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A dynamic landscape of allergen associations in delayed-type cutaneous hypersensitivity

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Abstract

Delayed-type hypersensitivity represents a significant clinical and public health challenge. Patients undergoing patch testing may exhibit positive reactions to more than one allergen. It is recognized that reactions to specific pairs of allergens are associated reflecting a combination of exposure

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patterns and structural similarity. Here, we explore the influence of time of testing, age, sex and atopy status on allergen pair associations in a series of 45110 consecutive patients tested over 30 years. This is the largest reported study of patch test allergen pair relationships. Our analysis shows a high degree of variability in allergen pair associations. Rigorous statistical analysis reveals a large number of differences between groups including an significant increase in the association between formaldehyde and multiple formaldehyde-releasing preservatives over the study period in addition to pair associations with cobalt and formaldehyde releasing preservatives that were present to a significantly greater extent in males compared to females. These observations extend our understanding of cutaneous allergy with implications both for clinical practice and for mechanisms of cutaneous hypersensitivity.

What is already known about this topic?

- Patients undergoing patch testing may exhibit positive test results to more than one allergen
- Positive results to specific pairs of allergens are associated

What does this study add?

- We have identified 243 statistically significant pair-wise allergen associations
- Allergen associations are highly dynamic and with variation according to date of testing, age, sex and atopy status
- There are statistically significant differences in the association of specific allergen pairs according to sex, age and atopy status.

Introduction

Allergic contact dermatitis reflects T-cell mediated hypersensitivity. Patch testing remains the most reliable method of identifying sensitisation to an allergen and patients sensitized to a single allergen have an increased risk of sensitization to additional allergens[1,2]. It has long been recognized that positive reactions to specific allergen pair combinations occur in excess of that predicted by chance[3,4]. More recently, systematic evaluation of allergen pair relationships has revealed a large number of associations[5-7] likely reflecting a combination of exposure patterns in addition to structural similarity. We have previously demonstrated that allergy to individual preservatives evolve independently over a 10 year time period[8], however the extent to which allergen pair associations evolve over time and the influence of other variables such as age, sex and atopy has not been explored. Here, we develop novel methods to visualize allergen pair associations and explore the influence of date, age, sex and atopy status on allergen pair associations in a series of 45110 consecutive patients tested over 30 years. This uniquely homogeneous patient population represents the largest single centre series reported to date and is a unique and powerful resource for addressing these questions.

Materials and methods

Study population

Patch test records of all patients undergoing testing with a modified European baseline series between 1985 and 2014 were retrieved from a database at St John's Institute of Dermatology at St Thomas' Hospital, London. Data recorded at the time of consultation included age, sex and atopy status. Patch testing was performed with aluminium Finn Chambers® (Bio-Diagnostics) with TROLAB® allergens. Reactions were read on days 2 and 4 according to the Menne and White criteria[9]. For each allergen it was recorded whether the allergen was tested and whether the result was positive or negative. Reactions recorded as +/++/+++ were regarded as positive. Reactions documented as negative, questionable or irritant were regarded as negative. A total of 45110 consecutive patients were recorded between 1985 and 2014. The composition of the baseline series evolved over this time period comprising a total of 38 allergens (Table 1).

Data analysis

Data analysis was performed with Python and R scripts in association with Numpy and Scipy[10] packages for statistical analysis and matplotlib[11] for data visualization. The prevalence of positive results for each allergen was defined as the number of positive tests divided by the number of times that the allergen was tested. For 38 allergens, there are 703 possible associations. For each allergen pair, where both members of the pair were tested in a patient, results were tabulated in a 2 x 2 contingency table. In keeping with previous studies[5,6], the strength of association was quantified by odds ratio with significance according to Fisher's exact test. Odds ratios were only reported where the number of observations exceeded 5 in all segments of the contingency table. Adjustment for multiple testing was performed with the Bonferroni correction, with an *a priori* significance level of 0.05 giving an adjusted p value threshold of 7.1×10^{-5} for significance. In addition we have calculated prevalence ratios and Cohen's kappa coefficient. The latter quantifies inter-rater agreement for qualitative categorical items. Positive values indicate an association between two allergens, with a maximum achievable value of 1 when two allergens give identical results in every patient tested. The kappa coefficient can achieve its maximum value of 1 only when the prevalence of positive results is the same for both allergens. In view of this we also report 'kappa maximum', the largest theoretically achievable kappa given the relative prevalence rates of the two allergens. In this analysis we are interested in a small excess of concordance over that predicted by chance and therefore high kappa values are not anticipated.

To investigate the effects of time of testing, age, sex and atopy status patients were assigned to groups. Time of testing was subdivided into 3 decades: 1985-1995, 1995-2005 and 2005-2014. Spearman rank correlation of odds ratios was 0.47 for 1985-1995 vs 1995-2005, 0.36 for 1995-2005 vs 2005-2014 and 0.10 for 1985-1995 vs 2005-2014. Patient ages were divided into three periods: 0-30 years, 30-60 years and >60 years. Spearman rank correlation was 0.34 for 0-30 vs 30-60; 0.32 for 30-60 vs 60-90 and 0.40 for 0-30 vs 60-90. Patients were also stratified according to sex and atopy status. The Spearman rank correlation between males and females was 0.45. Spearman rank correlation was 0.42 for atopic versus non-atopic individuals. The relationship between these variables is illustrated (Supplementary Figure 1). Differences in the association of allergens between these groups were quantified by the absolute difference in kappa coefficients. Additionally, in order to interdependency of variables, we stratified the comparison of kappa coefficients according to subgroups (Supplementary Table 1).

Data visualization

The prevalence ratios for association between n allergen pairs can be represented as an n x n matrix. To visualize this, data was plotted as 38 x 38 grid using the Python matplotlib package with a linear relationship between colour saturation and prevalence ratio. Allergen pairs for which the association was not found to be significant were not displayed. In order to visualize relationships as a network of interactions between allergens, the Python NetworkX package[12] was employed. Each allergen was plotted as a node and edges were added when both the odds ratio (arbitrarily) exceeded 8.0 and the relationship was statistically significant.

Results

A total of 45100 patients underwent patch testing between 1985 and 2014. Of these patients, 9800 patients exhibited reactions to 1 allergen and 8300 to 2 or more allergens. There is a log-linear relationship between the number of positive allergens and number of patients (Figure 1A) with a maximum of 10 positive reactions observed. To facilitate comparison, allergens were assigned a numeric code from 1-38 according to the prevalence of positive reactions in the overall dataset ie. the number of positive readings divided by the sum of positive and negative results (Table 1; Figure 1B). In accordance with previous studies[5], the highest prevalence of positive results was seen for nickel (0.17) and fragrance mix I (0.07). Cetostearyl alcohol (0.0032) and chlorocresol (0.0016) exhibited the lowest prevalence of positive reactions.

Allergen pair associations

For 38 allergens, there are a total of 703 possible pair-wise combinations. Odds ratios (OR), prevalence ratios and p values for each of these pairs were calculated with Fisher's exact test and adjusted for multiple testing with the Bonferroni correction. It was found that 243 pairs were associated in excess of that predicted by chance with odds ratios ranging from 1160 to 1.4. The top 100 associations (by odds ratio) are listed in Table 2. As anticipated, strong associations were observed for mercaptobenzothiazole and mercapto mix (OR 1160, CI 861-1600), both of which are rubber accelerators; imidazolidinyl urea and diazolidinyl urea (OR 910, CI 599-1457), both of which are formaldehyde-releasing preservatives; methylisothiazolinone and methylchloroisothiazolinone / methylisothiazolinone mix (OR 271, CI 159-492) and fragrance mix 2 and hydroxylisohexyl 3-cyclohexene carboxaldehyde (OR 154 CI 70-370). There were no examples of significant pair associations with an odds ratio less than zero and therefore no evidence to support negative associations between allergens. Whilst the majority of these associations are well characterised, several unexpected relationships were also observed including associations between colophonium and thiuram mix (OR 4.3, CI 3.6-5.0); primin and thiuram mix mix (OR 4.5, CI 3.0-6.5) and epoxy resin and sesquiterpene lactone (OR 5.5, CI 3.4-8.6). All of these associations were significant at the Bonferonni adjusted p value threshold.

To visualize all pair-wise allergen associations, allergens were plotted on a 38 x 38 grid in order of overall prevalence (Figure 1C). Thus, the most prevalent allergen – nickel – is represented by the lowermost row and left column and the least prevalent – chlorocresol – by the top row and right column of the grid. Colour saturation in the green channel is linearly correlated with prevalence ratio. Unlike odds ratio, the latter is dependent upon the order of the associations. Nevertheless, although there are minor variations, the matrix largely exhibits symmetry about the bottom-left to top-right axis indicating that the order of association generally has little impact upon associations and therefore that the odds ratio captures effectively the strength of associations. In order to clarify allergen pair relationships, a network was generated with the Python Networkx package[12]. Allergens are plotted as nodes and joined by edges where a significant odds ratio in excess of 8.0 was present (Figure 1D). It can be observed that allergens spontaneously arrange into recognized groups including fragrances, preservatives, metals, medicaments and rubbers (dashed lines).

Evolution of relationships over time

Next, we examined the stability of allergen associations over the 30 year study period. Over this time period, the number of patients undergoing patch testing per year in our centre has varied within the range of 1000-1900 (Figure 2A). There are considerable differences in allergen relationships over the three decades examined. This can be visualized by plotting the individual odds ratios for the 3 decades separately with saturation in the red (Figure 2B), green (Figure 2C) and blue (Figure 2D) colour channels. To facilitate comparison of these relations, the 3 colour channels were superimposed (Figure 2E). Where the three time periods exhibit complete overlap the relevant segment will appear white or grey, if one of the primary colours predominates then the allergen pair relationship predominates in this time period.

It is anticipated that differences in allergen associations over time will reflect a combination of changing patterns of exposure and changes in the composition of the test series. As expected, strong pair associations such as mercaptobenzothiazole and mercapto mix or Imidazolidinyl urea and Diazolidinyl Urea were consistent at all time periods. To identify significant differences we calculated the absolute difference in Cohen's kappa coefficient 'delta Kappa' between these time periods for each allergen pair. For comparison, odds ratios with confidence intervals for each time period are also shown (Table 3). The top 10 differences are listed in Table 3. A particularly striking observation is the increased strength of association between formaldehyde and formaldehyde-releasing preservatives between early and later time points. For the time periods 1985-1994 versus 1995-2004, there was an increase in the association of formaldehyde and diazolidinlyl urea, quaternium 15 and diazolidinyl urea, formaldehyde and imidizalidinyl urea and quaternium 15 and imidizalidinyl urea. This is consistent when the comparison is stratified according to age, sex, and atopy status (Supplementary Table 1). A similar increase in association was noted for quaternium 15 and diazolidinyl urea between 1985-1994 and 2005-2014.

Patient age

The age distribution for patients in our series exhibits a peak at approximately 25 years of age, with a shoulder at approximately 50 years of age (Figure 2F). This is consistent across the three decades of testing (Supplementary Figure 1J). A significant increase in the association of colophonium and sesquiterpene lactone was observed between age ranges 0-29 versus 60-100 and 30-59 versus 60-100. This strong association is present in both males and females, however interestingly the strength of association is lower in atopic compared to non-atopic individuals (Supplementary Table 1).

Another notable difference was the increased association of cobalt and thiuram mix between ages 0-29 and 60-100 and 30-59 and 60-100 (Table 3). In an analogous manner to Figure 2B-E, to facilitate a global comparison, the three age groups were plotted in separate colour channels (Figure 2G-J).

Effects of patient sex

We wished to investigate other variables governing allergen pair associations. First, we examined the effect of patient sex. In our series, 38% of patients were male (Figure 3A). A number of allergen pairs exhibited a significantly stronger association in males than females including cobalt and potassium dichromate, multiple formaldehyde-releasing preservatives – quaternium 15 and imidizalidinyl urea, quaternium 15 and diazolidinyl urea, formaldehyde and imidizalidinyl urea in addition to cobalt and sesquiterpene lactone (Table 3). The association between cobalt and potassium dichromate was particularly robust across all subgroups (Supplementary Table 1). To visualize sex-specific differences, allergen pair relationships were plotted in the red channel for males (Figure 3B) and in the blue channel for females (Figure 3C-D).

Effects of atopy status

30% of the patients in our series were classified as atopic by the assessing doctor (Figure 3E) according to the UK diagnostic criteria developed by Williams and Flohr[13]. Significant differences are listed in Table 3 and included an increased association between caine mix and PPD and quaternium 15 and PPD. Allergen pair relationships were plotted in red for atopic (Figure 3F) and blue for non-atopic (Figure 3G) individuals. A comparison is shown in Figure 3H.

Discussion

We have reported the largest single-centre study of patch test allergen pair associations. This uninterrupted 30 year series is of particular value in understanding the variables governing allergen pair relationships. Brasch et al[5] collated a series of 57822 patients from 32 German centres over a 6 year periods between 1993-1999. However data from only 32779 patients was analysed since the others had not undergone complete readings on all allergens. The duration of our study is greater, permitting comparison of allergen relationships in different time periods, moreover we have for the first time studied prevalence ratios and Cohen's Kappa statistic in addition to odds ratios.

Allergen associations reflect a combination of structural cross-reactivity[14] and exposure patterns. Common exposure can arise when allergens are present within the same products or are applied in combination to the same site. An example is leg ulcer patients, for whom sensitization to topical products is common[15]. Furthermore, it is possible that genetic predisposition lowers the threshold for sensitization or increases the risk of sensitization to specific allergens[16]. Dissecting the relative importance of these factors has been challenging. We have identified a total of 243 statistically significant allergen associations out of 703 possible associations. In keeping with previous studies[5,6,17], strong associations were observed between cobalt and Nickel, cobalt and potassium dichromate and formaldehyde and formaldehyde-releasing preservatives such as quaternium-15. These relationships are particularly apparent when plotted as a network, where it is apparent that members of allergen groups including fragrances, preservatives, rubbers, metals and medicaments self-associate. Whilst many of these relationships were expected, a number of unexpected relationships were also present. One could speculate on the cause of these associations; colophonium[18] and thiuram[19] may both be contained in surgical and sporting tape and footwear. Regarding thiuram and primin, thiuram chemicals are used as pesticides in the horticultural industry. Finally, with regard to the association of epoxy resin and sesquiterpene lactone mix, a sesquiterpene lactone in compositae with an epoxy side chain has been reported[20].

In order to establish the degree of variability in allergen pair associations we first examined changes over time. Since there have not been significant changes to the patch testing methodology over this period of time it is anticipated that changes in allergen pair associations over time will primarily reflect changes in exposure patterns and changes in the composition of the test series. A striking difference was the increased association of allergies to formaldehyde and formaldehyde-releasing preservatives over this time period and this may reflect an increased exposure to these products. It is noted that a reduction in the number of occasions that an allergen pair combination is tested will not reduce the magnitude of the odds ratio but could reduce the degree of statistical significance.

Next we looked at the impact of patient age on associations. Previous data regarding the impact of age upon contact allergy is complex with one study reporting a higher incidence of positive patch test results in an aged population without dermatitis[21], however a second study suggested that age effects may be allergen-specific[22]. We observed a large degree of age-specific variation, which included increases in the association of cobalt and thiuram mix and colophonium and sesquiterpene lactone. The latter is interesting as this combination of allergens is frequently encountered in patients with chronic actinic dermatitis who are typically older than 60. Alterations in allergen pair associations with age likely reflect a complex, allergen-specific interplay of allergen exposure and immunosenescence. There is evidence that the aged immune system exhibits a diminished delayed hypersensitivity response which may reflect reduced lymphokine production[23]. In addition there may be differences in T cells subsets present in the elderly[24].

Finally we examined the effects of patient sex and atopy status. Cobalt was associated with dichromate to a considerably greater extent in males compared to females. The reasons for this are unclear but might reflect occupational exposure. There was also an increased association of formaldehyde and formaldehyde-releasing preservatives in males compared to females. Previous studies have reported a higher incidence of nickel and cobalt allergy in females[22], and this may reflect greater sensitization as a consequence of jewellery exposure. We observed a number of alterations in allergen pair associations in atopic versus non-atopic individuals including greater association between PPD and both caine mix and quaternium 15 in atopic compared to non-atopic patients. A previous study found a similar frequency of positive patch test results in patients with or without atopic dermatitis[25], however a higher frequency of multiple sensitization was noted. A second study of patients with loss of function mutations in the filaggrin gene found increased sensitization to lanolin (wool alcohol) and PTBP resin[26].

In summary, this is the largest reported study of patch test allergen pair relationships. Our analysis reveals that allergen pair relationships are far more dynamic than previously appreciated with variation according to date of testing, age, sex and atopy status.

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Figure legends

Figure 1

Association of tested allergen pairs

A) Number of positive reaction per patient (log scale).

B) Overall prevalence of positive patch tests to each tested allergen. Allergens are displayed in order of overall prevalence. Allergen names are as listed in Table 1.

C) Pair-wise relationship of all tested allergens. Allergens are plotted in order of prevalence as listed in Table 1 from bottom-left to bottom-right and from bottom-left to top-left therefore the graph is symmetrical about the diagonal. Saturation in the green channel is proportional to prevalence ratio.

D) Network relationship of tested allergens. Allergens are plotted as nodes with edges plotted for all significant associations with an odds ratio in excess of 8.0.

Figure 2

Impact of time of testing and age of patient on pair-wise allergen associations

A) Number of patients undergoing patch testing per year. The number of patients undergoing patch tested is plotted per year from 1985-2014.

B-D) Pair-wise prevalence ratios are plotted in red, green and blue channels for patients undergoing patch testing from 1985-1995 (B), 1995-2005 (C) and 2005-2014 (D).

E) Comparison of pair-wise allergen prevalence ratios for the 3 tested time periods. Superimposing the 3 colour channels illustrates the extent to which allergen pair relationships differ between these time periods.

F) Age distribution of patients undergoing patch testing.

G-I) Pair-wise prevalence ratios are plotted in red, green and blue channels for patients aged <30 (G), 30-60 (H) and >60 (I).

J) Comparison of pair-wise allergen associations for these 3 age groups.

Figure 3

Impact of sex and atopy status on pair-wise allergen associations

A) Sex distribution of patients undergoing patch testing. Red indicates males and blue females.

B-C) Allergen pair prevalence ratios for males (B) and females (C). Colour saturation is linearly related to odds ratio.

D) Comparison of allergen pair relationships in males and females. Associations with complete overlap will appear purple.

E) Quantification of atopic (red) versus non-atopic (blue) patients undergoing patch testing.

F-G) Allergen pair prevalence ratios for atopic (F) and non-atopic (G) patients. Colour saturation is linearly related to odds ratio.

H) Comparison of allergen pair relationships in atopic and non-atopic patients. Associations with complete overlap will appear purple.

Tables

Table 1: Allergen names, numeric code and prevalence

Numeric code	Short name	Full name	Prevalence
1	NICKEL	Nickel	0.1703
2	PERFUME	Fragrance mix I	0.07
3	MI	Methylisothiazolinone	0.0624
4	COBALT	Cobalt chloride	0.0594
5	COLOPHONY	Colophonium	0.0411
6	NEOMYCIN	Neomycin	0.0359
7	PPD BASE 1	Paraphenylenediamine Base (1% petroleum)	0.0357
8	THIURAMS	Thiuram mix	0.0337
9	BALSAMPERU	Myroxylon pereirae	0.0297
10	SODIUM METABISULFITE	Sodium metabisulfite	0.029
11	DICHROMATE	Potassium dichromate (0.5%)	0.0268
12	FMII	Fragrance mix II	0.0241
13	FORMALIN	Formaldehyde	0.024
14	DOWICIL200	Quaternium-15	0.0195
15	WOOL ALC	Lanolin (Wood alcohol)	0.0158
16	KATHON	Methylchloroisothiazolinone : Methylisothiazolinone (3:1)	0.0155
17	LACTONE	Sesquiterpene lactone	0.0136
18	EUXYL	Methyldibromo glutaronitrile	0.0134
19	TIXOCORTAL	Tixocortol pivolate	0.0124
20	ETHYLENEDI	Ethylenediamine	0.0123
21	CAINES	Caine mix	0.0112
22	EPOXY	Epoxy resin	0.0106
23	MBT	Mercaptobenzothiazole	0.0104
24	LYRAL	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	0.0102
25	PTBP RESIN	PTBP resin	0.0098
26	MERCAPTO	Mercapto mix	0.0095
27	PPD	Paraphenylenediamine	0.009
28	GERMALL2	Diazolidinyl urea	0.0089
29	CARBA	Carba mix	0.0085

30	BRONOPOL	2-bromo-2-nitropropane-1,3-diol	0.008
31	GERMALL	Imidazolidinyl urea	0.0078
32	QUINOLINE	Quinoline (Clioquinol)	0.0068
33	YELLOW3	Disperse Yellow 3	0.0063
34	PARABENS	Paraben mix	0.0055
35	PRIMIN	Primin	0.0055
36	PPD RUBBER	N-isopropyl-N-phenyl-paraphenylenediamine	0.005
37	CETOSTERYL	Cetostearyl alcohol (Cetearyl alcohol)	0.0032
38	CHL CRESOL	Chlorocresol	0.0016

Table 2: Top 100 significant allergen associations

Uncorrected p values are reported. All displayed associations are significant with a Bonferonni corrected threshold for significance of 7.1×10^{-5}.

Allergen 1	Allergen 2	Odds ratio	CI lower	CI upper	P value	Kappa	Max kappa	Number double positive
Mercaptobenzothiazole	Mercapto mix	1200	860	1600	<5e-324	0.74	0.96	327
Imidizalidinyl urea	Diazolidinyl urea	910	600	1500	8e-302	0.67	0.87	157
Methylisothiazolinone / Methylchloroisothiazolinone	Methylisothiazolinone	270	160	490	2e-149	0.78	0.97	125
Fragrance mix 2	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	150	70	370	2e-39	0.37	0.51	28
Carba mix	Thiuram mix	140	100	210	4e-219	0.34	0.45	168
Quaternium 15	Formaldehyde	87	74	100	<5e-324	0.48	0.89	470
Quaternium 15	Diazolidinyl urea	46	35	61	2e-105	0.26	0.74	95
Formaldehyde	Diazolidinyl urea	36	27	47	3e-104	0.22	0.59	104
Chlorocresol	Quinoline	35	12	88	7e-08	0.056	0.31	6
Cetostearyl alcohol	Tixocortyl pivolate	32	18	54	9e-23	0.098	0.37	21
N-isopropyl-N-phenyl-paraphenylenediamine	Disperse yellow 3	29	15	50	2e-17	0.11	0.83	16

Caine mix	Disperse yellow 3	24	15	37	1e-28	0.13	0.74	30
Carba mix	Mercaptobenzothiazole	24	16	36	4e-34	0.15	0.94	36
Carba mix	Mercapto mix	23	15	34	7e-31	0.14	0.96	33
Carba mix	N-isopropyl-N-phenyl-paraphenylenediamine	22	12	36	3e-18	0.1	0.76	19
Balsum of Peru	Fragrance mix 1	21	19	24	<5e-324	0.3	0.59	648
Mercaptobenzothiazole	Thiuram mix	19	16	24	1e-130	0.16	0.46	171
Chlorocresol	Mercaptobenzothiazole	18	7.1	39	6e-08	0.039	0.26	8
Paraphenylenediamine Base (1% petroleum)	Disperse yellow 3	18	13	25	1e-44	0.095	0.25	59
Cetostearyl alcohol	Lanolin	17	10	28	1e-18	0.065	0.35	22
Chlorocresol	Mercapto mix	17	6.3	38	6e-07	0.037	0.29	7
Mercapto mix	Thiuram mix	17	14	21	1e-106	0.14	0.43	146
Cetostearyl alcohol	Parabens mix	16	6.4	33	1e-07	0.052	0.76	8
Formaldehyde	Imidizalidinyl urea	16	12	21	8e-58	0.12	0.49	78
Chlorocresol	Lanolin	15	6.2	31	5e-08	0.032	0.2	9
Quaternium 15	Imidizalidinyl urea	15	11	20	2e-48	0.11	0.57	65
Ethylenediamine	Neomycin	15	12	18	2e-121	0.15	0.5	180
Fragrance mix 2	Fragrance mix 1	15	9.3	23	2e-26	0.23	0.71	39
Mercapto mix	N-isopropyl-N-phenyl-paraphenylenediamine	15	9.3	23	1e-20	0.075	0.69	26
Parabens mix	Quinoline	15	8.5	25	5e-15	0.071	0.88	18
2-bromo-2-nitropropane-1,3-diol	Methylisothiazolinone / Methylchloroisothiazolinone	14	10	20	5e-41	0.11	0.65	56
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	Fragrance mix 1	14	8.1	25	5e-17	0.12	0.33	24
Cetostearyl alcohol	Primin	13	4.5	30	1e-05	0.041	0.82	6
Cobalt	Potassium dichromate (0.5%)	13	11	15	2e-276	0.22	0.61	477
Cobalt	Nickel	13	12	14	<5e-324	0.29	0.47	1764
Parabens mix	Lanolin	13	8.8	18	3e-28	0.077	0.52	40
Paraphenylenediamine Base (1% petroleum)	N-isopropyl-N-phenyl-paraphenylenediamine	13	9	19	2e-30	0.064	0.22	45
Quinoline	Tixocortyl pivolate	13	7.7	22	9e-15	0.073	0.58	19

Mercaptobenzothiazole	N-isopropyl-N-phenyl-paraphenylenediamine	12	7.2	18	2e-16	0.062	0.65	23
Balsum of Peru	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	11	5.6	21	6e-10	0.11	0.59	14
Caine mix	Parabens mix	11	6.9	18	1e-15	0.063	0.64	22
Caine mix	Paraphenylenediamine Base (1% petroleum)	10	8	13	3e-51	0.11	0.46	89
Cetostearyl alcohol	Ethylenediamine	10	4.8	20	1e-07	0.04	0.49	10
Neomycin	Tixocortyl pivolate	10	7.6	13	4e-43	0.11	0.57	75
Carba mix	Quinoline	9.7	3.7	21	2e-05	0.049	0.95	7
2-bromo-2-nitropropane-1,3-diol	Formaldehyde	9.6	6.9	13	6e-31	0.08	0.52	53
Carba mix	Paraphenylenediamine	9.5	5.2	16	1e-10	0.063	0.95	16
Neomycin	Quinoline	9.3	6.9	13	5e-35	0.069	0.32	63
Carba mix	PTBP resin	9.1	4.8	16	2e-09	0.058	0.97	14
Formaldehyde	Methylisothiazolinone / Methylchloroisothiazolinone	8.9	7.1	11	4e-55	0.11	0.79	103
N-isopropyl-N-phenyl-paraphenylenediamine	Primin	8.9	4.2	17	5e-07	0.038	0.95	10
2-bromo-2-nitropropane-1,3-diol	Methyldibromoglutaronitrile	8.7	5.4	13	3e-14	0.069	0.79	24
Caine mix	Tixocortyl pivolate	8.7	5.6	13	2e-16	0.077	0.95	28
Colophonium	Sesquiterpene lactone	8.7	6.9	11	4e-57	0.11	0.5	112
Sesquiterpene lactone	Thiuram mix	8.7	6.8	11	1e-51	0.11	0.56	100
Paraphenylenediamine	N-isopropyl-N-phenyl-paraphenylenediamine	8.3	3.7	17	3e-06	0.043	0.72	9
Fragrance mix 2	Lanolin	7.9	3.5	16	3e-06	0.096	0.73	10
Neomycin	Lanolin	7.9	6.5	9.5	8e-71	0.11	0.6	149
Parabens mix	Tixocortyl pivolate	7.8	3.9	14	2e-07	0.044	0.58	12
Carba mix	Parabens mix	7.6	3	17	7e-05	0.036	0.7	7
Chlorocresol	Neomycin	7.6	3.5	15	1e-06	0.016	0.085	11
Potassium dichromate (0.5%)	Sesquiterpene lactone	7.6	5.8	10	8e-35	0.093	0.68	71
N-isopropyl-N-phenyl-paraphenylenediamine	PTBP resin	7.6	4.1	13	6e-09	0.039	0.67	15

N-isopropyl-N-phenyl-paraphenylenediamine	Thiuram mix	7.3	5.1	10	2e-21	0.043	0.25	44
Caine mix	N-isopropyl-N-phenyl-paraphenylenediamine	7.2	3.8	12	4e-08	0.039	0.63	14
Sesquiterpene lactone	Primin	7.2	3.7	13	1e-07	0.037	0.49	13
Tixocortyl pivolate	Lanolin	7.1	4.7	11	9e-16	0.071	0.91	31
Caine mix	Quinoline	7	4.1	12	7e-10	0.045	0.74	18
Quaternium 15	Parabens mix	6.9	4.5	10	1e-14	0.044	0.44	29
Quinoline	Lanolin	6.9	4.3	11	7e-13	0.049	0.6	25
2-bromo-2-nitropropane-1,3-diol	Quaternium 15	6.8	4.6	9.9	3e-16	0.056	0.61	33
Balsum of Peru	Parabens mix	6.6	4.5	9.6	7e-17	0.042	0.3	36
Cetostearyl alcohol	Neomycin	6.5	3.7	11	2e-09	0.026	0.18	19
Mercapto mix	Primin	6.5	3.5	11	1e-07	0.035	0.73	14
2-bromo-2-nitropropane-1,3-diol	Mercaptobenzothiazole	6.4	3.6	11	7e-09	0.043	0.92	17
Mercaptobenzothiazole	Quinoline	6.4	3.5	11	5e-08	0.04	0.83	15
N-isopropyl-N-phenyl-paraphenylenediamine	Quinoline	6.4	2.7	13	6e-05	0.029	0.85	8
Parabens mix	Primin	6.3	2.7	13	7e-05	0.027	0.99	8
Chlorocresol	Fragrance mix 1	6.1	3.1	11	5e-07	0.011	0.044	15
Potassium dichromate (0.5%)	Mercapto mix	6.1	4.5	8.1	1e-24	0.059	0.52	58
Mercapto mix	PTBP resin	6.1	3.8	9.4	5e-11	0.045	0.98	23
Caine mix	Ethylenediamine	6	3.8	9.2	1e-11	0.049	0.98	25
Chlorocresol	Colophonium	6	2.7	12	3e-05	0.012	0.073	10
2-bromo-2-nitropropane-1,3-diol	Mercapto mix	5.9	3.2	10	2e-07	0.038	0.94	15
2-bromo-2-nitropropane-1,3-diol	Parabens mix	5.9	2.6	12	4e-05	0.029	0.8	9
Carba mix	Colophonium	5.9	4	8.4	1e-16	0.053	0.35	40
Cetostearyl alcohol	Colophonium	5.9	3.5	9.6	2e-09	0.023	0.14	21
Carba mix	Potassium dichromate (0.5%)	5.8	3.7	8.7	3e-12	0.052	0.49	28
Imidizalidinyl urea	Parabens mix	5.8	2.6	11	5e-05	0.029	0.83	9
Mercapto mix	Quinoline	5.8	3	10	1e-06	0.035	0.85	13

Balsum of Peru	Fragrance mix 2	5.7	2.8	11	3e-06	0.092	0.99	13
2-bromo-2-nitropropane-1,3-diol	Diazolidinyl urea	5.7	2.9	10	4e-06	0.038	0.98	12
Caine mix	Lanolin	5.7	3.8	8.2	4e-14	0.053	0.84	33
Potassium dichromate (0.5%)	Disperse yellow 3	5.7	3.3	9.2	1e-08	0.04	0.41	19
Quaternium 15	Methylisothiazolinone / Methylchloroisothiazolinone	5.7	4.3	7.5	3e-24	0.068	0.89	60
Ethylenediamine	Parabens mix	5.7	3.2	9.6	9e-08	0.033	0.62	16
Parabens mix	PTBP resin	5.7	3	10	1e-06	0.031	0.72	13
2-bromo-2-nitropropane-1,3-diol	Imidizalidinyl urea	5.5	2.7	10	1e-05	0.031	0.97	11
Caine mix	Neomycin	5.5	4.2	7.3	1e-25	0.062	0.49	67
Epoxy resin	Sesquiterpene lactone	5.5	3.4	8.6	9e-10	0.046	0.84	22

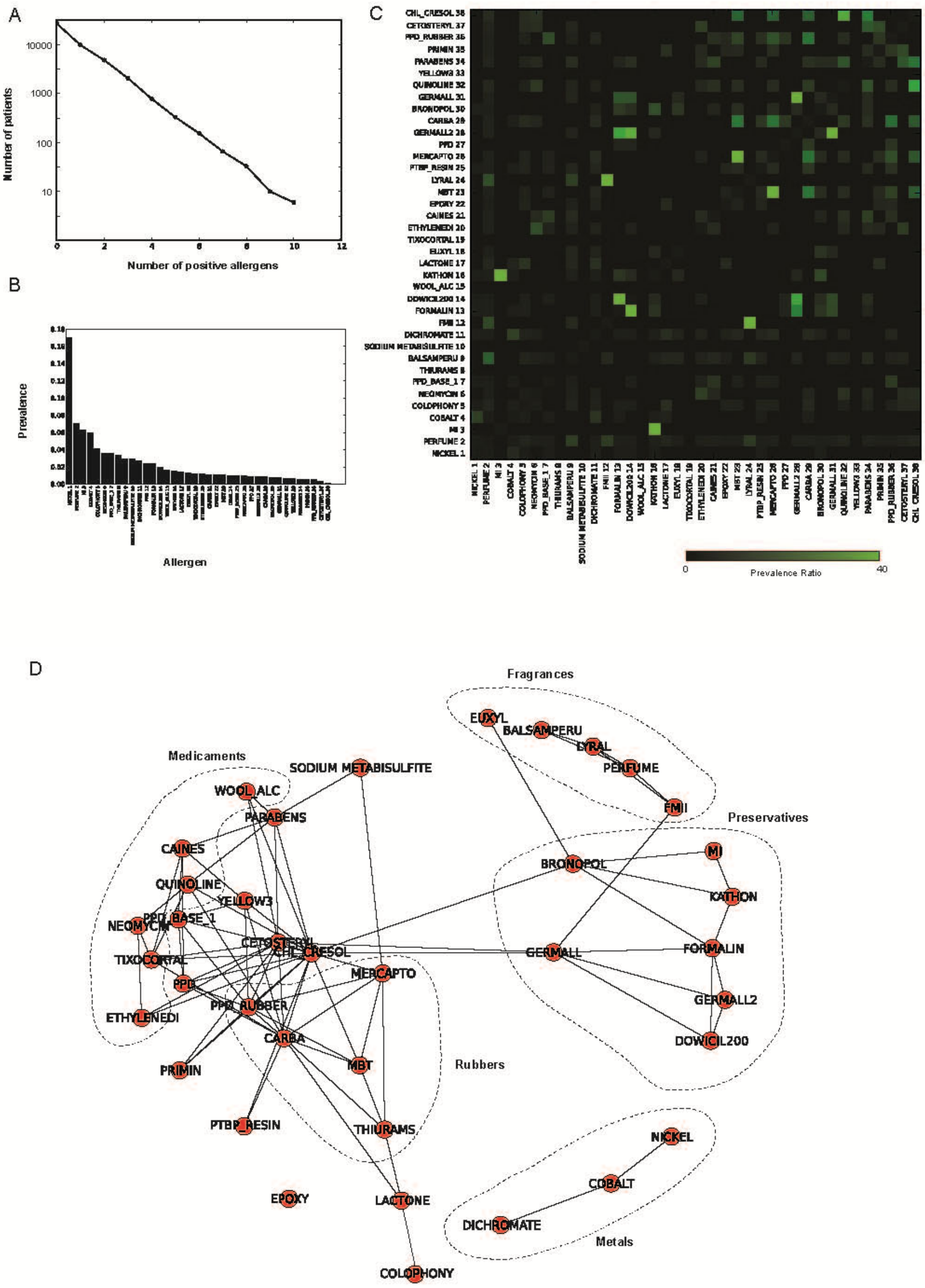
Table 3: Dynamic alterations in allergen pair associations (top 10 changes for each comparison)

Allergen 1	**Allergen 2**	**Kappa 1**	**Kappa 2**	**Delta Kappa**	**Odds ratio 1**	**CI 1 (lower)**	**CI 1 (upper)**	**Odds ratio 2**	**CI 2 (lower)**	**CI 2 (upper)**
1985-1994 vs 1995-2004										
Formaldehyde	Diazolidinyl urea	0.14	0.32	0.18	13	7.9	21	67	43	100
Quaternium 15	Diazolidinyl urea	0.19	0.31	0.12	21	12	34	61	39	95
Formaldehyde	Imidizalidinyl urea	0.1	0.17	0.069	10	6.9	15	33	19	57
Imidizalidinyl urea	Diazolidinyl urea	0.72	0.66	0.065	730	410	1500	1100	540	2400
Caine mix	Paraphenylene diamine Base (1% petroleum)	0.081	0.14	0.056	6.9	3.9	12	13	8.9	19
Quaternium 15	Imidizalidinyl urea	0.096	0.15	0.056	9.5	6.1	14	27	15	48
Colophonium	Sesquiterpene lactone	0.14	0.084	0.054	8.8	6.4	12	6.3	4.1	9.4
Ethylenediamine	Neomycin	0.18	0.13	0.052	16	12	20	15	9.8	24
Potassium dichromate (0.5%)	Disperse yellow 3	0.089	0.038	0.051	15	5.3	41	5.2	2.3	11

Mercaptobenzothiazole	Mercapto mix	0.75	0.71	0.049	1000	650	1600	940	530	1900
1995-2004 vs 2005-2014										
Formaldehyde	Diazolidinyl urea	0.32	0.2	0.12	67	43	100	57	31	100
Caine mix	Disperse yellow 3	0.11	0.21	0.1	17	8.2	33	48	25	90
Imidizalidinyl urea	Diazolidinyl urea	0.66	0.55	0.1	1100	540	2400	940	370	2300
Formaldehyde	Imidizalidinyl urea	0.17	0.095	0.079	33	19	57	26	12	54
Colophonium	Fragrance mix 1	0.13	0.069	0.065	4.7	3.8	5.9	3.4	2.3	4.8
Cobalt	Potassium dichromate (0.5%)	0.24	0.17	0.065	15	12	19	13	9.3	18
Paraphenylenediamine Base (1% petroleum)	Disperse yellow 3	0.12	0.06	0.064	25	15	42	10	5.1	19
Ethylenediamine	Neomycin	0.13	0.073	0.057	15	9.8	24	12	5.5	26
Epoxy resin	Sesquiterpene lactone	0.041	0.097	0.055	5	1.9	11	17	6.9	38
Neomycin	Tixocortyl pivolate	0.12	0.064	0.054	10	6.6	15	8.2	3.7	16
1985-1994 vs 2005-2014										
Imidizalidinyl urea	Diazolidinyl urea	0.72	0.55	0.17	730	410	1500	940	370	2300
Ethylenediamine	Neomycin	0.18	0.073	0.11	16	12	20	12	5.5	26
Colophonium	Fragrance mix 1	0.16	0.069	0.09	5.1	4.3	6.1	3.4	2.3	4.8
Quaternium 15	Diazolidinyl urea	0.19	0.27	0.083	21	12	34	87	47	160
Neomycin	Lanolin	0.11	0.034	0.081	7.7	5.7	10	3.9	1.5	8.4
Epoxy resin	Sesquiterpene lactone	0.02	0.097	0.077	2.4	0.87	5.6	17	6.9	38
Neomycin	Tixocortyl pivolate	0.13	0.064	0.071	7.8	4.8	12	8.2	3.7	16
Sesquiterpene lactone	Thiuram mix	0.12	0.059	0.066	7.9	5.6	11	7.6	3.4	15
Potassium dichromate (0.5%)	Thiuram mix	0.098	0.035	0.063	4.5	3.5	5.8	3	1.4	5.6
Formaldehyde	Diazolidinyl urea	0.14	0.2	0.062	13	7.9	21	57	31	100
Age 0-29 vs 30-59										
Cobalt	Potassium dichromate (0.5%)	0.16	0.27	0.11	12	9.5	16	15	13	18
N-isopropyl-N-phenyl-paraphenylenediamine	Disperse yellow 3	0.2	0.1	0.1	98	32	280	21	9.1	45

Caine mix	Disperse yellow 3	0.23	0.13	0.099	75	30	180	24	13	43
Colophonium	Thiuram mix	0.017	0.095	0.078	1.8	0.99	3.1	4.1	3.3	5.1
Imidizalidinyl urea	Diazolidinyl urea	0.66	0.59	0.068	1400	560	4200	640	370	1200
Carba mix	Thiuram mix	0.35	0.28	0.065	260	120	610	87	56	140
Quaternium 15	Formaldehyde	0.53	0.47	0.065	140	110	200	74	59	91
Formaldehyde	Diazolidinyl urea	0.18	0.23	0.051	50	25	100	43	29	63
Quaternium 15	Diazolidinyl urea	0.21	0.26	0.051	64	31	130	55	37	81
Mercapto mix	Thiuram mix	0.094	0.14	0.049	13	7.5	22	18	13	24
Age 30-59 vs 60-100										
Colophonium	Sesquiterpene lactone	0.055	0.24	0.18	5.5	3.6	8.2	9.5	6.8	13
Imidizalidinyl urea	Diazolidinyl urea	0.59	0.76	0.17	640	370	1200	750	360	1600
Carba mix	Thiuram mix	0.28	0.45	0.17	87	56	140	210	97	510
Potassium dichromate (0.5%)	Sesquiterpene lactone	0.057	0.18	0.13	5.7	3.5	9	8.7	5.8	13
Sesquiterpene lactone	Thiuram mix	0.067	0.18	0.12	6.5	4.3	9.7	6.4	4.6	8.8
Cobalt	Sesquiterpene lactone	0.039	0.16	0.12	3.9	2.6	5.8	5.9	4	8.4
2-bromo-2-nitropropane-1,3-diol	Methylisothiazolinone / Methylchloroisothiazolinone	0.089	0.2	0.11	11	7	18	24	13	44
Formaldehyde	Imidizalidinyl urea	0.11	0.21	0.096	17	11	25	16	9.6	25
Cobalt	Thiuram mix	0.049	0.13	0.084	2.3	1.8	2.9	4.6	3.4	6.3
Carba mix	Cobalt	0.0057	0.082	0.076	1.4	0.63	2.8	5	2.5	9.5
Age 0-29 vs 60-100										
Colophonium	Sesquiterpene lactone	0.045	0.24	0.19	14	5.7	33	9.5	6.8	13
Cobalt	Sesquiterpene lactone	0.011	0.16	0.14	3.6	1.2	9.2	5.9	4	8.4
Colophonium	Thiuram mix	0.017	0.16	0.14	1.8	0.99	3.1	4.9	3.7	6.5
Formaldehyde	Imidizalidinyl urea	0.069	0.21	0.14	16	7.4	31	16	9.6	25
2-bromo-2-nitropropane-1,3-diol	Methylisothiazolinone / Methylchloroisothiazolinone	0.078	0.2	0.12	12	5.2	23	24	13	44
Quaternium 15	Formaldehyde	0.53	0.42	0.11	140	110	200	61	40	94
Carba mix	Mercaptobenzothiazole	0.1	0.21	0.11	23	7.7	59	25	12	52

Cobalt	Thiuram mix	0.029	0.13	0.1	2.2	1.5	3.1	4.6	3.4	6.3
Carba mix	Thiuram mix	0.35	0.45	0.1	260	120	610	210	97	510
Imidizalidinyl urea	Diazolidinyl urea	0.66	0.76	0.099	1400	560	4200	750	360	1600
Male vs Female										
Cobalt	Potassium dichromate (0.5%)	0.38	0.15	0.24	30	25	37	10	8.7	13
Quaternium 15	Imidizalidinyl urea	0.21	0.078	0.13	40	25	64	9.3	6.2	14
Quaternium 15	Diazolidinyl urea	0.34	0.22	0.12	84	51	140	36	25	50
Balsum of Peru	Fragrance mix 1	0.37	0.26	0.12	26	22	32	19	16	22
Formaldehyde	Imidizalidinyl urea	0.2	0.087	0.11	35	22	55	10	7.1	15
Formaldehyde	Diazolidinyl urea	0.29	0.19	0.093	55	34	86	29	20	41
Caine mix	Tixocortyl pivolate	0.13	0.041	0.086	14	7.7	25	4.9	2.3	9.5
Neomycin	Tixocortyl pivolate	0.17	0.081	0.085	15	10	23	7.2	4.7	11
Cobalt	Sesquiterpene lactone	0.1	0.032	0.073	7.2	4.9	10	3	2.1	4.2
Potassium dichromate (0.5%)	Nickel	0.099	0.032	0.067	4	3.2	5.1	2.7	2.3	3.2
Atopic vs Not atopic										
Balsum of Peru	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	0.16	0.069	0.09	21	7.2	58	6.4	2.2	16
Caine mix	Paraphenylene diamine Base (1% petroleum)	0.17	0.087	0.084	20	13	31	7.8	5.6	11
Carba mix	Thiuram mix	0.29	0.36	0.068	200	91	480	130	89	190
Nickel	Sodium metabisulfite	0.093	0.031	0.062	8.2	2.3	30	1.6	0.71	3.4
Caine mix	Disperse yellow 3	0.17	0.11	0.06	36	17	72	20	11	35
Quaternium 15	Paraphenylene diamine Base (1% petroleum)	0.067	0.011	0.057	5.1	2.9	8.4	1.5	0.88	2.4
Parabens mix	Lanolin	0.037	0.092	0.055	7.6	2.6	18	14	9.4	21
Caine mix	Tixocortyl pivolate	0.041	0.095	0.055	4.7	1.6	11	11	6.7	18
Formaldehyde	Imidizalidinyl urea	0.15	0.1	0.05	25	15	41	13	8.8	18
Methyldibromoglutaronitrile	Methylisothiazolinone / Methylchlorois othiazolinone	0.089	0.04	0.049	8.5	4.5	15	3.7	2.1	6.2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Number of positive allergens
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Prevalence
Allergen
C
Prevalence Ratio
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40
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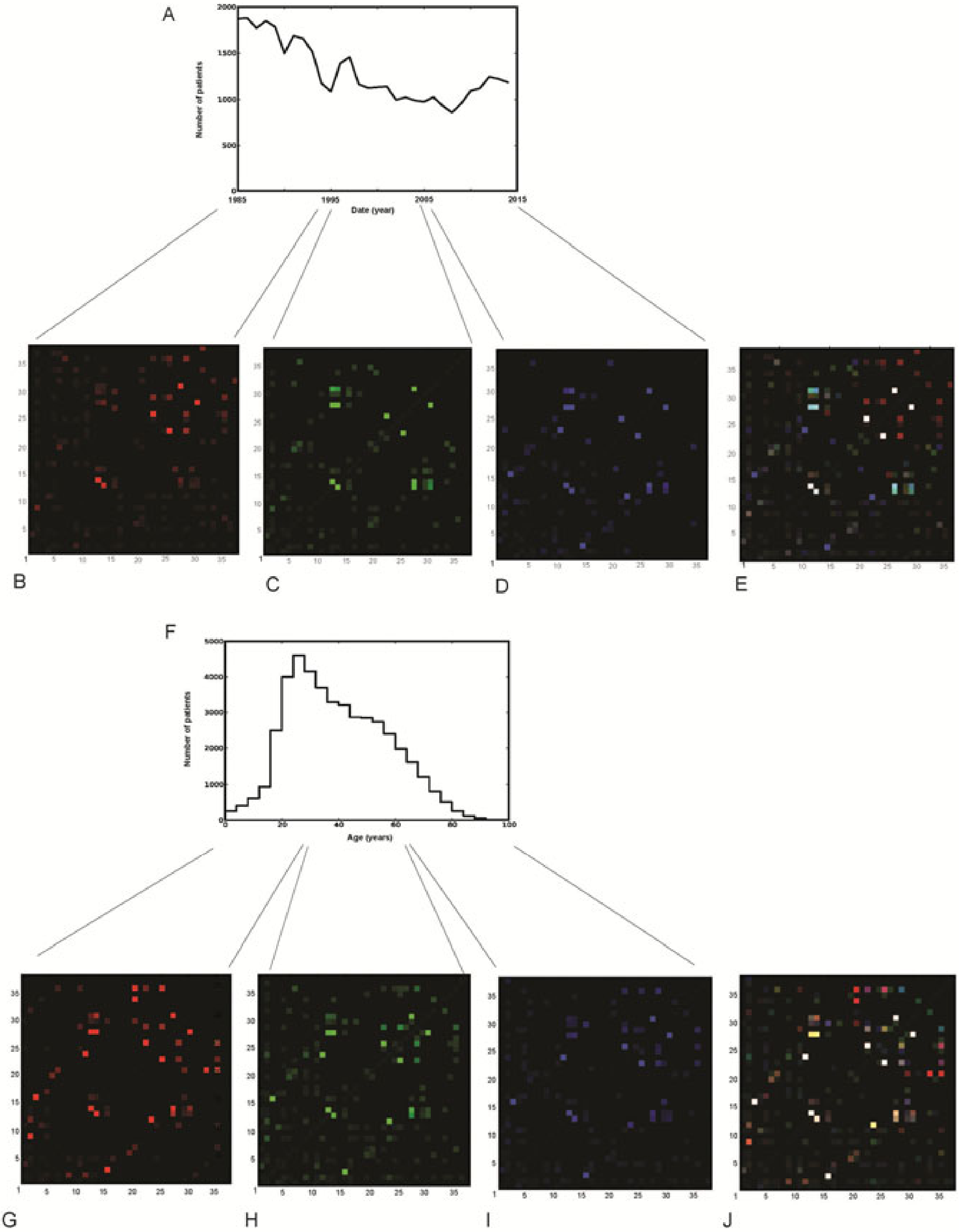
BALSAMPERU
LYRAL
PERFUME
FMII
Medicaments
WOOL_ALC
PARABENS
CAINES
QUINOLINE
YELLOW3
PPD_BASE_1
NEOMYCIN
TIXOCORTAL
CETOSTERYL
CHL_CRESOL
PPD
ETHYLENEDI
PPD_RUBBER
CARBA
PRIMIN
PTBP_RESIN
SODIUM METABISULFITE
MERCAPTO
MBT
THIURAMS
Rubbers
EPOXY
LACTONE
COLOPHONY
Preservatives
BRONOPOL
MI
KATHON
GERMALL
FORMALIN
GERMALL2
DOWICIL200
NICKEL
COBALT
DICHROMATE
Metals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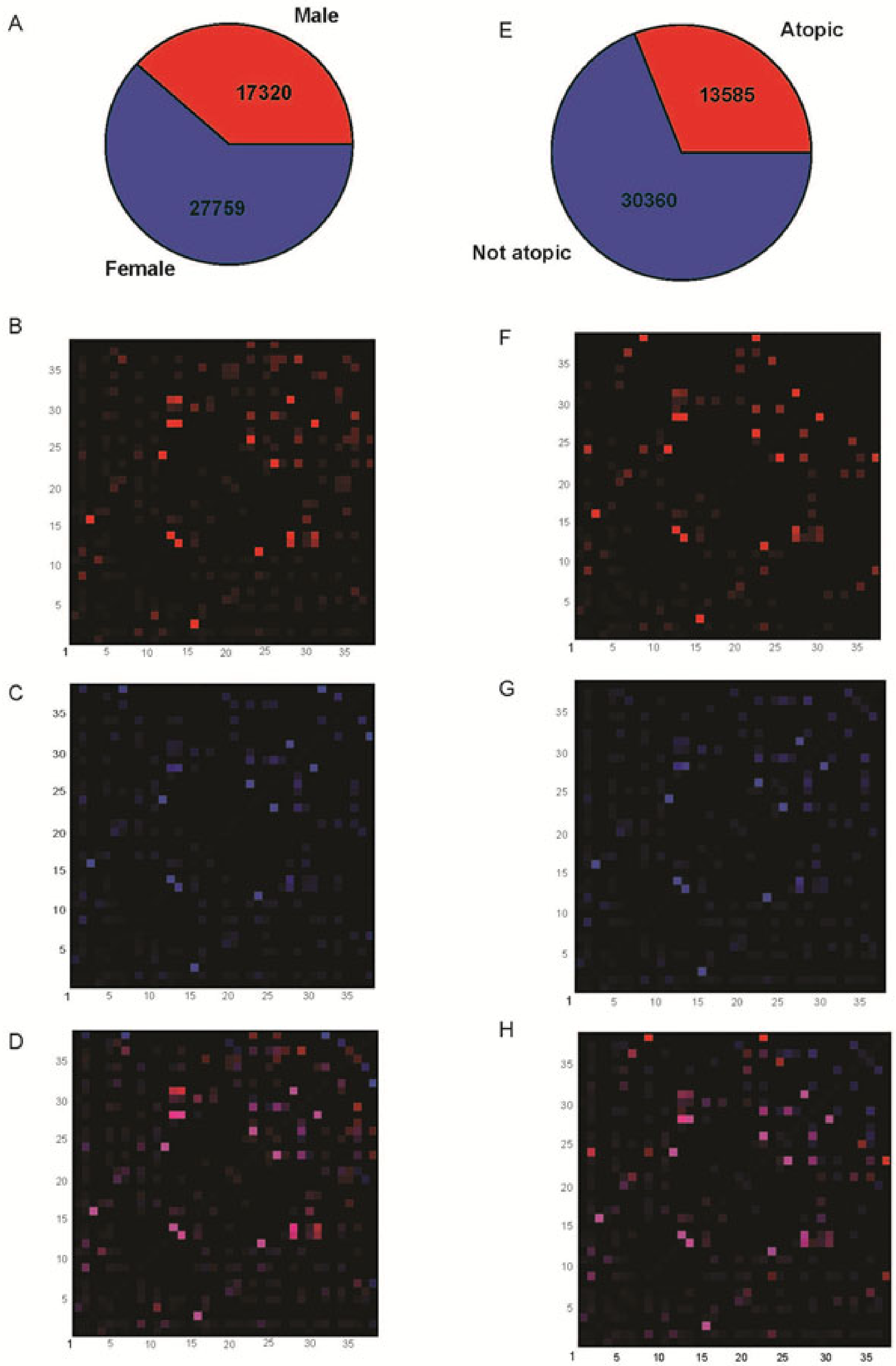
Date (year)
B
C
D
E
F
Number of patients
Age (years)
G
H
I
J

Figure 2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Female
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Atopic
13585
30360
Not atopic
B
C
D
F
G
H

Figure 3