GENETICS

WHAT DOES SHARED GENETICS MEAN?

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On Feb 7, 2020 I had the chance to hear a talk of Luke Jostins-Dean about Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD). While IBS had a substantial overlap of polygeneic risk scores with psychological features, IBD did not. Sounds logical but does this prove anything?

Two new medRxiv preprints [<u>Wendt</u> and <u>Marees</u>] throroughly examine also possible genetic correlates. Although I am quite sceptical that SES correlates should be tested at all (and also think that GWAS are not hypothesis free) here is the Marees explanation of the three possibilities we do have: PRS, MTAG, mtCOJO.

First, polygenic risk scoring (PRS) is a tempting approach; but PRS using mental health/disease to predict the same or different phenotypes from an independent dataset often explain very little variance in the outcome phenotype. PRS also cannot detect specific biology underlying each phenotype.

Second is multi-trait analysis of GWAS (MTAG), which jointly analyses GWAS summary statistics and adjusts per-SNP effect estimates and association p-values using the strength of the genetic correlation between phenotypes. Genetic correlations between EDU/SES and related phenotypes have, however, demonstrable biases from environmental confounders....

To disentangle the complex genetic overlaps between EDU/SES and mental health, we therefore used multi-trait conditioning and joint analysis (mtCOJO), which generates conditioned GWAS summary statistics for each phenotype of interest after correcting for the per-SNP effects of another phenotype). The mtCOJO approach is not based on genetic correlation; it is based on the causal relationship between trait pairs inferred by Mendelian randomization (MR).

mtCOJO seems the way to go although the usual restrictions apply.

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https://www.wjst.de/blog/sciencesurf/2020/03/what-does-shared-genetics-mean/ Page 2