Genetic Identification of Individuals with Increased Risk of Developing Occupational Skin Diseases

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Abstract

Our understanding of the complex genetic susceptibility to occupational contact dermatitis (OCD) is still in the early stage. The search for candidate susceptibility genes focused mainly on proteins involved in skin barrier and immune response which have a key role in both irritant and allergic contact dermatitis (respectively, ICD and ACD). Furthermore, for ACD genetic variations in enzymes involved in metabolism of contact allergens have been investigated. Among skin barrier genes, loss-of-function mutations in the filaggrin gene (*FLG*) have been identified as a risk factor for irritant contact dermatitis (ICD); the risk-modifying effect of *FLG* mutations was stronger in the presence of atopic dermatitis. In ACD, the impact of *FLG* mutations was allergen specific and dependent on the outcome measure and the exposure pattern. Several studies reported association of genetic polymorphisms in the metabolizing enzymes N-acetyltransferase and glutathione S-transferase with ACD; however the results are so far inconclusive. Among inflammatory genes, there appears to be an effect of *TNF*

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gene polymorphisms on susceptibility to both irritant and allergic CD, suggesting that they share some common pathways.

At present, the predictive value of genetic markers for the appearance of OCD is too low for reasonable identification of susceptible individuals in occupational health practice.

Further well-designed studies in larger cohorts with a well-defined disease phenotype and external exposure in the control as well as in the case group are needed to confirm and extend our knowledge of the impact of genetic variations on the susceptibility to OCD.

Keywords

Allergic contact dermatitis · Irritant contact dermatitis · Genetic susceptibilty · Occupational

1 Core Messages

- Our understanding of the complex genetic susceptibility to occupational contact dermatitis (OCD) is still in the early stage.
- Loss-of-function mutations in the filaggrin gene have been identified as a risk factor for irritant contact dermatitis (ICD), while data for allergic contact dermatitis (ACD) are less conclusive. Individuals with concomitant AD and *FLG* mutations have the highest risk of OCD.
- Among inflammatory genes, there appears to be a risk-modifying effect of *TNF* gene mutations on susceptibility to both irritant and allergic CD, suggesting that they share some common pathways.
- At present, the predictive value of genetic markers for the appearance of OCD is too low for reasonable identification of susceptible individuals in occupational health practice.
- Further well-designed studies in larger cohorts with a well-defined disease phenotype and external exposure are needed to confirm and extend our knowledge of the impact of genetic variations on the susceptibility to OCD.

2 Introduction

Skin diseases, mainly irritant and allergic contact dermatitis (respectively, ICD and ACD), are one of the most common work-related disorders (Belsito 2005; Diepgen and Kanerva 2006). In the occupational situation, CD tends to become chronic, often resulting in impaired quality of life and loss of work ability. Given its substantial prevalence in the workplace, particularly in high-risk professions, there is a pressing need to better understand underlying disease mechanisms and factors which predispose individuals to develop occupational contact dermatitis (OCD). Knowledge of the genetic factors which might modify the risk to OCD would lend more insight into the mechanisms which underlie its development. Furthermore, identifying of susceptible individuals might be useful in occupational health practice for the application of preventive measures and for career guidance for apprentices and workers in high-risk occupations.

The mechanisms underlying development of OCD and factors that predispose individuals to this skin disease are only partially understood. One of few, if not the only established predisposing factor for OCD, is having a history of atopic dermatitis (AD). Since genetic predisposition is a fundamental factor governing susceptibility to AD, it is likely that genetics also plays an important role in individual susceptibility to OCD.

While it is likely that many genes are involved in the pathogenesis of CD, historically the studies on genetic susceptibility to CD focused mainly on the variations in the genes involved in inflammatory response, in particular of the cytokine genes. Specifically for ACD, several studies investigated the role of polymorphisms in the genes responsible for the biotransformation of contact allergens and oxidative stress. Recent identification of loss-of-function mutations in the gene encoding epidermal structural protein filaggrin (*FLG*) as a major risk factor for AD has shifted the focus toward genes which are involved in the skin

barrier maintenance. The results of several recent genetic association studies have been summarized separately for ICD and ACD.

3 Genetic Susceptibility to ICD

3.1 Skin Barrier Genes

Inflammatory response in ICD is dose dependent; thus, it is plausible that the condition of the skin barrier may influence the amount of a skin-irritating substance that penetrates into the skin and consequently the individual susceptibility to ICD (English 2004; Fluhr et al. 2008). Defects in skin barrier can occur by a combination of factors, including a deficiency of skin barrier proteins, alteration in the composition and organization of the stratum corneum lipids, altered protease activity, and the lack of certain protease inhibitors (Proksch et al. 2008). So far, studies on the role of the skin barrier genes for the development of ICD have been focused on the loss-of-function mutations in the gene encoding for an epidermal protein, filaggrin. Filaggrin is thought to have an important role in the maintenance of the skin barrier and cutaneous hydration, although there may be other nonstructural functions of filaggrin yet to be defined (Thyssen and Kezic 2014). Loss-of-function mutations in the filaggrin gene (*FLG*) were identified in a large number of clinical studies as a major predisposing factor for atopic dermatitis (AD) (Weidinger and Novak 2016). In a case-control study, it has been found that individuals with loss-of-function mutations in the *FLG* gene have approximately two times higher risk to acquire chronic ICD (de Jongh et al. 2008a). Consistently, Timmerman et al. (2016) found that *FLG* mutations were more frequent in construction workers with contact dermatitis (89% were diagnosed as ICD). As *FLG* mutations are associated with AD, known as a strong risk factor for ICD, Visser et al. (2013, 2014) investigated the contribution and interaction of *FLG* mutations and AD in a case-control study and in a prospective cohort study in apprentice nurses. When adjusting for the history of AD, carriers of *FLG* mutations showed an increase in the risk for ICD in the case-control study (OR = 1.6; 95% CI 1.33–2.58) but not in a prospective cohort study. However, both studies of Visser et al. (2013, 2014) demonstrate that individuals with concomitant AD and *FLG* mutations have the highest risk of occupational CD. Next to a strong risk-modifying effect, *FLG* mutations were also shown to contribute to a particular subtype of chronic hand eczema which is characterized by a combination of ICD and ACD (Molin et al. 2009). Furthermore, individuals with excessive daily exposure to water or irritants who were carriers of *FLG* mutations had higher risk to develop chronic hand eczema than the individuals lacking these mutations. Interestingly, *FLG* mutations not only predispose for ICD but also influence the clinical course in ICD (Landeck et al. 2012b). Although the mechanisms by which *FLG* mutations modify the risk for ICD remain to be delineated, these findings provide evidence for the important role of an intact skin barrier in protecting against development of OCD (Kezic and Jakasa 2016). The role of other genes involved in the maintenance of the skin barrier still remains to be delineated.

3.2 Inflammatory Genes

Cytokines and chemokines which regulate immune response play an essential role in skin inflammation in ICD (Pastore et al. 2004; Esser and Martin 2017). One may assume therefore that the factors which influence the cutaneous levels of various cytokines, for example, due to functional polymorphisms in the cytokine genes, will modify individual risk for inflammation. De Jongh et al. (2008b) investigated in a case-control study whether polymorphisms in cytokine genes contribute to the occurrence of occupational chronic irritant contact dermatitis (CICD). Nine polymorphisms in the genes encoding pro-inflammatory cytokines interleukin (IL)-1 α, IL-1β, IL-8, and tumor necrosis factor (TNF) (also referred to as TNF-α) and of anti-inflammatory cytokine IL-10

were determined in the CICD and in the apprentices who served as controls. The results showed that these polymorphisms were not a substantial risk factor of CICD. The same research group reinvestigated the role of *TNF* gene polymorphisms on the prevalence of ICD in a larger cohort of patients and controls (Landeck et al. 2012a). The study revealed that carriers of *TNFA-308A* allele were more prone to develop ICD. Furthermore, in the same study, it has been shown that carriers of *TNFA-238A* allele have a lower risk to ICD. The risk-modifying effect of *TNF* gene polymorphism is consistent with the findings from an experimental irritation study showing lower irritation threshold to model irritants sodium lauryl sulfate and benzalkonium chloride in carriers of the variant *TNFA-308A* allele (Allen et al. 2000). Since *TNFA-308A* allele is associated with enhanced TNF production, this may indicate that higher cutaneous levels of TNF increase risk for CICD (Wilson et al. 1997). In the case-control study of Landeck et al. (2013), a trend of protective effect of *IL1A-889T* allele has been found (OR = 0.81; 95% CI: 0.65–1.00). Interestingly, carriers of a variant *IL1A-889T* allele had a reduced amount of IL-1α in their stratum corneum (de Jongh et al. 2008c). The release of IL-1α which is constitutively present in the SC is the first step in the inflammatory cascade (Fluhr et al. 2008; Elias and Schmuth 2009). The results from the studies of de Jongh et al. (2008b, c) and Landeck et al. (2013) suggest that lower levels of IL-1α in the SC due to genetic polymorphism in the *IL1A* gene have a protective effect in development of CICD.

4 Genetic Susceptibility to ACD

Several candidate genes have been studied because of their putative roles in the etiology of ACD. Most studies have focused on the genes that are involved in the pathways that influence individual immune response, skin barrier, or metabolic activation of prohaptens into immunogenic species (biotransformation genes). In addition to a limited number of studies in this research field, comparison of different studies is hampered by different definitions of ACD phenotype. Next to commonly used end points such as sensitization and ACD, some scientists proposed polysensitization (sensitization to three or more unrelated allergens) to contact allergens as a feasible phenomenon for studying effects of genetic susceptibility to ACD (Schnuch et al. 2011; Friedmann et al. 2015).

4.1 Skin Barrier Genes

While *FLG* mutations have consistently been identified as a risk factor for ICD, the association between *FLG* mutations and occurrence of ACD is less obvious (Brown and Cordell 2008). So far, a significant association between *FLG* mutations and contact sensitization to a specific contact allergen could not be identified (Lerbaek et al. 2007; Novak et al. 2008; Thyssen et al. 2010; Landeck et al. 2014). Nevertheless, *FLG* mutations seemed to increase risk for nickel sensitization and nickel ACD in specific exposure scenarios and subgroups. In a cross-sectional study, Novak et al. (2008) observed a significant association with nickel sensitization in combination with self-reported intolerance to fashion jewelry. Furthermore, in a general population study, Thyssen et al. (2010) identified a positive association between *FLG* mutations and nickel sensitization and nickel ACD but only in a subgroup of women who did not have ear piercing. These findings have been explained by reduced levels of filaggrin protein in the skin of the carriers of *FLG* mutations. As filaggrin is the main source of histidine in the skin, which is a strong nickel-chelating agent, reduced levels of filaggrin lead to enhanced penetration of nickel into the viable epidermis. In the individuals with ear piercing, chelation of nickel to filaggrin in the SC is bypassed, and the effect of *FLG* mutations might not have been detected.

In addition to filaggrin, several other proteins of the stratum corneum have been investigated for their possible role in susceptibility to ACD. The polymorphisms in the genes encoding for the proteins of the late cornified envelope (LCE) have previously been shown as a risk factor for psoriasis (de Cid et al. 2009).The combined deletions in

genes encoding late cornified envelope (*LCE3C_LCE3B*) showed a risk-modifying effect for ACD, and this effect was independent of external irritant damage or atopic dermatitis (Molin et al. 2011). These results have, however, been obtained in a small group of patients and controls and should be further investigated with larger study population (Molin et al. 2011). Next to the SC structural proteins, Ross-Hansen et al. (2013) studied genetic variations in the claudin-1 gene and risk for ACD. Claudin is an important protein of tight junctions contributing to the skin barrier function. The results showed a significant association of three *CLDN1 SNPs* with, respectively, nickel sensitization in individuals without ear piercings, contact sensitization to fragrances, and both organic compounds and nickel contact dermatitis.

4.2 Inflammatory Genes

Research on the risk-modifying effect of genes involved in inflammation have primarily focused on the cytokines which mediate a broad spectrum of immune response. One of the most investigated cytokine genes in this respect is the gene encoding TNF, in particular single-nucleotide polymorphisms *TNF-308G>A* and *TNF-238G>A*. The *TNFA-308A* allele has been shown to increase the risk for sensitization to the hair-dye component paraphenylenediamine (Blömeke et al. 2009a) and to chromate in cement workers (Wang et al. 2007). However, there was no difference in the distribution of *TNF-308* G/A genotypes between patients with nickel allergy and healthy controls (Colagiovanni et al. 2016). There was only one study that reported a promoting effect of *TNFA-308G* allele for ACD (Ertam et al. 2009). In the study of Westphal et al. (2003), the *TNFA-308 A* allele tended to be more prevalent in polysensitized patients, defined in that study as sensitization to para-substituted aryl compounds and at least one other structurally unrelated allergen. However, when investigating polysensitization to unrelated compounds, there was no significant difference in TNFA-308 between polysensitized patients and controls (Westphal et al. 2016). Enhanced risk for polysensitization, as compared to controls and/or monosensitized individuals, has been found for CXCL11*A/A genotype (Westphal et al. 2016) and a polymorphism in the gene encoding IL-16 (*IL16-295 *C/C*) (Reich et al. 2003).

4.3 Biotransformation Genes

Many contact allergens need metabolic activation in the skin to become immunogenic; however, for some contact allergens, metabolism represents a detoxification pathway. As both sensitization and elicitation are dose dependent, it is obvious that the activity in the biotransformation enzymes may confer individual susceptibility to ACD (Kimber et al. 2002; Koppes et al. 2017). Most of the existing studies on biotransformation enzymes have investigated the role of polymorphisms in N-acetyltransferase gene (NAT) in sensitization to p-phenylenediamine (PPD) and para-substituted aryl compounds. Variations in the NAT gene have been shown to cause differences in N-acetyltransferase 1 (NAT1) and N-acetyltransferase 2 (NAT2) protein levels and are associated with either a slow or rapid N-acetylation activity (Schnuch et al. 2011). NAT2 rapid acetylators were overrepresented in individuals positively patched for para-substituted arylamine as compared to the controls, while the slow acetylators phenotype with *NAT2*5b/2*6a* genotype showed an opposite pattern (Westphal et al. 2000a). An increased risk of ACD due to "rapid" NAT2 polymorphism has also been reported in studies of Nacak et al. (2006) and Najim et al. (2005). In contrast, a study of Blömeke et al. (2009b) could not confirm an increased risk for PPD-induced contact allergy due to acetylator status. Differences in study design, inadequate statistical power, and reported linkage disequilibrium between NAT2 *4 and NAT1 *10 might at least partly explain inconsistency in the findings reported in different studies (Westphal et al. 2000; Schnuch et al. 2011). Several studies have investigated the role of polymorphisms in the gene encoding for glutathione S-transferases (GSTs), a large family of conjugating enzymes which are critical in modulating

inflammatory processes and the detoxification of a wide range of reactive oxygen species. Deletion polymorphisms in two GST members, M1 and T1, are common in general population with major ethnic differences (Bolt and Thier 2006). Westphal et al. (2000b) reported a risk-modifying effect of *GSTM1* and *GSTT1* null genotypes in patients sensitized to mercury compounds. In a study conducted in the workers in cement industry, *GSTT1*0* was more frequent in chrome-sensitized workers as compared to non-sensitized workers; however there was no risk-modifying effect of GSTM1*0 (Wang et al. 2007). However, in a meta-analysis, a risk-modifying role of *GST* polymorphisms could not be confirmed in sensitization to PPD, chromate or thimerosal (Pot et al. 2011) or nickel and various organic contact sensitizers (Ross-Hansen et al. 2013). Another biotransformation enzyme that is involved in oxidative stress and was investigated in relation to individual susceptibility to ACD is manganese superoxide dismutase (MnSOD). Brans et al. (2005) investigated the association between two polymorphisms (*Ala9Val and Ile58Thr*) in the gene encoding MnSOD and the risk for sensitization to PPD. MnSOD is involved in the scavenging of potentially harmful oxidizing species and might play a role in the pre-immunological phase during the induction of ACD. The authors concluded from their data that the investigated polymorphisms had no strong impact on individual susceptibility to developing a sensitization to PPD.

5 Conclusion

Although several studies have reported several biologically plausible susceptibility genes, at present the genetic basis of increased susceptibility to OCD is largely unknown. The most important recent development is the well-established evidence that *FLG* loss-of-function mutations increase the risk for ICD and in certain subgroups and exposure patterns for Ni sensitization and Ni-induced ACD. These findings underscore the importance of the skin barrier in the pathogenesis of both ICD and ACD. This is further supported by studies in ACD showing a risk-modifying effects of genes for proteins involved in the skin barrier function such as claudin and the proteins of the late cornified envelope. Among the inflammatory genes, there appears to be a risk-enhancing effect of *TNFA-308A* allele on susceptibility to both ICD and ACD, suggesting that they share some common pathways. Less evidence is available regarding the protective effect of the *IL1A-889T* allele toward ICD and of the precipitating effect of the variants *IL16-295*C/C* and CXCL11*A/A genotype toward polysensitization; therefore, replication of these findings is needed to confirm these associations.

The effect of the polymorphisms in the biotransformation genes for the risk of ACD has been demonstrated for various contact allergens; however the reported findings have been conflicting. In general, the risk-modifying effect of the polymorphisms in the biotransformation genes is likely to be more substance specific than, for example, inflammatory or skin barrier genes.

In conclusion, our understanding of the complex genetic susceptibility to OCD is still in the early stage, and with exception of clear risk-enhancing effect of *FLG* mutations on ICD, there are no other genetic biomarkers that might be useful in identifying of susceptible individuals, e.g., for pre-employment guidance and consultation in occupational health practice. Given the complexity of the molecular mechanisms underlying development of ICD and ACD, it is not likely that the studies of isolated genes will be sufficient to provide genetic markers of sufficient predictive power. Further well-designed studies in larger cohorts with a well-defined phenotype and external exposure and choice of appropriate control group are needed to confirm and extend our knowledge of the impact of genetic variations on the susceptibility to OCD.

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