an affected relative. Several case reports mentioned a phenotypic concordance between monozygotic twins [12], but an absence of phenotypic concordance in monozygotic twins has also been published [13]. DD familial aggregation has recently been estimated in 92 British patients, by the use of the sibling (i.e. born from the same father and mother) recurrence risk. This parameter allows for the quantification of heritability by dividing the sibling recurrence risk by the general population prevalence. In this study, 41% of patients had a positive DD family history. The sibling recurrence risk was 2.9, confirming a DD genetic component [12]. In familial forms, no association with classical environmental risk factors was identified. However, the age of onset was earlier (49 years versus 55 years in the absence of family history) and the DD severity was higher (severity score of 23.1 versus 15.5 in the absence of family history) [12]. Moreover, in the presence of family history there was a non-significant trend towards a higher number of affected fingers and a more frequent extrapalmar involvement (Ledderhose's disease and knuckle pads).

3.2. Genetic transmission modes

The DD genetic transmission mode is not currently well understood and seems heterogeneous: most often autosomal dominant with variable penetrance, and rarely autosomal recessive or maternal (matrilinear), suggesting a mitochondrial heredity. A large number of DD patients probably have a sporadic form of multifactorial origin (i.e. a complex heredity determined by the presence of genetic factors of susceptibility, each one having a weak contribution to the genetic susceptibility, which may interact with environmental or lifestyle factors). In Peyronie's disease the most often reported genetic transmission mode is autosomal dominant with variable penetrance [14,15]. It is possibly the same for Ledderhose's disease, but its mode of genetic transmission remains largely unexplored.

Please cite this article in press as: Michou L, et al. Genetics of Dupuytren's disease. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.05.027

4. Dupuytren's disease, cytogenetic abnormalities and gene copy number

Cytogenetic abnormalities in the number and the structure of chromosomes, as well as a premature separation of centromeres, have been observed in fibroblasts from DD nodules. Karyotype abnormalities, including trisomies 8, trisomies 7 and loss of chromosome Y have also been identified [16]. Clonal or sporadic chromosomal abnormalities were reported in 69% of DD nodules: autosomal trisomies or monosomies, deletions, chromosomal insertions or translocations [17]. The absence of recurrence in the chromosomal abnormalities and in breakpoints may more likely suggest a chromosomal instability in the DD affected palmar fascia than a true cytogenetic signature [17]. Such cytogenetic abnormalities have indeed been reported in the kidney, the ureter and in atherosclerosis plaques. Recently, palmar aponevrectomy tissues from 18 DD patients were analyzed by comparative genomic hybridation (CGH) [18]. This technology searches for changes in the gene copy number. Although some studies have reported major abnormalities in the number and the structure of chromosomes in DD, no gene copy number disequilibrium was observed in genome-wide CGH [18]. These findings may suggest a selection bias of trisomic fibroblast in cultures, which may have had a higher proliferation capacity than fibroblast with normal karyotype in previous cytogenetic studies. However, a recent genome-wide search for gene copy number alterations, utilizing high resolution but with few patients, may suggest a gene copy number alteration in *10q22*, *16p12.1* and *17p12* in DD [19]. Nine other chromosomal regions, including *6p21* (*HLA* locus), may contain gene copy number polymorphisms in DD [19].

Finally, the follow-up of a Danish cohort of 4866 individual carriers of chromosomal rearrangements was conducted to search for autoimmune disease susceptibility loci and concluded that DD in several female patients carrier of rearrangements in chromosome 5 and on the long arm of chromosome 11, thus suggesting two novel DD genetic susceptibility loci [20].

5. Genetic linkage analysis

Only one genetic linkage study on DD has been published. This linkage analysis was performed in a Swedish family containing 17 DD affected individuals over five generations. The DD segregation in this family was consistent with an autosomal dominant transmission mode with high, but incomplete, penetrance at the age of 50 years [21]. This genome scan with microsatellite markers spaced about every 8 cM, led to a suggestion of genetic linkage with a 6 cM region located on the long arm of chromosome 16 (Table 1) [21]. The causal gene identification in this first and only known susceptibility locus, *DUPC1*, has not yet been published.

6. Genetic association studies

6.1. Association with TGFβ pathway genes

The first genetic association study with DD covered two promoter polymorphisms and two non-synonymous polymorphisms located in the first exon of *TFGβ1* gene [22] (Table 1). The *TFGβ1* gene is an excellent DD candidate gene since the TFGβ1 protein contributes to the development of the myofibroblast cellular phenotype from normal fibroblasts. Nevertheless, no genetic association of this gene with DD was observed [22]. Moreover, since *TFGβ2* gene expression variations may increase myofibroblast activity as well as the proliferation and induction of extracellular matrix synthesis, an insertion polymorphism in a regulatory region of *TFGβ2* gene has been studied in the same cohort [23]. However, this genetic association study with DD turned out to be negative [23]. A third analysis searched for association of genes coding for TGFβ receptors with DD [24]. These receptors, present in the DD affected tissue, were logically good candidate genes. Only one significant association of a polymorphism of the *TGFβRI* gene was observed in a recessive model [24]. Finally, one last study covered three polymorphisms of the *Zf9 (Kruppel-like factor 6, KLF6)* gene, a transcription factor increasing the tissular expression of TFGβ1. One of the polymorphisms located in a regulatory region of the *Zf9* gene, was significantly associated with DD (relative risk = 1.9 [1.2–2.9]) [25].

6.2. Association with HLA-DRB1gene

The HLA association with DD has been investigated several times in the literature with discordant or non-replicated results, from which follows a possible role in DD of the ancestral haplotype *HLA A1-B8-DR3* [1]. Recently, a case-control study in the British population showed a genetic association of DD with a group of alleles coding for the beta 1 subunit of the HLA-DR molecule. This *HLA-DRB1*15* allele group was present in 37% of patients versus 21% of healthy individuals, conferring a 2.3-fold higher risk for the development of DD in the carriers (Table 1) [26]. This genetic association has not yet been pathophysiologically explained. This *HLA-DRB1*15* allele group is already known to be associated with the genetic susceptibility to multiple sclerosis, narcolepsy and leprosy bacillus infection, and it may protect against rheumatoid arthritis.

6.3. Association with mitochondrial genome mutation

A systematic search for mitochondrial genome mutations was performed using denaturing high pressure liquid chromatography (DHPLC) in 20 DD affected patients with a family history suggestive of mitochondrial heredity and compared with 20 healthy individuals, [27]. In this study, the authors identified a *C2839A* mutation in the gene coding for the 16s ribosomal RNA in 90% DD affected patients and absent from healthy individuals (Table 1) [27]. However, the possible functional consequences of this mutation in DD have not been detailed.

6.4. Genome-wide association study in Dupuytren's disease (DD)

A first genome-wide association has recently been published in DD [28]. The study of 40 DD affected patients and 40 controls, all of Caucasian origin, has suggested an association of DD with regions in chromosomes 6, 11 and 16 (Table 1), the associated region on chromosome 6 being located within the *HLA* locus. The *16p13* region of the *HLA* locus was located at more than 36 cM from the *DUPC1* locus located in *16q* as reported during the linkage analysis of a large Swedish DD affected family.

7. Current pathophysiological concepts

7.1. The myofibroblast and the collagen extracellular matrix

The contractile myofibroblasts leading to the progressive and irreducible flexion of fingers are involved at every stage of DD. The early proliferation stage is characterized by the formation of a nodule with a high fibrinolytic activity leading to the progressive differentiation of almost all of the fibroblasts contained in the nodule into myofibroblasts [29]. At the involution stage, the myofibroblasts shrink and line up along the tissue constraint lines. At the residual stage, the irreducible flexion is reinforced by large amounts of extracellular type I, III and IV collagen deposits, whereas the number of myofibroblasts decreases. The myofibroblasts appear to originate from fibroblasts, and gain smooth muscle cell properties,

Please cite this article in press as: Michou L, et al. Genetics of Dupuytren's disease. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.05.027

Table 1
Main candidate genes and main Dupuytren's disease genetic susceptibility loci.

Chromosome	SNP/marker	Physical position in base pairs	Gene or nearby gene	Reference
1	rs12032381	219683699	LOC100132626	[28]
1	rs1903138	219719126	LOC100132626	[28]
3	rs7426655	197829546	FBXO45 LRRC33	[28]
4	rs4864039	132525024	CYCSP14	[28]
5	rs6897647	15957024	FBXL7	[28]
6	rs3132506	31284205	HCG27 HLA-C	[28]
6	rs3130473	31307187	HCG27 HLA-C	[28]
6	rs16895338	65267311	LOC727945	[28]
6	HLA-DRB1*15	32546546	HLA_DRB1	[26]
9	A > C	3′UTR	TGFBR1	[24]
10	rs114266304	3′UTR	Zf9 (KLF6)	[25]
11	rs2846236	123571837	OR10D3P OR8F1P	[28]
11	rs6590281	127224748	LOC100132514	[28]
16	rs1919060	5258657	LOC100129495	[28]
16	rs11649669	5293566	LOC100131502	[28]
16	D16S415	53670735	*DUPC1?*	[21]
17	rs1978136	29401811	ACCN1	[28]
23	rs17335275	3584538	PRKX	[28]
Mitochondrial DNA	C>A	2839	16S RNA	[27]

SNP: single nucleotide polymorphism.

notably the presence of actin-α-microfilaments following extracellular fibronectin fibrils. The myofibroblasts synthesize themselves this extracellular glycoprotein, which glues the myofibroblasts together [29] and to the collagen extracellular matrix thanks to an integrin.

The causes for myofibroblast proliferation in DD may involve self-sustained ischemic phenomena. The differentiation and proliferation of myofibroblasts may be stimulated by various cytokines, adhesion molecules, extracellular matrix components and growth factors such as TGFβ1, by inducing the accumulation of β-catenin and by its role in abnormal mechanotransduction of myofibroblasts [30], and by TGFβ2. The periostin, a TGFβ1-induced protein which regulates apoptosis, actin α proliferation and expression, may also contribute to the transformation of cellular phenotype of fibroblasts into myofibroblasts [31]. On the contrary, PDGF, FGF-b, high doses of TGF, interleukin 1α and interleukine 1β may conversely have an inhibitory effect on myofibroblast proliferation [4]. Finally, the presence of androgen receptors specifically in DD nodules suggests that androgens may play a role in myofibroblast proliferation in DD [32].

7.2. Contributions from gene expression profile studies

The surgical therapeutic management of DD yields large amounts of affected tissues and probably explains the large number of published gene expression works (Table 2). These analyses aim at identifying biomarkers for the prediction of the progression risk towards irreducible flexion in DD or of postoperative relapse.

Despite the major role of TGFβ in extracellular matrix protein transcription, in inflammation and fibrosis, only the *TGFβ2* gene seems to be significantly upregulated in DD cords [33]. Several analyses of expression of genes coding for matrix metalloproteinases (MMP) and their inhibitors have been performed, following clinical observations suggesting DD in patients who received these inhibitors in cancer therapeutic trials [34]. Several genes coding for these collagenases were upregulated, notably *MMP1, 2, 13* and *14* [34,35]. A disequilibrium between MMP and their natural inhibitors in DD has been observed. This disequilibrium increases the extracellular collagen synthesis and deposit despite the overexpression of collagenases which are supposed to reduce collagen deposits [35]. A correlation has been shown between the gene expression level of some MMP and related proteins (desintegrins and MMP with a thrombospontin motif or ADAMTs) and the risk of recurrence of flexion-fixed deformity in the year following a first aponevrectomy [36]. This gene expression profile of MMP and their inhibitors in DD seems to be shared with the one in Peyronie's disease [37].

A gene expression analysis over 1176 genes has shown, in DD affected tissues, an upregulation of five genes and a significant downregulation of 18 genes, notably the gene coding for the precursor of amyloid protein A4, the dihydrodiol dehydrogenase and the precursor of an intercellular adhesion molecule called ICAM2 [38]. The first genome-wide study using expression microchips compared fibroblasts from either DD cords or healthy palmar fascia [39]. An overexpression of more than 30 genes has thus been demonstrated, notably for fibronectin, tenascin-C, three TGFβ isoforms and type III, IV and VI collagen genes. Other genes involved in the extracellular matrix organisation and remodelling were also significantly upregulated, such as type V and XIV collagen genes as well as *NCAM1*, an adhesion molecule. Novel potential genes in DD pathophysiology have been identified, notably the *MafB* gene, coding for a transcription factor significantly upregulated in fibroblasts from DD cord [39]. Later on, other differentially expressed genes were identified, particularly those coding for proteoglycan 4, fibulin-1 and type XV collagen [40]. A bioinformatic analysis has shown that these genes come from common biological networks mainly involved in pathways for cell death, cellular proliferation and growth, and in cancer [40]. Recently, the gene expression profile comparison between DD nodules and cords has shown large differences: genes with differential expression alterations mostly came from biological pathways for cell growth, proliferation, differentiation, cell death regulation, cellular adhesion, extracellular matrix/receptor interaction, and cellular communication [41]. Novel signalling pathways involved in DD pathophysiology have then been identified, notably proteolysis, cytoskeleton development, lipid metabolism and inflammation [41]. By comparing gene expression data with database information, the six best candidate genes for DD would be the genes coding for a desintegrin (*ADAM12*), the aldehyde dehydrogenase (*ALDH1*), a development protein (*IRX6*), the proteoglycan 4 (*PRG4*), the tenascin C (*TNC*) and the periostin (*POSTN*) [42]. These genes expression, directly quantified in affected tissue, allowed for the demonstration that the *ADAM12*, *POSTN* and *TNC* genes constituted a kind of biological (or genetic) signature for DD development or postoperative relapse [42].

7.3. MicroRNAs expression profile studies

MicroRNAs, ribonucleic acid molecules consisting of about 20 nucleotides, play a major role in post-transcriptional regula-

Please cite this article in press as: Michou L, et al. Genetics of Dupuytren's disease. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.05.027

Table 2
Primary genes showing an expression profile deregulation in Dupuytren's disease affected palmar tissues.

Gene symbol	Official gene name	Studied palmar tissue	Reference
Downregulated genes			
ADH1B	Alcohol dehydrogenase 1B (class I), beta polypeptide	Nodule	[41]
ALDH1A1	Aldehyde dehydrogenase 1 family, member A1	Nodule, cord	[41]
ALDH2	Aldehyde dehydrogenase 2 family (mitochondrial)	Affected fascia	[38]
AKR1C1	Aldo-keto reductase family 1, member C1 (Dihydrodiol dehydrogenase)	Affected fascia	[38]
BMP-4	Bone morphogenetic protein 4	Nodule, cord	[45]
CLEC3B	C-type lectin domain family 3, member B (Tetranectin)	Affected fascia	[38]
CLU	Clusterin	Nodule	[41]
COL15A1	Collagen type XV, alpha-1	Affected fascia	[40]
CYP4F3	Cytochrome P450, family 4, subfamily F, polypeptide 3	Cord	[41]
FBLN-1	Fibulin-1	Affected fascia	[40]
GPX3	Glutathione peroxidase 3 (plasma)	Nodule, cord	[41]
HBA2	Hemoglobin, alpha-2	Cord	[41]
ICAM2	Intercellular adhesion molecule 2	Affected fascia	[38]
LSP1	Lymphocyte-specific protein 1	Affected fascia	[38]
MMP3	Matrix metallopeptidase 3 (stromelysin 1, progelatinase)	Cord	[41]
MYOC	Myocilin, trabecular meshwork inducible glucocorticoid response	Nodule, cord	[41]
MB	Myoglobin	Cord	[46]
PCOLCE2	Procollagen C-endopeptidase enhancer 2	Nodule, cord	[41]
PRG4	Proteoglycan 4	Affected fascia, cord	[40,41]
TNXB	Tenascin XB	Cord	[41]
TIMP1	TIMP metallopeptidase inhibitor 1	Nodule	[41]
Upregulated genes			
ACAN	Aggrecan	Nodule	[41]
ADAM12	ADAM metallopeptidase domain 12	Nodule	[41,42]
ADAMTS14	ADAM metallopeptidase with thrombospondin type 1 motif, 14	Nodule	[34]
APP	Amyloid beta (A4) precursor protein	Affected fascia	[38]
ARCN1	Archain 1	Affected fascia	[38]
ARL4 C	ADP-ribosylation factor-like 4 C	Nodule	[41]
CDH11	Cadherin 11, type 2, OB-cadherin (osteoblast)	Cord	[41]
CNTN1	Contactin 1	Cord	[39]
COL1A1	Collagen type I, alpha-1	Nodule, cord	[41]
COL5A1	Collagen type V, alpha-1	Nodule, cord	[41]
COL5A2	Collagen type V, alpha-2	Cord, nodule	[39,41]
COL8A1	Collagen type VIII, alpha-1	Cord	[39]
CSRP2	Cysteine and glycine-rich protein 2	Nodule, cord	[41]
FGFb	Basic fibroblast growth factor	Nodule	[47]
IL1α	Interleukin *1α*	Nodule	[47]
IL1β	Interleukin *1β*	Nodule	[47]
LRRC17	Leucine-rich repeat containing 17	Cord	[39]
LOXL2	Lysyl oxidase-like 2	Nodule, cord	[41]
MafB	V-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	Cord, nodule	[39,41]
MMP1	Matrix metallopeptidase 1	Nodule	[34]
MMP2	Matrix metallopeptidase 2	Nodule	[35]
MMP7	Matrix metallopeptidase 7	Nodule and cord	[34]
MMP13	Matrix metallopeptidase 13	Nodule	[34]
MMP14	Matrix metallopeptidase 14	Nodule	[34]
NT5DC2	5'-nucleotidase domain containing 2	Nodule	[41]
POSTN	Periostin	Nodule, cord	[41,42]
PRKX	Protein kinase, X-linked (protein kinase PKX1)	Affected fascia	[38]
ROR2	Tyrosine kinase-like orphan receptor 2	Cord	[46]
TCF4	Transcription factor 4 (SEF2-1B protein)	Affected fascia	[38]
TIMP1	TIMP metallopeptidase inhibitor 1	Nodule	[34,35]
TIMP2	TIMP metallopeptidase inhibitor 2	Nodule and cord	[35]
TGFβ1	Transforming growth factor *β1*	Nodule	[47]
TGFβ2	Transforming growth factor *β2*	Cord	[33]
TNC	Tenascin C	Nodule, cord	[41,42]

tion and are involved in many biological processes. A first study of microRNAs expression profile in 29 DD affected patients has shown a characteristic molecular signature, consisting of eight microRNAs involved in β-catenin pathway regulation [43].

7.4. Contributions from protein expression profile studies

The first proteomic study has been published in DD. By comparing the expression profile of fibroblast proteins coming from either affected tissues or healthy palmar fascia, expression differences have been observed in several proteins involved in intra- and extracellular signalling (e.g. TGFβ1), in oxidative stress (e.g. heat shock protein 70 kD), in the cytoskeleton (e.g. cytokeratin 9) and in the cellular metabolism (e.g. pyruvate kinase) [44]. A bioinformatic analysis of the interaction network between all these proteins, or interactome, allowed for better understanding of the role of autocrine regulation contributing to the excessive survival of DD affected fibroblasts [44].

8. Conclusion

Technological progress in genomics and post-genomics has allowed for improved pathogenic knowledge in DD. The generous pathological tissue accessibility during surgical treatment sets DD apart from the other musculoskeletal disorders. The numerous published genome-wide gene expressions studies will contribute

Please cite this article in press as: Michou L, et al. Genetics of Dupuytren's disease. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.05.027

to the identification of novel DD diagnosis and prognosis biomarkers and will facilitate the emerging of new-targeted treatments. Meanwhile, further searches for proven genetic factors in DD are required to improve current knowledge on its pathogenesis.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Shih B, Bayat A. Scientific understanding and clinical management of Dupuytren disease. Nat Rev Rheumatol 2010;6:715–26.
[2] Hueston J. Dupuytren's contracture. Edinburgh: E&S Livingstone; 1963. p. 51–120.
[3] Hindocha S, Stanley JK, Watson S, et al. Dupuytren's diathesis revisited: evaluation of prognostic indicators for risk of disease recurrence. J Hand Surg Am 2006;31:1626–34.
[4] Shaw Jr RB, Chong AK, Zhang A, et al. Dupuytren's disease: history, diagnosis, and treatment. Plast Reconstr Surg 2007;120:44e–54e.
[5] Hindocha S, McGrouther DA, Bayat A. Epidemiological evaluation of Dupuytren's disease incidence and prevalence rates in relation to etiology. Hand (N Y) 2009;4:256–69.
[6] McFarlane RM. On the origin and spread of Dupuytren's disease. J Hand Surg Am 2002;27:385–90.
[7] Slattery D. Review: Dupuytren's disease in Asia and the migration theory of Dupuytren's disease. ANZ J Surg 2010;80:495–9.
[8] Degreef I, Steeno P, De Smet L. A survey of clinical manifestations and risk factors in women with Dupuytren's disease. Acta Orthop Belg 2008;74:456–60.
[9] Burke FD, Proud G, Lawson IJ, et al. An assessment of the effects of exposure to vibration, smoking, alcohol and diabetes on the prevalence of Dupuytren's disease in 97,537 miners. J Hand Surg Eur Vol 2007;32:400–6.
[10] Logan AJ, Mason G, Dias J, et al. Can rock climbing lead to Dupuytren's disease? Br J Sports Med 2005;39:639–44.
[11] Geoghegan JM, Forbes J, Clark DI, et al. Dupuytren's disease risk factors. J Hand Surg Br 2004;29:423–6.
[12] Hindocha S, John S, Stanley JK, et al. The heritability of Dupuytren's disease: familial aggregation and its clinical significance. J Hand Surg Am 2006;31:204–10.
[13] Lyall HA. Dupuytren's disease in identical twins. J Hand Surg Br 1993;18:368–70.
[14] Nyberg Jr LM, Bias WB, Hochberg MC, et al. Identification of an inherited form of Peyronie's disease with autosomal dominant inheritance and association with Dupuytren's contracture and histocompatibility B7 cross-reacting antigens. J Urol 1982;128:48–51.
[15] Bias WB, Nyberg Jr LM, Hochberg MC, et al. Peyronie's disease: a newly recognized autosomal-dominant trait. Am J Med Genet 1982;12:227–35.
[16] Dal Cin P, De Smet L, Sciot R, et al. Trisomy 7 and trisomy 8 in dividing and non-dividing tumor cells in Dupuytren's disease. Cancer Genet Cytogenet 1999;108:137–40.
[17] Casalone R, Mazzola D, Meroni E, et al. Cytogenetic and interphase cytogenetic analyses reveal chromosome instability but no clonal trisomy 8 in Dupuytren contracture. Cancer Genet Cytogenet 1997;99:73–6.
[18] Kaur S, Forsman M, Ryhanen J, et al. No gene copy number changes in Dupuytren's contracture by array comparative genomic hybridization. Cancer Genet Cytogenet 2008;183:6–8.
[19] Shih BB, Tassabehji M, Watson JS, et al. Genome-wide high-resolution screening in Dupuytren's disease reveals common regions of DNA copy number alterations. J Hand Surg Am 2010;35:1172–83.
[20] Bache I, Nielsen NM, Rostgaard K, et al. Autoimmune diseases in a Danish cohort of 4866 carriers of constitutional structural chromosomal rearrangements. Arthritis Rheum 2007;56:2402–9.
[21] Hu FZ, Nystrom A, Ahmed A, et al. Mapping of an autosomal dominant gene for Dupuytren's contracture to chromosome 16q in a Swedish family. Clin Genet 2005;68:424–9.
[22] Bayat A, Watson JS, Stanley JK, et al. Genetic susceptibility in Dupuytren's disease. TGF-beta1 polymorphisms and Dupuytren's disease. J Bone Joint Surg Br 2002;84:211–5.
[23] Bayat A, Alansar A, Hajeer AH, et al. Genetic susceptibility in Dupuytren's disease: lack of association of a novel transforming growth factor beta(2) polymorphism in Dupuytren's disease. J Hand Surg Br 2002;27:47–9.
[24] Bayat A, Stanley JK, Watson JS, et al. Genetic susceptibility to Dupuytren's disease: transforming growth factor beta receptor (TGFbetaR) gene polymorphisms and Dupuytren's disease. Br J Plast Surg 2003;56:328–33.
[25] Bayat A, Watson JS, Stanley JK, et al. Genetic susceptibility to dupuytren disease: association of Zf9 transcription factor gene. Plast Reconstr Surg 2003;111:2133–9.
[26] Brown JJ, Ollier W, Thomson W, et al. Positive association of HLA-DRB1*15 with Dupuytren's disease in Caucasians. Tissue Antigens 2008;72:166–70.
[27] Bayat A, Walter J, Lambe H, et al. Identification of a novel mitochondrial mutation in Dupuytren's disease using multiplex DHPLC. Plast Reconstr Surg 2005;115:134–41.
[28] Ojwang JO, Adrianto I, Gray-McGuire C, et al. Genome-Wide Association Scan of Dupuytren's Disease. J Hand Surg Am 2010;35:2039–45.
[29] Al-Qattan MM. Factors in the pathogenesis of Dupuytren's contracture. J Hand Surg Am 2006;31:1527–34.
[30] Bisson MA, Beckett KS, McGrouther DA, et al. Transforming growth factor-beta1 stimulation enhances Dupuytren's fibroblast contraction in response to uniaxial mechanical load within a 3-dimensional collagen gel. J Hand Surg Am 2009;34:1102–10.
[31] Vi L, Feng L, Zhu RD, et al. Periostin differentially induces proliferation, contraction and apoptosis of primary Dupuytren's disease and adjacent palmar fascia cells. Exp Cell Res 2009;315:3574–86.
[32] Pagnotta A, Specchia N, Greco F. Androgen receptors in Dupuytren's contracture. J Orthop Res 2002;20:163–8.
[33] Zhang AY, Fong KD, Pham H, et al. Gene expression analysis of Dupuytren's disease: the role of TGF-beta2. J Hand Surg Eur Vol 2008;33:783–90.
[34] Johnston P, Chojnowski AJ, Davidson RK, et al. A complete expression profile of matrix-degrading metalloproteinases in Dupuytren's disease. J Hand Surg Am 2007;32:343–51.
[35] Ulrich D, Ulrich F, Piatkowski A, et al. Expression of matrix metalloproteinases and their inhibitors in cords and nodules of patients with Dupuytren's disease. Arch Orthop Trauma Surg 2009;129:1453–9.
[36] Johnston P, Larson D, Clark IM, et al. Metalloproteinase gene expression correlates with clinical outcome in Dupuytren's disease. J Hand Surg Am 2008;33:1160–7.
[37] Qian A, Meals RA, Rajfer J, et al. Comparison of gene expression profiles between Peyronie's disease and Dupuytren's contracture. Urology 2004;64:399–404.
[38] Pan D, Watson HK, Swigart C, et al. Microarray gene analysis and expression profiles of Dupuytren's contracture. Ann Plast Surg 2003;50:618–22.
[39] Lee LC, Zhang AY, Chong AK, et al. Expression of a novel gene, MafB, in Dupuytren's disease. J Hand Surg Am 2006;31:211–8.
[40] Satish L, Laframboise WA, O'Gorman DB, et al. Identification of differentially expressed genes in fibroblasts derived from patients with Dupuytren's Contracture. BMC Med Genomics 2008;1:10.
[41] Rehman S, Salway F, Stanley JK, et al. Molecular phenotypic descriptors of Dupuytren's disease defined using informatics analysis of the transcriptome. J Hand Surg Am 2008;33:359–72.
[42] Shih B, Wijeratne D, Armstrong DJ, et al. Identification of biomarkers in Dupuytren's disease by comparative analysis of fibroblasts versus tissue biopsies in disease-specific phenotypes. J Hand Surg Am 2009;34:124–36.
[43] Mosakhani N, Guled M, Lahti L, et al. Unique microRNA profile in Dupuytren's contracture supports deregulation of beta-catenin pathway. Mod Pathol 2010;23:1544–52.
[44] Kraljevic Pavelic S, Sedic M, Hock K, et al. An integrated proteomics approach for studying the molecular pathogenesis of Dupuytren's disease. J Pathol 2009;217:524–33.
[45] Shin SS, Liu C, Chang EY, et al. Expression of bone morphogenetic proteins by Dupuytren's fibroblasts. J Hand Surg Am 2004;29:809–14.
[46] Forsman M, Paakkonen V, Tjaderhane L, et al. The expression of myoglobin and ROR2 protein in Dupuytren's disease. J Surg Res 2008;146:271–5.
[47] Baird KS, Crossan JF, Ralston SH. Abnormal growth factor and cytokine expression in Dupuytren's contracture. J Clin Pathol 1993;46:425–8.

Please cite this article in press as: Michou L, et al. Genetics of Dupuytren's disease. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.05.027