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Review

Mendelian randomization: Its impact on cardiovascular disease

Masa-aki Kawashiri (MD, PhD, FJCC)*, Hayato Tada (MD, PhD), Akihiro Nomura (MD, PhD), Masakazu Yamagishi (MD, PhD, FJCC)

Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

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ABSTRACT

Cardiovascular diseases and their risk factors are inheritable. Single nucleotide polymorphisms in the human genome are found in around 1 in 1000 base pairs, and this may affect the genetic variety of individuals. During meiosis, any genetic information is randomized and is independent of other characteristics. In a Mendelian randomization study (MRS), a genetic variant associated with biomarker is used as a proxy for the biomarker, and the outcomes are compared between the groups harboring the effect alleles and a group with the reference allele.

An MRS using variants of both rare and modest effect sizes and variants of common and lower effect sizes provides an understanding of risk factors and their causality of cardiovascular disease; for example, an individual possessing an allele associated with lower low-density lipoprotein cholesterol (LDL-C) exhibits lower risk of coronary artery disease (CAD). Moreover, the log-transformed reduction rates of CAD are linearly correlated with the reduction value of LDL-C. High-density lipoprotein (HDL) removes cholesteryl esters from peripheral tissues, including atherosclerotic plaque to the liver. Numerous epidemiological studies have shown that HDL-cholesterol (HDL-C) levels are inversely associated with the frequency of the occurrence of CAD. However, genetic variants, which are only associated with higher HDL-C levels, do not decrease the frequency of myocardial infarction. This fact shows that HDL-C level is not a cause but a biomarker of CAD.

Discoveries of rare variants in Mendelian disorders resulted in the successful development of drugs for the general population. An MRS may also predict the pharmacological effectiveness and adverse side effects of novel drugs targeting specific molecules. An MRS could become a standard process to be performed before the development of novel drugs. Furthermore, future guidelines for the prevention of CAD should consider the genetic information of individuals, which will result in precision medicine for cardiovascular diseases.

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* Corresponding author at: Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa, 920-8641, Japan.
E-mail address: mk@med.kanazawa-u.ac.jp (M.-a. Kawashiri).

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Introduction

Coronary artery disease (CAD) and consequent sudden cardiac death and heart failure have long been the number one cause of death in the developed world, especially in Western countries [1]. The Framingham Heart Study that was initiated in 1948 was designed to seek a single essential cause of atherosclerotic cardiovascular disease (ASCVD). However, it soon became apparent that the etiology of ASCVD was multifactorial, and these factors were coined as "risk factors" by the Framingham Heart Study [2]. The Hisayama Study also found similar "risk factors" of CAD in Japanese populations [3]. To date, multiple risk factors for CAD have been identified by many epidemiological studies. However, they are not always the causes of CAD but merely the incidental occurrences.

For example, an association between having a cigarette lighter in the chest pocket and lung cancer is entirely confounded by smoking, and the lighter itself is not a carcinogen. Although the plasma ascorbic acid concentration was inversely related to mortality from cardiovascular disease, its supplementation failed to reduce the risk of cardiovascular mortality. This inconsistent result may have been derived from confounding factors such as socio-economics and a lifestyle habit; for example, people who ingest large amounts of ascorbic acid may have a habit of getting adequate exercise. Even though known confounding factors can be corrected, it is impossible to correct all the "unknown" confounding factors.

A prospective, randomized, double-blind, placebo-controlled trial is the sole method to prove the effects of a specific pharmacological therapy. However, this method takes a long time, huge effort, and a large amount of funding to get an appropriate result. In addition, it sometimes may be impractical or unethical in clinical studies to randomize patients to interventions. Recently, an MRS has been developed to detect the causality between a risk factor and an outcome. In this review article, the impact of an MRS on cardiovascular disease is discussed along with some examples.

Risk factors for CAD

Atherosclerosis is characterized by the subendothelial accumulation of cholesterol and involves a complicated cascade of chronic vascular inflammation. Hyper low-density lipoprotein (LDL) cholesterolemia is the most prognostic and primary risk factor for CAD. LDL is a carrier lipoprotein of cholesterol from the liver to peripheral tissues: therefore, it is reasonable that LDL-cholesterol (LDL-C) levels are positively associated with the frequency and severity of CAD. Several pharmacological and non-pharmacological studies about lowering LDL-C were carried out to reduce the occurrence of cardiovascular events, and most of them succeeded in reducing them according to the achieved LDL-C levels. These facts may suggest that cholesterol is a fundamental "causal" risk factor of CAD.

Conversely, epidemiological cohort studies revealed that the frequency of the occurrence of CAD is inversely and independently associated with the serum levels of high-density lipoprotein (HDL)-cholesterol (HDL-C). HDL removes cholesterol from peripheral tissues, including atherosclerotic plaque to the liver (reverse cholesterol transport system): therefore, it is believed to be anti-atherosclerotic. Elevated blood pressure, impaired glucose tolerance, and smoking are also recognized as traditional risk factors for CAD. However, the interventional approaches to these risk factors are not always successful in reducing cardiovascular events.

The principle of the MRS

Single nucleotide polymorphisms (SNPs) are defined as variants in deoxyribonucleic acid (DNA) sequences, the frequency of which is estimated to be more than 1% in the general population. SNPs in the human genome are found in around 1 in 1000 base pairs, and this may affect the genetic variety of individuals. It may also affect the occurrence of disease or quantitative varieties of blood levels of any biomarkers. During meiosis, when DNA is transferred from parents to children at the time of gamete formation, genetic information is randomized through an assortment of alleles (Fig. 1). In other words, the inheritance of any genetic variants in an individual's DNA is independent of other characteristics. Thus, individuals in a population could be divided by genotype that is associated with a difference in a biomarker, and those individuals should be similar in all aspects except for one particular biomarker.

The first MRS was described by Katan in 1986 [4]. In the article, Katan investigated the relationship between hypocholesterolemia and cancer observed in a cohort study using the genetic variant in the *APOE* locus, which is strongly associated with the plasma cholesterol level. There were several possibilities about how hypocholesterolemia was associated with cancer: (1) hypocholesterolemia itself was a cause of cancer, (2) cancer was a cause of hypocholesterolemia (reverse causality), and (3) there were confounding factors between hypocholesterolemia and cancer, such as smoking (confound). If hypocholesterolemia itself is causally related to an increased risk of cancer, apolipoprotein E2 carriers, which are strongly associated with hypocholesterolemia, are hypothesized to have a higher risk of cancer. Actually, subjects with the lowest third of plasma cholesterol levels at baseline had an increased risk of cancer incidence and mortality from cancer, relative to subjects with the highest third of plasma cholesterol. However, apolipoprotein E2 carriers did not have a higher risk of cancer compared with apolipoprotein E4 carriers, who were associated with hypercholesterolemia, suggesting that low plasma cholesterol was not a cause of cancer [5].

In an MRS, a genetic variant associated with a biomarker (such as LDL-C) is used as a proxy for the biomarker (Fig. 2). Outcomes are compared between the groups harboring the effect alleles and a group with the reference allele. Thus, an MRS is an analog of a randomized controlled trial (RCT) and regarded as a "natural" RCT.

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