Disclosure Slide

Financial Disclosure for:

Theo Dupuis

Quantifying the shared genetic effects on the regulation of expression and protein levels in family data

I have nothing to disclose

Quantifying the shared genetic effects on the regulation of expression and protein levels in family data

T Dupuis[1], JM Soria[2], JM Schwenk[3], ET Dermitzakis[4], A Viñuela[4,5], AA Brown[1]

1. Population Health and Genomics, University of Dundee School of Medicine 2. Instituto de Investigaciones Biomedicas Sant Pau (IIB-Sant Pau) 3. Division of Affinity Proteomics, Science for Life Laboratory, Department of Protein Science, KTH - Royal Institute of Technology 4. Department of Genetic Medicine and Development, University of Geneva Medical School 5. Institute of Genetic Medicine, International Centre for Life, Newcastle University

pdf version on github

Background

- Most disease associated variants fall in non-coding regions. Molecular studies are required to understand the mechanism by which they act.
- RNA-seq captures the whole spectrum of gene expression variation but transcript levels may not correlate with disease risk because of buffering and post-transcriptional modifications, which are captured by proteomic studies.
- The phenotypic correlation between proteins and transcripts has been shown to be low. However their degree of shared genetic architecture has still to be systematically quantified.

Objective

To measure the shared contribution of genetic variants to the regulation of expression and proteins.

Methods

- We used a pedigree consisting of 67 individuals in which the levels of 16748 transcripts were assayed by RNA-seq in blood. The levels of 90 proteins on the Olink CVDIII panel were also measured in plasma.
- We used linear mixed models to decompose the variance of these molecular phenotypes into the contributions of genetics (h^2), age, sex, smoking status and unknown environmental effects.
- We also measured the genetic correlation r_G in 46 pairs of matching transcripts and proteins.

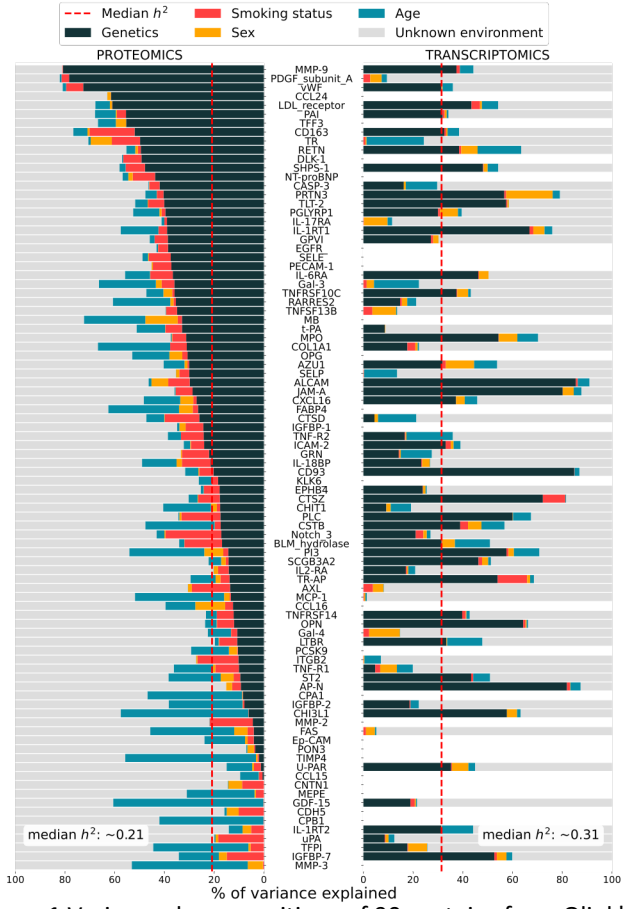

Figure 1 Variance decompositions of 90 proteins from Olink's CVDIII and corresponding transcripts ordered by proteins h^2

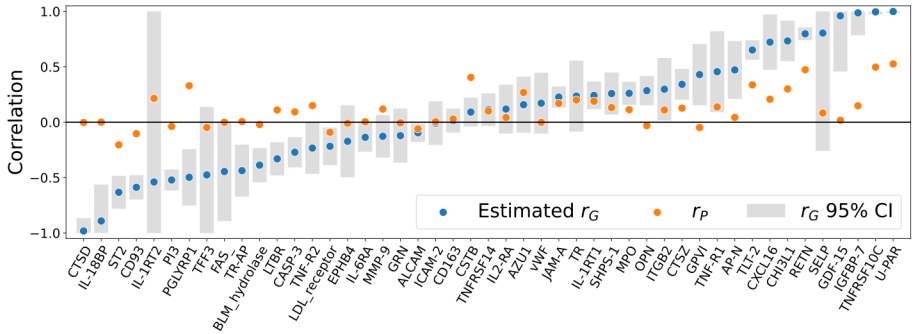

Figure 2 Estimates of r_G between proteins and transcripts levels and their corresponding phenotypic correlations r_P for 46 genes. The 95% confidence interval calculated using the jackknife is shown in grey.

Results

- The heritability of transcripts in the panel was higher than that of proteins (respective medians h^2 ~ 0.31 and ~ 0.21) as well as that of genome-wide transcripts (~ 0.20) (**Fig. 1**).
- We observed a low phenotypic correlation r_P between proteins and transcripts (median r_P ~0.11) but a 95% CI for r_G did not overlap 0 for 31/46 genes (**Fig.2**).

Conclusion

The important genetic correlations we observed between proteins and transcripts suggest that their regulation shares a similar genetic architecture. This is especially interesting as we observe high values of r_G even when the r_P is low. This could mean that the environmental component is the main driver of the difference between these two phenotypes.