

Early origins of allergic disease

In 1976, John W Gerrard observed that allergic diseases were more common in Saskatchewan amongst European immigrants than native families who had increased helminth, viral and bacterial diseases. These observations and subsequent work stimulated interest in the possibility that early-life exposures may promote or prevent allergic diseases, which vary according to cultural group and socio-economic status.^{1,2} From work published in the journal last year, we know that water hardness may be a relevant risk factor, at least for eczema,³ and that water softeners may be a feasible approach to preventing eczema.⁴ However, other approaches to infant skincare do not seem to impact allergic disease development.⁵ We also know that there is no causal association between serum vitamin D levels and risk of rhinitis or allergic sensitization, at least in a European-ancestry population⁶ and that while dietary antioxidants may promote improved lung function and respiratory health,⁷ the first randomized controlled trial of increasing fruit and vegetable intake in asthmatic children did not impact asthma exacerbations over a 6-month period.⁸ In this issue of the journal, we publish several articles which make important contributions to our understanding of the early-life origins of allergic conditions.

Kotsapas et al. used the well-characterized Manchester Asthma and Allergy Study (MAAS) cohort to better understand the relationship between early life skin and allergy health and the development of peanut allergy. Prospective cohort studies with well-characterized peanut allergy confirmed by oral food challenge are few and far between. The MAAS cohort has made important contributions to our understanding of peanut allergy development. In this new analysis, the MAAS team confirmed previous associations between filaggrin gene mutations and risk of peanut allergy, but interestingly only saw this in children without clinically manifest eczema. In children with eczema, filaggrin gene mutations did not confer an additional risk for peanut allergy beyond eczema itself. They also found associations between multiple IgE sensitization, persistent eczema and wheeze, and peanut allergy development, but peanut allergy was not associated with asthma severity. These findings suggest that children who develop peanut allergy have an immunological predisposition, manifested by persistent eczema and wheeze and multiple sensitizations, and have a cutaneous predisposition, displayed by filaggrin mutations in the population without clinically manifest eczema. This fits with our current understanding of genetic risk factors for peanut allergy and suggests that attempts to prevent peanut allergy should focus on both immune-directed interventions, where some progress has been made in recent years using oral tolerance induction, and skin-directed approaches, where we still lack an effective intervention (Figure 1).

The Isle of Wight Birth Cohort studies have made a major contribution to our understanding of allergic disease pathogenesis for more than 30 years, especially to the natural history of allergic conditions, and the UK ALSPAC cohort study has made broader contributions to our understanding of environmental influences on health and development. One of the strengths of these cohort studies is their longitudinal follow-up from birth through to adulthood. In this issue, Li et al. use the Isle of Wight Cohort, with replication in ALSPAC, to try to understand whether early epigenetic biomarkers, in this case DNA methylation in blood taken from a neonatal heel prick sample in the first days of life, are associated with future development of asthma through to early adulthood. We know that our genetic make-up is an essential contributor to asthma risk, but less well understood is the impact of environmental exposures on gene expression in relation to asthma risk.⁹ DNA methylation is one of the epigenetic processes through which transcription of a gene into messenger RNA (and subsequent translation into protein) is inhibited. In the Isle of Wight Cohort, Li et al. found no consistent relationship between early DNA methylation and future asthma risk in the population as a whole; however, when data were stratified by gender, the team identified eight sites where gene silencing through methylation was associated with asthma acquisition during adolescence or young adulthood in both cohort studies. These methylation sites were, in turn, linked to eight genes that are known to be associated with asthma. Thus, the Isle of Wight Cohort investigators have provided us with evidence for a pathway through which very early exposures may impact gene expression and influence the future development of asthma. These epigenetic markers can potentially be used as early biomarkers of future asthma acquisition in research studies (Figure 2).

Brandt et al. contribute to the growing evidence base surrounding parasite exposures and allergic disease development. Like other studies in low and middle-income settings, they found a high prevalence of allergic sensitization in South African schoolchildren. Although they could not confirm the relationship between parasite infection and reduced allergic sensitization that others have shown, they showed that helminth infection specifically and intensity of helminth infection was inversely associated with polysensitization. There has been considerable interest in the relationship between another group of intestinal microbes, the intestinal microbiota and its relationship with allergic disease development. Findings are not consistent between studies, but several prospective studies have found variations in the intestinal microbiota to be associated with allergic disease development. In this issue, Kielenniva et al. contribute an analysis of the microbiota of the very early lower intestine

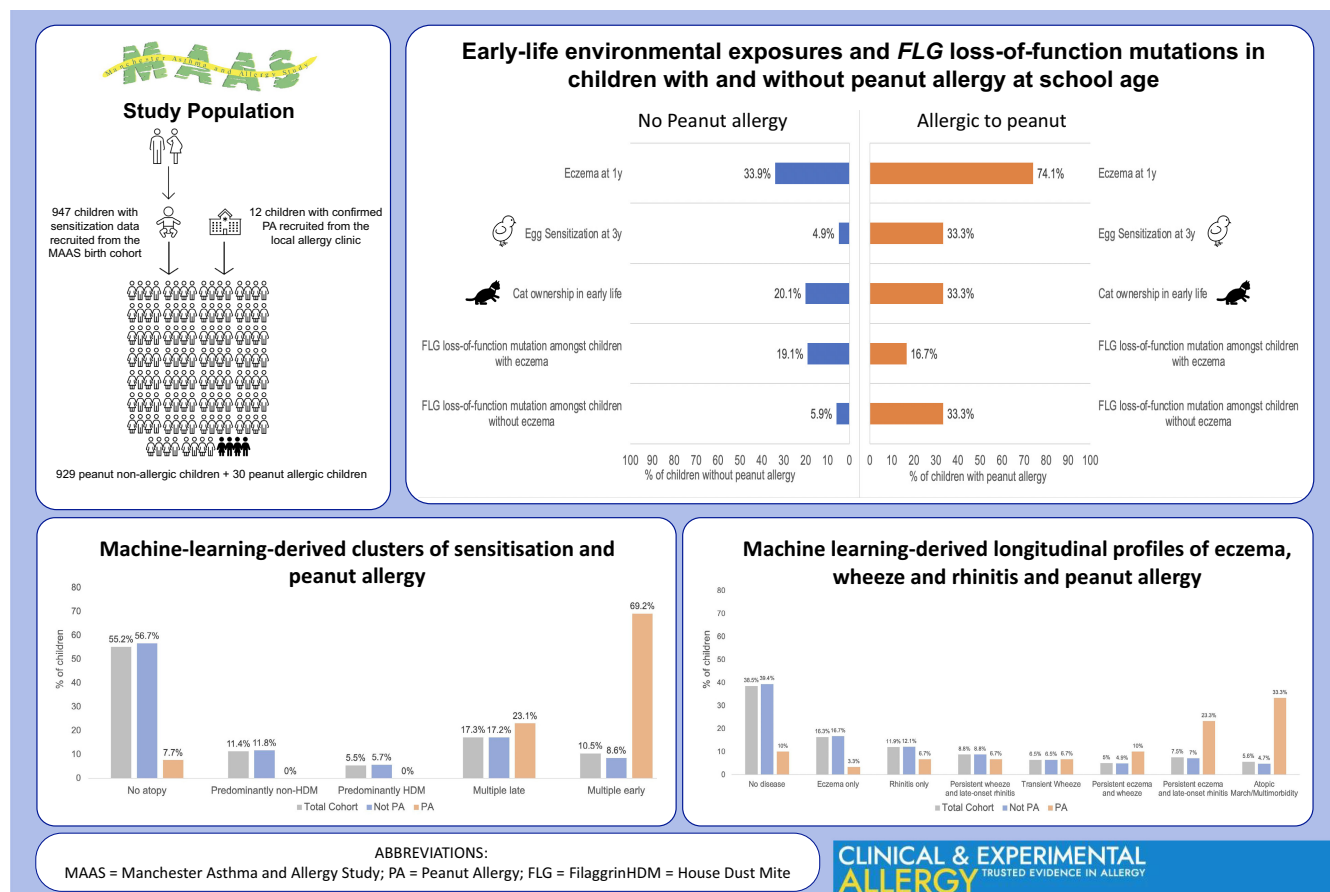


FIGURE 1 From Kotsapas et al. Peanut allergy was associated with multiple IgE-sensitization and early-onset persistent eczema and wheeze. FLG loss-of-function mutations were associated with peanut allergy in children without eczema

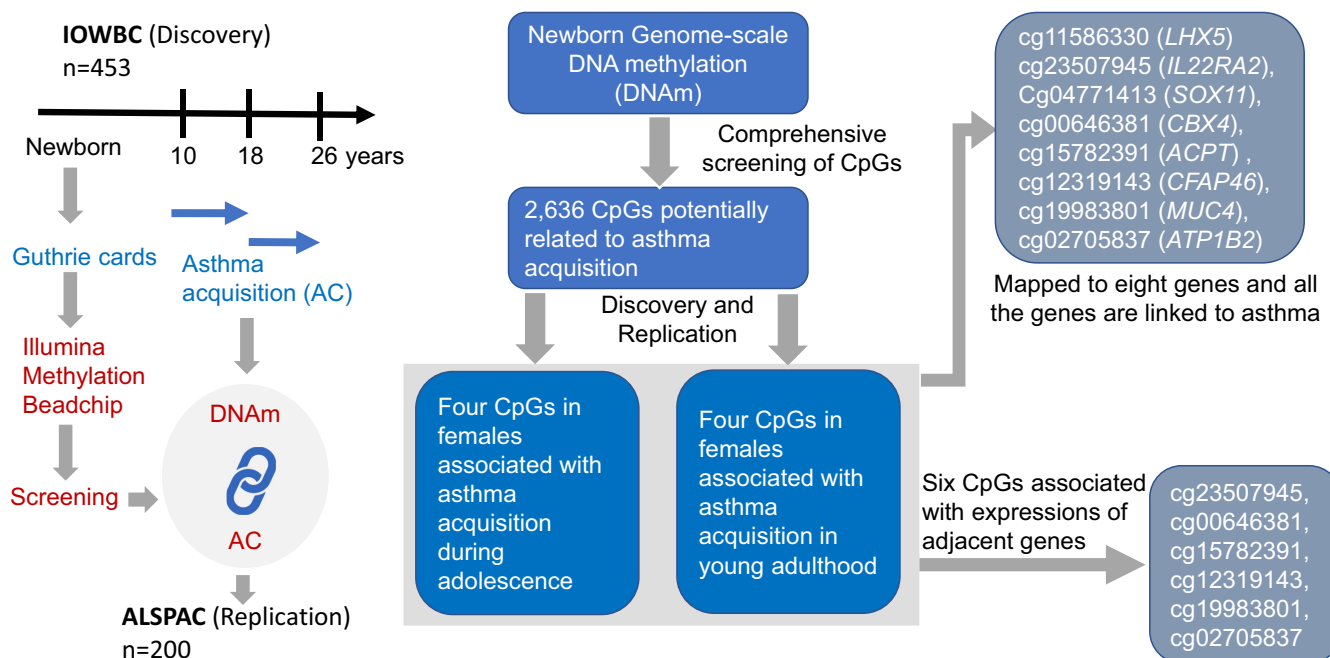


FIGURE 2 From Li et al. Little is known about the association of newborn DNAm with adolescence and young adulthood asthma acquisitions. This work examined individual CpGs and differentially methylated regions (DMR) at birth at the genome scale on their association with asthma acquisition in discovery and replication cohorts. The eight identified CpGs have the potential to serve as candidate epigenetic biomarkers for asthma acquisition in females

in the form of first-pass meconium analysis. They used a hospital-based cohort of over 300 children, followed for 4 years, and found no consistent relationship between meconium microbiota and allergic manifestations during the 4 years of follow-up.

Other work in the journal highlights some potentially harmful early interventions which may promote the development of food allergies. Seay et al. identify associations between the use of aluminium-containing antacids and IgE-mediated food allergy in the GMAP cohort study, and De Luca et al. highlight the potential danger for people with inflammatory skin conditions such as eczema of applying food-based skin products, which could promote the development of IgE-mediated allergy to these specific food antigens.

So the work presented in our May 2022 issue of Clinical and Experimental Allergy suggests that early life exposures are indeed important for priming or suppressing allergic disease development, and that the mechanism of action of some such exposures may be to suppress or promote the expression of key genes linked to allergic conditions.

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