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

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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 proteomics studies.
- The phenotypic correlation between proteins and transcripts has been shown to be low. However their degree of sharing of genetic architecture has still to be systematically quantified.

Objective

To measure the shared contribution of genetic variants on 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 from Olink CVDIII panel were also measured in plasma.
- We used linear mixed models to decompose the variance of these molecular phenotypes in 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 transcript and protein.

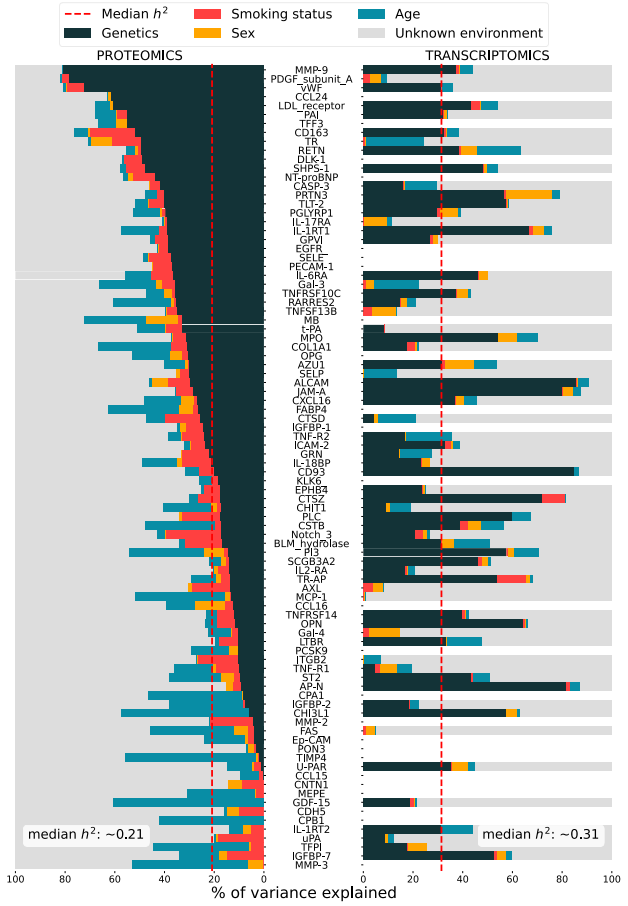

Figure 1 Variance decompositions of 90 proteins from Olink's CVDIII and corresponding transcripts ordered by proteins h^2

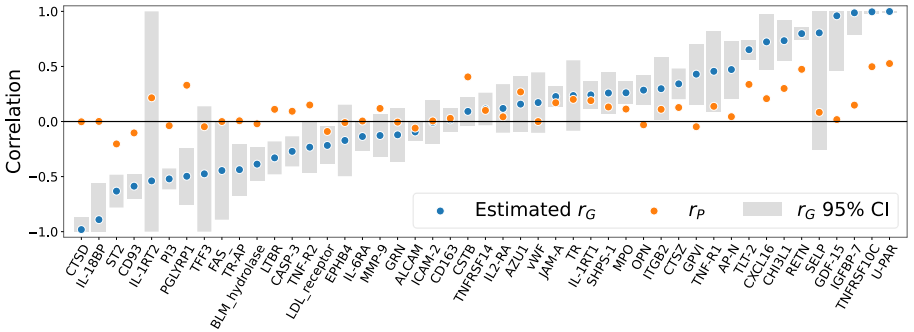

Figure 2 Estimates of r_G between proteins and transcripts levels and their corresponding phenotypic correlations r_P for 46 genes. The 95% confidence interval calculated using the jackknife is shown in grey.

Results

- The heritability of transcripts in the panel was higher than those of proteins (respective median h^2 ~ 0.31 and ~ 0.21) as well as those of genome wide transcripts (~0.197) (**Fig. 1**).
- The overall correlation between h^2 transcripts and h^2 proteins was low (r = -0.02)
- We observed a low phenotypic correlation r_P between proteins and transcripts (median r_P ~0.11) but significant r_G in 31/46 genes (**Fig.2**).

Conclusion

The important genetic correlations we observed between proteins and transcripts suggest that their regulation share a similar genetic architecture. This is especially interesting as we observe strong 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.