HHS Public Access

Author manuscript

Sex Med Rev. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Sex Med Rev. 2016 January 1; 4(1): 85–94. doi:10.1016/j.sxmr.2015.10.002.

The Genetic Basis of Peyronie's Disease: A Review

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Abstract

Introduction—Peyronie's disease (PD) is progressive fibrotic disorder of the penile tunica albuginea that results in fibrotic penile plaques and may lead to penile deformity. Characterized by aberrant fibrosis resulting in part from persistence of myofibroblasts as well as altered gene expression, the molecular factors underpinning Peyronie's disease and other related fibrotic diatheses are just being elucidated. A genetic link to PD was first identified using pedigree analyses three decades ago. However, the specific genetic factors that predispose patients to aberrant fibrosis remain unknown, and the relationships between these fibrotic conditions and other heritable diseases, including malignancy, are uncharacterized.

Aim—To review the current landscape linking molecular and genetic factors to aberrant fibrosis in PD as well as related fibrotic diatheses, including Dupuytren's disease.

Methods—Review and evaluation of the literature from 1970 to present examining the genetic factors associated with PD.

Main Outcome Measures—Data describing the genetic factors associated with PD.

Results—We describe the known structural chromosomal abnormalities and single nucleotide polymorphisms associated with fibrotic diatheses, and discuss the spectrum of differential gene expression data comparing normal tissues and those derived from men with Peyronie's or Dupuytren's diseases. Finally, we discuss epigenetic mechanisms that may regulate gene expression and alter predisposition to fibrosis.

Conclusion—Although our current understanding of the genetic factors associated with PD are limited, significant advances have been made over the last three decades. Further research is necessary to provide a more comprehensive understanding of the landscape of genetic factors responsible for the development of PD.

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Keywords

Adult; cell differentiation/genetics; cell division/genetics; fibroblast/pathology; Gene Expression Regulation/Physiology; Humans; Male; Oligonucleotide Array Sequence Analysis; Penile Induration/genetics*; Penile induration/pathology; penile induration/therapy; Transforming Growth Factor beta/genetics; Transforming Growth Factor Beta1

Introduction

Peyronie's disease (PD) is a progressive fibrotic disorder of the tunica albuginea (TA) of the penis that is defined by the presence of tunical plaques. Clinically, these plaques can result in penile pain and penile deformity including curvature, shortening, and narrowing.[1] PD plaques are thought to develop following either acute trauma or repeated external stress or microtrauma to the penis, causing delamination of the bilaminar TA. This initiates the inflammatory cascade and results in an abnormal persistence of myofibroblasts, leading to aberrant collagen accumulation, fibrin deposition, and disordered elastic fibers, ultimately resulting in tunical plaque formation and scarring.[2–6]

PD may be a localized manifestation of a systemic fibrotic disorder existing in the same spectrum as Dupuytren's disease (DD), which affects the palmar fascia of the hand, and Ledderhose disease (LD), which affects the plantar aponeurosis of the foot.[7–9] Concurrent fibrotic syndromes can be seen within the same individual, with 10–20% of men with PD also manifesting DD.[7]

Although the complete spectrum of etiologic factors for PD is unknown, multiple mechanisms have been proposed including trauma, impaired fibrin clearance, autoimmune and genetic factors.[6, 10–13] The evidence supporting a genetic predisposition in persons with PD has since been recognized through HLA associations, pedigree analyses confirming a familial inheritance pattern consistent with an autosomal dominant mode of transmission, and gene expression studies supporting a common pathogenetic mechanism.[12, 16] In this review, we summarize the literature evaluating genetic factors involved in fibrotic diatheses, with a focus on PD. It is our goal to provide an overview of the known genetic factors that may predispose to aberrant fibrosis, highlighting opportunities for investigation in this relatively unexplored space.

Epidemiology

PD is reported to have an incidence of 22.4 to 25.7 per 100,000 men, with the highest incidence in men 50 to 59 years old; the average age of presentation is 55 years old.[17, 18] Despite the higher incidence in older men, PD can affect men of all ages, from teenagers to men over 70 years old.[19–21] Reported prevalence rates of PD range from 0.4% to 13%, although these are likely underestimates due to an under-reporting bias; men are often reluctant to discuss this condition.[21, 22]

Although the roles of certain environmental risk factors in the development of PD, including smoking, obesity, and hypertension, have been determined, the epidemiologic impact of

genetic predisposition to PD and other fibrotic diatheses remains unknown, largely because genetic causes of PD remain to be determined.[23, 24]

Familial Aggregation and Genetic Transmission Modes

The initial indication that genetic factors may play a role in the pathogenesis of PD was demonstrated in 1982 by Bias et al.[12] through pedigree analysis of three families affected by both PD and DD. An autosomal dominant mode of inheritance with incomplete penetrance was identified in the three families, with one family exhibiting three generations of father-to-son transmission. The presence of a low frequency of affected family members despite the autosomal dominant transmission was later demonstrated by Nugteren et al.[7] who showed that of the 415 men in their study with PD, 89 (22.1%) also had DD, 5 (1.4%) had an affected father or brother, and 28 (6.7%) had a positive family history for DD.

Expanding on the finding of Willscher et al.,[16] who had previously shown an increased frequency of the HLA-B7 cross-reacting group in patients with idiopathic PD compared to the general population, Bias et al.[12] found that antigens of the HLA-B7 cross-reacting group were present among family members of all three families affected by PD. However, the familial segregation patterns suggested independent assortment of HLA loci, decreasing the likelihood that these loci contribute to the development of PD. Three studies analyzing the population frequencies of HLA antigens in the PD population have subsequently debunked the association between HLA antigen expression and PD.[25–27]

Chromosomal Abnormalities in Peyronie's Disease

Several fibroblast cell culture models have documented chromosomal abnormalities associated with PD. Early work by Somers et al[28] detected karyotypic abnormalities in PD plaque-derived fibroblasts in 7 of 12 PD patients. Chromosomal abnormalities detected include three numerical changes including duplication of chromosome 7 and 8 and deletion of chromosome Y in three patients. Structural chromosomal alterations included reciprocal translocations of 46XY,t(11;12)(q11,p11) and 46XY,t(1;5)(q25;q11), as well as inversion of 46XY,inv(7)(p22q36). These chromosomal abnormalities, importantly, were not present in cell cultures derived from adjacent TA, dermis and lymphocytes in men with PD, arguing against the presence of a heritable mutation in these men, but supporting genomic alterations in affected cells. In a series of fourteen patients with PD by Guerneri et al.,[29] plaque-derived cells from 9 were similarly found to have structural and numerical chromosomal abnormalities. Eight of the nine patients had aneusomies of the Y chromosome and three also had chromosomal translocations. Interestingly, structural rearrangements were observed during metaphase in two cases, suggesting the possibility of clonal evolution. Although the significance of these karyotypic changes remains to be determined, these numerical and structural changes may influence cell cycle regulation.

Mulhall and colleagues[30] demonstrated the presence of clonal evolution in fibroblasts of both PD plaque-derived fibroblasts as well as fibroblasts from uninvolved TA, supporting a potential field defect of the TA in PD. The temporal progression of the chromosomal abnormalities was demonstrated using fluorescent *in situ* hybridization (FISH) probes for chromosomes 7, 8, 17, 18, X, and Y. As plaque and nonplaque derived fibroblasts grew in

culture, they developed morphologic transformations (cell rounding and increased cytoplasm) as well as cytogenetic abnormalities. The most common chromosomal abnormalities detected were aneuploidy of chromosome 7 and 8, followed by chromosome 17 and 18 and lastly the Y and X chromosomes. Plaque-derived fibroblasts demonstrated chromosomal instability during early passages with four of five cell culture lines demonstrating aneusomy as early as the 3rd passage. These findings were in contrast to those in nonplaque-derived fibroblasts, which developed aneuploidy during later passages, albeit with the same pattern of aneuploidy observed in the plaque-derived fibroblasts. Overlapping patterns of chromosomal aberrations were identified in this study between fibroblasts from PD and DD lesions, including trisomy 7 and 8 and deletion of the Y chromosome, suggesting a shared pathway for aberrant fibrosis.

Single Nucleotide Polymorphisms Associated with PD and DD

Elevated levels of transforming growth factor beta 1 (TGFβ1) have previously been described in PD.[11]. The role of TGFβ1 in PD pathogenesis is supported by induction of PD in the rat model using recombinant TGFβ1 injected into the rat phallus, and the regression of fibrotic plaques via inhibition of the TGFβ1 type 1 receptor using a small molecule inhibitor of activin receptor-like kinase, which normally activates the TGFβ1 type 1 receptor via transphosphorylation.[34–37] Although the mechanism for elevated levels of TGFβ1 has not been elucidated, it is hypothesized that this increased expression is partly due to the presence of heritable single nucleotide polymorphisms (SNPs) that may impact gene expression. Several SNPs have been identified within the TGFβ1 gene, including rs1800469 (C–509T), rs1800471 (G915C), and rs1982073 (T+29C). Of these polymorphisms, only G915C has been associated with PD. The G915C SNP, which results in substitution of arginine to proline at position 25 in the TGFβ1 protein,[42] was shown in a prospective comparison of 111 men with PD to 100 healthy controls to have a significantly higher frequency in men with PD (p=0.04).[43]

A genome wide association study (GWAS) of 2,325 patients with DD revealed nine chromosomal loci associated with DD susceptibility.[44] Eleven SNPs showed significant associations with these chromosomal loci, and of these, six were associated with the wingless-type MMTV integration site (WNT) signaling pathway. In order to determine whether these SNPs were also present in men with PD, allele frequencies for the SNPs were assessed among 111 men with PD and compared to 490 unaffected controls.[45] Of the SNPs evaluated, a statistically significant association was observed with SNP rs4730775 at the WNT2 locus on chromosome 7. Taken together, these studies further implicate a common set of genetic factors for both PD and DD.

Gene Expression Profiles

The advent of microarray platforms and microarray gene expression profiling has permitted rapid analysis of gene expression on a genome-wide scale. Such differential gene expression pattern analysis has facilitated characterization of gene expression disparities between normal and pathologic tissue samples, and has also helped characterize molecular pathways,

furthering our understanding of disease progression and identifying novel therapeutic targets for numerous diseases.[46]

Differences in Gene Expression Between PD Lesions and Normal Tunica Albuginea

Some of the first studies evaluating gene expression in men with PD compared PD plaque tissue to either normal TA from control patients or unaffected TA from the same patient. Initial work by Magee et al. compared gene expression profiles between plaque tissue derived from 7 patients with PD and TA obtained from 5 unaffected patients.[47] Two complementary but non-overlapping microarray platforms, a Clontech DNA Microarray (Clontech, Palo Alto, California) and an Affymetrix DNA Microarray (Affymetrix, Santa Carla, California), were compared to identify a cost-effective approach to microarray analysis. The Clontech microarray, which analyzes functionally related families of genes, identified 8 up-regulated and 4 down-regulated genes that exhibited at least 2-fold relative difference in gene expression after normalization to global gene expression. The gene with highest level of differential expression in the PD plaque was pleiotrophin (PTN/OSF-1), a growth factor that induces fibroblast proliferation and osteoblast recruitment and osteogenesis (Table 1).[48] PTN/OSF-1 overexpression in postnatal bone has the dual effect of promoting differentiation of human bone marrow stromal cells to chondroblasts and inducing a higher bone mineral content.[49, 50] Intriguingly, calcification occurs in a subset of PD plaques, although why it occurs in one plaque and not another is currently unknown. The above data support differential gene expression profiles that likely result in variable predisposition to plaque calcification in some men with PD.

The monocyte chemotactic precursor protein 1 (MCP-1) gene, which not only recruits and activates peripheral blood monocytes but also drives the inflammatory cascade and promotes ossification, was the next most up-regulated gene.[51] Higher levels of MCP-1 mRNA have been observed in PD plaque-derived fibroblasts when compared to fibroblasts derived from normal TA following incubation with recombinant TGFβ1.[52] Lin et al. exposed three types of fibroblasts to TGFβ1 – PD plaque-derived fibroblasts, non-plaque derived fibroblasts from patients with PD, and fibroblasts from the TA of patients without PD – and subsequently measured MCP-1 expression.[53] The highest levels of MCP-1 expression were found in PD plaque-derived fibroblasts using immunohistochemistry, followed by non-plaque derived fibroblasts from the same man, and then in fibroblasts from men without PD.

Among the six remaining highly up-regulated genes identified by Magee et al. using the Clontech platform, five are functionally associated with general cell proliferation, including the genes for the human early growth response protein 1 (hEGR1), the c-myc oncogene (MYC), 60S ribosomal protein L13A (RPL13A), transforming protein rhoAH1b (RHOA), and prothymosin alpha (PTMA).[54, 55] The increased expression of these cellular proliferation genes, together with subsequent data from Mulhall and colleagues[56] showing a blunted p53 gene activation response following irradiation of PD plaque-derived fibroblast cultures compared to normal TA fibroblast cultures, underscores the aberrant growth potential of PD cells resulting from loss of cell cycle control. Although no reports of malignant degeneration in PD plaques exist, PD plaque-derived fibroblasts transplanted into subcutaneous tissue of severe combined immunodeficient (SCID) mice resulted in the

development of subcutaneous nodules containing multinucleated, pleomorphic cells with abundant cytoplasm and numerous mitotic figures.[57] In contrast, subcutaneous placement of fibroblasts derived from men with congenital penile curvature or neonatal foreskin did not result in formation of such subcutaneous nodules.

Of the four most significantly down-regulated genes identified using the Clontech platform, the Inhibitor of DNA binding 2 (ID2) was the most down-regulated, followed by calcineurin A subunit alpha (PPP3CA), transcription factor ATF4 (ATF4), and ubiquitin. ID2 belongs to a family of genes that regulate cell lineage commitment and help maintain the balance between cell growth and apoptosis by inhibiting basic-helix-loop-helix transcription factors such as myoD, myogenin, MASH, Tal, and E2A, as well as cell cycle regulatory proteins, namely the retinoblastoma tumor suppressor protein (pRB).[58] Levels of ID2 increase during cell proliferative states and decrease when cells reach a finite number of divisions and enter senescence.[59] Although the role of ID2 has not been evaluated in fibrosis associated with PD, ID2's role in cell fate determination and differentiation is well established in multiple tissue types including neural,[62] hepatobiliary,[65] and genitourinary.[66, 67] Moreover, its overexpression attenuates liver and pulmonary fibrosis.[68, 69]

Using the Affymetrix platform, which analyzes the expression of 7129 genes compared to the 1176 genes represented in the Clontech platform,[70] Magee et al.[47] identified 14 up-regulated and 7 down-regulated genes in PD plaque tissue. Up-regulated genes were responsible primarily for the differentiation of fibroblasts into myofibroblasts (fibroblast muscle type tropomyosin (TPM), 20-kDa myosin light chain (MYL), filamin (FLN), gamma-smooth muscle actin (ACTA2), smooth muscle alpha actin (ACTA2), desmin (DES), 22-kDa smooth muscle protein), fibroblast attachment and collagen production (cadherin, TGFβ1, and insulin-like growth factor binding protein-6), elastin degradation (elastase IIB24), and the cellular stress response (28-kDa heat shock protein). Down-regulated genes included mothers against decapentaplegic homolog 7 (SMAD7), SPARC/osteonectin, decorin collagenase IV, and the HLA-B antigen.

Notable among the up- and down-regulated genes in this study were elastase IIB and SMAD7, which had the largest differential expressions between PD and normal tissue. The overexpression of elastase may play a role in cell proliferation through the cleavage of insulin receptor substrate-1 (IRS1) and downstream activation of the phosphatidylinositol-3 kinase (PI3K) pathway.[71] Elastase may also promote cell proliferation via release of growth factors such as transforming growth factor-α (TGFα), platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).[72] Decreased expression of SMAD7 is likely to have a pro-fibrotic role in PD, given that SMADs are involved in TGFβ signaling.[73] SMAD7 expression is normally increased following TGFβ1-mediated signaling, and SMAD7 antagonizes TGFβ1 signaling in multiple ways including dephosphorylation and resulting inactivation of the type 1 TGF β1 receptor (TGFB1R), recruitment of SMAD2/3 and the ubiquitination and eventual degradation of the TGFβ1 type 1 receptor.[74–76] Although subsequent work by Szardening-Kirchner et al.[52] did not observe decreased SMAD7 expression following incubation of PD fibroblasts with recombinant TGFβ1, gene expression levels of SMAD2-4 did not change despite fibroblast stimulation with TGFβ1, suggesting potential dysfunction of SMAD7-mediated recruitment of SMAD2/3. The

potential under-expression or loss of function of SMAD7 may therefore remove an important checkpoint in the inflammatory cascade, predisposing to PD.

In contrast, overexpression of SMAD7 can limit the fibrotic response of PD fibroblasts to TGFβ1. Choi et al.[77] recently demonstrated the impact of SMAD7 overexpression in PD by isolating and transfecting fibroblasts from human PD plaques with either a vector containing the full-length human SMAD7 gene or an empty vector control. Fibroblasts transfected with SMAD7 demonstrated profound decreases in extracellular matrix protein expression, including decreases in plasminogen activating inhibitor-1 (PAI1), fibronectin, collagen I, and collagen IV when compared with PD plaque-derived fibroblasts transfected with empty vector. SMAD7 was also shown to have pro-apoptotic effects on both TGFβ1-stimulated and unstimulated PD plaque-derived fibroblasts through the decreased expression of cyclin D1.

In order to better understand the dysregulation of apoptosis in the PD plaque, Zorba et al.[78] recently compared gene expression in PD plaque tissue to that of adjacent grossly normal TA in 8 men undergoing plaque incision and grafting procedures. RNA expression levels were quantified for six pro-apoptotic genes – Fas, Fas Ligand, Bcl-2, p53, Caspase 3 and Caspase 8 – using reverse transcriptase PCR (RT PCR). There was no Fas expression and Fas Ligand had lower expression in PD plaque tissue compared with normal TA. In contrast, higher relative expression levels of Bcl-2, p53, Caspase 3 and Caspase 8 were observed in PD plaque tissue. However, as previously demonstrated by Mulhall et al.[30], PD may represent a TA field defect, and validation studies comparing gene expression of pro-apoptotic genes in PD plaque to normal-appearing TA derived from men without PD are needed.

Differences in Gene Expression Between PD and DD Lesions

Array-based gene expression analysis has been used to compare gene expression between PD and DD lesions, and genes with altered expression that overlap between the conditions have been identified. Qian et al.[79] compared the gene expression profiles of 9 patients with PD and 9 patients with DD to matched controls. Genes with at least a 2-fold relative difference in expression were considered significantly affected. The authors identified 15 genes with overexpression in the PD plaque, of which 8 were functionally related to fibrosis in tissue from both PD and DD lesions and included matrix metalloproteinase 2 (MMP2), MMP9, Thymosin Beta-10 (TMSB10), TMSB4, Cortactin/amplaxin/ems-1 oncogene (CTTN), Transforming protein RhoA H12 (RHOA), RhoGDP dissociation inhibitor 1 (ARHGDIA), and PTN/OSF-1. Among these eight genes, MMP2 and MMP9 were up-regulated in the PD plaque but not in the isolated PD fibroblasts.

The gene with the highest expression in PD plaque tissue in this study was MMP9. MMP9 belongs to the matrix metalloproteinase family of endopeptidases which catabolize gelatins, collagen type I, and collagen type III.[80] The expression of MMPs is stimulated by inflammatory cytokines including IL1 and TNFα, and regulated by the co-expression of tissue inhibitors of metalloproteinases (TIMPs). *In situ* activation of MMPs depends on thymosins, which were elevated in not only PD plaque but also PD plaque-derived fibroblasts isolated from the PD plaque and DD nodules.[81] Del Carlo et al. characterized the

expression of MMPs and TIMPs using MMP protein microarrays and Western blot analysis of PD fibroblasts following transcriptional induction using either IL1β or TGFβ. IL1β significantly increased the production of MMP1, 3, 10, and 13 and only mildly increased the production of MMP8 and MMP9.[82] Although TGFβ did not up-regulate MMP1, 8 or 13 and only mildly increased MMP9 levels, it resulted in significant up-regulation of TIMP 1–4. The authors also evaluated the relative expression of MMP1, 8, and 13 as well as TIMP 1–4 using Western blot analysis of plaque tissue samples obtained from 13 men with stable PD lesions compared with normal TA tissue from 6 men without PD. MMP1, 8 and 13 were detected in both PD and non-PD TA tissue. However, TIMPs 1–4 were readily detectable in TA from men with PD. These findings underscore the role of both MMPs and TIMPs in the fibrotic process of PD. MMPs may contribute to fibrosis through the altered function of extracellular matrix proteins following proteolysis or release of sequestered growth factors such as TGFα, PDGF, and VEGF, within the extracellular matrix.[72, 83] The local accumulation of TIMPs also promotes fibrosis by decreasing the net catabolic activity of MMPs and allowing the gradual buildup of collagen and other matrix proteins.[82]

Other over-expressed genes identified in either PD plaque tissue and/or PD plaque-derived fibroblasts that merit inclusion here include transcription factor AP1, hEGR1, MCP1, bone proteoglycan II precursor (PGS2)/decorin (DCN), T-Cell specific RANTES protein precursor, and integrin beta 1 (ITGB1).[79] AP1 plays a central role in the inflammatory cascade by regulating the transcription of cytokines, which influence immune cell proliferation, differentiation, migration, and apoptosis.[84, 85] The second and third most over-expressed genes included hEGR1 and MCP1, whose roles in the development of PD were discussed above.

Epigenetic Regulation

Epigenetic regulation refers to heritable alterations in gene expression that occur without altering the gene sequence, but rather dynamically alter the transcriptional potential of a cell. This type of gene regulation can occur at the transcriptional or post-transcriptional level through modifications of histone proteins, such as acetylation, methylation, and phosphorylation, or through noncoding RNA-based regulation that can modify chromatin structure. Histone deacetylases (HDACs) are enzymes that control the balance of histone acetylation/deacetylation and alter the transcriptional potential of a given gene by regulating access of its promoter to transcriptional regulatory proteins. HDACs selectively remove acetyl groups from the terminal lysine on histones, causing the DNA to tightly wrap around the histone protein, and limiting access to transcriptional machinery.[90] Importantly, HDACs have been implicated in the pathogenesis of multiple fibrotic disorders of the kidneys, bladder, lungs, heart and liver.[91–93]

Inhibition of HDACs can repress TGFβ-mediated signaling. In order to determine if inhibition of HDAC2 would limit the profibrotic response to TGFβ signaling in human PD plaques, Ryu et al. used RNA interference (RNAi) via small interfering RNA (siRNA) targeting HDAC2, comparing PD plaque-derived fibroblasts to control fibroblasts transfected with nonspecific scramble siRNA.[94] Protein expression levels of plasminogen activator inhibitor 1 (PAI1), fibronectin, collagens I and IV, smooth muscle α-actin, and

HDAC2 were assessed using Western blot following stimulation with TGFβ. The authors observed a 60% reduction in HDAC2 expression in PD plaque-derived fibroblasts transfected with the HDAC2-targeted siRNA, with similar reductions in expression of PAI1, fibronectin, collagens I and IV, and smooth muscle α-actin. Additionally, the conversion of fibroblasts into myofibroblasts, the causal cell type in aberrant fibrosis, was blocked in fibroblasts treated with HDAC2-targeted siRNA. Reduced phosphorylation and nuclear migration of SMAD2/3, which typically occurs following TGFβ-mediated stimulation of PD plaque fibroblasts, were also observed.

Kwon et al. corroborated these findings using adenovirus-encoded HDAC2 small hairpin RNA (ad-HDAC2 shRNA) in a rat model.[95] The authors observed that PD model rats receiving injections of Ad-HDAC2 shRNA had regression of fibrotic penile plaque, fewer intralesional inflammatory cells, impaired nuclear translocation of phosphorylated Smad3, inhibited differentiation of fibroblasts into myofibroblasts, and reduced collagen production. Furthermore, cultured rat fibroblasts from PD plaques exhibited reduced expression of cyclin D1, which blocked cell cycle entry and a propensity towards apoptosis in both basal and TGFβ-stimulated conditions.

Conclusions

The genetic underpinnings of fibrotic diatheses, including Peyronie's and Dupuytren's diseases, are just beginning to be understood. From studies 3 decades ago that established genetic links to these conditions, much progress has been made in defining the similarities between Dupuytren's and Peyronie's diseases, particularly on a cellular levels. However, the specific genetic factors that predispose patients to PD and/or DD are not currently known, nor are the relationships between PD/DD and other heritable conditions, including malignancy. While translation of our current understanding of the genetic factors predisposing to PD to clinical practice is in its infancy, future research will provide a more comprehensive understanding of the landscape of genetic factors responsible for the development of PD, and will facilitate development of novel biomarkers and therapies to allow earlier detection and treatment of those afflicted with PD. As such, the present represents an exciting time for elucidation of the genetic landscape of these conditions, towards the goal of an improved understanding of these related fibrotic diatheses, as well as an improved ability to risk stratify affected patients, and ultimately provide better care for them through more effective targeted therapies and disease prevention.

Acknowledgments

Funding: A.W.P. and A.S.H. are National Institutes of Health (NIH) K12 Scholars supported by a Male Reproductive Health Research Career (MHRH) Development Physician-Scientist Award (HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Program (to Dolores J. Lamb).

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Table 1

Genes with involvement in Peyronie's and Dupuytren's diseases

Gene	Gene Symbol	Chromosomal Location	Gene Function	Reference
Matrix metalloproteinase 2	MMP 2	16q12.2	Breakdown of extracellular matrix	88
Matrix metalloproteinase 9	MMP 9	20q13.12	Breakdown of extracellular matrix	88
Thymosin beta-10	TMSB-10	2p11.2	Prevents spontaneous globular actin monomer polymerization	88
Thymosin beta-4	TMSB-4	Xq21.3-q22	Actin sequestering protein	88
Cortactin; amplaxin	CTTN	11q13	Organizes cytoskeleton and cell adhesion structures	88
Transforming protein RhoA H12	RHOA	3p21.3	Regulates cytoskeletal dynamics	56, 88
RhoGDP dissociation inhibitor	ARHGDIA	17q25.3	Regulates Rho GTPase signaling	88
Pleiotrophin precuros; osteoblast specific factor 1	PTN/OSF-1	7q33	Stimulates mitogenic growth of fibroblasts and osteoblasts	56, 88
Amyloid A4 protein precursor; nexin II	PN-II	21q21.3	Cell surface receptor	88
Defender against cell death 1	DAD1	14q11.2	Prevents apoptosis	88
Heat Shock 27-kDa protein (HSP27)	HSP27	7q11.23	Actin organization and translocation from cytoplasm to nucleus upon stress induction	56, 88
Macrophage-specific stimulating factor	MCSF/CSF1	1p13.3	Controls the production, differentiation and function of macrophages	88
Transcription factor AP-1	AP1	1p32-p31	Key mediator of macrophage education and point of recruitment for immunosuppressive regulatory T cells	88, 105
human Early growth response protein 1	hEGR1	5q31.1	Promotes mitosis	88
Monocyte chemotactic protein 1	MCP1	17q11.2-q12	Chemotactic cytokine for monocytes and basophils	88
Bone Proteoglycan II precusor; Decorin	DCN	12q21.33	Matrix proteoglycan	56, 88

Gene	Gene Symbol	Chromosomal Location	Gene Function	Reference
T-Cell specific rantes protein precursor	RANTES	17q12	Chemoattractant for monocytes, memory T cells and eosinophils	88
Integrin Beta-1	ITGB1	10p11.2	Membrane receptor involved in cell adhesion and recognition in a variety of processes including immune response, tissue repair and hemostasis	56
Osteonectin	SPARC	5q31.3-q32	Matrix protein that facilitates collagen ossification	56
Ubiquitin	RBX1	6q25.2-q27	Targets substrate proteins for proteasomal degradation	56
Transcription factor ATF-4	ATF4	22q13.1	Transcriptional regulation of osteoblasts and down-regulates apelin to promote apoptosis	56, 106
Elastase IIB	ELA2B	1p36.21	Serine protease that hydrolyzes matrix protein	56
c-myc	MYC	8q24.21	Transcription factor that regulates cell cycle progression, apoptosis, and cellular transformations	56
60 S ribosomal protein L13A	RPL13A	19q13.3	Repression of inflammatory genes	56
Prothymosin alpha	PTMA	2q37.1	Influences chromatin remodeling, anti-apoptotic factor	56
Fibroblast tropomyosin	TPM1	15q22.1	Actin-binding protein involved in contractile system of striated and smooth muscle	56
Myosin light chain	MYL2	12q24.11	Regulatory light chain associated with myosin Beta heavy chain	56
Filamin	FLN	Xq28	Actin-binding protein that crosslinks actin filaments and links actin to membrane glycoproteins. Interacts with integrins	56
Calcineurin A subunit alpha	PPP3CA	4q24	Promotes cell migration and invasion and inhibits	56 107

Gene	Gene Symbol	Chromosomal Location	Gene Function	Reference
			apoptosis	
DNA binding protein inhibitor Id-2	ID2	2p25	Transcriptional regulator that inhibits the function of basic helix-loop-helix transcription factors by preventing their heterodimerization, negatively regulates cell differentiation	56
Smooth muscle gamma actin	ACTA2	10q23.3	Plays a role in cell motility, structure and integrity	56
Desmin	DES	2q35	Forms intracytoplasmic filamentous network connecting myofibrils	56
Cadherin FIB2	PCDHGB4	5q31	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing	56
Cadherin FIB1	DCHS1	11p15.4	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing	56
SMAD family member 7	SMAD7	18q21.1	Interacts with and promotes degradation of TGFBR1	56
Insulin-like growth factor binding protein 6	IGFBP6	12q13	Negative regulator of cellular senescence in human fibroblasts	56, 108
Collagen 1 alpha	COL1A1	17q21.33	Encodes pro-alpha 1 chains of type 1 collagen	56
Transforming growth factor, beta 1	TGFB1	19q13.1	Cytokine that regulates proliferation, differentiation, adhesion and cell migration	56