Weak Sensitizers May Be Associated with CD80 Polymorphisms: Implications for Systemic Contact Dermatitis

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Chronic irritant dermatitis predisposes to Th2 skewed allergic contact dermatitis. Chronic hand dermatitis due to wet work or childhood- onset irritant flexural dermatitis (AD) is associated with sensitization to weak or non-sensitizing antigens as defined by the local lymph node (LLN) assay. In about 15% of these patients, ingestion of allergens results in systemic contact dermatitis, defined as recall dermatitis at previous sites. In this large exploratory study, not even known associations (e.g. IL4R and AD) survived correction for tests of multiple associations. As such, we analyzed for associations using $p<0.005$ combined with OR >1.8 or <0.5. We found that positive patch tests to weak allergens were common with 3 polymorphisms of CD80. CD80 is a co-stimulatory molecule on several cell types including innate lymphoid group 2 cells (ILC2). ILC2 presentation may bypass education in the local lymph node, explaining the association of antigens classified as non-sensitizers in LLN assay with CD80, and the absence of symptoms of immediate type hypersensitivity in many of these patients. Food handlers with hand dermatitis and patients with atopic dermatitis should be patch tested to allergens in foods (e.g. propylene glycol, vanillin, nickel, cobalt, and chromates) and instructed on dietary restriction of these allergens.

Keywords: Allergic contact dermatitis, Atopic dermatitis, Food allergy, Innate lymphoid cells, Systemic contact dermatitis

INTRODUCTION

The classic view of allergic contact dermatitis (ACD) is delayed-type hypersensitivity from a potent allergen applied to healthy skin without pre-existing chronic dermatitis, resulting in presentation by conventional dendritic cells (cDCs) with innate lymphoid cell (ILC) group 1 activation. ILC1s migrate back and forth from the circulation to regional lymph nodes and promote a T helper (Th)1−type ACD response (Kabata et al, 2022). Sensitizers that cause Th1 reactions on healthy skin are generally classified as potent allergens in the local lymph node assay (LLNA).

In contrast, chronic irritant dermatitis disrupts the skin barrier, releasing alarmins such as IL-33, IL-25, and TSLP that instruct a Th2 response to contact allergens (Brys et al, 2020). ILC2s are involved in an alternative antigen-presenting pathway that results in release of IL-13 as in other Th2 responses to contact sensitizers. Atopic dermatitis (AD) encompasses childhood-onset irritant flexural and perioral dermatitis that predisposes to Th2-skewed ACD.

The LLNA is a tool to classify potency of allergens using the estimated concentration of the chemical required to produce a 3-fold increase (positive response) in draining lymph node cell proliferative activity (Gerberick et al, 2005). This correlates well to patch test reactions for most chemicals, but some chemicals, for example, propylene glycol, are positive in human patch tests yet classified as an extremely weak or nonsensitizer in the LLNA. Sensitization to these weak antigens is more common in patients with chronic irritant dermatitis such as AD or chronic hand dermatitis due to wet work (Kohli and Nedorost, 2016).

CD80 is expressed on many cells such as eosinophils and dendritic cells, including ILC2s, which may facilitate sensitization to antigens that are not processed through cDCs in the local lymph node (Bartemes and Kita, 2021). Therefore, a role for ILC2s would be expected for weak antigens that do not activate the local lymph node in the LLNA (Gerberick et al, 2005).

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Abbreviations: ACD, allergic contact dermatitis; AD, atopic dermatitis; cDC, conventional dendritic cell; DE, dyshidrotic eczema; ILC, innate lymphoid cell; LLNA, local lymph node assay; SCD, systemic contact dermatitis; Th, T helper

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ILC2s are critical to memory T-cell responses in the skin (Lloyd and Snelgrove, 2018). ILC2s may sometimes also participate in cross-talk with dendritic cells presenting antigen in the local lymph node, leading to Th2 cells and antigen-specific IgE (Lloyd and Snelgrove, 2018).

Systemic contact dermatitis (SCD) is defined as recall flares at previous sites of skin exposure upon ingestion or inhalation of the allergen (Jacob et al, 2019). Ingested allergens causing SCD are often non or weak sensitizers in the LLNA such as food or food additives. Positive patch tests to these allergens are more common in patients with respiratory atopy or occupational wet work (Scott et al, 2019) but also occur in many patients without immediate-type hypersensitivity symptoms of respiratory atopy (Ahuja et al, 2024).

Dyshidrotic eczema (DE) is another form of SCD that is often triggered by ingested metals, which are more potent allergens (Veien, 2011). The alarmin TSLP can trigger cDCs to educate Th2 cells in the local lymph node, leading to downstream antigen-specific immunoglobulins. Positive prick tests to nickel that are relevant to early reactions to jewelry have been documented even with negative patch tests, suggesting an Ig trigger (Saluja et al, 2016). DE is also associated with IgG administration (Voland et al, 2023).

We explored genetic variants important in cutaneous immunology in adult patients with clinically relevant positive patch tests at 2 tertiary, referral contact dermatitis clinics. We stratified patients with a history of early childhood flexural dermatitis as a marker for genetic barrier defects predisposing to chronic irritant dermatitis and patients with a history of DE.

Because innate signals from irritant dermatitis instruct the adaptive response, we also compared our genetic variant associations in this group of patients with ACD with a previously reported cohort of healthcare workers with and without chronic irritant hand dermatitis, analyzed using the same methods (Yucesoy et al, 2016). This allowed us to differentiate genetic variants important in the prerequisite irritant contact dermatitis from those facilitating sensitization to various groups of contact allergens.

Our a priori groupings for allergens on the standard screening series were intended to explore multiple hypotheses at once, including different antigen presentation for metal allergens, immunological differences in antigens metabolized in the skin, differences in polysensitized patients (sensitized to 3 or more chemically unrelated allergens), and differences in patients sensitized to weak antigens. In this study, we explored only the weak allergens (propylene glycol, vanillin, eugenol, and paraben mix); there are many other weak allergens in foods and food additives, but these were chosen because they were included on the standard screening series at both study sites.

We show all the 1450 genetic markers that we explored in the complete dataset (Nedorost et al, 2025). Because of the large number of markers studied, none of the individual analyses survived Bonferroni correction for tests of multiple associations, including the strongest association noted, which was between IL-4R and AD. The latter is well-accepted, and we looked for other associations with similar *P*-values ($P < .005$) and ORs (≥ 1.8 or ≤ 0.5). We use the term "associated" throughout this manuscript to indicate results that meet these criteria, even though no results survived correction for 1450 associations.

Table 1. Demographics of ACD Cohort (n = 358)

Characteristic	n	% or (Mean ± SD)
Age, y	358	49.9 ± 15.2
Sex		
Male	98	27.4
Female	260	72.6
History of childhood flexural dermatitis	358	22.1
History of dyshidrotic hand or foot eczema	358	13.4

Abbreviation: ACD, allergic contact dermatitis.

RESULTS

The mean age of the participants was 49.9 years, and 73% were female. A total of 239 participants were recruited from institution #1, and 119 were from institution #2. Of the 358 participants, 22.1% had a history of childhood flexural dermatitis (AD), and 13.4% had a history of DE (Table 1). There was a significant correlation between history of AD and DE ($r = 0.127$, $P = .0165$).

Patients often had positive patch test reactions in more than 1 group (Table 2). Of the 4 specified allergen groups, metal-sensitized group was the largest group with 225 participants, and weak allergens was the smallest with 45 participants. The category of sensitization to weak allergens had the most associated SNPs, followed by polysensitization and allergens metabolized in the skin. Twenty of our 45 (44%) weak allergen-sensitized participants were also allergic to at least 1 metal.

Genetic variants associated with the specified allergen groups and with history of AD and DE that met our criteria of $P < .005$ and OR ≥ 1.80 or ≤ 0.5 were extracted into Tables 3 and 4, respectively. We found association (Table 3) of positive patch tests with weak allergens with 3 polymorphisms of CD80 (*rs626364*, *rs7630595*, and *rs6808536*), 2 of which (*rs7630595* and *rs6808536*) have previously been associated with AD (Sharma et al, 2012).

No CD80 SNPs were associated with metals, polysensitization, or allergens metabolized in the skin, suggesting that ILC2s are not critical to sensitization for all allergens (Table 3). Metals are known to activate cDCs through a different innate immune mechanism involving toll-like

Table 2. Number of Patients in Each Allergy Group (Patients Could be Assigned to More Than 1 Group)

Allergen Group	n	Number with Positive Test	%
Sensitized to metals (Au > Ni > Co > Cr)	358	225	62.8
Polysensitized to more than 3 unrelated allergens	358	175	48.9
Sensitized to allergens metabolized in the skin	358	156	43.6
Sensitized to weakly potent allergens	358	45	12.6

The symbol % denotes percentage with positive patch test.

Table 3. Association of Gene Variants with Patch Test Outcomes

Clinical Outcome	Gene	SNP	Alleles	Frequency	*P*-Value	OR (95% CI)	Reported Dermatitis Associated with this Gene
Allergens metabolized in the skin	*HCG17*	rs928824	C/T	0.0781	.00438	1.81 (1.20–2.72)	
Polysensitization	*PTGS2*	rs2206593	G/A	0.0603	.003	2.35 (1.34–4.12)	
Weak allergens	*DDX39B*	rs2239709	C/T	0.0813	.000417	2.81 (1.58–4.98)	
	KIFC1	rs465223	G/C	0.365	.00032	2.06 (1.39–3.06)	In conjunction with RGS16 in a machine-learning program, differentiated irritant from allergic contact dermatitis (Fortino, 2020)
	IL22RA2	rs10484798	T/C	0.201	.000949	2.14 (1.36–3.35)	
	IL10	rs3024495	C/T	0.178	.00115	2.18 (1.36–3.49)	
	NTKR3	rs12594283	A/C	0.291	.00113	1.91 (1.29–2.83)	NTRK3; rs1347424 variant associated with irritant contact dermatitis owing to benzalkonium chloride (Yucesoy et al, 2016)
	NOD1	rs3823773	T/C	0.115	.00243	2.26 (1.33–3.81)	
	CD80	rs626364	A/G	0.514	.00268	2.63 (1.41–5.00)	
	CD80	rs6808536	G/T	0.149	.00398	2.04 (1.26–3.32)	**Same SNP associated with AD (Sharma et al, 2012)**
	CD80	rs7630595	G/A	0.112	.00478	2.21 (1.27–3.83)	**Same SNP associated with AD (Sharma et al, 2012)**
	FGF7	rs4407014	A/G	0.108	.00294	2.28 (1.33–3.94)	
	DNAH5	rs13154770	C/T	0.112	.00339	2.25 (1.31–3.87)	
	IL31RA	rs327240	C/A	0.793	.00365	3.70 (1.54–9.09)	

Abbreviations: AD, atopic dermatitis; CI, confidence interval.

SNPs rs9268766, rs4551215, and rs7382649 for weak antigens and rs3857558 for dyshidrotic eczema mapped to chromosome 6 but of unknown significance and were not included in the tables.

Alleles are displayed as protective/risk allele. The allele frequencies and ORs are calculated on the basis of the risk allele (second allele). Boldfaces indicate that the same variant has been previously associated with dermatitis.

Table 4. Association of Gene Variants with Demographic Variables of History of Childhood Eczema and History of Dyshidrotic Eczema

Category	Gene	SNP	Alleles	Frequency	*P*-Value	OR (95% CI)	Reported Dermatitis Associated with this Gene
History of childhood eczema	*IL4R*	rs1805015	C/T	0.86	.00401	2.08 (1.27–3.45)	Two other SNPs in IL-4R associated with AD and respiratory atopy (Tripathi et al, 2014)
	IL4R	rs2074570	T/C	0.0409	.000771	2.30 (1.42–3.73)	
	IP6K3	rs877187	C/T	0.193	.0000337	1.93 (1.42–2.64)	
	ACACB	rs10849968	A/C	0.76	.00313	2.00 (1.27–3.12)	
	CCL7	rs3091237	T/C	0.85	.00424	2.63 (1.35–5.26)	
History of dyshidrotic eczema	*TLR8*	rs4830805	G/A	0.261	.0000223	1.84 (1.39–2.44)	
	FGFR2	rs11199993	G/C	0.0638	.000794	2.37 (1.43–3.92)	
	NTRK3	rs7172184	T/C	0.53	.00188	2.17 (1.33–3.57)	
	TSLP	rs10062929	A/C	0.82	.0022	3.57 (1.59–8.33)	Multiple other SNPs associated with AD (Gao et al, 2010)
	VEGFA	rs3025010	C/T	0.64	.00325	2.22 (1.30–3.70)	
	IL13RA1	rs2154240	C/T	0.0567	.00517	2.09 (1.25–3.52)	
	Chr 6 NOS	rs2394401	T/C	0.136	.00163	1.91 (1.28–2.86)	
	IL17A	rs3819025	G/A	0.0747	.00302	2.27 (1.32–3.91)	**Same SNP associated with AD** (Shen et al, 2024)
	CX3CR1	rs2669845	C/T	0.131	.00424	1.94 (1.23–3.06)	
	PPP1R11	rs1150740	C/A	0.0857	.00438	2.20 (1.28–3.79)	
	KIFC1	rs3857558	T/G	0.0972	.00391	2.04 (1.26–3.32)	Fortino, 2020

Abbreviations: AD, atopic dermatitis; CI, confidence interval; TLR5, toll-like receptor 5.

Alleles are displayed as protective/risk allele. The allele frequencies and ORs are calculated on the basis of the risk allele (second allele). Boldface indicates that the same variant has been previously associated with dermatitis.

receptors (Rachmawati et al, 2013). Our participants with contact allergy to both metals and weak allergens demonstrated that both toll-like receptor and ILC2 innate immunity can facilitate sensitization to different allergens in the same patient.

A CXCL12 polymorphism (rs197452) was previously reported to be associated with chronic irritant hand dermatitis (Yucesoy et al, 2016) and, in this work, was associated with weak antigens with an OR of 1.86, which met our cut off, but with a $P = .009$, which did not meet our cut off of $P < .005$.

The IL-17A variant (*rs3819025*) associated with DE in our study has been previously associated with AD. IL-17A is thought to impair skin barrier components, including FLG (Furue, 2020a). An IL-31RA variant was associated with sensitization to weak antigens, although the variant we noted (*rs327240*) has not been associated with dermatitis in the literature.

There were SNPs in several additional genes associated with sensitization to weak allergens. Of these genes, *KIFC1* and *NTRK3* were also associated with DE, also a phenotype of SCD. Although each was a different SNP, *NTRK3* was previously associated with irritant dermatitis to benzalkonium chloride (Yucesoy et al, 2016). Publications relevant to dermatitis are noted in Tables 3 and 4, and reports involving the same variant are in bold face.

DE was not associated with polymorphisms in CXCL12 or CD80 but was associated with polymorphisms in TSLP (Table 4). Dermatitis without respiratory atopy—"intrinsic AD"—was most common in those with positive patch tests to weak allergens (7.8%) than in those with sensitization to the other 3 allergen categories (3.9%) (Table 5).

DISCUSSION

In chronic irritant dermatitis, as seen in AD or occupational wet work, damaged keratinocytes can release TSLP, prompting cDCs to present more potent antigens (eg, peanut, dust mite, or nickel) to the local lymph node where Th2 cells are educated and release IL-4, promoting B-cell isotype switching to create antigen-specific immunoglobulins (Furue, 2020b). This pathway leads to "extrinsic" AD with immediate-type hypersensitivity symptoms such as urticaria, respiratory atopy, or DE. The association of TSLP with DE in our data is consistent with this framework.

Alternatively, chronically damaged keratinocytes can release IL-33 and IL-25, which stimulate ILC2s to produce IL-13 causing dermatitis without IL-4 or antigen-specific antibodies (Jin et al, 2022; Oliphant et al, 2014). ILC2s identified in human skin to date are tissue resident, as opposed to ILC1s and cDCs, which both circulate to the regional lymph nodes. Therefore, ILC2s may be associated with sensitization to weak antigens that are defined as not activating the local lymph node. ILC2s participate in "trained immunity," a type of immune memory acquired outside of the local lymph node (Ebihara et al, 2021), although they may communicate with and amplify the effects of Th2 cells as well (Kabata et al, 2022).

The term "atopy," meaning generation of antigen-specific antibody, is not always relevant to our current understanding of the immune mechanisms in "atopic" dermatitis. As discussed earlier, TSLP-mediated dermatitis with cDCs educating Th2 cells in the local lymph nodes leads to antibody formation. However, chronic dermatitis may also produce IL-33 and IL-25 alarmins, leading to ILC2 antigen presentation and IL-13–mediated dermatitis that may not involve the local lymph node and antigen-specific immunoglobulins. SCD may be facilitated by cutaneous lymphocyte–associated antigen–positive T cells and NKT cells homing to areas of prior skin exposure in these 2 scenarios, respectively.

SCD triggered by ingestion of weak antigens responds to IL-13– as well as IL-4–blocking drugs (Jacob et al, 2019), as does AD (Figure 1). This is consistent with our observation that of the 3 polymorphisms of CD80 (rs626364, rs7630595, and rs6808536) associated with sensitization to weak antigens, 2 (rs7630595 and rs6808536) have previously been associated with AD without asthma (Sharma et al, 2012). Despite prior demonstration of association of weak antigens with AD (Kohli and Nedorost, 2016), there was no significant correlation between history of AD and sensitization to weak antigens in our data ($r = 0.062$, $P = .2391$), suggesting that the association of weak antigens with the identified variants in CD80 is independent of their association with AD.

In chronically inflamed skin, weak and moderately potent sensitizers can cause SCD that is clinically indistinguishable from AD (Ahuja et al, 2024). In patients with AD, it is even possible to sensitize to a potent allergen on perilesional unaffected skin and elicit simultaneous Th1 and Th2 reactions to the same antigen (Newell et al, 2013). The Th2 response is more durable in this scenario, in contrast to the more commonly recognized durable Th1 response to contact allergens sensitizing healthy skin.

Table 5 shows that patients sensitized to weak allergens were twice as likely to have "intrinsic AD," meaning dermatitis without antigen-specific IgE created downstream from

Table 5. Data on Respiratory Atopy (Available Only for Site 1)

Allergic Group	Sample Size (n)	History of Childhood Flexural Dermatitis (%)	"Intrinsic AD" without Respiratory Atopy (%)	History of Respiratory Atopy Only (%)	No History of Any Atopy (%)
Total cohort (sites 1 and 2)	358	22.1	N/A	N/A	N/A
Site 1 cohort only	235	18.3	4.3	26.0	55.7
Weak allergens (site 1 only)	39	30.8	7.7	18.0	51.3
Metal, metabolized, and polysensitized cohorts (site 1 only)	229	17.5	3.9	26.2	56.3

Abbreviations: AD, atopic dermatitis; N/A, not applicable.

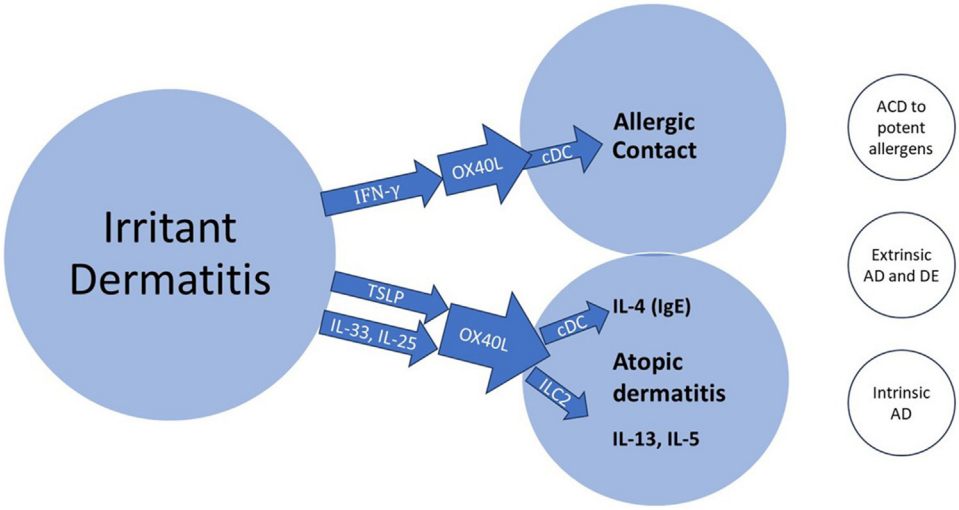

Figure 1. Acute versus chronic irritant dermatitis instructs Th1 versus Th2 ACD. Th1 skewed ACD occurs after sensitization on healthy skin. Th2 skewed ACD occurs after sensitizatin on chronically inflamed skin. TSLP promotes extrinsic AD often to medium potency allergens, whereas IL-33 and IL-25 promote intrinsic AD often to weak allergens. ACD, allergic contact dermatitis; AD, atopic dermatitis; cDC, conventional dendritic cell; DE, dyshidrotic eczema; ILC2, innate lymphoid cell group 2; SCD, systemic contact dermatitis; Th1, T helper 1; Th2, T helper 2.

education of Th2 cells in the local lymph node. Although the weak allergen group did have more participants with AD than the other groups, consistent with the known association of AD with sensitization to weak allergens (Kohli and Nedorost, 2016); the percentage with associated respiratory atopy was lower. Statistical significance of this is difficult to determine because these are not independent variables given that participants could be included in more than 1 allergen group, but the clinical application is that sensitization to weak antigens can occur either with or without history of Ig-mediated immediate-type hypersensitivity.

SCD induces recall inflammation at the sites of previous skin sensitization or elicitation after ingestion of the relevant allergen. ILCs are present in more superficial portions of skin than cDCs and, therefore, may be more likely to initiate sensitization to larger molecular-weight antigens such as food proteins known to cause SCD (Ahuja et al, 2024).

Cutaneous lymphocyte–associated antigen–positive memory cells are required for homing of the immune response to the site of previous encounters of allergen on the skin. Skin-resident NK T cells (cutaneous lymphocyte–associated antigen–positive memory cells connecting the innate and adaptive immune response) in patients with AD express CXCL4, which binds to CXCL12 on fibroblasts in areas of chronic skin barrier repair (Sun et al, 2021).

CXCL12 was previously shown to be associated with chronic hand dermatitis (Yucesoy et al, 2016) in a study of healthcare workers who developed irritant hand dermatitis in winter season compared with that in those who did not. NK T cells home to CXCL12 in areas of barrier repair and may explain recall reactions in skin that previously elicited ACD, including positive patch test sites, after ingestion of the relevant allergen. In other words, SCD and chronic irritant dermatitis, as seen in occupational wet work and shown to be associated with the *rs197452* variant of the *CXCL12* gene (Yucesoy et al, 2016), may instruct the adaptive recall response to weak antigens given the OR of 1.86 of association of weak antigen with this same *rs197452* variant (albeit with a *P*-value that did not meet our chosen criterion for association).

The IL-31 variant noted is of interest because IL-31–expressing T cells and IL-31RA–expressing sensory neurons may connect inflamed keratinocytes to itch. In addition, the IL-31 pathway is important in stimulating murine keratinocytes to recruit cutaneous lymphocyte–associated antigen–positive cells to the skin (Datsi et al, 2021), consistent with association with SCD.

Limitations

We assessed relevance for contact allergy at time of final reading. We estimate that 15% of the overall patient population in dermatitis clinics have SCD, but SCD cannot be diagnosed unless dermatitis clears with avoidance of skin contact and ingestion of the allergen(s) and then flares upon oral rechallenge. Therefore, we are not able to directly associate genetic polymorphisms with confirmed SCD. In addition, our study was limited to weak allergens widely tested in clinical practice, including the food additives propylene glycol and vanillin known to cause SCD; we did not include food proteins known to cause SCD (Ahuja et al, 2024) because these are not routinely tested.

The categorization of some patients into more than 1 allergen group did not allow analysis for allergen type as an independent variable. The OR and *P*-values chosen were based on established associations in our dataset such as IL-4R and AD (Tripathi et al, 2014), and limitations related to this are discussed in the statistical methods section.

Conclusions

In conclusion, although we did not envision a role for CD80 in sensitization to weak allergens at the outset of this exploratory study, our data support a role for CD80+ ILC2s in contact dermatitis to weak allergens. CXCL4+ NK T memory cells binding to CXCL12+ fibroblasts in areas of previous skin exposure are likely important in the recall phenomenon of

SCD. Because our study could not stratify patients with confirmed SCD, we hope that our results will inspire future work with a cohort of patients with SCD.

Future research designed around our hypothesis that ILC2s are involved in sensitization to weak allergens should aim for larger sample size and follow-up to determine whether avoidance of ingestion of the allergen was needed to clear dermatitis, the definition of SCD. Other applications would be to other protein allergens presented in the epidermis such as scabies mites, where CD80 variants may explain why only some patients sensitize to the mites.

The immediate application of our work is that patch testing should be used to investigate weak antigens such as foods and food additives suspected of triggering dermatitis and SCD even in the absence of respiratory atopy. These reactions are Th2 skewed, and patch testing should therefore be conducted when the patient is not treated with medications that inhibit Th2 cytokines.

MATERIALS AND METHODS

All patients of European ancestry by self-report or investigator observation aged >18 years with positive relevant patch tests were offered enrollment in this study. Inclusion was restricted to European ancestry because of emerging evidence during the study design interval suggesting that skin barrier protein variants such as in FLG may be more important in patient of European ancestry (Chiricozzi et al, 2023). IL-17 may be more important in Asian population with AD than in European population (Nomura et al, 2020), so we can speculate that ILC3s may be more important in that population. However, there is significant interplay between ILC2 and ILC3s (Alkon et al, 2022), which may allow some extrapolation to non-European populations.

Patch test allergens were obtained from Chemotechnique (Vellinge, Sweden) and SmartPractice Canada (Calgary, Canada). Patch tests were applied for 48 hours and interpreted at days 2−4 and 5−7 by experienced dermatitis experts, both of whom are coauthors. A positive patch test was defined as a 1+, 2+, or 3+ at any reading by the International Contact Dermatitis Research Group criteria or a doubtful reading that persisted to day 7. Relevance was defined as current definite or probable or past definite or probable by the North American Contact Dermatitis group standards (DeKoven et al, 2023). Patch test results considered possibly or not relevant did not warrant eligibility for the study. This is a more stringent standard than in most clinical studies, where "possibly relevant" is considered to be relevant.

The allergens chosen represented the metals (nickel, cobalt, chromate, and gold), allergens known to be metabolized in the skin (paraphenylenediamine and the topical corticosteroids budesonide, clobetasol, tixocortol pivalate, and triamcinolone acetonide), and allergens considered non or weak sensitizers in the LLNA (propylene glycol, vanillin, parabens, and eugenol) that were present on the standard series in the 2 participating clinics during the study interval. In addition, patients with 3 or more positive patch tests that were unrelated by chemistry (eg, formaldehyde-releasing preservatives would be considered related) or by historical coreaction (eg, neomycin and bacitracin) were considered polysensitized and also offered enrollment in the study. Some patients qualified for enrollment with positive tests in more than 1 category.

Patients with a history of childhood-onset flexural dermatitis, with or without respiratory atopy, were considered to have AD. Patients who reported intermittent itchy vesicles on their lateral digits and/or palms or soles were considered to have DE.

Genotyping

Whole-blood samples were collected for genetic analysis, and genomic DNA was extracted using the QIAamp blood kit (Qiagen, Chatsworth, CA). Genotyping was performed according to the Illumina Golden Gate instructions (Illumina, San Diego, CA). A total of 250 ng to 1 μg DNA was used for each assay depending on the source. Genotypes were autocalled using GenomeStudio software (Illumina). An oligonucleotide pool assay was designed by selecting candidate genes that are known and/or suspected to be involved in the irritant or ACD process. In SNP selection, 10 kb upstream and 10 kb downstream regions were included in accordance with design score validations, and SNPs closer than 60 bp to another SNP were excluded to accommodate the assay. The SNPs included in the oligonucleotide pool assay had a minor allele frequency >5% in HapMap/CEU population (Yucesoy et al, 2016).

Genotype data quality control was performed, and samples with a high missing rate (>5%) or excessive heterogeneity were excluded. Markers with a high missing rate (>5%) or significant deviation from Hardy−Weinberg equilibrium ($P < 5E\text{-}4$) were filtered out. Genetic principal component analysis of the study samples was examined using 1000 Genomes samples as references, and samples with substantial non-European ancestry were excluded from the final association tests.

Statistical methods

We estimated the required cohort size on the basis of nickel, the most common positive patch test in most standard series and positive in over 15% of the patch-tested population (DeKoven et al, 2023). By grouping other allergens in ways that they might be presented immunologically, we expected that we would have similar aggregate percentages of positive tests. We obtained the target 400 participants, but only 358 samples survived quality control.

Approximately 1450 markers were used. *FLG* genes were not included owing to a quality issue. Because this was meant to be an exploratory hypothesis-generating study, >1400 SNPs were examined, resulting in the potential for multiple associations, and none survived Bonferroni correction. Bonferroni correction is needed when multiple tests were conducted within the same experiment, and Bonferroni-corrected significance level (αB) is calculated by dividing the test-wise significance (α) level by the number of tests (k) ($\alpha B = \alpha/k$).

Because even known associations such as IL-4R variants with AD did not survive Bonferroni correction, we extracted from our data the associated SNPs for each group of allergens with an OR $\geq$ 1.8 or $\leq$ 0.5 and $P < .005$ as shown in Tables 3 and 4. We have referenced known functional associations between dermatitis and these SNPs in the tables.

We recognize that the results may be less reliable than planned using nickel as the target allergen and potentially lead to a failure to identify significant associations. For example, we demonstrated association meeting our criteria of the SNP *rs7630595* with weak antigens, and this SNP was previously linked to AD by others using similar statistical methods (Sharma et al, 2012), but in our data, association with history of childhood eczema yielded $P = .00953$ and an OR of 1.60 that did not meet our chosen reporting threshold for association.

ETHICS STATEMENT

Written informed consent was obtained from all patients and participants as approved by the institutional review boards below: University Hospitals Cleveland Institutional Review Board (number 01-11-16), patch test database (used for Table 5) institutional review board number (06-14-34), and Dartmouth Hitchcock Medical Center Institutional Review Board (number 21409).

DATA AVAILABILITY STATEMENT

Datasets related to this article can be found at https://doi.org/10.17632/dx39s9wf7k.1 hosted at Mendeley (Nedorost et al, 2025; "SNPs associated with allergic contact dermatitis to weak antigens, metals, antigens metabolized in skin, and polysensitization," Mendeley Data, V1). The clinical data that support the findings of this study are available from the corresponding author stn@case.edu upon request.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: SN, BY; Data Curation: BY, GZ; Formal Analysis: DF, GZ; Funding Acquisition: BY; Investigation: BY, SN, KF, BF, KZ, WW; Resources: BY; Software: BY; Supervision: BY, SN; Writing - Original Draft Preparation: SN, BY; Writing - Review and Editing: SN, BY, GZ, DF, EB, KZ

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMs)

The authors did not use AI/LLM in any part of the research process and/or manuscript preparation.

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