

REVIEW

# Dupuytren's: a systems biology disease

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## Abstract

Dupuytren's disease (DD) is an ill-defined fibroproliferative disorder of the palm of the hands leading to digital contracture. DD commonly occurs in individuals of northern European extraction. Cellular components and processes associated with DD pathogenesis include altered gene and protein expression of cytokines, growth factors, adhesion molecules, and extracellular matrix components. Histology has shown increased but varying levels of particular types of collagen, myofibroblasts and myoglobin proteins in DD tissue. Free radicals and localised ischaemia have been suggested to trigger the proliferation of DD tissue. Although the existing available biological information on DD may contain potentially valuable (though largely uninterpreted) information, the precise aetiology of DD remains unknown. Systems biology combines mechanistic modelling with quantitative experimentation in studies of networks and better understanding of the interaction of multiple components in disease processes. Adopting systems biology may be the ideal approach for future research in order to improve understanding of complex diseases of multifactorial origin. In this review, we propose that DD is a disease of several networks rather than of a single gene, and show that this accounts for the experimental observations obtained to date from a variety of sources. We outline how DD may be investigated more effectively by employing a systems biology approach that considers the disease network as a whole rather than focusing on any specific single molecule.

## Introduction

The quasi-neoplastic nodular palmar fibromatosis [1] called Dupuytren's disease (DD) often causes permanent

flexion contracture of the metacarpophalangeal and proximal interphalangeal joints of the digits [2,3] (Figure 1), leading to loss of function, deformity of the hand, and permanent contracture of the involved digits [2,4]. Although DD does not metastasize [5], it may invade locally within the palmar aponeurosis of the hand (sparingly supplied with blood vessels) and it is progressive with a high rate of recurrence after surgical excision [6], often requiring amputation of the affected digit [7-9]. The three stages of DD growth (proliferative, involutinal, and residual) appear to involve dysdifferentiation into myofibroblasts [10-12]. DD is associated with abundance of collagen, fibronectin, integrins, cytokines and many other growth factors [2,7,13-15], as well as altered expression of several genes [16-25], but unlike the involvement of known oncogenes and suppressor genes in cancer development [26], our knowledge of the exact aetiopathogenesis of DD remains poor despite significant understanding of its biology.

Systems biology combines mechanistic modelling with quantitative experimentation in studies of networks [27-34] and aims at understanding how the interaction of multiple components within a cell, tissue, organ or indeed individual leads to much of biological function and obfuscates correlations with single genes. Systems-level approaches have begun to help comprehension of network control, (dys-)regulation, and function [35-38]. This has improved the understanding of certain disorders [39], and has provided new rationales for drug discovery [40-42]. The complex biology of DD may constitute an invitation to a systems level approach. In this review, we outline such an approach.

## Dupuytren's disease and its many faces

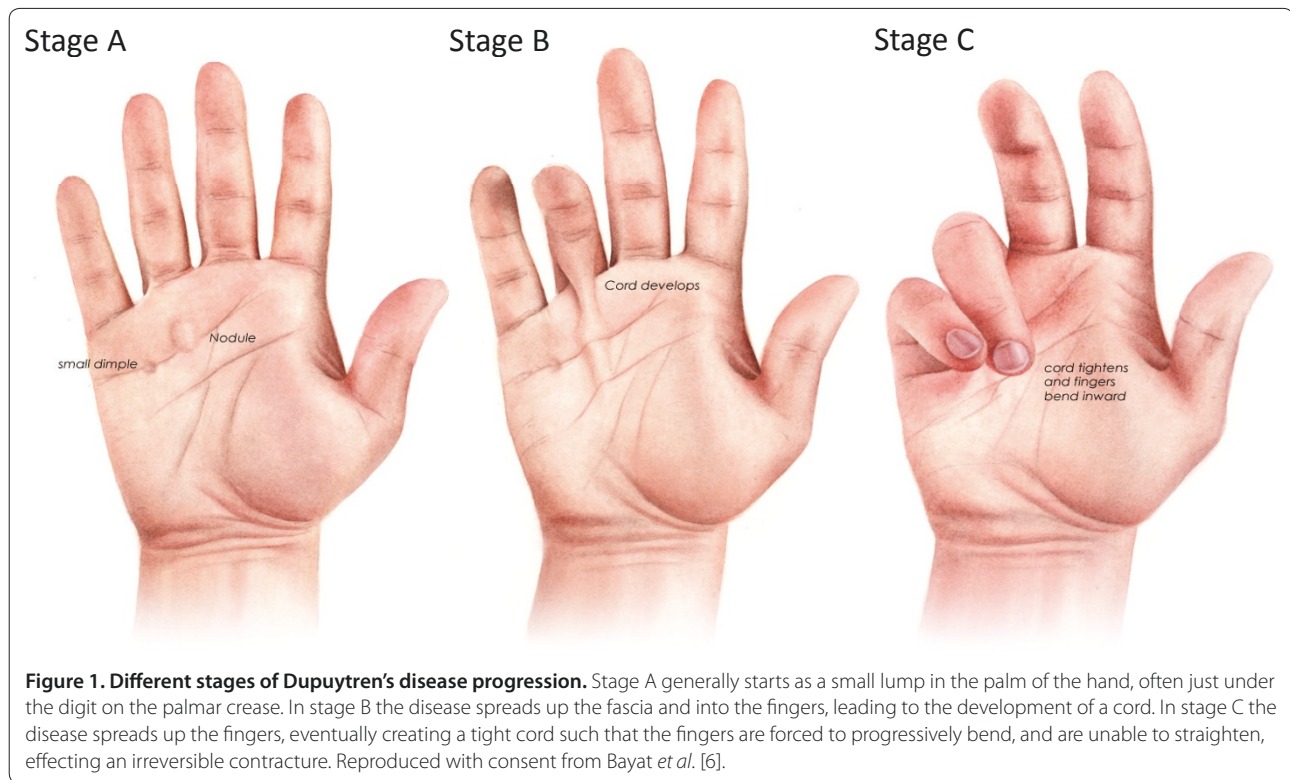
### Histopathology

Clinical examples of fibrosis include renal interstitial fibrosis [43], scleroderma [44], sarcoidosis [45], idiopathic pulmonary fibrosis [46], retroperitoneal fibrosis [47] and DD [48]. DD tissue shows increased deposition of collagen III relative to collagen I and increased levels of collagen hydroxylation and glycosylation [49]. DD is thought to arise either from a defect in the wound repair process or from an abnormal response to wounding. The presence of immune cells and related phenomena in DD tissue suggests DD may be immune-related [50-53].

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**Figure 1. Different stages of Dupuytren's disease progression.** Stage A generally starts as a small lump in the palm of the hand, often just under the digit on the palmar crease. In stage B the disease spreads up the fascia and into the fingers, leading to the development of a cord. In stage C the disease spreads up the fingers, eventually creating a tight cord such that the fingers are forced to progressively bend, and are unable to straighten, effecting an irreversible contracture. Reproduced with consent from Bayat et al. [6].

Cellularity (quantified as the cellular density) of the DD nodules (see below) is indicative of the activity of the disease [4]. DD has been classified into three stages co-existing in the same specimen, that is, proliferative, involutinal and residual, further subdivided into the essentially fibrous nodules, reactive tissue, and residual tissue. It contains two structurally distinct fibrotic elements: the nodule is a highly vascularised tissue containing many fibroblasts, with a high percentage being recognised as myofibroblasts due to their expression of the  $\alpha$ -smooth muscle actin; and the cord is relatively avascular, acellular, and collagen-rich with few myofibroblasts. The nodule may develop into the cord as the disease progresses over time or the two structures represent independent stages of the disease. Macroscopically, neither the deep retinacular tissue that includes the transverse palmar ligament or fascia, also known as 'Skoog's fibres', nor the fibrous flexor tendon sheaths appear to be involved in DD. Other areas are affected macroscopically but at irregular depth and distribution, with the more superficial layers and ulnar side of the palm being affected most.

The specialised mesenchymal cells expressing smooth muscle  $\alpha$ -actin may explain the contractility observed in DD [11,54-56]; they resemble the myofibroblasts of granulation tissue thought to be responsible for contraction during wound healing. The Dupuytren myofibroblast synthesizes fibronectin, an extracellular glycoprotein that

connects myofibroblasts and connects them to the extracellular stromal matrix through an integrin.

According to genome-wide gene expression profiles, fibroblasts come in various subtypes [57], perhaps due to 'topographic differentiation'; that is, distinct phenotypes persisted *in vitro* even when fibroblasts were isolated from the influence of other cell types [58]. Chang et al. [57] did not evaluate diversity or cell heterogeneity in DD. All of those evaluated had the morphology of elongated, spindle-shaped cells. Fibroblast cultures were uniformly positive for a mesenchymal immunofluorescence marker, but negative for markers of epithelial, smooth muscle, endothelial, perineural, and histiocytic cells. Different passages of the same fibroblast culture clustered with each other, indicating that their *in vitro* phenotypes were stable. Several components implicated as modulators of transdifferentiation of DD fibroblasts into myofibroblasts have been reported [59-69]. Among the cytokines, transforming growth factor- $\beta$  is thought to be a significant inducer of myofibroblast transdifferentiation because of its ability to up-regulate  $\alpha$ -smooth muscle actin and collagen in fibroblasts, both *in vivo* and *in vitro* [65].

#### Genetics

A study performed in a five generation Swedish family suggested that DD was inherited in an autosomal dominant pattern [70]. Linkage analysis implicated a single region of approximately 6 cM between markers D16S419

and D16S3032 at a logarithm of the odds (LOD) score >1.5. Genotyping of four siblings affected by the disease but from another branch of the family together with the use of additional microsatellite markers produced a maximal LOD score of 3.2 (for D16S415), with four other markers producing LOD scores >1.5. When a disease is dominant, it is likely to be caused by a single allele of a single gene, and by the molecule it encodes. From this perspective, the above findings would suggest that DD is a single gene disease. To date, however, linkage to a single gene has not been reported at a LOD that is much more significant than the marginal value of 3 in this Swedish study and the penetrance in this study was incomplete. In addition, the disease develops at an advanced age, there are many more sporadic cases of DD, and there are few such families for which the genetic analysis has been performed. Indeed, other studies have shown association of the disease with other loci, including a positive association with HLA-DRB1\*15 on chromosome 6 in Caucasians [71]. A study of 20 British DD patients with a maternally transmitted inheritance pattern demonstrated a mutation within the mitochondrial genome (mitochondrial 16S ribosomal RNA region) in 90% of patients [72]. The defective mitochondria generated abnormally high levels of free radicals and induced defects in apoptotic mechanisms.

#### **Reactive oxygen species**

A relation between localised ischaemia, reactive oxygen species (ROS) and DD was projected from a study in which palmar fascia from 10 DD individuals were subjected to 0 to 60 minutes of tourniquet ischaemia DD [73]. The concentration of hypoxanthine was six-fold higher in Dupuytren's palmar fascia compared to the palmar fascia from ten suitable control patients (having carpal tunnel decompression), implying that measuring metabolites directly in tissue could help understand DD. Xanthine oxidase catalyzes the removal of hypoxanthine, generating super oxide free radicals and hydrogen peroxide as by-products that would damage the perivascular connective tissue, which fibroblasts would attempt to repair. Upon addition of free radicals to fibroblast cultures from DD palmar fascia, lower concentrations of ROS stimulated fibroblast proliferation, explaining the observed increase in collagen type III [73]. The hypoxanthine was more abundant in nodular areas than in the tight fibrous cords. We propose that microvessel narrowing, leading to localised hypoxic conditions, may be one cause of DD, secondary to age, smoking and other environmental factors as discussed by Shih and Bayat [3].

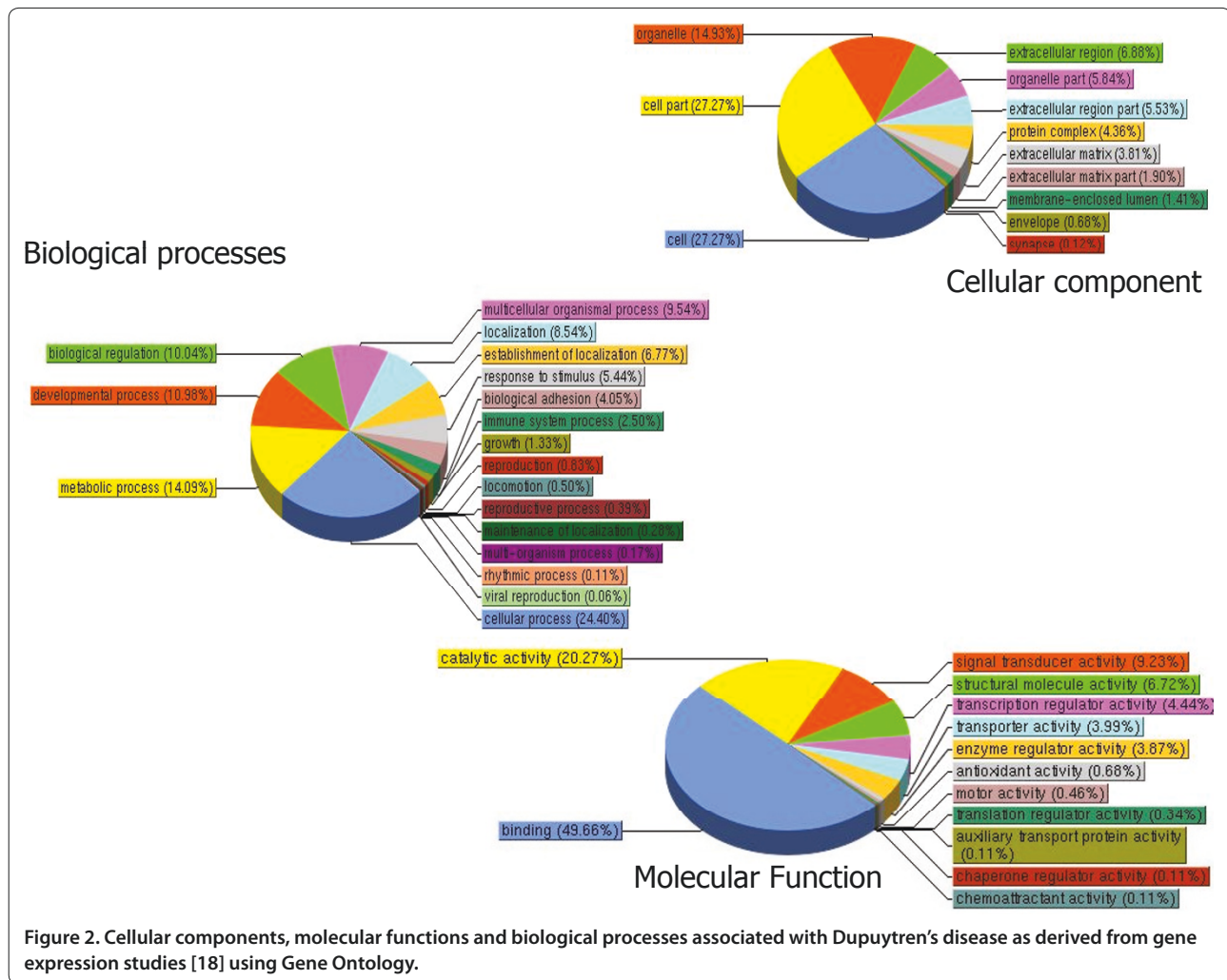
#### **Transcriptomics**

Alterations of gene expression in Dupuytren's nodules [25], Peyronie's plaques [74], and cultured fibroblasts

have been reported. Because of the complexity and heterogeneity of the disease, we carried out a new transcriptome analysis, optimizing for unbiased experimental design, sample size and sufficiently large data sets by considering the nodule and the cord as two separate entities, and by adding a pathway oriented approach. We compared diseased Dupuytren tissue biopsies (both nodules and cords) with corresponding healthy tissue (the transverse palmar fascia adjacent to the diseased site) from the same patients as well as with profiles from the palmar fascia of individuals not affected by DD [18]. The genes we confirmed and established as altered in expression in DD [13,60] are involved in the immune response, angiogenesis, apoptosis, cell adhesion and cell-matrix adhesion, cell cycle and proliferation, cell differentiation, transcription, development, signalling and signal transduction, protein synthesis and folding, oxygen transport, and carbohydrate metabolism (Figure 2). A study comparing fibroblasts isolated from DD patients with those from controls found tens of genes to be altered at the mRNA expression level, although these differed between the two microarray platforms used. The down-regulation of three of the genes was confirmed by quantitative PCR; these encode a proteoglycan, a fibulin and type XV collagen alpha 1 chain [75]. Also using PCR, Ulrich and colleagues [76] found that DD tissue amplified mRNA encoding one metalloprotease and two tissue inhibitors of metalloproteases. The genes localised between markers D16S419 and D16S3032 encode hemoglobin  $\alpha 1$  and 2, cadherin 11 type 2, OB-cadherin (osteoblast), matrix metalloproteinase 2, perioplakin, tryptase  $\alpha/\beta 1$ , and tryptase  $\beta 2$ . The transcriptomics results were therefore not particularly supportive of the early hypothesis that altered expression of a single autosomal gene on chromosome 16 is solely responsible for DD. The observation that genes with fairly obvious functional connections to DD, such as those encoding metalloproteases, proteoglycans and collagen components, have altered expression brings home the message that even if the disease were to have a single-gene origin, its aetiology is likely to involve multiple regulatory pathways and genes downstream. Up to now the hunt for the single DD gene has not only failed but also weakened its own motivation; many genes, both upstream and downstream, may be involved in causing DD.

#### **Proteomics**

The DD proteomics venture began in 2006 with the study of protein expression profiles in an attempt to identify potential disease biomarkers [77,78]. In one study, two-dimensional gel electrophoresis was performed to extract proteins from diseased tissue (nodule and cord), the Skoog's fibres, and normal control tissues. MALDI-TOF-MS (matrix-assisted laser desorption ionization time-of-flight mass spectrometry) generated a peptide mass



fingerprint that was used to search protein databases; however, the authors did not report names of identified proteomic changes in their abstract. SELDI-TOF-MS (surface enhanced laser desorption/ionization time-of-flight mass spectrometry) using Ciphergen's SELDI-TOF-MS Protein Biological System II (PBSII) ProteinChip reader [78] revealed several differentially expressed low molecular weight (<20 kDa) tissue proteins and identified three disease-associated protein features (4,600.8 Da, 10,254.5 Da, and 11,405.1 Da) that were elevated (5-, 12-, and 4-fold, respectively). Three potential low molecular weight protein markers (p4.6DC, p10DC, p11.7DC) for DD were identified. An integrative proteomic-interactomic approach [79] coupling two-dimensional gel electrophoresis with mass spectrometry compared the proteomic profile of DD tissue with that of unaffected patient-matched palmar fasciae tissue and found several proteins correlated with DD. The findings were used to create a protein-protein interaction network (interactome) map on the basis of the proposed interactions in the

Human Interactome Map (HiMAP) [80] and the Search Tool for the Retrieval of Interacting Proteins (STRING) [81]; however, several proteins were added to fill gaps in order to yield a complete network, which then involved extra- and intracellular signalling, oxidative stress, cytoskeletal changes, and alterations in cellular metabolism. In particular, ERBB-2 and insulin-like growth factor 1 receptor (IGF-1R) and the Akt signalling pathway emerged as novel components of pro-survival signalling in Dupuytren's fibroblasts. One should exercise care, however, not to over-interpret these results, as they are partly based on inference from other protein interaction data obtained in different contexts. In addition, increased activity of pathways need not involve increased protein levels [82] and increased pathway expression may be homeostatic rather than aetiological.

**The dilemma: more or less data - less or more understanding**  
 As more and more aspects associating with DD are revealed, we see less and less forest (understanding of the

disease) for the trees (its many molecules) [83]. Even if the disease were set in motion by a single genetic factor, its aetiology would involve many diverse processes such that DD will be co-determined by the many factors that regulate those processes. If indeed the networks governing differentiation of normal fibrocytes of the palm of the hand are perturbed irreversibly so that they differentiate into muscle-like tissue without the proper controllers of contraction and relaxation, then different sets of genetic perturbations could lead to DD. In this context DD may be much like cancer [39].

The dilemma is that although we now have an unprecedented set of methodologies for the identification and analysis of all the molecules in living cells, that methodology alone is not enough. We need something substantially more to understand how all those molecules interact to create functional networks. Seeing more molecules may not help our understanding; seeing the connections between them and more mechanism might.

#### **Systems biology disease versus molecular disease**

The disease in Figure 3a may seem to depend on a single molecule (gene) only, or at least that is how it is often conceived. But of course, a disease cannot depend on a gene (if defined as the corresponding DNA sequence) alone: it will depend on its gene product (F in Figure 3a), and in fact on the molecular function of the latter. For instance, a muscular dystrophy could result from a mutation in the gene encoding myosin, the molecular function of which is muscle contraction. If that muscular dystrophy were only found when the myosin gene has been mutated and if the severity of the disease was not influenced by other factors, then that muscular dystrophy would be a single-gene disease. In actuality there are many different genetic lesions that lead to similar muscular dystrophies, including lesions in mitochondrially encoded genes [84]. A better candidate for a mono-gene disease may be phenylketonuria, an inherited (autosomal recessive) metabolic disease that is largely due to mutations in the phenylalanine hydroxylase (*PAH*) gene [85]. However, its therapy (dietary restriction) shows that the disease can be influenced by external factors, mutations in genes involved in the synthesis of a cofactor of the phenylalanine hydroxylation reaction also lead to the disease, and there are multiple alleles of the *PAH* gene that confer different severities. Hence, even this disease exhibits characteristics of systems biology diseases.

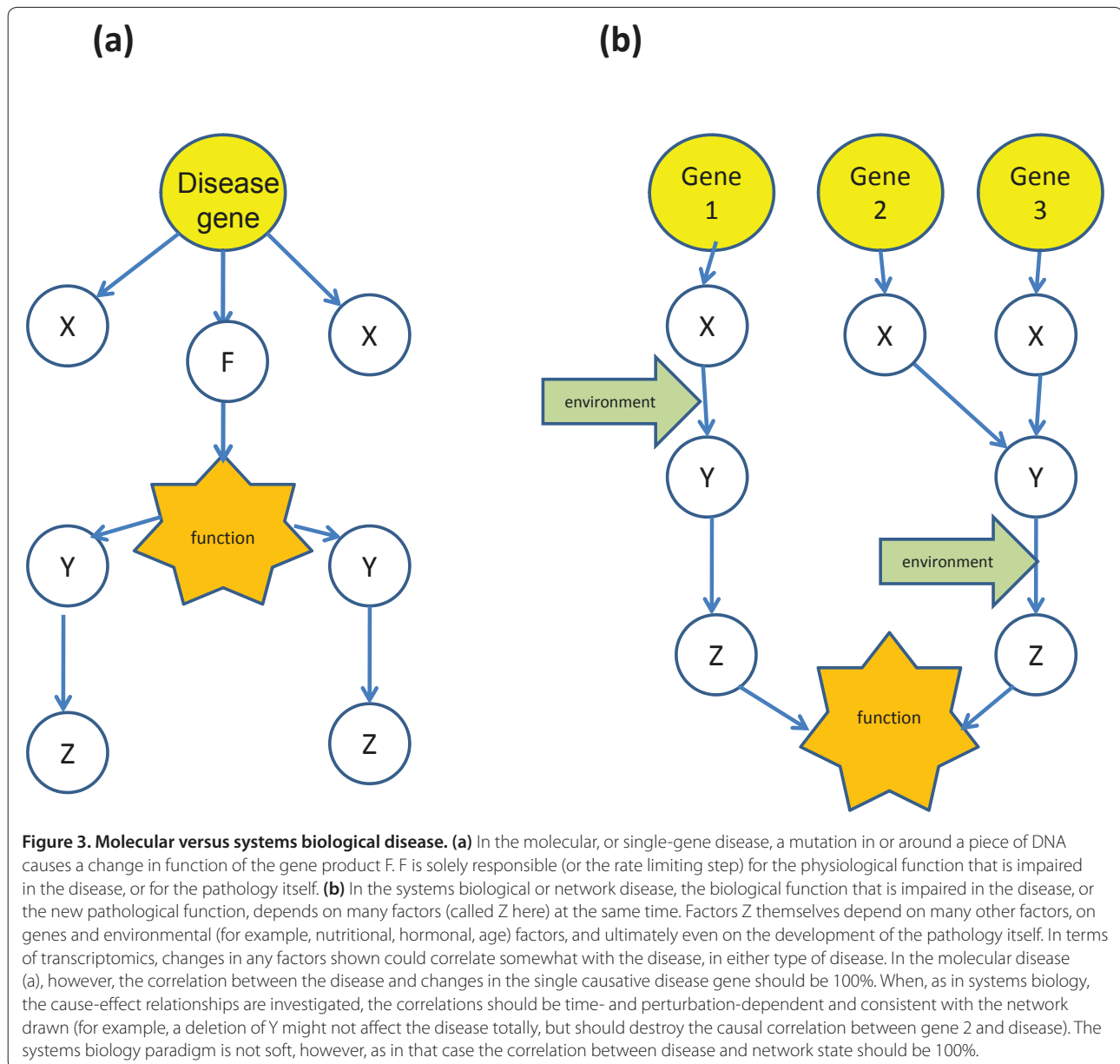
Most diseases have multiple genes associated with them. Such diseases might be considered to be a group of single-gene diseases; that is, many different diseases each being caused by a different single gene lesion, but all with similar phenotypes [86]. This would explain the association of multiple genes with the disease. In the case of a

group of single gene diseases, no other faulty molecules should be important for that individual disease and no other gene changes (for example, polymorphisms) or conditions (for example, diet) should influence the disease severity. Notably, a single patient's transcriptome should then show only changes in the single molecular culprit and not in other factors controlling the network leading to the disease; and in the transcriptomes of different patients suffering from the same disease group, that single molecular culprit should be different. For DD this is not what is observed (see above). As illustrated in Figure 3b, in a systems biology disease the function that is compromised depends cooperatively on a number of pathways, the functioning of each of which again depends on many cooperating molecular factors. In systems biology diseases one would typically find multiple changes in the transcriptome or proteome of each patient, differing between individual patients but such that all have a very similar disabling effect on network function. Identifying a disease as a systems biology or network disease does not dispel molecules from its pathology: molecules are always involved. The issue is whether the change in networking of the molecules is crucial for the disease, that is, whether the disease is more a consequence of faulty networking than of an individual malfunctioning molecule.

What difference should this all make for research, diagnosis and therapy? The answer is straightforward: when dealing with a network disease, one should deal with the network; when dealing with a molecular disease, one should concentrate on the molecule. For systems biology diseases, transcriptome patterns should be mapped onto the known cellular pathways, network fluxes, and the disease. The concept 'candidate pathway' or even 'candidate network' should be substituted for 'candidate gene'. In addition, one should investigate at the proteome, metabolome, and functional levels [87], and not each independently but all together, and then one may need to examine multiple network functions (Figure 4). Malignant cancer, for instance, may involve proliferation, lack of apoptosis, metastasis and multiple drug resistances.

#### **Is Dupuytren's disease a single-molecule or a systems biological disease?**

DD has been identified as a disease inherited in an autosomal dominant pattern [70] (and see above). It was linked to a single 6cM region on chromosome 16. This would suggest that all DD patients should have a mutation in this part of their genome, and that transcriptomes of DD patients should be altered in terms of the level of the transcripts encoded by this part of the genome or in terms of the coding sequence of one of those transcripts. However, the dominance was

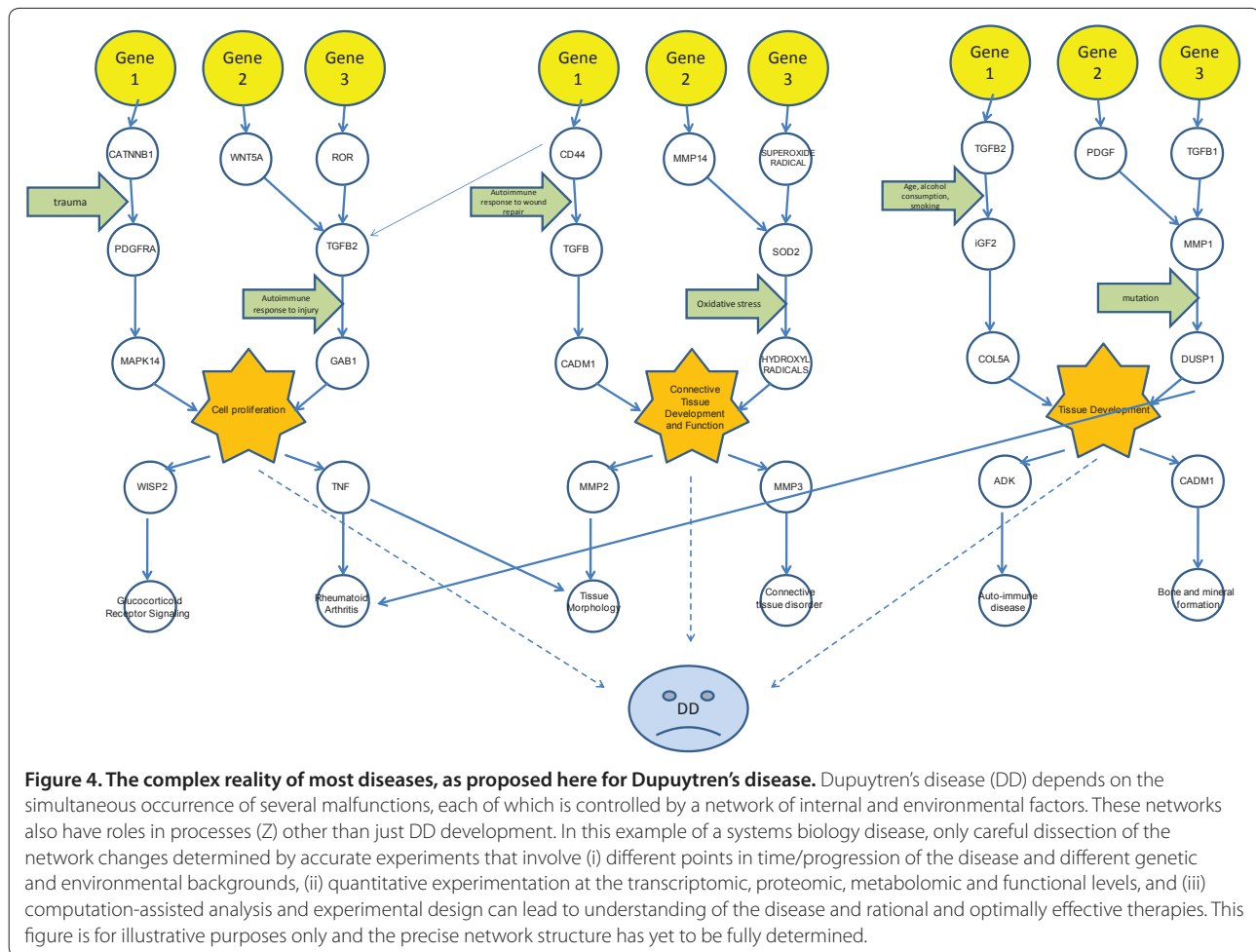


incomplete, weak, and has only been observed in a single Swedish family. This suggests that the genes on chromosome 16 are only dominant when other genes in the genome are of certain allelic forms. Moreover, in many other cases the expression levels of many other mRNAs were changed, although it remains to be analyzed whether in those studies there was always a change in mRNAs from the 6 cM region on chromosome 16. In our own studies, DD nodule transcriptomes of individual patients have all exhibited multiple changes in mRNA levels, and although these changes overlapped, they were not identical between individuals. The proteome did not point to a single causative protein either. The functional studies pointed to myofibroblast enrichment, although

not clearly as the sole cause, and neither was a causal relationship between a gene on chromosome 16 in the 6 cM region and differentiation of myofibroblasts established. This all shows that DD is not a single-gene disease and suggests that it is not just a group of pure single-gene diseases either. It is much more likely to be a systems biology disease.

#### Treatment

Surgical intervention is still the current mainstay of treatment for DD, usually involving fasciotomy, fasciectomy or dermofasciectomy [88]. A variety of non-operative techniques have been practiced but have failed to give long-lasting benefits. More recently, clinical



**Figure 4. The complex reality of most diseases, as proposed here for Dupuytren's disease.** Dupuytren's disease (DD) depends on the simultaneous occurrence of several malfunctions, each of which is controlled by a network of internal and environmental factors. These networks also have roles in processes (Z) other than just DD development. In this example of a systems biology disease, only careful dissection of the network changes determined by accurate experiments that involve (i) different points in time/progression of the disease and different genetic and environmental backgrounds, (ii) quantitative experimentation at the transcriptomic, proteomic, metabolomic and functional levels, and (iii) computation-assisted analysis and experimental design can lead to understanding of the disease and rational and optimally effective therapies. This figure is for illustrative purposes only and the precise network structure has yet to be fully determined.

investigation (phase II and III), including the use of clostridial collagenase injections, have shown encouraging results in some DD patients [89,90], but long-term follow-up results are required before this can be advocated as standard procedure in place of surgery.

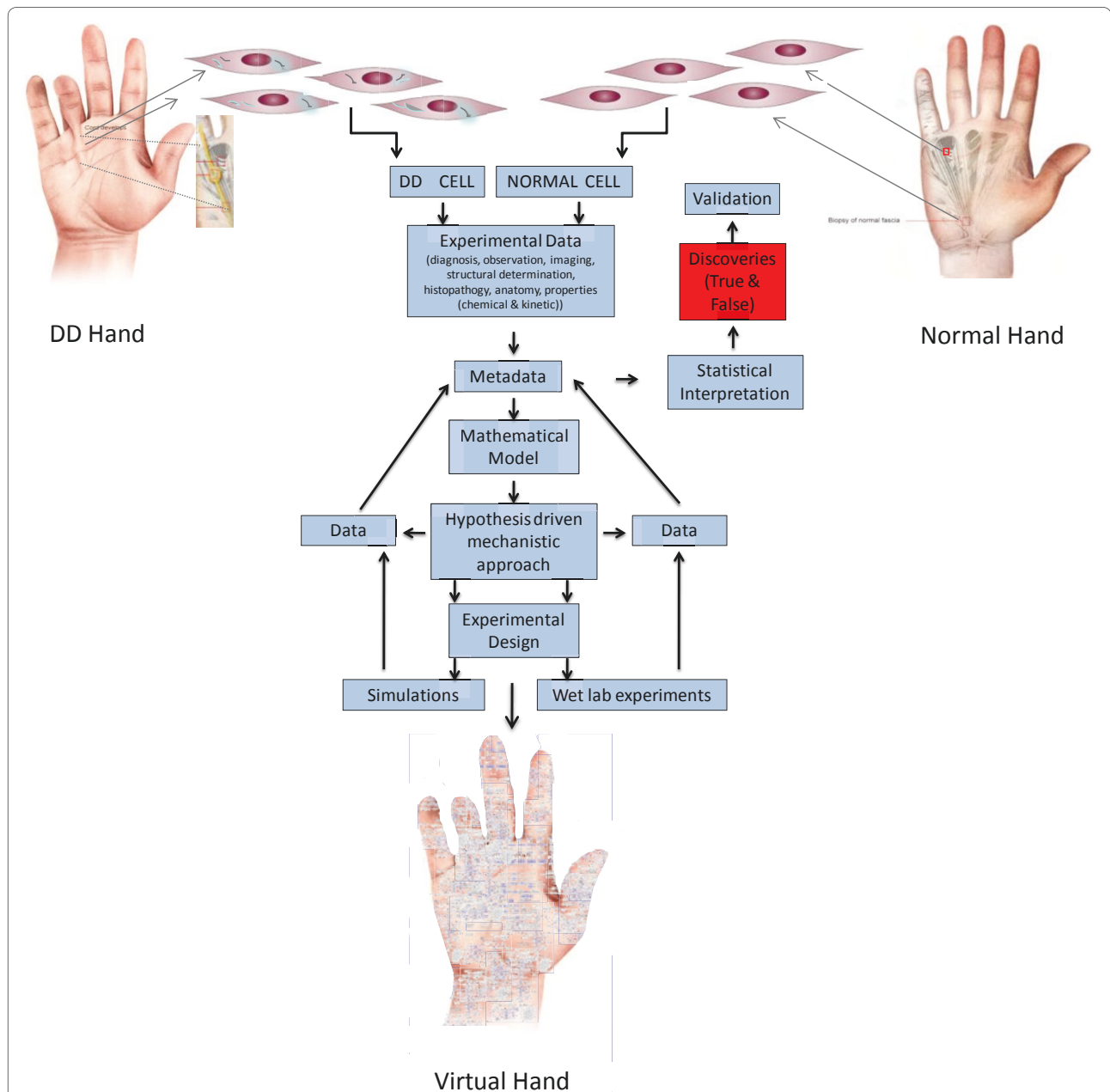
### Conclusion

Since association of DD with a single gene is inconclusive, the present mainstream research paradigm may be unlikely to lead to a full understanding of it. The experimental data appear to be more consistent with DD being a systems biology disease. Therefore, a different approach to the disease should be considered; analysis, diagnosis and therapy should target pathways rather than genes or their products. The concept of a 'candidate gene' should be replaced with that of 'candidate pathway(s)'. Studies should be aimed at elucidating cause-effect chains, rather than disease correlations. From the experimental data, alterations in pathways should be inferred. Using transgenic and antisense approaches in cell lines, these pathway alterations should then be induced and the predicted

development into a DD cellular phenotype tested. The pathways are expected to be integrals of gene expression, signalling and metabolic networks, as should be the approach and data analysis.

A hypothesis-driven systems biology would be based on *a priori* observations in human, *in vitro* or *in vivo* (linkage and expression studies, for example), or on knowledge of related diseases (such as plantar fibromatosis, peyronies, musculo-aponeurotic fibromatosis and even keloid disease). Inter-relationships would be sought between hypothesized underlying mechanisms governing these fibrotic disorders and physiological changes predicted based on molecular and environmental changes impacting on those mechanisms. This could then be extended to understand inter- versus intra-individual variability. Altering the networks using multiple molecular interventions in a tissue culture model system for DD would enable the hypotheses to be tested.

Such an approach should also help put into perspective existing inconclusive discoveries and maximize the utilization of data obtained from molecular approaches



**Figure 5. A proposed information flow for Dupuytren's disease research versus normal fibroblast biology research.** In the top-down branch of the systems biology approach, data maps generated by large scale experiments first need to be annotated and subjected to statistical analysis in order to extract biologically relevant information. That information should then be used to generate hypotheses concerning patterns of molecular behaviour or dynamic parameters of the networks. Phenomenological or partly mechanistic mathematical modelling can already help here to weed the impossible from the possible and to enable one to put multiple complex interactions into single testable hypotheses. Then, predictions can be made and tested. This may spiral through iterations of top-down systems biology into an ever improving set of hypotheses that may become more and more mechanistic. A bottom-up systems biology branch of the research may begin with proposed mechanisms (such as stimulation of fibroblast growth because of enhanced reactive oxygen species production) and develop mathematical models of these in order to assist with experimental design. By spirally testing and adjusting the hypothesis this will ultimately lead to a hypothesis that is better and better tested and involves more and more of the network. At each step, data will be consolidated, reducing the amount of unnecessary information while increasing their accuracy, quality and usefulness to improve and generate stronger models of the DD cell. A metabolic or signalling network can then be represented *in silico* and its properties studied using computer-simulated perturbations. For instance, the flux balance model could be applied to predict the behaviour of metabolic networks upon perturbation of the optimised metabolites within a metabolic pathway.



from molecular biology, perhaps in the sense of a live model repository [91]. Indeed, omics experiments generate heterogeneous data and metadata torrents. Systems biology modelling would serve as a way to organize the data rationally and efficiently. Emerging standard languages, such as the Systems Biology Markup Language (SBML) [92], Cell Markup Language (CellML) [93], Cell System Markup Language (CSML) [94], Biological Pathway Exchange (BioPAX) [95] and Systems Biology Graphical Notation (SBGN) [96], and modelling tools such as COMplex PATHway SIMulator (COPASI) [97], Cytoscape [98] and Pathway databases (for example, Ingenuity pathway analysis software) facilitate data representation and inter-operability from leading multidisciplinary research groups [99]. Additionally, the Java Web Simulation (JWS) facility, which quality controls kinetic models and puts them into a live repository, enables through-web experimentation *in silico* for scientists naive with respect to modelling, although it is experiment-dependent [100]. BioModels is a parallel model repository not built for *in silico* experimentation but focusing on annotation [101].

If we are right, and the systems biology research paradigm is adopted, the rewards should be substantial: no longer will the data collected in this field disappear into the diaspora of the experimental literature; they will be analyzed in terms of network models and, when informative, connected with proper data annotation [102]. Once the network hypotheses are proven, they will underpin the development of new rational biomarker strategies, and become the starting point for potential therapeutic interventions and prophylaxis.

More concretely, even though myofibroblasts obtained from different stages of DD may exhibit features that could trigger contraction and uncontrollable growth, neither the diversity of these cells nor the extent or nature of their local specificity *in situ* with regard to differentiation have been examined systematically. Remodelling of vascular connective tissue should be of fundamental importance as DD progresses over time and the ability of that tissue to be remodelled could be an important factor in the development of the disease. Matrix remodelling and matrix turnover are controlled by a complex network of cell-cell and cell-matrix interactions [103]. Mathematical modelling of these networks combined with targeted experimentation should help deduce the net outcome of the balance between proliferative and degradative processes.

Together, genomics, transcriptomics, proteomics, fluxomics, lipidomics, interactomics, glycomics and secretomics studies of biofluids within the DD system have the potential to improve our understanding of the disease immeasurably [104-106]; however, the 'together' concept requires an integration that is only plausible through systems approaches.

Investigating this complex deforming fibromatosis as part of a systems biology approach (Figure 5) will benefit not only understanding of the specific diseased phenotypes, but may also address the effects on the extracellular matrix and excreted by-products, and could offer further suggestions for early diagnosis.

Recognition of DD as a systems biology disease should also affect therapy. Treatment need not target the reversal of a molecular event but rather return a network affected by a combination of molecular culprits (for example, resulting from single-nucleotide polymorphisms) to its normal state. This return may be attempted by interventions in the network that may otherwise be unrelated to the molecular culprits. In this sense the recognition that DD is a network disease should increase the number of treatment options. More specifically, one should look at a number of intracellular networks (metabolic, signal transducing, or otherwise) affecting the disease and then consider treatment with combinations of existing drugs (and behavioural advice) that target all those networks. The relative dosages should be optimized, allowing for the optimum to differ between patients.

#### Abbreviations

DD, Dupuytren's disease; LOD, logarithm of the odds; ROS, reactive oxygen species.

#### Competing interests

The authors declare that they have no competing interests.

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