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The filaggrin gene mutation, atopic dermatitis and asthma

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Twin and family studies have shown that predisposition to eczema, allergic rhinitis and asthma is highly heritable.[1] Hitherto, the focus of studies investigating the development of atopic disorders has in the main been on mechanisms causing immune dysregulation. We describe here two recent important papers by Palmer and colleagues which focus on the role of the epidermis in atopic disease pathogenesis.

1. **Palmer CNA, Irvine AD, Terron-Kwiatowski A, *et al*. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.**
2. **Palmer CNA, Ismail T, Lee SP, *et al*. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007;120(1):64-8. doi: 10.1016/j.jaci.2007.04.001**

These studies have investigated two independent mutations in the gene encoding filaggrin (2282del4 and R501X) which are carried by 9% of people of European origin. These variants are known to cause complete loss of processed filaggrin product – which is expressed in the outer epidermis, oral and nasal mucosa, and which plays a role in the routine formation of epithelial barrier function, thereby impeding allergen entry.

An initial study of families with ichthyosis vulgaris found that a large proportion (76%) of patients with the severe form of this disease also presented with atopic dermatitis and were homozygous or compound heterozygous for a filaggrin null allele.[2] The null or 'loss of function' variety presents if a mutation results in a complete loss of function of the protein for which that allele codes. As a follow-up to this study, the authors studied a cohort of patients (aged 3-22 years) with physician-diagnosed asthma and controls who were recruited from the Tayside area of northeast Scotland as part of the BREATHE study. Seventy-two percent of those with asthma and carrying a filaggrin null allele were found to have atopic dermatitis as compared to 46% of those without the filaggrin variant. Individuals in this cohort with the co-dominant null filaggrin alleles were found to be significantly more likely to have asthma (odds ratio (OR) 1.8, 95% confidence interval (CI) 1.3-2.5).

Asthma severity was also analysed in this cohort of patients and this showed that patients were more likely to need aggressive management (British Thoracic Society asthma treatment steps 3-4 versus 0-2) if they had co-dominant (i.e. those in whom both alleles contribute equally to the disease expression or phenotype) (OR 1.73, 95%CI 1.19-2.52) or homozygous 2282del4 and R501x null alleles (OR 6.62, 95%CI 1.65-26.99).

These papers are excellent examples of well designed and conducted genetic epidemiology studies, whereby large cohorts of patients are used to detect novel genes and markers associated with disease susceptibility. A particular strength of this work is that findings were replicated in another European cohort of children – the Copenhagen prospective study on asthma in childhood (COPSAC) – this replication work now being an essential requirement for publication of genetic association studies in leading science journals. These papers are also ideal candidates for inclusion in the Human Genome Epidemiology Network (HuGENet) knowledge-based database, a resource which catalogues reported genetic associations.[3]

The authors acknowledge that further work is required: firstly, there is a need for additional replication in other cohorts to identify more accurately the relationship between filaggrin status, the general atopic state and specific intermediate phenotypes such as food allergy, bronchial hyperreactivity and house douse mite allergy; and secondly, there is a need for prospective longitudinal studies, which are less prone to confounding and bias, ideally from birth. This will require greater numbers of people to be studied, although given the high prevalence of these gene variants and disease outcomes

the numbers are unlikely to prove prohibitive. It is also important that these cohort studies have sufficiently long follow-up to assess the impact of developing all diseases of interest – including allergic rhinitis and asthma. This is likely to prove more challenging, both in terms of maintaining follow-up and in terms of cost implications. One novel solution to this is to link study records with a range of routine healthcare datasets; this has the potential significantly to reduce costs and thus make the mounting of such long-term follow-up feasible in the near future.[4]

Notwithstanding the need for this additional work, these studies have offered an extremely important new line of enquiry into the aetiology and pathogenesis of atopic conditions. This work has therefore quite appropriately attracted the attention of both the academic community and the international media.

Conflict of interest declaration

Professor Aziz Sheikh is an Assistant Editor of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article.

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The need for a biopsychosocial "gendered" perspective on food allergy

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DunnGalvin A, Hourihane JO, Frewer L, Knibb RC, Oude Elberink JN, Klinge I. Incorporating a gender dimension in food allergy research: a review. *Allergy* 2006;61: 1336-43.

National hospital discharge data suggest that the prevalence of food allergy in the UK is increasing.[1] There is, however, a large and possibly increasing discrepancy between self-reported prevalence rates and medically confirmed levels of food allergy in the general population, with self-reported rates exceeding confirmed rates by a factor of almost ten-fold.[2,3] This discrepancy has been shown to be particularly pronounced in females, for reasons that remain as yet poorly understood.[4] DunnGalvin and colleagues' quasi-systematic review is one of the few attempts to gather evidence surrounding this important issue and is therefore a welcome contribution to the literature.

In trying to disentangle the biological and psychosocial influences that might contribute to the disparate expression of medically-confirmed and perceived food allergy in males and females, the authors helpfully differentiate between studies that have investigated sex and those that have investigated gender. 'Sex' in this respect is conceptualised as being related to biological differences between males and females, whereas 'gender' is understood as being related to psychological, social and cultural factors. The methodology was a literature search from 1990 to 2006 using the terms sex, gender and food allergy.

The authors argue that, in order to get a suitably rounded understanding of the issues surrounding food allergy – whether perceived or real – there is a pressing need for integration of both biological and psychosocial factors.[5] With regards to biological factors, the review discusses the potential role of prenatal factors, sex hormones and sex steroids on mediating the risk of developing allergic conditions. With regards to gender considerations – which have in comparison received far less attention – the authors highlight the need for more work on food allergy and gender in relation to perceived (health-related) quality of life, information processing, risk perception, self-efficacy, and parental influences.

Whilst the focus of the paper is clearly on food allergy, in order to compensate for the paucity of psychosocial research in this area the authors have drawn appropriately on relevant research from wider long-term conditions – and specifically, literature on allergy – to support their arguments. Their paper represents a thoughtful and timely contribution to the subject. Its key strength lies in attempting to move beyond traditional explanations focusing on biological mechanisms in order to develop more credible explanations of sex differences in self-reported levels of food allergies.

What now needs to be done is to build on this work, investigating exactly which psychosocial factors play a role in