ENGLISH VERSION: CREATING A GENETIC DATABASE AS A STRATEGIC CHALLENGE OF MODERN MEDICAL RESEARCHES*

Vesnina L.,Kaidashev I.

Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics of Higher State Educational Establishment of Ukraine "Ukrainian Medical Stomatological Academy", Poltava, Ukraine

Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics among the first institutions in Ukraine had created a genetic database growing for the last few years. The creation of this database is necessary to monitor such common pathological conditions as metabolic syndrome, diabetes, arterial hypertension, coronary heart disease, allergic inflammation, urogenital infections, pathologies of immune and endocrine systems, and connective tissue. Creation of genetic monitoring system and identifying genetic markers of susceptibility to infectious agents and propensity to noninfectious origin diseases development will allow monitoring the level of morbidity in Ukraine by predicting the risk of developing certain pathological conditions, the nature and progression rate of pathological process, the formation of risk groups of possible morbidity since the childhood, and using effective prevention technologies. Development of targeted programs for early diagnosis and treatment taking into account a genetic predisposition will reduce the direct economic costs of medication, duration of outpatient and inpatient treatment by pharmacogenetic selection of main groups of drugs, decrease the incidence of complications and mortality level and will promote the introduction of individual strategies of preventive measures and improving health.

Keywords: databases, genetic samples, polymorphisms.

Rapid development of molecular and cell biology has significantly expanded our understanding of biochemical, physiological, molecular, and other processes in the healthy human body and allowed us to draw conclusions regarding subtle pathogenic mechanisms of particular clinical symptoms and diseases. World medical experience shows that the achievement in human genetics is no less important, and its potential could be fully realized in the collaboration of geneticists and physicians provided that the bioethical and deontological research norms will be met.

The need of medical diagnosis and genetic counseling of not only rare genetic diseases associated with severe disorders and complications but also the most common diseases such as diabetes, coronary heart disease, arterial hypertension, and atherosclerosis is currently a significant problem of practical medicine, that's why the creation of genetic database was assigned as a primary task. In the longer term, database and expert systems integration will significantly enhance the ability of doctors and increase the effectiveness of diagnostic decisions. Developing effective prevention programs becomes possible on the basis of genetic monitoring data; the use of such programs will prevent the development of diseases, maintain health and prolong people's lives, generally having a significant positive economic impact for society.

Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics among the first institutions in Ukraine had created a genetic database that is growing for the last few years. This database is necessary to monitor such common pathological conditions as metabolic syndrome, diabetes, arterial hypertension, coronary heart disease, allergic inflammation, urogenital infections, pathologies of immune and endocrine systems, and connective tissue pathologies. Despite different clinical manifestations, these diseases do not have completely certain aspects of etiology and pathogenesis making it difficult and sometimes making preventive and therapeutic measures quite ineffective.

Collecting samples was begun within "Diabetes", "Prevention and treatment of arterial hypertension in Ukraine", and "Prevention and treatment of dental diseases" state programs.

Database creation had been conducted in accordance with the subjects of scientific researches that were funded by government "Study of switching of immunoglobulin synthesis in patients with bronchial asthma for developing new methods of etiologic and pathogenetic therapy", № SR 0106U003241; "Development of methods for the prevention and treatment of diseases resulting from metabolic syndrome with drugs that stimulate the receptors, activating PPAR-γ, by improving diagnostic criteria", № SR 0107U01555; "Defining the role of polymorphisms in Toll-like receptors in the development of immune mediated diseases", № SR 0109U001629; "Study of genetic features of allergic inflammation and target organs formation", № SR 0110U003032; "Complex research of genetically determined characteristics of NF-kB-mediated signal transduction that specifies the development of chronic systemic inflammation in patients with metabolic syndrome and type 2 diabetes", № SR 0111U001774; "The role of inflammatory diseases of teeth-jaw apparatus in the development of diseases associated with systemic inflammation", № SR 0112U001538.

The purpose of creating genetic database of Ukraine's population representatives had become an urgent need to monitor and control the most common infectious and non-infectious diseases rate among Ukrainians, to define and substantiate the leading role of genetic factors contributing to their development, and, based on this, to develop targeted programs for early diagnosis and treatment, risk groups formation and predicting the nature and rate of progression of the pathological process.

Materials and methods

We received an approval of Bioethics Commission of Higher State Educational Establishment of Ukraine "Ukrainian Medical Stomatological Academy" to conduct the study. According to the standards of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) all patients signed an informed consent, and a voluntary consent was received from parents of children to the participation in the survey.

Biological materials (blood, serum, dried blood spots, epithelial scraping) were obtaining in the morning on an empty stomach using standard methods for storage or

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immediate examination. Samples had been stored for a long time using a low-temperature refrigeration (from -24º to -70º C).

During patients' registration, basic parameters were taken into account: passport information, sex, age, established diagnosis, survey results. Primary registration has been made in the current registration journals, and then the patient data and survey results were put into a Microsoft Office Excel 2007 database. Statistical analysis of the research results had been conducted using STATISTICA for Windows 7.0 (StatSoft Inc, USA).

Results and discussion

Main areas of study were identified from the beginning of genetic database creation: monitoring survey of relatively healthy persons (citizens of the Poltava region), patients with urogenital diseases; persons who were initially examined or treated by an endocrinologist for thyroid diseases; patients with signs of allergic inflammation; patients with disorder of lipid metabolism and features of metabolic syndrome; patients with connective tissue diseases.

Below we provide a brief overview of some samples and examples of their practical use.

Population control group was created in the first phase of research and consisted of relatively healthy persons of different age and sex (Table 1). For the cohort survey of population control group, an observation card in a form of questionnaire was pre-designed, each surveyed person should provide there detailed data on age, sex, nationality, social, occupational, genetic, epidemiological, allergy, therapeutic, and surgical anamneses, clinical status data at the time of inspection and objective data regarding various organs and systems. Later, card was supplemented with laboratory research data, and all information was fixed electronically.

Initially, population control group included 114 relatively healthy persons aged from 19 to 62 years. While forming, population control group was supplemented with 185 examples of citizens of Poltava region with different age and sex, who were considered as relatively healthy persons at the time of the survey. Group of people with urogenital diseases (chlamydia, ureaplasmosis, trichomoniasis, gardnerellosis, mycoplasmosis, and bacterial vaginosis) was formed of 156 patients. Overall, the total number of surveyed persons was 455 patients.

How can we use this material? Precisely using named samples, the prevalence of single nucleotide polymorphisms of TLR2 gene Arg753Gln with replacement of G to A at position 2258 (rs5743708), and TLR4 genes Asp299Gly with replacement of A to G at position 896 (rs4986790) and Thr399Ile with replacement of C to T at position 1196 (rs4986791) was investigated for the first time in Ukraine's population among healthy persons of Poltava region's population and among patients with common urogenital diseases [1].

We studied 299 persons from population control group (relatively healthy), balanced by sex, aged from 19 to 62 years, and 156 patients of different age and sex with urogenital infections. Study material was epithelial cells scraped from the urethra or cervix that were obtained via special sterile disposable urogenital probes.

We found a reliable correlation between the presence of mutant A allele in a genotype (GA and AA genotypes) of TLR2 gene and mutant G allele (AG and GG genotypes) of TLR4 gene and the increased risk of infection with common urogenital infections (χ^2=7.99; OR=2.01; CI=1.26-3.21; p=0.0047) that's why these single nucleotide polymorphisms can be considered as an additional prognostic indicator in pathogenetic studies.

Since 2008, we are collecting samples of patients with allergic inflammation (Table 1). Criteria for inclusion in the group are the signs and/or a clearly established diagnosis of allergic inflammation according to ICD-10 (bronchial asthma, allergic rhinitis, atopic dermatitis, urticaria). The number of samples is 620, creation of database is ongoing. Age range is from 6 months to 84 years, an average age of children is 4.3 ± 3.5 years.

The role of polymorphisms of the genes encoding TLR2 (rs5743708) and TLR4 (rs4986790, rs4986791) in increasing production of specific immunoglobulin E (IgE) and the development of allergic inflammation was determined [5]. We conducted genotyping of these three single nucleotide polymorphisms in the control group and in patients with allergic inflammation. Dry blood spots were used as biological material.

Group of patients consisted of 38 persons with allergic inflammations (19 persons with atopic asthma, 13 ones with atopic dermatitis, and 6 patients with atopic rhinitis). The selection criterion was the high level of allergen-specific IgE (from 3.5 to 100 kU/l) to at least one of allergens. To verify the IgE-dependent allergic inflammations, we studied specific IgE to 20 most important allergens [5]. Population control group consisting of 95 persons with a lack of allergic inflammation in history was used as a control.

As a study result, we established the relationship between TLR2 (rs5743708) and TLR4 (rs4986790) polymorphisms with elevated level of specific IgE production in patients with allergic inflammations that's why these single nucleotide replacements can be considered as an additional prognostic characteristic of individual susceptibility to these diseases.

We formed a separate group of 140 patients with allergic diseases (bronchial asthma, allergic rhinitis, atopic dermatitis), in whom were determined polymorphic variants of TLR2 and TLR4 genes and indicators of the immune system state [7, 9]. The study of polymorphic variants of TLR4 896A/G (rs4986790), 1196C/T (rs4986791) gene and TLR2 2258G/A (rs5743708) gene showed that exactly TLR4 gene 896A/G polymorphism causes the severity and complicated course of atopic dermatitis in children [8].

We are creating a database of patients who contacted Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics about screening for thyroid disease. 2547 samples amount the most significant part of the whole database now. Age range is from 20 to 80 years.

Within the state "Program of prevention and treatment of arterial hypertension in Ukraine" in cooperation with NRC "M. D. Strazhesko Institute of Cardiology" of NAMS of Ukraine, the direction with the purpose to study the pathogenesis of metabolic syndrome (MS) and chronic systemic inflammation was shaped.

Citizens of Poltava aged from 18 to 64 years were surveyed (896 persons in total: 579 women and 317 men). In Cherkasy 388 people were surveyed (222 women aged from 18 to 63 years and 166 men aged from 19 to 64 years) (Table 1).

Table 1

Genetic database structure of Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics

Groups	Number of samples	Sex		Age		Laboratory Methods
		M	F	M	F	
1	2	3	4	5	6	7
Relatively healthy persons	114	47	67	Aged 18-62 years	Aged 18-62 years	lipid metabolism, glucose, cytokines, polymorphisms 2258G/A TLR2 (rs5743708) 896A/G TLR4 (rs4986790)
Patients with urogenital diseases	341	195	146	Aged 20 - 80 years	Aged 20 - 80 years	polymorphisms 2258G/A TLR2 (rs5743708) 896A/G TLR4 (rs4986790) 1196C/T TLR4 (rs4986791)
Patients with thyroid diseases	2547	1018	1529	Aged 20 - 80 years	Aged 20 - 80 years	T3, T4, TSH, Ab to TPO, Ab to TSH
Patients with allergic diseases	620			Aged 6 months- 84 years	Aged 6 months- 84 years	Allergen-specific IgE
Patients with bronchial asthma	45	18	27	Aged 18 – 70 years	Aged 18 - 70 years	IgE, IL-4, IL-10, CD4, CD25, Foxp3 polymorphisms 2258G/A TLR2 (rs5743708), 896A/G TLR4 (rs4986790)
allergic rhinitis	45	23	22	Aged 19 - 65 years	Aged 19 - 65 years	$CD4^+$, $CD4^+/25^+$, $CD4^+/25^+$/Foxp3 polymorphism 896A/G TLR4 (rs4986790)
atopic dermatitis	50	24	26	Aged 2 - 7 years	Aged 2 - 7 years	CD3, CD4, CD8, CD16, CD20, IgA, IgM, IgG, IgE, CIC polymorphisms 2258G/A TLR2 (rs5743708), 896A/G TLR4 (rs4986790), 1196C/T TLR4 (rs4986791)
Patients with dyslipidemia	199	95	104	Aged 20 - 80 years	Aged 20 - 80 years	lipid metabolism, ceruloplasmin, polymorphism PPARγ (Pro12Ala)
Patients with metabolic syndrome	1441	567	874	Aged 18 - 75 years	Aged 18 - 75 years	lipid metabolism, glucose, glycosylated hemoglobin, cytokines, polymorphisms PPARγ (Pro12Ala), LPL (C→T, intron 6); LPDR (C→T, intron 15); MTHFR (Ala222Val)
Patients with combined pathology: metabolic syndrome, arterial hypertension	106	106	-	Aged 20 - 80 years	Aged 20 - 80 years	polymorphisms AGTR1 (A1166C); ACE (Alu Ins/Del I>D)
Patients with combined pathology: metabolic syndrome, coronary heart disease, bronchial asthma, endothelial dysfunction	102	69	33	Aged 40 - 75 years	Aged 40 - 75 years	lipid metabolism, glucose, cytokines, CRP, ICAM–1,VCAM–1 polymorphism PPARγ (Pro12Ala), expression NF-kB1, NF-kB2
Study on the genes of structural proteins	159	72	87	Aged 20 - 95 years	Aged 20 - 95 years	polymorphisms MMP12 (A-82G); MMP20 (g.16250T>A); KLK (g.2142G>A); ELN (g28197 A>G)
Patients with connective tissue disorders	53	22	31	Aged 20 - 80 years	Aged 20 - 80 years	Screening panel: Ro/SS-A, La/SS-B, Scl-70, PM-Scl-100, Jo-1, PCNA, dsDNA, rib.P-Protein, CENP-B, AMA-M2, PR3, MPO, TPO, tireohlobulin

Using the data of this line of research, the prevalence of lipoprotein lipase (LPL) gene PvuII polymorphism and the connection with arterial hypertension development were investigated in Cherkasy population [12].

85 men aged 19-66 years were selected among the patients of Cherkasy 1st clinical hospital to study the polymorphism of LPL gene and divided into two groups. Control group (n=47) consisted of persons with normal blood pressure <140/90 mmHg, main group (n=38) included patients with the level of blood pressure ≥140/90 mmHg or persons with an arterial hypertension in the anamnesis.

Distribution of LPL polymorphisms in a population control group and in a group of men with arterial hypertension in Cherkasy population was carried out for the first time. In the population of control group, genotype frequencies were as follows: CC – 29.79% CT – 51.06%, and TT – 19.15%; allele frequencies were: C – 55.32% and T – 44.68%. In men with hypertension, frequency of genotypes and alleles of the LPL gene was not significantly different from the population control group: CC – 34.21%, CT – 47.37%, and TT – 18.42%; C – 57.9% and T – 44.1% for alleles.

Relationship between PvuII polymorphism in the LPL gene and the development of arterial hypertension has not been established. But the findings suggest that it would be appropriate to study this polymorphism in patients with clearly defined features of metabolic syndrome.

Within the determination of genetic risk factors for essential hypertension, we studied the distribution of polymorphisms of angiotensin II type 1 receptor AGTR1

(A1166C) [4]. In healthy persons (n=100), the frequencies of genotypes and alleles were: AA – 51%, AC – 34%, and CC – 15%; A – 68% and C – 32% for alleles. An overwhelming prevalence of C allele and CC genotype in healthy people in the Ukrainian population was assumed. Genotype frequencies in patients with essential hypertension (106 persons) were: AA – 22.85% and AC – 51.9%; and allele frequencies were: CC – 25.3 %; A – 48.7% and C – 51.3%. It was concluded that the development of essential hypertension is associated with the presence of C allele and its homozygous variant, the severity and complications of hypertension depend on the presence of this allele in the genotype. Ukrainian population has a specific distribution of polymorphisms of angiotensin II type 1 receptor with a predominance of C1166 allele and CC genotype that is a risk factor for essential hypertension.

In general, it should be noted that while collecting samples of this trend, the need arose for division into groups allowing to more thoroughly investigate patients and focus on a particular pathology. Thus, we managed to investigate some polymorphic variants of a number of genes: angiotensin II type 1 AGTR1 (A1166C), angiotensin-converting enzyme (ACE) (Alu Ins / Del I> D), peroxisome proliferator-activated receptor (PPAR)-γ (Pro12Ala), lipoprotein lipase (LPL) (C → T, intron 6), lipoprotein receptor (LPDR) (C → T, intron 15) [2, 3]. Material is currently being collected to continue genetic studies of the pathogenesis of metabolic syndrome (Table 1).

The importance of using database to develop effective advanced schemes of therapy should be noted. Thus, while studying pharmacogenetic characteristics of metformin action in patients with coronary artery disease on the background of metabolic syndrome and type 2 diabetes taking into account Pro12Ala polymorphism of the PPAR-γ2 gene, we defined its high therapeutic efficacy in patients with coronary artery disease on the background of type 2 diabetes who have the Pro/Pro genotype, significantly enabling individualized therapy [6].

Sampling for further study of the role genetic polymorphisms of structural proteins genes in inflammatory and degenerative processes of organs and tissues is an interesting and promising trend. Matrix metalloproteinases (MMP12 (A-82G); MMP20 (g.16250T> A)), kallikrein (KLK (g.2142G> A)), elastin (ELN (g28197 A> G)) are among them to name a few (Table 1) [10].

Thus, we determined polymorphism of kallikrein 4 (KLK4) gene in exon 4 g.2142 G>A (AF228497) in 72 patients with excessive tooth wear of I-III degree (30 men, 42 women, aged 20-62 years) [11].

It was shown that more serious signs of excessive tooth wear are observed namely in carriers of A allele of g.2142 G>A polymorphism of KLK4 gene. The obtained data confirm the relationship between the presence of polymorphic A allele of KLK4 gene with excessive tooth wear. These data allow us to consider this polymorphism as an additional prognostic indicator of excessive loss of dental hard tissues, and the detection of mutant A allele of KLK4 gene enables purposefully carrying out prevention and treatment of patients with excessive tooth wear.

Data on patients with autoimmune connective tissue diseases such as scleroderma, rheumatoid arthritis, vasculitis, who were examined in the Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics by using modern screening panels, providing sighting diagnosis of disease and significantly improving the effectiveness of therapy, are of great practical significance (Table 1).

Work on creating genetic database continues. Such work is rather tedious, demanding, but the possibility of its practical use and value is difficult to estimate. We mentioned only some directions of data accumulation and some examples of their use in clinical practice. It should be noted, data on the prevalence of polymorphic variants of genes in the Ukrainian population are supplemented first of all step by step, theoretical foundation of medical genetics is being created, and certain levels of pathogenetic mechanisms are defining.

The creation of genetic databases will allow intensifying significantly medical studies. Systematization and registration of respondents forming groups of patients and population control group is going on using electronic documents that facilitates quick search, working with large data sets, adding additional inspection data, and research data in dynamics. The possibilities of using modern methods of statistical data processing, thorough analysis of frequency of distribution of polymorphic variants of genes in the general population and in selected groups of respondents also increase.

Standardization of methodical approaches to finding genetic markers of the most common diseases allows using modern certified reagents, test systems, and powerful scientific equipment. These factors significantly facilitate a scientific cooperation and interest in conducting joint researches on the collection and processing of data not only between research institutions, but also clinical genetics centers.

Creation of genetic monitoring system and identifying genetic markers of susceptibility to infectious agents and propensity to noninfectious origin diseases development will allow monitoring the level of morbidity in Ukraine by predicting the risk of developing certain pathological conditions, the nature and progression rate of pathological process, the formation of risk groups of possible morbidity since the childhood, and using effective prevention technologies. Development of targeted programs for early diagnosis and treatment taking into account a genetic predisposition will reduce the direct economic costs of medication, duration of outpatient and inpatient treatment by pharmacogenetic selection of main groups of drugs, decrease the incidence of complications and mortality level and will promote the introduction of individual strategies of preventive measures and improving health.

Ultimately, the prime importance of genetic databases is in the strategic direction of determining genetic markers of a number of common diseases that will be the basis for the conservation and sustainability of sanitary-epidemiological welfare of Ukraine. In our opinion, this achievement will bring a new level of basic and applied genetic researches in Ukraine and will deservedly contribute to increase the authority of our state among the scientific community.

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