GENERAL NOTIONS OF GENETIC EPIDEMIOLOGY REGARDING THE COMMUNICABLE DISEASES

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Abstract: *In the last two centuries, many observations have been gathered that pleaded for the existence of individual variations in the responsiveness or resistance to certain infections. Each individual has a unique genetic structure, made up of a huge and complex mixture of different kinds of genes that make up the human genome. Some variants may be associated with responsiveness to certain diseases, others produce resistance.*

Keywords: *epidemiology, genetics, cystic fibrosis, HLA genes*

Rezumat: *În ultimele două secole, s-au acumulat numeroase observaţii care pledau pentru existenţa unor variaţii individuale în receptivitatea sau rezistenţa la anumite infecţii. Fiecare individ are o structură genetică unică, formată din mixajul enorm şi complex al diferitelor variante ale genelor care alcătuiesc genomul uman. Unele variante pot fi asociate cu receptivitatea la anumite boli, altele produc rezistenţă.*

Cuvinte cheie: *epidemiologie, genetică, fibroză chistică, genele HLA*

INTRODUCTION

Genetic epidemiology is a new combination of epidemiology and genetics, which studies the diseases with complex etiology.

Having in view that its ultimate goal is the control and prevention of the frequent diseases, genetic epidemiology will play a predominant part in public health practice.

Genetic epidemiology was born in 1960 through a merger of several sciences: population statistics, classical genetics and molecular epidemiology. The pioneers of this new science were: Newton Morton, Douglas Falconer, Robert C Elston, Elizabeth A. Thompson and Neil Risch.

Studies of genetic epidemiology regarding the role of inheriting the causes of disease aim at detecting the inheritance pattern of a particular disease, gene locus and at finding a marker associated with disease susceptibility. Gene-gene and gene-environment interactions are also studied by genetic epidemiology.

Cohort studies and case-control studies can be used to assess genetic factors regarding the disease. There are several reasons: 1) unlike biological markers (e.g. occupational exposures, nutrition), genetic markers are stable indicators of host susceptibility, 2) case studies-control can provide an opportunity to review the effects of several genes, together with other risk factors, 3) case-studies are suitable to control many less common diseases, such as birth defects and cancer.

Two types of genetic markers can be used in epidemiological studies: markers, based on the encoded gene products, such as specific blood groups, HLA antigens, proteins and enzymes, and markers based on the direct analysis of the DNA. The assessment of the role of the genetic factors in the etiology of the disease generally refers to the "candidate gene", which examines the genetic variation in the known loci or in those suspected to play a part in the pathogenesis of the disease.

For example, in a case-control study of labio-palatine cleft, Ardinger et al. (1989) examined the differences of DNA markers from several selected candidate genes, suggesting the part played in the formation of the palate in rodents. By comparing 80 nonsyndrom cases, which had a lip-palate cleft and 102 control subjects, the authors have found an association between the genetic variation and the splice in the transformation of the growth factor alpha gene. Although, this association is modest in magnitude, it suggests that this gene plays an important part in the lip-palate cleft etiology in humans. Another example is the assessment of the association between the Alzheimer's disease and Apolipoprotein E (apo-E), alela E4. Evidence suggests that apo-E, alela E4 is strongly associated with late onset of the familial Alzheimer's disease and even more with the sporadic cases of the Alzheimer's disease. Regarding the families with increased risk of late debut of the Alzheimer's disease, it was proved that the risk increases with the number of E4 alleles. 47% of heterozygotes for E4 alleles and 91% of homozygots people for E4 alleles proved to be affected. The risk rates for heterozygots and homozygots were 2-8 and 8-1.

Numerous risk factors, such as smoking, alcohol consumption, obesity, physical inactivity and genetic factors are partly responsible for familial aggregation.

There were identified many genes associated to an increased receptivity to the pathogen microorganisms. Infections with various pathogens have shaped the human genome variability of today, for example cystic fibrosis, a genetic disease with autosomal recessive transmission.

Persons affected present various events, as a result of the exocrine glands dysfunction (intestine, pancreas, liver, mucous glands of the lungs, perspiratory glands). Cystic fibrosis is a common disease among the Caucasian population (1:2500 newborn babies), because in this population, 1:25 individuals is a heterozygote. They are healthy people but bearers of abnormal genes. Once the gene that brings about the disease is located on chromosome 7 and CFTR protein that forms a channel for chloride ion is identified, it is established that that Salmonella typhi uses this protein as a receptor to enter the intestinal epithelial cells. Although, there have been no final arguments, yet, it is assumed that heterozygots' selective advantage for cystic fibrosis was brought about by their resistance to typhoid fever (by altering the CFTR protein as a result of mutation).

The vulnerability of different individuals to microorganisms has been demonstrated through the methods of classical genetics: the study of different families and populations, the study of twins and adopted children. Some infections have a familial aggregation and are not necessarily correlated with the exposure to the pathogen. It is logical to assume that vulnerability genes are transmitted in the same family, and the study of leprosy, tuberculosis and other common diseases has led to the idea of a multifactorial model in which the I degree relatives have a risk of 2-5 times higher in comparison with the general population. These studies are accompanied by the studies of the differences in responsiveness to certain infections, regarding the different populations or ethnic groups, particularly tuberculosis. These are explained by the fact that each population has a common pool of genes, so including variability genes. Twin study is based on an assessment of the consistency monozygotic twins (with the same heredity) versus dyzygotic twins (with different heredity). Analysis of infections such as hepatitis B, tuberculosis, dropsies, polio and, more recently, the infection with Helicobacter pylori revealed a greater coefficient of concordance of the disease, regarding the monozygotic twins than the dyzygotic ones.

Certain studies have identified different gene variants (alleles) statistically significantly correlated with the vulnerability or resistance to certain infections.

The HLA (Human Leucocyte Antigens) is a multigenic and multifunctional system that plays an essential part in initiating and regulating the immune response. Component genes located on the short arm of the 6 chromosome (6p21.3) are grouped into three classes of genes:

- HLA class I gene (genes A, B, C and others) encode the glycoproteins expressed on the cell nuclei, for self and non-self recognition;
- HLA class II genes (DR, DP, DQ and others) encode the proteins expressed only on the surface of the antigen presenting cells, which have a crucial part in the cell cooperation regarding the immune response;
- HLA class III genes encode different proteins: complement, tumour necrosis factor etc.

Cytokine genes. Uncoding and understanding the regulating role of the different cytokines in the immune defence have led to the analysis of genes that encode them in various infections. The first studies concerned the gene for tumour necrosis factor (TNF), located in the HLA class III area. Increased production of TNF α or β, as a result of specific mutations in the gene promoter (a region with a regulating part regarding transcription and thus, of the TNF synthesis) was associated with responsiveness to trachoma or cerebral malaria in Africa, skin leishmaniasis in South America or persistent infection with hepatitis B virus in Europe.

Chemokine receptors. It has been recently discovered that for some chemokine receptors (CCR5 and CCR2) act as co-receptors for the invasion of macrophages and lymphocytes by HIV. Different mutations of genes for these receptors may alter the responsiveness capacity to the HIV infection and the disease progression to AIDS.

Mannose-binding lectin (MBL). Mannose-binding lectin is a serum protein, involved in immunity through two mechanisms:

1. are attached to carbohydrates (mannose and N-acetylglucosamine) on the surface of the microorganisms and facilitate their macrophages destruction;
2. activate the complement.

Inactivated mutations of this gene produce a substantial fall in the serum concentration of MBL and predispose to various infections with pneumococcus, meningococcus etc.

Natural resistance-associated macrophage protein (NRAMP I). The study of certain mouse lines, responsive to the infection with Salmonella, Leishmania, and certain mycobacteria, led to the identification of a major gene: natural resistance-associated macrophage protein (NRAMP I). Subsequently, the NRAMP I homologue of this gene was identified in humans, as well and it was established that some variants were associated with responsiveness to severe pulmonary tuberculosis in West Africa.

Anticipating the evolution for the next 5-10 years:

- The identification of the genetic factors that influence the prognosis of the disease is expected to be the greatest clinical relevance;
- The genetic study of the complex features will continue to identify specific genes, each representing only a small fraction of all cases;
- The relations between the genes known with risk factors will be clarified, allowing evidence-based preventive action in the people with high genetic risk and a better quantification of the risks in family members;
- The greatest progress will be made so that to understand the genetic contribution in the case of the intermediary phenotype regarding the relation between genes and disease and thus, the biology of disease, such as in the atherosclerotic disease.

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