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REVIEW

The role of genetics and environment in the rise of childhood food allergy

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Summary

Food allergy is a growing clinical and public health problem world-wide. The rising incidence is occurring more rapidly than changes to the genome sequence would allow, but it is yet to be determined whether environmental factors might act in interaction with genetic risk. That is to say, are environmental factors more likely to affect those genetically at risk? Family history is a strong risk factor for the development of food allergy as it co-aggregates with other atopic diseases and as such genetic factors do play an important role in food allergy risk. However, significant interest has now turned to the role of epigenetic modifications of the genome as the major mediator of gene–environment interaction. The consideration of the role of epigenetics in food allergy is likely to provide an insight into aetiological and biological disease mechanisms. This paper discusses the current state of knowledge regarding genetic and environmental risk factors for food allergy, and considers the potential for furthering our understanding of food allergy aetiology by examining the role of epigenetic variation.

Introduction

Food allergy, in particular IgE-mediated food allergy, is a growing clinical and public health problem world-wide, with concerns prevalent among patients and their families, schools, food producers and retailers, healthcare staff and government departments [1, 2]. There are limited publications on the prevalence of food allergy that report studies of uncertain quality, poor consistency and a lack of time series. However, while there are few clues as to why, there is emerging evidence that the prevalence is increasing, with most recently our own study showing a higher than expected prevalence of challenge-proven food allergy in 1-year-old infants in a population-based sample [3]. The key strength of the population-based food allergy studies now emerging (including Healthnuts [4] and Europrevall [5]) is the characterization of food allergy phenotype using the gold standard for outcome: oral food challenges. Objective outcomes and differentiation of distinct phenotypes is a clear advantage for the field of food allergy over investigation of other allergic outcomes such as asthma, and offers great advantages for the productivity of future research.

The prevalence of food allergy is significantly lower in developing countries, even though migrants from these countries are not protected from developing food allergies upon relocating to a developed country. In addition, the rising incidence is occurring more rapidly than changes to the genome sequence would allow. In combination, this suggests that the risk of food allergy is likely to be, at least partially, environmentally determined, with mounting evidence of a contribution of several factors associated with the 'modern lifestyle' [6]. However, it is yet to be determined whether environmental factors might act in interaction with genetic risk. That is – are environmental factors more likely to affect those genetically at risk than those without a family history of atopy? Certain atopic diseases that include asthma, allergic rhinitis (AR), eczema (atopic dermatitis) and food allergy aggregate within families but quantification of genetic risk for food allergy specifically has not yet been formally undertaken due to the dearth of population-based studies assessing food allergy using challenge-proven outcomes.

It is becoming clear that epigenetic modifications represent a major mediator of gene–environment interaction (G×E). The original definition of epigenetics by

Waddington in 1942 [7] referred to the processes by which phenotype (the expression of a functioning gene) arises from genotype (an individual's genetic code) during development [8–10]. More recently, epigenetic analysis encompasses the study of heritable changes in gene expression patterns independent of changes in DNA sequences [11]. In addition to the singular considerations of genes and environment, consideration of the role of epigenetics in diseases such as food allergy that appear to result from complex G×E is likely to provide an insight into aetiological and biological disease mechanisms, although the field is still very much in its infancy.

In this review, we discuss the current state of knowledge regarding genetic and environmental risk factors for food allergy and consider the potential for furthering our understanding of food allergy aetiology through the examination of the role of epigenetic variation. Although there are few studies of food allergy with regard to either genetic or epigenetic mechanisms, we aim to highlight key publications that inform risk for other allergic conditions such as eczema and asthma that closely co-aggregate in both individuals and families and therefore provide potential leads for associations with food allergy itself.

Mechanisms of IgE-mediated food allergy

Analysis of genetic variations associated with the activation of IgE mechanisms and development of food allergy and co-associated allergic diseases is likely to be a fruitful line of investigation for further understanding the causal pathways for food allergy. Sensitization refers to the evidence of IgE production to a food and is identified by either a positive skin prick test to an allergen or positive food allergen-specific serum IgE. Initial sensitization to a food allergen can occur through oral and gut mucosal exposure, cutaneous exposure or even exposure from aerosolized food [12]. IgE-mediated food allergy is characterized by evidence of a clinical response to the food (clinically by history or usually in research by an oral food challenge) in the presence of food-specific IgE. More is known about IgE-mediated food allergy compared with non-IgE-mediated allergy. Allergens that cross the mucosal or the gut/skin epithelium (the body's first line of defence) are taken up by antigen-presenting cells (APCs) – mainly dendritic cells, which will process the food antigen and present it on a major histocompatibility complex (MHC) class II receptor to the T cells, resulting physiologically in oral tolerance (the state of immunological non-response established after the first contact with the food antigens in the gut).

In atopic (genetically predisposed) individuals, exposure to an allergen causes the development of a T helper (Th)2 immune response, dominated by allergen-specific IgE antibody production [13]. The outcome of a skew towards Th2 cell development subsequently leads to the production and secretion of Th2 cytokines, IL-4, IL-5, IL-9 and IL-13, which contribute to sensitization and allergy. Genetic predisposition towards the production of a predominant Th2 cytokine may be caused by defects intrinsic to T cells or defects intrinsic to APCs [14]. Within the Th2-cytokine environment, allergen-stimulated B cells switch their antibody production towards IgE. Allergenic proteins absorbed through the gut encounter and conjugate with specific IgEs pre-bound to mast cells/basophils. This stimulates the cells to degranulate, releasing mediators (principally histamine) and synthesizing new mediators (prostaglandins, leukotrienes, cytokines), producing an immediate reaction within a few minutes [15]. Therefore, it is important to investigate the underlying genetic differences inherited by individuals predisposed to Th2 cell production in response to food allergens to elucidate the mechanisms or factors involved in determining the development of either tolerance or allergic sensitization.

Evidence for a heritable component

Family history is a strong risk factor for the development of food allergy [16–18], with evidence from twin studies suggesting that genetic variation is important, although not the only factor at play. One twin study of 58 twin pairs found that the concordance rate of peanut allergy among monozygotic (MZ) twins (64.3%) was significantly higher than that among dizygotic (DZ) twins (6.8%). This study estimated the heritability of peanut allergy to be as high as 81.6% [19]. Another twin study in a Chinese population examined sensitization (i.e. presence of food-specific antibodies) to common food allergens and found sensitization to peanut and shellfish to be influenced by both genetic and environmental factors [20]. In this study, the concordance rates for sensitization were found to be much higher in MZ twins than those in DZ twins. However, many MZ and DZ twin pairs were still discordant for sensitization to a specific allergen and any allergen, indicating that individual-specific environmental factors also play a role in sensitization. The study also estimated heritability of peanut and shellfish sensitization to be 51% and 54%, respectively [20].

Further studies have attempted to quantify the risk inferred by family history for the development of food allergy. In the United Kingdom, a study of 622 families found that a child with a peanut-allergic sibling had a fivefold increased risk of having peanut allergy [16]. Another study in the United Kingdom also showed similar findings, in which peanut allergy frequency is significantly higher in relatives of peanut-allergic individuals than in the general population (7% vs. 0.5%) [17]. However, none of these studies has investigated family history as a risk factor for food allergy in the context of a population-based study and as such the results might

reflect patients at the severe end of the spectrum with less generalizability to the general population.

A number of candidate gene association studies have been performed in an effort to elucidate genetic risk factors for food allergy. Candidate–gene association studies assess the association of genetic variants (allele) within and around a gene of interest with a disease. They are often performed by comparing affected cases to unrelated and unaffected control subjects. An understanding of disease pathophysiology (mechanisms underlying the disease) is usually required in order to choose a potential candidate gene for focused analysis [21]. Candidate genes for food allergy might encompass genes known to be associated with asthma and eczema, which are closely related atopic diseases. Studies in food allergy to date have utilized a candidate gene approach with little success. Relevant studies have investigated polymorphism(s) in genes including the MHC human leucocyte antigen (HLA class II gene family including *HLA-DRB1*, *HLA-DQB1* and *HLA-DPB1*), cluster of differentiation 14 (*CD14*), forkhead box P3 (*FOXP3*), signal transducer and activator of transcription 6 (*STAT6*), serine protease inhibitor Karzal type 5 (*SPINK5*), interleukin-10 (*IL-10*) and interleukin-13 (*IL-13*). Each of these genes was found to be associated with the incidence or the severity of food allergy in single studies. However, most of these associations have yet to be replicated in independent populations and thus a specific, confirmed locus for FA risk has not been identified. Table 1 summarizes the genes associated with food allergy and food sensitization.

The currently popular and highly successful hypothesis-free approach to unravelling the genetics of complex disease is the genome-wide association study (GWAS). A GWAS is generally performed as a very large case–control study that involves rapidly scanning and comparing hundreds of thousands of single nucleotide polymorphisms (SNPs) across the human genome to identify variations associated with complex disease. GWAS has its strengths and limitations. Large sample sizes and good-quality phenotypic data are necessary to provide sufficient power to overcome the large multiple testing burden, and to detect variants of a modest effect that appear to be commonplace for complex disease.

Additionally, to ensure that the findings are robust, confirmation of associations in further large sample sets is required. Current GWAS approaches are targeted at assessing the independent effects of single genes, and methodologies for gene×gene and G×E analyses require further development [22]. GWAS for complex traits covering the knowledge gained, areas of consensus and challenges have been comprehensively reviewed [23]. GWAS has not yet been utilized in the search for food allergy genes. This is most likely because the population prevalence, which, until recently, has appeared low, has prevented the assembly of large, carefully phenotyped, population-based samples to allow for a sufficiently powered study. However, GWAS has been performed in related allergy fields, including for eczema, asthma and total serum IgE levels [24–33]. There is emerging evidence that infantile food allergy is part of the first step of the 'atopic march' in the development of other allergic disease such as asthma [34]. Furthermore, children with eczema are at a significantly increased risk of developing food allergy [35] and as such genetic factors found to be associated with other allergic disease should be investigated in food allergy studies.

The first and only GWAS to date on eczema found a highly significant association with rs7927894 on chromosome 11q13.5 [$P = 7.6 \times 10^{-10}$, combined odds ratio (OR) = 1.22, 95% CI = 1.15–1.30] [24]. This association was replicated in an Irish case–control study ($P = 0.0025$; OR = 1.27; 95% CI = 1.09–1.49) [25]. GWA studies in asthma have found an association with ORM1-like 3 (*ORMDL3*) [26], phosphodiesterase 4D (*PDE4D*) [27], chromosome 9q21.31 [28], DENN/MADD domain containing 1B protein (*DENND1B*) [29] and *RAD50IL13* and *HLA-DR/DQ* regions [30], while GWAS of asthma in an African-ancestry population found no replication of the SNPs implicated in the discovery population [31]. A pooling-based GWAS identified several susceptibility loci associated with atopy that needed to be replicated and fine-mapped [32]. The GWAS performed for the total serum IgE level found an association with two functional variants (rs2251746 and rs2427837) in the gene encoding the alpha chain of the high-affinity receptor for IgE (*FCER1A*) on chromosome 1q23 [33]. *STAT6* was also confirmed as a susceptibility locus that modulates IgE levels [33].

Genetic risk factors for eczema and their association with food allergy

Food allergy and eczema often co-exist and there is a higher prevalence of food allergy among children with atopic disorders [36, 37]. A double-blind, placebo-controlled, oral food challenge, the gold standard in diagnosing food allergy, showed that food allergy is found in about 35–80% of children with moderate to severe eczema [38]. The gene most convincingly associated with eczema to date is the filaggrin (*fil*ament-*agg*regating prote*in*) gene (*FLG*), with more than 20 studies reporting positive associations; however, there are no studies that investigate the association between *FLG* mutations and the risk of developing food allergy [39].

FLG has a key role in epidermal barrier function. *FLG* encodes pro-FLG, which is proteolytically cleaved to produce 10, 11 or 12 copies of the FLG peptide [40]. FLG aggregates keratin filaments within the cytoskeleton of keratinocytes, helping in their squame shape formation during cornification (a unique form of programmed cell death) [41]. The cornified cell envelope formed acts an

Table 1. Genes associated with the incidence or the severity of food allergy and eczema

Association	Gene	Locus	Variant	References
Food allergy	*HLA Class II*	6p21	DRB1	[74]
			HLA-DQB1	
			HLA-DPB1 DRB1*07	[75]
	STAT6	12q13	G allele in G2964A	[76]
	FOXP3	Xp11.23	1300-base pair deletion in the non-coding region of the FOXP3	[77]
			rs5906761	[78]
			rs2294021	
			rs2294019	
			rs6609857	
			rs3761548	
	TNF	6p21	−308 GA/AA	[52]
Food allergy and eczema	*SPINK5*	5q32	1258AA or 1258AG*	[79]
			G-206A†	[80]
			Glu420Lys†	[81]
			His396His†	[82]
			IVS12-26C/T†	
			IVS12-10A/G†	
			IVS13-50G/A†	
			IVS14119G/A†	
	IL-13	5q31	C-1055 T*,†	[83, 84]
			C-1112 T†	[85]
			Arg130Gln†	
			G4257A†	[86]
	CD14	5q31	C-159 T*,†	[87, 54]
	IL-10	1q31-q32	−1082AA*	[88]
			T-819C†	[89]
			A-592C†	
	GSTP1	11q13	Ile105Val/Val105Val*,†	[52, 90]
Eczema	*FLG*	1q21.3	R501X	[91]
			2282del4	
			R2447X	
			S3247X	
			3702delG	
	IL-4	5q31.1	C-589 T (C-590 T)	[92]
			C-3112 T	[93]
			T-1803C	
			C-327A	
			A-326C	
			G-186A	
	IL4R	16p12.1–11.2	G186A	[93]
			A326C	
			C327A	
			T1803C	
			C3112 T	
			Glu 551Arg	[94]
			C3223 T	[95]
	CMA1	14q11.2	BstXI	[96]
			rs1800875	[97]
	C11orf30LRRC32 intergenic region	11q13.5	rs7927894	[24, 25]

*Gene variant associated with food allergy.

†Gene variant associated with eczema.

important permeability barrier to water, microbes and allergens and helps maintain skin integrity [42]. Subsequently, FLG proteins are degraded into hygroscopic amino acids (part of the 'natural moisturizing factor'), which can retain water, therefore increasing the flexibility of the cornified layer. Besides the skin, FLG immunoreactivity has been observed in orthokeratinized and parakeratinized areas of the human oral epithelium (hard palate,

buccal mucosa) and the conjunctiva [43–45]. *FLG* is a good candidate for food allergy, as mutation in genes predisposing to eczema may increase the risk of food allergy as the skin or the mucosal barrier is more permeable to food allergen. Lack et al. [12] found that sensitization to peanut protein may occur in children through the application of peanut oil to inflamed skin. This suggests that skin barrier defects may mediate sensitization and possibly contribute to food allergy. Examination of *FLG* may therefore provide clues as to an underlying food allergy genetic predisposition.

Besides the *FLG* gene, there are at least 46 other genes reported with a positive association to eczema. Among these, only 13 genes have been reported in at least two different studies and five of them (*IL-4, IL4R, SPINK5, CMA1* and *IL-13*) have been reported in at least four different studies. Barnes [46] has recently reviewed the genetics of eczema and summarized the positive and negative genetic associations published. Interestingly, there are a few genes found to be associated with both eczema and food allergy in separate studies, including *SPINK5*, *IL-13*, *CD14*, *IL-10* and *GSTP1*. Those genes associated with eczema, but have not been examined in relation to food allergy, remain candidates worthy of consideration. Table 1 also compares the main genes investigated in food allergy, eczema and both conditions, with a positive association.

Environmental factors and their interaction with genes

Because the rise in the prevalence of allergic diseases has occurred more rapidly than can be accounted for by population-based changes in genetic sequence, it is most likely due to environmental factors. However, the rising incidence may be primarily occurring in those genetically at risk. The continuous dialogue between the genome and the environment (G×E) is important for the pathogenesis of complex diseases, which exhibit a heritable component but do not follow Mendel's laws [47–49]. Food allergy, like other complex diseases, is presumed to be caused by a combination of subtle genetic and environmental factors.

The G×E reflects how environmental exposures (including lifestyle and diet) interact with genetic predisposition to modify disease risk and/or outcome. An interaction is indicated when the simultaneous influence of two or more factors on a phenotype is not additive [50]. Thus, the presence of one factor affects the influence (manifestation of risk) associated with a second [51]. For example, the effect of air pollution on allergic sensitization to inhalant and/or food allergens appears to be modified by the *GSTP1* Ile105Val polymorphism [52] while genetic polymorphisms in the *NQO1* gene have been linked to asthma susceptibility among those exposed to local traffic-related air pollution [53]. Additionally, the influence of the C-159 T polymorphism on the *CD14* gene could depend on the microbial stimulation from the environment [54–56], with individuals carrying the TT genotype appearing to have increased protection from eczema with dog exposure [54].

Our population-based study (HealthNuts) has investigated the association between egg allergy in 12-month-old infants and lifestyle factors such as the timing of introduction of egg and solids as well as the duration of breastfeeding and found that early introduction of egg appears to protect against egg allergy. The study showed that introducing egg into the diet at either 10–12 months or after 12 months was associated with higher risks of egg allergy [with adjusted ORs of 1.6 (95% CI, 1.0–2.6) and 3.4 (95% CI, 1.8–6.5), respectively], compared with introduction at 4–6 months. These findings have been adjusted for family history of allergy (genetic risk) and they persisted even in children without risk factors [OR, 3.3 (95% CI, 1.1–9.9); 10–12 months] [57].

Environmental factors that have commonly been considered in interaction with genetic risk factors include Vitamin D (which has known direct genetic effects), smoking, air pollution and microbial exposures. However, other environmental factors for which there is evidence of involvement in allergic diseases have not been considered in interaction with genetics. For example, a recent study has suggested that dietary antioxidants may play a role in the development of allergic sensitization, as increased beta-carotene intake was associated with a reduced risk of allergic sensitization and lower IgE levels, in 5- and 8-year-old children [58]. A Swedish birth cohort study suggested that supplementation with multivitamins during the first years of life may impart a reduced risk of allergic disease in school-age children, because children who started taking multivitamins before or at age 4 years had a decreased risk of sensitization to food allergens (OR: 0.61; 95% CI: 0.39, 0.97) and tendencies towards inverse associations with AR [59]. Therefore, it would be useful to consider factors such as diet, food supplement, sun exposure (and Vitamin D levels), pet ownership and exposure to diesel exhaust particle (DEP) in relation to genetic risks such as *FLG* mutations.

While there is considerable work to be carried out to explore the role of G×E in determining food allergy, the evidence presented above provides impetus to also consider the mechanisms through which genes and environment work together to determine risk.

Epigenetics – the interface of genetics and environment

While substantial evidence exists for a role of both genetic and environmental factors in specifying the risk of allergy, it is becoming clear that epigenetic modification represents a major mechanism through which these factors interact. Epigenetics refers to the 'structural adaptations of chromosomal regions so as to register, signal, or

perpetuate altered activity states' [10]. Epigenetic mechanisms regulate gene expression changes accompanying cell differentiation and represent a major mechanism underpinning the majority of environmentally mediated changes to gene expression. The epigenome can change and adapt to environmental stimuli over a relatively short timescale and is also subject to epigenetic 'drift' over the life course in response to both environmental and stochastic factors [60].

Mounting evidence suggests that early development (*in utero* and early postnatal) represents an especially sensitive time for epigenetic disruption (reviewed in [10]). One of the most studied maternal environments with regard to epigenetics is diet, which, as discussed above, may be an important factor in the development of food allergy. There is now evidence that nutrition is an important environmental modifier of methylation. Low methionine intake leads to changes in methylation in mice and humans while increased consumption of folic acid, vitamin B12, choline and betaine during pregnancy has been shown to increase methylation in mice offspring, affecting the expression of coat colour gene [61]. Besides methyl donors, other dietary factors like polyphenols, isothiocyanates, genistein, selenium and butyrate, which mediate effects independent of folate metabolism, may also influence epigenetic patterns [62, 63]. Famine during the prenatal period leads to methylation changes in the insulin-like growth factor 2 (*IGF2*) gene, which persist into adulthood [64]. Methylation is also associated with smoking [65, 66], another important modifiable lifestyle factor. In children exposed to maternal smoking *in utero*, global methylation levels are decreased [67], with differences in global methylation being associated with the glutathione S-transferase mu 1 (*GSTM1*) genotype. Figure 1 shows the potential genetic, epigenetic and environmental factors contributing to an increase in IgE-mediated food allergy.

Epigenetic alterations in immune/allergic disease

Unfortunately, there are no studies to date that have formally investigated the role of epigenetics in food allergy, although many (including our own) are currently underway. Many believe that the disruption of appropriate allergic pathways such as Th cell differentiation (and the corresponding cytokine expression profile) in the early postnatal period represents an important potential pathway to the development of allergy. Several studies have demonstrated that DNA methylation and the resulting changes in chromatin structure are the primary regulators of naïve Th cell differentiation. At birth, there is a skew towards a pro-allergic Th2 profile with its associated cytokine profile (including IL-4) [68], but this normally does not persist, with increasing differentiation of naïve Th0 cells down the Th1 lineage (with a concomitant increasing expression of IFN-γ). This is associated with an increasing level of methylation of the *IL-4* gene and loss of methylation at *IFN-γ* regulatory regions in Th1 cells. Conversely, methylation of the *IFN-γ* gene attenuates transcription and is associated with Th2 polarization [69]. Animal models have revealed that inhalation of environmental toxins can alter methylation of both *IL-4* and *IFN-γ* promoter regions, in association with altered IgE levels [70]. In this study, BALB/c mice underwent a 3-week course of inhaled DEP exposure while undergoing intranasal sensitization to *Aspergillus fumigatus*. The total IgE production was increased following intranasal sensitization to *A. fumigatus* and was further augmented following combined exposure to *A. fumigatus* and DEP exposure. Inhaled DEP exposure and intranasal *A. fumigatus* induced hypermethylation at CpG^{-45}, CpG^{-53} and CpG^{-205} sites of the *IFN-γ* promoter and hypomethylation at CpG^{-408} of the *IL-4* promoter.

In addition to the potential changes in Th1/2-cell profile, epigenetic dysregulation may also play an important role in specifying the levels of other important immune cells. For example, the specification of regulatory T cells is driven primarily by *FOXP3* expression, which in turn is regulated by the levels of DNA methylation at key regulatory sequences [71].

Measuring the effect of epigenetics to understand their role in food allergy

The potential to identify distinct epigenetic biomarkers associated with food allergy has not been explored. Future food allergy studies should investigate DNA methylation status as it the most robust and readily measured epigenetic modification. DNA methylation can be seen as a phenotype and smaller sample sizes are required in genome-wide searches for disease-associated epigenetic change, compared with GWAS [72]. Only small amounts of genomic DNA with little specialized sample processing are needed, and a wide range of fresh and archived tissues can be used [73]. For methylation analysis in food allergy, immune cells can be easily isolated from blood, which is generally readily available or easily obtained. As for histone proteins and non-coding RNAs, more technically challenging methods are involved and cells need to be cryopreserved, snap-frozen in liquid nitrogen or stored in RNA preservative [73].

Conclusion

Studies currently in progress hold great promise in identifying the mechanisms through which genetic and environmental factors jointly contribute to disease risk and thus should be considered in any comprehensive study that aims to fully understand the aetiology of food allergy. Cohort-driven food allergy research with abundant epidemiological data has the potential to address key questions,

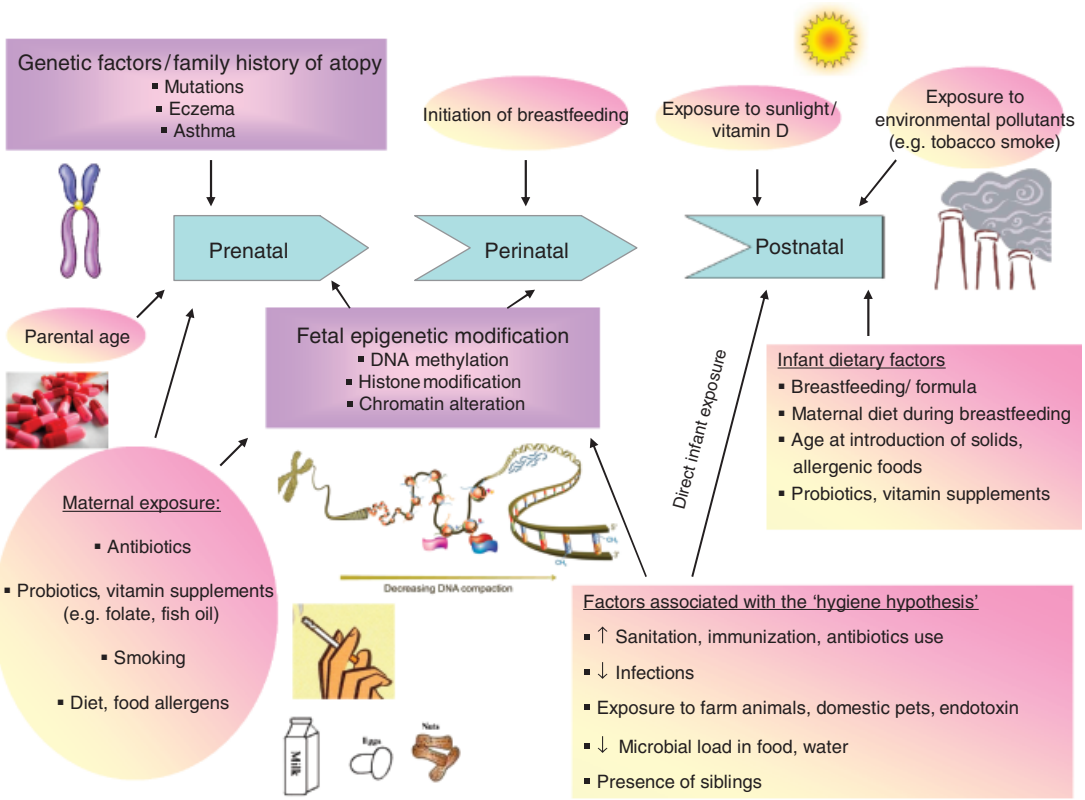

Fig. 1. The potential genetic, epigenetic and environmental factors contributing to an increase in IgE-mediated food allergy, in prenatal, perinatal and postnatal phases. Genetic factors or family history of atopy, parental age and maternal exposure to antibiotics, probiotics, supplementary food, food allergens and smoking may act at the prenatal stage. Epigenetic modification may play a role during prenatal and perinatal periods, while breastfeeding starting at the perinatal stage and infant's dietary factors and exposure to sunlight, environmental pollutants and factors related to the hygiene hypothesis may have an effect on food allergy development at the postnatal stage.

such as those concerning the influence of timing of exposure, dose of exposure, diet and ethnicity, on susceptibility to the development of food allergy and helps in shaping disease risk profiles.

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