Universität Zürich[UZH]

JACOBS CENTER

THE JACOBS CENTER RESEARCH SEMINAR SERIES

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MENDELIAN RANDOMIZATION INTEGRATING GWAS AND EQTL DATA REVEALS GENETIC DETERMINANTS OF COMPLEX AND CLINICAL TRAITS

Interpretation of GWAS results is challenging, as most of the associated variants fall into regulatory regions and overlap with expression-QTLs (eQTLs), indicating their potential involvement in gene expression regulation.

To address this challenge, we propose an advanced transcriptome-wide summary statistics-based Mendelian Randomization approach (called TWMR) that uses multiple SNPs jointly as instruments and multiple gene expression traits as exposures, simultaneously.

When applied to 43 human phenotypes it uncovered 2,369 genes whose blood expression is putatively associated with at least one phenotype resulting in 3,913 gene-trait associations; of note, 36% of them had no genome-wide significant SNP nearby in previous GWAS analysis. Using independent association summary statistics (UKBiobank), we confirmed that the majority of these loci were missed by conventional GWAS due to power issues. Noteworthy among these novel links is educational attainment-associated BSCL2, known to carry mutations leading to a mendelian form of encephalopathy. We similarly unravelled novel pleiotropic causal effects suggestive of mechanistic connections, e.g. the shared genetic effects of GSDMB in rheumatoid arthritis, ulcerative colitis and Crohn's disease. We then explored whether sex-specific eQTLs lead to sex-specific complex trait association and conversely if sex-specific trait associations were due to sex-specific eQTLs or sex-specific causal effects.

In summary, our advanced Mendelian Randomization unlocks hidden value from published GWAS through higher power in detecting associations. It better accounts for pleiotropy and unravels new biological mechanisms underlying complex and clinical traits.

Friday, May 17th, 2019, 10:00 h

At the Jacobs Center for Productive Youth Development
Andreasstrasse 15, 4th floor, AND 4.19, 8050 Zürich

Individual meetings with Dr. Eleonora Porcu are available,
if interested please contact Maria Schönholzer at maria.schoenholzer@jacobscenter.uzh.ch