# Identification of genetic regulation at the proteomic level in the long-term stroke outcome: A Proteome-Wide Association study

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## Background and Aims

The stroke outcome is highly variable and depends on multiple factors, including genetics. Proteome-Wide Association studies (PWAS) could help to identify how genetic variants are affecting the stroke outcome through the modulation at the proteomic level.
To identify new protein biomarkers for the long-term outcome (modified Rankin scale at three months (mRS3)) combining genomics and proteomics data.

## Methods

We performed a four-stage PWAS using FUSION. Discovery: dorsolateral prefrontal cortex (dPFC) proteomic data from the ROS/MAP cohort (1,475 heritable proteins; 376 subjects) and the GODS stroke outcome GWAS (N=1,791 and 8,895,027 SNV)).

- Replication 1: dPFC proteomic dataset from the Banner Sun Health Research Institute (1,139 proteins; 152 subjects)
- Replication 2: ROS/MAP proteomic dataset with a new mRS3 GWAS (N=688; 7,502,471 SNV).

We validated the results' causality with a Bayesian colocalization analysis and Summary-based-data Mendelian Randomization (SMR).
All the PWAS were meta-analyzed with the adaptively weighted Fisher's method.

## Results

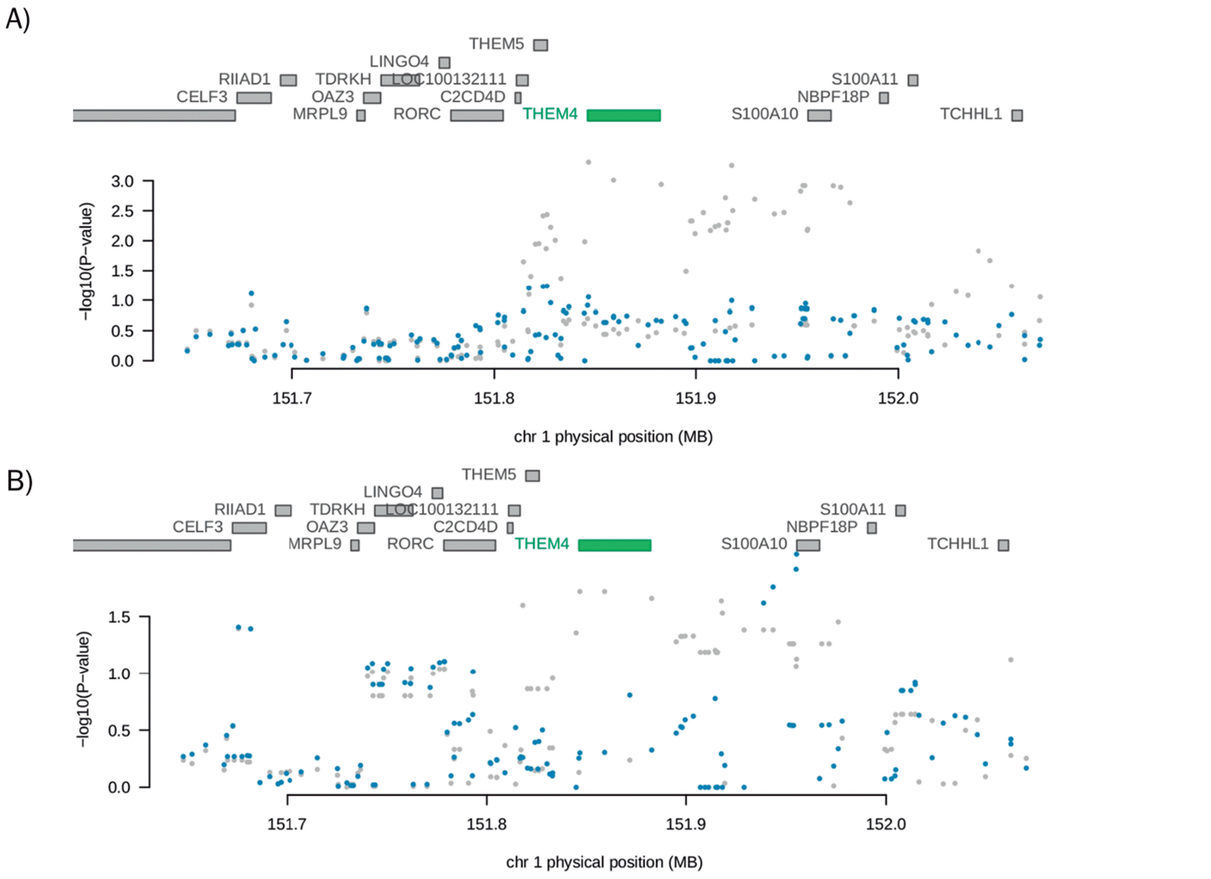
Three proteins were significantly associated with the mRS3 ($P < 0.05$) in the discovery with high posterior probability 4 in the colocalization. The three proteins were significant in the Replication1 but only THEM4 in the Replication2 (Table 1 and Figure 1). THEM4 and APOL2 were significant after Bonferroni adjustment in the meta-analysis (Table 1).

The SMR results confirmed the causal association of THEM4 and APOL2 with the stroke outcome (Table 2).

**Table 1: Significant PWAS results in the Discovery, Replication 1, Replication 2 and meta-analysis**

| | DISCOVERY | | | | | REPLICATION1 | | | | REPLICATION2 | | | | META-ANALYSIS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | pQTL | pQTL Z | PWAS Z | PWAS P | COLOC PP4 | pQTL | pQTL Z | PWAS Z | PWAS P | pQTL | pQTL Z | PWAS Z | PWAS P | P | Q-value |
| THEM4 | rs16833668 | -10.7 | 3.04 | 2.35E-03 | 0.5 | rs16833668 | -8.69 | 2.84 | 4.51E-03 | rs168336668 | -10.8 | 2.3 | 2.35E-02 | 1.51E-04 | 6.93E-03 |
| GSTP1 | rs7941648 | -8.99 | -2.56 | 1.04E-02 | 0.7 | rs1695 | -9.13 | -2.06 | 3.93E-02 | rs7941648 | -9 | -0.06 | 9.55E-01 | 1.40E-02 | 6.42E-01 |
| APOL2 | rs8136528 | -6.19 | -2.37 | 1.77E-02 | 0.8 | rs9619597 | -6.5 | -3.31 | 9.32E-04 | rs8136528 | -6.2 | 0.6 | 5.28E-01 | 8.66E-04 | 3.98E-02 |

**Figure 1: Conditional analysis**




*Conditional analysis for the GODS GWAS used in the discovery (A) and for the new GWAS with GODS criteria used in the Replication 2 (B).*

**Table 2: Significant SMR results**

| Gene | b_SMR | se_SMR | p_SMR |
|---|---|---|---|
| THEM4 | 0.62 | 0.21 | 2.85E-03 |
| APOL2 | -0.84 | 0.32 | 9.40E-03 |

## Conclusion

**Our results indicated that the stroke outcome is modulated by genetic variants through a cis-regulation at the proteomic level.**

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