# Inflammation pQTLs – findings from the SCALLOP consortium

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## Contact information

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## Abstract

BACKGROUND. METHODS. FINDINGS. INTERPRETATION.

## Introduction

Proteins play central role in many biological processes and large-scale protein-wide genomic analysis (PGWAS) became an important source of information (Sun et al. 2018).

The objectives of the study are as follows

* Identification of pQTLs in SCALLOP discovery cohorts
* Study of pQTLs in replication cohorts
* Investigation of the mechanistic basis of identified cis- and trans-pQTL by functional annotation
* Examination of pQTL pleiotropic effects
* Evaluation over the causal role of INF proteins disease outcomes such as CHD and stroke
* Other downstream analysis

## Data and analysis

### The SCALLOP consortium

The contributing cohorts are listed in Table.

We report pQTLs associated with OLINK/INF1 panel, using cohorts in the SCAndinavian coLLaboration for Olink plasma Protein genetics (SCALLOP) consortium, a collaborative framework for discovery and follow-up of genetic associations with proteins on the Olink Proteomics platform.

### Proteins

The Olink INFlammation panel of 92 proteins,

### SNPs

1000 genomes imputation, build 37 (hg19) positions. Quality control on aspects such as SNP/sample call rates, gender mismatch, abnormal inbreeding coefficient, failed cryptic relatedness test, ancestry outlier, heterozygosity and Hardy-Weinberg equilibrium test.

### Association analysis

Rank-based inverse normal transformation on the raw measurement of proteins including those below lower limit of detection. Multiple linear regression for all samples including sex, age, principal components and other cohort specific covariates. Additive genetic model. For case-control data, cases and controls were analysed separately – results were merged at meta-analysis stage. As individual level data from KORA study, the protein normalization and association testing were done centrally.

Software which account for genotype uncertainty, such as SNPTEST were used but due to the relatively large number of proteins, results based on PLINK were also accepted, both amended with outputs from qctool –snp-stats.

## Meta-analysis

Meta-analysis were performed centrally using the inverse-N weighted analysis of regression betas and standard errors, as implemented in the software METAL. Filters such as MAF, HWE, and imputation quality filters were applied at the meta-analysis. Genomic control were considered. The Bonferroni threshold for the genome-wide analyses is 5 x 10-10. The results were replicated in independent cohorts. Independent loci were assessed by PLINK and GCTA and cis/trans classifications were obtained using customized R functions. Finemapping experiment was conducted on summary statistics via several software including finemap and JAM using approximately independent LD blocks. The reference panels included 1000Genomes release 3 as well as INTERVAL.

For annotation of the variants, PhenoScanner was used.

## Results

The list of variants is shown in Table. The Q-Q, Manhattan and LocusZoom plots are shown in Figure. The cis/trans classification is shown in Table along with circular plot in Figure.

## Discussions

We were able to assess the protein-genetic association in the OLINK panel. It is particularly interesting to see the cis/trans effects. Findings on OPG are in line with earlier report (Kwan et al. 2014). Significant variants across different proteins gave evidence of pleiotropy. The significant variants offered useful instruments for causal inference through Mendelian randomization. An inflammation score could also be built. The results further facilitate construction of biological pathways.

We were also be able to develop relevant functions in Bash as well as R.

## Acknowledgements

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## References

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Kwan JSH, et al. (2014). Meta-analysis of genome-wide association studies identiﬁes two loci associated with circulating osteoprotegerin levels. Hum Mol Genet 23(24): 6684–669.

Sun BB, et al. (2018). Genomic atlas of the human plasma proteome. Nature 558: 73–79.

## Supplementary information

Additional information about this investigation is available from GitHub, <https://github.com/jinghuazhao/INF>.

URL: SCALLOP, <https://www.olink.com/scallop/>; OLINK/INF1 panel, <https://github.com/jinghuazhao/INF/blob/master/doc/olink.inf.panel.annot.tsv>; METAL <https://github.com/statgen/METAL>; PLINK, <http://zzz.bwh.harvard.edu/plink>; R/gap. <https://cran.r-project.org/web/packages/gap/index.html>; Uniprot, [https://www.uniprot.org](https://www.uniprot.org/):