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CONTACT DERMATITIS

Review Article

Patients with multiple contact allergies: a review

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Patients with multiple contact allergies, also referred to as polysensitized, are more frequent than predicted from prevalence of single sensitivities. The understanding of why some people develop multiple contact allergies, and characterization of patients with multiple contact allergies is limited. This review presents the current knowledge on the topic and discusses the evidence and characteristics of an increased susceptibility factor, possible causes to and genetic markers for the increased susceptibility, composition of the patient group and identification of patients at risk of developing multiple contact allergies. Evidence of allergen clusters among polysensitized individuals is also reviewed. The literature supports the idea that patients with multiple contact allergies constitute a special entity within the field of contact allergy. There is no generally accepted definition of patients with multiple contact allergies. We suggest that contact allergy to 3 or more allergens are defined as multiple contact allergies.

Key words: individual susceptibility; multiple contact allergies; patch tests; polysensitization.

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Development of contact allergy is the result of interplay between environmental exposures and individual susceptibility, as only a fraction of individuals exposed get sensitized. Among these, some develop clinically manifest allergic contact dermatitis. Within the group of sensitized individuals, a subgroup exists of individuals with multiple allergies. They may also be designated polysensitized individuals. The understanding of why some patients develop multiple contact allergies is limited and mainly based on assumptions. It is generally believed that this group of patients constitutes the extreme end of the contact allergy spectrum with widespread, long-lasting, and hard-to-treat eczema. Treatment and prevention are not specifically directed at this patient subgroup and it is not possible today to identify patients at risk of developing multiple contact allergies. Furthermore, it is not known if patients with multiple contact allergies constitute a special entity within the field of allergic contact dermatitis, or if they represent the end of a continuum. Are these patients a result of high exposure to environmental allergens, or do they have a special susceptibility to develop contact allergy? If so, is the susceptibility because of a genetic disposition or a consequence of previously developed allergies?

It is not well established when a patient should be regarded as having multiple contact allergies. Some authors use 2 or more, others 3 or more, contact allergies as cut point. The lack of definition contributes to the uncertainty regarding patients with multiple contact allergies.

This review discusses the evidence of increased susceptibility, the prevalence, composition, and identification of patients with multiple contact allergies, and patterns of allergen combinations.

Prevalence of Polysensitized Patients in a General Population and in Eczema Populations

In populations of patients with suspected contact dermatitis in hospital-based dermatology clinics, the total sensitivity rate amounts to 28–37%, and patients with multiple contact allergies constitute 4–7% (1–4). Consequently, 1 out of every 6 to 7 patients sensitized has multiple allergies. The rate of patients with multiple contact allergies was stable over a 20-year period in 1 study (4). In a general population study, the total sensitivity rate was 15%, and the rate of patients with multiple contact allergies was 0.7% (5), which gives a rate of 1 out of every 21 with multiple allergies. Thus, the

rate of multiple allergies is much higher in eczema populations than in the general population. The observed overrepresentation in eczema populations might be related to chronic or recurrent severe eczema caused by multiple eliciting environmental allergens in combination with repeated exposures, or difficulty in identifying or avoiding eliciting allergens. These factors lead to a need for medical attention and also lead to repeated dermatology visits and repeated testing that often identifies new allergies.

Further, in the general population (5) and 1 eczema population study (1), multiple contact allergies were more frequent than predicted from the prevalence of single sensitivities indicating that patients with multiple contact allergies constitute a special entity and are not just random occurrences within the field of contact allergies.

Groups of Polysensitized Patients

The composition of patients with multiple contact allergies is unknown except from 4 out of 5 patients being women, and the rate of patients with multiple contact allergies increases with age (4). Polysensitized individuals are mainly described in case reports. Most of these reports include patients, who can be divided in 1 of 4 groups: patients exposed to topical drugs other than leg ulcer patients (6–8), patients with leg ulcers and exposures related to wound treatment (9–12), patients with work-related exposure (13–15), and patients with allergies to ubiquitous allergens and without specific exposure (16–18). Ubiquitous allergens are allergens, which the magnitude of the general population is exposed to. They are present in the common environment. Subdivision into 2 groups is possible: a group where the multiple contact allergies are the product of high environmental exposure to specific allergens and a group where high-risk exposure is not present.

Patients with high exposure to topical drugs, leg ulcer patients, and those with work-related exposure constitute the 1st subgroup. They have a long-lasting and intense exposure to certain compounds. It is not surprising that these patients develop multiple allergies. All individuals, exposed under extreme conditions, can get sensitized (19, 20). Patients with leg ulcer are exemplary as 63–80% get sensitized, and 51–57% get polysensitized (9–12). It is a reasonable assumption that massive environmental exposure is a major contributor to development of allergies and multiple allergies in these cases.

The second subgroup is constituted of patients with only a general base-line environmental exposure who acquire multiple contact allergies to more ubiquitous allergens. This group has no evidence of any extraordinary exposure. They seem to have a special ability to develop allergies as the broad range of the population is exposed to the same allergens but do not develop an allergy, less likely multiple allergies.

The classification of polysensitized individuals needs to be confirmed in other studies.

Susceptibility

The hypothesis has been put forward that patients with multiple contact allergies have an inherent increased susceptibility. In 1985, Moss et al. (1) compared the ability to get sensitized to dinitrochlorobenzene (DNCB) among 3 groups: patients with $\geq$3 contact allergies, mono-allergic patients, and healthy controls. Patients sensitized by occupational exposure to an allergen or with leg ulcers were excluded. With increasing induction dose, significantly more individuals got sensitized in all 3 groups. At an induction dose of 500 μg, 100% of the healthy controls were sensitized, while a dose of 250 μg sensitized all individuals with multiple contact allergies. At challenge, the degree of reaction increased for all 3 groups with increasing elicitation dose. The distance between the elicitation dose–response curves for each group remained parallel.

Moss et al. (1) concluded that patients with multiple contact allergies had an increased susceptibility towards developing contact allergies as they got sensitized more easily and to a greater extent than mono-allergic and healthy individuals. Furthermore, this propensity lied in the induction phase as the amplification of the induction dose–response curve was much steeper for the multiple-allergic individuals than mono-allergic and healthy controls, while the elicitation dose–response curve increased parallel for all 3 groups with increasing elicitation dose.

Further, it is seen that patients with multiple contact allergies had greater elicitation responses to DNCB at every eliciting dose than mono-allergic patients and healthy controls, suggesting a tendency to develop more severe clinical manifestations in individuals with multiple contact allergies.

Susceptibility – a Graded Phenomenon

The increased susceptibility of multiple-allergic patients seems to be a graded phenomenon. The mono-allergic individuals in the study of Moss et al. (1) expressed intermediate values in both induction and elicitation implying a graded susceptibility. In the same study, the ratio of

observed versus predicted prevalence of combination of allergies was calculated as a measure of relative susceptibility. The ratio increased with rarity and number of the combinations of allergies. A comparison of the ratio with the response to DNCB showed, that the greater the ratio, the greater the relative susceptibility, the greater was the response to DNCB. The gradient suggests different degrees of susceptibility not only between patients with no allergies, with mono/double allergies and with multiple allergies, but also within the group of patients with multiple contact allergies. The number of allergies may perhaps be regarded as an indirect expression of the degree of inherent susceptibility.

Possible Causes to Increased Susceptibility

Environmental exposure is a necessary and the most important factor in development of allergies and multiple contact allergies. Intense exposure situations such as leg ulcer treatment and certain occupations (21) with high sensitization rates, and legislative regulations which effectively decrease sensitization rates (22), emphasize the important role of the environment in the development of contact allergies. In development of multiple contact allergies, cumulative environmental exposure seems to be necessary (4). The nature of the exposure; relating to type, potency and dose of allergen (23, 24), occlusion, extent and duration (19, 25), simultaneous exposure to more than 1 allergen (26, 27) or irritants (28, 29), inflamed, or damaged skin (19), all influence the risk of and can increase susceptibility towards development of contact allergy and multiple contact allergies. Under controlled settings, the reported increased susceptibility among multiple-allergic patients may be an expression of a changed or up-regulated state in the immune system caused by the acquisition of allergies or the inflammation.

Also, genetics play a role for the individual susceptibility. Women get sensitized more easily than men and display a larger response for each elicitation dose (30). Contact allergy is strongly decreased in 1 animal model (31), and variation in the degree of sensitivity can be established by controlled breeding (32). Children of parents, both sensitized to strong allergens, were sensitized with a greater probability than children of parents, who were not sensitized (33).

If the susceptibility is caused by the acquisition of allergies and a subsequent change in the immune system, then the observed decreased threshold for DNCB sensitization should be a general feature of all patients with multiple contact allergies. Both Moss et al. (1) and Friedmann et al. (34) referred to a comparison of DNCB sensitization between a multiple-allergic group because of occupational high exposure and a multiple-allergic group because of ubiquitous base-line exposure. Only the last group expressed a decreased sensitization threshold making a strong case against susceptibility being caused by earlier contact sensitization. Additionally, the reported increased susceptibility was not a consequence of inflammation as all patients were eczema-free at the time of testing. Moss et al. (1) even stated that it was not related to extent and severity of the eczema in the past, but no results were presented to support this statement.

In conclusion, genetics seems to be an important contributor to the increased susceptibility for a non-high-risk exposure subgroup of patients with multiple allergies. There is no evidence to determine the relative influence of inherent susceptibility and environmental exposure, respectively, on development of contact allergies within this subgroup. In a twin study, the heritability of nickel allergy has been calculated to 60% (35). The balance may not be fixed. Extreme environmental exposures in the subgroup of patients with an increased susceptibility may overrule the influence of inherent susceptibility, just as the environment is the major contributor in development of multiple contact allergies in the high-risk exposure group. In low-risk exposure situations, the susceptibility might have a greater influence but likely also differ in this situation as the degree of susceptibility varied between individuals in the group. Under low-risk circumstances, no evidence exists of specific environmental factors or situations being decisive for the development of multiple allergies.

Overall, environmental exposure is the most important factor in development of contact allergy. Without environmental exposure, contact allergy cannot be induced. An increased susceptibility lowers the threshold for induction.

Genetic Markers for Increased Susceptibility

The evidence for increased susceptibility raises the hypothesis that genetic factors are more prominent in polysensitized individuals. So far, susceptibility for contact allergy has been shown to be associated with rapid acetylator polymorphisms of *N*-acetyltransferase (NAT) (36–38), interleukin 16-295 (IL) promoter polymorphism (39), and high secretor tumour necrosis factor-alfa-308 (TNF) polymorphisms (40). For all the polymorphisms the difference between proportion of cases and controls with the respective polymorphism is small. Only the IL-16-295 and the TNF-alfa-308

polymorphism have been shown to be overrepresented in polysensitized individuals compared with healthy non-eczematous patients. Additionally, the TNF-alfa-308 polymorphism is associated to both allergic and irritant contact dermatitis (40, 41), and the IL 16-295 polymorphism is associated to both allergic contact dermatitis and non-allergic eczema patients without further specification (39). Both polymorphisms likely represent more general markers for increased skin immune reactivity. No studies have been performed on NAT-2 polymorphisms and irritant contact dermatitis or polysensitization, but rapid acetylator NAT-2 polymorphisms are positively associated with early onset psoriasis (42) and might also be a more general marker.

All study participants in the above mentioned genetic marker studies were included based on specific allergies. Extrapolating the results to other contact allergens should be performed with care as the observed polymorphism might be substance-specific and not a general feature of contact allergy as shown for the substance-specific polymorphism of glutathione S-transferase M1 (43).

Polymorphisms of manganese superoxide dismutase (44), IL-1 beta, IL-1 receptor antagonist, IL-6 (40), IL-4, and TNF-beta (45) were not associated with allergic contact dermatitis. Furthermore, no difference in number or morphology of Langerhans cells or human leucocyte allergen associations has been noticed among polysensitized individuals versus healthy controls (46–48). The genetic markers investigated and their association to allergic and irritant contact dermatitis and polysensitization, respectively, are given in Table 1.

Genetic markers for increased susceptibility are a highly complex field. A world of cytokines and cells interact in the process of an allergic response and likely involve the interaction of a number of genes. Only selected polymorphisms have been investigated so far.

Allergens in Combination

Cross-reactivity between chemically related allergens or concomitant exposure to 2 allergens in the same environment or product are 2 mechanisms by which simultaneous reactions occur (49). Simultaneous reactivity can also occur if 1 allergen is metabolized to a compound or releases a compound similar to another allergen for example formaldehyde and formaldehyde releasers.

Table 1. Association between various genetic markers and allergic contact dermatitis, irritant contact dermatitis, and polysensitization

		Associations		
	Examined genetic markers	Allergic contact dermatitis (references)	Irritant contact dermatitis (references)	Polysensitization/≥2 contact allergies (references)
Xenobiotic-metabolizing enzymes	NAT1*10	− (37)		
	NAT2*4	+ (36, 37)		
	NAT2*4/1*10	+ (37)		
	NAT2*4/*4	+ (36)		
	GST M1-	+[a] (43)		
	GST T1-	− (43)		
	GST M1-/T1-	+[a] (43)		
Anti-oxidative enzyme	MnSOD-47	− (44)		
	MnSOD-339	− (44)		
Cytokines	IL 1 beta–511	− (40)		− (40)
	IL 1 beta+3953	− (40)		− (40)
	IL 1 receptor antagonist-VNTR in intron 2	− (40)		− (40)
	IL 4-590	− (45)		
	IL 6-174	− (40)		− (40)
	IL 16-295	+ (39)	+[b] (39)	+ (39)
	TNF alfa-238	− (40, 45)		− (40)
	TNF alfa-308	+ (40, 45)	+ (41)	+ (40)
	TNFbeta 1064-1069	− (45)		
Human leucocyte antigens	HLA-class I	− (46–48, 62)		− (46–48)
	HLA-class II	− (46, 62, 63)		− (46)
Epidermal Langerhans cells	Amount/number	− (46)		− (46)
	Morphology	− (46)		− (46)

+, significant association found; −, no association found; HLA, human leucocyte antigen; IL, interleukin; MnSOD, manganese superoxide dismutase; NAT, *N*-acetyltransferase; TNF, tumour necrosis factor; VNTR, variable number of tandem repeats.
[a]Specifically associated to thimerosal allergy.
[b]Increased in patients with non-allergic eczema without further specification.

False-positive reactions because of hyper-reactivity (the angry back syndrome) are a source of error of simultaneous positive patch tests, but the arrangement of the patches on the back seems not to be decisive for development of positive patch tests to neighbouring patch tests (50–52). If cross-reactivity explained the development of polysensitization or the angry back syndrome was a frequent source of error, the research in an inherent susceptibility would be less interesting.

The majority of allergen cluster-studies focus on allergens from the standard series. Varying numbers of statistically significant associated duplet allergen combinations have been identified ranging from 13 to 166 combinations in single papers (53–56). Mechanisms other than random coincidence are common in duplet combinations; however, they do not explain all duplet combinations. Total number of associations to each allergen in the present European Standard Series is shown in Fig. 1.

Nickel sulfate, fragrance mix, and Balsam of Peru were the 3 allergens in the European Standard Series with most associations to other allergens (Fig. 1). They are also the most frequent sensitizers (57). Interestingly, wool alcohols and paraben mix are the allergens with the 2nd most associations. They are weak sensitizers with very low sensitization rates (4). The likelihood of finding statistically significant associations to these allergens is small. The relatively high number of associations and lack of known cross-reactions to these allergens raises the hypothesis that paraben mix and wool alcohols as specific allergens or as representatives of weak sensitizers in general might be associated with multiple contact allergies. The risk of contact allergy to the weak sensitizer neomycin sulfate increased with additional positive reactions to other standard allergens supporting the hypothesis (58).

Only a few reported triplet allergen associations have been identified (Table 2). No combinations of allergens larger than 3 have been identified.

Allergen patterns in multiple contact allergies, here referring to a definition of ≥ 3 allergies, appear to occur at random (1, 2). The propensity for a particular allergen to occur in combination or isolated varies between allergens (2). Combined with the lack of specific allergen triplet clusters, the development of polysensitization appears antigen-*in*dependent supporting the idea of an inherent general susceptibility. Whether or not a particular allergen or subgroup of allergens – a marker – triggers a cascade of *unrelated* secondary allergies in polysensitization is unknown. The order in which the allergies are acquired has not been investigated.

Identification and Prevention

Identification of patients at risk of developing multiple contact allergies is needed for primary

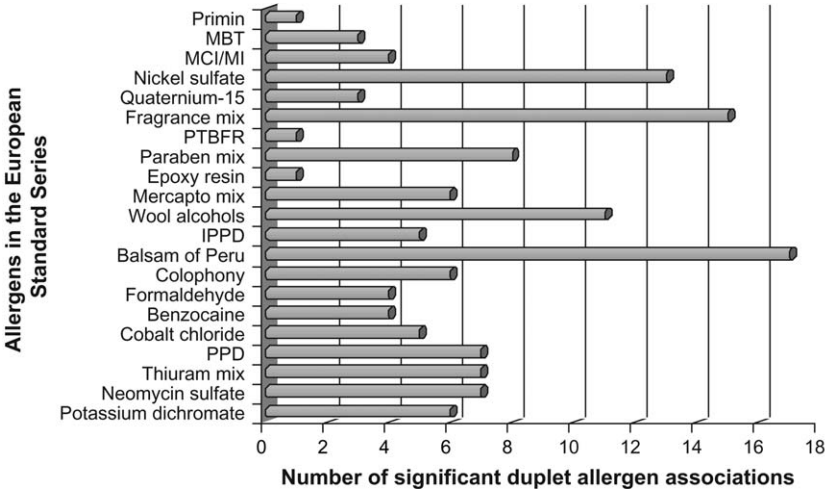

Fig. 1. Number of statistically significant allergen associations to allergens attained in the present European Standard Series. Data is pooled from 4 papers with the objective to identify significantly associated pairs of allergens starting from a large pool of allergens (53–56). Varying numbers of allergens were examined in the different papers, and not all allergens were examined in all 4 papers. Mostly substances found on standard screening trays were examined. Sesquiterpene lactone cocktail and clioquinol were not examined in any of the 4 papers. The papers did not focus on any specific allergen associations. Only associations to allergens in the *present* European Standard Series are illustrated. All associated allergens were counted when a statistically significant association to 1 of the allergen in the present European Standard Series was found. Some of the associated allergens are, therefore, not attained in standard screening trays. MBT, mercaptobenzothiazole; MCI/MI, Cl(Me) isothiazolinone; PTBFR, *p-tert*-butylphenol-formaldehyde resin; IPPD, *N*-isopropyl-*N′*-phenyl-*p*-phenylenediamine; PPD, para-phenylenediamine.

Table 2. Reported triplet cluster allergen associations

Triplet allergen clusters	References
Nickel sulfate/cobalt chloride/potassium dichromate	(3, 64)
Para-phenylenediamine/*N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine/benzocaine	(65, 66)
Colophony/fragrance mix/compositae mix	(67)
Colophony/fragrance mix/Balsam of Peru	(68)
Thiuram mix/mercapto mix/mercaptobenzothiazole	(65)
Nickel sulfate/para-phenylenediamine/benzocaine	(2)
Thiuram mix/carba mix/mercapto mix	(2)

prevention. Patients with leg ulcers are beyond dispute at risk. Despite new topical treatments with low sensitizing potency, contact allergies continues to occur and increase, emphasizing the importance of continuous awareness in choice of materials in this high-risk subgroup (11). Whether specific high-risk occupations exist or if specific treatment other than wound treatment or other eczema locations constitute a high risk is plausible but still not documented.

Can we recognize patients at risk of developing multiple allergies who are not in a high-risk environment and are only exposed to the ubiquitous allergens? Several standard allergens do occur in combinations but the combinations are unrelated. Weak sensitizers such as paraben mix and wool alcohols may be indicators of multiple contact allergies but the presumed association needs to be investigated properly. With the current knowledge, identification via allergens is impossible.

Strong patch test reactions have been shown to be associated with additional allergies and with strong reactivity to the additional contact allergens (53, 59). Concomitant exposures and cross-reactivity were excluded as explanation supporting an antigen-*in*dependent association. Therefore, patients who respond with strong patch test reactions might exhibit a general increased susceptibility. Another explanation could be a general and high environmental exposure load increasing the likelihood of strong patch test reactions and additional allergies. The authors concluded that preventive strategies to minimize further exposure to known sensitizations and other ubiquitous allergens should be executed when expressing strong patch test reactions (59). A general advice to avoid ubiquitous standard contact allergens is an ambitious and probably unrealistic intervention in everyday life for the average patient and probably leads to reduced life quality. Numerous patients with 1 strong patch test reaction, who are not at risk of developing more allergies, would be affected by such a recommendation.

Mainly patients with chronic and recurrent dermatitis are subjected to additional patch testing. Additional patch testing is associated with an increased rate of patients with multiple contact allergies (4). Chronic and recurrent dermatitis may be used as a marker of increased risk of having multiple contact allergies but again is too general an indicator and would affect many patients not at risk, if preventive strategies were based on this observation. No other markers for identification of patients at risk of developing multiple contact allergies are available today.

Preventive strategies may take 2 approaches: individual protection measures to minimize exposure to known sensitizations and general exposure regulation. Individual protection has a discouraging compliance (60, 61), and allergen avoidance may be unrealistic when suffering from several contact allergies. In contrast, general exposure regulation in form of legislative regulations has proven effective (22). Combined with the lack of identification of patients at risk of developing multiple allergies, it may well be the most optimal prevention strategy for polysensitized individuals.

Conclusion

The literature supports the idea that patients with multiple contact allergies constitute a special entity in the field of contact allergy, and they may be divided into 2 groups. An increased susceptibility seems to be characteristic for the subgroup of multiple-allergic patients without high-risk exposure. It may be an inherent ability rather than a result of multiple allergies and is graded from normal individuals through mono- and double allergies to multiple allergies but also graded within the group of patients with multiple contact allergies. The balance between the influence of inherent susceptibility and environment, respectively, is likely variable and dependant on the type of environmental exposure. Under low-risk circumstances, no specific environmental factors or situations are known decisive for the development of multiple contact allergies. Cross-reactions as mechanism only explain a minor part of all patients with multiple contact allergies.

Besides high-risk leg ulcer patients, it is not possible to identify patients at risk of developing multiple contact allergies. No specific sensitivities are uniquely associated with polysensitization. The 2 genetic markers associated with polysensitization are also associated with dermatitis of other causes.

Disease duration and disease severity of this patient group is still not described but indications support the general assumptions of severe, long-lasting, and hard-to-treat eczema.

No generally accepted definition of patients with multiple contact allergies exists. Many duplet allergen combinations but only a small number of triplet allergen combinations exists. To reduce the group within patients with multiple contact allergies where cross-reactivity is the solitary explanation, we suggest that multiple contact allergies are defined as contact allergy to 3 or more allergens. The definition seems reasonable when focusing on patients with suspected increased susceptibility.

References

1. Moss C, Friedmann P S, Shuster S, Simpson J M. Susceptibility and amplification of sensitivity in contact dermatitis. *Clin Exp Immunol* 1985: 61: 232–241.
2. Dickel H, Taylor J S, Bickers D R, Merk H F, Bruckner T M. Multiple patch-test reactions: a pilot evaluation of a combination approach to visualize patterns of multiple sensitivity in patch-test databases and a proposal for a multiple sensitivity index. *Am J Contact Dermat* 2003: 14: 148–153.
3. Hegewald J, Uter W, Pfahlberg A, Geier J, Schnuch A. A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. *Allergy* 2005: 60: 372–378.
4. Carlsen B C, Menne T, Johansen J D. Twenty years of standard patch testing in an eczema population with focus on patients with multiple contact allergies. *Contact Dermatitis* 2007: 57: 76–83.
5. Nielsen N H, Menne T. Allergic contact sensitization in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Acta Derm Venereol* 1992: 72: 456–460.
6. Gonzalo M A, Revenga F. Multiple cutaneous sensitization to nonsteroidal anti-inflammatory drugs. *Dermatology* 1996: 193: 59–60.
7. Oh C S, Lee J Y. Contact allergy to various ingredients of topical medicaments. *Contact Dermatitis* 2003: 49: 49–50.
8. Lewis F M, Gawkrodger D J, Bleehen S S, Nelson M E. Multiple contact sensitivity to eyedrops. *Contact Dermatitis* 1993: 28: 246–247.
9. Tavadia S, Bianchi J, Dawe R S et al. Allergic contact dermatitis in venous leg ulcer patients. *Contact Dermatitis* 2003: 48: 261–265.
10. Saap L, Fahim S, Arsenault E, Pratt M, Pierscianowski T, Falanga V, Pedvis-Leftick A. Contact sensitivity in patients with leg ulcerations: a North American study. *Arch Dermatol* 2004: 140: 1241–1246.
11. Machet L, Couhe C, Perrinaud A, Hoarau C, Lorette G, Vaillant L. A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975-2003 data. *Br J Dermatol* 2004: 150: 929–935.
12. Zmudzinska M, Czarnecka-Operacz M, Silny W, Kramer L. Contact allergy in patients with chronic venous leg ulcers–possible role of chronic venous insufficiency. *Contact Dermatitis* 2006: 54: 100–105.
13. Bleasel N, Tate B, Rademaker M. Allergic contact dermatitis following exposure to essential oils. *Australas J Dermatol* 2002: 43: 211–213.
14. Kanerva L, Jolanki R, Estlander T. Occupational epoxy dermatitis with patch test reactions to multiple hardeners including tetraethylenepentamine. *Contact Dermatitis* 1998: 38: 299–301.
15. Alvarez M S, Brancaccio R R. Multiple contact allergens in a violinist. *Contact Dermatitis* 2003: 49: 43–44.
16. Mathelier-Fusade P, Aissaoui M, Chabane M H, Mounedji N, Leynadier F. Chronic generalized eczema caused by multiple dye sensitization. *Am J Contact Dermat* 1996: 7: 224–225.
17. Fowler J F Jr. Allergy to cocamide DEA. *Am J Contact Dermat* 1998: 9: 40–41.
18. Paulsen E, Andersen K E, Hausen B M. An 8-year experience with routine SL mix patch testing supplemented with Compositae mix in Denmark. *Contact Dermatitis* 2001: 45: 29–35.
19. Kligman A M. The identification of contact allergens by human assay. II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol* 1966: 47: 375–392.
20. Friedmann P S, Moss C, Shuster S, Simpson J M. Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects. *Clin Exp Immunol* 1983: 53: 709–715.
21. Rasmussen K, Carstensen O, Ponten A, Gruvberger B, Isaksson M, Bruze M. Risk of contact allergy and dermatitis at a wind turbine plant using epoxy resin-based plastics. *Int Arch Occup Environ Health* 2005: 78: 211–217.
22. Johansen J, Menne T, Christophersen J, Kaaber K, Veien N. Changes in the pattern of sensitization to common contact allergens in denmark between 1985-86 and 1997-98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000: 142: 490–5.
23. Friedmann P S. Graded continuity, or all or none – studies of the human immune response. *Clin Exp Dermatol* 1991: 16: 79–84.
24. Marzulli F N, Maibach H I. The use of graded concentrations in studying skin sensitizers: experimental contact sensitization in man. *Food Cosmet Toxicol* 1974: 12: 219–227.
25. Basketter D A, Jefferies D, Safford B J et al. The impact of exposure variables on the induction of skin sensitization. *Contact Dermatitis* 2006: 55: 178–185.
26. McLelland J, Shuster S. Contact dermatitis with negative patch tests: the additive effect of allergens in combination. *Br J Dermatol* 1990: 122: 623–630.
27. Johansen J D, Skov L, Volund A, Andersen K, Menne T. Allergens in combination have a synergistic effect on the elicitation response: a study of fragrance-sensitized individuals. *Br J Dermatol* 1998: 139: 264–270.
28. McLelland J, Shuster S, Matthews J N. 'Irritants' increase the response to an allergen in allergic contact dermatitis. *Arch Dermatol* 1991: 127: 1016–1019.
29. Smith H R, Basketter D A, McFadden J P. Irritant dermatitis, irritancy and its role in allergic contact dermatitis. *Clin Exp Dermatol* 2002: 27: 138–146.
30. Rees J L, Friedmann P S, Matthews J N. Sex differences in susceptibility to development of contact hypersensitivity to dinitrochlorobenzene (DNCB). *Br J Dermatol* 1989: 120: 371–374.
31. Shornick L P, De T P, Mariathasan S, Goellner J, Strauss-Schoenberger J, Karr R W, Ferguson T A, Chaplin D D. Mice deficient in IL-1beta manifest impaired contact hypersensitivity to trinitrochlorobenzone. *J Exp Med* 1996: 183: 1427–1436.
32. Chase M W. Inheritance in guinea pigs of the susceptibility to skin sensitization with simple chemical compounds. *J Exp Med* 1941: 73: 711–726.
33. Walker F B, Smith P D, Maibach H I. Genetic factors in human allergic contact dermatitis. *Int Arch Allergy Appl Immunol* 1967: 32: 453–462.
34. Friedmann P S. The immunology of allergic contact dermatitis: the DNCB story. *Adv Dermatol* 1990: 5: 175–195.
35. Menne T, Holm N V. Nickel allergy in a female twin population. *Int J Dermatol* 1983: 22: 22–28.
36. Nacak M, Erbagci Z, Aynacioglu A S. Human arylamine N-acetyltransferase 2 polymorphism and susceptibility to allergic contact dermatitis. *Int J Dermatol* 2006: 45: 323–326.
37. Westphal G A, Reich K, Schulz T G, Neumann C, Hallier E, Schnuch A. N-acetyltransferase 1 and 2 polymorphisms in para-substituted arylamine-induced contact allergy. *Br J Dermatol* 2000: 142: 1121–1127.

38. Schnuch A, Westphal G A, Muller M M et al. Genotype and phenotype of N-acetyltransferase 2 (NAT2) polymorphism in patients with contact allergy. *Contact Dermatitis* 1998: 38: 209–211.
39. Reich K, Westphal G, Konig I R, Mossner R, Kruger U, Ziegler A, Neumann C, Schnuch A. Association of allergic contact dermatitis with a promoter polymorphism in the IL16 gene. *J Allergy Clin Immunol* 2003: 112: 1191–1194.
40. Westphal G A, Schnuch A, Moessner R, Konig I R, Kranke B, Hallier E, Ziegler A, Reich K. Cytokine gene polymorphisms in allergic contact dermatitis. *Contact Dermatitis* 2003: 48: 93–98.
41. Allen M H, Wakelin S H, Holloway D, Lisby S, Baadsgaard O, Barker J N, McFadden J P. Association of TNFA gene polymorphism at position -308 with susceptibility to irritant contact dermatitis. *Immunogenetics* 2000: 51: 201–205.
42. Reich K, Westphal G, Schulz T, Muller M, Zipprich S, Fuchs T, Hallier E, Neumann C. Combined analysis of polymorphisms of the tumor necrosis factor-alpha and interleukin-10 promoter regions and polymorphic xenobiotic metabolizing enzymes in psoriasis. *J Invest Dermatol* 1999: 113: 214–220.
43. Westphal G A, Schnuch A, Schulz T G et al. Homozygous gene deletions of the glutathione S-transferases M1 and T1 are associated with thimerosal sensitization. *Int Arch Occup Environ Health* 2000: 73: 384–388.
44. Brans R, Dickel H, Bruckner T, Coenraads P J, Heesen M, Merk H F, Blomeke B. MnSOD polymorphisms in sensitized patients with delayed-type hypersensitivity reactions to the chemical allergen para-phenylene diamine: a case-control study. *Toxicology* 2005: 212: 148–154.
45. Dai Y, Leng S, Li L, Niu Y, Huang H, Cheng J, Zheng Y. Genetic polymorphisms of cytokine genes and risk for trichloroethylene-induced severe generalized dermatitis: a case-control study. *Biomarkers* 2004: 9: 470–478.
46. White S I, Friedmann P S, Stratton A. HLA antigens and Langerhans cell density in contact dermatitis. *Br J Dermatol* 1986: 115: 447–452.
47. Dumont-Fruytier M, Van N D, De B M, Tennstedt D, Lachapelle J M. Nickel contact sensitivity in women and HLA antigens. *Arch Dermatol Res* 1980: 269: 205–208.
48. Liden S, Beckman L, Cedergren B, Groth O, Goransson K, Wahlby L. Lack of association between allergic contact dermatitis and HLA antigens of the A and B series. *Acta Derm Venereol* 1981: 61: 155–157.
49. Benezra C, Maibach H. True cross-sensitization, false cross-sensitization and otherwise. *Contact Dermatitis* 1984: 11: 65–69.
50. Brasch J, Geier J, Schnuch A, Uter W. A high-positive patch test load correlates with further positive patch test reactions irrespective of their location. *Allergy* 2006: 61: 1411–1415.
51. Brasch J, Kreilgard B, Henseler T, Aberer W, Fuchs T, Pfluger R, Hoeck U, Gefeller O. Positive nickel patch tests do not intensify positive reactions to adjacent patch tests with dichromate. Results from a double-blind multicentre study of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG). *Contact Dermatitis* 2000: 43: 144–149.
52. Andersen K E, Liden C, Hansen J, Volund A. Dose-response testing with nickel sulphate using the TRUE test in nickel-sensitive individuals. Multiple nickel sulphate patch-test reactions do not cause an 'angry back'. *Br J Dermatol* 1993: 129: 50–56.
53. Brasch J, Uter W, Geier J, Schnuch A. Associated positive patch test reactions to standard contact allergens. *Am J Contact Dermat* 2001: 12: 197–202.
54. Edman B. Computerized analysis of concomitant contact allergens. *Contact Dermatitis* 1991: 24: 110–113.
55. Albert M R, Chang Y, Gonzalez E. Concomitant positive reactions to allergens in a patch testing standard series from 1988-1997. *Am J Contact Dermat* 1999: 10: 219–223.
56. Holness D L, Nethercott J R, Adams R M et al. Concomitant positive patch test results with standard screening tray in North America 1985-1989. *Contact Dermatitis* 1995: 32: 289–292.
57. Bruynzeel D P, Diepgen T L, Andersen K E et al. Monitoring the European standard series in 10 centres 1996-2000. *Contact Dermatitis* 2005: 53: 146–149.
58. Menezes de Padua C A, Schnuch A, Lessmann H, Geier J, Pfahlberg A, Uter W. Contact allergy to neomycin sulfate: results of a multifactorial analysis. *Pharmacoepidemiol Drug Saf* 2005: 14: 725–733.
59. Brasch J, Schnuch A, Uter W. Strong allergic patch test reactions may indicate a general disposition for contact allergy. *Allergy* 2006: 61: 364–369.
60. Jungbauer F H, Van D V, Groothoff J W, Coenraads P J. Irritant hand dermatitis: severity of disease, occupational exposure to skin irritants and preventive measures 5 years after initial diagnosis. *Contact Dermatitis* 2004: 50: 245–251.
61. Noiesen E, Larsen K, Agner T. Compliance in contact allergy with focus on cosmetic labelling: a qualitative research project. *Contact Dermatitis* 2004: 51: 189–195.
62. Silvennoinen-Kassinen S, Ilonen J, Tiilikainen A, Karvonen J. No significant association between HLA and nickel contact sensitivity. *Tissue Antigens* 1979: 14: 459–461.
63. Emtestam L, Zetterquist H, Olerup O. HLA-DR, -DQ and -DP alleles in nickel, chromium, and/or cobalt-sensitive individuals: genomic analysis based on restriction fragment length polymorphisms. *J Invest Dermatol* 1993: 100: 271–274.
64. Ruff C A, Belsito D V. The impact of various patient factors on contact allergy to nickel, cobalt, and chromate. *J Am Acad Dermatol* 2006: 55: 32–39.
65. Andersen K E, White I R, Goossens A. Allergens from the Standard Series. In: *Contact Dermatitis*, 4th edition, Frosch P J, Menne T, Lepoittevin J-P (eds): Berlin Heidelberg, Springer-Verlag, 2006: 453–492.
66. Sosted H, Johansen J D, Andersen K E, Menne T. Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006: 54: 87–91.
67. Paulsen E, Andersen K E. Colophonium and Compositae mix as markers of fragrance allergy: cross-reactivity between fragrance terpenes, colophonium and compositae plant extracts. *Contact Dermatitis* 2005: 53: 285–291.
68. Wohrl S, Hemmer W, Focke M, Gotz M, Jarisch R. The significance of fragrance mix, balsam of Peru, colophony and propolis as screening tools in the detection of fragrance allergy. *Br J Dermatol* 2001: 145: 268–273.

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