

## Concept Paper Template

**Provisional Paper Title:** Genetic Markers of the Inflammatory Biomarker Soluble Urokinase Plasminogen Activator Receptor (suPAR) in a Population of Healthy Blood Donors

**Proposing Author:** Joseph Dowsett

**Author's Email:** joseph.dowsett@regionh.dk

**P.I. Sponsor:**

Terrie E. Moffitt and Avshalom Caspi

**Today's Date:**

---

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

**Objective of the study:**

The plasma protein soluble urokinase plasminogen activator receptor (suPAR) is a non-specific biomarker for low-grade inflammation. Previously suPAR has been found to predict various negative conditions, including incident cancer, cardiovascular disease, diabetes, depression and mortality<sup>1,2</sup>. Though there is a wide range of negative outcomes associated with suPAR, the genetics of suPAR remain unexplored.

A recent genome-wide association analysis (GWAS) meta-analysis of the well-known inflammatory marker C-reactive protein (CRP) identified 58 associated genetic loci and consequently provided new insight into the genetic aetiology of chronic inflammation<sup>3</sup>. However, CRP and suPAR reflect different aspects of low-grade inflammation despite both being used as inflammatory biomarkers<sup>4</sup>. Additionally, unlike CRP, suPAR is a stable biomarker in the sense that circadian changes in plasma suPAR are minimal<sup>5,6</sup>.

Therefore, performing a GWAS on suPAR in a population of otherwise healthy blood donors may reveal genetic variants that affect this inflammatory marker's systemic expression. The findings may provide new insight into the aetiology of low-grade inflammation.

We have conducted a suPAR GWAS using log-transformed suPAR values and adjusting for sex, age, smoking status, BMI and 10 principal components (N= 12,236). The results from the GWAS discovered 8 genome-wide significant loci.

We wish to replicate the findings in independent cohorts by using the suPAR measurements and genomic (SNP) data available from the Dunedin Study and the E-Risk Longitudinal Twin Study.

### **Data analysis methods:**

Additive genetic association tests between suPAR levels and each of the available SNPs will be performed using the R package “SNPassoc”. Briefly, the following model will be employed:

$$\text{suPAR} \sim \text{SNP} + \text{sex} + \text{PCs}_{1-10}$$

SNP genotypes will be coded as number of risk alleles (0,1,2).

### **Variables needed at which ages:**

Dunedin: suPAR and SNP data at age 38.

E-Risk: suPAR and SNP data at age 18.

### **Significance of the Study (for theory, research methods or clinical practice):**

To our knowledge, a GWAS on suPAR has never been attempted, and datasets with suPAR measurements and genomic data are extremely limited. As we have already identified several genome-wide significant SNPs, a replication study in Dunedin and E-risk would naturally complement the GWAS and strengthen the study. suPAR is a stable biomarker for low-grade inflammation with many associated negative conditions, highlighting the potential importance of the findings from this study. Identifying genetic markers associated with plasma suPAR levels may provide essential insight into the aetiology of low-grade inflammation.

### **References cited:**

- 1 Eugen-Olsen, J. et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. *Journal of internal medicine* 268, 296-308, doi:10.1111/j.1365-2796.2010.02252.x (2010).
- 2 Haastруп, E. et al. Soluble urokinase plasminogen activator receptor as a marker for use of antidepressants. *PLoS One* 9, e110555, doi:10.1371/journal.pone.0110555 (2014).
- 3 Ligthart, S. et al. Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *American journal of human genetics* 103, 691-706, doi:10.1016/j.ajhg.2018.09.009 (2018).
- 4 Lyngbaek, S. et al. CRP and suPAR are differently related to anthropometry and subclinical organ damage. *International journal of cardiology* 167, 781-785, doi:10.1016/j.ijcard.2012.03.040 (2013).
- 5 Andersen, O., Eugen-Olsen, J., Kofoed, K., Iversen, J. & Haugaard, S. B. Soluble urokinase plasminogen activator receptor is a marker of dysmetabolism in HIV-infected patients receiving highly active antiretroviral

therapy. *Journal of medical virology* 80, 209-216, doi:10.1002/jmv.21114 (2008).

- 6 Sier, C. F. et al. Presence of urokinase-type plasminogen activator receptor in urine of cancer patients and its possible clinical relevance. *Laboratory investigation; a journal of technical methods and pathology* 79, 717-722 (1999).

## CONCEPT PAPER RESPONSE FORM

### A

Provisional Paper Title	Genetic Markers of the Inflammatory Biomarker Soluble Urokinase Plasminogen Activator Receptor (suPAR) in a Population of Healthy Blood Donors
Proposing Author	Joseph Dowsett
Other Contributors	DK: Henrik Ullum, Jesper Eugen-Olsen, Lise Wegner Thørner, Kristoffer Sølvsten Burgdorf, Sisse Rye Ostrowski, Erik Sørensen, Christian Erikstrup, Karina Banasik, Søren Brunak, Ole Birger Vesterager Pedersen IS: Hreinn Stefánsson + 5 US/NZ/UK: Karen Sugden, Line Jee Hartmann Rasmussen, Avshalom Caspi, Terrie E. Moffitt, Richie Poulton, Louise Arsenaault
Potential Journals	
Today's Date	
Intended Submission Date	

***Please keep one copy for your records and return one to the proposing author***

### B. To be completed by potential co-authors:

<input type="checkbox"/>	Approved
<input type="checkbox"/>	Not Approved
<input type="checkbox"/>	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

<input type="checkbox"/>	Conceptualizing and designing the longitudinal study
<input type="checkbox"/>	Conceptualizing and collecting one or more variables
<input type="checkbox"/>	Data collection
<input type="checkbox"/>	Conceptualizing and designing this specific paper project
<input type="checkbox"/>	Statistical analyses
<input type="checkbox"/>	Writing
<input type="checkbox"/>	Reviewing manuscript drafts
<input type="checkbox"/>	Final approval before submission for publication
<input type="checkbox"/>	Acknowledgment only, I will not be a co-author

**Signature:**

\_\_\_\_\_

