Genome-wide association studies (GWAS) have resulted in an unprecedented leap in our understanding of the common genetic variation associated with common diseases and traits. Work performed predominantly in the last 2 years means there are now more than 200 common DNA variants associated with human traits, at levels of statistical significance, which means less than 1 in 20 will be false positives. This contrasts with the situation before 2006, where, in total, less than 20 common variant–trait associations was considered robust.

Despite this progress, GWAS studies have been recently criticized as not providing the biological or clinical insight predicted. Some commentators have suggested that the associations between a single base-pair change and a human trait or disease have not told us a great deal. This is a legitimate concern, given that often, associated DNA variants occur in the middle of several genes and it is unclear which gene is important. Those involved have pointed out that the concern is unfounded; that often variant–disease associations are merely the first step towards a better understanding of biological processes and that translation will take >2 years. Even so, GWAS studies are already providing real biological insights. Type 2 diabetes provides a good example of how results from GWAS studies can be used to increase our understanding of disease. This is through using common DNA variants known to associate with a trait as ‘tools’ or ‘instruments’ to assess the likely causal nature or otherwise of observational epidemiological associations. This approach, termed Mendelian Randomization, has been used before and is based around the principle that case–control-based associations between gene variants and traits are much less likely to be biased or confounded than traditional epidemiological studies. Probably the best proof of principle comes from the fact that rare and common variants in genes that alter low-density lipoprotein cholesterol alter the risk of coronary artery disease—something we know from randomized controlled trials of statins, but genetic studies provide the same answer. Brennan et al. have now taken the Mendelian Randomization approach a step further by using it to test an association that is much more poorly understood—adiposity and cancer. They tested the association between the body mass index (BMI) and obesity-associated variant in the FTO gene in a series of cancer case–control studies. They reasoned that this would provide an

Commentary: A new dawn for genetic epidemiology?

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unbiased, unconfounded estimate of the association between obesity and cancers. They point out that studying the association between obesity and cancer is normally extremely troublesome due to the likely many confounding factors involved and weight changes before and during the disease process. Furthermore, their study provides an example of how it is not necessarily critical to have identified the causal variant or causal gene behind the association to provide biological insight.

Brennan et al. used three series of cancer case studies—of lung cancer, upper aerodigestive tract (UADT) cancer and kidney cancer, consisting of 2250, 811 and 954 cases, respectively, and compared these with 3000 shared age and sex frequency-matched controls. They first noted that the average BMIs of their cancer patients were as expected compared with controls given previous evidence—lower in lung and UADT and higher in kidney cancer. As the authors acknowledge, the main results are marginal, but in the expected directions given the epidemiological associations. The FTO allele associated with lower BMI is associated with lung cancer, at borderline levels of significance, and there is a trend towards the FTO allele associated with higher BMI increasing the risk of kidney cancer. In sub-analyses, there is a suggestion that the association with lung cancer gets stronger in lung cancers with a squamous cell histology, and in never smokers, and a suggestion that the association with kidney cancer is stronger in younger onset cases. These sorts of sub-analyses need to be treated with caution, but the direction of effects suggests further studies are warranted. If replicated, the results will provide important evidence for a causal role of increased adiposity in an increased risk of kidney cancer and a decreased risk of lung cancer.

There are two caveats to their study. The first, readily acknowledged by the authors, is a lack of power. They have calculated that they would need closer to 10 000 case–control pairs to provide 90% power to detect the expected effect of the FTO variant on lung cancer. It has previously been pointed out that large sample sizes will be needed to detect expected effects of FTO gene variants on traits related to adiposity, assuming that adiposity is causal to those traits, and this is a potential downside to Mendelian randomization studies.20 However, two developments mean a lack of power is likely to be less of a problem in future studies. First, DNA collections and consortia of DNA collections now mean that sample sizes in the order of 10 000s are available for many traits. Secondly, as more variants are discovered for the same trait, these can be combined to provide a more powerful ‘instrument’ with which to test associations—notably there are now 11 common variants that are associated with obesity.21–23

A second caveat to their study is that the biology of the FTO gene is not fully understood. It is possible that an association between FTO and cancer could be driven by a mechanism other than adiposity, if the FTO gene has effects other than on adiposity. For example, mice lacking the FTO gene have increased metabolic rates and reduced adiposity,14 but it is possible that FTO could alter cancer risk by its effect on an aspect of metabolism other than adiposity (assuming the mechanism behind the FTO–adiposity association in humans is the same as that in mice). Consistency of direction and size of effects with those expected will provide some reassurance regarding this caveat. Even if concerns remain as to the mechanisms, a robust association between FTO variants and lung cancer will still indicate that there is likely to be a biological basis to the epidemiological association between reduced BMI and lung cancer, as opposed to an epidemiological artefact.

In summary, Brennan et al. provide an important example of how FTO variation specifically, and common genetic variation in general, can be useful in contributing to understanding disease mechanisms. The caveats to the Mendelian randomization approach mean that these studies should be treated in the context of a body of evidence, rather than definitive proof of causality on their own, but as more genetic association studies reveal more common variants associated with human traits, genetic epidemiologists will have more tools to help understand disease.

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References


