

Conflicts of interest

None to declare.

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What substances are allergenic and in whom?

DOI: 10.1111/bjd.15101

Linked Article: Lynch et al. *Br J Dermatol* 2017; **176**:184–196.

The question has a dynamic answer but allows us to focus and apply a structure to the nature of allergy in terms of factors determined by the substance itself and the host that is allergic to it. In a landmark paper by Lynch et al.¹, the team have explored trends in allergen associations in 45 110 patients over a period of 30 years. Extensive analyses of associations of allergens in patient groups and time periods has identified many interesting trends that may now help us to focus our enquiries about the nature of type IV allergy and the substances that cause them.

Contact dermatitis accounts for 4–7% of dermatology consultations and has a significant impact on the patient's quality of life.² An allergen diffuses through the skin and is picked up by an antigen-presenting cell which then triggers the immune response when it presents to the immune system.³ The coming together of the host immune system and the external allergen is different in each situation but this extensive analysis has found patterns that could shed more light on this complex mechanism.

For the 38 allergens tested, there are a possible 703 pairs of allergen combinations in the patients tested. Many of us are used to seeing coexistent reactions between similar allergens and the study confirmed this. Methylisothiazolinone and chloromethylisothiazolinone would react together as did the rubber accelerators mercapto mix and mercaptobenzothiazole.

However, seemingly unrelated substances, such as colophonium (rosin) and thiuram mix (a rubber accelerator) would react together more than would be expected by chance [odds ratio (OR) 4.3], as did epoxy resin and the plant mix of sesquiterpine lactone (OR 5.5). The authors suggest these odd combinations could be due to frequent co-exposure of allergens (such as ointments and dressings in leg ulcer care) and perhaps similar chemical structures as has been reported in a case where a patient allergic to a foam dressing also reacted to local anaesthetics and hair dye.⁴ Greater details of concomitant reactions are displayed in two-dimensional colour diagrams. These are explored further and changes of associations over the decades are displayed, particularly changes in the frequency of formaldehyde and formaldehyde releaser concomitant reactions. Some of this may reflect changes in regulations.⁵

The allergen itself is not the only factor for allergenicity. The Coopman classification for steroid cross-reaction has now been superseded by a new method of looking at steroids, as well as the patient group the steroid affects.⁶ Similarly, this study found the younger age group had a greater association of colophonium and sesquiterpine lactone as well as cobalt and thiuram mix. Allergen pairs were more likely in males than females and atopic individuals were more likely to pair paraphenyldiamine (PPD) and caine mix as well as PPD and quaternium 15 (a formaldehyde releaser).

The large wealth of data presented in this paper will help to focus future research into the mechanisms of contact dermatitis.

Acknowledgment

Avad A. Mughal would like to acknowledge Drs Natalie Stone and Mabs Chowdhury for their help in reviewing and critique of this commentary.

Conflicts of interest

None to declare.

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Mosaicism in the skin: lumping or splitting?

DOI: 10.1111/bjd.15042

Linked Article: Kuentz et al. *Br J Dermatol* 2017; **176**:204–208.

Cutaneous mosaicism is a common phenomenon resulting from postzygotic mutations that manifests as persistent, stable skin lesions and may be accompanied by abnormalities of other organs.¹ The clinical presentations are manifold, including pigmentary, vascular, verrucous or keratotic lesions with various distributions, e.g. punctate, patchy, segmental, linear or unilateral. The concept of cutaneous mosaicism was established several decades ago,² and various complicated and mainly descriptive names have been given to apparently distinct clinical entities over the years.

We are now fortunate to witness a revolution in the understanding of cutaneous mosaicism, which is possible through the technological progress of next-generation sequencing (NGS). NGS with deep sequence coverage enhances sensitivity and allows for accurate quantification of the level of mosaicism, detecting mutations in very low numbers of cells within the tissues.³ The big surprise is that many of the apparently distinct clinical entities result from mutations in the same gene or even from the same mutation. The phenotypic diversity and variety is determined by the time point when the mutation occurs during development and by the affected cell. If mutations occur early in embryogenesis in stem cells that give rise to several organs, then skin lesions are accompanied by the involvement of the respective organs. If the mutational event takes place late in cutaneous precursor cells, then only the skin is affected.

The repertoire of genetic defects underlying cutaneous mosaicism is also surprising. For example, pigmentary mosaicism (so-called 'hypomelanosis of Ito') can be caused by various chromosomal anomalies or monogenic defects.⁴ In contrast, in naevoid lesions, affected genes often disturb signalling pathways involved in cell growth and survival. For instance, keratinocytic epidermal naevi harbour postzygotic mutations in *FGFR3*, *PIK3CA*, *HRAS*, *NRAS* and *KRAS*, while sebaceous naevi are caused by postzygotic *KRAS* and *HRAS* mutations (Table 1).^{5,6}

Table 1 Molecular basis of epidermal naevi

Histological type of epidermal naevus	Affected genes
Keratinocytic naevi	<i>FGFR3</i> <i>FGFR2</i> <i>PIK3CA</i> <i>NRAS</i> <i>HRAS</i> <i>KRAS</i>
Epidermolytic keratinocytic naevi	<i>KRT1</i> , <i>KRT10</i>
Naevus sebaceous	<i>HRAS</i> <i>KRAS</i> <i>FGFR2</i>
Naevus comedonicus	<i>NEK9</i>
Acne naevus	<i>FGFR2</i>
Porokeratotic eccrine naevus	<i>GJB2</i>

Kuentz et al.⁷ report that *FGFR2* postzygotic mutations underlie papillomatous pedunculated sebaceous naevus. The authors performed whole-exome sequencing in two unrelated fetuses with this rare condition and found the activating mutation c.1144T>C, p.Cys382Arg in the *FGFR2* gene, encoding the fibroblast growth receptor 2 (*FGFR2*), in affected skin but not in the unaffected organs or in the DNA from the parents. Activation of the tyrosine kinase receptor *FGFR2* sequentially activates the Ras–Raf–MEK (mitogen-activated protein kinase/extracellular regulated kinase) pathway or the phosphoinositide-3 kinase–Akt signalling cascade.⁸ Germline *FGFR2* mutations cause a spectrum of craniosynostosis syndromes, which can be associated with acne, cutis verticis gyrata and acanthosis nigricans. Thus, acne naevi are caused by postzygotic activating *FGFR2* mutations affecting keratinocytes above and around the dilated infundibula.⁹ Almost simultaneously with Kuentz et al., Toll et al.¹⁰ reported somatic embryonic *FGFR2* mutations in keratinocytic epidermal naevi. These findings suggest that *FGFR2* mutations may cause different types of epidermal naevi, depending on the affected progenitor cells and types of keratinocytes (e.g. interfollicular, follicular or both), respectively.

The precise identification of the cellular populations, which harbour the postzygotic mutations, by using laser-dissection microscopy and deep targeted sequencing, will illuminate remaining questions. Thus, epidermal naevi and associated syndromes may be considered as a spectrum of disorders and be classified according to molecular criteria, rather than splitting them by clinical or histological aspects. Finally, many postzygotic mutations associated with naevi are commonly found as somatic mutations in cancers and can be targeted by specific drugs. However, new treatment approaches are required for epidermal naevi, which may be extensive and cause significant aesthetic and psychological burden.

Funding sources

No external funding.