Mendelian Randomisation Points to a Potential Role of OX40 in Mediating the Effects of Smoking Initiation on Palmoplantar Pustulosis

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Background

Palmoplantar Pustulosis

Pathology

Palmoplantar Pustulosis (PPP) is a severe pustular form of psoriasis, characterized by sterile pustules on the palms and soles. Multiple pathways are upregulated in the skin and blood of PPP patients, largely corresponding to TH2- and TH17-mediated immune responses.

Epidemiology

PPP is very rare, with a prevalence of 0.05-0.10%. PPP patients are predominantly smokers or previous smokers (40-100%), and a causal association between Smoking Initiation and PPP has been previously identified, however this relationship is poorly understood.

Objective

The aim of this project was to assess whether the plasma levels of 160 different immune-related proteins might mediate the relationship between Smoking Initiation and PPP, using a two-step MR analysis.

Methods

Mendelian Randomisation

Two sample Mendelian Randomisation (MR) is a statistical method that tests for a directional casual relationship between two traits using separate GWASes. The rationale behind MR is that if one trait is casual for another, genetic variants casual for the first trait will be proportionally associated with the second trait.

Assumptions

An important assumption that is made during an MR analysis is that a genetic variant chosen to model the exposure trait (an instrumental variable; IV) only effects the outcome trait through the exposure trait. If an IV also influences the outcome trait independently, this is known as horizontal pleiotropy.

Two other key assumptions are that the IVs must be strongly associated with the exposure trait, and that the IVs are not associated with confounders.

Two-Step MR

Two-step MR involves performing two MR analyses sequentially, to try and infer if a causal relationship (such as between smoking and PPP) might be mediated by other factors.

Methods: Follow-Up Analyses

Genetic Correlation

As MR only uses a few selected genetic variants, a useful follow-up method is computing the genetic correlation between two traits. While a strong genetic correlation cannot confirm a causal relationship, it can indicate whether the genetic architecture for two traits is similar.

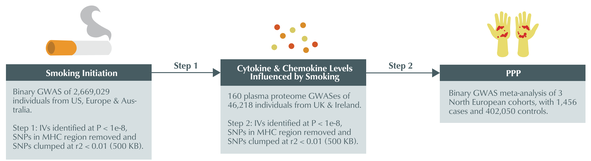
Investigating Pleiotropy

A key issue when applying MR to multiple different mediators is the risk of pleiotropy: while MR could indicate a strong effect of a specific protein on a particular outcome, some of the genetic IVs selected for the protein may also effect the outcome via other pathways.

To try and assess the extent of pleiotropy where any relationship between protein level and PPP was detected in our project, we looked at whether the genetic variants associated with the protein level were also associated with other protein levels.

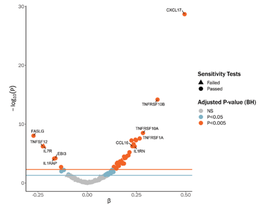
Study Design

We performed a two-step MR, first by investigating whether each plasma proteome level is influenced by smoking initiation, and then by investigating whether the plasma levels of any proteins identified in Step 1 are predicted to have a causal effect on PPP.

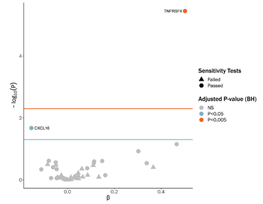


Results: Mendelian Randomisation

Step 1



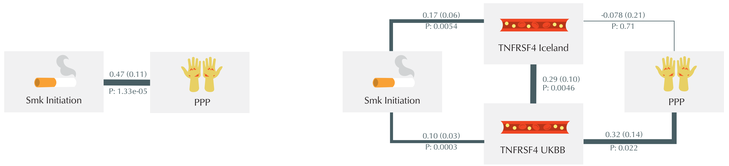
Step 2



In Step 1, we identified 48 proteins that were predicted to be affected by smoking initiation, that also passed MR sensitivity tests; in Step 2, one of these proteins (TNFRSF4, or 0X40) was predicted to effect PPP development with the same direction of effect seen in Step 1.

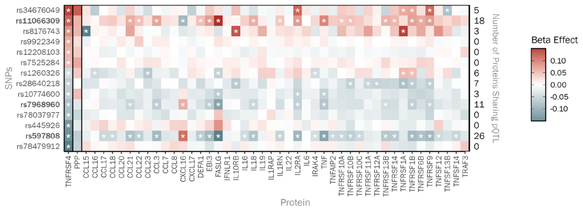
Results: Follow-Up Analyses

Genetic Correlation



Using LDSC, we identified a strong genetic correlation between Smoking Initiation and TNFRSF4 levels (using UKBB data), and between TNFRSF4 levels and PPP. However, the relationship between TNFRSF4 and PPP was not replicated using a seperate GWAS for TNFRSF4 levels from an Icelandic population; MR could not be performed using this GWAS due to a lack of strong IVs.

Investigating Pleiotropy



We found that while 3 of the genetic IVs used for TNFRSF4 MR were highly pleiotropic, the remainder did not appear to consistently influence other protein levels, meaning we can be moderately confident that the detected effect is not due to pleiotropy.

Conclusions

Summary

- Using blood proteome GWASes from the UKBB, we identified a causal relationship from Smoking Initiation to TNFRSF4 levels, and from TNFRSF4 levels to PPP.

Limitations

- This finding could not be replicated using a seperate GWAS due to a lack of strong IVs, which may be due to a difference in protein detection method.
- Our finding may be affected by pleiotropy; while there is a minimal level of pleiotropy when looking at other UKBB protein GWASes, there may be unmeasured pleiotropic factors.
- The PPP GWAS has a small case size, limiting the power to detect causal effects using MR.

References

1. Brunasso & Massone (2021) Dermatology Practical & Conceptual 9(2):105-110.
2. Saunders et al. (2022) Nature 612:720–724.
3. Eldjarn et al. (2023) Nature 622:348–358.
4. Yoshiji et al. (2023) Nature Metabolism 5(2):248-264.
5. Hemani et al. (2018) eLife 7:e34408.
6. Bulik-Sullivan et al. (2015) Nature Genetics 47:291–295.
7. Bulik-Sullivan et al. (2015) Nature Genetics 47:1236–1241.