How to search for the role of gene-environment interactions for lipids in humans

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To target the interventions to the requirements of the individuals we need to identify the genes and the alleles which show variations in response pattern. For example, a lipid-lowering diet is effective for most people, but not so for everyone. The search for genetic polymorphisms that affect the response of LDL cholesterol to diet in humans has been disappointing up till now, and is the first hurdle to take. In addition, it should be realized that the phenotype of serum lipid is not only indicated by the blood level, but is multifaceted.

A complication of gene-environment interactions is that in the chain of environmental factor, intermediate phenotype, and pathogenetic process we have the possibility of genetic variability at all levels.

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Introduction

The response to environmental factors is variable among individuals and we can usually distinguish three types of response as depicted in figure 1. Here the "normal' responses in individuals with the alleles A and B are similar, starting from a difference in level that is maintained (Fig. 1A); the allele C shows an increased response and can be denoted as hyper response allele (Fig. 1B); the allele D shows a poor response and can be denoted as poor response allele (Fig. 1C). We are particularly interested in the alleles C and D since the carriers of the hyper response genotype may benefit more from intervention and the poor responders will not respond very much to intervention in the environmental factor at all.

It is thus obvious that there is a desire to identify the genes and the alleles of the hyper and poor responding types to target the interventions to the characteristics of the individuals. At the same time the mechanisms of risk become more apparent and help to identify the individuals at risk and to design the prevention strategy.

Low-density lipoprotein cholesterol

One of the environmental factors affecting lipids is diet, and a lipid-lowering diet which is low in dietary cholesterol and saturated fat is frequently used to normalize

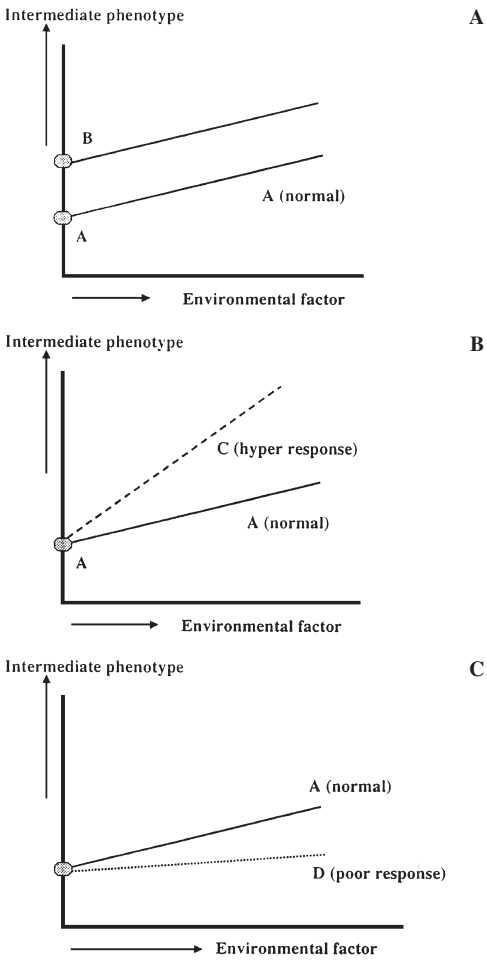

Figure 1. *Patterns of response of an intermediate phenotype or analyte (for instance blood LDL cholesterol) to an environmental factor (for instance fat).* A: *allele A is the wild type allele; allele B exemplifies coding for a higher level only.* B: *allele C codes for stronger or hyper response to the environmental factor.* C: *allele D codes for poor response to the environmental factor.*

increased lipid levels. However, even though a lipid-lowering diet is effective for most people, it is not so for everyone.

The search for genetic polymorphisms that affect the response of LDL cholesterol to diet in humans has been disappointing up till now. A summary of the data for traditional lipid candidate genes and polymorphisms (10 genetic polymorphisms in ApoA1, ApoA4, ApoB, ApoE, and colesteryl ester transfer protein) only reveals a small effect of these genetic polymorphisms on serum lipid response to diet[1]. Thus the identification of better candidates is the major hurdle to overcome and the increased knowledge about our genome and the ability to generate genotypes will facilitate this research.

It is essential to select functional polymorphisms that are involved in response variability (the C and D type of alleles in figure 1B and 1C) and to demonstrate in experimental studies the responses in well defined genotype groups.

However, although lipid levels are strongly heritable, the fear is that not a few important major contributions exist but that numerous genes with a small contribution are involved in the complex phenotype of serum lipid concentrations[2]. In addition, besides the involvement of lipid genes also hormones and the mechanisms involved in obesitas and insulin resistance are contributory.

Not only low-density lipoprotein cholesterol

It should be realized that the phenotype of serum lipid is multifaceted. Lipids appear in multiple forms and compositions; regulation involves various enzymes, receptors and apolipoproteins; lipid particle size may be of relevance; in blood these particles are amenable to modification such as oxidation and glycation; lipid particles carry various proteins (e.g. serum amyloid A, paroxanase, factor XIIa, thrombin activatable fibrinolysis inhibitor) and participate in multiple pathways suggested to be of importance in the pathogenesis of atherothrombosis. Lipid levels can show temporary changes, such as in the post-prandial phase which quantitatively and qualitatively may be of relevance above the basal level. It is important to define carefully the analyte or intermediate phenotype including apolipoprotein, LDL cholesterol, HDL cholesterol, triglyceride-rich lipoproteins, small dense LDL, lipoprotein(a) or oxidized or glycated LDL for which a pathogenetic role has been implied. When selecting analytes such as oxidized or glycated LDL the genes that may be involved in hyper and poor response are likely of oxidation- and glycation-related processes and possibly less so of lipid metabolism. The incorporation of non-lipid processes such as oxidation is introducing roles for other environmental factors and other possibilities of intervening with such processes.

In addition to the selection of a specific intermediate phenotype the selection of the disease process should be detailed and involve the pathogenetic mechanism in which the selected analytes participate as a significant element. In practice the clinical and epidemiological studies involving genetic analyses will be more demanding than usually in both laboratory diagnosis and documentation of pathogenetic processes. The move from syndromes to specific disease processes is essential in genetic studies and different genes may be important in different mechanisms[3,4].

Total approach includes also genetics of the environmental effect and pathogenetic process

The discussion of environment-gene interaction for intermediate phenotypes is only part of the discussion needed for individual targeting or treatment. In the chain of "environmental factor → intermediate phenotype → pathogenetic process", we also have to deal with genetics in the effectiveness or bioavailability of the environmental factor and with the genetics of the susceptibility of the vascular pathogenetic process for the effects of the intermediate phenotype.

A recent example of an environmental factor being sensitive to genetic variability for its effect concerns alcohol. The effect of alcohol on HDL levels appeared closely linked to the rate of alcohol metabolism[5]. Here genetic variation in alcohol dehydrogenase modulates the effect of the environmental factor and it implies that recording environmental factors alone is not sufficient in all cases.

Conclusion

Among lipid intermediate phenotypes several candidate analytes are of relevance from the point of view of pathogenetic hypotheses, and should be evaluated separately. The search for the role of gene-environment interactions for these lipid analytes in humans is presently primarily in need of identification of candidate genes with significant quantitative effects and clearly defined functional polymorphisms involved in response variation. For results applicable to individual treatment the genetics of effectiveness or bioavailability of environmental factors and the susceptibility of the vascular pathogenetic process for the intermediary phenotype should be included in the total evaluation.

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