

Unravelling the genetic basis of contact allergy

Sheila M. McSweeney^{a, b}, Ian R. White^a, John P. McFadden^a, Christos Tziotzios^a, John A. McGrath^a

^aDepartment of Cutaneous Allergy, St. John's Institute of Dermatology, London, United Kingdom

^bCorresponding author

Corresponding author address: St. John's Institute of Dermatology, Guy's Hospital, Great Maze Pond, London, SE1 9RT, United Kingdom

Corresponding author telephone number: +44 (20) 71886353

Corresponding author e-mail: sheila.mcsweeney@kcl.ac.uk

Word count: 729

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Keywords: allergic contact dermatitis, genetics, genome-wide association study, gene-environment interaction

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/cod.13983](https://doi.org/10.1111/cod.13983)

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Contact allergy occurs due to cutaneous interaction with environmental allergens that result in T-cell mediated inflammation.¹ Exposures to allergens could, therefore, be presumed to be the sole determinant of contact allergy. However, many contact allergens are ubiquitous in the environment and multiple human and animal studies have demonstrated inter-individual variability in the development of contact allergy under uniform conditions of allergen exposure.¹ Consequently, there exists a need to consider the factors influencing the development of contact allergy in relation to inter-individual susceptibility.

Inter-individual susceptibility to many diseases is driven by genetic factors, which can be investigated by classic studies of heritability.² For contact allergy, Menné and Holm examined the frequency of nickel allergy in 115 female twin pairs, identifying an increased pairwise concordance rate among monozygotic (0.32) compared to dizygotic (0.14) twin pairs and estimating a heritability for nickel contact allergy of 60%.³ Bryld *et al.* also examined nickel contact allergy among 630 Danish female twin pairs, demonstrating a slightly increased odds of nickel contact allergy (adjusted odds ratio 1.28, 95% confidence interval 0.33-5.00) in monozygotic compared to dizygotic twin pairs.⁴ Although this study did not demonstrate statistical significance, it is important to note that proband selection was based on the presence of hand eczema and thus, selection bias may have affected the results. Similar heterogeneity has been observed in family studies of contact allergy.⁵ Walker *et al.* experimentally sensitised parents and children in 99 families with dinitrochlorobenzene and p-nitrosodimethylaniline, observing that sensitization of children by p-nitrosodimethylaniline, but not dinitrochlorobenzene, was more frequent in the presence of concomitant parental sensitization (51% versus 29%, $p < 0.01$).⁶ Likewise, Forsbeck *et al.* patch-tested 404 relatives of 94 patients with confirmed contact allergy to a series of common contact allergens, demonstrating that patch-test positivity was seen more frequently only in female relatives (30%) compared to healthy controls (18%).⁷

Such observations of heritability in contact allergy could be used as evidence to refute the relevance of genetic predisposition to its development. However, studies of heritability are *per se* imperfect due to concerns regarding the definition of heritability,² while contact allergy is a highly heterogeneous entity, in which a myriad of environmental parameters, including allergen exposure, are known to affect whether a specific contact allergy develops.¹ It seems more logical, therefore, to consider the development of allergen-specific contact allergy as a distinct complex trait, with allergy to each substance being determined by a unique combination of genetic and environmental factors. Nevertheless, major insights into key genetic determinants of contact allergy might be gained by examining those who demonstrate increased risk of contact allergy, irrespective of allergen structure or class. Such polysensitised individuals, termed “polysensitisers”, are broadly defined as having three or more confirmed contact allergies across different classes of allergen.⁸ Furthermore, their unique susceptibility to contact allergy has been confirmed by studies demonstrating that polysensitisation

occurs at greater frequencies in patch-tested populations than would be predicted based on the frequency of single contact allergies in the same population.⁹

If investigation of the genetic aetiology of polysensitisation could be the first step in determining the genetic basis of contact allergy, the next is selection of an appropriate genetic study design. This choice is predicated on hypotheses surrounding the genetic architecture of polysensitisation, as different study designs are used to detect common and rare causal variants, respectively.¹⁰ Moreover, as polysensitisation is a relatively common trait affecting ~7% of patients in patch-tested populations,¹¹ it can be inferred under the “common disease-common variant hypothesis” that it is driven by multiple common genetic variants, which are best identified via genome-wide association studies (**Figure 1**).¹²

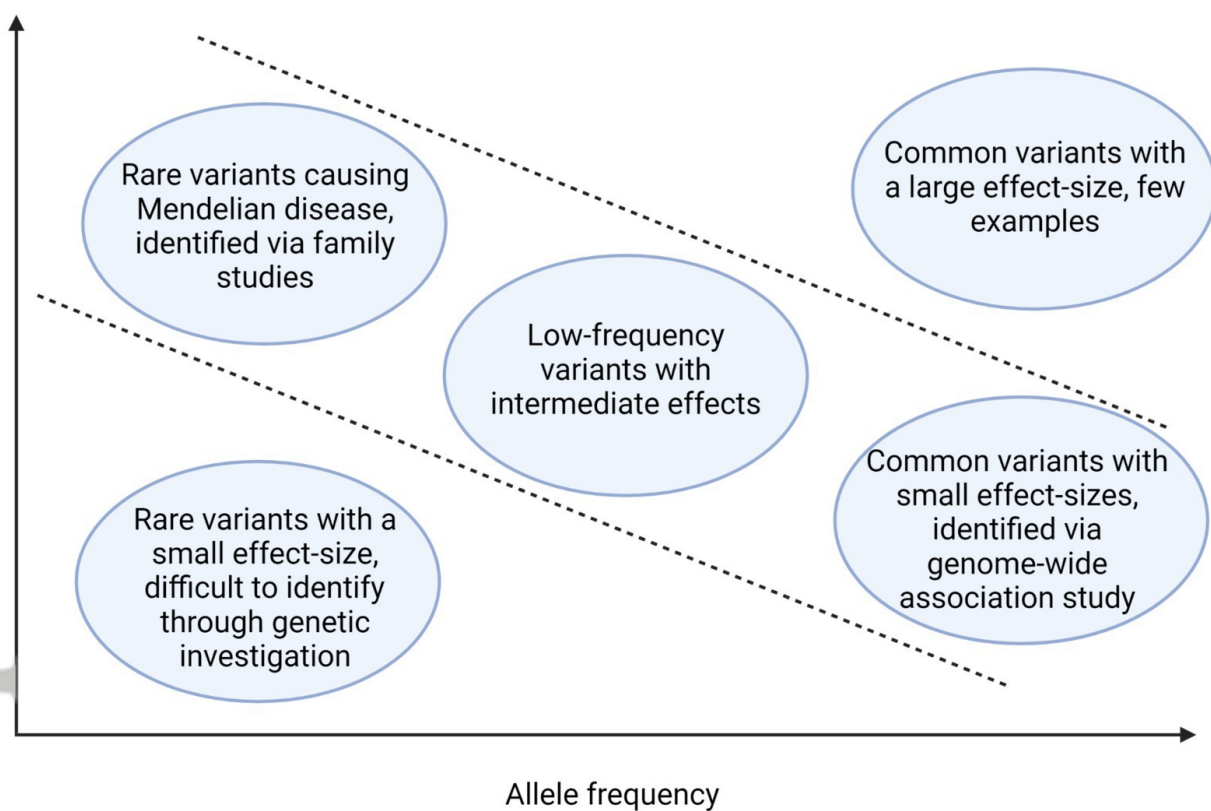
A genome-wide association study (GWAS) of polysensitisation could, therefore, provide important insights into the genetic aetiology of contact allergy and its key pathomechanisms. However, it is also important to highlight the wider benefits of the genetic investigation of contact allergy. Understanding major pathomechanisms that drive contact allergy may facilitate development of better *in vitro* and even *in silico* testing systems for the screening of new potential contact allergens. Similarly, incorporating estimates of inter-individual susceptibility into acceptable exposure level calculations will also improve their accuracy and allow industry stakeholders to formulate a wider, safer variety of products containing potential contact allergens. Therefore, with our understanding of the epidemiology of contact allergy and the explosion in genetic technologies and investigation, there has never been a better time to investigate its genetic basis.

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Figure Legends

Figure 1. The relationship between genetic variant frequency, effect-size and the study designs used to detect them. Created using Biorender.com



COD_13983_Figure 1.jpg

Questions on 5-point Likert Scale						
		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I feel that the doctor was able to understand and address my medical concern.	 	☐	☐	☐	☐	☐
reset						
I feel that my visit took place in a timely fashion.	 	☐	☐	☐	☐	☐
reset						
I feel satisfied with my visit.	 	☐	☐	☐	☐	☐
reset						
I would prefer a telemedicine visit to an in-office visit if I had a similar medical concern in the future.	 	☐	☐	☐	☐	☐
reset						
I feel that a virtual visit would be more convenient than an in-office visit.	 	☐	☐	☐	☐	☐
reset						
I would recommend a telemedicine visit to a friend or family member who has a similar medical concern.	 	☐	☐	☐	☐	☐
reset						