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Genes, factor X, and allergens: what causes allergic diseases?

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Genetic disposition and allergen exposure play the main roles in the development of allergic diseases. Another factor that could be involved is the nutritional intake of vitamin D.

The prevalence of allergies is increasing in many parts of the world, and asthma has become the most common chronic disease in childhood (1).

Genes seem to play a major role, as can be concluded from numerous family and twin studies (2). A recent study suggested the existence of a major gene with a population frequency of 24.2% but very low penetrance (3). Many attempts are now being undertaken to identify chromosomal locations and to test polymorphisms of the newly identified genes for association with asthma. Nevertheless, genetic factors cannot explain the sharp increase in prevalence during the last three decades. Allergen exposure is a *sine qua non* condition, and many other environmental factors are also under discussion. Specific infections and pollution exposure all influence the clinical course of disease; however, there is considerable doubt that these factors are the only cause of the increase of allergies. Therefore, there is probably a still unidentified risk factor X (Fig. 1) that acts on individuals with one or more of the susceptibility genes during a critical time period.

Recent research indicates that already at 22 weeks of gestation the fetus can mount IgE antibodies against various environmental allergens such as egg, milk, or house-dust mites (4), a fact which implies an antenatal immune activation. As the interferon-gamma (IFN- γ) levels in the cord blood of future atopic children are low, the current theory assumes a programming for allergen responsiveness

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very early during the perinatal period (5). The antigen-specific memory that develops at this time period is the result of a T-cell selection process that leads in normal individuals to allergen-specific T-memory cells of the CD4+ Th₁ pattern. Cytokines secreted by Th₁ cells suppress the growth of the allergy-inducing Th₂-type cells. However, if these protective antigen-reactive Th₁ memory cells fail to develop, the subsequent proliferation of Th₂ cells can trigger allergic reactions.

Therefore, the assumed factor X should have a potent immunomodulatory function already in early pregnancy. It could either direct the clonal expansion of the immunologically naive Th₀ precursor into one of the main pathways or affect the clonal deletion of responder T cells (6). Unfortunately, there are virtually hundreds of risk factors that have emerged in the last 30 or 40 years, all associated with the so-called Western lifestyle. We hypothesize now that early vitamin D exposure could be factor X.

Infantile rickets was common in many countries when addition of cholecalciferol to national sources of dried milk in the early 1950s virtually eliminated the disease (7). This is now a common practice in many countries, while others supply supplemental vitamin D as tablets. The World Health Organization has defined international units (IU) of vitamin D₃. Thus, 1.0 IU of vitamin D₃ is 0.025 mg, which is equivalent to 65 pmoles. Since vitamin D₃ is produced in the skin after exposure to sunlight, there is no requirement for vitamin D intake when sufficient sunlight is available. However, vitamin D does become an important nutritional factor in the absence of sunlight. The current recommended vitamin D dose of the US Food and Nutrition Board of the Commission on Life Sciences of the National Research Council is 200 IU/day (8). For pregnant and lactating women, the recommended vitamin D dose is 400 IU, reflecting their greater calcium needs. For infants from birth to 6 months of age, the daily requirement is set at 300 IU. Actual vitamin D exposure is different to estimate not only because of the variable endogenous production but also

because of the highly variable content in milk, which ranges from nil to the fourfold amount that may be labeled on the bottle (9). The supply of vitamin D *in utero*, rather than that in breast milk, seems to be the main determinant of vitamin D status in early life (10).

The elements of the vitamin D endocrine system include photoconversion of 7-dehydrocholesterol to vitamin D₃ in the skin or dietary intake of vitamin D₃ and conversion of 25(OH)D₃ by the kidney to produce the two principal dihydroxylated metabolites, 1,25(OH)₂D₃ (calcitriol) and 24R,25(OH)₂D₃ (11). Interestingly, 1,25(OH)₂D₃ inhibits the secretion of interleukin (IL)-12, which itself leads to the activation and differentiation into Th₁ cells. Therefore, the inhibition of IL-12 directs toward a Th₂-like cell response in mice (12). In addition, cholecalciferol inhibits IFN-γ secretion by Th₁ clones in a dose-dependent manner (13). In the same study, human T helper cell subsets showed a 50% inhibition of IFN-γ, but not IL-4, in the dose range of 10–100 nM, which is in the physiologic range of 150–1500 IU. In studies of patients with schistosomiasis, cholecalciferol showed a significant increase in circulating lymphocytes and percentage of vacuolized eosinophil cells (14).

In addition to the biological evidence, several facts or observations support an association of vitamin D exposure and allergic disease in the population:

- The time course of additional vitamin D intake during the last 30 years runs in parallel with the prevalence increase of allergic diseases (15).
- The geographic trend of higher disease prevalences in more developed countries goes along with early vitamin D exposure (16).
- The unexplained clustering of asthma in families by socioeconomic level (17) could be related to better adherence to vitamin D supplementation recommendations.
- The probandwise concordance rate of dizygous twins is considerably higher for asthma and allergic rhinitis than for siblings (18), a difference which may indicate sharing of a common early environmental factor.
- Children born abroad have less asthma than their counterparts born in the UK where vitamin D supplementation has been more common (19).
- The prevalence of children with allergic diseases is slightly higher in the summer when endogenous vitamin D exposure may be additive (20).

Further hypothesis-driven experimental, clinical, and epidemiologic studies are needed to clarify the relationship of any putative factor X and the allergy epidemic.

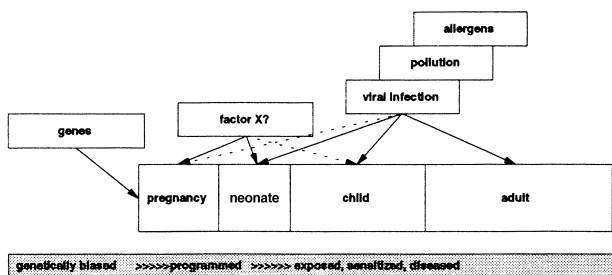


Figure 1. Relation of genes, factor X, and other risk factors for allergic diseases.

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