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Review

Modifiable and Non-Modifiable Predictors of Dupuytren's Disease

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Abstract: Dupuytren's disease (DD) is a common multifactorial disease accompanied by deformity of the hand with flexion contracture of one or more fingers, limitation of their mobility and a fixed lesion. This disease refers to disorders of the connective tissue. **Objective:** to generalize the results of studies of environmental risk factors for DD and update existing ideas about modifiable and non-modifiable predictors of the disease in adults. **Methods.** We searched for full-text English-language publications in the PubMed, Springer, Scopus, Clinical Keys, Oxford Press, Google Scholar, eLIBRARY. **Results.** The most significant modifiable predictors of the development of DD include (top 5): occupation; hobby; lifestyle; comorbid diseases; drugs. Non-modifiable predictors include (top 5): gender; age; ethnos; race; genetics. Genetic predictors of DD are not well understood, but the number of candidate genes responsible for the development of DD is increasing and reaches the top 50 or more candidate genes with a statistically significant association with the risk of developing DD in adults. The most studied candidate genes are *DUPC1*, *MMP2*, *MMP9*, *TIMP1*, *TIMP2*, *WNT4*, *WNT7B*. **Discussion.** Primary and secondary prevention of DD requires accounting of the mutual influence of modifiable and non-modifiable predictors in the disease development, as well as a personalized approach in planning and choosing non-surgical and surgical treatment, as well as the carriage of single nucleotide variants (SNVs) candidate genes associated with the development of DD. A promising direction in the prevention of disabling complications of DD may be the development of decision-making information programs (personalized algorithms) that take into account non-genetic and genetic predictors in a particular person, and their implementation in real clinical practice. **Conclusion**. Large multicenteral studies of the influence and mutual influence of modifiable and non-modifiable predictors with a single design are required in the future.

Keywords: *Dupuytren's contracture; Dupuytren's disease; Viking disease; sclerosing ligamentitis; risk factor.*

Introduction

Dupuytren's disease (DD) (ICD-10 M72.0) is a common multifactorial polygenic disease accompanied by deformity of the hand with flexion contracture of one or more fingers, limitation of their mobility and a fixed position [1]. Thus, one of the manifestations of DD is progressive fibrous hyperplasia of the structures of the palmar and digital fascia, presented in the form of nodes and cords, the final stage of which is secondary progressive and irreversible flexion contractures of the finger joints (Figure 1).

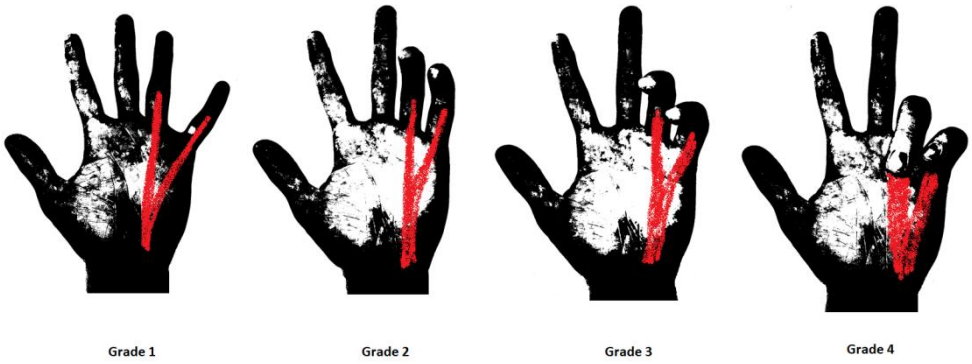

Figure 1. Progression of Dupuytren's disease (drawed by A.V. Petrov)

Apart from the high prevalence of DD in the Scandinavian countries, no objective scientific evidence has been found to support an exclusively "Nordic" origin of DD. Thus, with the exception of a high prevalence in northern European populations, so far there are no real genetic factors indicating the occurrence of DD predominantly in the Scandinavian population. Global prevalence of DD [2] in most countries of the world demonstrates that the origin and spread of the disease occurred much earlier than previously thought, and population migration patterns support the hypothesis that DD is a genetically determined disease. Indeed, DD has been found to be most common among residents of Northern Europe and the Caucasus, where it is one of the most commonly inherited connective tissue diseases, with a prevalence reaching 30% in the population of Norway and other Nordic countries over the age of 60 and 28% among non-indigenous Australians over 60 years of age [3]. In contrast, the prevalence of DD in the UK male population is just over 16% [3]. These specific rates of DD prevalence have been reported in many publications [3]. It is believed that DD is almost always found in Caucasians and only sporadically in people of African or Asian origin [4, 5]. Thus, the DD is more common than previously thought, has a higher prevalence and geographical representation in the world. This may be due to population migration and genetic drift, as well as changes in environmental risk factors as civilization develops, which contributes to the implementation of a genetic predisposition to a pathological phenotype in various ethnic and racial groups.

The development of DD depends not only on the race and ethnicity of individuals, but also on modifiable and unmodifiable risk factors. Translation of the results of studies of DD risk factors is important for the development of new strategies for the prevention and early diagnosis of DD at the primary health care level, because it can allow the patient to prescribe pathogenetic and symptomatic pharmacological therapy and/or minimally invasive surgical treatment at the early stages of the disease.

Objective

The purpose of this thematic review is to generalize the results of studies of environmental risk factors for DD and update existing ideas about modifiable and non-modifiable predictors of the disease in adults.

Materials and Methods

We searched for full-text English-language publications in the PubMed, Springer, Scopus, Clinical Keys, Oxford Press, Google Scholar, eLIBRARY databases using the keywords and their combinations: "Dupuytren's contracture"; "Dupuytren's disease"; "Viking disease"; "sclerosing ligamentitis"; "primary prevention"; "secondary prevention"; "risk factor"; "predictor". The review included original studies, meta-analyses, Cochrane

reviews, case reports. In addition, the review included publications of historical interest. Despite a comprehensive search, it is not excluded that some studies of recent years have been missed.

In total, we analyzed 678 publications, of which the objectives of this study corresponded to 63 publications.

Results

The results of the studies we analyzed suggest that DD can be primary (idiopathic) [6] and secondary (against the background of comorbid diseases, for example: diabetes mellitus (DM); thyroid disease; cardiac ischemia; hyperlipidemia; epilepsy; gout; rheumatoid arthritis; arterial hypertension (AH); malignancy; asthma and chronic obstructive pulmonic disease (COPD); Human Immunodeficiency Virus (HIV); sympathetic dystrophy; cancer) [3]. DD has been associated with multiple fibroproliferative conditions, including: Peyronie's disease (PD); knuckle pads; congenital generalized fibromatosis; juvenile fibromatosis; frozen shoulders [7]. The least studied is the multifactorial form of DD, including the lack of a common understanding of the etiology and pathogenesis, the contribution of non-genetic and genetic predictors [8].

Mechanisms of Dupuytren's Disease Development

To understand the role of modifiable and non-modifiable DD risk factors, several mechanisms for the development of this disease have been proposed (Table 1), but so far none of these mechanisms is the only recognized or leading one.

Table 1. Mechanisms of Dupuytren's disease development

Reference	Mechanism	Key proteins/enzymes
[9, 10]	The hypoxia theory: ROS production following hypoxia, microangiopathy, stimulation of fibroblasts proliferation.	HIF1α NOX DUOX1/2 NADH-CoQ
[11, 12]	The collagens degradation disorders: change balance between MMPs and their natural inhibitors; MMP activators dischange.	TIMP1 TIMP2 MMP2 MMP9 Thymosin TM-β4 TM-β10 OSF1 OSF2 RhoGDI TGF-β1
[13-15]	The theory of persistent low-grade inflammation: local activation of macrophages, lymphocytes or dendritic cells; increase of pro-inflammatory cytokines; discovery of dense T-cell infiltrates; increase of T-helper cells population in nodules; transformation of growth factor (PDGF); selectively upregulation of profibrotic genes (*COL1A1* and *ACTA2*) and proteins in palmar dermal fibroblasts by TNF.	TNF IL-6 IL-8 IL-1β PDGF
[16, 17]	The activation of WNT signaling: increase of expression of the Wnt signalling protein Wnt7β in nodules; decrease of SFPR4 secretion; promotion of fibroblast activation; predisposition or fibrosis.	Wnt7β SFPR4
[18]	The theory the extracellular matrix homeostasis disorders: matrix remodeling including discoid domain receptor (DDR2), matrix metalloprotease 14 (MMP14) and integrin alpha-11 (ITGA11): DDR2 synergized and potentiated the action of TGF-β1 and fibrillar collagen in stimulating myofibroblast differentiation; activation of fibroblast and induction of collagen deposition in the palmar fascia; increase of MMP14 fibroblast inhibition.	DDR2 MMP14 ITGA11 TGF-β1
[19, 20]	The theory of mechanical forces: promotion of development and progression of fibrosis: elucidation of the pathways governing cellular mechanotransduction; increase of key mechanotransduction molecules	YAP1 TAZ

	including the transcriptional co-activators Yes-associated protein 1 (YAP1), transcriptional co-activator with PDZ-binding motif (TAZ); change of YAP1 regulation of myofibroblast phenotype and transduction of signals from the mechanical environment in several fibrotic conditions.	
[21]	The cell theory: the growth factor TGF-beta 1 combined with mechanical stress can promote the differentiation of fibroblasts into myofibroblasts. Agonists, such as LPA and thrombin, can promote the contraction of myofibroblasts through specific intracellular signaling pathways that regulate levels of phosphorylated myosin light chain.	TGF-beta 1
[22]	The vascular theory: microangiopathy and increased collagen production.	β-catenin

Note: HIF1α – hypoxia inducible factor 1 subunit alpha; NOX – NADPH oxidase; DUOX1/2 – dual oxidase; NADH-CoQ – NADH-coenzyme Q; TIMP1 – tissue inhibitor of metalloproteinase 1; TIMP2 – tissue inhibitor of metalloproteinase 2; MMP2 – matrix metallopeptidase 2; MMP9 – matrix metallopeptidase 9; TM-β4 – thymosin β4; TM-β10 – thymosin β10; OSF1 – osteoblast-specific factor 1; OSF2 – osteoblast-specific factor 2; RhoGDI – Rho GDP-dissociation inhibitor 1; TGF-β1 – transforming growth factor beta; TNF – tumor necrosis factor; IL-6 – interleukin-6; IL-8 – interleukin-8; IL-1β – interleukin-1β; PDGF – platelet-derived growth factor; Wnt7β – Wnt family member 7β; SFPR4 – secreted frizzled related protein 4; DDR2 – discoidin domain receptor tyrosine kinase 2; MMP14 – matrix metallopeptidase 14; ITGA11 – integrin subunit alpha 11; YAP1 – yes-associated protein 1; TAZ – tafazzin.

According to McFarlane's Intrinsic theory (1974), pathological changes in the normal fascia lead to the formation of diseased cords [23]. Cords occur along routes determined by the normal fascial anatomy and arise from fascial precursors. However, this does not explain the commonly observed central cord which may occur in DD [24].

According to Hueston's Extrinsic theory (1985), the process of fibrosis begins with nodule formation. Nodules arise de novo from the metaplasia of fibro-fatty tissue [25]. Nodules then develop into cords which lie superficial to the palmar aponeurosis and eventually spread to form cords which lie superficial to the palmar aponeurosis. This theory provides a rational explanation for the presence of nodules. It also explains why recurrence occurs following fascial excision and why rates of recurrence are lower after dermofasciectomy [24].

According to Gosset's Synthesis theory (1985), cords and nodules are different forms of the same disease process [26]. Nodules are thought to arise *de novo* and cords from the palmar fascia. Studies by Strickland and Leibovic support this theory [27].

Murell's theory of free radicals (1992) is based on the hypothesis of local ischemia leading to the formation of free radicals [28]. Narrowed microvessels and thickening of the lamina basalis, as in diabetic patients, have been reported in patients with DD. It is believed that the release of free radicals is a stimulus for the excessive proliferation of fibroblasts, as occurs in DD.

According to Andrew's Macrophage hypothesis (1991), macrophages present at the initial stages of the disease release growth factors, that leads to endothelial proliferation as well as local proliferation of fibroblasts [29]. Proliferation of fibroblasts is thought to lead to microvascular occlusion, hypoxia, free-radical release and fibroblast proliferation as described by Murrell [28].

According to Goldblum's hypoxia theory (2016), atherosclerosis, cigarette smoking, hyperglycemia in poorly controlled diabetes and work-related hand micro-trauma have vascular damage as a common result. This fits with the hypoxia theory of DD pathogenesis, stating that microangiopathy may stimulate fibroblasts proliferation through ROS production following hypoxia [9, 30].

Despite the improvement of methods of surgical treatment of DD, the frequency of postoperative relapses is high and can reach a third of cases or more [31]. Conservative treatment (pharmacotherapy, physiotherapy, radiotherapy, etc.) [32] is limited, but actively studied and expanded as our knowledge of non-genetic and genetic predictors (risk factors) of this disease improves.

Modifiable Predictors of Dupuytren's Disease

Modifiable predictors are risk factors that can be influenced by lifestyle changes or medications. The most significant (top 5) modifiable predictors of the development of DD

include: profession (designer, pianist, carpenter, artist, sculptor, surgeon, etc.); hobbies (drawing, embroidery, knitting, etc.); lifestyle (smoking, alcohol abuse, fatty food, etc.); comorbid diseases (cardiac ischemia, arterial hypertension, hyperlipidemia, 1 type and 2 type diabetes, epilepsy, etc.); drugs (phenobarbital, phenytoin beta adrenergic blocking agents, etc.) (Table 2).

Table 2. Modifiable predictors of Dupuytren's disease

Modifiable predictor	Characteristics
Occupation [30, 33-38]	Occupational daily vibration exposure. Daily heavy manual work. Musicians (pianists, violinists, rock musicians, etc.), painters, sculptors, medical professionals (surgeons, physiotherapists).
Hobby [33]	Preparing food, writing, playing musical instruments, knitting, embroidery, drawing, etc.
Food preferences [33]	Fatty foods high in cholesterol, foods high in fast-digesting carbohydrates.
Comorbid diseases [1, 30, 39-41]	Cardiac ischemia, arterial hypertension, hyperlipidemia, 1 type and 2 type diabetes, epilepsy, gout, rheumatoid arthritis, malignancy, asthma, chronical obstructive pulmonic disease, Human Immunodeficiency Virus infection, sympathetic dystrophy, cystic fibrosis, etc. Associations with Ledderhose's disease and Peyronie's disease are well known.
Lifestyle [33, 42, 43]	Alcohol abuse, tobacco exposure.
Leading hand [33]	Right hand (more often).
Hand injury [33-35, 38]	Acute and chronic occupational and non-occupational trauma to hand and wrist (microdamage).
Medical and drug histories [33, 44]	Beta adrenergic blocking agents (beta blockers), anti-epileptic drugs (phenytoin, phenobarbital), certain supplements (glucosamine /chondroitin and large doses of supplemental vitamin C).

Non-Modifiable Predictors of Dupuytren's Disease

Non-modifiable predictors are those risk factors that can't be changed (for example, age, gender, race and ethnicity, genetic burden). However, the selection of these predictors into a separate group allows you to identify patients at high risk of DD who need the appointment of preventive measures and control of modifiable risk factors.

Non-modifiable predictors of DD include (top 5): gender (usually male); age (more often after 40-50 years); ethnos (Caucasians from Northern Europe, Scandinavia, Australia); race (European); genetics (family predisposition, candidate genes) (Table 3).

Table 3. Non-modifiable predictors of Dupuytren's disease

Predictor	Characteristics
Sex [7]	Male
Age [42, 43, 45]	Over 40 years old
Nationality [46]	Europeans (Scandinavians, Australians)
Race [45, 47]	Caucasians
Genetics [1, 17, 48]	Monogenic Dupuytren's disease (the *DUPC1* gene). Multifactorial Dupuytren's disease (the *MMP2*, *MMP9*, *TIMP1*, *TIMP2*, *WNT4*, *WNT7B* genes, etc)

DD can develop in both men and women. However, most of the previous studies indicate that this disease affects men more often than women in a ratio of 3:1 [7].

Univariate analysis revealed associations of age, range 40-92. Among men, the following were significantly associated with DD: age. The mean age for men was 68 years. In men, DD most often occurs after age 50. In women, it tends to appear later and be less severe. However, DD can occur at any time of life, including childhood [42, 43, 45]. The percent of people with DD in each age group goes up with age, but the number of people in each age group goes down with age (Figure 2) [49].

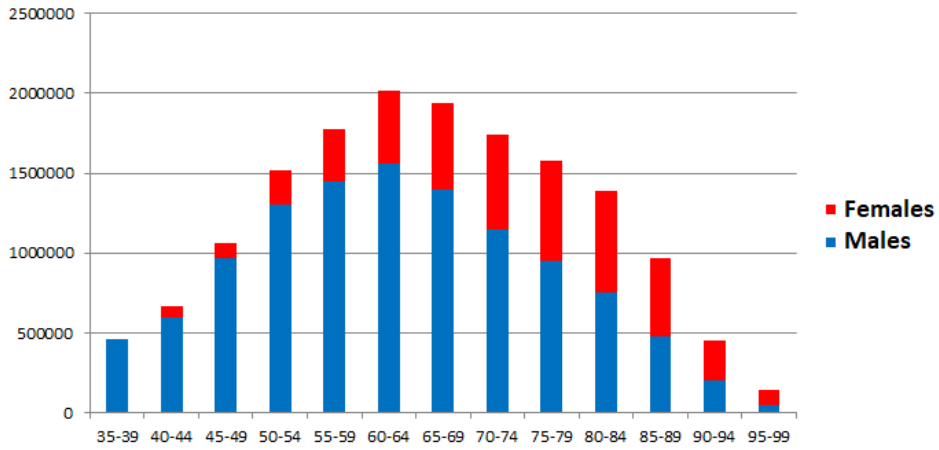

Figure 2. The incidence of Dupuytren's Disease in men and women depending on age (USA, 2010) [49, modification by A.V. Petrov et al., 2022]

DD more commonly affects Northern European Caucasians [1]. The condition is 3 to 10 times more common in people of European descent than in those of non-European [45]. It has been generally agreed that DD is more common in people of the white northern European population (Caucasians), especially from Celtic descent [50, 51]. With the inclusion of close relatives, the incidence in Celtic families have been reported to be as high as 74% [50]. Also, in areas where Caucasians have emigrated to, a high incidence can be found [4]. DD is the most common hereditary disease of the connective tissue preferentially affecting Caucasians originating from Northern Europe [1]. 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 [52, 53].

Summary, DD is 3 to 10 times more common in people of European descent than in those of non-Europeans [45]. It afflicts predominantly white males of northern European origin [47].

DD is the most common hereditary disease of the connective tissue preferentially affecting Caucasians originating from Northern Europe. For many centuries, doctors and scientists have paid attention to familial cases of DD, therefore, clinical and genealogical analysis (pedigree method) [54-56] and twin method [37, 57, 58] were previously used to analyze and generalize the accumulated knowledge. However, our understanding of the genetics of DD is changing with the introduction of modern methods of molecular diagnostics [1, 59-61].

Genetic predictors (biomarkers) of this disease have not been studied enough, but the number of candidate genes responsible for the development of DD is increasing and exceeds the number of 50 [62]. The most studied candidate genes are: the *DUPC1* [1, 48] gene responsible for the monogenic form of DD and the *MMP2*, *MMP9* [48, 63], *TIMP1*, *TIMP2* [48, 63], *WNT4*, *WNT7B* [17] genes - for multifactorial forms of DD.

Discussion

Our review of modifiable and non-modifiable DD's predictors indicates that those factors should be taken into account when planning the provision of medical and preventive care, including preliminary and periodic medical examinations of the population for the time-sensitive diagnosis of the disease, an adequate solution to the issue of admission of individuals with high professional risk and family history for certain types of professional activities. Undoubtedly, the study of genetic predictors can help predict the risk of developing DD in various ethnic and age groups of the population.

However, the results of the available associative genetic- and genome-wide studies indicate that the translation of the results of fundamental science into real clinical practice is currently difficult. The reasons are variable: the difference in studies' design; small sample sizes in most studies; the lack of a unified approach to the clinical interpretation of the results; a large number of candidate genes, single nucleotide variants and polymorphisms of which predispose to the development of DD. At the same time, for the implementation of a genetic predisposition into a pathological phenotype, an additional influence of environmental predictors and epigenetic mechanisms is necessary. There is no doubt that the continuation of research into the genetics of DD is relevant due to the high prevalence of the disease in Europeans, including those living in the Russian Federation, the growing importance of environmental predictors of technogenic DD (professions, hobbies, housework, etc.) and an increase in prevalence of comorbid diseases that increase the risk of DD (DM, atherosclerosis, hypertension, etc.), an increase in the number of cases of prescribing drugs for comorbidities that increase the risk of DD (beta adrenergic blocking agents, anti-epileptic drugs (phenytoin, phenobarbital), certain supplements (glucosamine/chondroitin and large doses of supplemental vitamin C, etc.)).

Despite many years of studying modifiable and non-modifiable predictors of DD, expanding our understanding of the development and recurrence of this disease, there is currently no single hypothesis for the development of DD. However, due to the high prevalence of the disease and its progressive type of course that impairs hand function, it is necessary to develop personalized algorithms for diagnosing and wide prophylactic observation of individuals at risk and patients with early stages of DD, taking into account the cumulative contribution of modifiable and non-modifiable predictors, as well as the development of a unified interdisciplinary strategies of treatment and preventive care for the considered group of patients with the participation of primary health care physicians (general practitioners, therapists, surgeons) and a specialized link (orthopedists, traumatologists, plastic surgeons, microsurgeons).

Conclusions

Our narrative review demonstrated that DD is a medical problem not only in the Scandinavian countries, but also in the global population as a whole. This may be due not only to population migration, but also to the increasing prevalence of modifiable risk factors for DD, such as DM, atherosclerosis, hypertension, etc. The authors suggest that taking into account the predictors of DD systematized in this review can help modify the approach to conducting preliminary and periodic medical examinations of the population in high-risk groups and, thereby, improve the quality and timing of primary diagnosis of the disease in the Russian Federation.

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