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REVIEW

Early life precursors, epigenetics, and the development of food allergy

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Abstract Food allergy (FA), a major clinical and public health concern worldwide, is caused by a complex interplay of environmental exposures, genetic variants, gene–environment interactions, and epigenetic alterations. This review summarizes recent advances surrounding these key factors, with a particular focus on the potential role of epigenetics in the development of FA. Epidemiologic studies have reported a number of nongenetic factors that may influence the risk of FA, such as timing of food introduction and feeding pattern, diet/nutrition, exposure to environmental tobacco smoking, prematurity and low birth weight, microbial exposure, and race/ethnicity. Current studies on the genetics of FA are mainly conducted using candidate gene approaches, which have linked more than 10 genes to the genetic susceptibility of FA. Studies on gene–environment interactions of FA are very limited. Epigenetic alteration has been proposed as one of the mechanisms to mediate the influence of early life environmental exposures and gene–environment interactions on the development of diseases later in life. The role of epigenetics in the regulation of the immune system and the epigenetic effects of some FA-associated environmental exposures are discussed in this review. There is a particular lack of large-scale prospective birth cohort studies that simultaneously assess the interrelationships of early life exposures, genetic susceptibility, epigenomic alterations, and the development of FA. The identification of these key factors and their independent and joint contributions to FA will allow us to gain important insight into the biological mechanisms by which environmental exposures and genetic susceptibility affect the risk of FA and will provide essential information to develop more effective new paradigms in the diagnosis, prevention, and management of FA.

Keywords Genetics · Environmental exposure · Epigenetics · Food allergy

Abbreviation

ACSL	Actyl-CoA synthetase long-chain family, member 3
AIMs	Ancestry informative markers
BBC	Boston Birth Cohort
CTLA4	Cytotoxic T lymphocyte-associated protein 4
CYP24A1	Cytochrome P450, family 24, subfamily A, polypeptide 1
DCs	Dendritic cells
DNMT	DNA methyltransferase
ETS	Environmental tobacco smoke
FA	Food allergy
FCER1G	Fc fragment of IgE, high affinity I, receptor for gamma polypeptide
FLG	Filaggrin
FOXP3	Forkhead box P3
FS	Food sensitization
GSTP1	Glutathione S-transferase pi 1
GWA	Genome-wide association
HDACs	Histone deacetylase
IFNG	Interferon, gamma
IgE	Immunoglobulin E
IL	Interleukin

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IL12RB1	IL12 receptor, beta 1
IL4RA	IL4 receptor alpha
LBW	Low birth weight
MS4A2	Membrane-spanning 4-domains, subfamily A, member 2
NHANES	National Health and Nutrition Examination Survey
NLRP3	NLR family, pyrin domain containing 3
PGE2	Prostaglandin E2
PTPRO	Protein tyrosine phosphatase receptor type O
LC-PUFAs	Long-chain polyunsaturated fatty acids
SPINK5	Serine peptidase inhibitor, Kazal type 5
STAT6	Signal transducer and activator of transcription 6
TNFα	Tumor necrosis factor, alpha
T reg	T regulatory
TSLP	Thymic stromal lymphopoietin
TLR	Toll-like receptor
VDD	Vitamin D deficiency

Introduction

Food allergy (FA), defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" in the recent National Institute of Allergy and Infectious Diseases-sponsored expert panel report [1], is emerging as a major clinical and public health problem not only in USA, but worldwide [2, 3]. FA affects more than 1–2 % but less than 10 % of the population [4]. More significantly, FA is the most frequent single cause of emergency room visits for anaphylaxis. FA impacts not only the affected individual but also those providing care and nourishment for the food-allergic individual, thus its effect on family and society is enormous [5–8]. Strict allergen avoidance, which is exceedingly difficult, is the current approach to the management of FA.

The prevalence of FA may vary by age, geographic location, and possibly race/ethnicity [9]. While conclusive data are lacking, many experts believe that the actual prevalence of FA has risen substantially over the past decade, in parallel with the rise previously seen for other atopic conditions [2, 3, 10, 11]. Although the cause for the rise in prevalence remains unclear, it may partly be due to changes in environmental exposures. To date, while epidemiologic studies have linked a broad range of early life environmental factors to the risk of FA, these findings await further replication in independent studies. Recent advances in environmental epigenetics research hold great potential to explain how early life environmental exposures affect the incidence of diseases later in life. In this review, we will summarize pertinent literature on early life environmental exposures and genetic susceptibility for FA, with a particular focus on potential epigenetic alterations related to the immune system and the development of FA. We will also discuss critical knowledge gaps and future directions in the field, as well as the need to integrate multi-level factorial variables and apply cutting-edge science and technology in FA research.

A critical time window to understand the development of food allergy

Most cases of FA develop in the first few years of life, suggesting that early life is a critical window for the development of FA. While production of immunoglobulin E (IgE) in the first year of life is cyclical, IgE titers trend positively in those who are later sensitized [12]. Also, children who go on to develop allergy by age 5 have higher T_h2 cytokine responses by the age of 1 year [12], suggesting that allergen-specific immunologic responses within the first year of life correlate with the development of allergy. The prenatal period also is believed to be a critical window for programming, which is supported by recent findings on the relationships between maternal environmental exposures (such as smoking, diet, and microbe exposure) during pregnancy and the risk of FA in offspring [13–16]. Furthermore, infants who later developed egg sensitization were found to release less interferon-gamma and less interleukin (IL)-10 from PHA-stimulated cord blood mononuclear cells [17]. While controversy exists concerning the relative impact of pre- vs. postnatal events, early life is clearly a time when immune deviation and atopy are determined.

Key nongenetic factors associated with the development of food allergy

There is an increasing number of epidemiologic studies focused on the relationships between environmental exposures and the risk of FA during childhood and adolescence; however, most of these studies have led to inconsistent findings. Lack [18] reviewed the possible nongenetic risk factors for the development of FA and came out several hypothesis, which include: (1) dual-allergen-exposure hypothesis, which posits that food sensitization (FS) can occur through low-dose cutaneous exposure and that early consumption of food protein induces oral tolerance; (2) hygiene hypothesis, which suggests that early exposures to microbial pathogens could protect against subsequent atopic diseases; (3) dietary fat hypothesis, which suggests that higher intakes of ω-6 and lower intakes of ω-3 fatty acids lead to increased production of prostaglandin E2 (PGE2) and thus the development of FA; (4) antioxidant hypothesis, which stresses the anti-inflammatory effects of antioxidants in allergic diseases; and (5) vitamin D hypothesis, which takes

two opposite forms: the vitamin D excess hypothesis, which suggests that vitamin D is a risk factor for allergy, while the vitamin D deficiency (VDD) hypothesis argues the opposite. The following paragraphs summarize the recent findings on the relationships between nongenetic factors and the risk of FA.

Feeding pattern and the timing of food introduction

The ability to avoid FA by manipulating the diet during pregnancy or early infancy remains controversial. Many studies have investigated the role of breastfeeding on the risk of atopy and FA, with results varying from a protective [19–21] or neutral effect [22–26] to a disease-promoting effect [27–29]. The review by Host et al. in 2008 supports the effectiveness of dietary regimen in preventing allergic diseases, including exclusively breastfeeding for at least 4–6 months, or, in the absence of breast milk, formula with documented reduced allergenicity for at least the first 4 months, combined with avoidance of solid food and cow's milk for the first 4 months [30]. However, the American Academy of Pediatrics has withdrawn their recommendations about food avoidance during pregnancy and early infancy and replaced them with comments regarding the lack of current evidence related to delaying the timing of the introduction of complementary foods beyond 4 to 6 months of age in preventing the occurrence of atopic disease [31]. Some other studies have shown that prolonged breastfeeding and/or delayed introduction of these food allergens may increase the risk of FA. For example, Koplin et al. found that delayed introduction of egg appears to be a risk factor for egg allergy, although no association was found for duration of breastfeeding and age at introduction of the solid food [32]. Similar results were found between the introduction of milk and milk allergy [33], the introduction of peanut and peanut allergy [34], as well as the introduction of cereal grain and wheat allergy [35].

The inconsistent results for the relationships of breastfeeding and the timing of food introduction with the risk of atopy and/or FA may partly be due to the fact that these relationships are modified by other factors including a child's age [36], gender [37], family history of allergy [37, 38], the existence of other allergic diseases [39, 40], and genetic backgrounds [41]. In a cohort composed of 594 maternal–infant pairs, Joseph et al. reported that complementary food introduced at <4 months of age was associated with a reduced risk of peanut sensitization by age 2 to 3 years, but only for children with a parental history of asthma or allergy [40]. Our study showed that, in a family-based Chicago Food Allergy cohort, later formula and later solid food introduction was associated with a lower risk of FA in children without eczema, but not in children with eczema [39]. In our inner city, multi-ethnic prospective Boston Birth Cohort (the BBC), we reported that prolonged breastfeeding was associated with increased FS, and that such a positive association was dependent on functional genetic variants in the *IL12 receptor beta 1* (*IL12RB1*), *thymic stromal lymphopoietin* (*TSLP)*, and *toll-like receptor (TLR) 9* gene. This study underscores the importance of evaluating the effects of breastfeeding in the context of individual genetic backgrounds [41].

Nutritional/dietary factors

Vitamin D is increasingly recognized as an important regulator of immune response [42–44]. It may have a number of tolerogenic effects on DCs [45] and on the differentiation of T regulatory (T reg) cells [46, 47] and may have direct effects on B cells to promote IL-10 production and decrease IgE production [48]. Vitamin D has been proposed to mediate the observed associations between season of birth and childhood FA [49] and/or food-induced anaphylaxis [50], as there is inadequate UVB intensity for the synthesis of active vitamin D in winter. The role of vitamin D has also been indirectly reflected by geographic studies, which indicate that a higher prevalence of allergic disease occurs in areas further away from the equator [51–55]. This evidence, however, was not completely supported by studies using supplemental intake and/or a direct measurement of plasma/serum vitamin D level. Elevated serum 25(OH)D was not associated with sensitization to common aeroallergens and food allergens (milk and egg) in the National Health and Nutrition Examination Survey (NHANES) III [56]. In comparison, results from the NHANES in 2005–2006 showed that 25(OH)D deficiency (<15 ng/mL) was associated with increased sensitization to peanut, ragweed, and oak when compared with sufficient vitamin D levels of >30 ng/mL [57]. Nwaru et al. found that maternal intake of vitamin D during pregnancy was inversely associated with FS [16]. Gale et al. found that maternal 25(OH)D in late pregnancy was positively associated with eczema and asthma when children were 9 months and 9 years old, respectively [58]. These conflicting results may support two opposite hypotheses. Wjst postulated that excess vitamin D might be associated with increased risk of allergic diseases based on its effects on the T_h1/T_h2 shift to T_h2 dominance, and parallel patterns of increased vitamin D supplementation, and a "Western lifestyle" [59, 60]. In contrast, Litonjua and Weiss [61] postulated that vitamin D might protect against allergies because both VDD and allergic diseases are associated with African American race, obesity, higher latitude, and immigration to westernized countries, which should not be considered a coincidence. Additionally, 1,25(OH)D has been demonstrated to maintain mucosal barrier integrity

[62], and thus, lower vitamin D status could lead to an exposure to abundant food allergens. Our recent study in the BBC reported that cord blood VDD (<11 ng/mL) increased the risk of FS only among children carrying the CC/CT genotype in the *IL4* gene (rs2243250), which may indicate that the relationship between vitamin D and FS may be modified by genetic variants [63].

Dietary fat is another nutritional factor that may play an important role in regulating the immune system. It has been suggested that ω-6 long-chain polyunsaturated fatty acids (LC-PUFAs) may lead to the production of PGE2, which can inhibit the production of T_h1 cytokines [64] and promote synthesis of T_h2 cytokines [65]. In comparison, ω-3 LC-PUFAs may inhibit PGE2 synthesis. A decrease in consumption of ω-3 or ω-3/ω-6 LC-PUFAs has been proposed to account for the increased prevalence of allergic diseases, which has been supported by some but not all studies. For example, ω-3 LC-PUFAs supplementation during pregnancy is reported to be associated with decreased mRNA levels of T_h2-related molecules in the fetus [66]. Kull et al. in a large prospective birth cohort (n=4,089) found that regular fish consumption (the main source of ω-3 LC-PUFAs) during the first year of life was associated with a decreased risk of allergic disease and FS by 4 years of age [67]. A randomized placebo-controlled trial, in which 145 pregnant women received daily maternal supplementation with either 1.6 g eicosapentaenoic acid and 1.1 g DHA (ω-3 LC-PUFAs group) or a placebo from the 25th gestational week to an average of 3–4 months of breastfeeding, showed that infants in the ω-3 LC-PUFAs group had a lower prevalence of FA than those in the placebo group during the first year of life [14]. Inconsistently, a multicenter, randomized controlled trial showed that the incidence of parent-reported FA over the first 18 months of life was comparable in preterm infants (>33 weeks gestation) who were breastfed by the mother taking either tuna oil (high-docosahexaenoic acid (DHA) diet) or soy oil (standard-DHA diet) [68]. A study by Saarinen and Kajossari found that early introduction of fish had no influence on fish allergy [69]. The meta-analysis conducted by Anandan also suggests that ω-3 or ω-6 LC-PUFAs may be unlikely to play an important role in preventing FA and/or other allergic diseases [70].

Antioxidant supplements include vitamin C, E, and β-carotene. Vitamin E is reported to suppress IL-4 levels in human peripheral blood T cells by blocking the binding of transcription factors to two important IL-4 promoter binding sites [71]. Data from the NHANES III showed that allergic skin sensitization were less common in participants with higher serum level of vitamin E [72]. However, another study reported that vitamin E intake was associated with an increased risk of allergic sensitization at age 5 [73]. Sato et al. demonstrated that mice-fed with β-carotene produced more T_h1 cytokines and less T_h2 cytokines than those in the control group, suggesting that β-carotene may contribute to T_h1/T_h2 balance, which leads to reduced IgE production [74]. Using a semiquantitative food frequency questionnaire, β-carotene intake was found to be associated with a reduced risk of allergic sensitization at age 5 and with decreased total IgE level [73]. A higher concentration of vitamin C in breast milk was also associated with a reduced risk of atopy in infants [75]. Children who reported taking multivitamins before or at age 4 years had a decreased risk of FS [76]. Early vitamin supplementation also was significantly associated with a decreased risk of FA in exclusively formula-fed children [77]. Other nutritional/dietary factors, such as vitamin A, zinc, and a Mediterranean diet have been reported to protect against asthma [78]. Hollingsworth et al. reported that in mice, a maternal diet supplemented with methyl donors may exacerbate the severity of allergic airway disease [79]. However, several studies in humans reported no associations of maternal folic acid supplementation during pregnancy with atopy [80], asthma [81], or FA [82]. The associations of these dietary factors with the risk of FA warrant further investigation.

Environmental tobacco smoke

Kulig et al. reported that children pre- and postnatally exposed to environmental tobacco smoke (ETS) had a significantly higher risk of FS during the first 3 years of life [15]. Lannero et al. demonstrated that, although there was no association for maternal smoking during pregnancy, a dose–response effect was revealed between parental smoking in early infancy and an increased risk of IgE sensitization to inhalant and/or food allergens [83]. In a German prospective multicenter birth cohort, Keil et al. found that maternal smoking during pregnancy significantly increased the risk of allergic sensitization in children with one or two allergic parents [84]. Inconsistently, Raherison et al. reported that children with exposure to maternal ETS during pregnancy were at a higher risk for sensitization to house dust mites, but not for FS [85]. Strachan and Cook reported that parental smoking, either before or immediately after childbirth, is unlikely to increase the risk of allergic sensitization in the child [86]. In a Finnish population, maternal smoking was even found to be associated with a decreased risk of cow's milk allergy in infants up to 2 years of age [87].

Prematurity and low birth weight

Prematurity is proposed to be associated with increased intestinal permeability and increased food antigen uptake [88, 89], which may lead to an increased risk of IgE-mediated FA in premature children. Very low birth weight

(LBW) preterm infants also are considered to have a wide range of immature digestive and absorptive functions, which might cause increased macromolecular absorption [90], leading to FA. Lucas et al. reported that LBW infants who received cow's milk formula developed latent systemic sensitization more rapidly than infants born at term [91]. A recent study in a national sample of US children showed that children aged 6–12 years who were born with very LBW were more likely to have reported FA compared to children with normal birth weight [92]. However, findings from other studies have questioned the role of prematurity/LBW in the development of FA. de Martino et al. compared 80 preterm infants with 80 sex-matched- and age-matched full-term infants at a mean age of 16 months and found no difference in frequency of positive skin tests to foods between the two groups [93]. In the 1995 Manitoba birth cohort composed of 13,980 children, Liem et al. found no association for prematurity and LBW with the risk of FA in childhood [94]. Similarly, in the BBC, we found that prematurity was associated with an increased risk of recurrent wheezing, while no such associations were found for either FA or eczema [95]. In a Japanese study, the prevalence of FA in LBW infants (8.1 %) was found to be significantly lower than that in infants with normal birth weight at 18 months of age (11.2 %) [96].

Microbial exposure and the hygiene hypothesis

The revised hygiene hypothesis proposes that changes in the intestinal colonization pattern during infancy are an important reason for the increased prevalence of allergy [97, 98]. These changes can be caused by Cesarean delivery, presence of siblings, antibiotic use, child care, and pet/farm exposure. From a German prospective multicenter birth cohort of 2,500 infants, Negele et al. reported a significant positive association between Cesarean delivery and specific food IgE [99]. The meta-analysis by Bager et al. showed that Cesarean delivery was associated with increased risk of FA and other allergic phenotypes [100]. Metsala et al. found that Cesarean delivery was associated with increased risk of cow's milk allergy in infants up to 2 years of age in the Finnish population [87]. Similar results were found by other studies for milk allergy [101] and egg allergy [102]. Using a logistic regression model, Dioun et al. found that being first born was an independent predictor of FA [103]. However, another study showed that having an older brother may delay the onset of IgE sensitization but may not prevent IgE sensitization [104]. Treatment with antibiotics in early infancy was also found to contribute to an increased risk of atopy in children [105]. Pet exposure at 0–2 years and at 0–5 years may protect against IgE sensitization until 5 years of age [106]. In an animal model, Lewis et al. provided direct evidence that an early life farm environment, by affecting microbial colonization, is associated with both local development of regulatory components of the mucosal immune system and immune responses to food proteins at weaning [107]. Ege et al. showed that prenatal exposure to stables may significantly protect against atopic sensitization and upregulate the expression of receptors of the innate immune system including *TLR2*, *TLR4*, and *CD14* [13]. Schaub et al. reported that maternal farm exposure during pregnancy increases the number and function of cord blood T reg cells associated with lower T_h2 cytokine secretion and lymphocyte proliferation on innate exposure [108], all suggesting that farm environment exposure may affect the susceptibility of FA.

Sleep duration

In school-age children (especially adolescents), sleep duration has decreased over the last several decades [109, 110]. This decrease has occurred in parallel with an increase in both obesity [111] and FA [112, 113]. Epidemiologic studies have linked altered short sleep duration to systematic inflammation [114, 115] and immune regulation [116]. Van Leeuwen et al. reported that sleep restriction resulted in an elevated production of pro-inflammatory cytokines [117] (IL-1β, IL-6, and IL-17), which may play important roles in immune defense [118]. Indeed, short sleep duration may even set up a positive feedback loop with inflammation since IL-13 and IL-4 given exogenously act to decrease sleep in animal models [119, 120]. In a Chinese twin cohort, we were the first to investigate the potential relationship between sleep duration and allergen sensitization, and we demonstrated that short sleep duration was associated with increasing sensitization to food allergens and aeroallergens in a dose–response manner [121]. These findings require further validation.

Antacid medications

Antacid medications may increase the gastric pH and substantially interfere with the digestive function of the stomach, leading to the persistence of labile food protein during gastric transit, which may have a major effect on the development of FA [122]. Results from a mouse model suggest that the use of antacids lead to an enhanced risk for FA [123–126]. In 152 adult patients, Untersmayr et al. reported that the relative risk to develop food-specific IgE after antacid treatment was 10.5 (95 % CI 1.4–76.5) [127].

Race/ancestry

Non-White race [128] and non-Hispanic Black race [129, 130] have been reported as potential risk factors for FA. In telephone surveys, shellfish allergy was reported at a significantly higher rate among Black subjects than White subjects (3.1 vs. 1.8 %) [130]. Yet, self-identified ethnicity and reported origin of parents and grandparents is imprecise compared to a genetic estimation of individual ancestry [131, 132]. The use of ancestry informative markers (AIMs) allows genetic ancestry to be easily and inexpensively estimated in admixed populations such as African Americans and Latinos [133–135]. In the BBC, we previously reported that African ancestry (estimated based on 150 AIMs markers) was associated with an increased risk of FS, and with an increased odds of egg, sIgE levels are ≥2 kUA/L and peanut sIgE levels ≥5 kUA/L [136].

Other factors

Boys appear to be at a higher risk for FA than girls [128, 129]. *Obesity* may be an inflammatory state associated with increased risk for FA [137]. *Alcohol consumption* is a documented risk factor for increased specific IgE levels against food antigens in adults [138]. *Air pollution exposure* during the first year of life was associated with an increased risk of FS at year 8 [139]. In a nested case–control study in Finland composed of infants up to 2 years of age, *low socioeconomic status*, *high maternal age*, and *number of previous deliveries* and/or *previous pregnancies* were all associated with the risk of cow's milk allergy [87]. In the BBC, we found that *gestational diabetes* was associated with both FS and cord blood IgE independent of fetal growth and maternal obesity [140]. A recent study further reported that *US-born* children and adolescents had higher odds of FS than foreign-born children, and among the US-born group, children of immigrants were at the highest risk [141].

Genetics and G×E interactions associated with the risk of FA

As we reviewed previously [142], FA is under strong genetic control, while the genetic variants accounting for the susceptibility of FA remain largely unknown. Candidate gene association studies, which have focused on one or more candidate genes selected based on an understanding of biological mechanisms underlying the disease, represent the main approach used to map genetic variants associated with FA. One of the major limitations of these candidate gene association approaches is that it depends on *a priori* knowledge to select promising candidate genes, which ultimately is unsuccessful in identifying novel genetic variants relevant to complex traits. To date, more than 10 genes have been linked to FS and/or FA in at least one single study. These genes include the HLA class II gene family (*HLA-DRB1* [143, 144], *HLA-DQB1* [143], *HLA-DPB1* [143]), *CD14* [145], *forkhead box P3* (*FOXP3*) [146, 147], *signal transducer and activator of transcription 6* (*STAT6*) [148], *SPINK5* [149], *IL10* [150], *IL13* [151], *NLRP3* [152], and *FLG* genes[153]; most of which may be involved in antigen presentation and/or a shift of the immune system towards a T_h2 response. Further replications in different populations are needed for these genes. We expect that the use of the state-of-art, hypothesis-free genome-wide association (GWA) approach in FA research will potentially lead to a steeper increase in the identification of novel genetic variants associated with the susceptibility of FA.

It has been recognized that the process of identifying the genetic markers of human complex traits is highly time-consuming and labor-intensive, which, even worse, will potentially lead to a small number of confirmed susceptibility genes, leaving a long list of genes with inconclusive findings. One potential explanation for these difficulties might be the presence of gene–environment and/or gene–gene interactions. A few studies have reported that the genetic susceptibility of atopy and/or allergic phenotypes is dependent on environmental exposures such as birth order [154], prenatal or postnatal exposure to ETS [155, 156], air pollution [157, 158], day care [159], diet [41, 63], and microbial exposures [160–164]. In comparison, only limited studies have been designed and conducted to particularly focus on FS and/or FA. For example, the *GSTP1* Ile105Val polymorphism has been shown to modify the effect of air pollution on allergic sensitization to inhalant and/or food allergens [157]. In addition, our group recently reported that breastfeeding was associated with an increased risk of FS, and that this effect was significantly modified by genetic variants in the *IL12RB1* (rs425648), *TLR9* (rs352140), and *TSLP* (rs3806933) genes, individually. More importantly, we found that the interaction between the combined genotypes of the three SNPs and breastfeeding on FS was even stronger [41]. In the same cohort, we also found that VDD significantly interacted with the *IL4* gene polymorphism on the risk of FS. Similar but weak interactions were also found for SNPs in the *MS4A2* (rs512555), *FCER1G* (rs2070901), and *CYP24A1* genes, and when all four SNPs were simultaneously considered, a strong gene–VDD interaction was evident [63]. An even smaller number of studies have been carried out to explore the role of gene–gene interaction on the susceptibility of FS and/or FA. Liu et al. reported that, among unrelated German children from a multicenter atopy study, the effect of *IL13*-1112TT genotype on FS was modified by polymorphisms in the IL4 receptor alpha *(IL4RA)* gene [151]. Clearly, based on the important evidence

uncovered through these limited studies, further studies to explore the role of G×E and G×G interactions in determining FA will help to elucidate the mechanisms through which genes and environment work together to determine the risk of FA.

Epigenome: an epicenter for understanding human health and disease

Epigenetic modifications, which are heritable changes in gene expression other than those in the DNA sequence [165, 166], fall into three main categories: *DNA methylation*, a covalent modification at the carbo-5 position of cytosine in the CpG dinucleotide; *histone modifications*, which affect alterations in nucleosomal packaging and high-order folding of chromatin; and *aberrant expression of microRNAs*, which is capable of post-transcriptionally regulating the expression of a cohort of cognate target genes [167]. The epigenome can change and adapt to environmental stimuli over a relatively short time period and is also subject to epigenetic "drift" over the life course in response to both environmental and stochastic factors [168]. The plasticity of the epigenome has been demonstrated in many elegant models showing how variation in early life environmental exposure can profoundly alter the phenotype of genetically identical offspring through epigenetic effects [169, 170]. Both animal models and human studies implicate the intrauterine period as a sensitive time for the establishment of epigenetic variability [169, 171, 172], which in turn influences risk for a range of disorders that develop later in life. There is growing recognition that epigenetic mechanisms are critical to normal human development and play an important role in complex human diseases [173–175]. Two of the most comprehensively studied epigenetically regulated phenomena in mammals are genomic imprinting and X-chromosome inactivation.

Immune development is under epigenetic regulation

The kinetics and balance of naïve $CD4^+$ T cell differentiation into T_h1 or T_h2 effector cells is critical to the development of FA, since a relatively T_h2-skewed status predisposes an increased risk of allergy [176]. A growing body of studies support that T_h2 cell differentiation is under epigenetic regulation [177–184]. Methylation of the *IFNG* gene promoter, which can be reversed with a DNMT inhibitor in vitro and in vivo [177], is the main epigenetic control of T_h1 lineage commitment. CpG sites −295, −186, and −54 upstream to the transcription start site of the *IFNG* promoter in cord CD4+ T cells were demethylated under T_h1-polarizing conditions, whereas the majority of these sites were methylated under T_h2-polarizing conditions [178]. After allergen sensitization/challenge, DNA methylation at the *IFNG* promoter was significantly increased, which was correlated with decreased *IFNG* cytokine expression [177], leading to a T_h2-skewed response. In comparison, demethylation of T_h2-associated cytokines, such as IL-4, may be critical to T_h2 lineage commitment. Lee et al. reported that the 5′ region of the IL-4 locus was hypermethylated in naïve T cells and became specifically demethylated in T_h2 cells [179]. Among the four Dnase I hypersensitive sites in the T_h2 cytokine locus control region, rad50 hypersensitive site 7 undergoes rapid T_h2-specific demethylation on TCR stimulation [180]. DNA methylation is also involved in STAT6 expression in human T cells [185], which is an important transcriptional factor implicated in the T_h2 commitment linkage. Current evidence also indicates that DNA hypomethylation is a prerequisite for *FOXP3* expression and T reg differentiation [181–183]. The level of *FOXP3* demethylation in cord blood is associated with the more efficient suppressive capacity of T reg cells and is positively correlated with T_h2 cytokines (IL5 and IL13) following LpA stimulation [184].

The role of histone acetylation/deacetylation in regulating T cell development and function has been previously reviewed [186, 187]. Multiple histone deacetylase (HDACs) that regulate chromatin remodeling, gene expression, and protein function are expressed in Foxp3+ T reg cells. Administration of an HDAC inhibitor in vivo may lead to increased *FOXP3* gene expression, as well as the production and suppressive function of T reg cells [188, 189]. Recent studies also support the involvement of microRNAs in regulating the immune system [190–193]. For example, miR-146, an NF-kappaB-dependent gene, is involved in the negative regulation of TLRs and cytokine signaling [190]. miR-155 may play a role in the in vivo control of specific differentiation processes in the immune response [191]. This gene is overexpressed in patients with atopic dermatitis and may contribute to chronic skin inflammation by increasing the proliferative response of T_h cells through downregulating the production of CTLA-4 [192]. miR-126 suppresses the effector function of T_h2 cells and the development of allergic airway disease [194]. Other miRNAs, such as miR-21 [195], miR-181a [196], miR-133b [197], and miR-206 [197] may also play a role in the regulation of immune cell development and function.

Limited studies are available that directly investigate the associations between epigenetic alterations and allergic phenotypes. Pascual et al. found that three characterized populations, including house dust mite allergic subjects, and aspirin-intolerant asthmatics and controls, had different methylation patterns at limited numbers of loci in $CD19^+$ B lymphocytes. Among these loci, *CYP26A1* is one of the genes that may play a role in the immune system [198]. In

mice, Liu et al. demonstrated that altered methylation in two genes, *IL-4* and *IFNG*, was significantly correlated with a change in IgE levels. Breton and colleagues were the first to study DNA methylation levels in the asthma-specific candidate genes and demonstrated that DNA methylation levels in the *arginase* gene, but not the *nitric oxide synthase* gene, were inversely associated with exhaled nitric oxide in children with asthma, suggesting a possible role of DNA methylation in the regulation of nitric oxide production [199]. Consistent differences in methylation and expression patterns were also observed for the prostaglandin D2 receptor gene between asthmatic patients and controls [200]. No studies have directly investigated the role of epigenetics in FA.

Epigenetics as a potential mechanistic link between environmental exposures and FA

Epigenetic alterations are among the mechanisms by which prenatal and early childhood environmental exposures affect disease risk later in life. Such environmental stimuli include diet/nutrition [201–204], xenobiotic chemicals [205, 206], maternal behavior [207], tobacco smoke [208, 209], and psychosocial stress [210]; some of which are the potential risk factors of atopy and FA. Despite the lack of direct evidence, our current understanding of environmental epigenetics supports the hypothesis that epigenetic alterations are one of the mechanisms mediating the effect of pre- and postnatal environmental exposure on the development of FA. Below, we summarize the findings regarding the epigenetic influences associated with the environmental risk factors of FA.

Nutrition/diet Dietary methyl donors and cofactors, such as folic acid, vitamins B12, B6, B2, and zinc, are necessary to one-carbon metabolism, which provides the methyl group for DNA methylation. Hollingsworth and colleagues reported that in mice, in utero supplementation with methyl donors is associated with altered DNA methylation of 82 gene-associated loci and decreased transcriptional activity. One of the genes was runt-related transcription factor 3, which may negatively regulate allergic airway disease. This study strongly suggests that dietary factors can modify the heritable risk of allergic airway disease through epigenetic mechanisms during a vulnerable period of fetal development in mice [79]. It remains unknown whether other dietary factors, such as vitamin D, fatty acids, and dietary antioxidants, act on immune function and/or the development of FA via epigenetic mechanisms.

Exposure to ETS Exposure to ETS prenatally has been linked to aberrant global methylation in the placenta and cord blood, as well as in children and adults by several [208, 211–213] but not all [214] studies. In buccal cells of 348 children, Breton et al. reported that children who are prenatally exposed to ETS may have aberrant global and gene-specific DNA methylation levels [208]. Among the eight genes with differential DNA methylation levels between exposed and non-exposed children, *AXL* and *PTPRO* genes were further validated using pyrosequencing [208]; however, it is unclear whether these two genes are involved in the development of the immune system. Exposure to ETS has also been found to reduce HDAC2 expression and HDAC activity, which may account for the enhanced expression of inflammatory mediators (GM-CSF, IL-8, and TNFα) by ETS [215]. This study may indirectly indicate an epigenetic mechanism linking exposure to ETS and FA, since TNFα and IL-8 are involved in the regulation of the immune/inflammatory mechanism [215].

Microbial exposure and the hygiene hypothesis Although further validation is needed, low microbial exposure during early life has been proposed to increase the risk of allergic disease by reducing demethylation of the *IFNG* gene of naïve T cells [216]. A recent study by Brand et al. showed that asthma-protective effects by prenatal A lwoffii F78 exposure were dependent of altered *INFG* production, and that such prenatal exposure may be associated with a significant change in H4 acetylation at the *IFNG* and *IL4* promoters, which were positively associated with IFN-γ and *IL4* protein level [217]. Additionally, offspring of mothers with farm milk exposure during pregnancy were found to have increased *FOXP3* demethylation; in parallel, cord blood T reg cell counts in these offspring were increased with maternal farming exposure and associated with higher FOXP3 [108].

Air pollution It is also likely that the effects of pollutants on immune function are mediated by epigenetic modification. Exposure to black carbon, a tracer of traffic particles, has been linked to decreased DNA methylation of long interspersed nucleotide element-1, but not of Alu repeat elements, although whether such a change could affect immune function and/or allergic susceptibility remains to be determined [218]. Perera et al. reported that prenatal exposure to polycyclic aromatic hydrocarbons, measured from backpacks worn by pregnant women, was positively and significantly associated with methylation of the 5′-CpG islands in the actyl-CoA synthetase long-chain family member 3 (ACSL3) gene, a member of the ACSL gene family which encodes key enzymes in fatty acid metabolism [219]. Due to the anti-inflammatory and immune-modulating effect of several fatty acids such as dietary ω-3 and ω-6 LC-PUFAs, it is possible that hypermethylation of this gene in T helper cells may affect the susceptibility to allergy. A mouse

model undergoing intranasal sensitization to *Aspergillus fumigatus* demonstrated increased total IgE resulting from combined exposure to inhaled diesel exhaust particles and *A. fumigatus*, which is significantly associated with hypermethylation at CpG^{-45}, CpG^{-53}, and CpG^{-205} sites of the *IFNG* promoter and hypomethylation at CpG^{-408} of the *IL4* promoter [220]. By studying asthmatic children living in either the highly polluted Fresno area or lesser polluted Stanford areas of California, Nadeau et al. reported that children with greater exposure to air pollution were more likely to have increased DNA methylation of the *FOXP3* locus and impaired T reg function [221]. The epigenetic regulation of responses to ambient air pollutants and their associations with the development of allergic disorders also has been reviewed by Hong et al. [222].

Epigenetics in relation to immune-related genetic variations and G×E interaction

Epigenetic marks are heritable and appear to be associated with DNA variants [169, 223–225]. A study of DNA methylation in monozygotic twins highlighted the contribution of both intrauterine environmental and underlying genetic factors to the establishment of the neonatal epigenome [169]. Some studies demonstrated that allele-specific DNA methylation is widespread across the genome, most of which can be strongly influenced by the sequence of adjacent SNPs [223, 224]. By integrating SNP data from GWAs and DNA methylation data, a study reported that numerous CpG sites are regulated by genetic variants in *cis* and/or *trans* manner [225]. Moreover, genetic variants in genes involved in the one-carbon metabolism pathway, phases 1 and 2 detoxification, DNA repair pathway, or genes encoding chromatin protein and chaperone protein may also influence DNA methylation [226]. A recent study on *CD14* gene polymorphisms, one of the candidate genes of FA [227], reported that the reduced effect of *CD14* polymorphisms on sCD14 levels from early to late childhood parallel a small but significant increase in *CD14* methylation during the same period [227], suggesting that DNA methylation may mediate the effect of genetic variants on the development of FA via altered protein expression.

Epigenetic status also may be influenced by G×E interactions. For instance, homozygosity (TT) for the functional variant (C677T) of the methylenetetrahydrofolate reductase gene, which encodes a thermolabile protein with reduced enzymatic activity, is associated with reduced global DNA methylation but only in the presence of low folate levels [228]. Another study demonstrated that prenatal exposure to ETS was associated with global and gene-specific DNA methylation; this association varied by detoxification gene variations (*GSTM1* and *GSTP1*). These studies have provided indirect evidence that epigenetic alteration is one of the mechanisms by which to explain G×E interactions identified for the allergic phenotypes.

Research gaps and future directions

A major challenge in FA research and prevention is that FA is a complex trait and there is limited knowledge regarding early life precursors that can be reliably used for the purposes of early risk assessment, prediction, and prevention of FA. Despite the fact that most FA and FS develop in a critical period during the first few years of life, most previous FA studies have only focused on older age groups or children who have already developed FA. It also is critical to perform randomized, controlled interventional studies to determine the relative causal effects of identified environmental risk factors on the incidence of FA. Studies focused on the genetic susceptibility and gene–environmental interactions of FA are very limited. Given the complex biological pathways and mediators involved in FA, a comprehensive genome-wide search is the best available approach to identify novel genes that would not naturally be suspected due to our very limited understanding of the immune mechanisms of FA and lack of candidate genes. Future studies focused on the epigenetic and epigenomic alterations of FA hold tremendous promise for translational medicine, much due to the reversible nature of epigenetic alterations and the promise of therapies that may restore the "normal epigenome" by activating or silencing disease-related genes.

Our current knowledge supports the understanding that FA, like other complex diseases, is caused by a complex interplay of multiple factors including well-recognized epidemiological and clinical factors, genetic variants, gene–environment interactions, and epigenomic marks. Thus, studies which only address one or two factors or aspects at a time will not be able to fully explore the etiology and biological mechanisms underlying the development and progression of FA. This underscores the need for large-scale prospective birth cohort studies to simultaneously identify the interrelationships of early life adversities, genetic susceptibility, epigenomic alterations, and the development of FA. The identification of these key factors will allow us to gain important insight into the biological mechanisms by which environmental exposures and genetic susceptibility affect immune function and then the risk of FA and will contribute to the development of new paradigms for the diagnosis, prevention, and management of FA.

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References

1. Boyce JA, Assa'ad A, Burks AW et al (2010) Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 126(6 Suppl):S1–S58
2. Sampson HA (2004) Update on food allergy. J Allergy Clin Immunol 113(5):805–819, quiz 820
3. Gupta R, Sheikh A, Strachan DP et al (2007) Time trends in allergic disorders in the UK. Thorax 62(1):91–96
4. Chafen JJ, Newberry SJ, Riedl MA et al (2010) Diagnosing and managing common food allergies: a systematic review. JAMA 303(18):1848–1856
5. Primeau MN, Kagan R, Joseph L et al (2000) The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy 30(8):1135–1143
6. Sicherer SH, Noone SA, Munoz-Furlong A (2001) The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol 87(6):461–464
7. Avery NJ, King RM, Knight S et al (2003) Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol 14(5):378–382
8. Cohen BL, Noone S, Munoz-Furlong A et al (2004) Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 114(5):1159–1163
9. Sicherer SH (2011) Epidemiology of food allergy. J Allergy Clin Immunol 127(3):594–602
10. Ninan TK, Russell G (1992) Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. BMJ 304(6831):873–875
11. Peat JK, van den Berg RH, Green WF et al (1994) Changing prevalence of asthma in Australian children. BMJ 308 (6944):1591–1596
12. Holt PG, Rowe J, Kusel M et al (2010) Toward improved prediction of risk for atopy and asthma among preschoolers: a prospective cohort study. J Allergy Clin Immunol 125(3):653–659, 659 e651-659 e657
13. Ege MJ, Bieli C, Frei R et al (2006) Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol 117(4):817–823
14. Furuhjelm C, Warstedt K, Larsson J et al (2009) Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr 98(9):1461–1467
15. Kulig M, Luck W, Lau S et al (1999) Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. multicenter allergy study group, Germany. Allergy 54(3):220–228
16. Nwaru BI, Ahonen S, Kaila M et al (2010) Maternal diet during pregnancy and allergic sensitization in the offspring by 5 years of age: a prospective cohort study. Pediatr Allergy Immunol 21(1 Pt 1):29–37
17. Neaville WA, Tisler C, Bhattacharya A et al (2003) Developmental cytokine response profiles and the clinical and immunologic expression of atopy during the first year of life. J Allergy Clin Immunol 112(4):740–746
18. Lack G (2008) Epidemiologic risks for food allergy. J Allergy Clin Immunol 121(6):1331–1336
19. Saarinen UM, Kajosaari M (1995) Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet 346(8982):1065–1069
20. Oddy WH, Holt PG, Sly PD et al (1999) Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. BMJ 319(7213):815–819
21. Kramer MS, Chalmers B, Hodnett ED et al (2001) Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. JAMA 285(4):413–420
22. Kramer MS, Matush L, Vanilovich I et al (2007) Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. BMJ 335(7624):815
23. Kucukosmanoglu E, Yazi D, Yesil O et al (2008) Prevalence of egg sensitization in Turkish infants based on skin prick test. Allergol Immunopathol (Madr) 36(3):141–144
24. Venter C, Pereira B, Voigt K et al (2009) Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. Pediatr Allergy Immunol 20(4):320–327
25. Nwaru BI, Erkkola M, Ahonen S et al (2010) Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. Pediatrics 125(1):50–59
26. Lack G, Fox D, Northstone K et al (2003) Factors associated with the development of peanut allergy in childhood. N Engl J Med 348(11):977–985
27. Mihrshahi S, Ampon R, Webb K et al (2007) The association between infant feeding practices and subsequent atopy among children with a family history of asthma. Clin Exp Allergy 37 (5):671–679
28. Linneberg A, Simonsen JB, Petersen J et al (2006) Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. J Allergy Clin Immunol 117 (1):184–189
29. Sears MR, Greene JM, Willan AR et al (2002) Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet 360 (9337):901–907
30. Host A, Halken S, Muraro A et al (2008) Dietary prevention of allergic diseases in infants and small children. Pediatr Allergy Immunol 19(1):1–4
31. Greer FR, Sicherer SH, Burks AW (2008) Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 121(1):183–191
32. Koplin JJ, Osborne NJ, Wake M et al (2010) Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 126(4):807–813
33. Katz Y, Rajuan N, Goldberg MR et al (2010) Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol 126(1):77–82, e71
34. Du Toit G, Katz Y, Sasieni P et al (2008) Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 122(5):984–991
35. Poole JA, Barriga K, Leung DY et al (2006) Timing of initial exposure to cereal grains and the risk of wheat allergy. Pediatrics 117(6):2175–2182
36. Matheson MC, Erbas B, Balasuriya A et al (2007) Breast-feeding and atopic disease: a cohort study from childhood to middle age. J Allergy Clin Immunol 120(5):1051–1057
37. Mandhane PJ, Greene JM, Sears MR (2007) Interactions between breast-feeding, specific parental atopy, and sex on development of asthma and atopy. J Allergy Clin Immunol 119(6):1359–1366

38. Pesonen M, Kallio MJ, Ranki A et al (2006) Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. Clin Exp Allergy 36(8):1011–1018
39. Kumar R, Caruso DM, Arguelles L et al (2010) Early life eczema, food introduction, and risk of food allergy in children. Pediatr Allergy Immunol Pulmonol 23(3):175–182
40. Joseph CL, Ownby DR, Havstad SL et al (2011) Early complementary feeding and risk of food sensitization in a birth cohort. J Allergy Clin Immunol 127(5):1203–1210, e1205
41. Hong X, Wang G, Liu X et al (2011) Gene polymorphisms, breast-feeding, and development of food sensitization in early childhood. J Allergy Clin Immunol 128(2):374–381, e372
42. Adams JS, Hewison M (2008) Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab 4(2):80–90
43. Baeke F, Takiishi T, Korf H et al (2010) Vitamin D: modulator of the immune system. Curr Opin Pharmacol 10(4):482–496
44. Vassallo MF, Camargo CA Jr (2010) Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children. J Allergy Clin Immunol 126(2):217–222
45. Szeles L, Keresztes G, Torocsik D et al (2009) 1,25-dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. J Immunol 182(4):2074–2083
46. Dimeloe S, Nanzer A, Ryanna K et al (2010) Regulatory T cells, inflammation and the allergic response—the role of glucocorticoids and vitamin D. J Steroid Biochem Mol Biol 120(2–3):86–95
47. Unger WW, Laban S, Kleijwegt FS et al (2009) Induction of Treg by monocyte-derived DC modulated by vitamin D3 or dexamethasone: differential role for PD-L1. Eur J Immunol 39(11):3147–3159
48. Heine G, Niesner U, Chang HD et al (2008) 1,25-dihydroxyvitamin D(3) promotes IL-10 production in human B cells. Eur J Immunol 38(8):2210–2218
49. Vassallo MF, Banerji A, Rudders SA et al (2010) Season of birth and food allergy in children. Ann Allergy Asthma Immunol 104 (4):307–313
50. Vassallo MF, Banerji A, Rudders SA et al (2010) Season of birth and food-induced anaphylaxis in Boston. Allergy 65(11):1492–1493
51. Camargo CA Jr, Clark S, Kaplan MS et al (2007) Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. J Allergy Clin Immunol 120 (1):131–136
52. Mullins RJ, Clark S, Camargo CA Jr (2009) Regional variation in epinephrine autoinjector prescriptions in Australia: more evidence for the vitamin D-anaphylaxis hypothesis. Ann Allergy Asthma Immunol 103(6):488–495
53. Mullins RJ, Clark S, Camargo CA Jr (2010) Regional variation in infant hypoallergenic formula prescriptions in Australia. Pediatr Allergy Immunol 21(2 Pt 2):e413–e420
54. Wjst M, Dharmage S, Andre E et al (2005) Latitude, birth date, and allergy. PLoS Med 2(10):e294
55. Rudders SA, Espinola JA, Camargo CA Jr (2010) North—south differences in US emergency department visits for acute allergic reactions. Ann Allergy Asthma Immunol 104(5):413–416
56. Wjst M, Hypponen E (2007) Vitamin D serum levels and allergic rhinitis. Allergy 62(9):1085–1086
57. Sharief S, Jariwala S, Kumar J et al (2011) Vitamin D levels and food and environmental allergies in the United States: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol 127(5):1195–1202
58. Gale CR, Robinson SM, Harvey NC et al (2008) Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr 62(1):68–77
59. Wjst M (2008) Allergy risk of vitamin D supplements has been described in various settings. J Allergy Clin Immunol 12 (4):1065–1066, author reply 1066
60. Wjst M, Dold S (1999) Genes, factor X, and allergens: what causes allergic diseases? Allergy 54(7):757–759
61. Litonjua AA, Weiss ST (2007) Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 12(0):1031–1035
62. Kong J, Zhang Z, Musch MW et al (2008) Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am J Physiol Gastrointest Liver Physiol 294(1): G208–G216
63. Liu X, Wang G, Hong X, et al. (2011) Gene–vitamin D interactions on food sensitization: a prospective birth cohort study. *Allergy*
64. Betz M, Fox BS (1991) Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines. J Immunol 146 (1):108–113
65. Snijdewint FG, Kalinski P, Wierenga EA et al (1993) Prostaglandin E2 differentially modulates cytokine secretion profiles of human T helper lymphocytes. J Immunol 150(12):5321–5329
66. Krauss-Etschmann S, Hartl D, Rzehak P et al (2008) Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. J Allergy Clin Immunol 12(2):464–470, e466
67. Kull I, Bergstrom A, Lilja G et al (2006) Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy 61(8):1009–1015
68. Manley BJ, Makrides M, Collins CT et al (2011) High-dose docosahexaenoic acid supplementation of preterm infants: respiratory and allergy outcomes. Pediatrics 128(1):e71–e77
69. Saarinen UM, Kajosaari M (1980) Does dietary elimination in infancy prevent or only postpone a food allergy? A study of fish and citrus allergy in 375 children. Lancet 1(8161):166–167
70. Anandan C, Nurmatov U, Sheikh A (2009) Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy 64(6):840–848
71. Li-Weber M, Giaisi M, Treiber MK et al (2002) Vitamin E inhibits IL-4 gene expression in peripheral blood T cells. Eur J Immunol 32(9):2401–2408
72. McKeever TM, Lewis SA, Smit H et al (2004) Serum nutrient markers and skin prick testing using data from the third national health and nutrition examination survey. J Allergy Clin Immunol 114(6):1398–1402
73. Patel S, Murray CS, Woodcock A et al (2009) Dietary antioxidant intake, allergic sensitization and allergic diseases in young children. Allergy 64(12):1766–1772
74. Sato Y, Akiyama H, Suganuma H et al (2004) The feeding of beta-carotene down-regulates serum IgE levels and inhibits the type I allergic response in mice. Biol Pharm Bull 27(7):978–984
75. Hoppu U, Rinne M, Salo-Vaananen P et al (2005) Vitamin C in breast milk may reduce the risk of atopy in the infant. Eur J Clin Nutr 59(1):123–128
76. Marmsjo K, Rosenlund H, Kull I et al (2009) Use of multivitamin supplements in relation to allergic disease in 8-y-old children. Am J Clin Nutr 90(6):1693–1698
77. Milner JD, Stein DM, McCarter R et al (2004) Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. Pediatrics 114(1):27–32
78. Nurmatov U, Devereux G, Sheikh A (2011) Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol 127(3):724–733, e721-730
79. Hollingsworth JW, Maruoka S, Boon K et al (2008) In utero supplementation with methyl donors enhances allergic airway disease in mice. J Clin Invest 118(10):3462–3469

80. Bekkers MB, Elstgeest LE, Scholtens S, et al. (2011) Maternal use of folic acid supplements during pregnancy and childhood respiratory health and atopy: the PIAMA birth cohort study. *Eur Respir J*
81. Martinussen MP, Risnes KR, Jacobsen GW et al (2012) Folic acid supplementation in early pregnancy and asthma in children aged 6 years. Am J Obstet Gynecol 206(1):72, e71-77
82. Binkley KE, Leaver C, Ray JG (2011) Antenatal risk factors for peanut allergy in children. Allergy Asthma Clin Immunol 7:17
83. Lannero E, Wickman M, van Hage M et al (2008) Exposure to environmental tobacco smoke and sensitisation in children. Thorax 63(2):172–176
84. Keil T, Lau S, Roll S et al (2009) Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. Allergy 64(3):445–451
85. Raherison C, Penard-Morand C, Moreau D et al (2008) Smoking exposure and allergic sensitization in children according to maternal allergies. Ann Allergy Asthma Immunol 100(4):351–357
86. Strachan DP, Cook DG (1998) Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. Thorax 53(2):117–123
87. Metsala J, Lundqvist A, Kaila M et al (2010) Maternal and perinatal characteristics and the risk of cow's milk allergy in infants up to 2 years of age: a case–control study nested in the Finnish population. Am J Epidemiol 171(12):1310–1316
88. Weaver LT, Laker MF, Nelson R (1984) Intestinal permeability in the newborn. Arch Dis Child 59(3):236–241
89. Roberton DM, Paganelli R, Dinwiddie R et al (1982) Milk antigen absorption in the preterm and term neonate. Arch Dis Child 57(5):369–372
90. McNeish AS (1984) Enzymatic maturation of the gastrointestinal tract and its relevance to food allergy and intolerance in infancy. Ann Allergy 53(6 Pt 2):643–648
91. Lucas A, McLaughlan P, Coombs RR (1984) Latent anaphylactic sensitisation of infants of low birth weight to cows' milk proteins. Br Med J (Clin Res Ed) 289(6454):1254–1256
92. Chandran U, Demissie K, Echeverria SE, et al. (2012) Food allergy among low birthweight children in a national survey. *Matern Child Health J*
93. de Martino M, Donzelli GP, Galli L et al (1989) Food allergy in preterm infants fed human milk. Biol Neonate 56(6):301–305
94. Liem JJ, Kozyrskyj AL, Huq SI et al (2007) The risk of developing food allergy in premature or low-birth-weight children. J Allergy Clin Immunol 119(5):1203–1209
95. Kumar R, Yu Y, Story RE et al (2008) Prematurity, chorioamnionitis, and the development of recurrent wheezing: a prospective birth cohort study. J Allergy Clin Immunol 121(4):878–884, e876
96. Hikino S, Nakayama H, Yamamoto J et al (2001) Food allergy and atopic dermatitis in low birthweight infants during early childhood. Acta Paediatr 90(8):850–855
97. Wold AE (1998) The hygiene hypothesis revised: is the rising frequency of allergy due to changes in the intestinal flora? Allergy 53(46 Suppl):20–25
98. Noverr MC, Huffnagle GB (2005) The 'microflora hypothesis' of allergic diseases. Clin Exp Allergy 35(12):1511–1520
99. Negele K, Heinrich J, Borte M et al (2004) Mode of delivery and development of atopic disease during the first 2 years of life. Pediatr Allergy Immunol 15(1):48–54
100. Bager P, Wohlfahrt J, Westergaard T (2008) Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy 38(4):634–642
101. Sanchez-Valverde F, Gil F, Martinez D et al (2009) The impact of caesarean delivery and type of feeding on cow's milk allergy in infants and subsequent development of allergic march in childhood. Allergy 64(6):884–889
102. Eggesbo M, Botten G, Stigum H et al (2003) Is delivery by cesarean section a risk factor for food allergy? J Allergy Clin Immunol 112(2):420–426
103. Dioun AF, Harris SK, Hibberd PL (2003) Is maternal age at delivery related to childhood food allergy? Pediatr Allergy Immunol 14(4):307–311
104. Turner SW, Palmer LJ, Gibson NA et al (2005) The effect of age on the relationship between birth order and immunoglobulin E sensitization. Clin Exp Allergy 35(5):630–634
105. Johnson CC, Ownby DR, Alford SH et al (2005) Antibiotic exposure in early infancy and risk for childhood atopy. J Allergy Clin Immunol 115(6):1218–1224
106. Sandini U, Kukkonen AK, Poussa T et al (2011) Protective and risk factors for allergic diseases in high-risk children at the ages of two and five years. Int Arch Allergy Immunol 156(3):339–348
107. Lewis MC, Inman CF, Patel D, et al. (2012) Direct experimental evidence that early-life farm environment influences regulation of immune responses. *Pediatr Allergy Immunol*
108. Schaub B, Liu J, Hoppler S et al (2009) Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol 123(4):774–782, e775
109. Liu X, Liu L, Owens JA et al (2005) Sleep patterns and sleep problems among schoolchildren in the United States and China. Pediatrics 115(1 Suppl):241–249
110. Ouyang F, Lu BS, Wang B et al (2009) Sleep patterns among rural Chinese twin adolescents. Sleep Med 10(4):479–489
111. Hedley AA, Ogden CL, Johnson CL et al (2004) Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. Jama 291(23):2847–2850
112. Sicherer SH, Munoz-Furlong A, Godbold JH et al (2010) US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 125(6):1322–1326
113. Rudders SA, Banerji A, Vassallo MF et al (2010) Trends in pediatric emergency department visits for food-induced anaphylaxis. J Allergy Clin Immunol 126(2):385–388
114. Teramoto S, Yamamoto H, Yamaguchi Y et al (2005) Obstructive sleep apnea causes systemic inflammation and metabolic syndrome. Chest 127(3):1074–1075
115. Vgontzas AN, Zoumakis E, Bixler EO et al (2004) Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 89 (5):2119–2126
116. Bryant PA, Trinder J, Curtis N (2004) Sick and tired: does sleep have a vital role in the immune system? Nat Rev Immunol 4 (6):457–467
117. van Leeuwen WM, Lehto M, Karisola P et al (2009) Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One 4(2):e4589
118. Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A et al (2007) Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol 8(9):942–949
119. Kubota T, Fang J, Kushikata T et al (2000) Interleukin-13 and transforming growth factor-beta1 inhibit spontaneous sleep in rabbits. Am J Physiol Regul Integr Comp Physiol 279(3):R786–R792
120. Kushikata T, Fang J, Wang Y et al (1998) Interleukin-4 inhibits spontaneous sleep in rabbits. Am J Physiol 275(4 Pt 2):R1185–R1191
121. Zhang S, Liu X, Kim JS et al (2011) Association between short sleep duration and the risk of sensitization to food and aero allergens in rural Chinese adolescents. Clin Exp Allergy 41 (4):547–555
122. Untersmayr E, Jensen-Jarolim E (2008) The role of protein digestibility and antacids on food allergy outcomes. J Allergy Clin Immunol 121(6):1301–1308, quiz 1309-1310

123. Scholl I, Ackermann U, Ozdemir C et al (2007) Anti-ulcer treatment during pregnancy induces food allergy in mouse mothers and a Th2-bias in their offspring. FASEB J 21(4):1264–1270
124. Scholl I, Untersmayr E, Bakos N et al (2005) Antiulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. Am J Clin Nutr 81(1):154–160
125. Untersmayr E, Scholl I, Swoboda I et al (2003) Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. J Allergy Clin Immunol 112(3):616–623
126. Pali-Scholl I, Herzog R, Wallmann J et al (2010) Antacids and dietary supplements with an influence on the gastric pH increase the risk for food sensitization. Clin Exp Allergy 40(7):1091–1098
127. Untersmayr E, Bakos N, Scholl I et al (2005) Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J 19(6):656–658
128. Sicherer SH, Wood RA, Stablein D et al (2010) Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. J Allergy Clin Immunol 126 (6):1191–1197
129. Liu AH, Jaramillo R, Sicherer SH et al (2010) National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 126(4):798–806, e713
130. Sicherer SH, Munoz-Furlong A, Sampson HA (2004) Prevalence of seafood allergy in the United States determined by a random telephone survey. J Allergy Clin Immunol 114(1):159–165
131. Yaeger R, Avila-Bront A, Abdul K et al (2008) Comparing genetic ancestry and self-described race in African Americans born in the United States and in Africa. Cancer Epidemiol Biomarkers Prev 17(6):1329–1338
132. Goldstein DB, Hirschhorn JN (2004) In genetic control of disease, does 'race' matter? Nat Genet 36(12):1243–1244
133. Hoggart CJ, Parra EJ, Shriver MD et al (2003) Control of confounding of genetic associations in stratified populations. Am J Hum Genet 72(6):1492–1504
134. Rosenberg NA, Li LM, Ward R et al (2003) Informativeness of genetic markers for inference of ancestry. Am J Hum Genet 73 (6):1402–1422
135. Tang H, Peng J, Wang P et al (2005) Estimation of individual admixture: analytical and study design considerations. Genet Epidemiol 28(4):289–301
136. Kumar R, Tsai HJ, Hong X et al (2011) Race, ancestry, and development of food-allergen sensitization in early childhood. Pediatrics 128(4):e821–e829
137. Visness CM, London SJ, Daniels JL et al (2009) Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the national health and nutrition examination survey 2005-2006. J Allergy Clin Immunol 123(5):1163–1169, 1169 e1161-1164
138. Bakos N, Scholl I, Szalai K et al (2006) Risk assessment in elderly for sensitization to food and respiratory allergens. Immunol Lett 107(1):15–21
139. Gruzieva O, Bellander T, Eneroth K et al (2012) Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. J Allergy Clin Immunol 129 (1):240–246
140. Kumar R, Ouyang F, Story RE et al (2009) Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. J Allergy Clin Immunol 124(5):1031–1038, e1031-1034
141. Keet CA, Wood RA, Matsui EC (2012) Personal and parental nativity as risk factors for food sensitization. J Allergy Clin Immunol 129(1):169–175, e161-165
142. Hong X, Tsai HJ, Wang X (2009) Genetics of food allergy. Curr Opin Pediatr 21(6):770–776
143. Howell WM, Turner SJ, Hourihane JO et al (1998) HLA class II DRB1, DQB1 and DPB1 genotypic associations with peanut allergy: evidence from a family-based and case–control study. Clin Exp Allergy 28(2):156–162
144. Senechal H, Geny S, Desvaux FX et al (1999) Genetics and specific immune response in allergy to birch pollen and food: evidence of a strong, positive association between atopy and the HLA class II allele HLA-DR7. J Allergy Clin Immunol 104(2 Pt 1):395–401
145. Woo JG, Assa'ad A, Heizer AB et al (2003) The −159 C→T polymorphism of CD14 is associated with nonatopic asthma and food allergy. J Allergy Clin Immunol 112(2):438–444
146. Bottema RW, Kerkhof M, Reijmerink NE et al (2010) X-chromosome Forkhead Box P3 polymorphisms associate with atopy in girls in three Dutch birth cohorts. Allergy 65(7):865–874
147. Torgerson TR, Linane A, Moes N et al (2007) Severe food allergy as a variant of IPEX syndrome caused by a deletion in a non-coding region of the FOXP3 gene. Gastroenterology 132 (5):1705–1717
148. Amoli MM, Hand S, Hajeer AH et al (2002) Polymorphism in the STAT6 gene encodes risk for nut allergy. Genes Immun 3(4):220–224
149. Sharabrin OI (1968) Changes in the hamatopoietic system in swine with hog cholera. Veterinariia 45(7):38–41
150. Alberto EJ, Shimojo N, Suzuki Y et al (2008) IL-10 gene polymorphism, but not TGF-beta1 gene polymorphisms, is associated with food allergy in a Japanese population. Pediatr Allergy Immunol 19(8):716–721
151. Liu X, Beaty TH, Deindl P et al (2004) Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. J Allergy Clin Immunol 113(3):489–495
152. Hitomi Y, Ebisawa M, Tomikawa M et al (2009) Associations of functional NLRP3 polymorphisms with susceptibility to food-induced anaphylaxis and aspirin-induced asthma. J Allergy Clin Immunol 124(4):779–785, e776
153. Brown SJ, Asai Y, Cordell HJ et al (2011) Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol 127(3):661–667
154. Ogbuanu IU, Karmaus WJ, Zhang H et al (2010) Birth order modifies the effect of IL13 gene polymorphisms on serum IgE at age 10 and skin prick test at ages 4, 10 and 18: a prospective birth cohort study. Allergy Asthma Clin Immunol 6(1):6
155. Panasevich S, Lindgren C, Kere J et al (2010) Interaction between early maternal smoking and variants in TNF and GSTP1 in childhood wheezing. Clin Exp Allergy 40(3):458–467
156. Li H, Romieu I, Sienra-Monge JJ et al (2006) Genetic polymorphisms in arginase I and II and childhood asthma and atopy. J Allergy Clin Immunol 117(1):119–126
157. Melen E, Nyberg F, Lindgren CM et al (2008) Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic-related air pollution for development of childhood allergic disease. Environ Health Perspect 116(8):1077–1084
158. Castro-Giner F, Kunzli N, Jacquemin B et al (2009) Traffic-related air pollution, oxidative stress genes, and asthma (ECHRS). Environ Health Perspect 117(12):1919–1924
159. Custovic A, Rothers J, Stern D et al (2011) Effect of day care attendance on sensitization and atopic wheezing differs by Toll-like receptor 2 genotype in 2 population-based birth cohort studies. J Allergy Clin Immunol 127(2):390–397, e391-399
160. Eder W, Klimecki W, Yu L et al (2005) Opposite effects of CD 14/-260 on serum IgE levels in children raised in different environments. J Allergy Clin Immunol 116(3):601–607
161. Leynaert B, Guilloud-Bataille M, Soussan D et al (2006) Association between farm exposure and atopy, according to the CD14 C-159T polymorphism. J Allergy Clin Immunol 118(3):658–665

162. Roduit C, Wohlgensinger J, Frei R et al (2011) Prenatal animal contact and gene expression of innate immunity receptors at birth are associated with atopic dermatitis. J Allergy Clin Immunol 127 (1):179–185, 185 e171
163. Penders J, Thijs C, Mommers M et al (2010) Host–microbial interactions in childhood atopy: toll-like receptor 4 (TLR4), CD14, and fecal *Escherichia coli*. J Allergy Clin Immunol 125 (1):231–236, e231-235
164. Simpson A, John SL, Jury F et al (2006) Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. Am J Respir Crit Care Med 174(4):386–392
165. Jaenisch R, Bird A (2003) Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 33(Suppl):245–254
166. Bird A (2007) Perceptions of epigenetics. Nature 447(7143):396–398
167. Rodriguez A, Griffiths-Jones S, Ashurst JL et al (2004) Identification of mammalian microRNA host genes and transcription units. Genome Res 14(10A):1902–1910
168. Jirtle RL, Skinner MK (2007) Environmental epigenomics and disease susceptibility. Nat Rev Genet 8(4):253–262
169. Ollikainen M, Smith KR, Joo EJ, et al. (2010) DNA methylation analysis of multiple tissues from newborn twins reveals both genetic and intrauterine components to variation in the human neonatal epigenome. *Hum Mol Genet*
170. Wong CC, Caspi A, Williams B et al (2010) A longitudinal study of epigenetic variation in twins. Epigenetics 5(6)
171. Gluckman PD, Hanson MA, Cooper C et al (2008) Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 359(1):61–73
172. Hanson MA, Gluckman PD (2008) Developmental origins of health and disease: new insights. Basic Clin Pharmacol Toxicol 102(2):90–93
173. Feinberg AP (2007) Phenotypic plasticity and the epigenetics of human disease. Nature 447(7143):433–440
174. Waterland RA, Michels KB (2007) Epigenetic epidemiology of the developmental origins hypothesis. Annu Rev Nutr 27:363–388
175. Reik W, Dean W, Walter J (2001) Epigenetic reprogramming in mammalian development. Science 293(5532):1089–1093
176. Prescott SL, Macaubas C, Smallacombe T et al (1999) Development of allergen-specific T-cell memory in atopic and normal children. Lancet 353(9148):196–200
177. Brand S, Kesper DA, Teich R, et al. (2012) DNA methylation of T(H)1/T(H)2 cytokine genes affects sensitization and progress of experimental asthma. *J Allergy Clin Immunol*
178. White GP, Hollams EM, Yerkovich ST et al (2006) CpG methylation patterns in the IFNgamma promoter in naive T cells: variations during Th1 and Th2 differentiation and between atopics and non-atopics. Pediatr Allergy Immunol 17(8):557–564
179. Lee DU, Agarwal S, Rao A (2002) Th2 lineage commitment and efficient IL-4 production involves extended demethylation of the IL-4 gene. Immunity 16(5):649–660
180. Fields PE, Lee GR, Kim ST et al (2004) Th2-specific chromatin remodeling and enhancer activity in the Th2 cytokine locus control region. Immunity 21(6):865–876
181. Polansky JK, Kretschmer K, Freyer J et al (2008) DNA methylation controls Foxp3 gene expression. Eur J Immunol 38 (6):1654–1663
182. Polansky JK, Schreiber L, Thelemann C, et al. (2010) Methylation matters: binding of Ets-1 to the demethylated Foxp3 gene contributes to the stabilization of Foxp3 expression in regulatory T cells. *J Mol Med*
183. Huehn J, Polansky JK, Hamann A (2009) Epigenetic control of FOXP3 expression: the key to a stable regulatory T-cell lineage? Nat Rev Immunol 9(2):83–89
184. Liu J, Lluis A, Illi S et al (2010) T regulatory cells in cord blood —FOXP3 demethylation as reliable quantitative marker. PLoS One 5(10):e13267
185. Kim EG, Shin HJ, Lee CG et al (2010) DNA methylation and not allelic variation regulates STAT6 expression in human T cells. Clin Exp Med 10(3):143–152
186. Bhavsar P, Ahmad T, Adcock IM (2008) The role of histone deacetylases in asthma and allergic diseases. J Allergy Clin Immunol 121(3):580–584
187. Wang L, Tao R, Hancock WW (2009) Using histone deacetylase inhibitors to enhance Foxp3(+) regulatory T-cell function and induce allograft tolerance. Immunol Cell Biol 87(3):195–202
188. Tao R, de Zoeten EF, Ozkaynak E et al (2007) Deacetylase inhibition promotes the generation and function of regulatory T cells. Nat Med 13(11):1299–1307
189. de Zoeten EF, Wang L, Butler K et al (2011) Histone deacetylase 6 and heat shock protein 90 control the functions of Foxp3(+) T-regulatory cells. Mol Cell Biol 31(10):2066–2078
190. Taganov KD, Boldin MP, Chang KJ et al (2006) NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci U S A 103(33):12481–12486
191. Thai TH, Calado DP, Casola S et al (2007) Regulation of the germinal center response by microRNA-155. Science 316 (5824):604–608
192. Sonkoly E, Janson P, Majuri ML et al (2010) MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative responses by targeting cytotoxic T lymphocyte-associated antigen 4. J Allergy Clin Immunol 126(3):581–589, e581-520
193. Baltimore D, Boldin MP, O'Connell RM et al (2008) MicroRNAs: new regulators of immune cell development and function. Nat Immunol 9(8):839–845
194. Mattes J, Collison A, Plank M et al (2009) Antagonism of microRNA-126 suppresses the effector function of TH2 cells and the development of allergic airways disease. Proc Natl Acad Sci U S A 106(44):18704–18709
195. Lu TX, Hartner J, Lim EJ et al (2011) MicroRNA-21 limits in vivo immune response-mediated activation of the IL-12/IFN-gamma pathway, Th1 polarization, and the severity of delayed-type hypersensitivity. J Immunol 187(6):3362–3373
196. Li QJ, Chau J, Ebert PJ et al (2007) miR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell 129(1):147–161
197. Haas JD, Nistala K, Petermann F et al (2011) Expression of miRNAs miR-133b and miR-206 in the Il17a/f locus is co-regulated with IL-17 production in alphabeta and gammadelta T cells. PLoS One 6(5):e20171
198. Pascual M, Suzuki M, Isidoro-Garcia M et al (2011) Epigenetic changes in B lymphocytes associated with house dust mite allergic asthma. Epigenetics 6(9)
199. Breton CV, Byun HM, Wang X et al (2011) DNA methylation in the arginase-nitric oxide synthase pathway is associated with exhaled nitric oxide in children with asthma. Am J Respir Crit Care Med 184(2):191–197
200. Isidoro-Garcia M, Sanz C, Garcia-Solaesa V et al (2011) PTGDR gene in asthma: a functional, genetic, and epigenetic study. Allergy 66(12):1553–1562
201. Steegers-Theunissen RP, Obermann-Borst SA, Kremer D et al (2009) Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child. PLoS One 4(11):e7845
202. Waterland RA, Jirtle RL (2004) Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 20(1):63–68
203. Kovacheva VP, Mellott TJ, Davison JM et al (2007) Gestational choline deficiency causes global and Igf2 gene DNA

hypermethylation by up-regulation of Dnmt1 expression. J Biol Chem 282(43):31777–31788
204. Waterland RA, Lin JR, Smith CA et al (2006) Post-weaning diet affects genomic imprinting at the insulin-like growth factor 2 (Igf2) locus. Hum Mol Genet 15(5):705–716
205. Dolinoy DC, Huang D, Jirtle RL (2007) Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci U S A 104 (32):13056–13061
206. Bromer JG, Zhou Y, Taylor MB et al (2010) Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. FASEB J 24(7):2273–2280
207. Weaver IC, Cervoni N, Champagne FA et al (2004) Epigenetic programming by maternal behavior. Nat Neurosci 7(8):847–854
208. Breton CV, Byun HM, Wenten M et al (2009) Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. Am J Respir Crit Care Med 180(5):462–467
209. Launay JM, Del Pino M, Chironi G et al (2009) Smoking induces long-lasting effects through a monoamine-oxidase epigenetic regulation. PLoS One 4(11):e7959
210. Donkena KV, Young CY, Tindall DJ (2010) Oxidative stress and DNA methylation in prostate cancer. Obstet Gynecol Int 2010:302051
211. Guerrero-Preston R, Goldman LR, Brebi-Mieville P et al (2010) Global DNA hypomethylation is associated with in utero exposure to cotinine and perfluorinated alkyl compounds. Epigenetics 5(6)
212. Terry MB, Ferris JS, Pilsner R et al (2008) Genomic DNA methylation among women in a multiethnic New York City birth cohort. Cancer Epidemiol Biomarkers Prev 17(9):2306–2310
213. Suter M, Abramovici A, Showalter L et al (2010) In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. Metabolism 59(10):1481–1490
214. Michels KB, Harris HR, Barault L (2011) Birthweight, maternal weight trajectories and global DNA methylation of LINE-1 repetitive elements. PLoS One 6(9):e25254
215. Ito K, Lim S, Caramori G et al (2001) Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. FASEB J 15(6):1110–1112
216. Vuillermin PJ, Ponsonby AL, Saffery R et al (2009) Microbial exposure, interferon gamma gene demethylation in naive T-cells, and the risk of allergic disease. Allergy 64(3):348–353
217. Brand S, Teich R, Dicke T et al (2011) Epigenetic regulation in murine offspring as a novel mechanism for transmaternal asthma protection induced by microbes. J Allergy Clin Immunol 128 (3):618–625, e611-617
218. Baccarelli A, Wright RO, Bollati V et al (2009) Rapid DNA methylation changes after exposure to traffic particles. Am J Respir Crit Care Med 179(7):572–578
219. Perera F, Tang WY, Herbstman J et al (2009) Relation of DNA methylation of 5′-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. PLoS One 4(2):e4488
220. Liu J, Ballaney M, Al-alem U et al (2008) Combined inhaled diesel exhaust particles and allergen exposure alter methylation of T helper genes and IgE production in vivo. Toxicol Sci 102(1):76–81
221. Nadeau K, McDonald-Hyman C, Noth EM et al (2010) Ambient air pollution impairs regulatory T-cell function in asthma. J Allergy Clin Immunol 126(4):845–852, e810
222. Ji H, Khurana Hershey GK (2012) Genetic and epigenetic influence on the response to environmental particulate matter. J Allergy Clin Immunol 129(1):33–41
223. Schalkwyk LC, Meaburn EL, Smith R et al (2010) Allelic skewing of DNA methylation is widespread across the genome. Am J Hum Genet 86(2):196–212
224. Kerkel K, Spadola A, Yuan E et al (2008) Genomic surveys by methylation-sensitive SNP analysis identify sequence-dependent allele-specific DNA methylation. Nat Genet 40(7):904–908
225. Zhang D, Cheng L, Badner JA et al (2010) Genetic control of individual differences in gene-specific methylation in human brain. Am J Hum Genet 86(3):411–419
226. Feinberg AP, Ohlsson R, Henikoff S (2006) The epigenetic progenitor origin of human cancer. Nat Rev Genet 7(1):21–33
227. Munthe-Kaas MC, Torjussen TM, Gervin K et al (2010) CD14 polymorphisms and serum CD14 levels through childhood: a role for gene methylation? J Allergy Clin Immunol 125(6):1361–1368
228. Friso S, Choi SW, Girelli D et al (2002) A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. Proc Natl Acad Sci U S A 99(8):5606–5611