# ROLE OF PHENOTYPES IN ALLERGIC DISEASES

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**Annotation**

The variety of causes that cause the development of allergic diseases, the complex pathogenesis, and the unequal response of patients to therapy have become the basis for identifying phenotypes and endotypes of allergic diseases. Such a high interest in this problem is due to the fact that modern advances in the diagnosis and treatment of allergic diseases do not always satisfy patients, and many of them experience ineffectiveness of the standard treatment [1]. As a result, all the signs and properties of the organism develop, which make up its phenotype. Thus, a phenotype is a product of the implementation of the genetic program contained in the genotype. However, the genotype does not unambiguously determine the phenotype: to a greater or lesser extent it also depends on external conditions. Sometimes phenotypes differ extremely dramatically in different conditions. Various methods of carrying out this type of immunotherapy have been proposed: oral, subcutaneous, etc., but the question of its appropriateness for food allergies requires further study.

***Key words****: oral, allergy syndrome, phenotype, endotype, therapy*

**Introduction**. The variety of causes that cause the development of allergic diseases, the complex pathogenesis, and the unequal response of patients to therapy have become the basis for identifying phenotypes and endotypes of allergic diseases. Such a high interest in this problem is due to the fact that modern advances in the diagnosis and treatment of allergic diseases do not always satisfy patients, and many of them experience ineffectiveness of the standard treatment [1]. All this served as a reason for studying the phenotypes and endotypes of allergic diseases, which make it possible to explain the clinical, pathophysiological, functional, and sometimes genetic characteristics of each individual patient and to select personalized therapy for him [2, 3]. To date, the phenotypes of bronchial asthma have been described in most detail [4, 5]. For the first time, the term “phenotype” (phenotype from the Greek phaino - I show, discover and typos - imprint, form, sample) was proposed by the Danish scientist Wilhelm Johansen in 1909, who explained that under the influence of environmental factors the genotype of an organism (hereditary predisposition) is realized into any symptom inherent in a given organism, or disease.

Each biological species has a phenotype unique to it. It is formed in accordance with the hereditary information contained in the genes. However, depending on changes in the external environment, the state of traits varies from organism to organism, resulting in individual differences - genetic variability, which can be combinative and mutational. Combinative variability arises as a result of the exchange of homologous regions of homologous chromosomes, which leads to the formation of new gene associations in the genotype. Mutational variability (mutations) causes changes in the genotype, is inherited by offspring and is not associated with crossing and recombination of genes. There are chromosomal and gene mutations. Chromosomal mutations are associated with changes in the structure of chromosomes. This may be a change in the number of chromosomes, a multiple or not a multiple of the haploid set. Gene mutations affect the structure of the gene itself and entail changes in the properties of the organism and occur in both somatic and germ cells. Phenotypic characteristics are not transmitted from parents to offspring, only the reaction norm is inherited, i.e. the nature of the response to changes in environmental conditions. And if the totality of all the genes of an organism constitutes its genotype, then the totality of all its characteristics (anatomical, morphological, functional, etc.) constitutes its phenotype. During life, the phenotype of an organism can change, while the genotype remains unchanged. Each phenotype has its own molecular markers (endotypes), which require further decoding. Endotypes are precisely those biomarkers that determine the pathogenesis and characteristics of the phenotype of a patient with a particular disease. So, a phenotype is the totality of all the characteristics and

properties of an organism, which is formed in the process of its individual development as a result of the interaction of the genotype and environmental conditions.

**Results**. The set of chromosomes received from the parents carries a set of genes that are characteristic of a given species in general and a given organism in particular. These genes carry information about proteins that can be synthesized in this organism, as well as about the mechanisms that determine the synthesis itself and its regulation. During development, genes are sequentially turned on and the proteins they encode are synthesized (gene expression). As a result, all the signs and properties of the organism develop, which make up its phenotype. Thus, a phenotype is a product of the implementation of the genetic program contained in the genotype. However, the genotype does not unambiguously determine the phenotype: to a greater or lesser extent it also depends on external conditions. Sometimes phenotypes differ extremely dramatically in different conditions. Phenotype can be defined as the "carrying out" of genetic information towards environmental factors. In light of the above, the identification and study of food allergy phenotypes as a trigger and etiological factor in many allergic diseases is of great importance for clinical practice [6, 7]. Food allergy is characterized by polymorphism of clinical manifestations and complex immunological mechanisms. It has a high and uneven prevalence in different regions of the globe, due to specific dietary traditions and the unique impact of environmental factors on the child's body [8, 9, 10]. The heterogeneity of food allergies with all the variety of clinical manifestations, differences in severity and, in special cases, resistance to traditional treatment makes it possible to distinguish individual food allergy phenotypes based on clinical signs and a number of immunological markers. Currently, this issue is controversial and requires further discussion. Food allergies underlie many allergic diseases: atopic dermatitis, urticaria, angioedema, gastrointestinal symptoms, allergic rhinitis, bronchial asthma, anaphylaxis. In most cases, food allergies are caused by overproduction of IgE antibodies with the formation of chronic inflammation in the shock target organ [11]. The main role in it is played by various immunocompetent cells, among which are lymphocytes, dendritic cells, eosinophils, mast cells and basophils. In patients with IgE-mediated reactions, there is an imbalance of the Th2/Th1 cytokine profile with a predominance of the activity of Th2 lymphocytes with the generation of pro-inflammatory cytokines. The cause of polarization of Th1 cells may be the excretion by dendritic cells of a large number of antigenic peptides with high affinity for the major histocompatibility complex (HLA) class II and their production of IL-12. With delayed maturation of the innate immune system, polymorphic variants of Toll-like receptor genes and decreased production of IL-12 are observed. The reason for the insufficiency of the Th1 immune response may be a decrease in the functional activity of T-regulatory lymphocytes (CD4+CD25+FOXP3+, Tr1, Th3), which may cause hyperactivation of Th2 lymphocytes. IL-4 plays a significant role in the development of immune Th2/Th1 imbalance; the predominance of the Th2 immune response leads to increased production of IgE antibodies. In addition to IgE-mediated reactions, non-IgE-mediated and cell-mediated reactions, responsible for the development of various clinical manifestations in many organs and systems of the body, can play an important role in the pathogenesis of food allergies [12]. The formation of clinical phenotypes of food allergy can occur with the participation of pathophysiological processes at the molecular level. Today, when identifying individual phenotypes of food allergy, one should focus on a description of its clinical manifestations, the most significant triggers (food allergens), as well as the response to standard therapy.

Thus, with regard to the differences in clinical manifestations of food allergy, cutaneous, gastrointestinal and respiratory phenotypes of food allergy are distinguished. In patients with food allergies, several phenotypes may be present, and one phenotype may transform into another. The cutaneous phenotype of food allergy can manifest itself as atopic dermatitis, urticaria, and angioedema. Atopic dermatitis is the most common manifestation of food allergy in children during the first 3 years of life. At this age, the predominance of the exudative component of inflammation on the skin is characteristic. As the child grows older, the clinical picture of atopic dermatitis changes; pruriginous and lichenoid skin manifestations predominate. When exposed to food

allergens, urticaria and allergic swelling (angioedema) may develop. The causes of the development of the skin phenotype of food allergies are cow's milk, eggs, fish, seafood, wheat, soy, peanuts, nuts, carrots, beets, tropical fruits (kiwi, mango, avocado, bananas), citrus fruits. The gastrointestinal phenotype of food allergy is manifested in children by periodic vomiting, abdominal pain, and recurrent diarrhea. There may be weight loss and blood in the stool. A number of patients have oral allergic syndrome, characterized by rapidly occurring itching and swelling of the lips, sometimes of the oral mucosa and the back wall of the pharynx. Causes any food products. Most often, cow's milk, wheat, fish, seafood, soy. The respiratory phenotype of food allergy is manifested by acute rhinoconjunctival syndrome in the form of itching in the nose, rhinorrhea, sneezing, difficulty in nasal breathing, signs of conjunctivitis, and bronchial asthma. Caused by apple, tomato, carrot, fresh fruits, vegetables, peanuts, fish, seafood. The presence of various immunological mechanisms influencing the development and course of food allergies gave rise to the identification of pathogenetic phenotypes. Today, the basic developmental mechanisms underlying food allergies are known. These are IgE-, non-IgE- and cell-mediated mechanisms.

Potential triggers (food allergens) and accompanying conditions determine the clinical picture and course of food allergies. Food allergies occur when consuming a wide variety of foods, among which are food allergens of animal origin [cow's milk and the milk of other domestic animals; eggs of chickens and other birds; fish, crustaceans (crayfish, crabs, shrimp) and other seafood] and food allergens of plant origin [cereals (wheat, barley, rye, oats, corn, sorghum, millet, rice); umbrella crops (carrots, celery, parsley, dill); nightshade crops (tomato, potato, pepper, eggplant, coffee); fruits (kiwi, banana, tangerines, oranges, lemon, apple, peach) and berries (strawberries, strawberries, watermelon); plants of the cruciferous family (cabbage, radish, radishes, turnips, mustard, horseradish); legumes (peanuts, soybeans, green peas); nuts (hazelnut, chestnut, coconut)]. With regard to the time of onset of food allergies, the duration and severity of the course, food allergies should be distinguished in young children and in older children. There is a certain age sequence to food allergies. Thus, in children of the first years of life, the leading causes of food allergies are cow's milk proteins, gluten from cereal products, eggs, soy, and a number of vegetables and fruits. At older ages, nuts, seafood, herbs, spices, etc. play a significant role in the exacerbation of food allergies [8, 9]. At the stage of diagnosing food allergies, it is very important to establish an individual causally significant food allergen or allergenic fractions of this product responsible for the manifestation of allergic symptoms. The preparation of individual elimination diets taking into account the age of the child and the determination of allergen-specific IgE antibodies in the blood serum not only to whole food protein, but also to its allergenic fractions is always more justified than the empirical exclusion of a food product from the diet. It should be noted that cross-allergy - reactions to food products in patients with pollen or fungal allergies - is an additional factor that modifies the phenotype of food allergy. In case of pollen allergy (hay fever), symptoms may occur when eating fruits or other parts of allergenic plants, as well as other foods containing common antigenic determinants. In patients with fungal allergies, allergy symptoms may occur when consuming products that have been subjected to fungal fermentation during manufacturing. Currently, groups and families of plant allergens that play an important role in the formation of cross-reactions have been identified and studied. These include PR proteins, or “protection proteins,” as well as storage proteins; 2S-albumin; thiol proteases; protease inhibitors [13–15]. PR proteins are low molecular weight proteins. They are synthesized in plants under the influence of stressful situations, such as infection, ultraviolet rays heat, unfavorable meteorological conditions, some chemicals, mechanical damage. In the pollen or fruits of some plants, the accumulation of these proteins is especially high. They can be compared to acute phase proteins in mammals; they provide the first phase of plant protection from infections and other irritants. PR proteins are classified into 14 different groups, of which 8 have allergenic activity. In the process of cross-reaction formation, the most significant are defense proteins of groups 2, 3, 4, 5, 10 and 14 (Table 3). PR type 2 includes β-1,3-glucanases, the action of which is aimed at destroying the cell

wall of fungi (protection against mold fungi). One of these enzymes, which has a pronounced sensitizing activity, was isolated from natural latex obtained from the Hevea brasiliensis tree (Hevea brasiliensis - the main source of natural rubber), and was characterized as one of the latex allergens Hev b 2. Homologous peptides contain many fruits and vegetables , especially avocados, bananas, kiwis, figs, chestnuts, tomatoes and potatoes. They are responsible for the development of "fruit-latex syndrome". Type 3 PRs are predominantly class I chitinases. They have the ability to break down chitin, the main structural element of the exoskeleton of insects and the cell wall of most fungi (antifungal protection). Chitin-binding proteins include latex allergens - prohevein (Hev b 6.01) and hevein (Hev b 6.02), as well as the main avocado allergen (Pres a 1), banana and chestnut allergens, which can cause fruit-latex syndrome. PR type 4 includes chitinases found in latex (Hev b), potatoes and turnips. The main function of these chitinases is protection against wound damage. Type 5 PRs are found in the fruits of the shrub plant of the genus Thaumatococcus daniellii (a natural source of thaumatin). They were first isolated from apples (Mal d 2). They may cross-react with cherry, apple, black pepper and mountain cedar. The main function of PR-5 protein is antifungal protection, protection against drought and frost. Group 8 PRs are class III chitinases. Contains latex minor allergen – hevamin. Allergies to fruits, vegetables and nuts are often combined with sensitization to birch pollen. Betv 1 belongs to PR type 10 and is the main allergen of birch pollen. Proteins homologous to it are present in most flowering plants: Cor a 1 - the main allergen of hazel pollen, MaI d 1 - the main allergen of apple, allergens of cherry - Pru av 1, apricot - Pru ar 1, pear - Pr c 1, celery - Api g 1, carrots – Dau with 1. Homologous Bet v 1 proteins are also found in parsley and potatoes. Homologues of the birch allergen Bet v 1 form the basis of cross-reactions in the development of food allergies in patients with sensitization to tree pollen. PR type 14 are polypeptides with a molecular weight of 9 kDa, consisting of 90–95 amino acid residues, resistant to proteases. They belong to lipid transfer factors (LTP), and their biological function is to transfer phospholipids from liposomes to mitochondria. They have antimicrobial and antifungal activity. Allergens of fruits of rosaceous plants (Pru p 3 peaches, Pru ar 3 apricots and Mal d 3 apples) are TFL. IgE antibodies to TPL were found in patients who have allergic reactions to these fruits, but are not sensitized to pollen allergens. Allergenic proteins that cause cross-reactions also include profilins. They are low molecular weight proteins and are found in all plant cells. They play an important role in the development of birch-wormwood-fruit-vegetable syndrome. The presence of profilin in pollen and in food is one of the reasons for cross-reactivity to various vegetables in patients with pollen allergy. Profilin in latex, which causes latex fruit syndrome, is also officially called latex allergen Hev b 8. Profilin can cause severe anaphylactic reactions to peanuts and soy. Preparation of personalized diet therapy taking into account identified individual causally significant food allergens, the severity of food sensitization (from + to ++++), the presence of cross-reactivity with other allergens significantly increases the effectiveness of treatment and improves the patient's quality of life, eliminating the inconvenience that he experiences while following a strict elimination diet. Thus, eliminating a food product and replacing it with another product of the same calorie content and the same protein content is usually not difficult. For example, if a food allergy develops to rarely consumed foods (strawberries, strawberries, chocolate, crab, etc.), elimination may be considered the only effective treatment method. If the spectrum of allergens is fully identified, an elimination diet can maintain a satisfactory condition of the patient without additional therapy. Exclusion from the diet of such important foods as milk, meat, potatoes and grains should be sufficiently justified (only with a clearly proven intake-response relationship). Elimination requires excluding from the diet not only a specific allergen food product, but also any others that contain it, even in trace quantities. When following an elimination diet, the child's age-specific energy and micronutrient needs should be taken into account. At the same time, the diet should contain a minimum of foods with a high allergenic potential; To reduce allergenic activity, food products must be thoroughly cooked; exclude extractive substances, hot seasonings, salty dishes, broths; limit the consumption of mono- and disaccharides. When prescribing complementary foods and dishes, you should select products

with relatively low allergenicity and consistently include them in the diet from monocomponent to multicomponent.

**Conclusion**. As for pathogenetic treatment such as allergen-specific immunotherapy, it has not yet found widespread use in clinical practice. Various methods of carrying out this type of immunotherapy have been proposed: oral, subcutaneous, etc., but the question of its appropriateness for food allergies requires further study. Thus, the identification of food allergy phenotypes in children is of great practical importance for the selection of effective therapy that prevents the development of some of its clinical manifestations that are resistant to traditional treatment, reducing the development of a severe course and the frequency of exacerbations of the disease.

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