GENETIC SUSCEPTIBILITY TO DUPUYTREN’S DISEASE
– A REVIEW

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Dupuytren’s Disease (DD) or contracture (shortening DD), is a benign, fibroproliferative disease of the palmar aponeurosis (syn. palmar fascia) of unknown etiology. Factors that predispose to the development of the disease include alcohol abuse, smoking, anti-seizure medication, diabetes and cirrhosis of the liver, but the significance of any of these has not been definitively confirmed (1, 2). The prevalence of DD is geographically and racially variable with the greatest morbidity in northern Europe, more commonly affecting whites than other ethnicities and more frequently occurring in men than in women (2, 3). Family clusters affected by the disease were identified, suggesting the possible role of its genetic background (1, 4). Initial investigations indicated an autosomal dominant pattern of inheritance with variable penetration of the gene as being responsible for the development of DD (5). However, no single gene has yet been identified and it is supposed that DD may have a complex etiology, arising from a combination of environmental and multiple genetic factors; in this type of genetic predisposition, occurrence of the disease depends on the simultaneous presence of multiple alleles (6).

Previous investigations have allowed the identification of genes for fibronectin, α-smooth muscle actin, α₅β₁ integrin, laminin and tenascin C as major components of the cellular apparatus for generating signals transmitted to the extracellular matrix, leading to contracture formation (7, 8). Novel findings indicate matrix metalloproteinases and their inhibitors in sera and tissue as factors which may have effect on development of fibrosis on the palmar aponeurosis (9). Indirect evidence on the role of TGF β transformin growth factor in the pathogenesis of PD was found (6). Investigations of gene expansion in diseased palmar aponeurosis allowed identifying those, which may be implicated in metabolic processes which lead to fibrosis (1). Since Dupuytren’s disease has been recently a subject of many genetic and molecular investigations, we found it as reasonable to review contemporary evidence on the role of genetic susceptibility to DD.

Transforming growth factor beta (TGF β)

Proliferation of myofibroblasts is thought to be directly responsible for the development of pathological changes in palmar fascia, and these cells play a key role in the initiation and progression of the disease. Several factors, including transforming growth factor β, have been implicated in differentiation of myofibroblasts during wound healing and in some fibrocontractive conditions. Indirect evidence has been found in some studies, suggesting a contribution of TGF β₁ isoforms in the pathogenesis of Dupuytren’s contracture. These isoforms were found intracellularly within myofibroblasts in the proliferative and involutional stages of DD. In contrast, they are not present in myofibroblasts of normal palmar fascia (6, 10).
TGF β belongs to the family of multifunctional cytokines regulating cell proliferation and differentiation and has a key role in development, tissue turnover and repair. TGF β regulates synthesis of many proteins, such as collagen, fibronectin, glycoaminoglycans and integrins. This factor is released from many cell types that are involved in inflammation and fibrosis, i.e. lymphocytes, macrophages, endothelial cells, smooth muscle cells and fibroblasts. Compared to TGF β1, the TGF β2 isoform has a stronger effect on proliferation of myofibroblasts in DD and can also enhance the production of tissue matrix proteins such as collagen, fibronectin and polyglycan (10, 11). The TGF β2 isoform has been found in fibroblasts, myofibroblasts and endothelial cells of Dupuytren’s tissue (11). Receptors of TGF β isoforms, which are termed TGF βR I-III, are located on chromosomes 9q22, 3p22 and 1p32, respectively, and are found in myofibroblasts of Dupuytren’s tissue. Strong expression of TGF βR I-II has been found in granulation tissue of healing wounds. It is suspected that failure of the process of elimination of TGF β receptor-overexpressing myofibroblasts leads to a feedback loop resulting in excessive fibrosis during wound healing (6). In light of these findings, TGF βR I-III receptors may be suspected to be responsible for susceptibility to Dupuytren’s contracture.

Bayat et al. investigated the association of single nucleotide polymorphisms in TGF β receptors at risk of development of Dupuytren’s contracture. DNA blood samples from 183 patients with DD and from 181 controls were examined for the presence of the above-mentioned polymorphisms by DNA sequencing. For each single nucleotide polymorphism, association with Dupuytren’s contracture was investigated by comparing the distribution of genotype frequencies of Dupuytren cases with controls. Statistical analysis revealed a borderline level correlation (chi-square test, p=0.048) in genotype frequency distribution between Dupuytren’s cases and controls for TGF βR I polymorphisms in the recessive model. The genotype frequencies for TGF βR I polymorphisms in the dominant and co-dominant model were not statistically significant in Dupuytren’s cases and controls. Similarly, the genotype frequency for TGF βR III polymorphisms did not differ significantly in the examined or control groups. The investigations failed to find TGF βR II polymorphisms in either group. The authors consider that these findings do not show a definitive causative correlation between TGF βR I polymorphism and risk of Dupuytren’s contracture, and that the mechanisms of susceptibility to the disease appears to be more complex (6).

In their other study, Bayat et al. investigated correlation between TGF β2 gene polymorphisms in the 5’ untranslated regions of the 9q22, 3p22 and 1p32 chromosomes and development of DD. They did not find a statistically significant difference in three gene and two allele frequency distributions between the Dupuytren’s and control group, which failed to confirm an initially assumed association (10).

Genes that can contribute to fibrosis of the palmar aponeurosis

Pan et al. analysed gene expression in Dupuytren’s tissue taken from six affected patients and in normal fascia taken from two healthy controls using microarray analysis. The authors found 23 genes that were over- or underexpressed in Dupuytren’s tissue compared to the normal fascia. Nine of the 23 genes were selected for further investigation based on expression levels differing by at least approximately twice that of control levels. These genes were further identified by reverse transcription-polymerase chain reaction. The products of these genes, their direction and their level of expression are listed in tab. 1. Two of these genes, aldehyde dehydrogenase and dihydrodiol dehydrogenase, are involved in alcohol metabolism. The former dehydrogenase is an enzyme in the mitochondrial oxidative degradation of ethanol, while the latter catalyses the reduction of aldehydes or ketones to an alcohol. The authors believe that overexpression of these two genes may be associated with an increased incidence of DD in alcohol abusers; however, this correlation has not been confirmed in recent studies (1, 2). The gene for protein kinase PKX1, a regulatory enzyme in the phosphorylation of proteins is localised on the sex chromosome, with some evidence of Xp and Yp recombination and may be associated with a higher incidence of DD in men than in women. Tetranectin is a protein that binds plasminogen in the fibrinotic pathway. Amyloid A4 precursor, which was fo-
was also overexpressed in samples of both disease conditions. Osteoblast-specific factor 2 (OSF2) is involved in actin/cell membrane interactions required for fibroblast and myofibroblast contractile ability. Other genes included cortactin (amplaxin), which is involved in collagen breakdown and thyromosin peptides, which are activators of MMPs. Similarly, the expression of amyloid A4 protein precursor gene was increased in samples of both diseased tissues compared to controls. Differential alterations in expression between Peyronie’s Disease and Dupuytren’s contracture were found in four proteins associated with apoptosis, proteolysis and inflammation. The authors believe that these findings definitively confirm a role of genetic factors in the development of both diseases. They also provide targets for potential therapeutic strategies by identifying the downregulation of the genes responsible for excessive fibrosis or upregulation of their inhibitors (block differentiation of myofibroblasts or stimulate their apoptosis) (gene therapy) (12).

Numerical chromosome changes, as a predisposing factor to DD

Karyotype investigations of patients with DD revealed a more frequent occurrence than in healthy subjects of the following numerical chromosome changes: loss of Y chromosome and trisomy of chromosomes 7 and 8 (13, 14). Dal Cin et al. analysed the karyotype of Dupuytren’s tissue cells in 40 samples taken from 36 patients affected by the condition. A positive familial history was noted in nine of the 36 patients (25%). The authors found the following numerical abnormalities: trisomy of chromosome 7 in 13 samples (32%), of which one had associated trisomy 4 and one had loss of chromosome Y. Trisomy of chromosome 8 was observed in seven samples (17%). The presence of both trisomies 7 and 8 in the same sample was not found (15). Trisomy 7 is not associated specifically with DD, but it has been observed in normal tissue cells and in different solid tumors, both malignant and benign. Trisomy 8 is associated with the occurrence of deep

Table 1. List of products of genes, which expression levels differing at least approximately twice that of control levels (1)

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Direction of expression</th>
<th>Level of expression</th>
</tr>
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<tbody>
<tr>
<td>Aldehyde dehydrogenase 2</td>
<td>decreased</td>
<td>1,9-25,5</td>
</tr>
<tr>
<td>Amyloid A4 precursor</td>
<td>increased</td>
<td>1,7-2,4</td>
</tr>
<tr>
<td>Archaen</td>
<td>increased</td>
<td>3-5</td>
</tr>
<tr>
<td>Dihidrodiol dehydrogenase</td>
<td>decreased</td>
<td>2,6-11,8</td>
</tr>
<tr>
<td>Intracellular adhesion molecule 2</td>
<td>decreased</td>
<td>4</td>
</tr>
<tr>
<td>Lymphocyte-specific protein 1</td>
<td>decreased</td>
<td>2,5</td>
</tr>
<tr>
<td>Protein kinase PKC,</td>
<td>increased</td>
<td>1,8-3,4</td>
</tr>
<tr>
<td>SEF-1B protein</td>
<td>increased</td>
<td>2-5,5</td>
</tr>
<tr>
<td>Tetranectin</td>
<td>decreased</td>
<td>2,2-11</td>
</tr>
</tbody>
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Und initially in the brain tissue of Alzheimer’s patients, is a glycoprotein presented in myoblasts and myotubes. Lymphocyte-specific protein is involved in lymphocyte signal transduction. The last two products of the genes may play a role in modulation of contractile properties of cells, i.e. fibroblasts. The authors state that this is only the beginning of the profiled studies on the selection of genes associated with DD (1).

Qian et al. compared expression of the selected genes in patients affected by DD and Peyronie’s disease. Peyronie’s disease is a localized fibromatosis in the tunica albuginea of the penis, leading to penile deformation. The authors investigated gene expression in Dupuytren’s tissue taken from nine patients with DD and in tunica albuginea taken from nine patients with Peyronie’s Disease. Normal flexor tendon and tunica albuginea taken from two healthy volunteers were used as control tissues. Gene expression profiling was performed by microarray analysis. It was found that a series of 15 genes were upregulated and none were downregulated in the tunica albuginea of patients with Peyronie’s Disease, when compared to normal tunica albuginea. In the Dupuytren’s tissue samples, 16 genes were upregulated and three were downregulated when compared to normal tendon. Nine genes were upregulated in both Peyronie’s Disease and Dupuytren’s contracture. Of these genes, the most predominantly expressed were matrix metalloproteinases MMP-2 and MMP-9, which are involved in collagen breakdown and thyromosin peptides, which are activators of MMPs. Other genes included cortactin (amplaxin), a gene involved in actin/cell membrane interactions required for fibroblast and myofibroblast contractile ability. Osteoblast specific factor 2 was also overexpressed in samples of both diseased tissues compared to control tissues. Similarly, the expression of amyloid A4 protein precursor gene was increased in samples of both diseased tissues compared to controls. Differential alterations in expression between Peyronie’s Disease and Dupuytren’s contracture were found in four proteins associated with apoptosis, proteolysis and inflammation. The authors believe that these findings definitively confirm a role of genetic factors in the development of both diseases. They also provide targets for potential therapeutic strategies by identifying the downregulation of the genes responsible for excessive fibrosis or upregulation of their inhibitors (block differentiation of myofibroblasts or stimulate their apoptosis) (gene therapy) (12).

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seated fibromatosis such as desmoid tumors. Results of contemporary studies failed to provide definitive evidence to confirm a direct relationship between the aforementioned aberrations and DD, but also did not exclude it (15).

Review of the literature indicates a considerable contribution of genetic factors in the initiation process of fibrosis of the palmar aponeurosis, resulting in Dupuytren’s contracture. Many genes were identified, by which altered function may stimulate metabolic processes leading to excessive fibrosis. This process can be enhanced by the upregulation of the stimulated genes or by downregulation of inhibited genes. A relationship of transforming growth factor beta and risk of DD occurrence was also shown. Although the range of genetic investigations is impressive and their results are convincing, it seems that there is not yet definitive evidence to propose a single pathogenetic mechanism for DD, which is rather more complex in its nature.

REFERENCES


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