

Nickel Sensitization, Hand Eczema, and Loss-of-Function Mutations in the Filaggrin Gene

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Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease. Recently, it was demonstrated that a large proportion of individuals with AD have an epidermal expression deficiency of filaggrin (FLG). This unique finding may have great implications for our understanding of nickel sensitization because nickel is chelated in the epidermis and perhaps to FLG. This review aims to briefly present the current knowledge about nickel sensitization in relation to FLG deficiency and speculate on its possible implications. The new knowledge concerning loss-of-function mutations in the *FLG* gene (the lack of specific nickel-chelating power in the stratum corneum and a generally defective skin barrier) suggests that an additive effect from irritants and nickel may aggravate hand eczema in individuals with loss-of-function mutations in the *FLG* gene. This hypothesis calls for a reevaluation of the potential risk of nickel sensitization through the establishment of cohorts with and without such mutations.

NICKEL SENSITIZATION is frequent in the western hemisphere.¹ Exposure to nickel-releasing items such as buttons,² earrings,^{3,4} tools,⁵ and cell phones⁶ is a known risk factor. The most important factor for the induction and elicitation of nickel sensitization is the amount of nickel per skin unit area present in the epidermis⁷ although area size also matters.⁸ Furthermore, corrosion caused by human sweat on nickel-plated surfaces and alloys may release free nickel ions.^{9,10} A recent review summarized published studies evaluating genetic factors in the development of allergic nickel dermatitis¹¹; however, no definite conclusions could be reached.

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that often develops during the first year of life. The prevalence of AD varies widely between different populations but appears to be increasing.¹² The exact pathomechanisms of AD remain to be fully elucidated, but it is believed that both genetic and environmental factors are causative. Recently, it was demonstrated that a large proportion of individuals with AD had an epidermal expression deficiency of filaggrin (FLG).¹³ This unique finding may have great implications

for our understanding of nickel sensitization because nickel is chelated in the epidermis¹⁴ and perhaps to FLG. Thus, it is probable that we need to rethink the relative potency of nickel as a contact allergen depending on the presence or absence of loss-of-function mutations in the profilaggrin gene (*FLG* gene). The aims of this review are to (1) briefly present the current knowledge about nickel sensitization in relation to FLG deficiency and (2) speculate on its implications.

The Profilaggrin Gene and Its Functions

FLG, a highly phosphorylated histidine-rich polypeptide, is the processed product of the *FLG* gene.¹⁵ The *FLG* gene is located on human chromosome 1q21, which contains the human epidermal differentiation complex.¹⁶ FLG aggregates keratin filaments and is a crucial component of the terminal differentiation of the epidermis. It prevents epidermal water loss and also impedes the entry of microorganisms, allergens, and chemicals.¹⁷ Loss of FLG expression may lead to deficiencies in the terminal formation of the stratum corneum and disrupt skin barrier function. Furthermore, FLG acts as a source of hygroscopic amino acids and their derivatives, known as natural moisturizing factors (NMFs).¹⁸ Loss-of-function mutations in the *FLG* gene may therefore lead to a reduced level of NMFs in the stratum corneum and consequent dryness of the skin.¹⁸

So far, two heritable diseases have been linked to loss-of-function mutations in the *FLG* gene: ichthyosis

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vulgaris¹⁹ and AD.¹³ A total of 22 known mutations in the *FLG* gene have been documented so far.²⁰ The two most frequent loss-of-function mutations are R501X and 2282del4, which lead to a deficiency of FLG in the upper part of the epidermis.¹⁵ It is estimated that approximately 10% of the general population have loss-of-function mutations in the *FLG* gene and that heterozygote carriers have a three-times elevated risk of AD in comparison to individuals without mutations.^{13,15} Among individuals with AD, the frequency of these mutations is between 17 and 50%.^{13,20–23} Early onset of AD and persistence into adulthood seem to be closely associated with these mutations.²⁴ *FLG* mutations are also associated with atopic diseases such as asthma and allergic rhinitis in combination with AD.^{20,25} The knowledge of the *FLG* gene will most likely revolutionize how we classify, diagnose, and evaluate AD. However, the disease entity remains extremely complex, and there are other possible candidate genes and several causative environmental factors.

Nickel Sensitization and Loss-of-Function Mutations in the Profilaggrin Gene

Recently, Novak and colleagues confirmed the association between *FLG* gene mutations and AD but also identified an association between loss-of-function mutations in the *FLG* gene and dry skin, nickel sensitization, and nickel sensitization combined with an intolerance to costume jewelry.²⁶ Surprisingly, these findings could not be replicated with other contact allergens although the prevalence of contact allergy to fragrance mix (15.9%) was higher than the prevalence of nickel allergy (13.1%).²⁶ Hence, Novak and colleagues speculated that hyperreactivity to contact allergens could be explained by either genetic predisposition (eg, in regard to nickel) or environmental exposure.²⁶ Furthermore, they speculated on whether *FLG* deficiency increases the amount of nickel in the epidermis and predisposes the patient to nickel sensitization. However, we believe that the increased risk of nickel allergy is explained by a more rapid transport of nickel through the epidermis rather than by a build-up of nickel. As we will describe, this hypothesis is based on past research results as well as the metal-chelating abilities of FLG.

Chelation of Nickel to Filaggrin

FLG gene mutations may be important confounders of our understanding of nickel sensitization because it is likely that *FLG* gene mutations lead to specific changes in the accumulation and metabolism of nickel in the skin. FLG is

a highly phosphorylated histidine-rich polypeptide that is gradually cleaved by proteolytic enzymes in the stratum corneum.¹⁵ Previous studies have established that nickel is accumulated in the stratum corneum and that only minor amounts are found in the lower layer of epidermis.^{14,27} More than 90% of the available nickel is in a bound state.¹⁴ Fullerton and colleagues hypothesized that a local reservoir of nickel was gradually built up in the epidermis and that, when the binding capacity was saturated, nickel ions were free to permeate the skin.^{14,27} However, the permeation of nickel ions also depends on the oxidizing capacity of sweat.²⁸ Histidine and histidine-rich polypeptides have been shown to be strong nickel-chelating agents. It is therefore likely that the accumulation of nickel in the upper part of the stratum corneum is caused by FLG and other histidine-rich polypeptides in this layer. Thus, we speculate that individuals with loss-of-function mutations in the *FLG* gene may have a completely different level of nickel absorption through the skin. Nickel may permeate the epidermis more rapidly (due to the lack of FLG) and lead to sensitization.

Nickel Sensitization and Atopic Dermatitis

The association between nickel sensitization and AD is controversial.^{29–34} Patch-test results may be difficult to interpret because papulopustular reactions occur in response to nickel sulfate in some patients with AD.³² Furthermore, patients with AD may also develop severe irritant reactions when tested with nickel sulfate 5%.³⁵ We hypothesize that these reactions may occur because of extreme nickel absorption through the epidermis in individuals with loss-of-function mutations in the *FLG* gene. Furthermore, it has been proposed that a down-regulation of cell-mediated immune responses may occur in patients with AD.^{7,36,37} In a population-based study, no association was identified between contact sensitization and elevated serum immunoglobulin E (IgE).³⁸ As 20 to 30% of individuals with AD exhibit normal serum IgE levels, this finding does not definitively exclude an association between AD and, for example, nickel sensitization.³⁹ In conclusion, no past studies have convincingly presented evidence of an association or dissociation between nickel sensitization and AD. Perhaps future studies may show that subpopulations with loss-of-function mutations in the *FLG* gene have greater prevalences of nickel sensitization than subpopulations without these mutations.

Nickel Sensitization and Genetic Studies

Fleming and colleagues identified an increased familial disposition (risk ratio, 2.83) to develop nickel sensitization

among first-degree relatives of probands with nickel allergy.⁴⁰ They concluded that the risk ratio was low compared to, for example, that for insulin-dependent diabetes but did not reflect more on this finding. We speculate that a significant proportion of nickel-sensitized families had loss-of-function mutations in the *FLG* gene. Such familial clustering supports the evidence for a genetic basis of nickel sensitization. Furthermore, an early Danish twin study demonstrated that nickel sensitization could be influenced by genetic factors because nickel sensitization was apparently more common in monozygotic than dizygotic twins.⁴¹ However, a recent twin study showed that nickel sensitization is mainly explained by environmental factors and only to a lesser degree by genetic factors.⁴² These contradictory results may be explained by different routes of exposure. In the study by Bryld and colleagues, the majority of twins had been sensitized by ear piercing.⁴² Due to perforation of the earlobe, the route of nickel exposure was independent of nickel-chelating proteins (such as *FLG*) in the stratum corneum. Thus, an effect from loss-of-function mutations in the *FLG* gene was “bypassed,” and nickel was exposed directly to Langerhans’ cells in the lower epidermis. In the study by Menné and colleagues, the primary nickel exposure was related to suspenders; hence, nickel did not “bypass” the *FLG* system.⁴¹ Thus, an analysis of loss-of-function mutations may have altered the outcomes of such studies.

Nickel Sensitization, Loss-of-Function Mutations, and Hand Eczema

Whether nickel sensitization is a risk factor for hand eczema has repeatedly been discussed.^{1,10,43–53} Menné and colleagues identified an increased risk of developing hand eczema among women with nickel sensitization, but they also demonstrated that women with hand eczema had an increased risk of developing nickel sensitization.⁴⁶ It is possible that a significant proportion of these individuals had loss-of-function mutations in the *FLG* gene. Hence, they were at the same time at risk of developing nickel sensitization as well as hand eczema. If this is true, loss-of-function mutations were important confounders in this study.

Although no general consensus has been reached about the association between hand eczema and nickel sensitization, occupational exposure to high concentrations of nickel undoubtedly leads to hand eczema. In addition, systemic nickel exposure may lead to vesicular hand eczema.⁵⁴ In a double-blind placebo-controlled study,

Nielsen and colleagues established that repeated non-occlusive skin exposure to very low nickel concentrations was clinically relevant among patients with nickel allergy and hand eczema.⁵⁵ Finally, studies have indicated that the prognosis of hand eczema can be improved if metal-skin contact is strongly limited in nickel-sensitized patients.^{56,57}

AD is a well-established risk factor for hand eczema.⁴³ Surprisingly, Lerbaek and colleagues established that the inheritance of hand eczema was not only explained by comorbidity with AD.⁵⁸ A new investigation indicated that hand eczema was associated with *FLG* gene mutations in patients with AD (although this was not significant).²¹ Furthermore, Lerbaek and colleagues found that 5 of 29 patients with nickel allergy had loss-of-function mutations in the *FLG* gene (A. Lerbaek, personal communication, April, 2008). These near-significant findings are likely caused by a lack of statistical power; thus, future studies should be performed with larger study groups. Finally, de Jongh and colleagues examined whether chronic irritative hand eczema was associated with *FLG* mutations.⁵⁹ Among 206 patients and 217 controls, no difference was identified.

Perspectives

The new knowledge concerning loss-of-function mutations in the *FLG* gene (the lack of specific nickel-chelating

Table 1. Proposed Studies on the Role of Loss-of-Function Mutations of the Filaggrin Gene in Nickel Allergic Contact Dermatitis and Hand Eczema

Suggested study populations
• Individuals from the general population ²⁶
• Twins (unselected and with dermatitis) ²¹
• Consecutive dermatitis patients
• Atopic dermatitis patients
• Hand eczema patients (both allergic ²¹ and irritant ⁵⁹)
• Polysensitized dermatitis patients
• Occupational dermatitis patients
Suggested studies in individuals with and without filaggrin gene deficiency
• Nickel absorption rate (transdermal and transmucosal)
• Genetic expressions to irritants and/or contact allergens
• Function of Langerhans’ cells in the epidermis (quantitative and qualitative differences possible)
• Cytokine and T-cell responses to irritants and/or contact allergens
• Skin lipid changes
• Histologic changes to irritants and/or contact allergens
• Dose-response patch testing

power in the stratum corneum and a general defect skin barrier) suggests that an additive effect from irritants and nickel may aggravate hand eczema in individuals with loss-of-function mutations in the *FLG* gene. This hypothesis calls for a reevaluation of the potential risk of nickel sensitization through the establishment of cohorts with and without such mutations (Table 1). An investigation of the nickel-binding capacity of the stratum corneum in these cohorts will be of major interest, as will dose-response studies of individuals with and without loss-of-function mutations in the *FLG* gene. A knowledge of the effect of nickel exposure on individuals with and without these mutations is crucial for the understanding of nickel dermatitis. The accumulation of such new knowledge may give us new insight into the etiology and prognosis of nickel dermatitis in patients with hand eczema and atopic dermatitis.

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