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Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal Type 2 signalling? The MeDALL hypothesis

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Short title: Phenotypes of quantitative IgE-mediated sensitization

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Abstract

Allergic diseases (asthma, rhinitis and atopic dermatitis) are complex. They are associated with allergen-specific IgE and non-allergic mechanisms that may coexist in the same patient. In addition, these diseases tend to cluster and patients present concomitant or consecutive diseases (multimorbidity). IgE sensitization should be considered as a quantitative trait. Important clinical and immunological differences exist between mono or polysensitized subjects. Multimorbidities of allergic diseases share common causal mechanisms that are only partly IgE-mediated. Persistence of

allergic diseases over time is associated with multimorbidity and/or IgE polysensitization. The importance of the family history of allergy may decrease with age. This review puts forward the hypothesis that allergic multimorbidities and IgE polysensitization are associated and related to the persistence or re-occurrence of foetal Type 2 signalling. Asthma, rhinitis and atopic dermatitis are manifestations of a common systemic immune imbalance (mesodermal origin) with specific patterns of remodelling (ectodermal or endodermal origin). This paper proposes a new classification of IgE-mediated allergic diseases that allows the definition of novel phenotypes in order to (i) better understand genetic and epigenetic mechanisms, (ii) better stratify allergic preschool children for prognosis, and (iii) propose novel strategies of treatment and prevention.

Key words: allergy, IgE, asthma, rhinitis, atopic dermatitis, polysensitization

Abbreviations

AD: atopic dermatitis
BAMSE: Barn (Children), Allergy, Mileu, Stockholm, Epidemiology
ECA: Environment and Childhood Asthma
ECRHS: European Community Respiratory Health Survey
EGEA: Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy
EoE: Eosinophilic gastroenteritis
FcεRI: high affinity receptor for IgE
FcγRIIB: low affinity receptor for IgG
GA^{2}LEN: Global Allergy and Asthma European Network
ILC: Innate lymphoid cell
MAAS: Manchester Asthma and Allergy Study
mAb: monoclonal antibody
MAS: German Multicenter Allergy Study
MeDALL: Mechanisms of the Development of ALLergy
MHC: major histocompatibility complex
SAE: *Staphylococcus aureus* superantigen
SPT: skin prick test
WAO: World Allergy Organization

Introduction

IgE-mediated allergic diseases were defined by the World Allergy Organization (1) and include allergic rhinitis (2), allergic asthma (3), atopic dermatitis (AD) (4) and food allergy. However, IgE-mediated allergy is not always involved in the symptoms of these diseases (5-8) including non-allergic rhinitis, non-allergic asthma and eosinophilic esophagitis (EoE) (9-11).

In the present document, allergic diseases refer to an immune-mediated mechanism. Only IgE associated mechanisms are considered and allergic diseases refer to IgE-mediated allergic diseases.

IgE-associated allergic diseases are very complex since (12):

i) IgE sensitization is characterized by the presence of allergen-specific IgE to environmental allergens as demonstrated by serum allergen-specific IgE or skin prick test (SPT), but not all sensitized individuals present symptoms (13).

ii) Allergic and non-allergic mechanisms have been described for the same target organ and often coexist in the same patient (8).

iii) Serum-specific IgE and SPT reactivity do not have the same biological and clinical relevance and patients with dissociated tests may represent a different phenotype (14).

iv) The role of family history is complex. Allergic parents usually have children with allergic diseases (15) but the majority of allergic children in the birth cohorts do not have allergic parents.

v) The definition of atopy by Coca and Cooke was proposed in 1923 (16) and included a genetic determinant. However, many components of this definition do not currently apply. The definition of atopy was modified by Pepys (17) who proposed that atopy is "a form of immunological reactivity of the subject in which reaginic antibody, now identified as IgE antibody, is readily produced in response to ordinary exposure to common allergens of the subject environment."

vi) The relationship between asthma and IgE sensitization is not clear (18, 19).

vii) Allergic diseases tend to cluster and patients present concomitant or consecutive diseases. The term co-morbidity is commonly used but multimorbidity might be more appropriate. Comorbidity is the presence of one or more additional diseases co-occurring with a primary disease or the effect of such additional disorders or diseases. Multimorbidities is a term which means co-occurring diseases in the same patient. In most studies, the co-occurrence of a primary disease (e.g. asthma, rhinitis) has been studied and the term co-morbidity was correct. However, in MeDALL, we studied the co-occurrence of allergic diseases without clear information on the primary disease and the term multimorbidity appears to be more appropriate except in the case of the allergic march.

viii) IgE directed against allergens such as *Staphylococcus aureus* enterotoxins may play an important role (20-23).

Complex interactions of structural and inflammatory cells, cytokines, chemokines, growth factors, mediators of inflammation and remodeling are involved in allergic diseases. It is possible that a common mechanism leads to multimorbidities and IgE sensitization although IgE sensitization does not explain the majority of multimorbidities in young children (24).

The MeDALL project (Mechanisms of the Development of ALLergy) may help to understand the links between multimorbidities and IgE polysensitization in allergic diseases using a dual approach: hypothesis-driven (classical approach) and data-driven (novel approach) (25-27).

The present paper is based on a thorough review of the literature. It also includes the novel information found in the MeDALL studies and is therefore able to (i) assess the links between allergic multimorbidities and IgE sensitization since these associations have rarely been studied and (ii) propose hypotheses for a unified approach on multimorbidities and IgE polysensitization.

1- From allergen-specific IgE to IgE-mediated disease

In sensitized subjects, allergen-specific IgE is the initial trigger of a complex inflammatory cascade leading to symptoms and repair processes that differ between the various target organs. However, some subjects with specific IgE are asymptomatic.

1-1- Basophil activation

Basophils, mast cells, epithelial and dendritic cells represent the first cells to interact with allergens. The basophil activation test may add some information on specific IgE in certain allergic reactions such as cypress pollen (28), food challenges (29, 30), or asthma severity (31, 32).

1-2- Allergen-specific IgE and skin tests in epidemiologic studies

IgE sensitization can be assessed using either serum-specific IgE (33) or SPT or both, whereas in epidemiologic studies, although they show considerable overlap, they do not have the same value for the interpretation of the allergic risk (34, 35).

1-3- Asymptomatic subjects with IgE sensitization

Serum allergen-specific IgE or positive skin tests to common aeroallergens are observed in asymptomatic subjects (36-43). Using passive transfer tests, it has been shown that these antibodies are functional (36, 37). In the Dutch ECRHS (European Community Respiratory Health Survey) study, 43% of the subjects with IgE to inhalant allergens did not present respiratory symptoms (42). Positive skin tests in non-symptomatic subjects precede the onset of allergic symptoms including asthma (44-49).

Asymptomatic subjects are often monosensitized (50) and have lower serum allergen-specific IgE levels than symptomatic patients for inhalant (39, 40, 51) and food allergens (52-59). Moreover, skin test reactivity to inhalant allergens is reduced in asymptomatic subjects by comparison to symptomatic patients (39).

An allergen microarray containing 103 allergen molecules has detected a high prevalence of asymptomatic IgE sensitizations to tropical pollen-derived cross-reactive carbohydrate determinants (60, 61). The MeDALL allergen-chip contains 176 allergen molecules including seven cross-reactive carbohydrate determinants against which IgE are likely to be clinically irrelevant (62). The MeDALL chip has revealed that one mechanism of natural clinical tolerance to peanuts can be IgE to low allergenic peanut (63).

Allergen-specific IgE is necessary for the development of an allergic disease but many subjects have developed an IgE sensitization without symptoms.

2- Multimorbidities of IgE-mediated allergic diseases

2-1- Multimorbidities

Major IgE-mediated chronic diseases (rhinitis, asthma, AD) often cluster in multimorbidities. However, many unsolved problems remain:

i- The hypothesis of an atopic march suggests that atopic dermatitis or sometimes food allergy is the first manifestation of allergic diseases, followed by asthma and rhinitis (64, 65). However, this is not very common in certain populations (66).
ii- Atopic dermatitis is highly prevalent in preschool children and tends to be less prevalent later in life when rhinitis becomes more common. However, this is not always the case (67, 68).
iii- Atopic dermatitis is seldom present in patients with severe asthma (69), but adolescents with a severe form of AD are prone to having asthma and rhinitis (70).
iv- Lung function is lower at birth among children with co-morbid diseases after 10 years of age, as compared to all other children with asthma alone (71).
v- Genome-wide association analysis has identified new risk genes for asthma and rhinitis co-morbidity (72).

Using the "classical" hypothesis-driven approach (24), MeDALL has discovered that, at 4 and 8 years, the coexistence of AD, rhinitis and asthma in the same child is more common than expected by chance, both in the presence and absence of IgE sensitization. This discovery suggests that these diseases share causal mechanisms. Although IgE sensitization is independently associated with excess co-morbidity of AD, rhinitis and asthma, its presence accounted for only 38% of co-morbidity. This suggests that IgE sensitization cannot be considered the dominant causal mechanism of co-morbidity for these diseases at 4 and 8 years. The results of the study have been confirmed by the "novel" data-driven approach (J Garcia Aymerich, submitted).

Multimorbidities of allergic diseases may share common causal mechanisms and risk factors that are only partly IgE-mediated.

2-2- Importance of multimorbidities on trajectories of allergic diseases

In one of the cohort studies from the 12 European birth cohort studies participating in MeDALL, a longitudinal analysis modelled the relation between co-morbidity at age 4 years and disease at age 8 years (24). Children with multimorbidities at 4 years with or without IgE sensitisation had higher relative risks of co-morbidity at 8 years than those with a single disease. The stability was observed in the ECA study through puberty (67). Furthermore, in the ECA study, children with co-morbid asthma, rhinitis and AD had significantly more bronchial hyperresponsiveness and signs of allergic inflammation at 16 years than children with asthma alone.

Multimorbidities of allergic diseases are associated with persistence of disease irrespective of IgE sensitization.

2-3- Co-morbid allergic diseases without IgE sensitization

Many children and adults have symptoms resembling allergy but do not have any IgE sensitization. In children, asthma, rhinitis and AD multimorbidities prevail (24), whereas in adults, AD co-morbidity appears less common. In adults, chronic rhinosinusitis may be associated with severe asthma (73, 74). Another disease associated to this group is EoE. This disease exists at all ages (9, 10) and is characterized by a Th2 eosinophilic inflammation.

Multimorbidities of allergic diseases may occur in the absence of IgE sensitization

3- Mono and polysensitization against allergens

3-1- Characteristics of mono and polysensitization

Exposed to a common environment, the IgE-mediated immune response differs among sensitized subjects. Some react towards one or a limited number of allergens (mono or pauci-sensitized) whereas others are sensitized to a wide array of allergens (polysensitized) (13, 75) (Table 1). However, the limit between pauci and polysensitization is still unclear.

Table I: Definition of polysensitization

- At the extract level: IgE reactivity to several non-related (or not obviously related) allergenic source materials
- At the molecular level: IgE reactivity to several non-related (or not obviously related) allergenic molecules

Pepys categorized atopic status into 0, 1, 2 or 3 or more groups according to the number of positive skin prick tests to a small battery of allergens (pollens, house dust mites, cat and a locally important mould allergen) (17, 76). Taking cross-reactivities between allergens and panallergens (62, 77) into consideration in clinical studies, a minority of symptomatic patients are monosensitized, whereas over 70% are polysensitized (78, 79). Similar results are found in epidemiologic studies in adults. On the other hand, polysensitization increases with age in birth cohorts (33, 80, 81). IgE sensitization patterns differ for rhinitis and AD between 4 and 16 yrs. In rhinitis, the level of specific IgE increases whereas for AD there is an increase in polysensitization. For asthma, there is an increase in polysensitization as well as in IgE levels (33).

The discrimination between mono- and polysensitized subjects is optimally achieved using purified natural or recombinant allergens (82-88). New techniques for the determination of IgE reactivity profiles using microarrays improve the characterization of allergenic sensitization (86, 89). Different allergy patterns of PR-10 and LTP have been found according to the geographic location of the patients (90).

The characteristics of mono and polysensitization may differ using allergen extracts or allergen components.

3-2- Allergic diseases and multimorbidities in mono and polysensitized subjects

In subjects with respiratory allergic symptoms, indoor allergen sensitization is strongly associated with asthma. Sensitization to pollens is mostly associated with rhinitis (91) and less with asthma (92), whereas polysensitization is more commonly associated with asthma and rhinitis co-morbidity (91).

In a New Zealand cohort, in 13-year old children, the prevalence of diagnosed asthma increased with increasing numbers of positive SPT. However, hay fever without asthma was little affected above one positive skin-test (93). In a cross-sectional study, asthma was associated with polysensitization and significantly higher total IgE levels than rhinitis (94). Polysensitization was also associated with the development of asthma and its severity in the MAAS (Manchester Asthma and Allergy Study) cohort (81).

The EGEA (Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy) study examined the number of inhalant allergens assessed by SPT in subjects with rhinitis (95). The number of positive SPT was increased in subjects with asthma co-morbidity (Burte et al, submitted).

Bronchial hyper-responsiveness to non-specific stimuli was associated with allergen exposure (e.g. pollens) (96, 97) and was increased in subjects with both mite and pollen allergy, but not in those with a single allergenic sensitization (98). Increased bronchial hyper-responsiveness was also associated with asthma, rhinitis and AD co-morbidity in the ECA (Environment and Childhood Asthma) study (67).

Rhinitis is usually associated with mono or polysensitization, whereas asthma is more often associated with polysensitization and multimorbidities.

3-3- Severity of symptoms depending on sensitization

The impact of polysensitization on the severity of symptoms has been examined in a few studies. Nasal challenge with orchard grass induced similar symptoms and mediator release in the mono- and polysensitized subjects (99). Overall, clinical symptoms are equally severe in polysensitized and monosensitized individuals both in adults and children (78, 79, 100, 101). However, some monosensitized adults have more severe symptoms than polysensitized subjects during the ragweed or tree pollen seasons (102, 103).

Some allergen components (non-prevalent sensitizing allergen molecules) may be associated with symptom severity (104) and/or response to allergen immunotherapy, as suggested in children, but this requires further demonstration.

Mono or polysensitization as an individual criterion cannot differentiate the severity of allergic symptoms.

3-4- Trajectories of IgE-sensitization

Allergy in wheezing infants starts by monosensitization (105), but case histories of rapid onset of polysensitization are common (BAMSE: Barn/Children, Allergy, Milieu, Stockholm, Epidemiology). In childhood, most monosensitized subjects develop polysensitization, but there may be cases of transient sensitization later in life. In the MAS (German Multicenter Allergy Study) cohort, the IgE response against grass pollen molecules can start years before disease onset as a weak monosensitization or paucisensitization (106). The same data were found for birch pollen sensitization in the BAMSE study (107). Polysensitization, especially in early childhood, is a major risk for developing allergic diseases (108, 109). The number and level of IgE to the major PR-10 protein Bet v 1 (major birch pollen allergen molecule) at 4 yrs is related to the prevalence and severity to birch pollen related allergy at 8 and 16 years (107). IgE may increase in serum concentration and complexity through a "molecular spreading" process during preclinical and early clinical disease stages (106). Parental allergy was shown to reinforce IgE to pollen as a pre-clinical biomarker of hay fever in childhood (110).

In clinical studies in adults, most monosensitized subjects with symptoms are likely not to develop new sensitizations (103, 111-114).

In young children, monosensitization is often followed by polysensitization. In adults with rhinitis, monosensitization tends to persist.

3-5- IgE immune response

Mono- and polysensitized patients differ in terms of their immune response. By comparison to polysensitized patients, monosensitized subjects usually have lower serum total IgE levels (94, 112, 115, 116) and lower serum allergen-specific IgE levels (112, 117). In grass pollen allergy, monosensitized patients usually react to one or two allergenic proteins of orchard grass pollen (immunoprint) whereas polysensitized patients have IgE against a large number of them (99, 100). The same was found in mite allergy for *Dermatophagoides pteronyssinus* (118). In MeDALL, the immunoprint data on mono and polysensitization (99, 100, 118) have been reinforced, showing that polysensitization is associated with a greater number of components for the same allergen and a higher level of IgE for each component (107, 119).

Clonality implies the state of a cell or a substance being derived from one source or the other. Thus there are terms like (i) *polyclonal* - derived from many clones; (ii) *oligoclonal* - derived from a few clones; and (iii) *monoclonal* - derived from one clone. Although many patients are only sensitized to one allergen, at the clonal level the immune response is polyclonal.

The IgE immune response differs between mono and polysensitized patients suggesting a dichotomy in low and high IgE responders

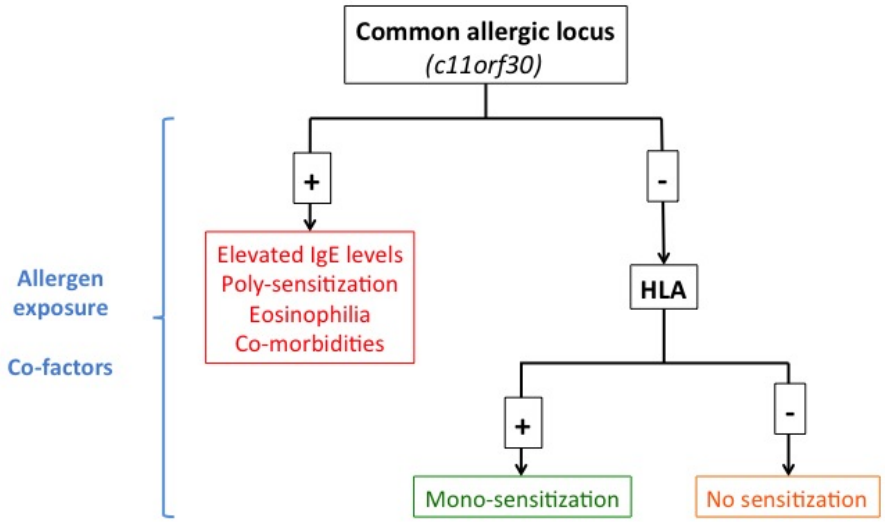
3-6- Genetic associations depending on the sensitization patterns or total serum IgE levels

The immunogenetic mechanisms underlying heightened IgE responsiveness seen in allergic diseases may be divided into two types: antigen-specific and non-specific. IL-4 regulates IgE (120). Genome wide association studies have investigated groups of subjects with one or more skin tests or specific IgE positive. These studies have therefore identified genes for the non-antigen specific response.

HLA plays a role in the development of the IgE response to allergens, but genetic regulation appears to differ in mono- and polysensitized patients. Associations between HLA haplotypes or HLA-DQ/DR molecules and allergen sensitivity were confirmed only in patients either with low total serum IgE levels or monosensitised (121-125). Recent data suggest strong associations between HLA-DQ/DR variants and peanut allergy (126), but less clear associations with other food allergies such as milk or egg. In low-IgE responder patients (low total IgE and/or monosensitized), the allergic sensitization depends more closely on HLA-DR or DQ molecules than in patients with high total IgE or polysensitized (127, 128). In another study, the *Parietaria* IgE antibody response was associated with DRB1*1104 in patients with low total IgE and with DRB1*1101 in patients with high total IgE (129). Genetic restrictions of Ole e1 are associated with total serum IgE levels (130).

The *C11orf30-LRRC32* region may represent a common locus for allergic diseases through biological pathways involved in the regulation of IgE (131), polysensitization (132), eosinophilic inflammation (133) and co-morbid allergic diseases (134) (Figure 1)

Figure 1: Differences in genetic associations between mono- and polysensitized subjects



Epigenetic associations between serum IgE concentrations and methylation at loci concentrated in CpG islands genome wide were studied in 95 nuclear pedigrees. Methylation at these loci differed significantly in isolated eosinophils from subjects with and without asthma and high IgE levels (135).

The different patterns of IgE and Type 2 immunity associated with co-sensitization between biologically unrelated allergens indicates that mono- and polysensitisation are the expression of distinct IgE-associated phenotypes. We hypothesize that they are also associated with different genetic regulation

4- Developmental origin of allergic diseases

4-1- Embryologic origin of IgE co-morbid diseases

The embryologic development of the upper and lower airways begins during the fourth week of gestation and continues for many years after birth. The nose and the skin develop from the ectoderm and mesoderm whereas the lungs develop from the endoderm and the mesoderm (136-138). The epithelial structures of the skin, i.e., the epidermis (surface and infundibular), apocrine units, sebaceous units, hair follicles, eccrine units and nail units, all come from ectoderm. Melanocytes, nerves, and specialized sensory receptors develop from neuroectoderm (139). Other elements of the nose, lung and skin, i.e., inflammatory cells, fibrocytes, blood vessels, lymph vessels, muscles and adipocytes, all originate from mesoderm. The extra-cellular matrix (ECM) interacts with cells to regulate diverse functions, including proliferation, migration and differentiation. ECM remodelling is crucial for regulating the morphogenesis of the lung (140) (Figure 2). We hypothesize that these morphogenetic capacities are being reused during chronic inflammatory disease with remodelling.

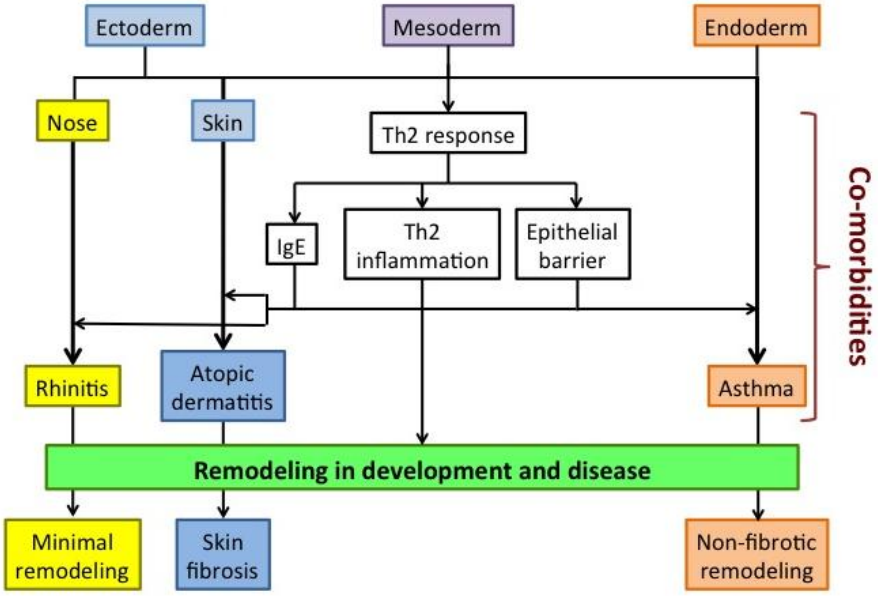
The Developmental Origins of Health and Disease (DOHaD) hypothesis refers to the concept that malnutrition and other environmental factors during the foetal period induce a nature of thrift in foetuses, such that they have a higher change of developing non-communicable diseases, such as obesity, diabetes or allergic diseases (141, 142). DOHaD should be viewed as part of a broad

biological mechanism of plasticity by which organisms, in response to cues such as nutrition, pollution or hormones, adapt their phenotype to environment (143, 144).

Common causal mechanisms of allergic multimorbidities may be associated with foetal genes from mesoderm (Th2 signalling) or from genes regulating/interacting with ectoderm and/or endoderm (145, 146). On the other hand, genes regulating remodelling differ from inflammatory genes (147, 148) and are associated with endoderm (asthma, EoE) or ectoderm (AD, rhinitis) (Figure 2).

We hypothesize that common causal mechanisms of multimorbidities may be associated with foetal genes from mesoderm. Individual diseases are likely to be associated with foetal genes of endoderm and ectoderm.

Figure 2: Embryologic origin of co-morbid allergic diseases



4-2- Peri-natal and early life events

Pre- and peri-natal events play a fundamental role in health, in the development of diseases and in ageing (149). Allergic diseases, the most common disorders in children, begin early in life and persist across the life cycle.

The immunology of pregnancy is complex. The mother must tolerate the "foreign" foetus requiring some immunosuppression whilst needing to maintain immune function to fight off infection. Successful pregnancy maintenance associates a switch from Th1 to the Th2 profile and Treg interaction (150, 151).

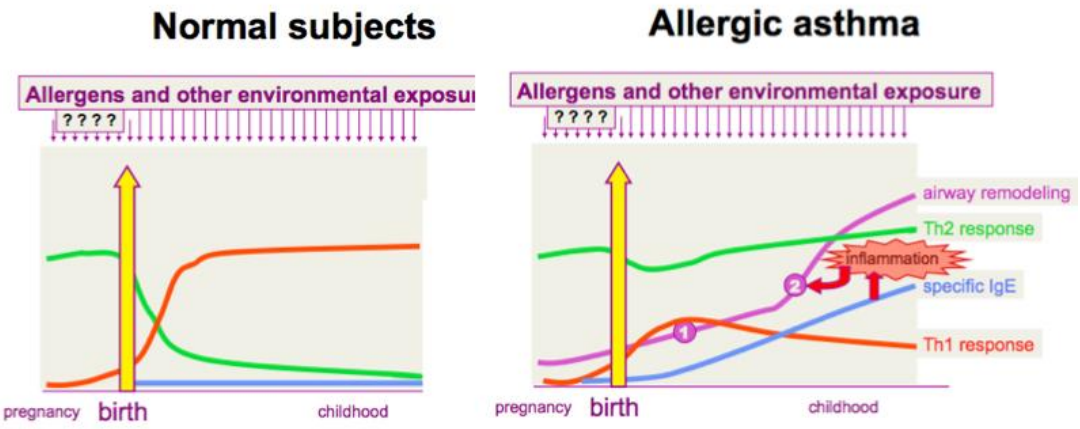
The process of immune deviation already begins *in utero* (152, 153). IgE is produced by the foetus (154, 155), and its level in cord blood is associated with the further development of allergic diseases in childhood. The effect may be weaning in adults (15, 156). The affinity of IgE may be low in cord blood (157). The continuation of foetal allergen-specific Th2 responses during infancy appears to be

a feature of the inductive phase of allergic disease, although more data are needed to fully understand the kinetics of Th1 and Th2 cytokines in infancy (158-160). Reduced IFN-γ and enhanced IL-4-producing CD4+ cord blood T cells are associated with a higher AD risk at 2 yrs (161). The first 6 months of life are also critical for the development of the Th2 response and allergic diseases (162). IL-4 production at 3 months is associated with IgE levels at 5 years (163). Birth cohort studies are relevant for the investigation of the environmental and lifestyle determinants of asthma and IgE-associated diseases as well as the absence of such diseases (164, 165) (Figure 3).

Several sets of genes are likely to interact with the environment for the development of allergic diseases and asthma: genes governing the IgE immune response, remodeling (166), inflammation and oxidative stress (167) as well as those involved in the epithelial barrier function (168, 169). Genes encoding Th2 cytokines such as IL-4 and IL- 13 (170-172) or remodeling are conserved foetal genes persisting across the life cycle (172) (Figure 3). Several asthma susceptibility genes are differentially expressed during lung development, which suggests common mechanisms underlying lung morphogenesis and pathogenesis of asthma and allergic diseases (173). Moreover, these genes interact in these diseases and multimorbidities (174). One example is the Th2 (IL-4, IL-13) involved in IgE production, the regulation of the epithelial barrier function in the skin (175) and the airways (176), remodeling and fibrosis (177).

The allergy epidemic may have resulted from recent environmental changes interacting with genes. Epigenetic mechanisms may help to understand the epidemics of allergic diseases and asthma, such as the important role of pre- and post-natal environmental factors that may programme an individual towards disease (178). Epigenetic phenomena may contribute to a Th1 and Th2 imbalance (179). As epigenetics mediates genomic imprinting during embryogenesis, it may be involved with the multigenerational transmission of allergic diseases and asthma (180).

Figure 3a & 3b: Foetal gene persistence in allergic diseases and asthma (from (179)).



Several sets of un-silenced foetal genes act in combination to induce an IgE immune inflammation, remodeling and multimorbidities. Epigenetic mechanisms are at the forefront of the development of allergic diseases.

5- Importance of Type 2 signalling in inflammation and remodelling in allergic diseases

5-1- Asthma and rhinitis

Asthma is an inflammatory disease of the entire airways and airway wall remodelling (181-183). In response to allergen presentation by airway dendritic cells, Th cells of the adaptive immune system control many aspects of the disease through the secretion of IL-4, IL-5, IL-13, IL-17, and IL-22. These are counterbalanced by cytokines produced by Treg cells (184). IL-4, IL-13, IL-33 and thymic stromal lymphopoietin (TSLP) (185) play a key role in allergic disease by their ability to initiate, maintain and augment Th2 responses (186-188). Many innate immune system cells (mast cells, basophils, neutrophils, eosinophils and lymphoid type 2 cells ILCs) have an important role. ICLs produce IL-5 and IL-13 (189). The bronchial epithelium protects the internal milieu of the lung from noxious agents by forming a physical barrier involving adhesive complexes and a chemical barrier (190). It can release cytokines and chemokines (191-193), is a sense exposure to allergens and may result in IgE sensitization.

In asthma and rhinitis, the inflammation of nasal and bronchial mucosa appears to be sustained by a similar inflammatory infiltrate including eosinophils, mast cells, T-lymphocytes and macrophages (194), as well as similar pro-inflammatory mediators (histamine, Cysteinyl Leukotrienes), Th2 cytokines and chemokines. However, there are differences between the two sites and both unique and shared genetic factors for asthma and rhinitis have been identified (195). The importance of the Th2 pathway in eosinophilic asthmatics is supported by the efficacy of a mAb against IL4/IL-13 (196).

Remodelling is present in the airways of most if not all asthmatics (181, 197) and is only partly associated with a Th2 inflammation (181)**.** Remodeling exists very early in life in asthma. On the other hand, although the epithelial mesenchymal trophic unit exists in rhinitis, nasal remodelling in rhinitis seems to be far less extensive than in the bronchi of asthmatics (198). Tissue remodelling exists in rhinosinusitis (199). Epithelial barrier and remodelling features close to those of asthma are found in EoE, a Th2 often non-IgE associated disease of an endodermic organ (9, 200-204).

Periostin, an extracellular matrix protein belonging to the fasciclin family, plays a critical role in remodeling during development or repair (205). It is a downstream molecule of IL-4 and IL-13 and a component of subepithelial fibrosis in asthma (206). Periostin expression is minimally increased in the nasal mucosa of patients with allergic rhinitis whereas it is highly increased in rhinosinusitis (207).

Type 2 inflammation has a central role in asthma and rhinitis. Remodeling is extensive in asthma whereas it is less extensive in rhinitis.

5-2- Atopic dermatitis

In AD, abnormalities in terminal differentiation of the epidermal epithelium, leading to a defective stratum corneum, allow enhanced allergen penetration and systemic IgE sensitization (208). Causes of this abnormal skin barrier are complex and driven by a combination of genetic, environmental and immunologic factors. Mutations in filaggrin (FLG), a structural protein fundamental in the development and maintenance of the skin barrier, are the best identified. However, variants

associated with AD exist in genes encoding for other proteins involved in the skin barrier (209). FLG variants also increased risk of allergic multimorbidities, which may represent more severe and complex clinical phenotypes. Allergic sensitization and AD modulated the association between FLG variants, asthma and food allergy (210) but less with rhinitis (211, 212).

The pathogenesis of AD is complex and includes a Th2 deviation, a role for specialized dendritic cells as well as Th17 and Th22 cells (213). Periostin is also involved in AD (214, 215). Dupilumab, a Mab against IL-4/IL-13, is effective in AD. It improves molecular signature (216, 217) suggesting that IL-4 and IL-13 drive a complex, Th2-centered inflammatory axis in patients with AD. Skin fibrotic remodeling is a major feature in AD, but as a consequence of skin irritation.

AD is associated with a defective skin barrier function and a complex immune response in which Type 2 signalling plays an important role.

6- Integration of concepts

6-1- Type 2 co-morbid phenotypes

6-1-1- IgE associated phenotypes

IgE-associated allergy with eosinophilic inflammation is a common feature of allergic asthma, allergic rhinitis, some forms of atopic dermatitis and allergic EoE (218, 219). Three extreme phenotypes appear to co-exist with intermediate phenotypes and non-sensitization. These phenotypes may vary with age.

1- **Non-sensitized asymptomatic individuals**

2- **IgE response restricted to one environmental allergen with no family history: low IgE responders** (number of components and level of IgE)

a. Non symptomatic subjects who are unlikely to develop symptoms over time.
b. Symptomatic subjects (symptoms similar to polysensitized subjects):
   - These subjects become sensitized because there is a substantial level of allergen exposure and subsequent exposure to co-factors (e.g. traffic-related air pollutants) (220). This is the case for tree pollens (cypress, birch) or new pollens (ragweed in Northern Italy) (103) and soybean outbreaks (221).
   - There is usually no family history.
   - In cypress pollen allergic patients, at the beginning of the disease, skin tests are not positive between seasons, only during season.
   - Patients mostly suffer from rhinitis (the case of cypress and birch pollen allergy) (222).

3- **Polyclonal IgE response to environmental allergens with family history: high IgE responders** (number of components and level of IgE). Most subjects are symptomatic, with an early life onset, a high rate of multimorbidities and persistence of the disease over time.

4- **Non-allergic polyclonal IgE without family history: Late-onset disease and local polyclonal IgE:** Some patients develop asthma late in life. In these patients, positive skin prick tests or serum IgE antibodies to inhalant allergens are not common but there is often an increase in total serum IgE (223). These patients frequently suffer from co-morbid upper airway disease (rhinosinusitis) (73) and more severe asthma (224). In chronic rhinosinusitis with nasal polyps (CRSwNP), significantly associated with asthma co-morbidity, there is a local IgE production in the upper airway mucosa (225) and a strong polyclonal mucosal local

IgE production (IgE antibodies to several hundred allergens) which is functional upon allergen exposure (226). Together with specific IgE to inhalant allergens, IgE antibodies to *Staphylococcus aureus* enterotoxins (SE-IgE) can be demonstrated in the mucosa. The presence of this antibody and a high increase in total IgE are significantly associated with asthma co-morbidity (22). In asthmatics, serum SE-IgE correlates with total IgE and is associated with the severity of the disease (227, 228). A Th2 immune response has been demonstrated in the nasal polyps of these patients (22).

5- **Intermediate phenotypes**
   a. Polyclonal IgE response without family history. The role of co-factors (pollutants, viruses) needs to be better understood.
   b. IgE response restricted to few allergens.

6-1-2- Non-IgE associated phenotypes

Eosinophilic diseases without IgE-mediated allergy exist both in children and adults. They include asthma, rhinitis, rhinosinusitis, some forms of atopic dermatitis and non-allergic EoE.

6-2- Temporal integrations of Type 2 co-morbid phenotypes

Allergens and environmental co-factors (inhaled (220, 229), nutritional, bacterial and viral infections (165, 230, 231), microbiome (232-235) …..) act at different times of pregnancy and the life cycle in subjects with a variable genetic predisposition to develop an IgE-mediated disease. Moreover, the trajectories of subjects with an IgE response vary widely. It is known that environmental factors can act *in utero* and may have more impact in early life rather than in later life. However, their role is still unclear.

Allergic diseases are highly heterogeneous including many different and overlapping phenotypes which may however be theoretically simplified in a few scenarios (Figure 4):

1- **Early onset atopic dermatitis and subsequent comorbidities included in the atopic march**. A few children follow the typical atopic march pattern (66) and, in these subjects, it may be considered that foetal life Type 2 signalling persists throughout life from birth (236).

   In the other groups, Type 2 signalling re-occurs in response to allergen and the effect of co-factors, increasing with age. The importance of the family history of allergy decreases with age but genetic factors cannot be ruled out even in subjects developing allergy in adulthood.

2- **Early development of sensitization to an inhalant allergen present in very high amounts in early life.** Neo-natal birch pollen exposure can induce the development of birch pollen allergy in some (237-241) but not all studies (242). The effect may also be seen with other allergens (241). High-dose exposure to an inhalant allergen (birch pollen) is needed for the development of sensitization and allergic disease in high-risk children (239). The window of allergic risk may be around 3 months after birth. Exposure of the mother during pregnancy to inhalant allergens is less likely to result in sensitization in the child than exposure of the child in early infancy (243). In foods, an opposite mechanism may be found.

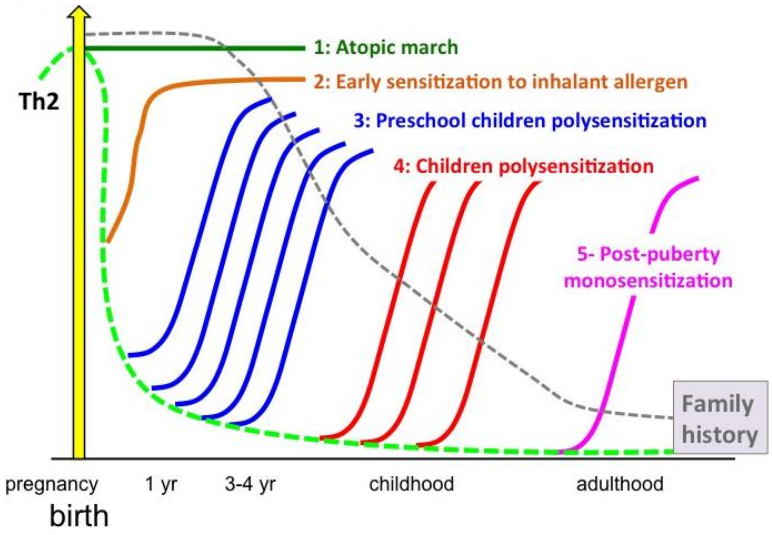
3- **Preschool children polysensitization:** Children with a family history of allergic diseases develop polysensitization and multimorbidities in early childhood. The influence of co-factors should be investigated. The disease will persist over life. Some of the children may only be monosensitized for a few years. One of the potential mechanisms may be associated with the *C11orf30-LRRC32* region involved in the regulation of IgE (131), polysensitization (132), eosinophilic inflammation (133) and co-morbid allergic diseases (134). Interestingly, *C11orf30* interacts with the Zinc finger

MYND domain-containing protein 11 (ZMYND11). The protein encoded by this gene binds the adenovirus E1A protein. The protein localizes to the nucleus. It functions as a transcriptional repressor, and the expression of E1A inhibits this repression (244).

4- **Polysensitization later in life** Children with or without a family history of allergic diseases develop polysensitization and multimorbidities later in childhood. The disease will persist over life. However, some of the children may only be monosensitized for a few years.

5- **Monosensitization after puberty:** In cypress and tree pollen allergy, many monosensitized individuals with an oligoclonal IgE response develop allergic symptoms (and probably sensitization) after puberty and sometimes a long time later. Co-factors (e.g. pollutants) may be of importance.

Figure 4: Phenotypes of IgE-mediated allergic diseases



Conclusion and implications of novel phenotypes of allergic diseases

This review has compiled evidence that allergic diseases are frequently associated as allergic multimorbidities and that IgE polysensitization increases the risk of allergic comorbidity. Though the origin of allergic comorbidity and its link with polysensitization is still unclear, we hypothesize that the persistence or re-occurrence of foetal Type 2 signalling genes plays an important role. The integration of comorbidities and polysensitization has resulted in a new classification framework of allergic diseases which could help to improve the understanding of genetic and epigenetic mechanisms of allergy as well as better manage allergic diseases (Table I). Asthma, rhinitis, AD and EoE are manifestations of a systemic immune imbalance, and a comprehensive approach should be taken for prevention and treatment (245).

Many of the hypotheses raised in this paper can be currently tested by the novel classification of allergic diseases using data already available, in particular in the MeDALL study.

Table I : Implications of the novel definition of IgE-mediated allergic diseases

Subphenotyping of allergic diseases: Phenotyping subtypes can be used to characterize allergic diseases, severity and progression, and may help identify unique targets for prevention and treatment.
Clinical practice: An updated definition provides a framework to inform decisions relating to treatment priorities and to indicate need for improvement in health care and delivery through better organisation for prediction, diagnosis and treatment. The prediction of allergic disease trajectories in preschool children is essential.
Clinical trials: Clarity on definitions is essential for clinical trials, evaluating efficacy and safety. The stratification of patients by sensitization and co-morbidity is essential in allergen immunotherapy (both for treatment and prevention).
Research on mechanisms and genetics: The new definition is likely to change the concepts of the mechanisms of allergic disease and to propose novel mechanisms.
Population studies: In longitudinal epidemiological population studies, standardised definitions are required to be able to compare cohorts across time and place and to develop dynamic models capturing risk factors which predict transitions through different stages of health.
Public health planning: For public health purposes, a comprehensive definition is needed (i) to identify the prevalence, burden and costs incurred by all phenotypes ; (ii) to improve quality of care and optimise health care planning and policies ; and (iii) to model the economic and social benefits of specific interventions to improve or maintain health.
Social welfare planning: For social welfare purposes, a phenotypic definition is also needed to predict the burden and costs at an early age in order to model the individual and collective economic and social benefits of specific interventions.
Applicability to high and low-income countries: A uniform allergy definition should be applicable to the local and geographical conditions of all countries, phenotypes, risk factors, availability and affordability to treatment differing widely around the world. This would help to better understand mechanisms specific to different environments and interactions with parasitic diseases in particular
Development of novel preventive approaches and therapies: Detailed cellular and molecular phenotyping is needed to identify novel primary and secondary prevention strategies, as well as new targets for the development of novel therapies. Ultimately, novel therapies studied in clinical trials should help define IgE-mediated pathways and determine the importance of the intervention in large patient populations or in sub-populations of patients based on the concept of distinct phenotypes. The life course approach of allergic diseases is of great interest since it may lead to health promotion strategies.

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