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Pregledni članak

GENE–ENVIRONMENT INTERACTION: A GENETIC-EPIDEMIOLOGICAL APPROACH

INTERAKCIJA GEN–SREDINA: GENETSKO-EPIDEMIOLOŠKI PRISTUP

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Summary: Classical epidemiology addresses the distribution and determinants of diseases in populations, and the factors associated with disease causation, with the aim of preventing disease. Both genetic and environmental factors may contribute to susceptibility, and it is still unclear how these factors interact in their influence on risk. Genetic epidemiology is the field which incorporates concepts and methods from different disciplines including epidemiology, genetics, biostatistics, clinical and molecular medicine, and their interaction is crucial to understanding the role of genetic and environmental factors in disease processes. The study of gene–environment interaction is central in the field of genetic epidemiology. Gene–environment interaction is defined as »a different effect of an environmental exposure on disease risk in persons with different genotypes,« or, alternatively, »a different effect of a genotype on disease risk in persons with different environmental exposures.« Five biologically plausible models are described for the relations between genotypes and environmental exposures, in terms of their effects on disease risk. Therefore, the study of gene–environment interaction is important for improving accuracy and precision in the assessment of both genetic and environmental factors, especially in disorders of less defined etiology. Genetic epidemiology is also applied at the various levels of disease prevention.

Keywords: genetic epidemiology, gene–environment interaction, prevention

Kratak sadržaj: Klasična epidemiologija se bavi izučavanjem distribucije i determinanti bolesti i faktora koji doprinose njenoj pojavi s ciljem da se bolest prevenira. Kako genetski tako i faktori sredine mogu doprineti tome da osoba bude podložna datoj bolesti, ali se još uvek nedovoljno zna o njihovim interakcijama i uticajima na rizik od oboljenja. Genetska epidemiologija inkorporira koncepte i metode različitih disciplina, uključujući epidemiologiju, genetiku, biostatistiku, kliničku i molekularnu medicinu, što ima ključnu ulogu u razumevanju zajedničkih uticaja genetskih i sredinskih faktora u procesu nastanka bolesti. Izučavanje interakcije gen–sredina zauzima centralno mesto u genetskoj epidemiologiji. Definiše se kao »različit efekat izloženosti faktorima sredine za pojavu bolesti u osoba sa različitim genotipovima«, ili, ekvivalentno, kao »različit uticaj genotipa na rizik od bolesti u osoba sa različitom izloženošću faktorima sredine«. Opisano je pet biološki prihvatljivih modela koji povezuju genotipove i izloženost faktorima sredine u smislu njihovih zajedničkih efekata na rizik od bolesti. Proučavanje interakcije gen–sredina doprinosi povećanju tačnosti i preciznosti procene uloge genetskih i faktora sredine, posebno kod zdravstvenih poremaćaja čija etiologija nije dovoljno poznata. Genetska epidemiologija igra značajnu ulogu na različitim nivoima prevencije bolesti.

Ključne reči: genetska epidemiologija, interakcija gen–sredina, prevencija

Introduction

Classical epidemiology addresses the distribution and determinants of diseases in populations, and the factors associated with disease causation with the aim of preventing disease. Both genetic and environmental factors may contribute to susceptibility, and it is still unclear how these factors interact in their influence on risk of disease. Therefore, genetic epidemiology is defined as the study of the role of genetic factors and their interaction with environmental factors in the occurrence of disease in human populations (1). Genetic epidemiology is the field which incorporates concepts and methods from different disciplines including epidemiology, genetics, biostatistics, clinical and molecular medicine, and their interaction is crucial to understanding the role of genetic and environmental factors in disease processes (2).

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The three basic steps are included in a genetic epidemiologic research: a) establishing that there is a genetic component of the disorder; b) establishing the relative size of that genetic effect in relation to other sources of variation in disease risk (environmental effects such as physical and chemical effects, as well as behavioral and social aspects); c) identifying the gene(s) responsible for the genetic component.

Genetic epidemiology is a young but rapidly expanding research field, although the implications of findings from such studies for individual or population health are still unclear (3). Many developments have contributed to the rapid growth of genetic epidemiology in the past decade. Extensive information about the human genome can now be included in genetic epidemiology studies (4, 5). Technological and other advances will allow the establishment of large population-based resources for such studies, such as biobanks.

Gene–environment interaction

Gene–environment interaction is defined as »a different effect of an environmental exposure on disease risk in persons with different genotypes,« or, alternatively, »a different effect of a genotype on disease risk in persons with different environmental exposures« (6). The essential in the gene–environment interaction is that the risk of disease which is conditioned by mutations or a genetic polymorphism might by modified by exposure to environmental risk factors. Therefore, the study of the gene–environment interaction is central in the field of genetic epidemiology. Additionally, this is important for improving accuracy and precision in the assessment of both genetic and environmental factors, especially in disorders of less defined etiology. However, it is also important to underline that in a case when an environmental factor causes gene mutation, gene–environment interaction is not necessarily present. In some disorders, mutation determines risk of disease without any influence of environmental factors.

Ruth Ottman (6, 7) defined the five biologically plausible models which described the relationships between genotypes and exposure to environmental risk factors, in terms of their effects on disease risk.

In model A, the effect of the genotype is to produce, or increase expression of an environmental risk factor, i.e. the genetic susceptibility does not cause disease directly, but acts by increasing the level of expression of the risk factor.

In model B, the genotype intensifies the effect of the environmental risk factor, but there is no effect of the genotype in unexposed individuals. In that situation the genetic susceptibility has no effect in the absence of the environmental risk factor, but the risk factor can act by itself to increase risk of disease.

In model C, the exposure to the environmental factor aggravates the effect of the genotype, but there is no effect of the exposure in individuals with the low-risk genotype.

In model D, neither the genetic susceptibility nor the risk factor can influence disease risk by itself, but risk of disease is increased when both are present.

In model E, environmental exposure and genotype each have some effect on disease risk, and the combined effect of the two may be different from the effect of each acting alone.

In order to test these models, several genetic and epidemiological studies can be used, such as studies of genetic markers, segregation analysis, case-control and cohort studies.

Some methodological aspects of genetic epidemiological studies

Case-control studies are the most commonly used design to evaluate the gene–environment interaction, and they are particularly useful for common exposures and genotypes (8). In these studies an exposure is classified as being either present or absent, and the underlying susceptibility genotype is also classified as present or absent. In these conditions the genotype could reflect the presence of one or two alleles at one locus or a combination of alleles at multiple loci. The reference group in the calculation of odds ratio (OR) should comprise unexposed subjects with no susceptibility genotype (*Table I*).

There are several possible problems in case-control design in genetic epidemiology (8). The case

Table I Calculation of odds ratio in gene–environment interaction analysis by using a case-control study.

Exposure	Susceptibility genotype	Cases	Controls	Odds ratio (OR)
absent	absent	A– –	B– –	OR=1.0*
absent	present	A–+	B–+	OR–+=A–+B– –/A– –B–+
present	absent	A+–	B+–	OR+–=A+-B– –/A– –B+–
present	present	A++	B++	OR++=A++B– –/A– –B++

* Reference group

group should be representative for all cases. Inclusion of those identified at a hospital clinic may not be appropriate, especially if the disease requires medical attention only in some cases. Therefore, recruitment from a hospital will be selective, usually for severe cases. Additionally, if there is a survival effect of the disease (for example, in Alzheimer's disease and ApoE), and if the associated allele also modifies the risk of death from competing causes, the age-dependent frequencies will be different.

The controls should be comparable to cases except for having the disease. Local, contemporary controls should be selected via the same routes as the cases. Furthermore, the age- and sex-matching (by frequency or one-to-one) of cases and controls becomes particularly important.

One potential problem is that the estimates of genetic effect are subject to confounding when cases and controls differ in their ethnic backgrounds (population stratification bias or confounding by ethnicity). This can occur when both disease risk and genetic mutation frequencies vary among ethnic groups. To avoid the problem of population stratification bias, matching of cases to controls on ethnic background can be used (9).

The pitfalls of conventional epidemiologic studies such as selection bias, information bias and confounding are equally obvious in genetic epidemiological research (10–12). Therefore, special attention has been paid to the confounding control measures in these studies. Restriction and matching provide protection against confounders in the design of case-control studies, while stratification analysis and mathematical models such as logistic regression should be used to avoid confounding in the data analysis (13).

Applications of genetic epidemiology in prevention

Genetic epidemiological research contributed to a better understanding of the etiology of different diseases, especially common multifactorial disorders or complex genetic diseases that are likely to result from the interaction of genes and the environment. The identification of previously unknown proteins involved in disease pathogenesis will enable the development of new diagnostic tests and investigation of protein targets for drug development (14, 15). Besides that, this concept also has important implications for predicting disease rates and consequently, for all three levels of disease prevention.

A genetic example of primary prevention would be screening programs to detect carriers of disease in high-risk populations. Classical model of secondary prevention is the screening of newborns for congenital anomalies, resulting in early intervention. Finally, tertiary prevention is concerned with minimizing the effects of disease by preventing complication and deterioration (16–18).

In recent years, genetic screening provided most of the opportunities for a potential interaction between genetics and epidemiology. Genetic screening can take several forms, such as recessive carrier screening, recessive disease screening, autosomal dominant disease screening, pharmacogenetic risk screening, employment risk screening, and complex genetic disease screening (3).

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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