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Editorial

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Genetic Variations, Triglycerides, and Atherosclerotic Disease

Hayato Tada and Masa-aki Kawashiri

Division of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

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Understandings from Causal Associations between Biomarkers and Clinical Outcomes

To establish a causal association between a biomarker and an outcome, randomized controlled trials (RCT) are the gold standard. On the other hand, the Mendelian randomization trial is a technique that uses genotypes as instruments to assess causal associations between biomarkers and outcomes[1]. In a Mendelian randomization trial, a genetic variant associated with a particular biomarker is used as a proxy for the biomarker. Outcomes are compared between the group with the effect allele and a group with the reference allele. This approach can be considered a proxy for an RCT, in which the randomized groups have similar confounding variables. Accordingly, a Mendelian randomization trial can be regarded as a natural RCT. Using this technique, a causal association between LDL cholesterol and atherosclerotic diseases have been firmly confirmed. With respect to triglycerides, they have been associated with atherosclerotic diseases in numerous epidemiological studies[2]. Establishing triglyceride as a causal factor of atherosclerotic diseases has been difficult because it is difficult to distinguish the effects of triglyceride on atherosclerotic diseases from those of LDL cholesterol and HDL cholesterol by RCT or by Mendelian randomization trials. To overcome this issue, an interesting study creating a framework to observed whether triglyceride causally influences the risk of atherosclerotic diseases was published in 2013[3]. They constructed a model adjusting for the effects of LDL cholesterol and/or HDL cholesterol levels on the risk of atherosclerotic diseases, and found that the genetic impact of single nucleotide polymorphisms (SNPs) on triglyceride levels was independently associated with the risk of atherosclerotic diseases. This study suggested that triglycerides causally affect the risk of atherosclerotic diseases. In this issue, Liu *et al.* described an extremely rare case of severe hypertriglyceridemia caused by lipase maturation factor 1 (*LMF1*) mutations exhibiting atherosclerotic changes[4]. In addition, rare as well as common genetic variations in lipoprotein lipase (*LPL*) and apolipoprotein C3 (*APOC3*) genes have been associated with coronary artery disease[5, 6]. We strongly believe that consistent directions regarding the effects on phenotype between common as well as rare genetic variations definitely ascertain the truth of nature (**Fig. 1**). Those observations collectively suggest that triglyceride could be regarded as a causal factor for atherosclerosis, rather than a biomarker.

Biology, Genetics, and Outcomes

Although human genetics could potentially illustrate the causal associations between biomarkers and outcomes, underlying biology should also be considered. We have previously shown that rare genetic variations lowering triglyceride were consistently associated with lowering the risk for coronary atherosclerosis, although we could not have enough power to show this favorable association in *LMF1* gene (**Table 1**)[7]. Interestingly, the effect on the risk of developing diabetes were inconsistent across those genes, suggesting that functions based on biology should be carefully considered when assessing such genetic association studies.

Conclusion

Dyslipidemias, including hypertriglyceridemia,

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Address for correspondence: Hayato Tada, Division of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa, 920-8641, Japan E-mail: ht240z@sa3.so-net.ne.jp

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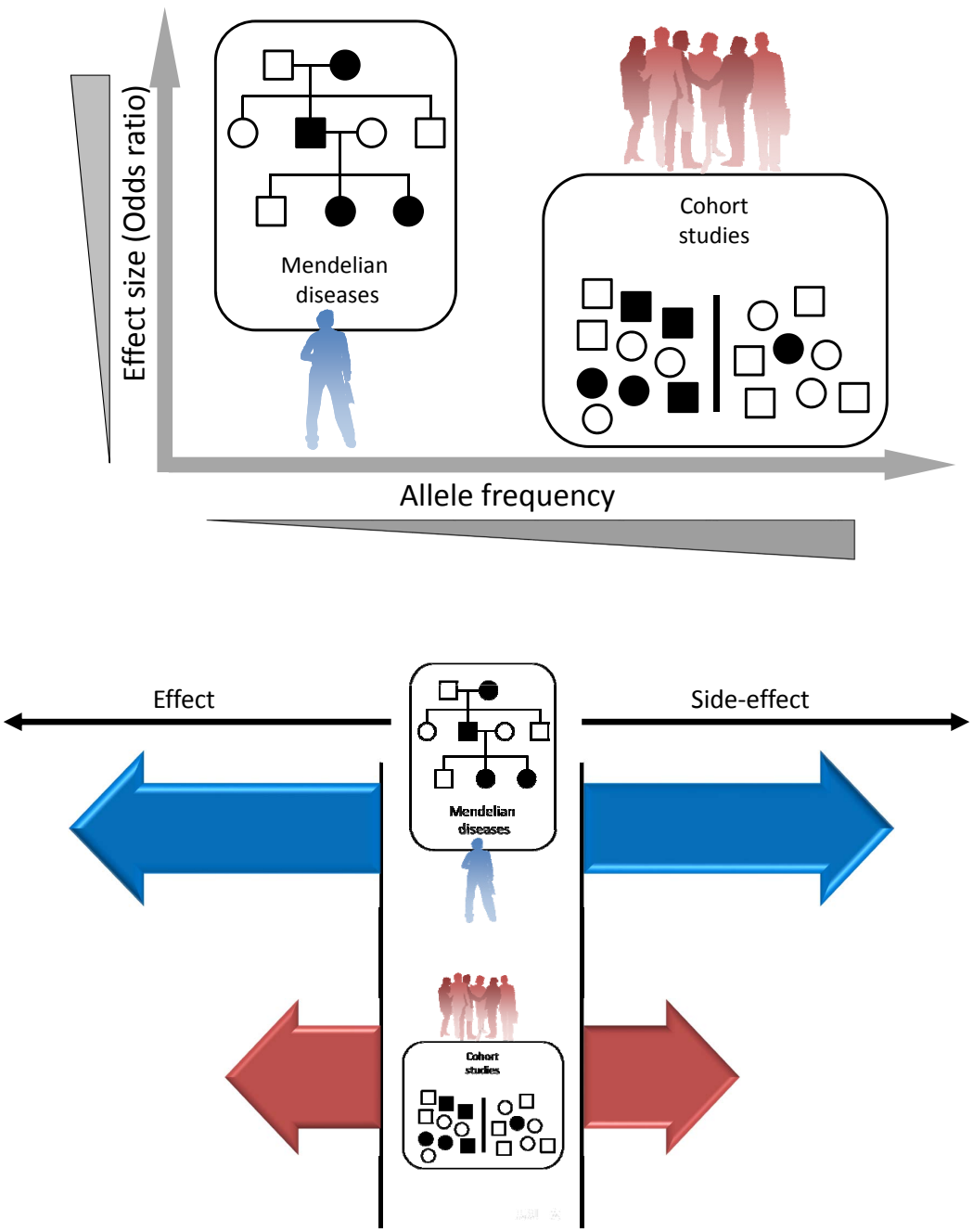

Fig. 1. Scheme of human genetic variations and diseases

Upper panel. X-axis represents allele frequency. Y-axis represents effect sizes.
Lower panel. Consistent directions between rare as well as common genetic variations definitely ascertain the truth of nature.

are important causal factors of atherosclerosis. Genetic analyses in Mendelian dyslipidemias as well as Mendelian randomization trials using common genetic variants have contributed to our understanding of lipids and atherosclerotic diseases. Investigation on extreme cases caused by rare genetic variants can lead to the development of novel drugs for the general population, especially when the on-target/off-target directions of rare variants and common variants exhibit the same directions[8]. We do hope that such cases could be verified in other genes, including *LMF1*, based on the accumulations of those extreme cases.

Table 1. Impact of triglyceride lowering genes on CAD and T2DM

Gene	Number of variants	Triglyceride	HDL cholesterol	LDL cholesterol	CAD Odds ratio	T2DM Odds ratio
LPL	7	-0.138 ± 0.002 ($<1.0\times10^{-237}$)	0.939 ± 0.011 ($<1.0\times10^{-237}$)	0.025 ± 0.012 (0.03)	0.66	0.8
ANGPTL4	1	-0.273 ± 0.01 (4.2×10^{-175})	0.891 ± 0.035 (4.8×10^{-146})	-0.014 ± 0.036 (0.7)	0.6	0.67
APOA5	7	-0.227 ± 0.002 ($<1.0\times10^{-237}$)	0.453 ± 0.009 ($<1.0\times10^{-237}$)	-0.145 ± 0.009 (8.4×10^{-59})	0.76	0.88
APOC3	3	-1.069 ± 0.032 (3.2×10^{-237})	0.695 ± 0.03 (9.0×10^{-120})	-0.106 ± 0.03 (4.7×10^{-4})	0.85	1.07
ANGPTL3	1	-0.077 ± 0.003 (6.1×10^{-170})	-0.136 ± 0.035 (1.2×10^{-4})	-0.588 ± 0.037 (4.8×10^{-58})	0.89	1.18
ANGPTL8	1	-0.353 ± 0.051 (2.8×10^{-12})	1.221 ± 0.141 (5.0×10^{-18})	-0.167 ± 0.146 (0.25)	0.74	1.58

Value are expressed as effect size ± S.E. (*p*-value). LPL = lipoprotein lipase; ANGPTL4 = angiopoietin-like 4; APOA5 = apolipoprotein A5; APOC3 = apolipoprotein C3; ANGPTL3 = Angiopoietin-like 3; ANGPTL8 = Angiopoietin-like 8; CAD = coronary artery disease; T2DM = type 2 diabetes mellitus

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Conflict of Interest

None.

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