



Published in final edited form as:

J Arthroplasty. 2020 November ; 35(11): 3343–3352. doi:10.1016/j.arth.2020.05.070.

Human Fibrosis: Is There Evidence for a Genetic Predisposition in Musculoskeletal Tissues?

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Abstract

Background: Pathologic fibrosis is characterized by dysregulation of gene expression with excessive extracellular matrix production. The genetic basis for solid organ fibrosis is well described in the literature. However, there is a paucity of evidence for similar processes in the musculoskeletal (MSK) system. The purpose of this review is to provide an overview of existing evidence of genetic predisposition to pathologic fibrosis in the cardiac, pulmonary, and MSK systems, and to describe common genetic variants associated with these processes.

Methods: A comprehensive search of several databases from 2000 to 2019 was conducted using relevant keywords in the English language. Genes reported as involved in idiopathic fibrotic processes in the heart, lung, hand, shoulder, and knee were recorded by 2 independent authors.

Results: Among 2373 eligible studies, 52 studies investigated genetic predisposition in terms of variant analysis with the following organ system distribution: 36 pulmonary studies (69%), 15 hand studies (29%), and 1 knee study (2%). Twenty-two percent of gene variants identified were associated with both pulmonary and MSK fibrosis (ie, *ADAM*, *HLA*, *CARD*, *EIF*, *TGF*, *WNT*, and *ZNF* genes). Genetic variants known to be involved in the MSK tissue development or contractility properties in muscle were identified in the pulmonary fibrosis.

Conclusion: Despite shared genetic variations in both the lung and hand, there remains limited information about genetic variants associated with fibrosis in other MSK regions. This finding

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LD: Conceptualization, Investigation, Methodology, Formal analysis, Visualization, Writing—original draft, Writing—review and editing. AO: Investigation, Methodology, Formal analysis, Visualization, Writing—original draft, Writing—review & editing. JWB: Visualization, Writing—original draft, Writing—review & editing. JDB: Writing—review & editing. PCA: Visualization, Writing—original draft, Writing—review & editing. JPK: Visualization, Methodology, Writing—original draft, Writing—review & editing. MEE: Conceptualization, Writing—original draft, Writing—review & editing. JSS: Conceptualization, Writing—original draft, Writing—review & editing. DJB: Conceptualization, Writing—review & editing. AVW: Conceptualization, Methodology, Formal analysis, Writing—review & editing. MPA: Conceptualization, Methodology, Project administration, Writing—original draft, Writing—review & editing

Investigation was performed at the Mayo Clinic, Rochester, MN.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to <https://doi.org/10.1016/j.arth.2020.05.070>.

establishes the necessity of further studies to elucidate the genetic determinants involved in the knee, shoulder, and other joint fibrotic pathways.

Level of evidence: Level III.

Keywords

arthrofibrosis; genetic predisposition; theragnostic; Dupuytren disease; musculoskeletal; total knee arthroplasty

Fibrotic diseases represent a major source of morbidity and mortality in contemporary healthcare [1–5]. It has been estimated that up to 45% of all deaths are related to fibroproliferative processes [6]. Fibrogenesis is a complex, dynamic molecular process involving numerous pathways and cell types [6]. In simple terms, fibrogenesis begins as a primary insult to an organ system that elicits activation of effector cells followed subsequently by deposition of extracellular matrix (ECM) to stabilize and repair the compromised tissue. In the nonpathologic state, this matrix is resorbed and replaced by healthy host tissue. In the pathologic state—characterized by continued injury stimulus—there is ongoing deposition of ECM coupled with insufficient resorption, resulting in a fibrotic phenotype. Fibrotic phenotypes alter the form of the tissue with resultant dysfunction. Tissue dysfunction is tolerated to varying degrees depending on the organ system involved, and likewise different organ systems exhibit varying abilities to recover from the fibrotic insult. Interestingly, there is substantial evidence that profibrotic molecular pathways of disease pathogenesis remain conserved across different organ systems, including the heart, lung, liver, pancreas, kidney, bone marrow, and skin, among others [6,7].

Understanding the molecular mechanisms underlying fibrogenesis has led to emerging therapies targeted at halting and reversing the course of disease with variable success [8,9]. Despite these advancements, the efficacy of such therapies is limited by the ability to identify and target at-risk cohorts. More recently, genome-wide association studies have been used to identify genetic variants associated with various fibrotic diseases. Genetic variants have been used to predict disease onset and severity, therefore facilitating risk stratification and early targeted intervention [10].

A subclass of fibroproliferative diseases represents a unique clinical and therapeutic challenge, as the pathologic state arises in the absence of continued injury stimulus. These processes are designated idiopathic and are the focus of this review. Of great interest is arthrofibrosis after total knee arthroplasty (TKA), an idiopathic fibrotic process in patients with well-fixed and well-aligned components and no known modifiable or nonmodifiable risk factors [11]. Despite the success of contemporary TKAs, arthrofibrosis remains a major failure mode affecting 4%–10% of patients undergoing primary TKA [11]. Risk factors such as limited preoperative range of motion, delayed physical therapy, and complexity of initial surgery have been described. However, it is unclear why these factors lead to debilitating arthrofibrosis in some patients, yet result in acceptable joint range of motion and clinical outcomes in others [12].

A potential explanation is that there may be a genetic predisposition to arthrofibrosis in a subset of patients. So far, however, there is no evidence to directly substantiate this hypothesis. Based on previous work demonstrating conserved molecular processes of fibrogenesis in different solid organs, the goal of the current review is to establish if there are identifiable overlapping genetic determinants of fibrosis across multiple organ systems—namely the cardiac, pulmonary, and musculoskeletal (MSK) systems. We focused on cardiac and pulmonary processes because of their synovial and encapsulated organization analogous to the joint organization. The current review aims to (1) identify the presence of a genetic predisposition in different organ systems by evaluating the idiopathic fibrotic disease processes in each system, (2) evaluate the type and function of genes implicated in each organ system, and (3) identify overlapping genetic predisposition between systems.

Materials and Methods

A protocol was designed for this systematic review to identify shared genetic determinants of human idiopathic fibrotic diseases in the cardiac, pulmonary, and MSK systems. This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology.

Data Sources and Search Strategies

A comprehensive search of several databases from January 1, 2000, to October 7, 2019, was conducted in the English language. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian. Controlled vocabulary supplemented with keywords was used to search for the genomics of fibrosis in the cardiac, pulmonary, and MSK systems in humans. Pulmonary processes included idiopathic pulmonary fibrosis (IPF). MSK processes emphasized in our review included Dupuytren disease, adhesive capsulitis of the shoulder, and arthrofibrosis of the knee, as these idiopathic conditions are most clinically relevant. The research strategy, including all search terms and combinations used, is available in Appendix A.

Study Selection

Two authors (LD and ARO) independently reviewed all titles and abstracts using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The quality of the studies was assessed according to the Newcastle—Ottawa quality assessment scale (Appendix B) [13]. Discordances in study inclusion were resolved by evaluation discussion and consensus. Studies about fibrosis in anatomic locations other than the selected organs were excluded, as were studies about true hereditary or chronic diseases (nonidiopathic or sporadic fibrosis such as cystic fibrosis and scleroderma), studies emphasizing confounding factors such as smoking, nonspecific fibrotic processes (eg, atrial fibrillation, sarcoidosis, myositis), nongenetic studies (genomic expression without gene variant discovery), imaging or therapeutic articles, and animal studies. Editorials, reviews, symposia, case reports, and case series also were excluded.

Data Extraction

The studies included were reviewed and separated by organ systems, namely the cardiac, pulmonary, and MSK-related studies. Data were extracted manually to provide an overview of the evidence of a genetic predisposition in idiopathic fibrotic processes in the organ systems of interest.

Results

There were 2373 potentially eligible articles with 2134 (90%) being unrelated to the study question. These studies investigated genomic expression without genetic variant determination and were thus excluded. The full texts of 69 studies were reviewed, and 17 studies were subsequently excluded secondary to the above exclusion criteria (Fig. 1).

Ultimately, 52 studies (2.1%) were selected for inclusion in the systematic review. The 52 studies selected for this investigation contained data about genetic discovery and predisposition with the following organ system distribution: 36 pulmonary studies (69%), 15 hand studies (29%), and one knee study (2%) [14]. No evidence was found in this review for cardiac or shoulder idiopathic fibrosis according to our inclusion and exclusion criteria. Seven studies (13%) evaluated the genetic determinants in relation to disease severity (6 studies in the pulmonary literature [15–20] and 1 study in the hand literature [21]).

The genes involved in the fibrotic processes were summarized and divided into 2 categories: organ-specific genes (Table 1) and fibroproliferative genes (Table 2). The function of each fibroproliferative gene was identified and reported as follows: (1) ECM remodeling and fibroblast regulation, (2) immune system dysfunction, and (3) profibrotic mediators. *MUC* gene variants (mucosal tissue) were identified as a lung-specific entity predictive of IPF risk and disease severity [17,19,22–26]. Some MSK-specific genes were also identified in this review: *ACAN* gene (encodes an ECM protein in cartilaginous tissue) and *EBF2* gene (a transcriptional regulator of osteoclast differentiation) [27].

We extracted 129 fibrotic gene variants for the pulmonary system and 100 fibrotic gene variants for the hand. Among these fibroproliferative genes, 51 gene variants (22%) were associated with both pulmonary and MSK fibrosis (Table 3). Overlapping gene families included the following: *ADAM* [28,29], *HLA* [14,21,29–32], *CARD* [27,28], *EIF* [27,33,34], *TGF* [20,35,36], *WNT* [27,34,35,37], and *ZNF* genes [27,29,33,34,38] (Table 3). The majority of overlap was shared between IPF and Dupuytren disease pathologic states. However, *HLA* variants did overlap across IPF, Dupuytren disease, and knee arthrofibrosis [14]. The subsets of genetic variants from genes known to be involved in the MSK tissue development [28] or contractility properties in muscle tissue [33] were identified in IPF studies; however, these genes were not even examined in available MSK investigations. Genes with unknown fibrotic function were summarized in Appendix C.

Discussion

The identification of genetic determinants of fibroproliferative processes is required for a more robust understanding of how fibrosis in multiple tissues is caused at the cellular level

in humans. Advancing our understanding of genetically controlled cellular mechanisms that mediate fibrosis will be key to guide patient-specific strategies to predict, diagnose, and control the risk of pathologic fibrogenesis [39]. Previous investigations have highlighted the “two-hit disease” as the hallmark of fibrotic diseases that are not hereditary—a patient’s genetic predisposition is the first hit, but is not activated until a second hit occurs—that is an environmental stressor that ultimately tips the balance from normal homeostasis to pathologic fibrosis [40]. Largely, these studies have focused on the solid organ fibrosis [8,9] and so far, no literature review has investigated the possibility of an overlapping genetic predisposition between cardiac, pulmonary, and MSK systems. The present systematic review provides a comprehensive evaluation of the existing literature and important information about shared genetic variations among pulmonary and hand systems.

Evidence of Genetic Predisposition

To evaluate evidence of genetic predisposition, the present investigation sought to identify genetic variation at the DNA level. Contemporary studies most often evaluate these differences via a genome-wide association study and report findings in terms of associated variants [19,23,26,27,30,32,35,41–43]. With these specific criteria, there was a large mismatch between the studies included for screening ($n = 2373$ articles) and those included for final analysis ($n = 52$ articles). Despite our narrow focus, this review was able to demonstrate shared genetic variation between the pulmonary and MSK systems. Genomic research is more prevalent and advanced for pulmonary fibrotic diseases compared to MSK disorders. The skewed representation of pulmonary fibrosis studies is secondary to the catastrophic clinical course and high mortality associated with this disease [8]. Nevertheless, the findings of the present study suggest that the current understanding of the genetic variation of fibroproliferative processes among the included systems is limited to data on IPF and Dupuytren disease. Despite clinical evidence and established molecular pathways, the present review identified only a single study related to knee fibrosis [14] and no studies related to cardiac or shoulder fibrosis.

It should be noted that failure to discover genes related to cardiac and shoulder diseases may be related to the study design. A dearth of information regarding cardiac fibrosis was in relation to ventricular fibrosis after chronic cardiomyopathy (ie, congestive heart failure, arrhythmia, or myocarditis). These disease states did not represent the idiopathic nature this review aimed to identify, and hence were excluded. There have been prior studies that have revealed an association between patients who are *HLA-B27* positive and have adhesive capsulitis of the shoulder (when compared to controls) [44–48], but our current investigation and others did not identify the genetic predisposition in relation to adhesive capsulitis of the shoulder. These older studies were not included in the present investigation because they were published before the human genome sequence was established and used methodology that is no longer considered state of the art. Lastly, MeSH terms using genetic predisposition were associated with a different focus that included inheritance in family relatives, positive family history, and genomic expression that did not correspond to gene discovery.

Genes Involved in the Fibrotic Pathway

Pathways leading to idiopathic fibrosis have been largely overlooked in the literature. Excluding pulmonary-specific genes, this review highlighted a common pathway supported by genetic variants found in IPF and Dupuytren disease, including ECM remodeling and fibroblast regulation, immune dysfunction and profibrotic mediators. Although Friedman et al [9] highlighted core features shared by chronic pathology among multiple solid organs (including the lung, liver, skin, and kidney), this review demonstrated that the same core features are shared by the pulmonary and MSK systems. Several responses to injury summarize what is understood about the fibrotic process [9]. Firstly, the genes involved in cell death and apoptosis regulation were very common in the literature and consistent in the lung and hand in our review. *CARD*, *EIF*, and *ZNF* genes are involved in apoptotic signaling and similar genes appear to be involved in the different organ systems [20,27–29,33–36]. Secondly, cell stress causes dysregulation of the metabolic pathways. Although markers of endoplasmic reticulum stress have been identified in the alveolar epithelial cells (IPF), some genes involved in the endoplasmic reticulum signaling were expressed in the hand, including *SERP2* [27], *TMEM* [27], *SDR16C5* [33], and *SLN* variants [33]. Genes involved in changes in adenosine 5' triphosphate generation were also associated with this metabolic dysregulation. Furthermore, *TGFβ* plays a central role in the epithelial to mesenchymal transition and interaction with integrins. Some overlapping profibrotic mediators were found in this study and TGFβ-related variants (ie, *TGFβ1*, *TGFβ2*, and *TGFβ3*) also were found in the lung and hand [20,35,36]. Lastly, immune system dysfunction is another common pathway identified in the literature: immune modulation via HLA complex [14,21,29–32] and inflammatory response via interleukin genes [15,22,49–54]. So far, only HLA genes were commonly reported in literature regarding the fibrosis in the lung, hand, shoulder, and knee.

Perspectives in MSK Research

Importantly, genetic variants associated with profibrotic processes of the knee and shoulder were underrepresented in this review when compared to the robust evidence observed in the hand. This lack of evidence does not mean genetic variants exist, and instead represents an opportunity for investigation in MSK research in humans [55]. In the knee, there is a body of molecular evidence demonstrating the differential expression of genes throughout the pathogenesis of arthrofibrosis in animal models [56–59]. Our laboratory has recently identified 380 genes most significantly upregulated or downregulated within the first 2 weeks after traumatic insult and immobilization leading to severe permanent contracture in the rabbit [57]. In the shoulder, the genomic expression of an intercellular adhesion model was found in adhesive capsulitis [60]. The same fibrotic pathways have been validated using microarray data and quantitative reverse transcription polymerase chain reaction analysis: cell-cell adhesion, apoptosis, protein kinase activity, or inflammatory response.

So far, there are no studies specifically addressing the genetic determinants of arthrofibrosis in the context of TKA. A few clinical studies indirectly acknowledged a predisposition to arthrofibrosis via reports of the bilateral occurrence of arthrofibrosis [61,62] or manipulation under anesthesia after primary TKA in a subset of patients [63]. As suggested by Clement et al, stiffness could be a predictor of stiffness for staged TKA [63] and genetic predisposition

may lead to a cumulative incidence of manipulations under anesthesia for bilateral procedures [64].

Although the pathogenesis of arthrofibrosis after TKA is incompletely understood, translational work has been critical to identifying the importance of myofibroblast and related cellular pathways at play in the process [56]. Under pathologic conditions, myofibroblasts are activated by local growth factors (eg, *TGFβ*) resulting in increased collagenous and noncollagenous (eg, fibronectin, decorin) ECM production. This dysregulated accumulation of ECM elements results in tissue deformation and loss of function after TKA.

Despite an improved understanding of the fundamentals of arthrofibrosis over the past decade, understanding of the specific genes that activate cellular pathways and insights into the modulation of those pathways remains elusive. Recently, in an effort to better understand the pathogenesis of arthrofibrosis at the molecular level, investigators in our laboratory used the RNA-sequencing analysis of posterior capsular tissue to identify differential gene expression between arthrofibrotic and nonarthrofibrotic knees [65]. Importantly, this study demonstrated that differentially expressed genes were enriched in ECM organization pathways that participate in cell-to-cell adhesion, wound healing, and post-translational collagenous protein modification [65]. Although this represents significant progress and enables identification of druggable pathways, it requires action after diagnosis. Future endeavors investigating changes at the level of DNA are required to identify patients at risk for arthrofibrosis development to foster the development of preventative strategies.

Taken together, these findings identify specific genes that play a role in fibrotic processes, and identification of variants within these genes holds both therapeutic and diagnostic benefits. For the very first time, cellular direct reprogramming and molecular targets could indeed be a part of novel therapeutic options, also known as theragnostic (a treatment strategy that combines therapeutics with diagnostics). Theragnostics in MSK fibrosis, including arthrofibrosis after TKA, may become a successful component of personalized medicine.

Conclusion

Despite shared genetic variations in both the lung and hand, there remains limited information about genetic variants associated with fibrosis in other MSK regions. This finding establishes the necessity of further studies to elucidate the genetic determinants involved in the knee, shoulder, and other joint fibrotic pathways.

Acknowledgments

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under Award Number AR072597 (Principal Investigator Matthew P. Abdel, MD) and the Anna-Maria and Stephen Kellen Foundation (Principal Investigator Matthew P. Abdel, MD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Louis Dagneaux, MD, also reports funding from Société Française de Chirurgie Orthopédique et Traumatologique (SOFOT) and the University of Montpellier (MUSE Explorer#2).

Appendix A

Ovid

Database(s): EBM Reviews—Cochrane Central Register of Controlled Trials August 2019, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 3, 2019, Embase 1974 to October 4, 2019, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 4, 2019 Search Strategy:

#	Searches	Results
1	exp Fibrosis/ge [Genetics]	1551
2	exp Pulmonary Fibrosis/ge [Genetics]	1419
3	exp Endomyocardial Fibrosis/ge [Genetics]	80
4	exp Dupuytren Contracture/ge [Genetics]	166
5	(arthrofibroses or arthrofibrosis or fibroses or fibrosis).ti,ab,hw,kw.	547,154
6	Genetics/	704,070
7	Genomics/	104,087
8	exp Genetic Predisposition to Disease/	281,969
9	(gene or genes or genetic or genetics or genomic or genomics).ti,ab,hw,kw.	7,915,383
10	6 or 7 or 8 or 9	7,915,383
11	exp Joint Diseases/ge [Genetics]	16,780
12	exp Joints/	668,503
13	exp Shoulder Joint/ or exp Shoulder/	94,461
14	exp Hand/ or exp Hand Joints/	175,741
15	exp Knee/ or exp Knee Joint/	133,234
16	exp Heart Diseases/ge [Genetics]	47,024
17	(arthrofibroses or arthrofibrosis or cardiac or dupuytren* or endomyocardial or hand or hands or heart or joint or joints or knee or knees or lung or lungs or myocardial or pulmonary or shoulder).ti,ab,hw,kw.	8,874,025
18	11 and (1 or 5)	133
19	12 and (1 or (5 and 10))	607
20	13 and (1 or (5 and 10))	91
21	14 and (1 or (5 and 10))	103
22	15 and (1 or (5 and 10))	118
23	16 and (1 or 5)	1933
24	(arthrofibroses or arthrofibrosis or fibroses or fibrosis).ti. and 10 and (arthrofibroses or arthrofibrosis or cardiac or dupuytren* or endomyocardial or hand or hands or heart or joint or joints or knee or knees or lung or lungs or myocardial or pulmonary or shoulder).ti.	8844
25	1 and 17	346
26	2 or 3 or 4 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	12,326
27	(case* adj3 report*).mp,pt.	4,842,191
28	exp Genetic Diseases, Inborn/	1,707,136
29	("Alagille Syndrome*" or "alpha 1-Antitrypsin Deficienc*" or "Ataxia Telangiectasia*" or "Autoimmune Lymphoproliferative Syndrome*" or "Brugada Syndrome*" or CADASIL or "Camurati-Engelmann Syndrome*" or "CHARGE Syndrome*" or Cherubism or "Chromosome disorder*" or Ciliopath* or "congenital Adrenal Hyperplasia*" or "congenital Angioedema*" or "congenital Autoinflammatory Disease*" or "congenital Eye Disease*" or "congenital hemolytic Anemia*" or "congenital hypertrophic Cardiomyopath*" or "congenital hypoplastic Anemia*" or	471,956

#	Searches	Results
	"congenital Multiple Lipomatos*" or "Congenital Myasthenic Syndrome*" or "congenital NeoplasticNeoplastic Syndrome*" or "Congenital Pain Insensitivity" or "Costello Syndrome*" or "Cystic Fibros*" or "Donohue Syndrome*" or Dwarfism or "familial Adrenal Hyperplasia*" or "familial Angioedema*" or "familial Autoinflammatory Disease*" or "familial Eye Disease*" or "familial hemolytic Anemia*" or "familial hypertrophic Cardiomyopath*" or "familial hypoplastic Anemia*" or "Familial Multiple Lipomatos*" or "familial Myasthenic Syndrome*" or "familial NeoplasticNeoplastic Syndrome*" or "familial Pain Insensitivity" or "Frasier Syndrome*" or "GATA2 Deficienc*" or "genetic Skin Disease*" or "Graves Ophthalmopath*" or "Hajdu-Cheney Syndrome*" or "Hemoglobinopath*" or "hereditary Adrenal Hyperplasia*" or "hereditary Angioedema*" or "Hereditary Autoinflammatory Disease*" or "hereditary Eye Disease*" or "hereditary hemolytic Anemia*" or "hereditary hypertrophic Cardiomyopath*" or "hereditary hypoplastic Anemia*" or "hereditary Multiple Lipomatos*" or "hereditary Myasthenic Syndrome*" or "Hereditary NeoplasticNeoplastic Syndrome*" or "hereditary Pain Insensitivity" or "Heredodegenerative disorder*" or "Hyper-IgM Immunodeficiency Syndrome*" or "Inborn Errors of Metabolism" or "inborn Genetic Disease*" or "inherited Blood Coagulation disorder*" or "Kallmann Syndrome*" or "Kartagener Syndrome*" or "Lennox Gastaut Syndrome*" or "Loeys-Dietz Syndrome*" or "Marfan Syndrome*" or "Muscular Dystroph*" or "Nail-Patella Syndrome*" or "Oculocerebrorenal Syndrome*" or "Orofaciodigital Syndrome*" or Osteochondrodysplasia* or "Osteogenesis Imperfecta" or "Pelger-Huet Anomaly" or "Primary hypertrophicOsteoarthropath*" or Pycnodysostosis* or "rheumatoid disease*" or scleroderma* or "Werner Syndrome*" or "X-Linked Genetic Disease*" or "Yellow Nail Syndrome*" or "Y-Linked Genetic Disease*"),ti,ab,hw,kw.	
30	exp Atrial Fibrillation/	116,660
31	"atrial fibrillation*".ti,ab,hw,kw.	223,252
32	exp Sarcoidosis/	58,514
33	sarcoidosis.ti,ab,hw,kw.	70,450
34	Myositis/	22,687
35	myositis.ti,ab,hw,kw.	37,853
36	exp Epigenomics/	74,627
37	(epigenetic* or epigenomic*).ti,ab,hw,kw.	208,463
38	exp Smoking/	520,985
39	smoking.ti,ab,hw,kw.	761,622
40	or/27-39	7,503,536
41	26 not 40	8531
42	limit 41 to english language [Limit not valid in CDSR; records were retained]	8210
43	limit 42 to yr="2000 -Current"	7798
44	(exp animals/ or exp nonhuman/) not exp humans/	10,852,970
45	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanzee or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects orjellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.	9,357,844
46	43 not (44 or 45)	4075

#	Searches	Results
47	limit 46 to (letter or conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR, CDSR,Embase, Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	976
48	46 not 47	3099
49	remove duplicates from 48	2390

Scopus

1. TITLE(arthrofibroses OR arthrofibrosis OR fibroses OR fibrosis)
2. TITLE-ABS-KEY(gene OR genes OR genetic OR genetics OR genomic OR genomics)
3. TITLE(arthrofibroses OR arthrofibrosis OR cardiac OR dupuytren* OR endomyocardial OR hand OR hands OR heart OR joint OR joints OR knee OR knees OR lung OR lungs OR myocardial OR pulmonary OR shoulder)
4. PUBYEAR AFT 1999 AND LANGUAGE(english)
5. 1 and 2 and 3 and 4
6. TITLE-ABS-KEY((case* W/3 report*) OR "Alagille Syndrome*" OR "alpha 1-Antitrypsin Deficienc*" OR "Ataxia Telangiectasia*" OR "atrial fibrillation*" OR "Autoimmune Lymphoproliferative Syndrome*" OR "Brugada Syndrome*" OR CADASIL OR "Camurati-Engelmann Syndrome*" OR "CHARGE Syndrome*" OR Cherubism OR "Chromosome disorder*" OR Ciliopath* OR "congenital Adrenal Hyperplasia*" OR "congenital Angioedema*" OR "congenital Autoinflammatory Disease*" OR "congenital Eye Disease*" OR "congenital hemolytic Anemia*" OR "congenital hypertrophic Cardiomyopath*" OR "congenital hypoplastic Anemia*" OR "congenital Multiple Lipomatos*" OR "Congenital Myasthenic Syndrome*" OR "congenital NeoplasticNeoplastic Syndrome*" OR "Congenital Pain Insensitivity" OR "Costello Syndrome*" OR "Cystic Fibros*" OR "Donohue Syndrome*" OR Dwarfism OR epigenetic* OR epigenomic* OR "familial Adrenal Hyperplasia*" OR "familial Angioedema*" OR "familial Autoinflammatory Disease*" OR "familial Eye Disease*" OR "familial hemolytic Anemia*" OR "familial hypertrophic Cardiomyopath*" OR "familial hypoplastic Anemia*" OR "Familial Multiple Lipomatos*" OR "familial Myasthenic Syndrome*" OR "familial NeoplasticNeoplastic Syndrome*" OR "familial Pain Insensitivity" OR "Frasier Syndrome*" OR "GATA2 Deficienc*" OR "genetic Skin Disease*" OR "Graves Ophthalmopath*" OR "Hajdu-Cheney Syndrome*" OR Hemoglobinopath* OR "hereditary Adrenal Hyperplasia*" OR "hereditary Angioedema*" OR "Hereditary Autoinflammatory Disease*" OR "hereditary Eye Disease*" OR "hereditary hemolytic Anemia*" OR "hereditary hypertrophic Cardiomyopath*")

OR “hereditary hypoplastic Anemia*” OR “hereditary Multiple Lipomatos*” OR “hereditary Myasthenic Syndrome*” OR “Hereditary NeoplasticNeoplastic Syndrome*” OR “hereditary Pain Insensitivity” OR “Heredodegenerative disorder*” OR “Hyper-IgM Immunodeficiency Syndrome*” OR “Inborn Errors of Metabolism” OR “inborn Genetic Disease*” OR “inherited Blood Coagulation disorder*” OR “Kallmann Syndrome*” OR “Kartagener Syndrome*” OR “Lennox Gastaut Syndrome*” OR “Loeys-Dietz Syndrome*” OR “Marfan Syndrome*” OR “Muscular Dystroph*” OR myositis OR “Nail-Patella Syndrome*” OR “Oculocerebrorenal Syndrome*” OR “Orofaciodigital Syndrome*” OR Osteochondrodysplasia* OR “Osteogenesis Imperfecta” OR “Pelger-Huet Anomaly” OR “Primary hypertrophicOsteoarthropath*” OR Pycnodysostosis* OR “rheumatoid disease*” OR sarcoidosis OR scleroderma* OR smoking OR “Werner Syndrome*” OR “X-Linked Genetic Disease*” OR “Yellow Nail Syndrome*” OR “Y-Linked Genetic Disease*”)

7. 5 and not 6
8. TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR “c elegans” OR “Caenorhabditis elegans” OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR “D melanogaster” OR “dairy calf” OR “dairy calves” OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR “Drosophila melanogaster” OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR “fruit flies” OR “fruit fly” OR “G mellonella” OR “Galleria mellonella” OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR “orang-utan” OR orangutans OR “orang-utans” OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR “zebra fish” OR zebrafish) AND NOT (human OR humans or patient or patients))

9. 7 and not 8
10. DOCTYPE(le) OR DOCTYPE(ab) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11. 9 and not 10
12. INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
13. 11 and not 12

Appendix B

Level of Evidence and Quality Assessment According to the Newcastle—Ottawa Quality Assessment Scale.

Authors, Year	LOE	Selection	Comparability	Exposure
Xaubet et al 2003 [20]	III	**	*	**
Jonsson et al 2013 [21]	III	***	**	**
Ng et al 2017 [27]	III	***	**	**
Huang et al 2014 [28]	III	***	**	**
Shih et al 2010 [29]	III	**	*	*
Fingerlin et al 2016 [30]	III	***	*	**
Xue et al 2011 [31]	III	****	*	**
Ojwhang et al 2010 [32]	III	***	-	**
Cecchini et al 2018 [33]	III	**	*	**
Anderson et al 2013 [34]	III	***	**	**
Bayat et al 2003 [36]	III	***	*	**
Dolmans et al 2011 [37]	III	***	*	**
Bayat et al 2003 [38]	III	***	*	**

Newcastle—Ottawa Quality Assessment Scale Case Control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of 2 stars can be given for comparability.

Selection

1. Is the case definition adequate?
 - yes, with independent validation \emptyset
 - yes, eg, record linkage or based on self-reports
 - no description.

Appendix C

Genes with Unknown or Nonspecific Fibrotic Function From the Literature Review.

Lung (Idiopathic Pulmonary Fibrosis)	Hand (Dupuytren's Disease)
<i>AHNAK2, ATP8A1, C1orf162, CTD-2245O6.1, F11, FMO5, LNX2, LRP2, MOP-1, NECAB1, OBFC1, PARN, PDLIM3, PHACTR1, PRUNE2, PTAFR, RPI3-870H17.3, RSAD2, SDR16C5, hTERT, TERC, TERT, TMEM38A, TXLNGY, WARS</i>	<i>ALDH2, ATL1, BOP1, C8orf34, CFDP1, CHST6, CYCSP14, DHDH, DUXA, GNB1, HSD17B7, LINC01230, LOC100129495, LOC100131502, LOC100132514, LOC100132626, LOC100132627, LOC100505718, LOC727945, MIR8079, MIRLET7BHG, OR10D3P, OR8F1P, RAB31, SM1M2, SULF1, SUMO4</i>

2. Representativeness of the cases
 - consecutive or obviously representative series of cases Ø
 - potential for selection biases or not stated.
3. Selection of controls
 - community controls Ø
 - hospital controls
 - no description.
4. Definition of controls
 - no history of disease (endpoint) Ø
 - no description of source.

Comparability

1. Comparability of cases and controls on the basis of the design or analysis
 - study controls for _____ (Select the most important factor.) Ø
 - study controls for any additional factor Ø (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1. Ascertainment of exposure
 - secure record (eg, surgical records) Ø
 - structured interview where blind to case/control status Ø
 - interview not blinded to case/control status
 - written self-report or medical record only
 - no description.

2. Same method of ascertainment for cases and controls
 - yes Ø
 - no.
3. Nonresponse rate
 - same rate for both groups Ø
 - nonrespondents described
 - rate different and no designation.

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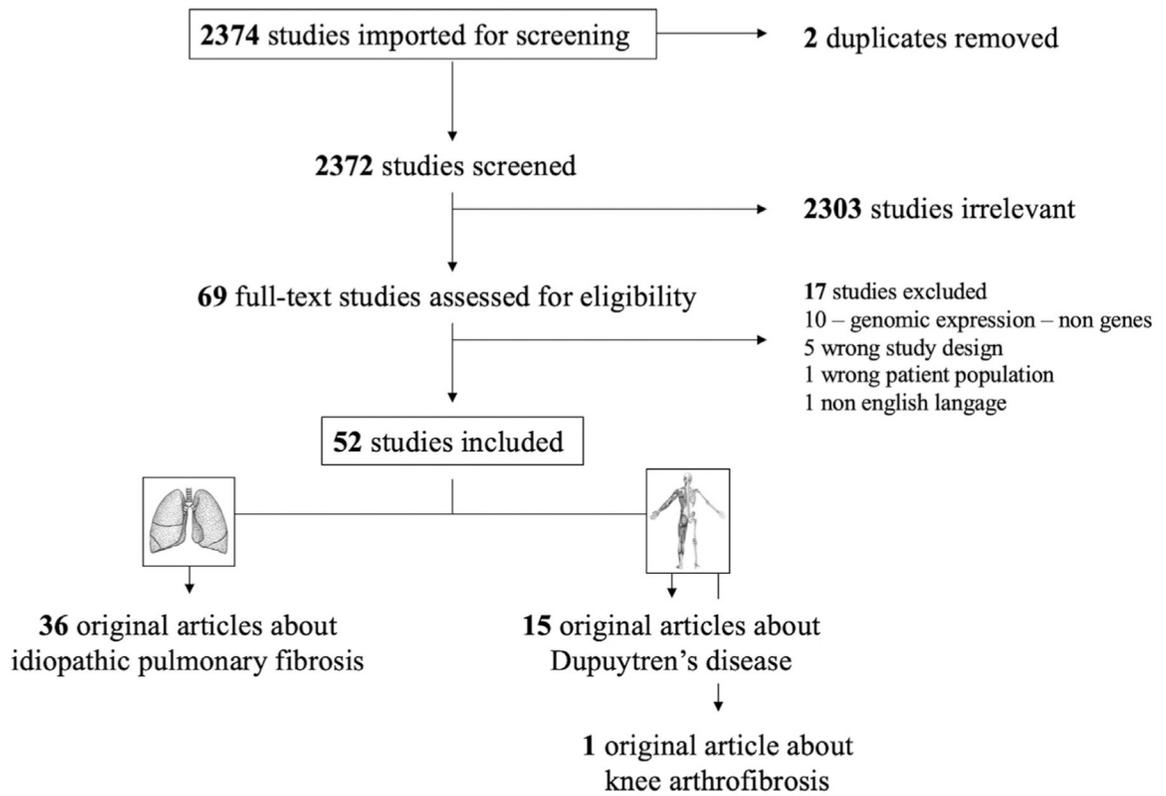


Fig. 1. Flow diagram of the systematic research method for detecting genes predisposition in the heart, lung, hand, shoulder, and knee.

Table 1

Organ-Specific Genes Involved in Idiopathic Fibrosis in the Lung and Musculoskeletal Tissue From Our Review.

Lung-specific genes	
Alveolar epithelial dysfunction	<i>MUC2, MUC5AC, MUC5B, SFTPC, SFTPA2</i>
Musculoskeletal specific genes	
Extracellular matrix in cartilaginous tissue	<i>ACAN</i>
Osteoclast differentiation	<i>EBF2</i>

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Table 3
Overview of Putative Functions of the Most Relevant Fibrotic Genes Overlapping in IPF and DD.

Genes Family	Variants	Pathway	Samples ^a	Age ^a	Male ^a	Race ^a	Tissue	Methods	Significance ^b	Putative Function
<i>ADAM</i> genes	<i>ADAMTSL5</i> [28]	IPF	6/6	49(18)	55	NHW's	Lung biopsy	Sequencing	$P = 7.68E-04$	Cell adhesion and protease,
	<i>ADAM3A</i> [29]	DD	13/11	69 (4)	100	NHW's	Palmar fasciectomy	Expression array	-	degradation of ECM
<i>HLA</i> genes	<i>X89654</i> [29]	IPF	878/2017	-	-	NHW's	Lung biopsy	GWAS	$P = .02$	Immune system regulation
	<i>HLA(rs3117116)</i> [30]									
	<i>HLA-DRB1*15</i> [31]	IPF	79/196	67(1)	73	-	Lung tissue/molecular	Molecular typing	$P = .004$	
	<i>HLA-A</i> [29]	DD	13/11	69 (4)	100	NHW's	Palmar fasciectomy	Expression array	-	
	<i>HLADRB1</i> [21]	DD	121/51	-	100	NHW's	Blood	PCR-SSPs	$P = .02$	
	<i>HCG27/HLA-C (rs3132506)</i> [32],	DD	40/40	60 (11)	72	Caucasians	Saliva	GWAS	$P = 5.84E-05$	
	<i>rs3130473</i> [32])	DD	13/11	69 (4)	100	NHW's	Palmar fasciectomy	Expression array	$P = 5.31E-05$	
	<i>HCG2P7</i> [29]									
	<i>HCG4P6</i> [29]									
<i>CARD</i> genes	<i>CARD10</i> [28]	IPF	6/6	49 (18)	55	NHW's	Lung biopsy	Sequencing	$P = 6.73E-04$	Apoptosis signaling
<i>EIF</i> genes	<i>CARD11</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = 2.89E-08$	
	<i>EIF-1AY</i> [33]	IPF	22/11	62 (6)	77	-	Lung tissue	Expression array	$P < .0001$	Apoptotic pathway in fibroblast
<i>TGF</i> genes	<i>EIF-3E</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = 3.7E-19$	
	<i>TGF-B1</i> [20]	IPF	128/140	66 (10)	63	Whites	-	-	$P = .002$	Cell proliferation, stimulates sustained
	<i>TGFβ1-3'UTR</i> [36]	DD	184/181	63 (10)	82	Caucasians	Blood	PCR-RFLP	$P = .048$	production of collagen
	<i>TAB2</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = 2.03E-08$	
<i>ZNF</i> genes	<i>ZFY</i> [33]	IPF	22/11	62 (6)	77	-	Lung tissue	Expression array	$P < .0001$	Transcription repressor and apoptosis signaling
	<i>ZNF385B</i> [33]									
	<i>DMRT1</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = .0237$	

Genes Family	Variants	Pathway	Samples ^a	Age ^a	Male ^a	Race ^a	Tissue	Methods	Significance ^b	Putative Function
	<i>DMRT2</i> [27], (<i>rs10809650</i> [37]) <i>rs1080964</i> [37]),	DD	960/3117	-	-	Caucasians	Blood/Saliva	GWAS	$P = 6.2E-09$	
	<i>DMRT3</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = 1.2E-08$	
	<i>ZNF160</i> [29]	DD	4/10	69 (4)	100	Whites	Nodules	Expression array	$P = 9.76E-12$	
	<i>ZNF264</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	-	
	<i>ZBTB40</i> [27]								$P = 1.42E-13$	
	<i>ZC3H12D</i> [27]								$P = 7.68E-12$	
	<i>ZI9-3'</i> [38]	DD	138/255	61 (11)	86	Caucasians	Blood	PCR-RFLP	$P = 2.03E-08$	
	<i>ZIM3</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = .0025$	
WNT genes	<i>FZD5</i> [33]	IPF	22/11	62 (6)	77	-	Lung tissue	Expression array	$P = 1.42E-13$	Wnt signaling regulating cell growth and differentiation in specific cell types, including regulation of cell fate and
	<i>WNT2</i> (<i>rs4730775</i> [34])	DD	960/3317	-	-	Caucasians	Blood/Saliva	GWAS	$P = .0237$	
	<i>WNT4</i> (<i>rs7524102</i> [34])								$P = 3.0E-08$	
	<i>WNT7B</i> (<i>rs8140558</i> [34], <i>rs6519955</i> [34])								$P = 2.8E-09$	patterning during embryogenesis.
	<i>RSP02</i> (<i>rs611744</i> [34])								$P = 1.2E-22$	
	<i>SFRP4</i> (<i>rs16879765</i> [34])								$P = 3.2E-33$	
	<i>EBF2</i> [27]	DD	5408/9961	-	-	-	Blood	GWAS	$P = 7.9E-15$	
									$P = 5.6E-39$	
									$P = 3.14E-11$	

ADAM, ADAM metalloproteinase; CARD, caspase recruitment domain; DD, Dupuytren disease; ECM, extracellular matrix; EIF, eukaryotic translation initiation factor; GWAS, genome-wide association study; HLA, major histocompatibility complex; IPF, idiopathic pulmonary fibrosis; NHW, non-Hispanic white; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSPs, polymerase chain reaction-sequence-specific primers; TGF, transforming growth factor; ZNF, zinc finger protein.

^aSamples: number of inclusions (fibrosis/control) and demographics from fibrosis group when noted. Age expressed as mean and standard deviation (SD), Male gender expressed in %.

^bSignificance: P -value after correcting population if available. In cases of genes significance involved in several articles, the lowest P -value is reported.