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Review

# GENETIC RISK FACTORS FOR OCCUPATIONAL CONTACT DERMATITIS

**A.M. Amromina, D.R. Shaikhova, I.A. Bereza**

Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, 30 Popov St., Yekaterinburg, 620014, Russian Federation

*Occupational contact dermatitis is an important current occupational health problem with serious economic and social consequences. Among possible risk factors for this disease, researchers pay attention to genetic predisposition. Identification of polymorphisms associated with the occupational pathology will allow specialists to establish risk groups, carry out timely preventive measures, and adjust treatment, guided by a personalized medicine approach.*

*The purpose of this review was to summarize the results of studying genetic risk factors for occupational contact dermatitis. Three researchers did an independent search in the PubMed, Google Scholar, eLibrary, and CyberLeninka databases and further analysis of scientific literature on genetic predisposition to occupational dermatitis published in 1990 to 2023. Of 88 papers analyzed, 32 articles were included in this review.*

*We established that genetic risk factors for occupational contact dermatitis were usually studied in metallurgical workers with a focus on potential candidate genes among skin barrier function-related genes, pro-inflammatory and anti-inflammatory genes, and xenobiotic metabolism and biotransformation genes. The most compelling evidence for the use of genetic polymorphisms as risk factors for occupational contact dermatitis has been demonstrated for the filaggrin (FLG) gene, which is involved in maintaining the skin barrier, and tumor necrosis factor alpha (TNF-α), which is involved in protecting the body and cells from inflammation and apoptosis. However, the data available are insufficient to use genetic polymorphisms as risk factors for occupational skin diseases. Further studies that take into account the mechanism of interaction of different genes during the development of occupational contact dermatitis are required.*

***Keywords:*** *genetic risk factors, genetic predisposition, allergic contact dermatitis, irritant contact dermatitis, occupational contact dermatitis, gene polymorphisms, candidate genes.*

Occupational contact dermatitis registered by dermatologists during periodic medical examinations of industrial workers is an important current issue of occupational health. In European countries, the proportion of occupational contact dermatitis reaches 45 % of all occupational disorders [1, 2]. At the same time, both domestic and foreign researchers note its poor detection rate attributed to the desire of patients to hide the problem and difficulties in diagnosis [3].

Occupational contact dermatitis has serious economic and social consequences, especially in industrialized countries. Significant economic losses include sick leave payments, treatment costs, compensation, etc. The development of this disease leads to a deterioration in the quality of workers' life, a decrease in income and working efficiency [4].

Occupational contact dermatitis is known to be induced by dermal exposure to work-related chemical, physical and/or biological agents. Not all workers, however, develop the disease following the exposure to comparable levels of allergens and irri-



**Anna M. Amromina** – Junior Researcher at the Department of Molecular Biology and Electron Microscopy (e-mail: amrominaam@ymrc.ru; tel.: +7 (343) 253-87-54; ORCID: https://orcid.org/0000-0001-8794-7288).

**Daria R. Shaikhova** – Researcher at the Department of Molecular Biology and Electron Microscopy (e-mail: darya.boo@mail.ru; tel.: +7 (343) 253-87-54; ORCID: https://orcid.org/0000-0002-7029-3406).

**Ivan A. Bereza** – Researcher at the Department of Molecular Biology and Electron Microscopy (e-mail: berezaia@ymrc.ru; tel.: +7 (343) 253-87-54; ORCID: https://orcid.org/0000-0002-4109-9268).

tants. In addition, obvious differences in clinical manifestations of the disease and the severity of its symptoms have been noted. These features may indicate genetic predisposition in some workers and their increased susceptibility to occupational contact dermatitis.

The search for genetic biomarkers of susceptibility to occupational dermatitis has been lasting for over 20 years now [5–9]. Data on genetic risk factors for dermatitis will make it possible to establish the mechanisms of its occurrence and take preventive steps even before the disease onset. Identification of polymorphisms associated with the occupational disease will help specialists reveal risk groups among industrial workers, assess individual risks, carry out timely preventive measures and treatment adjustments, which will ultimately allow for effective management of occupational risks.

The development of genetics and availability of genetic technologies have allowed this area of knowledge to penetrate into all fields of medicine, including occupational health and medicine. The accumulated experience is necessary for the development of a personalized approach in medicine aimed at maintaining health and improving the quality of life of the working-age population.

**The purpose** of the review is to summarize the accumulated results of studying genetic risk factors for occupational contact dermatitis.

**Materials and methods.** For this review, the available scientific literature and results of studying genetic predisposition to work-related contact dermatitis in employees of different occupations and industries were analyzed. Three authors did an independent search for literary sources published in 1990–2023 in the PubMed, Google Scholar, eLibrary, and CyberLeninka databases using the following keywords both in Russian and English: “genetics of occupational contact dermatitis”, “genetics of occupational allergic contact dermatitis”, “genetics of occupational irritant contact dermatitis”, “genetic predisposition to occupational dermatitis”, and “gene polymorphism in occupational dermatitis”.

The criteria for exclusion were the lack of information about work-relatedness of the disease or occupational exposure to a skin irritant or allergen, the absence of a genetic part in the study, and reviews. Of 88 papers analyzed, 56 were rejected given the above criteria. From the remaining 32 publications, data were extracted into an Excel spreadsheet.

Here we apply division of cases of occupational contact dermatitis by the mechanisms of the disease occurrence, as it is of fundamental importance for establishing genetic associations and does not correspond to the 10$^{th}$ revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

**Results and discussion.** Occupations posing a high risk of work-related contact dermatitis include hairdressers, construction workers, welders, healthcare workers, dentists, and metal workers [2]. We noted that genetic predisposition to the disease was most often studied in workers engaged in metallurgy (25 %), construction (19 %), and healthcare (16 %) (Figure 1).

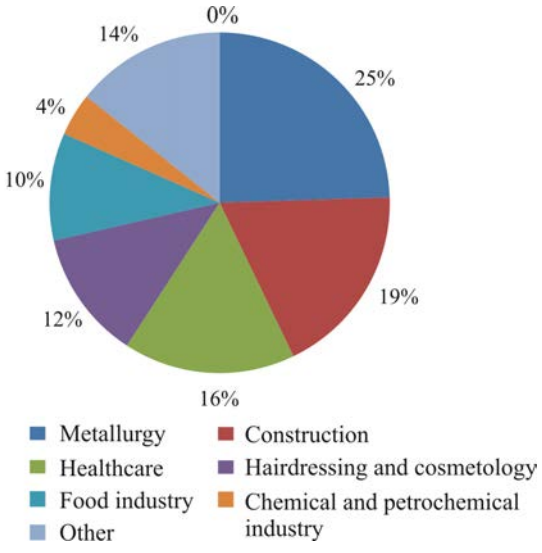


Figure 1. Industry-specific distribution of genetic studies on occupational contact dermatitis, %

Occupational contact dermatitis can be divided into two large groups owing to fundamental differences in the mechanisms of the disease occurrence: allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). ACD is characterized by preliminary sensitization to the allergen, and the development of the disease follows the type of delayed hypersensitivity. ICD, in its turn, is an inflammatory response resulting from direct contact with an irritant [1]. Our findings show that researchers are almost equally interested in the genetic predisposition to occupational ACD (37 %) and ICD (30 %) (Figure 2). It is worth noting, however, that most articles devoted to work-related ACD belong to Russian researchers, while foreign colleagues mainly focus on ICD. We assume that these differences can be explained by a high (ca. 90 %) proportion of ICD registered among all cases of occupational contact dermatitis abroad, while in Russia over 50 % are ACD cases [1, 10].

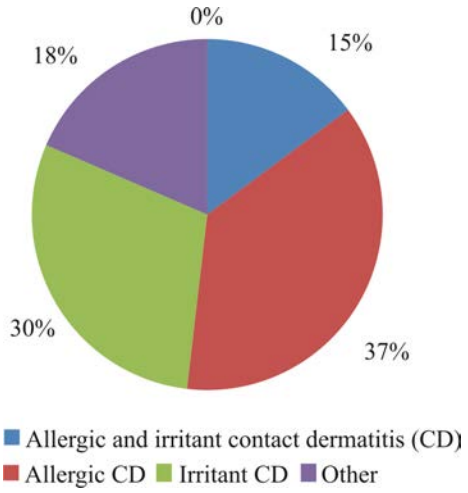


Figure 2. Percentage distribution of articles on genetic predisposition to occupational contact dermatitis by type

Figure 3 shows genes, polymorphisms of which are studied in connection with individual susceptibility to occupational contact dermatitis in workers. Among them, three large groups can be distinguished: skin barrier function genes (FLG – 18 %), pro- and anti-inflammatory genes (IL – 17 %, TNF-α – 15 %), and detoxification genes (GSTM1 – 15 %, GSTT1 – 5 %, CYP1A1, and CYP3A4).

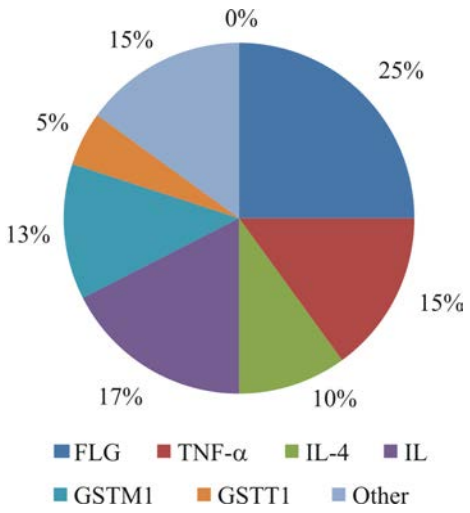


Figure 3. Percentage distribution of genes studied as potential predictors of occupational contact dermatitis: FLG, filaggrin; TNF-α, tumor necrosis factor alpha; IL, interleukin; GSTM1, glutathione S-transferase Mu 1; GSTT1, glutathione S-transferase theta 1

Table 1 shows that the genes, polymorphisms of which are considered as possible predictors of occupational dermatitis, do not differ significantly between ACD and ICD, with the exception of the genes for xenobiotic metabolism which are considered only in relation to ACD.

**Skin barrier-related genes.** Among the skin barrier-related genes presumably involved in the development of contact dermatitis, attention is paid to polymorphisms of the LCE3B and LCE3C, CLDN1, SPINK5, and FLG genes [6, 11, 12].

The filaggrin (FLG) gene encodes the protein that aggregates keratin intermediate filaments in mammalian epidermis, being the key component of the stratum corneum [13]. Reduction or loss of filaggrin function supposedly leads to skin barrier defect and increased passage of antigens, allergens and chemicals through the epidermis, thereby contributing to dermatitis [14]. More than 20 loss-of-function mutations in the FLG gene are known, some of the key ones are

Table 1

The genes, polymorphisms and alleles of which are considered as potential biomarkers of susceptibility to occupational contact dermatitis

| | Disease / Function | Allergic contact dermatitis | Irritant contact dermatitis | Allergic and irritant contact dermatitis |
|---|---|---|---|---|
| Genes | Skin barrier | FLG | FLG | FLG, SPINK5 |
| | Inflammation | TNF-α, IL4, IL33, IL5, IL16, IL10 | TNF-α, IL1A, IL4 | TNF-α, HLA-B, HLA-DRB1, HLA-DQA1, HLA-DQB1, IL4, IL31, IL-1Ra, IL1A |
| | Biotransformation of xenobiotics | GSTM1, GSTT1, CYP1A1, CYP3A4, EPHX1 | | NAT1, NAT2, GSTT1, GSTM1 |

associated with deletions of certain parts of the gene and are most often considered by researchers in the context of genetic predisposition to occupational dermatitis, namely R501X, 2282del4, S3247X, and R2447X [6, 13].

In a Dutch study, the relationship between mutations in the FLG gene and occupational dermatitis in 506 construction workers exposed to skin irritants including cement, epoxy resins, solvents, and abrasives was examined. The researchers found that the carriage of mutations in the FLG gene was significantly associated with both mild and severe occupational dermatitis (OR = 5.71; 95 % CI: 1.63–20.06, and OR = 8.26; 95 % CI: 2.32–29.39, respectively). It is worth noting, however, that in this study, four filaggrin loss-of-function mutations were genotyped (R501X, 2282del4, S3247X, and R2447X), and their carriage was established only in 32 workers [6]. Similar results were obtained in yet another study of Dutch construction workers suffering from occupational contact dermatitis where the carriage of FLG loss-of-function variants contributed to the development of CD and severity of its course (OR = 4.34; 95 % CI: 1.64–11.47, and OR = 5.83; 95 % CI: 1.64–20.78, respectively) [15].

Another study examined the association between two FLG polymorphisms (R501X and 2282del4) and chronic irritant contact dermatitis (CICD) among the patients employed in various occupational fields, including healthcare, metallurgy, construction, hairdressing and cosmetology, food industry, etc. Apprentices in vocational training for the respective high-risk occupations for CICD were chosen as controls. The study results showed that "…heterozygotes for R501X and 2282del4, FLG null alleles, were more frequent among patients with CICD (12.5 %) compared with controls (6.9 %), resulting in an odds ratio of 1.91 (95 % CI: 1.02–3.59)." The findings also showed that "in the apprentice group, signs of dermatitis before the start of the vocational training were four times more prevalent in carriers (43 %) than in noncarriers (10 %; $p < 0.001$)" [16]. This conclusion was partially confirmed by the results of other authors, who revealed the influence of the heterozygous genotype of the 2282del4 polymorphism on the development of occupational dermatitis ($\chi^2 = 8.622$; $p < 0.01$) [17].

Visser et al. [18] demonstrated that patients with occupational ICD were carriers of four loss-of-function mutations in the filaggrin gene (OR = 2.09; 95 % CI: 1.33–3.28), while the proportion of patients carrying null mutations was 8.5 %. The association with the development of occupational ICD was also noted in carriers of null variants of the

R501X and 2282del4 polymorphisms (OR = 2.25; 95 % CI: 1.07–4.75 and OR = 2.02; 95 % CI: 1.17 –3.49, respectively) [18]. Similar results were obtained in another study, in which carriage of null mutations was also associated with the severity of the clinical course of dermatitis [19].

Not all studies, however, confirm the impact of filaggrin gene polymorphisms on the development of occupational contact dermatitis [8, 20]. The study examining occupational ACD demonstrated no effect of FLG gene polymorphisms on the disease manifestation. The researchers explain this result by a low prevalence of deletion variants in the Croatian population [20]. The study of ACD among oil workers also failed to prove the relationship between the loss-of-function null mutation 282del4 in the skin barrier gene and ACD [8]. It should be noted that the FLG gene polymorphisms under consideration are rare in the European population, so the frequency of occurrence of null mutations R501X and 2282del4 is less than 9 % [14].

Among the genes involved in the skin barrier function, SPINK5 (serine peptidase inhibitor) is also identified, which is involved in the morphogenesis of skin and hair, as well as in the anti-inflammatory and antimicrobial protection of the mucosal epithelium. SPINK5 dysfunction can lead to abnormal keratinocyte differentiation and epidermal barrier dysfunction [21]. In the study of atopic eczema and non-atopic hand dermatitis in hospital nurses, rs6892205 G allele of SPINK5 gene was associated with the development of non-atopic hand dermatitis ($p$ = 0.00086). The G allele increased the risk of dermatitis (assuming dominant model; OR = 3.79; 95 % CI: 1.55–9.28; $p$ = 0.0036) and might be a biomarker of susceptibility to developing the disease among medical personnel [22].

**Genes for xenobiotic metabolism.** Polymorphisms of genes, protein products of which are involved in the biotransformation of allergens and xenobiotics, may contribute to individual differences in the occurrence and development of occupational dermatitis. The most extensive research on this topic has been carried out with respect to genetic polymorphisms of cytochrome P450 enzymes, glutathione S-transferases, and N-acetyltransferases.

Among N-acetyltransferases, polymorphisms of two genes are considered: NAT1 (N-acetyltransferase 1) and NAT2 (N-acetyltransferase 2). Cytosolic enzymes encoded by these genes catalyze acetylation reactions. These proteins are believed to be involved in the metabolism of drugs and xenobiotics, and their role in the metabolism of allergens is also assumed [23]. It is in connection with this function in the human body that polymorphisms of these genes have been studied as possible risk factors for the development of occupational contact dermatitis.

The study of Chinese workers diagnosed with hypersensitivity dermatitis showed that polymorphisms in the NAT2 gene, but not NAT1, were associated with the risk of developing the disease induced by trichlorethylene exposure. Patients with one or two mutant alleles (intermediate or slow acetylators) of NAT2 "…had a 2.01 fold higher risk for the disease than subjects with the fast acetylators" [7].

Deletion polymorphisms of glutathione S-transferase M and T enzymes are considered in numerous studies in connection with predisposition to various diseases, including occupational dermatitis [24–26]. The proteins of these genes are involved in phase 2 reactions of xenobiotic detoxification. The presence of deletion polymorphism in the GSTM1 and GSTT1 genes indicates the absence of enzyme activity, which is associated with a possible reduced ability to eliminate toxic compounds in the body [27]. Genes of the human cytochrome P450 1A (CYP1A) subfamily play a

critical role in the metabolism of endogenous substrates and exogenous compounds, including various xenobiotics and drugs. SNPs causing loss of function of the cytochrome P450 enzymes CYP1A1 or CYP1A2 are associated with lower ability to inactivate xenobiotics and disease risk [27–29].

In the study examining occupational dermatitis in construction workers exposed to cement that contains hexavalent chromium or its compounds, both being skin allergens, the effect of the GSTT1 null (deletion) genotype, but not GSTM1, on the development of the disease and increased sensitivity to chromium compounds was established (OR = 5.5; 95 % CI: 1.4–36.2) [24]. The lack of association between occupational dermatitis and GSTM1 deletion genotype was demonstrated in yet another study [30]. However, the latter revealed the influence of GSTM1 polymorphism on the severity of clinical symptoms of ACD; GSTM1 deletion was associated with severe disease, development of comorbidity and early manifestation. Similar results were obtained in another work [28]. The effect of the GSTM1 null genotype on the development of ACD was not established in the study of this pathology in oil workers [8].

The analysis of cytochrome gene polymorphisms in patients with occupational allergic contact dermatitis demonstrated that carriage of the A/G heterozygote of the CYP1A1*2C polymorphism is more common in patients with a history of this disease ($\chi^2$ = 9.27; $p < 0.01$), compared with the population control group (19.5 %) [28], just as the A/G heterozygote of the EPHX1 A415G polymorphism ($\chi^2$ = 3.86; $p < 0.05$), which is responsible for biotransformation of epoxides as a result of degradation of aromatic compounds.

**Pro-inflammatory and anti-inflammatory genes.** The immune response plays an important role in the inflammatory response in the development of occupational contact dermatitis. The latter can be influenced by genes that modulate skin inflammation. In this regard, when identifying genetic predisposition, the focus is made on the study of cytokine gene polymorphisms.

The TNF-α gene (tumor necrosis factor) encodes a multifunctional pro-inflammatory cytokine, is involved in protecting the body and cells from inflammation and apoptosis, and plays a vital role in maintaining immune homeostasis [31]. It has been proven that the TNF-α gene and its polymorphisms make a significant contribution to the development of skin diseases [31, 32].

In a Chinese study of dermatitis induced by occupational exposure to trichlorethylene, workers with the heterozygous TNF-α-308 genotype were found to have a lower risk of developing dermatitis compared with those with the homozygous genotype (OR = 0.398; 95 % CI: 0.164–0.967) [33]. This finding indicates possible contribution of the TNF-α-308 gene polymorphism to the pathogenesis of dermatitis related to trichlorethylene exposure and the protective role of the heterozygous genotype. However, the study of exposure to chromate in construction workers, on the contrary, showed that carriers of the TNF-α-308 heterozygous genotype had increased risk of chromate sensitization compared to carriers of the homozygous GG genotype (OR = 3.9; 95 % CI: 1.1–13.2) [24]. A higher frequency of the A allele and carriage of homo- and heterozygous TNF-α-308 genotypes were found in patients with occupational ACD compared to the control group ($\chi^2$ = 8.75; $p < 0.005$) [9]. Another study on patients with low levels of occupational skin exposure to irritants showed that the A allele of the TNF-α-308 polymorphism was associated with an increased risk ($p = 0.024$) of developing chronic ICD and an increased prevalence of eczema [34]. However, another polymorphism, TNF-α-238, was not associated with the onset and development of chronic ICD.

The incidence of dermatitis in people carrying the TNF-α-308 polymorphic variant (OR = 1.33; 95 % CI: 1.05–1.74) was confirmed in another study of 478 cases of the occupational disease working in healthcare, metallurgy, and cosmetology. In the same work, the researchers also found that carriers of the TNF-α-238 polymorphic variant are less likely to suffer from ICD (OR = 0.57; 95 % CI: 0.34–0.97), which indicates the protective effect of the A allele [35]. The association of the A allele with dermatitis was demonstrated in the study of medical personnel. Healthcare workers diagnosed with chronic ICD and carriers of the TNF-α-308 A allele were noted for increased susceptibility to skin irritation, poor response to treatment, and slow recovery [36].

Interleukins are a major subclass of cytokines that plays a central role in immune responses and inflammatory processes. Genes and polymorphisms of various interleukins are associated with predisposition to diseases and affect individual susceptibility to allergens and irritants [37–39].

Findings of the study of ACD in Bashkortostan demonstrated the contribution of the rs3939286 polymorphism of the IL33 gene to the development of this pathology. Carriage of the T allele accounted for a 1.5-fold increase in the risk of ACD ($\chi^2$ = 4.48; OR = 1.56; $p$ = 0.03) [39]. In another work, the same team of scientists established the effect of the rs2069812 polymorphism of the IL5 gene on the development of occupational allergic dermatitis; the frequency of the T allele was higher in the group of patients compared to the controls (43.0 % against 32.5 %; $\chi^2$ = 4.223; $p$ = 0.04) [40].

The analysis of the relationship between the rs4778889 polymorphism of the IL16 gene and the diagnosis of ACD among Egyptian construction workers revealed a tendency to carry CC/CT genotypes and the C allele in cases compared to controls ($p$ = 0.08). This study also demonstrated a high incidence of CC/CT genotypes in patients responding to formaldehyde exposure ($p < 0.05$) [41].

When an irritant comes in contact with skin, it provokes the release of IL1A in the stratum corneum at the first stage of the inflammatory process. In this regard, the IL1A-889 polymorphism (rs1800587) was examined as a risk factor for the occurrence of occupational ICD among patients working in different industries. The results showed a potential protective effect of the T allele against ICD ($p$ = 0.06) [42].

Kuzmina et al [9] demonstrated a statistically significant increase in the frequency of carriage of cytokine gene polymorphisms IL4 C589T ($\chi^2$ = 19.29; $p < 0.001$), IL10 C819T ($\chi^2$ = 21.04; $p < 0.001$), and IL10 G1082A ($\chi^2$ = 26.05; $p < 0.001$) in workers diagnosed with occupational ACD. In addition, they found that in 80 % of cases, carriage of the AA homozygous genotype of the IL10 gene contributes to early manifestation of the disease after the first exposure to an occupational risk factor.

The analysis of the relationship between polymorphisms in the IL-1Ra and IL4 genes (rs2234663 and rs79071878, respectively) and dermatitis related to occupational exposure to metal alloys based on methyl methacrylate demonstrated a statistically significant difference between the case and control groups in the severity of dermatitis symptoms [43]. Despite the accumulated data on the influence of interleukin polymorphisms on the development of occupational contact dermatitis, there are also studies that refute this relationship [24, 33, 34].

The human leukocyte antigen (HLA) genes play an important role in regulating the immune system. They are characterized by a high degree of allelic polymorphism. There is published evidence of the association between HLA variants and allergic and autoimmune diseases, including dermatitis and hypersensitivity to chemicals [44]. The

study on Chinese workers exposed to trichlorethylene demonstrated the risk of developing TCE-induced hypersensitivity dermatitis in the subjects with the HLA-B*1301 allele (OR = 27.5; 95 % CI: 13.5–55.7) [5]. This allele, however, is present only in the Asian population and cannot be therefore considered a specific biomarker for the working population as a whole.

In addition, by sequencing 1,074 SNPs in 188 genes in US medical personnel, the researchers established the association between several more gene polymorphisms and predisposition to ICD. Yucesoy et al. [45] showed that polymorphisms in the EGF (rs10029654), EGFR (rs12718939), CXCL12 (rs197452), and VCAM1 (rs3917018) genes were associated with hand dermatitis in health care workers [45]. The members of the epidermal growth factor (EGF) family are involved in cutaneous immune/inflammatory responses, and EGFR is a transmembrane tyrosine kinase receptor involved in cell proliferation and keratinocyte differentiation [46, 47]. VCAM1 is an adhesion molecule that also plays a role in skin inflammatory responses [48]. In addition, Yucesoy et al. [45] established links between gene polymorphisms and skin reactions to various stimuli: the ACACB SNPs (rs2268387, rs16934132 and rs2284685) showed association with response to low and high levels of sodium lauryl sulfate, the IL-22 rs1179251 SNP was associated with skin response to 1 % NaOH, and the PLAU rs2227564 and rs6593202 SNPs were associated with skin responses to medium and high levels of NaOH, respectively.

**Conclusions.** The studies of individual predisposition to developing occupational contact dermatitis have focused on three main groups of genetic polymorphisms associated with 1) the skin barrier function; 2) inflammation and immune response, and 3) biotransformation of xenobiotics, with the latter considered in the development of occupational ACD. The focus is made on polymorphisms of the FLG and TNF-α genes as possible predictors of disease development. Despite proven links between polymorphisms and occupational contact dermatitis, the accumulated data are still insufficient to use genetic polymorphisms as risk factors for occupational skin conditions. It is important to take into account sex, age, and ethnicity of workers under consideration, the frequency of polymorphism in this population, as well as the chemical inducing occupational contact dermatitis, its form and concentration for the high predictive value of the identified genetic promoter of the pathology. In this regard, further research is needed to confirm already known and establish new genetic predictors of occupational contact dermatitis. In the future, these data will enable identification of the genetic predisposition of workers at the pre-employment stage for further assessment of the individual risk and timely prevention of occupational skin diseases.

A complex mechanism of interaction between different genes is involved in the formation and development of occupational contact dermatitis; this particular approach might help identify workers at risk based on genetic predisposition with a sufficient degree of probability and provide them with the necessary preventive and preclinical care.

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