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HUMAN GENETICS

Syntropic Genes of Allergic Diseases

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Abstract—Common (syntropic) genes of allergic diseases (ADs) *HLA-DQB1*, *HLA-DRB1*, *IL4*, *IL4RA*, *MS4A2*, *HLA-DQA1*, *LTC4S*, *IL13*, *IL10*, and *TGFB1* have been identified on the basis of information from the HuGENet internet database. The functional realm of these genes is associated mainly with the initiation and regulation of an immune response and inflammation. Importance of these processes in the development of ADs is underlined. The results of cluster analysis of allergic diseases obtained using the data on common genes predisposing to their development are presented. Genetic clusterization of ADs confirms their accepted clinical classification.

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INTRODUCTION

In 1921, the German pediatricians M. Pfaundler and L. von Seht, who studied the problem of polypathia (manifestation of several diseases simultaneously in one patient), advanced the concept of syntropic and dystropic diseases on the basis of information about 30000 case histories. Under syntropy they meant predisposition of two diseases to concurrent manifestation and under dystropy their mutual rejection [1]. In the authors' opinion, the basis of syntropia is common pathogenesis. At the end of the 19th century, analogous considerations were advanced by the French pathologist Ch. Bouchard to his arthritism concept [2].

A present-day definition of syntropic diseases is as follows [3]: syntropy is a natural generic phenomenon of combination of two and more pathological conditions (nosologies or syndromes) in an individual and his close relatives, which is nonrandom and evolutionarily and genetically determined. A distinctive feature of this definition is the statement about the common hereditary nature of syntropic diseases. The nonrandom character of combination of individual forms of pathology (nosologies, syndromes) having similar pathogenesis suggests the possibility of involvement of some common genes determining predisposition to the development of individual pathological components and to the formation of a particular syntropy. Genes responsible for the development of syntropia are referred to as syntropic genes [3, 4]. In the strict sense, syntropic genes form a set of functionally interacting coregulated genes localized throughout the whole human genome that are involved in the biochemical and physiological pathways common for a given syntropy. In case the regulatory interactions lead to a mutual exclusion of certain phenotypes on the clinical level (dystropy), such genes should be called dystropic with respect to such phenotypes.

Applied to the present-day genomic studies of multifactorial diseases, the concept of syntropia/dystropia can be productive by permitting an approach to be developed for a more focused analysis of the genetic diversity of candidate genes and their markers (and for reducing their spectrum) considered to play a role in predisposition to diseases. Moreover, the genetic component of the concept of syntropic diseases can contribute to the solution of the problem of molecular classification of pathologies clearly formulated for the first time in the late 1960s by V. McKusick who called researchers classifying pathological phenotypes on the basis of cytogenetic and molecular genetic methods lumpers and splitters [5]. The contemporary systematicians of human pathologies also follow the principles deduced in discussions of genetic nosology [6, 7].

In this publication, we present the results of searching for syntropic genes of allergic diseases on the basis of information from the HuGE Navigator internet resource and the results of cluster analysis of ADs with the use of the data on common and specific genes associated with them.

MATERIALS AND METHODS

We analyzed common genes associated with allergic diseases that are considered as examples of syntropy: bronchial asthma (BA), atopic dermatitis (AD), allergic rhinitis (AR), food allergy (FA), drug allergy (DA), pollynosis (P), and urticaria/Quincke's edema (U/QE). In addition, the level of immunoglobulin E (IgE) was analyzed.

Information on genes was obtained from the HuGE Navigator database (http://www.hugenaviga-

tor.net) through making corresponding retrieval requests (English names of diseases). The basis of the project are publications presented in PubMed [8]. The program ranks sought-for genes in accordance to the score calculated by the formula:

$$\text{Score} = H/\Sigma H_i + GA/\Sigma GA_i + GWAS/\Sigma GWAS_i + MA/\Sigma MA_i + GT/\Sigma GT_i,$$

where H is a total number of publications in PubMed in which a given gene was studied in a given disease; ΣH_i is a total number of publications in the database devoted to a given disease; GA is the number of genetic association studies with the involvement of a given gene in a given disease; ΣGA_i is a total number of association studies for a given disease; $GWAS$ is the number of genome-wide association studies with the involvement of a given gene in a given disease; $\Sigma GWAS_i$ is a total number of genome-wide association studies for a given disease; MA is the number of publications on meta-analysis of associations with the involvement of the given gene in the given disease; ΣMA_i is a total number of publications on meta-analysis of associations for the given disease; GT is the number of publications on genetic testing with the involvement of the given gene in the given disease; ΣGT_i is a total number of publications on genetic testing for the given disease.

Only genes for which the score was not lower than 0.01 are considered in this work.

The data on associations of genes with ADs were used to construct a dendrogram demonstrating the vicinity/remotedness of diseases on the basis of the proportion of common genes involved in their development. The dendrogram was constructed using a hierarchic cluster analysis. The calculations were made using the unweighted pair-group means method and Euclidean distance as a measure of linkage. Analysis was carried out with the STATISTICA software package for Windows 7.0 (Statsoft, United States).

RESULTS AND DISCUSSION

The search for syntropic and dystropic genes for specific groups of syntropic diseases and their characterization is not a trivial task, but it can at least partially be solved by analyzing available database information on the association of genes with clinical phenotypes. One of such resources is HuGE Navigator—as an integrated database on genetic associations and human genome epidemiology. HuGE Navigator is a part of the project The Human Genome Epidemiology Network (HuGENet) and provides free access to the data on human genetic epidemiology, including information on the population frequency of genetic variants, associations of genes with diseases, gene–gene and gene–environment interactions, and also information on the efficiency of genetic tests [8].

A recent study aimed at searching for syntropic genes of diseases of the cardiovascular continuum [4] confirmed a high information capacity and suitability of HuGE Navigator for such studies.

In the present paper, the results of searching for common (syntropic) genes are given for another widespread group of allergic diseases considered as examples of syntropy: BA, AD, AR, FA, DA, P, and U/QE. In addition, the level of IgE was analyzed, since allergies mediated by antibodies of this class are most frequent.

A common characteristic of pathogenesis of allergic diseases is immediate hypersensitivity that can be realized through different mechanisms: IgE-mediated (reaginic), cytotoxic, or immunocomplex. The reaginic type of allergy, or atopy, seems to be most frequent; at the same time, clinically similar ADs can have different molecular mechanisms of pathogenesis, including nonimmunological ones (pseudoallergy), and the clinical classification of ADs is not therefore a simple task [9]. The common characteristics of ADs are, as a rule, familial accumulation, which suggests the importance of genetic factors in their etiology and pathogenesis, and the tendency towards their concurrent expression [10–14]. For instance, examination of 2270 children in the United States showed that in the case of BA the relative risk of another allergic disease varies from 1.8 to 4.8; in the case of AR it is 2.0–12.9 [13]. Similar results were obtained after examination of 3916 patients in France; however, a tendency was observed towards a higher risk of expression of ADs of similar types: for example, diseases with predominantly dermal symptomatology (AD, U/QE, contact dermatitis) or diseases of the respiratory tract (BA, AR, sinutitis, nasal polyps) are combined most often [11]. Finally, ADs can sequentially alternate in ontogenesis; in typical cases, a spectrum of atopic diseases defined as "atopical march" develops with age in a patient with atopy: early in the life, gastrointestinal and dermal eczematous symptoms, often caused by food allergens, prevail, and later on asthma and rhinitis develop in response to inhalatory allergens [9, 15].

These data permit ADs to be regarded as syntropia, assuming the existence of common (syntropic) genes presumably responsible for common components of pathogenesis (predisposition to allergies in general) and genes specific for different groups of diseases that determine a relation of the tendency towards allergy to a particular shock organ. The current genetic and genomic investigations support this point of view, demonstrating an existence of at least three groups of genes whose effects with respect to ADs permit them to be considered as genes of atopy (IgE expansion), genes of inflammation, and genes of organ specificity [16].

At the time of our study (November 2008), the number of known genes in the HuGE Navigator database was 417 for BA, 82 for AD, 85 for AR, 39 for P, 30 for U/QE, 20 for FA, 51 for DA, 203 for IgE. The criterion used to prove the association of a gene with a disease in HuGE Navigator is the score calculated on

Syntropic genes of allergic diseases and IgE

Gene	Gene product	Chromosomal localization	Score*
IL13	Interleukin-13	5q31	0.198 (0.109–0.625)
IL4RA	α-Chain of interleukin-4 receptor	16p12.1-p11.2	0.177 (0.081–0.338)
HLA-DRB1	Histocompatibility antigen of class II, DRβ1	6p21.3	0.166 (0.044–0.486)
IL4	Interleukin-4	5q31.1	0.165 (0.045–0.311)
HLA-DQB1	Histocompatibility antigen of class II, DQβ1	6p21.3	0.121 (0.044–0.338)
LTC4S	Leukotriene-C4-synthase	5q35	0.096 (0.022–0.256)
IL10	Interleukin-10	1q31-q32	0.092 (0.023–0.153)
MS4A2	Fc fragment of high-affinity IgE receptor	11q13	0.083 (0.022–0.167)
TGFB1	Transforming growth factor β1	19q13.2	0.055 (0.015–0.113)
HLA-DQA1	Histocompatibility antigen of class II, DQα1	6p21.3	0.053 (0.019–0.081)

* The mean score value and a spread (in parentheses) of the score values (the score is an index of association of a gene with a disease calculated by the HuGE Navigator program for the ADs under study); genes in the table are listed in order of decreasing mean score value.

the basis of a number of parameters (see Materials and Methods). In this publication, only genes for which the score was not lower than 0.01 are considered; there were 110 such genes for the diseases studied. The highest score value for BA was 1.761 (*ADRB2* gene), for AD 1.393 (*FLG*), for AR 0.158 (*CD14*), for P 0.188 (*FLG*), for DA 1.081 (*NAT2*), for FA 0.338 (*HLA-DQB1*), for U/QE 0.486 (*HLA-DRB1*), for IgE level 1.253 (*CD14*).

Five genes proved to be common for all ADs and IgE: *HLA-DQB1, HLA-DRB1, IL4, IL4RA, MS4A*2 (table). These genes can be considered syntropic when applied to ADs. In addition, five more genes (*HLA-DQA1, LTC4S, IL13, IL10,* and *TGFB1*) were common for IgE and all ADs except one (table): *HLA-DQA1* and *LTC4S* are not associated with FA, *IL10* and *TGFB1* with P, and *IL13* is not associated with U/QE. Taking into account insufficient knowledge of genes in respect of their association with a particular pathology, it can be assumed that these five genes are also syntropic for ADs. Indeed, no references were found in the HuGE Navigator database as to the association of *HLA-DQA1* and *LTC4S* to FA, *IL13* to U/QE, *IL10* and *TGFB1* to P.

It should be noted that the functional realm of all genes of ADs defined as syntropic is initiation and regulation of an immune response (mainly humoral) and inflammation. In particular, the HLA genes of class II (*HLA-DQB1, HLA-DRB1, HLA-DQA1*) are involved in the recognition of antigens and control the interactions of antigen-presenting cells with T lymphocytes by initiating an immune response. The HLA complex genes are clustered on chromosome 6p21 in a region for which linkage and associations with numerous immune-mediated diseases (including allergic, autoimmune, and infectious) were repeatedly shown [17].

The genes *IL4* and *IL13* encode cytokines of the same name that are critical in IgE-mediated reactions and initiate a Th2 immune response characteristic of atopic allergies. These genes are located in chromosome region 5q31 for which the linkage with ADs was also repeatedly proved [16]. Both cytokines contact with target cells through specific receptors for which a common subunit is the product of the *IL4RA* gene. This determines overlapping of the IL-4 and IL-13 signals and similarity of their biological effects [18]. The *IL4RA* gene is located in chromosome 16 in a locus linked with atopic diseases and the IgE level; some of its polymorphisms have a considerable effect on the signal function of IL-4 and IL-13 by predisposing to hyperproduction of IgE [19, 20].

The *MS4A2* gene encodes the β-subunit of a high-affinity IgE receptor responsible for initiation of an allergic response: it binds allergens with IgE attached via the receptor to the surface of mast cells and basophils and initiates a release of mediators of inflammation leading to allergy [21]. The gene is located in region 11q13, which is one of the first mapped loci of IgE and atopy [22].

Leukotriene-C4-synthase encoded by the *LTC4S* gene participates in the synthesis of cysteinilic leukotrienes that are important factors of tissue inflammation in the case of allergy. Hyperexpression of *LTC4S* in the case of aspirin-induced asthma is the main determinant of a respiratory response to aspirin; the promoter region of the gene was found to display polymorphisms associated with the allergic phenotype of aspirin intolerance expressed in BA and U/QE [23, 24].

The IL-10 and TGF-β cytokines encoded by the *IL10* and *TGFB* genes, respectively, play an important role in the inhibition of an allergic immune response under the action of viruses, some microbes, and helminths. Their increased expression is thought to explain a paradoxic situation when the helminth invasion stimulating Th2 immunity appears to be a protective factor against ADs [25]. In connection with this, it is concluded that it is the *IL10* and *TGFB* promoter

polymorphisms, which decrease the level of expression of the genes, that are associated with ADs and their severity [26–29].

For generalized characterization of the hereditary component of different ADs according to the HuGE Navigator data, we used a cluster analysis differentiating ADs into groups on the basis of common and specific genes associated with them. Two large clusters were revealed (figure): the first one includes IgE, BA, and AD. The second cluster is divided in two subclusters: the first one includes seasonal ADs, such as AR and P, and the second one includes U/QE, FA, and DA.

It is clear that the clustering of IgE and ADs supports the existing views on the etiology and pathogenesis of these diseases as well as the system of diagnosis of allergic diseases accepted in clinical practice.

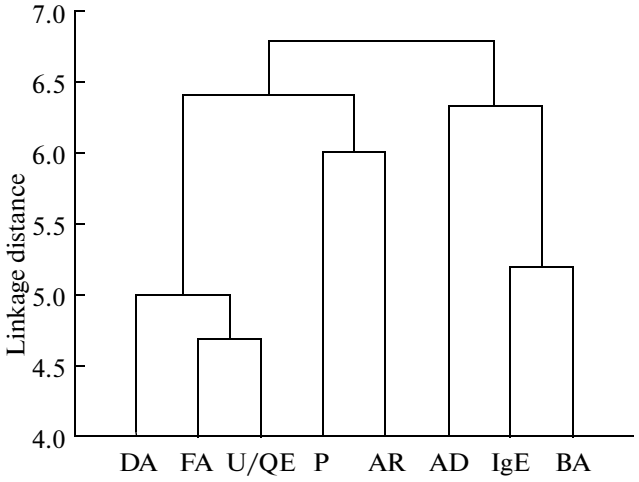
AD often accompanies BA and is its risk factor due to the common pathogenetic mechanism of development characterized by the "atopic march"; these diseases display the most pronounced association with atopy as compared to other ADs. According to expert estimations, BA is among diseases that are the most frequent comorbidities associated with AD [10]. It should be noted that in the first cluster the level of IgE is closer to BA by the proportion of common genes. It is probably because critical for AD is also the role of genes whose products determine epithelium permeability and regulation of inflammation unrelated to reagin antibodies, especially at the chronic stage of the disease [31].

Clustering of AR and P is obviously associated with the common allergens and seasonal expression. In addition, pollynosis is a synomym of the rhinoconjuctival syndrome, i.e., AR and P are in fact the same disease.

Finally, the differentiation of U/QE, FA, and DA into one subcluster is likely to be due to the same pathway by which allergens are taken in (alimentary) and with other common mechanisms of pathogenesis, including those having no relation to IgE (e.g., with the involvement of the complement system). Moreover, urticaria and Quincke's edema are known as frequent symptoms of FA [32–34].

Thus, clusterization of ADs by the degree of similarity of their hereditary components based only on the data on genetic associations wihout any a priori assumptions confirms the validity of the clinical classification and its natural character.

This approach can be applied to any other groups of syntropic diseases. Interesting results can be obtained from analysis of genetic clusterization of the whole diversity of human nosologies having the purpose to construct a natural genetic system of their classification, which in the first place will provide a deep insight into their etiology and pathogenesis and in the second place will become a prerequisite for a more successful therapy.



Clusterization of allergic diseases on the basis of common genes associated with them. BA, bronchial asthma; AD, atopic dermatitis; AP, allergic rhinitis; P, pollynosis; DA, drug allergy; FA, food allergy; U/QE, urticaria/ Quincke's edema; IgE, IgE level.

A problem is insufficient knowledge of associations of genes with diseases. However, the rapid development of new technologies of large-scale genotyping, sequencing, transcriptomics, bioinformatics and the inclusion in the study of other diseases, such as rare forms of pathology, as well as an increasing number of international projects for a unified analysis of a lot of diseases at once or one disease in a lot of populations give a hope that this gap will soon be closed. A recent study performed by the Wellcome Trust Case Control Consortium [35] can be cited as an impressive example of genome-wide association analysis of seven diseases: 14000 patients (2000 patients in each disease group) with bipolar disorder, ischemic heart disease, Crohn's disease, hypertension, rheumatoid arthritis, and type 1 and 2 diabetes were examined in comparison to 3000 controls. The study was performed with the use of a mapping Affymetrix microchip that allows typing of about 500000 single-nucleotide markers simultaneously.

Closer to the idea of syntropic genes of syntropic diseases is a recent study of three autoimmune diseases (ankylosing spondylitis, autoimmune thyroiditis, multiple sclerosis) and breast cancer performed by the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondylitis Consortium. One thousand patients from each group with a pathology were examined in comparison to 1500 controls for an association of the diseases with 14500 single-nucleotide markers of the main histocompatibility complex. Interestingly, in this study a close association with the markers was discovered for all autoimmune diseases, while no association was observed for breast cancer.

The concept of pathological phenotype in terms of nonrandom combinations of symptoms forming syntropy does not coincide with the clinical tradition

when attention is focused on diagnosis, nosology. The syntropic approach implies the selection from the phenome, presenting an infinitely large number of symptoms, of such associated symptoms that are controlled by common genes. The hypothesis of existence of a single field of action for a finite large number of genes predisposing to syntropic diseases can be of use not only in verifying the etiology and pathogenesis of these diseases, but also in determining the spheres of competence of the genes studied, their polymorphisms, and ensembles of genes/polymorphisms, i.e., in solving essential problems of functional genomics.

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