Review paper

Genetic aspects of food allergy

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Abstract

The increasing prevalence of food allergy is a growing problem. This review examines recent developments in the genetic factors of food allergy. The use of genomic information, accelerated by the sequencing of the human genome and the advent of new tools and technologies, has raised widespread hope that food allergy genetics can significantly contribute to the prediction, prevention, and treatment of food allergy.

Key words: food allergy, peanut allergy, FOXP3, genetics.

Introduction

Allergy to food is defined as a hyper-reactive immunological response to particular components of a diet. These allergies may be mediated by antibodies and cells. The antibodies most commonly involved in food allergy belong to the immunoglobulin E (IgE) class [1].

In addition to the concept of food allergy, abnormal responses to food are also described as food intolerance and toxic reactions to ingested food. Epidemiological data show that food intolerance is the most common, estimated to occur in 15-20% of the population, while food allergy affects 2% to 5% of the general population. In the case of allergy to food, it is necessary to make a further distinction between allergies occurring in children and in adults. The prevalence of food allergy in children ranges from 5% to 8%, while in adults it is 1% to 5% [2]. As in the case of other allergic conditions, observations over the past decade indicate there is a rising trend in the prevalence of food allergy [3]. Epidemiological studies conducted in Great Britain and in the United States have revealed a particularly high increase in the incidence of peanut allergy [4]. The most common food allergens in early childhood are: cow's milk, eggs, wheat, soy, peanuts, nuts, fish, and shellfish. During puberty, symptoms of food allergy following contact with allergens in milk, eggs, wheat, and soy tend to subside most often, while allergies to peanuts, nuts, fish and shellfish tend to be lifelong. According to Fleischer *et al.* [5], only 20% of children with allergy to peanuts develop tolerance to these allergens, while in the case of nuts, the percentage of children who develop tolerance to this fruit is even lower and amounts to 9% of the whole population allergic to these allergens.

Faced with the statistical data, the issue of food allergy is becoming increasingly important and requires intensive studies, which will make it possible to gain an understanding of the mechanisms underlying the development of such conditions.

Genetic predisposition to food allergy

Available studies on the incidence of allergic diseases indicate that genetic predisposition plays a significant role in the development of diseases such as bronchial asthma, atopic rhinitis, or atopic dermatitis. In the case of bronchial asthma and atopic rhinitis, a specific genetic defect responsible for the development of these diseases has not yet been identified. It has been suggested that there is an association with multiple genes, whose mutations may contribute to excessive IgE production, bronchial hyper-reactivity, or bronchial remodelling [6]. In the case of atopic dermatitis, numerous studies emphasize the association between this disease and chromosome 1q21 and filaggrin coding genes. A defect in the gene coding filaggrin is considered to be largely responsible for the development of atopic dermatitis [7].

As opposed to food allergy, investigations into the genetic causes of non-allergic food hypersensitivity are often successful, since they are the result of the mutation

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of single genes, responsible for the expression of individual enzymes. Examples of such genetic defects, responsible for non-allergic hypersensitivity, are presented in Tab. 1 [8].

In view of the complex mechanism of development of allergic diseases, Holloway *et al.* [9] are of the opinion that development of these diseases is determined by a gene complex. In addition to the genetic component, emphasis is also being placed on the role of environmental factors in the occurrence of allergies.

As in the case of other allergic conditions, food allergy tends to be familial [10]. Studies conducted in Great Britain confirm this theory. An analysis of 622 British families revealed that if one child is allergic to peanuts, the risk of a similar allergy developing in subsequent siblings increases as much as five-fold [11]. Other studies estimate the prevalence of peanut allergy in the general population at approximately 0.5%, while in families affected by this allergy the risk increases to 7% [12].

Genetic predisposition to developing food allergy has been demonstrated convincingly in studies involving twins. The concordance rate for inheriting the predisposition to develop an allergy to peanuts among monozygotic twins was 64.3%, while in dizygotic twins the concordance rate was approximately 6.8%. It appears that the risk of inheriting a predisposition to peanut allergy in twins is similar to the heritability of bronchial asthma, allergic rhinitis, or atopic dermatitis [13].

Suspect genes

Genetic studies currently underway aim to identify the gene or genes that play a key role in the development of allergic reactions. However, these studies only indicate candidate genes, whose role is limited to certain specific mechanisms of allergy.

A factor under consideration in the case of food allergy is the association with human leukocyte antigen (HLA) system genes. According to Howell *et al.* [14], peanut allergy may be linked to HLA-DRB1, HLA-DQB1, and HLA-DPB1 antigens. Apple allergy, meanwhile, may be associated with HLA-DRB1 antigens. However, these reports remain within the sphere of conjecture and have not been sufficiently documented [15]. Other studies suggest there is a link between developing bronchial asthma and food allergy and mutation within the promoter of the cluster of differentiation 14 (CD14) lipopolysaccharide receptor protein gene. However, once again, there is no consensus about the significance of genetic changes within CD14 with regard to predisposition towards allergy [16].

More conjectures relate to the genes encoding the transcription factor for Forkhead box P3 (FOXP3), located on chromosome Xp11.23. Torgerson *et al.* [17] reported that a 1300-base pair deletion in the gene coding FOXP3 results in abnormalities in protein production in lymphocytes, particularly in regulatory T-lymphocytes. According to the above-mentioned authors, this type of mutation is responsible for severe food allergy, enteropathy, and may lead to severe immunological defects. A syndrome associated with the X chromosome has been identified, described by the acronym IPEX, characterized by high IgE levels, atopic dermatitis, eosinophilia, and food allergy [18]. Some very interesting observations regarding FOXP3 and heritability of the predisposition to develop food allergy have been made by Bottema *et al.* [19]. Cohort studies conducted in a population of 3062 Dutch children at ages 1, 2, 4, and 8 years confirmed the involvement of FOXP3 and mutations within this gene in the development of food allergy to eggs and cow's milk, and allergy to such aeroallergens as house dust mite, and dog and cat allergens. The studies show that girls aged 1 and 2 years with single polymorphism of the FOXP3 gene have significantly increased levels of IgE specific to egg allergens and to the aforementioned aeroallergens. The authors of the studies in question specifically indicate the type of FOXP3 polymorphism that is associated with the development of specific allergic hypersensitivity. The findings reveal that 5 different FOXP3 polymorphisms, all of which concern

Tab. 1. Non-allergic food hypersensitivity caused by enzymatic defects [8]

Enzyme	Substrate	Mode of inheritance
β-galactosidase	Lactose	Autosomal recessive
Saccharase (invertase) and α-glucosidases	Saccharose	Autosomal recessive
Maltase (α-glucosidase)	Maltose	Autosomal recessive
Galactase	Galactose	Autosomal recessive
Aldolase B	Fructose	Autosomal recessive
Alcohol dehydrogenase	Ethanol, acetic aldehyde	
Glucose-6-phosphate dehydrogenase (G6PD)	Catalyses the first reaction of the pentose phosphate pathway	Mutation of the G6PD gene on the X chromosome
Di-amine oxidase (histaminase)	Histamine	Autosomal recessive

girls, are responsible for hypersensitivity to eggs, milk and some aeroallergens. These studies have demonstrated the significance of gender in the heritability of allergy to eggs and milk. It would appear that boys are affected by only one type of FOXP3 polymorphism. Also, there are differences between the evolution of food allergy in boys and girls. In the group of 8-year-olds, only boys were found to experience a remission of food allergy. An explanation for this phenomenon may be provided by studies conducted by Lemos *et al.* [20], who demonstrated the regulatory effect of the Y chromosome on the expression of genes on the X chromosome.

The aforementioned filaggrin possesses documented importance for the normal functioning of the skin. It is estimated that mutation of the coding gene for this protein is present in 10% of the population of Western Europe and North America and is a significant factor in the development of atopic dermatitis. Recent genetic studies reveal that mutations of the filaggrin gene may also be responsible for the development of bronchial asthma, allergic rhinitis, and food allergy [21].

Marenholz *et al.* [22] noted that mutation of the filaggrin gene and associated atopic dermatitis and concurrent food allergy are very significant factors in the development of bronchial asthma.

Geneticists' interest has been sparked by genes encoding cytokines, which play an important role in allergic reactions. Point mutations present in the interleukin-10 (IL-10) cytokine's genes have not been found to have any significance in the development of food allergy. Interleukin-13 gene polymorphism in both bronchial asthma as well as food allergy was found to play a significant role in the occurrence of these types of diseases. Next, an analysis of STAT6 transcription factors responsible for the production of IL-4 and IL-13, cytokines that activate IgE synthesis, revealed an association with development of bronchial asthma [23]. However, STAT6 polymorphism has not been found to contribute significantly to the occurrence of food allergy [24].

According to Kabesch [24], research into the causes of genetic allergic diseases should focus on studies of polymorphism in multiple genes involved in allergies. An example is the simultaneous discovery of genetic changes in the genes encoding IL-4, IL-13, IL-4RA, and STAT6, where such mutations increase the risk of IgE hyper-production 11-fold and of developing bronchial asthma as much as 16.8-fold compared to individually analysed polymorphisms of these genes. Studies on bronchial asthma confirm the difficulties involved in research into genes responsible for the development of allergies. The number of suspect genes that may be associated with development of this disease currently stands at 100 [25].

Studies into the development of food allergy point to epigenetic mechanisms, which are defined as changes in gene expression that are the result of causes other than mutations. Chromatin modifications and DNA methylation may affect Th lymphocyte differentiation, cytokine production and IgE synthesis [26]. Epigenetic alterations are induced by different environmental factors. In food allergy, emphasis is laid on the significance of various types of chemical substances added to food products, environmental pollution, and exposure to various types of microorganisms [27].

Elimination of allergens responsible for inducing allergic reactions is of fundamental importance in the treatment of food allergy. In nut allergy, particularly allergy to peanuts, such recommendations are often difficult to put into practice. The problem of allergy to peanuts is particularly troublesome in the United States, where an estimated 1.1% of Americans (which amounts to approximately 4 million people) suffer from allergies to various types of nuts [28]. According to Dodo *et al.* [29], transgenic plants may alleviate this problem. Using genetic engineering, the authors of this idea succeeded in reducing the expression of genes encoding Ara h 2, the principal allergen in peanuts, responsible for 85% of allergic reactions. This study, while representing a somewhat novel approach to solving the issue of food allergy, nonetheless touches upon the controversial issue of genetically modified food. Keeping this in mind, there is still the very large group of animal-derived allergens and a parallel should most certainly not be drawn between this group and plant-derived allergens.

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