Mendelian Randomization Analyses Reveals a Casual Effect of Gut Microbiome in the Development of ARDS

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RATIONALE: Gut-associated bacteria enrichment of the lung microbiome has been recently associated to the clinical diagnosis of ARDS. In spite of this evidence, the causal role of gut-microbiome in ARDS pathogenesis was rarely explored. Mendelian randomization (MR) is an established epidemiological approach that uses genetic variants (SNPs) associated with an exposure as “instruments” to estimate a causal effect of the exposure on the outcome of interest. In this study, we performed a comprehensive MR analysis to explore the cascaded relationship among gut microbiome, clinical traits, and ARDS. METHODS: Two-sample Mendelian Randomization (MR) analytic framework was conducted to obtain causal estimates of exposures on outcome. Exposures included 77 gut microbes and over 34,000 clinical traits. Genetic instruments for the exposure and outcome were derived from publicly available GWAS summary statistics. ARDS GWAS summary statistics was calculated using GWAS datasets from iSPAAR and MESSI in European populations. Independent genetic instruments were selected for MR analysis based on strict criteria of minor allele frequency > 0.05, linkage disequilibrium ($r^2 <$ 0.001), and beyond genome wide significance ($P< 5\times10^{-8}$ or suggestive significance at $P < 10^{-6}$). Inverse-variance weighted (IVW) and Wald ratio methods were mainly used for causal estimation. MR Egger method was used as sensitivity analyses to detect the pleiotropy of genetic instruments. Heterogeneity was estimated using MR Egger and IVW methods. RESULTS: Among 77 gut microbes, two microbial traits were causally associated with ARDS development ($b_{IVW} = 0.118$ and $P_{IVW} = 0.036$ for Genus Dialister; $b_{Wald} = 0.449$ and $P_{Wald} = 0.032$ for Phylum Firmicutes). When decomposing the genetic associations using clinical traits, we found 2,271 significant associations between the two ARDS-associated microbes and clinical traits. In addition, 1,614 clinical traits exhibited significant relationships with ARDS. Among the total 3,885 cascaded associations, clinical traits could be grouped into subcategories of protein biomarkers, immune traits, and aging traits, etc., to link the relationship of gut microbes and ARDS. For example, Genus Dialister seemed to cause an increase in plasma KLK11 levels ($b = 0.137$) to promote ARDS development as plasma KLK11 could increase ARDS risk at $b = 0.093$. CONCLUSIONS: Our work represents the first estimate of gut microbiome causal effect on development of ARDS cascaded via clinical traits. Future studies aim to expand the catalogue of loci contributing to human gut microbiome will be necessary to start bridging the gap in the mechanistic understanding linking gut microbiome and the development of ARDS

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