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N.K. Altynova[1*], O.K. Khamdiyeva[1], Zh.A. Zhaniyazov[1], A.A. Garshin[1], G.S. Baratzhanova[1], A.S. Amirgaliyeva[1], K. Yergali[1], D.N. Artygaliyeva[2], D.Zh. Talgatbekova[2], S.S. Tokmurzina[1], M.S. Abdullayeva[1], G.S. Zhunussova[1], L.B. Djansugurova[1]

[1]Institute of Genetics and Physiology, Almaty, Kazakhstan
[2]Medical center "Allergo Clinic", Almaty, Kazakhstan
*e-mail: naz10.79@mail.ru

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A genome-wide association study for different types of allergic diseases

Abstract. All over the world, there is an active search for genes that are responsible for the formation of predisposition to allergic diseases, which is associated both with the undoubted relevance of studying risk factors for the development of allergies, and with the emergence of new opportunities for genetic research. In addition, anthropogenic impact can cause allergic reactions and modifications in the functions of antioxidant defense cells and the immune system. Due to the fact that in the cohort of the population of Almaty and the Almaty region (going forward we will say Almaty to include the region also), respiratory diseases with an allergic component, such as bronchial asthma, bronchitis, allergic rhinitis, are common, we consider it is appropriate to conduct an epidemiological study of candidate genes for allergic diseases – cytokines and their receptors (*IL4, IL4RA , IL12B, IL13, TNFA, CCL5*), adrenoreceptor (*ADRB2*), transcription factors involved in T-lymphocyte differentiation (*STAT6, GATA3, TBX21*), major histocompatibility complex (*HLA-DRB1, HLA-DQB1*). The aim of our study is to conduct genome-wide genotyping in people with allergic diseases and to search for marker genes that affect the risk of developing allergies as well as to identify genes that are involved in the pathogenesis of allergic diseases. We performed genome-wide microarray genotyping of 25355 SNPs on the iScan platform of 103 samples with allergic diseases and 108 control DNA samples using the kit (Infinium® ImmunoArray٢٤- v٢,٠ BeadChip Kit). The results obtained, using the GWAS analysis, which considers numerous polymorphisms, showed the involvement of some genes in the development of allergic diseases (rs20541-asthma, allergic rhinitis, rs841718-atopic dermatitis, rs3212227-immunodeficiency).

Keywords: allergy, marker genes, Allergic rhinitis (AR), Bronchial asthma (BA), Atopic dermatitis (AD), GWAS-genome-wide genotyping, single nucleotide polymorphism (SNP).

Introduction

Allergies, "alien reactions" of human immunity, are the plague of the third millennium. Allergies are one of the diseases of peacetime and a distinctive marker of the state's well-being. For the past 25 years, WHO has been seriously concerned about the epidemic spread of allergies, as well as the fact that among all the main causes of death, mortality caused by respiratory diseases continues to grow [1]. Despite the undoubted achievements in the fight against allergic diseases, it must be admitted that no country in the world has so far managed to reduce the prevalence of allergies in general. The main concern is the fact that allergic diseases affect people of working age, children, and also affect the gene pool. If urgent measures are not taken at the national level, allergies might become a threat to the health and well-being of the nation and cause huge financial losses. In the Republic of Kazakhstan, respiratory diseases take first place in the general disease pattern which, in absolute terms, is about 2.5 million cases and includes such diseases as: allergic rhinitis, bronchial asthma, pneumonia, bronchitis, emphysema. About 1 million suffer only from bronchial asthma and the highest prevalence is noted in children [2]. Intensive anthropogenic pollution of the natural environment affects the state of plant and animal populations, as

well as human health. It is known that people's health is 12% dependent on the level of healthcare, 18% on genetic predispositions and 70% on lifestyle, not least of which is the ecological environment and nutrition [3]. The relationship of genetic polymorphism with the individual sensitivity of the human genome to the action of mutagenic environmental factors, in particular, to pesticide pollution, is being actively studied in the world.

Genome-wide association studies (GWAS) are the basis for the search for candidate genes for monogenic and multifactorial diseases, including allergic diseases, coronary heart disease, vascular diseases, and others. In some cases, GWAS results allow for not only the understanding of the pathophysiological basis of diseases, but can also serve as an impetus for the creation of new therapeutic agents and drugs [4]. Predicting the occurrence of allergic manifestations can help prevent the spread in high-risk individuals. The first GWAS of asthma were studied in Germany and England, showing the association of single nucleotide polymorphisms localized in the 17q12-q21 region (*ORMDL3* and *GSDMB* genes) [5]. In recent years, asthma GWAS have been carried out in various populations of the world, new genes associated with the development of asthma in individuals of European origin – *DENND1B, PDE4D, RAD50, IL-1RL1 / IL18R1, HLA-DQ, IL33, IL6R, SMAD3* and *IL2R*B have been discovered; African origin – *ADRA1B, PRNP* and *DPP10*; Mexicans – *TLE4*; Koreans – *CTNNA3* (http://www.genome.gov/GWAStudies/) [6]. A GWAS is conducted to identify genetic variants specifically for allergic rhinitis (AR) in an ethnic Chinese population [7], and two GWAS results for AD were published that revealed an association with the SNP of the 11q13.5 regions in individuals of European origin [8]. Recent data from scientists have shown that *NPSR1* and *CTLA4* may serve as genetic links between AR and asthma [9].

It is known that the genes that regulate antioxidants and immune systems play a key role in the mechanisms of allergy manifestation. Recent research has focused on the role of oxidative stress and antioxidants in allergic rhinitis and asthma. Some studies have examined whether specific oxidative markers are associated with specific diseases and performed cluster analysis to compare the clinical relevance of oxidative stress markers and the correspondence between diseases [10]. According to the literature, the most common markers for a genetic association with asthma were IL4 (91 refs), followed by IL13 (75 refs) and TNF (73 refs). Significant associations of SNPs in IL4 with asthma have been reported in 15 different populations. The following 14 genome-wide genes have been associated with the diagnosis of asthma in more than three independent study populations: *ADAM33, CCL5, CD14, DPP10, EDN1, GPR154, GSTP1, IL12B, IL13, IL4, IL4R, PTGDR, TNF*. [11]

Most of these studies are devoted to the study of polymorphism of genes encoding xenobiotic metabolizing enzymes, DNA repair defense systems, cell cycle control, antioxidant protection and immune response, which are indicators of hereditary individual sensitivity.

To search for genes responsible for predisposition to allergic diseases, we conducted a molecular genetic study using microarray genotyping of genes of the antioxidant and immune systems: cytokines (*IL4, IL4RA, IL12B, IL13, TNFA*), major histocompatibility complex (*HLA-DRB1*), 2-adrenergic receptors (*ADRB2*), transcription factors involved in T-lymphocyte differentiation (*STAT6, GATA3, TBX21*), CYP gene polymorphisms (CYP2D6, CYP2B6, CYP2C19), xenobiotic biotransformation enzymes (*GSTM1, GSTP1, GCLM, NAT2*) in patients with allergic diseases and in control group individuals on the example of the three most common allergic diseases – Allergic rhinitis (AR), Bronchial asthma (BA) and Atopic dermatitis (AD). The choice of candidate genes for association analysis is based on the significance of their protein products in the etiopathogenesis of allergy and literature data. Many believe that diseases of the upper and lower respiratory tract, such as allergic rhinitis, chronic rhinosinusitis, and asthma, often coexist (the "single airway concept") [12,13]. Most patients with asthma suffer from allergic rhinitis, and many patients with rhinitis have asthma [14,15].

The aim of our study is to conduct genome-wide genotyping on the iScan™ System platform using high-resolution Infinium® ImmunoArray-24v2.0 BeadChipKit biochips of people with allergic diseases and to search for marker genes that affect the risk of developing allergies along with the identification of genes that are involved in pathogenesis of allergic diseases. Such an associative analysis will help determine the genetic risk in people with allergic diseases, identifying causal mutations in cohorts of allergic patients, giving more definite answers on the mechanisms of disease development, suggesting measures for diagnosis, personalized treatment, prevention of environmentally dependent diseases, and suggesting new ways of health correction.

Materials and methods

Research objects. The object of the study were patients in Almaty, with various types of allergic diseases (103 people), who complained to the private clinic "Allergo clinic". The diseases were diagnosed by qualified pulmonologists, allergists and dermatologists on the basis of data from clinical, general laboratory and additional research methods in accordance with the criteria of program documents for the diagnosis, treatment and prevention of diseases. As a control, a cohort of apparently healthy individuals (108 people) from Almaty and Almaty region was chosen. Questionnaires, EDTA-treated frozen (-20°C) peripheral blood samples, peripheral blood samples, accompanied by personal data and clinical health survey data, served as the materials for the study. When selecting biomaterials from conditionally healthy people, the absence of a history of oncological, cardiovascular, neurological, autoimmune and allergic diseases, diabetes, metabolic disorders and thyroid function was considered.

Molecular genetic analysis of people was carried out on the basis of existing voluntary informed consents and approvals of local ethical commissions (Protocol No. 52 from 05.09.2017 LEK NUO Kazakh-Russian Medical University).

DNA extraction. DNA was isolated from frozen (-20°C) EDTA-treated peripheral blood samples using the GeneJet Genomic DNA Purification Kit (Thermo Scientific, USA) and ReliaPrep™ Blood gDNA Miniprep System (Promega, USA) according to the manufacturer's protocols. DNA samples were stored at –20°C. Quantitative and qualitative evaluation of isolated DNA was performed spectrophotometrically (BioPhotometer Plus, Eppendorf, Germany; NanoDrop 2000, Thermo Fisher Scientific, USA) and fluorometrically (Qubit Fluorometric Quantification, Thermo Fisher Scientific, USA). DNA samples with a purity factor of 1.75–1.80 were used for analysis. Samples contaminated with RNA (factor 1.8–2.0) and samples with protein contamination (1.5–1.7) were additionally washed and reprecipitated with ethanol until the desired purity of the preparation was obtained.

SNP genotyping by microarray. Preparation of DNA samples for microarray genotyping was carried out using the Infinium Automation Kit – 8 Tip Tecan Non LIMS automated sample preparation station. Microarray genotyping of the target population cohorts was carried out on the iScan System platform (Illumina, USA) using the Infinium® ImmunoArray-24 v2.0 BeadChip Kit (Illumina, USA) according to the Infinium HTS Automated Workflow protocol.

Initial microarray genotyping data were processed using Illumina GenomeStudio v.2.05 software. Software (Illumina, USA), PLINK, RStudio. Samples with quality less than 98% (percentage of progenotyped SNPs expressed in terms of call rate) were excluded from the analysis.

Bioinformatic analysis. Bioinformatic analysis of the results of microchip SNP genotyping included determining the reliability of data, determining the genetic status – homozygosity / heterozygosity for the identified changes, detection and analysis of identified mutations and polymorphisms by comparing the found mutations with mutations identified as pathogenic in well-known databases and scientific articles. For annotation and interpretation of genetic variants obtained using iScan, the Genome-Wide Association Studies data catalog (GWAS catalog – https://www.ebi.ac.uk/gwas/), single nucleotide polymorphisms database (dbSNP, https:// www.ncbi.nlm.nih.gov/snp/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar) and 1000 Genomes (1000G – https://www.internationalgenome.org/1000- genomes-browsers).

Statistical methods for data analysis. Traditional methods of variation statistics were used to assess the fit of case-control cohorts on key population characteristics such as age, gender, ethnicity, and bad habits. Differences were regarded as significant at $p<0.05$. Significance level (P) was determined using Chi2 ($\chi 2$) and Student's t-test.

Compliance with the Hardy-Weinberg equilibrium ($\chi 2$) was assessed in all cases of SNP genotyping.

Statistical analysis of the association of polymorphisms of the studied genes was performed using the Software GraphPad Instat™ software (V. 2.04. Ralf Stahlman, Purdue University) and the "Calculator for calculating statistics in case-control studies" provided by the website of the Tapotili company of the Laboratory of Molecular Diagnostics and genomic fingerprinting of the State Scientific Center of the Russian Federation "GosNII genetics" (http://www.tapotili.ru).

The relative risk index (OR) was calculated using the standard formula:

$$OR = a/b \times d/c,$$

where:

a is the number of people in the allergy group with the mutant genotype;

b is the number of people in the allergy group who have a normal genotype;

c is the number of people in the control group with the mutant genotype;

d is the number of people in the control group with a normal genotype.

The reliable confidence interval was calculated by the formulas:

CImin=exp(lnOr-1,96Ö(1/a+1/b+1/c+1/d))
CImax=exp(lnOr+1,96Ö(1/a+1/b+1/c+1/d))

Results and discussion

Health assessment. Allergic diseases have a complex multifactorial nature and develop through the interaction of environmental factors and hereditary predisposition. All over the world, researches are working to identify genes responsible for the formation of allergic predispositions. For the first time, we used a genome-wide analysis of associations in the study of allergic diseases in the population of Almaty, represented by a mixed population: Kazakhs (73.79%), Russians (14.56%) and others (12%).

To determine candidate genes for allergy predisposition, blood samples were collected from patients with various allergic diseases (103 people). When collecting material, a questionnaire was simultaneously conducted and voluntary informed consent was issued. Personal data and clinical and morphological characteristics of diseases were studied (Supplement, Appendix A). The selection of the control group was carried out considering previous studies of the state of human health, which materials are presented in the genetic bank of the Laboratory of Molecular Genetics of the Institute of Genetics and Physiology. The control group was formed from apparently healthy individuals, based on gender, ethnicity and age, and bad habits. Analysis of personal data in the control group showed no history of oncological, cardiovascular, neurological, autoimmune and allergic diseases. Table 1 reflects representative data for the study group with allergic diseases and in the control group.

Table 1 – Main characteristics of cohorts “case-control”

Characteristics		Study group, %	Control group, %
n		103	108
Age (years)		35.58±6.79	36.67±7.77
Gender, n (%)	Male	33 (32.04)	33(30.56%)
	Women	70 (67.96)	75(69.44)
Nationality, n (%)	Kazakhs	76 (73.79%)	100 (92.59%)
	Other nationalities		
	Russians	15(14.56%)	5(4.63%)
	Uighurs	4 (3.88%)	3 (2.79%)
	Koreans	5(4.85)	0
	Tatars	3(2.9%)	0
Smokers		21(20.39)	10(9.30)
Non-smokers		82(79.61)	98(90.74)

On the basis of the results obtained it may be concluded that the obtained and analyzed groups of people with allergic diseases and apparently healthy people can be considered suitable for this molecular epidemiological study based on the case-control method.

Regarding the types of allergic diseases, that were established based on clinical examinations, the following groups of patients with category of diagnoses were distinguished: 52 – allergic rhinitis, 13 – atopic dermatitis, 19 – urticaria, 9 – drug allergy, 1 – acute bronchitis, 10 – bronchial asthma, 1 – toxic erythema, 7 – Quincke’s edema, 3 – allergic conjunctivitis, 1 – solar urticaria, 5 – food allergy. Figure F.1 presents data on the types of diseases occurring in patients with allergic diseases. 44% were patients suffering from allergic rhinitis, and there was also an increase in atopic dermatitis (11%) and urticaria (16%).

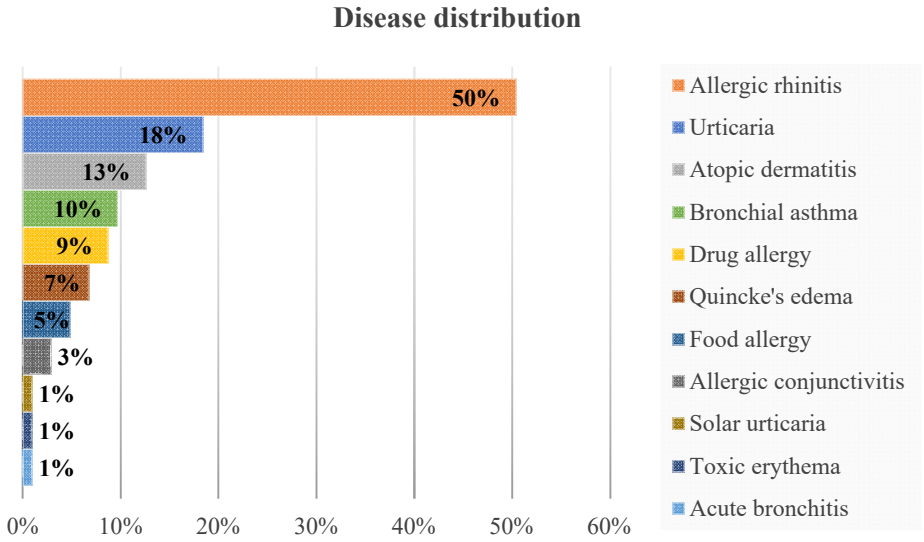

Figure 1 – Dynamics of allergic diseases in study group

The highest percentage of morbidity (50%) falls on allergic rhinitis. It is known that allergic rhinitis (AR) is the main chronic respiratory disease and the most common allergic disease with a worldwide prevalence of 10-25% [16]. AR is a disease characterized by IgE-mediated inflammation that develops as a result of allergens entering the nasal mucosa. According to statistics, the incidence of allergic rhinitis ranges from 10% to 40% of the population in various countries. The problem of allergic rhinitis is also relevant for Kazakhstan, primarily because of the continental climate with severe winters and a long flowering period. It has long been recognized that the development of AR depends on the interaction between genetic and environmental factors and that genetic factors play an important role, with an estimated heritability of AR as high as 70-90% [17,18]. A large number of studies have identified more than 100 single nucleotide polymorphisms (SNPs) associated with AR, but few of them have been successfully replicated.

Bronchial asthma (BA) is a chronic inflammatory disease of the airways in which many cells and cellular elements play a role. Asthma is well known to be closely associated with AR, as a significant proportion of people with asthma also have symptoms of AR, and patients with AR have a 5- to 6-fold increased risk of developing asthma [19-21]. According to statistics, in 2018 in Kazakhstan, the prevalence of BA among children under 17 years old is 23.5%, 105365 cases of BA were registered among adults [22]. The genetics of asthma has been extensively studied and many genes have been linked to the development or severity of the disease. It is currently believed that about 300 million people suffer from asthma worldwide, and these numbers are projected to rise in the coming years. Asthma is a syndrome with a heterogeneous pathophysiology and various asthma phenotypes differ in age of onset, environmental risk factors, clinical manifestations, prognosis, and response to therapy. Comorbidities have been reported between asthma and other allergic diseases (especially allergic rhinitis and atopic dermatitis) [23]. Clinical and epidemiological evidence suggests that asthma and allergic diseases are related and may share a common genetic etiology.

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that can affect 20% of children and 3% of adults. Atopic dermatitis (AD) is most often the first manifestation of allergy in a child, can continue into adulthood and leads to physical and emotional maladjustment of the patient. Almost half of the children against the background of AD subsequently develop bronchial asthma or allergic rhinitis. The prevalence of AD in children is 15-20%, in the adult population – 2-10% [24].

Thus, the next 10-15 years will be accompanied by an inevitable increase in allergies in general and chronic allergic diseases in particular. At the moment, the official statistics for the Republic of Kazakhstan is as follows – according to scientific research (including the own data of the Republican Allergy Center), the approximate figures for the incidence of bronchial asthma in urban residents are approaching 5-6%, in rural areas – 1-2%. For allergic rhinitis – 15-20% and 10-15%, respectively. At the same

time, the proportion of asthma in the pool of patients with chronic respiratory diseases (chronic bronchitis, COPD, asthma, etc.) is at least 40%. Moreover, all these indicators are growing in full accordance with global trends [25]. According to the World Allergy Organization, about 30-40% of the world's population suffer from various allergic diseases (World Allergy Organization).

Genotyping for candidate SNPs of a cohort of patients and healthy individuals. One of the most promising modern methods for studying complex traits is the Genome-wide Association Studies (GWAS) method, which involves genotyping and testing the association with the disease of hundreds of thousands of single nucleotide polymorphisms (SNPs) [6]. To identify genetic disorders of candidate allergy genes, the genes of cytokines – interleukins *(IL4, IL13, IL4R, 1L12B, STAT*) – the main molecular mediators of triggering, development and regulation of allergic inflammation, the major histocompatibility complex (HLA-DRB1) – playing a key role in the development acquired immune response to foreign protein antigens, beta-2 adrenergic receptor (ADRB2) – receptor-protein ion channel, polymorphisms of markers of the CYP2B6 family, xenobiotic biotransformation enzymes (*GSTM1, GSTP1, GSTT1*), genes of a polyprotein (APOE)-associated with human immunity etc., found in a genome-wide association analysis. We performed genome-wide microarray genotyping for 25355 SNPs on the iScan platform of 103 samples with allergic diseases and 108 control DNA samples using the kit (Infinium® ImmunoArray-24 v2.0 BeadChip Kit. Microarray genotyping data were processed using Illumina GenomeStudio v.2.05 software. Software, PLINK, RStudio 23 samples with poor reading quality of SNPs (call rate <95%) were excluded from the analysis (Supplement, Appendix B). The mean genotyping efficiency of the remaining 83 samples was 96%. In the control group, a total of 43 genes were analyzed, 43 polymorphisms associated with allergic diseases were identified, of which 14 were in the exon part, 8 were assessed as missense mutations (sense), 1- as synonymous, 34 polymorphisms were in non-coding regions of genes. SNPs genotypes were read in almost all case and control samples with exception of 23 persons because of call rate less then 95%. Heterozygosity/homozygosity, as well as the frequency of identified alleles and genotypes are presented in Table 2. Analysis of literature data and analysis using the program http://www.ncbi.nlm.nih.gov/projects/SNP made it possible to identify genes associated with allergic rhinitis, bronchial asthma, atopic dermatitis, such as the *IL13* (rs20541, rs848),*STAT6* gene (rs1059513, rs841718), *ADRB2* (rs1042714), *IL4R* (rs1805015), *IL12B* (rs2569254, rs3212227),etc. We pay special attention to SNPs of these genes.

For each SNP, the odds ratio for separate allelic variants and for genotypes was estimated using multiplicative, dominant, and recessive models.

Table 3 presents only significantly identified associations with the development of allergic diseases. According to the multiplicative inheritance model, for the total sample, the relative risk is expressed for individual alleles of the *IL12B* gene with different SNPs: rs2569254 – OR=1.79, CI95%=1.08 – 2.96, $\chi2$=5.174, p=0.023, rs2853694 – OR=1.97, CI95% =1.24 – 3.13, $\chi2$=8.287, p=0.004, rs3213094 – OR=1.87, CI95%=1.20-2.91, $\chi2$=7.652, p=0.006, rs3212227-OR=11.78 CI95%=5.43-25.54, $\chi32$=53., p=0.00; for the *IL13* gene: rs1295686 – OR=5.08, CI95%=2.89-8.96, $\chi2$=35.24, p=0.000), rs20541-OR=4.46, CI95%=2.54 -7.83, $\chi2$=29.731, p=0.000); for the *CYP2B6* gene: rs2279345 – OR=1.30, CI95%=0.81-2.07, $\chi2$=20.67, p=0.000).

According to the multiplicative model, rs1805015 of the *IL4R* gene (OR=0.20), rs841718 of the *STAT6* gene (OR=0.62), rs3789453 of the *GCLM* gene (OR=0.83) exhibit protective properties both in the homozygous state and in the heterozygous state (in combination with the risk allele risk lowered). It should be noted that the involvement of some SNPs in the development of specific allergic diseases was determined: rs20541 is significantly associated with the development of asthma and allergic rhinitis, rs841718 – atopic dermatitis, rs3212227 – immunodeficiency.

An analysis of the association of individual genotypes according to the general model of inheritance (Table 4) determined an increased relative risk of the influence of homozygotes on the development of allergic diseases in the general population and which are consistent with the GWAS database in the *IL13* gene with the following polymorphisms: rs1295686(OR=7.38, CI95% 3.69-14.74, $\chi2$=35.56, p=0.000); rs20541(OR=4.92, CI95% 2.51-9.64, $\chi2$=28.69, p=0.000); in the *IL12B* gene rs3212227(OR=14.61, CI95% 6.27-34.08, $\chi2$=49.58, p=0.000); rs2853694 (OR=3.41, CI95% 1.82 -6.37, $\chi2$=16.84, p=0.000); rs3213094 (OR=2.52,CI95% 1.35-4.72, $\chi2$=8.74, p=0.01); rs2569254 (OR=2.27, CI95% 1.23-4 .19, $\chi2$=7.03, p=0.03); for the *IL4R* gene rs1805015 (OR=1.16, CI95% 0.08-0.32, $\chi2$=28.69, p=0.000); for the *CYP2B6* gene rs2279345 (OR=2.15), rs707265(OR=2.51); *GATA3* rs3824662(OR=2.19, p=0.018);

GATA3 rs3824662(OR=2.19, CI95% 1.19-4.01, $\chi2$=86.05, p=0.018). However, rs3789453 for gene *GCLM* (OR=0.90, CI95%=0.49-1.64, $\chi2$=1.36, p=0.5) and rs6107696 gene *SRXN1* (OR=0.72, CI 95%=0.26-1.98, $\chi2$=3.70, p=0.157) show protective properties.

Table 2 – Detected SNP-genotyping data

Gene(s)	Chr	Name	Mutatio	AA	Hom	Hete	Hom	1000 G	TOPMed	gnomAD	An	Alleles
SPON1	11	rs1025412	Silent	NM_006108.4:c.826-18582G>A	22	42	19	G: 0.466	0.489214	G: 0.490	G	[A/G]
ADRB2	5	rs1042714	Missens	NC_000005.10:g.148826910G>A	9	36	38	0.46	G=0.304575	G=0.316528	G	[G/C]
ADRB2	5	rs1042718	Synonyn	NM_000024.6:c.523C>A	46	30	7	A=0.2977	A=0.246658	A=0.225180	C	[A/C]
NFE2	12	rs10506328	Silent	NC_000012.11:g.54687232A>C	0	18	65	A=0.1212	A=0.236458	A=0.248348	A	[A/C]
STAT6	12	rs1059513	Silent	NC_000012.11:g.57489709T>C	75	8	0	C=0.0701	C=0.083547	C=0.080376	T	[T/C]
SPON1	11	rs12146558	Silent	NC_000011.9:g.14237921T>G	83	0	0	G=0.0062	G=0.013748	G=0.015900	T	[T/G]
SPON1	11	rs12575169	Silent	NM_006108.4:c.239-6586A>C	57	26	0	C=0.1072		C=0.169706	A	[A/C]
IL13	5	rs1295686	Silent	NC_000005.9:g.131995843T>C	7	38	38	T=0.4219	T=0.386448	T=0.377092	T	[T/C]
APOE	19	rs140808909	Missens	NM_001302688.2:c.862G>A	83	0	0	A=0.0006	A=0.000045	A=0.000057	G	[A/G]
IL4R	16	rs1805015	Missens	NM_000418.4:c.1507T>C	66	15	2	C=0.2017	C=0.226907	C=0.225574	T	[T/C]
APOE	19	rs201672011	Missens	NM_001302688.2:c.169G>A	83	0	0	A=0.0006	A=0.000045	A=0.000057	G	[A/G]
IL13	5	rs20541	Missens	NM_002188.3:c.431A>G	38	39	6	A=0.2700	A=0.225479	A=0.226468	G	[A/G]
IL13	5	rs2066960	Silent	NM_002188.3:c.174+383C>A	54	27	2	A=0.1993	A=0.161090	A=0.156756	C	[A/C]
TNFAIP3	6	rs2230926	Missens	NM_001270508.2:c.380T>G	80	3	0	G=0.1396	G=0.140202	G=0.134318	T	[T/G]
CYP2B6	19	rs2279345	Silent	NC_000019.9:g.41515702T>C	9	31	43	T=0.2652	T=0.309460	T=0.326698	T	[T/C]
IL12B	5	rs2569254	Silent	NC_000005.9:g.158751249C>T	50	26	7	T=0.1160	T=0.139892	T=0.150169	C	[T/C]
IL12B	5	rs2853694	Silent	NC_000005.9:g.158749088G>T	12	41	30	G=0.3560	G=0.392240		G	[T/G]
HLA-DQB1	6	rs2854275	Silent	NC_000006.11:g.32628428C>A	71	11	1	A=0.0649		A=0.095787	C	[A/C]
IL4R	16	rs3024658	Silent	NC_000016.9:g.27370454A>G	0	8	75	A=0.1569	A=0.135234	A=0.134652	A	[A/G]
IL12B	5	rs3212227	Silent	NC_000005.9:g.158742950T>G	42	33	8	G=0.3590	G=0.280502		T	[T/G]
IL12B	5	rs3213094	Silent	NC_000005.9:g.158750769C>T	42	33	8	T=0.3626	T=0.281813		C	[T/C]
TNFAIP3	6	rs3757173	Silent	NC_000006.11:g.138190154A>G	72	11	0	G=0.2055	G=0.211999	G=0.199752	A	[A/G]
GCLM	1	rs3789453	Silent	NC_000001.10:g.94374026C>T	6	29	48	C=0.2504	C=0.262892	C=0.276436	C	[T/C]
TNFAIP8	5	rs3797343	Silent	NM_014350.4:c.31+72A>C	47	30	6	C=0.3305	C=0.378953	C=0.388604	A	[A/C]
GATA3	10	rs3824662	Silent	NM_001002295.2:c.779-1748C>A	46	28	9	A=0.1959	A=0.185417	A=0.173865	C	[A/C]
HLA-DRB1	6	rs3830135	Silent	NG_002432.1:g.127955G>A	69	14	0	A=0.0647		A=0.114891	G	[A/G]
GATA3	10	rs444929	Silent	NC_000010.10:g.8110024C>T	2	26	55	C=0.1358	C=0.189871	C=0.198814	C	[T/C]
TNFAIP3	6	rs5029939	Silent	NM_001270508.2:c.296-259C>G	80	3	0	G=0.1396	G=0.139907	G=0.133958	C	[G/C]
GATA3	10	rs569421	Silent	NC_000010.10:g.8108592T>C	34	39	10	C=0.2953	C=0.291787	C=0.293257	T	[T/C]
TNFAIP3	6	rs582757	Silent	NC_000006.11:g.138197824C>T	2	26	55	C=0.2584	C=0.289716	C=0.296668	C	[T/C]
TNFAIP3	6	rs610604	Silent	NC_000006.11:g.138199417G>T	2	34	47	G=0.3866	G=0.427236	G=0.423267	G	[T/G]
SRXN1	20	rs6107696	Silent	NC_000020.10:g.630970A>C	7	49	27	A=0.3183	A=0.305622	A=0.294738	A	[A/G]
TNFAIP3	6	rs643177	Silent	NC_000006.11:g.138195693T>C	2	27	54	T=0.2574	T=0.289588	T=0.296607	T	[T/C]
TNFAIP8	5	rs6878879	Silent	NM_001077654.3:c.2-45722C>T	49	32	2	T=0.1577	T=0.192958	T=0.204891	C	[T/C]
CYP2B6	19	rs707265	Silent	NC_000019.9:g.41524087A>G	10	28	45	A=0.2602	A=0.301817		A	[A/G]
SPON1	11	rs7104613	Silent	NM_006108.4:c.479+16730C>T	75	8	0	T=0.0805	T=0.075643	T=0.073234	C	[T/C]
TNFAIP3	6	rs719150	Silent	NC_000006.11:g.138192761A>G	72	11	0	G=0.2057	G=0.212426	G=0.200240	A	[A/G]
HLA-DRB1	6	rs72850287	Silent	NC_000006.11:g.32553841A>C	69	14	0	C=0.0705		C=0.17621	A	[A/C]
APOE	19	rs7412	Missens	NM_001302688.2:c.604C>T	76	7	0	T=0.0751	T=0.078122	T=0.079856	C	[T/C]
APOE	19	rs769455	Missens	NM_001302688.2:c.565C>T	83	0	0	T=0.0074	T=0.007847	T=0.007012	C	[T/C]
STAT6	12	rs841718	Silen	NC_000012.11:g.57492996G>A	20	44	19	A=0.4249	A=0.491337	A=0.495373	G	[A/G]
IL13	5	rs848	Silent	NC_000005.9:g.131996500A>C	6	39	38	A=0.3724	A=0.330553	A=0.326017	A	[A/C]
PON1	7	rs854570	Silent	NC_000007.13:g.94952692C>A	15	42	26	A=0.4866	C=0.484661	C=0.477169	C	[A/C]

Table 3 – Association of genomic-wide genotyping data with the risk of developing allergic diseases

Multiplicative model of inheritance

RS	Chromo-some	Gene	Mutation	Allergy			Control			OR Allele A (CI)	OR Allele B(CI)	χ2	p	Population frequency	Ancestral	Alleles
				Wild type	Hetero	Homo mutation	Wild type	Hetero	Homo mutation					1000 G		
rs1295686	5	IL13	Silent	66	15	2	30	45	12	5.08(2.89 -8.96)	0.20 (0.11 -0.35)	35.24	0.000	T = 0.421925/2113	T	[T/C]
rs1805015	16	IL4R	Missense	38	38	7	75	13	1	0.20 (0.11 – 0.38)	4.96 (2.66 – 9.24)	28.71	0.000	C = 0.201677/1010	T	[T/C]
rs20541 Asthma, susceptibility to/ Allergic rhinitis	5	IL13	Missense	66	15	2	41	36	16	4.46 (2.54 -7.83)	0.22 (0.13 – 0.39)	29.73	0.000	A = 0.269968/1352	A	[A/G]
rs2569254	5	IL12B	Silent	54	27	2	41	47	3	1.79 (1.08 – 2.96)	0,56 (0.34 – 0.93)	5.17	0.023	T = 0.116014/581	C	[T/C]
rs2853694	5	IL12B	Silent	50	26	7	28	56	7	1.97 (1.24 -3.13)	0.51 (0.32 -0.81)	8.28	0.004	G = 0.35603/1783	G	[T/G]
rs3024658	16	IL4R	Silent	30	41	12	84	5	1	0.06(0.03 -0.14)	15.91 (7.02 -36.02)	65.18	0,000	A = 0.156949/786		[A/G]
rs3212227 Immunodeficiency	5	IL12B	Silent	75	8	0	34	41	12	11.78 (5.43-25.54)	0.08 (0.04 – 0.18)	53.34	0.000	G = 0.359026/1798	T	[T/G]
rs3213094	5	IL12B	Silent	42	33	8	26	49	15	1.87 (1.20-2.91)	0.54 (0.34 – 0.84)	7.65	0.006	T = 0.36262/1816	C	[T/C]
rs841718 Atopic dermatitis	12	STAT6	Silent	20	44	19	34	38	13	0.62 (0.40 – 0.96)	1.62 (1.05 – 2.50)	4.72	0.03	A = 0.4249 (2128/5008)	G	[A/G]
rs3789453	1	GCLM	Silent	48	29	6	55	33	3	0.83(0.50-1.37)	1.20(0.73-1.98)	0.52	0.469	0.250	T	[T/C]
rs707265	19	CYP2B6	Silent	45	10	28	26	54	1	1.30(0.81-2.07)	0.77(0.48-1.23)	20.67	0.000	0.26 (A)	G	[A/G]
rs769455	19	APOE	Missense	83	0	0	89	2	1	0	0	3.65	0.056	0.007388	C	[T/C]

Table 4 – General model of inheritance

RS	Chromosome	Gene	Mutation	Allergy group			Control			OR genotype A/A(CI)	OR allele A/B	OR allele B/B	$\chi 2$	p
				wild genotype	Hetero-zygous	Homo-zygous	wild genotype	Hetero-zygous	Homo-zygous					
rs1295686	5	IL13	Silent	66	15	2	30	45	12	7.38 (3.69 – 14.74)	0.21 (0.10 – 0.41)	0.15(0.03-0.71)	35.56	0,000
rs1805015	16	IL4R	Missense	38	38	7	75	13	1	1.16 (0.08 – 0.32)	4.94 (2.38 – 10.24)	8.11(0.98 -67.37)	28.69	0,000
rs20541 Asthma, susceptibility o/Allergic rhinitis	5	IL13	Missense	66	15	2	41	36	16	4.92 (2.51 – 9.64)	0.35 (0.17 – 0.70)	0.12 (0.03-0.53)	24.88	0,000
rs2569254	5	IL12B	Silent	54	27	2	41	47	3	2.27 (1.23-4.19)	0.45 (0.24 – 0.84)	0.72 (0.12 – 4.45)	7.03	0.03
rs2853694	5	IL12B	Silent	50	26	7	28	56	7	3.41 (1.82 -6.37)	0.29 (0.15 – 0.53)	1.11 (0.37 – 3.30)	16.84	0.000
rs3024658	16	IL4R	Silent	30	41	12	84	5	1	0.04 (0.02 – 0.10)	1.16 (6.11 -45.08)	15.04 (1.91 – 118.46)	62.88	0.000
rs3212227 Immunodeficiency	5	IL12B	Silent	75	8	0	34	41	12	14.61 (6.27 – 34.08)	0.12 (0.05 – 0.28	0	49.58	0.000
rs3213094	5	IL12B	Silent	42	33	8	26	49	15	2.52(1.35 -4.72)	0.55 (0.30 – 1.01)	0.53 (0.21 – 1.33)	8.74	0.013
rs3824662	10	GATA3	Silent	46	28	9	33	50	8	2.19 (1.19 -4.01)	0.42 (0.23 – 0.77)	1.26 (0.46 – 3.44)	86.05	0.018
rs2279345	19	CYP2B6	Silent	43	31	9	29	49	6	2.15(1.16-4.00)	0.46(0.25-0.85)	1.05(0.40-2.80)	6.68	0.035
rs707265	19	CYP2B6	Silent EXON	45	10	28	26	54	1	2.51(1.33-4.73)	0.25(0.13-0.49)	10.96(1.37-87.72)	20.67	0.000
rs3789453	1	GCLM	Silent	48	29	6	55	33	3	0.90(0.49-1.64)	0.94(0.51-1.76)	2.29(0.55-9.45)	1.36	0.504
rs6107696	20	SRXN1	Silent	7	49	27	10	39	39	0.72(0.26-1.98)	1.81(0.99-3.32)	0.61(0.32-1.13)	3.70	0.157

Throughout the world, in the molecular genetic study of allergic diseases, cytokines, especially interleukin 4 (IL 4) and interleukin 13 (IL 13) [6], play an important role in controlling all stages of development and maintenance of allergic reactions and inflammation [6]. IL 4 was first described by M. Howard et al. in 1982 as a factor that stimulated the proliferation of B lymphocytes and their synthetic activity, therefore it was originally called B cell growth factor, B stimulating factor and B cell differentiating factor. It was then found that this mediator also stimulates the proliferation and functional activity of certain types of T lymphocytes. In 1986, this cytokine was given the name "IL 4". [26]. According to the literature, the IL4Rα gene is actively studied as a candidate gene for AD. There are at least 14 SNPs in coding exons that lead to amino acid substitutions and are associated with AD and atopy, for example, Val50, Glu375, Gln551, Cys406, Ser478, [27–28]. IL 13 has biological activity, in many respects similar to the activity of IL 4. Studying their biological functions showed fundamental differences between the two cytokines. IL 13 and IL 4 similarly stimulate the function in lymphocytes and monocytes/macrophages, however IL 13 has absolutely no effect on T lymphocytes, since T cells do not express their receptors [26]. In particular, the signal from IL 4 and IL 13 is transmitted using the STAT6 protein.

However, in recent years, researchers believe that the cause of allergic diseases are disorders in the immune system, which is associated with increased unbalanced activation of allergen-specific clones of type 2 helper T-lymphocytes. And here, the cytokines involved in the triggering and regulation of allergies are synthesized by epithelial cells, various types of leukocytes, innate lymphoid cells, and allergen-activated T-helper lymphocyte clones. After interacting with allergens, epithelial cells synthesize cytokines that cause inflammation, activation of dendritic cells (DCs), and recruitment of many types of leukocytes to the submucosal layer of the epithelium. The following cytokines are most important in these processes: thymic stromal lymphopoietin (TSLP), interleukins IL-25 and IL-33, which determine a special variant of activation of antigen-presenting DCs that direct the differentiation of T-lymphocytes of helpers (Th), activated by the allergen, according to proallergic Th2 and Th9 pathways. [29-30]. N.I. Baranova et al. (2014) showed an association of genetic polymorphisms of IL-4, IL-10 and IL-17 in the pathogenesis of allergic diseases, with a quantitative deviation of cytokines and the formation of one or another form of an allergic disease [31].

In recent years, AD GWAS have been carried out in various populations of the world, new genes associated with the development of AD in individuals of European origin have been discovered – DENND1B, PDE4D, RAD50, IL1RL1/IL18R1, HLA-DQ, IL33, IL6R, SMAD3 and IL2RB; African origin – ADRA1B, PRNP and DPP10; Mexicans – TLE4, Koreans – CTNNA3 (http://www.genome.gov/GWAStudies/). The results of two GWAS for AD have been published, which revealed an association with SNPs of the 11q13.5 regions in individuals of European origin [8], and SNPs localized in the 5q22.1, 20q13.33 and 1q21.3 regions (FLG) in the Chinese [32]. In general, genetic studies have shown that many functionally interconnected genes are involved in the etiopathogenesis of allergy. It is known that immunological mechanisms underlie the development of allergies, including drugs. CYP2D6 has been found to be responsible for the metabolism of 20-30% of drugs [33]. CYP2B6 is a highly inducible and polymorphic enzyme that is expressed in the brain, mainly in neurons and astrocytes. It metabolizes not only clinically important drugs (e.g. bupropion, cyclophosphamide, efavirenz, propofol, selegiline) but also many chemicals. Goodwin et al. Have shown that transcription of human CYP2B6 is directly regulated by the human pregnane X receptor (PXR) [34]. Transactivation of CYP2B6 by PXR is mediated by a region of the PBREM gene. This 51 bp amplifier module regulates constitutive androstane receptor (CAR) mediated induction of CYP2B6 [35]. PBREM contains two DR4 (four base pair direct repeat) elements that are capable of binding PXR-Rxr. In addition, the distal region of the CYP2B6 promoter, together with PBREM, mediates drug-induced transcription of CYP2B6. Wang et al. Showed that this distal response area could be activated by PXR [36].

Tripeptide glutathione (GSH; γ-glutamylcysteinylglycine) is one of the most abundant cellular thiols. GSH is a major player in cellular defense against ROS as it nonenzymatically scavenges both singlet oxygen and hydroxyl radicals and is used by glutathione peroxidase and glutathione transferases to limit the levels of certain reactive aldehydes and peroxides in the cell. The enzyme consists of two subunits, a large (73 kDa) catalytic subunit (GCLC) and a smaller (31 kDa) modifier or regulatory subunit (GCLM), which are encoded by separate genes [37]. GCLC provides catalytic activity and is the site of GSH feedback inhibition. The GCLC gene has been shown to contain oxidative stress sensitive elements in the promoter/enhancer region, and polymorphisms associated with reduced GCLC expression are sug-

gested to be important determinants of susceptibility to oxidative stress and DNA damage [38].

The results of genome-wide studies make it possible to discover a number of new loci and genes associated with allergic diseases, however, the results of these works are contradictory, in many studies the results of GWAS do not coincide with each other. Perhaps one of the reasons for this inconsistency is both the ethnic component of the genetic component (features of haplogroups of different populations, different allele frequencies of susceptibility genes) and the environmental component (differences in the structure of allergic sensitization, microbial and helminth environment). This dictates the need for GWAS to study AD in ethnically different populations. World achievements in genetics are widely used in Kazakhstan, however, often without considering the specifics of Kazakhstani genotype. Data on the genetic diversity of Kazakh populations are fragmentary and not systematized.

Research carried out by Rogers et al. (2009) showed that 160 associated SNPs from 39 genes from the Illumina 550k array in 422 families successfully replicated 10 SNPs in six genes [39]. At the gene level, they found additional association support in 15 of 39 genes, but none were significant after adjusting for multiple comparisons. Ober and Hoffjan (2006) listed 118 genes that were reported to be associated with phenotypes associated with asthma or atopy [40]. Of these genes, 25 were positively associated with asthma in six or more independent studies and thus were highly implicated as true genes for susceptibility to asthma-associated phenotypes. Initial associations have been identified in many different types of studies; linkage studies, positional cloning and association of candidate genes, and have subsequently been replicated mainly through association studies.

Conclusion

Thus, we evaluated the genes of allergic diseases using the GWAS technology. However, our sample is not large enough for such studies and needs to be continued with a larger sample. In addition, GWAS does not represent all candidate genes in its arrays and this requires additional direct genotyping. We hope that as the number of available GWAS for AR, AD, AD increases, we will soon be able to pool results from multiple cohorts and thus have enough power to answer more definitively whether these SNPs are indeed allergy susceptibility loci. Determination of individual genetic risks underlying personalized predictive medicine will allow primary prevention of diseases. To date, Kazakhstan does not produce a single diagnostic test system based on genomic information that is in demand on the domestic or foreign market. In this regard, the creation of genetic banks and national information databases that integrate information about the genome of Kazakhstanis seems to be a strategically important direction in the development of fundamental and applied science in Kazakhstan.

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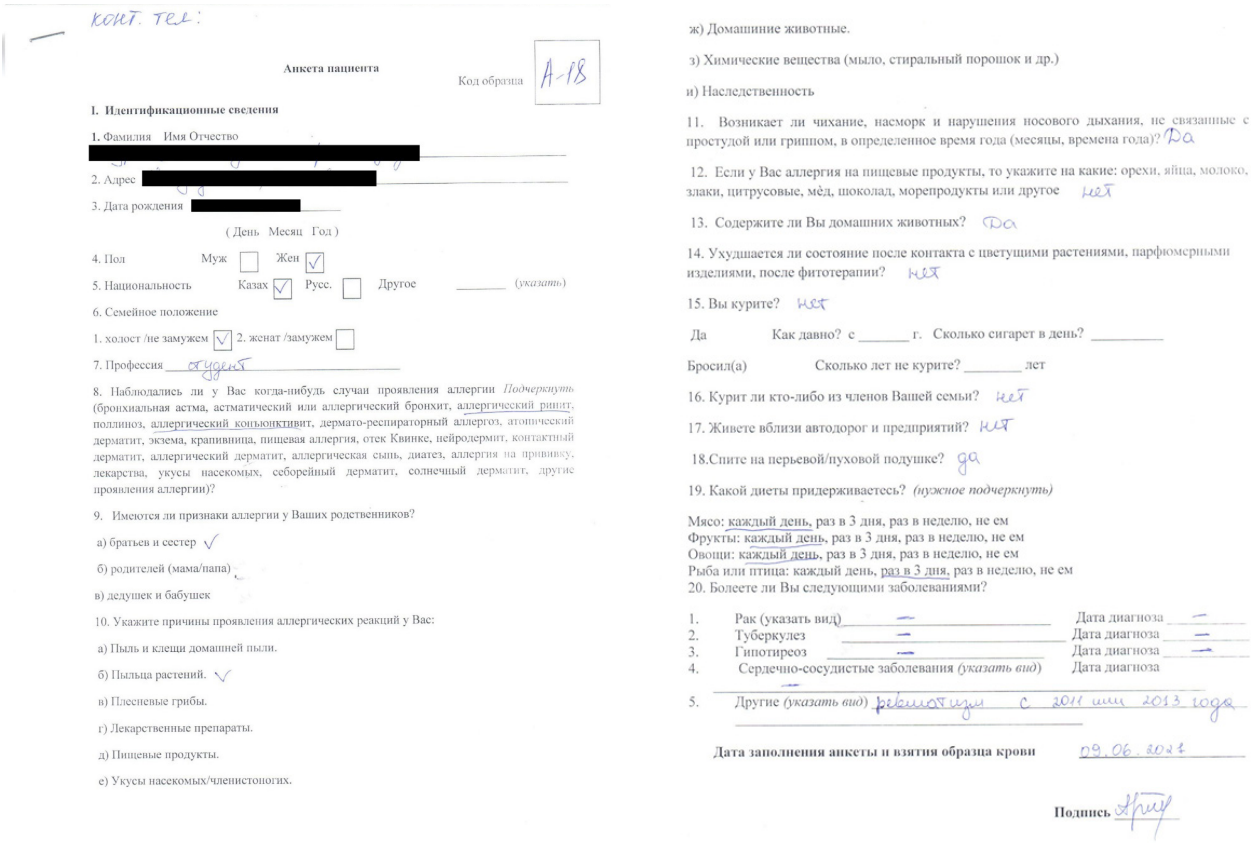
Appendix A – Example of a health questionnaire



конт. тел:

Анкета пациента Код образца A-18

1. Идентификационные сведения

1. Фамилия Имя Отчество [redacted]

2. Адрес [redacted]

3. Дата рождения [redacted]

(День Месяц Год)

4. Пол Муж ☐ Жен ☑

5. Национальность Казах ☑ Русс. ☐ Другое _____ (*указать*)

6. Семейное положение

1. холост /не замужем ☑ 2. женат /замужем ☐

7. Профессия студент

8. Наблюдались ли у Вас когда-нибудь случаи проявления аллергии *Подчеркнуть* (бронхиальная астма, астматический или аллергический бронхит, аллергический ринит, поллиноз, аллергический конъюнктивит, дермато-респираторный аллергоз, атопический дерматит, экзема, крапивница, пищевая аллергия, отек Квинке, нейродермит, контактный дерматит, аллергический дерматит, аллергическая сыпь, диатез, аллергия на прививку, лекарства, укусы насекомых, себорейный дерматит, солнечный дерматит, другие проявления аллергии)?

9. Имеются ли признаки аллергии у Ваших родственников?

а) братьев и сестер ✓

б) родителей (мама/папа)

в) дедушек и бабушек

10. Укажите причины проявления аллергических реакций у Вас:

а) Пыль и клещи домашней пыли.

б) Пыльца растений. ✓

в) Плесневые грибы.

г) Лекарственные препараты.

д) Пищевые продукты.

е) Укусы насекомых/членистоногих.

ж) Домашние животные.

з) Химические вещества (мыло, стиральный порошок и др.)

и) Наследственность

11. Возникает ли чихание, насморк и нарушения носового дыхания, не связанные с простудой или гриппом, в определенное время года (месяцы, времена года)? Da

12. Если у Вас аллергия на пищевые продукты, то укажите на какие: орехи, яйца, молоко, злаки, цитрусовые, мёд, шоколад, морепродукты или другое нет

13. Содержите ли Вы домашних животных? Da

14. Ухудшается ли состояние после контакта с цветущими растениями, парфюмерными изделиями, после фитотерапии? нет

15. Вы курите? нет

Да Как давно? с _____ г. Сколько сигарет в день? _____

Бросил(а) Сколько лет не курите? _____ лет

16. Курит ли кто-либо из членов Вашей семьи? нет

17. Живете вблизи автодорог и предприятий? нет

18. Спите на перьевой/пуховой подушке? да

19. Какой диеты придерживаетесь? *(нужное подчеркнуть)*

Мясо: каждый день, раз в 3 дня, раз в неделю, не ем
Фрукты: каждый день, раз в 3 дня, раз в неделю, не ем
Овощи: каждый день, раз в 3 дня, раз в неделю, не ем
Рыба или птица: каждый день, раз в 3 дня, раз в неделю, не ем

20. Болеете ли Вы следующими заболеваниями?

1. Рак (указать вид) — Дата диагноза —
2. Туберкулез — Дата диагноза —
3. Гипотиреоз — Дата диагноза —
4. Сердечно-сосудистые заболевания *(указать вид)* Дата диагноза
5. Другие *(указать вид)* ревматизм с 2011 или 2013 года

Дата заполнения анкеты и взятия образца крови 09.06.2021

Подпись [signature]

Examples of examinations of doctors with a diagnosis

03.08.2021 Печать A-14

ALLERGO clinic

Клиника "ALLERGO CLINIC"
ул. Навои, д. 208
+7 (727) 311 58 22
http://allergoclinic.kz (http://allergoclinic.kz)

Скачать приложение для пациентов
Вы сможете записаться на прием, получить записи по вашему приему, оставить отзыв или задать вопрос
(https://medelement.com/health)
epz.kz

Записи по приему # 544923101621938261
27.05.2021 / 09:30 - 10:00 / Амбулаторно
Аллерголог: Талгатбекова Динара Женисбековна (кабинет "Аллерголог")
Пациент: [redacted]

Жалобы
на заложенность носа, зуд в носу , в глазах, чихание

Anamnesis morbi
Вышеизложенные симптомы в течение нескольких лет, сезонно с июня по сентябрь

Объективный осмотр
Общее состояние. Общее состояние пациента удовлетворительное
Самочувствие (общая оценка). Самочувствие не страдает
Сознание. Сознание ясное
Дыхание через нос умеренно затруднено . Риноскопия - отечность слизистой носовой полости . выделения слизистого характера
По органам без патологии

Диагнозы

Диагноз/Код МКБ	Вид диагноза
Основное заболевание: Аллергический ринит (Другие сезонные аллергические риниты (J30.2))	Клинический (Впервые установлен)

Рекомендации
1. аллергообследование (общий ИГЕ, спец ИГЕ с ингаляцион аллергенами)
2. фексет 120 мг по 1 таб х1 раза вдень №10
3. монтигет 10 мг по 1 таб х1 раза в день 21 часов №14
4. снуп по 1 впр х3 раза вдень № 7 при заложенности
5. промывание водно-солевым раствором х3 раза вдень №10
6. в нос спрей флутинекс по 2 впр х2 раза вдень №10 , по 1 впр х2раза в день №10 , по 1 впр х1 р № до 1 месяца
7 . Натрия хлорид 0.9%- 200. + дексаметазон 8 мг - 6 мг -4 мг в/в кап 3 дня
8. в динамике через 5 дней

Акт выполненных работ
Сумма указана согласно прайса, с учетом скидок. Услуги оказаны в полном объеме. Претензий к качеству нет.

Пациент: _____
Специалист: _____

Медицинская информационная система - www.medelement.com, 03.08.2021 15:20, МО № 572750971476764532

Appendix B – Genome-Wide Analysis of Allergic People Based on Microarray SNP Genotyping Call Rate Analysis Examples