

Novel information on the genetic factors involved in the development of diseases

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Abstract. Nowadays full-genome sequencing allows achieving revolutionary progress in the modern medicine. As the result of a huge work on the study of the human genome and based on the results obtained, one can conclude that the single nucleotide polymorphisms are the reasons of the vast majority of non-communicable diseases as well as the diseases other than injuries and poisoning, i.e. the diseases where the cause is not obvious. To clarify the role of single nucleotide polymorphism in the occurrence of atrophic gastritis, it is required to perform full-genome sequencing and human genome scanning with a simultaneous mass serological screening of atrophic gastritis. As a result, it will be possible to establish which single nucleotide polymorphism is responsible for mild, moderate, and severe mucosal atrophy in the antrum and the body of the stomach. Serological screening of mild, moderate, and severe mucosal atrophy in the antrum and the body of the stomach can be made using GastroPanel.

Key Words

Atrophic gastritis, Serological screening, Single nucleotide polymorphism, Population.

firm, a time trial begins in order to track down the source of the infection and prevent its spread. The method of full-genome sequencing allowed tracking down this episode in a couple of days¹.

Using the new technique, scientists were able to identify a gene transforming normal cells into cancer cells. A team of researchers from the Case Western Reserve University School of Medicine has identified a gene, the overexpression of which makes normal cells behave like cancer cells, by using the new method of verified insertional mutagenesis. The discovery of FAM83B gene was made using the model of breast cancer cells. During the observation of tumor formation, researchers were able to identify gene overexpression that turns normal cells into cancer cells, causing independent cell growth of mammary epithelial cells. The discovery of new oncogenes provides opportunities for the development of new drugs aimed at inhibiting the FAM83A gene in the patients having aggressive forms of cancer, which are too complicated for conventional treatment².

Materials and Methods

Introduction

Nowadays full-genome sequencing allows achieving revolutionary progress in the modern medicine. This technology helped specialists from the National Human Genome Research Institute in the US to cope with hospital infection. The method of bacterial genome sequencing successfully allowed us to track nosocomial pneumonia episodes. Gram-negative bacteria *Klebsiella pneumoniae* is the main cause of hospital infections, particularly among the immunocompromised patients. When the episode is con-

Singapore researchers have identified three new genetic polymorphisms associated with primary angle-closure glaucoma. Scientists from more than thirty research sites have conducted a genome-wide analysis of the DNA samples from five databases collected in Asia [1854 patients with primary angle-closure glaucoma, and 9608 subjects in the control group]. As the result three previously unknown loci on 8q chromosome associated with high risk of developing primary angle-closure glaucoma were identified: rs11024102 locus in PLEKHA7 gene, rs3753841 locus in COL11A1 gene and rs1015213 locus located between PCMTD1 and ST18 genes³.

The international team of researchers led by Janusz Jankowski, Professor of the Blizard Institute of Cell and Molecular Science at Queen Mary, University of London studied the genomic variants in 1852 British and other people suffering from Barrett's esophagus and compared their data with about 6,000 people that did not have the disease. As a result, they found two genetic determinants associated with this disorder. Two single nucleotide polymorphisms in the chromosomal regions 6r21 and 16q24 showed correlation with Barrett's esophagus. Based on the results of this study, scientists will be able to develop a system of genetic screening of the 35% of the UK population who complain of acid reflux. In one of each 5 subjects, it will be possible to predispose Barrett's esophagus and prevent the development of esophageal cancer⁴.

A large group of authors conducted the Genome-Wide Association Study (GWAS). It enrolled 7410 prospectively and retrospectively selected patients with severe osteoarthritis, as well as 11,009 people without osteoarthritis living in the UK who are not their relatives. We replicated the most likely areas of the genetic material in independent samples of 7473 patients with osteoarthritis and 42,938 people without the disease, received during a number of studies conducted in Iceland, Estonia, Netherlands and the UK. All the patients suffering from osteoarthritis and participants of the study without this disease were the Europeans. The strongest association with osteoarthritis was found for rs6976 gene variant on chromosome 3 being in complete disequilibrium linkage with rs11177 gene variant. This single nucleotide polymorphism [SNP] causes missense polymorphism in GNL3 gene responsible for nucleostemin production. Elevated nucleostemin level was observed in chondrocytes of patients with osteoarthritis during the functional studies. Another important site located in the FTO gene was involved in the regulation of body weight, which is a significant risk factor of osteoarthritis development⁵.

Meta-analysis of 15 cohorts of patients with ischemic stroke was conducted. It included a total number of 12,389 patients and 62,004 healthy subjects without the disease being in the control group [all the study participants were the Europeans]. For the associations that conform to the relevant criterion of genome-wide significance according to the METASTROKE study, additional analysis based on the single nucleotide polymorphism was conducted in each area associated

with the disease. The newly identified regions of the genome, presumably associated with the disease, have been replicated at 13,347 stroke patients and 29,083 study participants without the disease. Previously discovered genetic associations in the cardioembolic stroke have been confirmed for PITX2 and ZFHX3 genes, as well as associations of stroke caused by blockage of the large vessels in 9p21 locus and HDAC9 gene. In addition, it was confirmed that all the associations are typical for specific stroke subtypes. Conditional analysis of the three areas in which associations were complied with the criterion of genome-wide significance [PITX2, ZFHX3 and HDAC9] showed that all the important areas in each region could be associated with one haplotype, which increases the risk of disease. 12 new potentially significant loci were also revealed. However, none of these new associations could be replicated in the cohort of the subjects, in whom the genome was replicated. These results indicate that despite the possibility of the gene polymorphisms detection in the patients with ischemic stroke (compared with the control group) all the confirmed associations were typical for specific stroke subtypes. This result allows us to make two conclusions. Firstly, to maximize the success of genetic studies of ischemic stroke, one should select the stroke subtypes. Secondly, different subtypes of stroke are apparently caused by various genetic pathophysiological mechanisms⁶.

The purpose of the study conducted by the members of the Consortium of Psychiatric Genomics was to identify the specific genetic variations underlying common genetic mechanisms of five diseases: Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Bipolar Disorder, Major Depressive Disorder and Schizophrenia. Full-genome analysis of single nucleotide polymorphism was performed among 33,332 patients with these five diseases and among 27,888 healthy subjects from the control group [all the study participants were the Europeans]. In order to describe the effect of individual alleles in the development of each disease, we used multinomial logistic regression in order to identify the model that reflects the relationship between genotype and phenotype in the optimal way. Influence of the loci corresponding to the genome-wide significance and previously identified criteria among the patients with bipolar disorder and schizophrenia on the development of the mentioned mental illnesses was studied. In addition, a risk analysis of polygenic diseases was performed in order to

study the impact of a number of common genetic polymorphisms on these mental illnesses. The analysis of signaling cascades was performed in order to identify biological links underlying common genetic mechanisms of the development of all five diseases. Also in the postmortem samples of the brain tissue the expressive representation of quantitative trait loci [eQTL] was analyzed in order to identify the prevalence of the presented SNP in regulatory regions among the SNPs associated with the occurrence of the studied mental disorders. The primary analysis revealed four SNPs loci exceeding the genome-wide significance level: in chromosomal regions 3p21 and 10q24, as well in the genes encoding two subunits of voltage-gated L-type calcium channel [and CACNB2]. Analysis of the selected models confirmed the impact of these loci on the development of several diseases. Loci that were previously associated with schizophrenia or bipolar disorder had different diagnostic specificity. Associations between risk assessments of polygenic diseases and the studied disorders were identified, especially those emerging in the adulthood. Signal cascades analysis confirmed that calcium channels genes are involved in the development of all five diseases. Finally, the analysis of the postmortem brain tissue samples revealed that among the SNPs associated with the development of the studied psychiatric disorders eQTL markers were very common. The findings obtained suggest a strong association between the individual SNPs and the number of mental illnesses that occur among adults or children. In particular, calcium channel gene variations seem to have pleiotropic effects, causing the occurrence of various mental disorders. The obtained data can be used to transit from the describing system of psychiatric syndromes to the nosological classification of mental illness based on their causes. In addition, the researchers from the Max Planck Institute of Psychiatry in Munich have found that the trauma happened in childhood lead to the change in the regulation of DNA methylation. This violates the mechanism of the stress hormones production. The individuals having traumatic experience in the childhood were significantly more likely to develop depression and anxiety disorders during their life. In the process of the DNA analysis of 2000 African-Americans often experiencing serious traumatic events in their childhood and adulthood, it was noted that the development of posttraumatic stress disorder among these patients was associated with the

presence of the specific subtype of FKBP5 gene. FKBP5 gene determines the effectiveness of the body's response to stressful stimuli and controls the entire system of the stress hormones. Severe stressful event occurred in the childhood leads to epigenetic changes in the structure of gene and dysregulation of the stress hormones. However, epigenetic changes in DNA do not occur in all the individuals suffered serious childhood trauma, but only in those who have genetic predisposition to a particular violation in FKBP5 gene. This study contributes to a better understanding of the mechanisms of psychiatric diseases, as well as awareness of the differences between innate and acquired factors leading to this pathology. It is expected that the results of this research will help to choose correct methods of treatment for patients who experienced a severe stress situation in their childhood^{7,8}.

Reitz et al⁹ conducted a meta-analysis of data obtained from a survey that enrolled the African-Americans and found that Alzheimer's disease was often associated with the SNPs in ABCA7 and other genes that were common in the Europeans suffering from Alzheimer's disease. Majounie et al¹⁰ also confirmed the association of neurological disorders genes with amyotrophic lateral sclerosis (ALS).

It was possible to establish an association between the mutations in genes associated with prolongation of QT interval and previously unexplained cases of fetal death. Intrauterine fetal death occurs in one of every 160 pregnancies. At the same time, 25-40% of cases of fetal death cannot be explained by such factors as chromosomal abnormalities, fetal infection, fetoplacental insufficiency, or comorbidities of the mother. A recent study conducted by the Mayo Clinic explained some of the fetal deaths (previously considered idiopathic) by mutations in the genes responsible for the proper function of ion channels and cells associated with prolongation of the QT interval. In order to evaluate the effect of mutations of genes associated with QT interval prolongation syndrome on the fetal death, the researchers have analyzed genetic material received from 91 cases of intrauterine death resulted from the unknown factors. The average gestational age at the time of fetal death was 26.3 weeks. The use of liquid chromatography showed that three specific missense mutations in KCNQ1 and KCNQ2 genes (associated with prolonged QT interval syndrome) were present in 3 studied fetuses. Thus, the frequency of these mutations among

the deceased fetuses was 3.3%. The frequency of heterozygotes according to the mutations in the general population is 0.05%. In addition, researchers have discovered 5 rare mutations of SCN5A gene, allegedly causing poly arrhythmic violations in heart. Mutations associated with the syndrome of prolonged QT are also recorded in 10% children deceased from the sudden infant death syndrome. Such significant difference in the incidence of the syndrome of prolonged QT interval among the cases of embryo fetal death as well as among the children with the syndrome of sudden infant death and adult population substantiates the necessity for screening pregnant women for the presence of specific mutations¹¹.

The researchers at the Cardiff University and the Sanger Institute in Cambridge have found that every healthy person is a carrier of about 400 nucleotide polymorphisms, representing a potential threat to health, and 2 nucleotide polymorphisms directly associated with diseases. They showed that 1 out of every 10 participants in the study could develop a genetic disease as the result of carrying of such nucleotide polymorphisms. It is not the first decade when genetic specialists are aware of the fact that every human gene contains pathological variants of DNA that have almost no effect on health. The authors made the first quantitative assessment of the content of such variants in the genomes of healthy individuals. For doing this, they compared the information contained in the two databases: full-genome DNA sequences of 179 participants of the pilot project involving 1000 genomes with a low degree of probability of any obvious symptoms of the genetic diseases at the time of blood withdraw for the DNA analysis; and the detailed catalog of mutations associated with various human diseases described in the scientific literature. Figure of 400 will likely increase along with the increase in the efficiency of the methods for the SNPs studying. Conduction of such works raises ethical issues related to the anonymity of participation in genetic studies and casual findings. In many cases, pathological or damaged genes represent "recessive" genetic variants which have no influence on the health of the carrier as they are presented in combination with a normal copy of the gene. Destructive effects of recessive genetic variants occur only if there are two pathological genes - one in each pair of chromosomes. However, as it turned out, one out of every 10 participants in the study is a carrier of two copies of the recessive pathological changes of the same gene or a dominant abnor-

mal genetic variant. [Dominant genetic variants are those that can cause symptoms in the presence of even a single copy of the genome]. Clinical manifestations of genetic diseases in these people were either mild or completely absent. The researchers suggested that in case of their absence clinical symptoms may appear in the later stages of life. According to the authors, their results made it clear that even in normal healthy organisms many proteins can be represented by abnormal or even completely inactivated forms without any significant damage to the health. It is extremely difficult to predict the clinical effects of the presence of nucleotide polymorphism in each particular case. The only way to alleviate this problem is the further development of databases containing information associated with various diseases of genetic variants. Such databases have been developed in the past two decades. However, the work on their creation is far from the end. In general, abnormal genetic variants are quite rare and in many populations, their search had not been performed. The genetic material used in this study was collected anonymously, so the participants cannot get any information about the risk of development of certain genetic abnormalities. Such situations cause growing concern in the researchers because of their ethical ambiguity¹².

Results and Discussion

The project resulted in a multinational consortium of researchers called "1000 Genomes" and the standard distribution of the SNPs has been defined. As a part of this work, we have sequenced the genomes of 1092 representatives in 14 different populations. The ultimate goal of this five-year study was to provide biologists and clinicians with the information that will help them to understand the spectrum of normal nucleotide polymorphisms that make up human genome. This in its turn will interpret the information contained in the genome in a wider context. The analyzed populations were selected based on their migration history and genetic relationship with each other. Healthy donors, that were not relatives, were randomly selected in each population. Cells lines precursors suitable for endless storage and reproduction were isolated from the collected blood samples. DNA was sequenced using isolated cells and the data obtained was listed in public databases. After the sequence of

the first sequenced human genome was published in 2003, it became clear that contrary to the traditional view, 98.5% of human genetic material does not encode proteins. The scientists are currently familiar with the function of a number of non-coding regions of the genome, but most of the genetic sequence is still an enigma. There is a reason to believe that at least part of genetic material is responsible for variability and susceptibility to disease. Nucleotide polymorphisms identified in the representatives of the analyzed populations were divided into the categories depending on the frequency of occurrence. Variants detected in more than 5% of the samples were considered as common, in 0.5-5% of the samples – as less common, and in less than 0.5% of the samples – as rare. 14 analyzed populations were divided into 4 groups: the Europeans, Africans, East Asians, and Americans. As was expected by the researchers, the majority of common variants were previously identified, with a little variation of their frequency depending on the origin of the group. In contrast, 58% and 87% of less common variants were described for the first time. In some cases, rare variants occurred in a particular population twice more common than in the wider group, including this population. A different number of rare variants was identified in different populations. Their greatest variety was typical for the Spanish, Finnish and African-American populations. It was a total surprise that in case of some rare variants the study participants were healthy carriers of 130-400 gene variants changing the structure of protein molecules; 10-20 gene variants depriving the ability of proteins encoded by them to perform their essential function; 2-5 gene variants that violate protein function; and 1-2 variants associated with malignant tumors. This means that healthy people, regardless of ethnic origin are the carriers of approximately the same amount of rare gene variants being harmful to health.

According to Aravinda Chakravarti, Professor from the Johns Hopkins University and one of the study leaders, there are several factors that ensure the survival of people despite the presence of so many errors in their genomes. One of the mechanisms is that, despite the presence of two variants of each gene, our body needs only one normal gene variant for the normal life. Another factor is the presence of “reserve” genes in our genome. In some cases, these “reserve” genes can compensate the effects of a nonfunctional protein. The first phase of “1000 Genomes” proj-

ect was completed in 2008. It was planned as a preliminary study of the genomes sequenced for the second phase of the project and demonstrated the feasibility of the search of genetic markers of various diseases. As a part of the final phase of the project, it is planned to sequence the genomes of another 1,500 people from 11 previously uncovered populations. The project has involved more than 100 scientists from 111 research sites all over the world¹³.

As a result of a huge work on the study of the human genome and based on the results obtained it can be concluded that single nucleotide polymorphisms are the reason of the vast majority of non-communicable diseases. And of course, the role of prevention of conditions that can be avoided becomes apparent for timely prophylactic measures.

This finding allows Juengst E.T., Flatt M.A., Settersten R.A. Jr. to make a conclusion that genetic medicine can cause patients to change their lifestyle. It is possible that patients will become more responsible for their own health. The introduction of genetic medicine could markedly change the standard approach to the treatment. Its widespread acceptance will lead to the fact that patients will be able to self-monitor their own health. Gene diagnostics allows assessing the pharmacogenomic information, which is the reaction of the patient to a particular therapy and genetic susceptibility, showing the probability in which patient is exposed to the disease. Supporters of genomic medicine (from private research centers to the National Institute of Health) are interested to deliver this information to patients. Although the question of how the results of gene diagnostics can affect patient and his attitude to their own health remains open. Pharmacogenomic information can make people follow your doctor’s instructions more closely, as the results of the molecular analysis can make the prescriptions more accurate and authoritative. Genetic medicine allows revealing a significantly larger amount of risks for the patient, which is a key factor in the treatment of diseases and general health assessment. The benefits of genetic susceptibility studies can be misinterpreted. Nowadays the use of genomic data allows only calculating the risk of some disease in the group of people. Often, the division into groups by ethnic or racial factors does not allow determining the likelihood of developing the disease in every particular patient being in the risk group. Also, we can note that the development of the disease is often determined

by a person's lifestyle. The role of the physician is to point to the potential risks while much of the responsibility for the occurrence of the disease is on the patient. Thus, the use of the data of gene therapy in medical practice leads to "delegation of powers" from the physician to the patient. Experts point out that further studies are necessary to determine whether the data of gene diagnostic can encourage patients to adopt a healthier lifestyle¹⁴. Recent advances in genetics suggest that single nucleotide polymorphisms can cause any diseases other than infectious diseases, as well as those caused by obvious reasons [trauma, poisoning, etc.]. However, the reasons of single nucleotide polymorphism are not clear. This individual SNPs could be inherited from parents (i.e. it has an inherited nature), it could also appeared in an individual's life (i.e. it has an acquired character). In order to clarify this, one needs to conduct special studies to identify a particular single nucleotide polymorphism in the genome simultaneously in healthy and diseased cells of the affected organ in particular human diseases, such as Barrett's esophagus or breast cancer. If such nucleotide polymorphisms are detected in diseased cells and cells still being normal, as well as in normal cells of other organs and tissues of the individual, it is likely that nucleotide polymorphism is inherited. If the nucleotide polymorphism is detected only in the affected cells of the patient's body while it is not detected in other cells of the individual, we can say that nucleotide polymorphism possibly has an acquired character.

Conclusions

To clarify the role of single nucleotide polymorphism in the occurrence of atrophic gastritis, it is required to perform the full-genome sequencing of the human genome with a mass simultaneous serological screening of atrophic gastritis. As a result, it will be possible to establish which single nucleotide polymorphism can cause mild, moderate, and severe mucosal atrophy in the antrum and the body of the stomach. Serological screening of mild, moderate, and severe mucosal atrophy in the antrum and the body of the stomach can be performed using GastroPanel¹⁵⁻¹⁹.

Conflict of Interests

The Authors declare that they have no potential conflict of interests.

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