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Mendelian randomization: A powerful tool to illuminate pathophysiological mechanisms

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Understanding the important risk factors for specific diseases is a key goal in clinical medicine. Accurate understanding of true causality can both illuminate pathophysiologic processes as well as identify robust targets for possible interventions designed to prevent disease progression. Two traditional and powerful methods to achieve this goal include careful analysis of large observational cohorts and controlled trials that include interventions designed to modify the putative risk factor. However, both have potential limitations and weaknesses. Observational studies that suggest association can be affected by confounders that are unrecognized, incompletely measured, and/or difficult to control for in the statistical analyses. Identifying large cohorts with robust and consistent measurements of potential risk factors can also be a challenge, and the greater the number of confounders the larger a data set is necessary for constructing accurate regression models. Randomized controlled trials remain the gold standard to establish a causal relationship between putative risk factors and a disease process. In this strategy, study groups are randomized into comparable groups except for the exposure of interest, typically a therapeutic intervention designed to mitigate the risk factor in the treatment group. However, randomized controlled trials can be costly or impractical, and can still have inconclusive results if the chosen intervention does not have a robust effect on the risk factor, or if important confounders are not adequately accounted for in the randomization protocol.

With the explosion of large genetic data sets over the last decade, a powerful third tool has emerged to evaluate potential risk factors: Mendelian randomization. The key underlying concept is that genetic variants are present from birth and non-modifiable, thus mitigating concerns related to reverse causation [1]. Thus, if one can identify genetic factors (most often single nucleotide variants or SNVs) that are associated with the risk factor of interest, these can serve as a surrogate for robust statistical analysis. Most often, multiple SNVs in one or more genes are combined to construct a genetic instrumental variable (GIV). This GIV must fulfill 3 criteria: 1) The GIV is reproducibly and strongly associated with the risk factor; 2)

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the GIV cannot be associated with known confounders; 3) the GIV is only associated with the outcome through the risk factor of interest. A careful Mendelian randomization study will present data to support all 3 points.

In the current issue of the Mayo Clinic Proceedings, Tsao and colleagues report a good example of a Mendelian randomization study used to study the association between uric acid and the risk of chronic kidney disease (CKD) progression taking advantage of genetic and medical data of 140,070 individuals in the Taiwan biobank [2]. Multiple observational epidemiologic studies have identified uric acid as an independent risk factor for incident CKD as well as progressive loss of kidney function [3, 4]. In addition, animal models suggest that increased serum uric acid can accelerate chronic kidney disease progression, perhaps via endothelial dysfunction, activation of the renin angiotensin aldosterone system, and/or oxidative stress [5, 6]. Despite this body of evidence, results of randomized controlled trials to reduce serum uric acid levels have been disappointing to date failing to demonstrate amelioration of CKD progression [7, 8].

Consistent with prior observational studies, in the current report participants with hyperuricemia at baseline had a higher cumulative incidence of incident CKD after adjusting for age, sex, hypertension, diabetes, hyperlipidemia, and estimated glomerular filtration rate (eGFR). A total of 21 SNVs that strongly associated with serum uric acid levels in East Asian populations in available data bases were then identified for the subsequent Mendelian randomization analysis. These 21 SNVs were used to construct 7 different GIVs, including one that included only a single variant in *SLC2A9* since the proximal tubular GLUT9 transporter this gene encodes is known to be the single largest contributor to genetic control of serum uric acid. The resulting analysis fulfilled all 3 pre-conditions of a valid Mendelian randomization study, and no causal relationship between serum uric acid and CKD risk was suggested by analyses with any of the 7 GIVs.

The current study adds important evidence to support the hypothesis that serum uric acid does not directly mediate CKD progression in this East Asian population, and is consistent with a recent large Mendelian randomization study in Western European populations [9]. Together, these results provide a potential explanation for negative results in studies that employed therapies that reduce serum uric acid with a goal of CKD prevention and suggest that the design of better pharmacologic agents or more robust studies designs that are solely focused on uric acid may not yield different results. This is not to say that serum uric acid could not still be an important risk factor for CKD progression. Evidence from another Mendelian randomization study suggested a causal relationship between uric acid and metabolic syndrome components including serum lipids [10, 11]. Thus, it is possible that serum uric acid could influence other intermediate factors than in turn impact CKD progression.

In conclusion, the current study provides a nice case study regarding the power of large genetic data sets to illuminate possible disease pathways in a cost efficient way. Analyses of these data sets using methods such as Mendelian randomization can help researchers prioritize targets for intervention that are more likely to be effective, and ultimately save money and accelerate the pace of successful development of therapeutics.

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