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Novel role of TYK2 mechanism in SLE pathogenesis via T-cell and B-cell pathways

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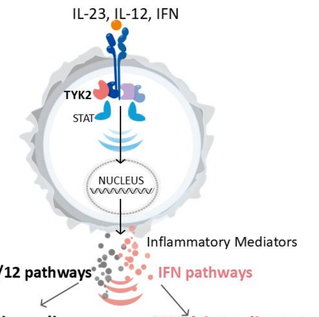
Background

New therapies are needed for SLE

- Systemic Lupus Erythematosus (SLE) is a chronic inflammatory multi-organ disease that affects >3.4 million people worldwide.[1]
- The biological heterogeneity in SLE leads to suboptimal results with conventional therapies, which causes the need for better understanding of pathological mechanisms and for development of new SLE targeted approaches.[2]

TYK2 modulates key inflammatory pathways of SLE

- Genome Wide Association Studies (GWAS) identified SLE-related variants at the *Tyrosine Kinase 2* (*TYK2*) locus.[3]
- Human **TYK2 loss-of-function variants protect** from a wide array of immune-mediated diseases, including SLE.[4]
- TYK2 mediates signaling from key proinflammatory cytokines, including **IL-23, IL-12, and type I IFN through STAT phosphorylation**.
- TYK2-mediated effects in other pathways are less studied.



Objectives

This study aimed to reveal **new TYK2-mediated pathways in SLE** by integrating **SLE GWAS** summary statistics and **proteomics** data made available through UK Biobank.

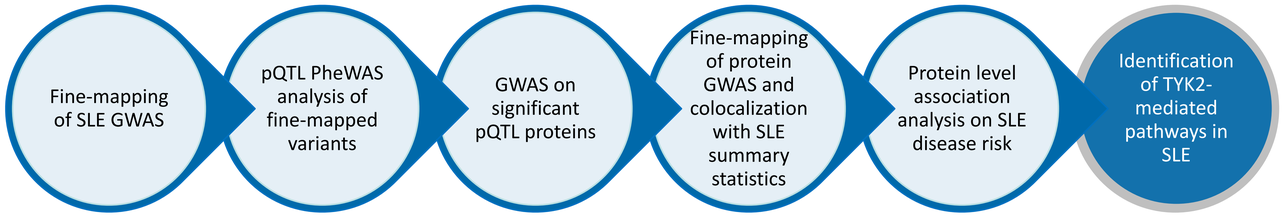
Methods

Databases

- **SLE GWAS** summary statistics from NHGRI-EBI GWAS Catalog.[5]
- Trans-protein-quantitative trait locus (**pQTL**) Phenome-wide association study (**PheWAS**) using Olink data from UK Biobank.[6]
- Protein level association analysis on SLE disease risk database from UK Biobank.[6]

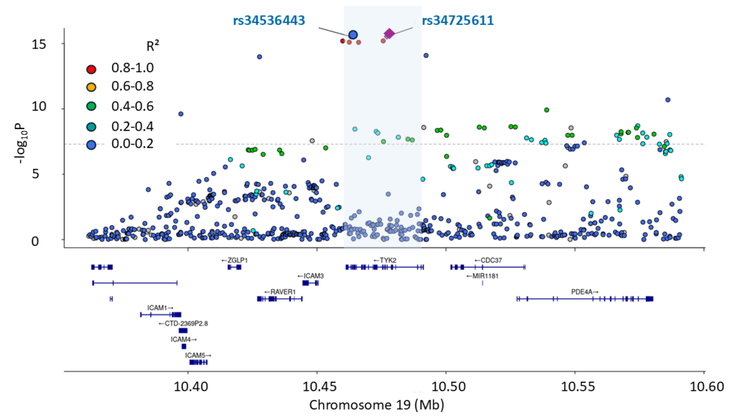
Statistical interaction methods

- Fine-mapping using susieR package.[7]
- Colocalization with Coloc R package.[8]



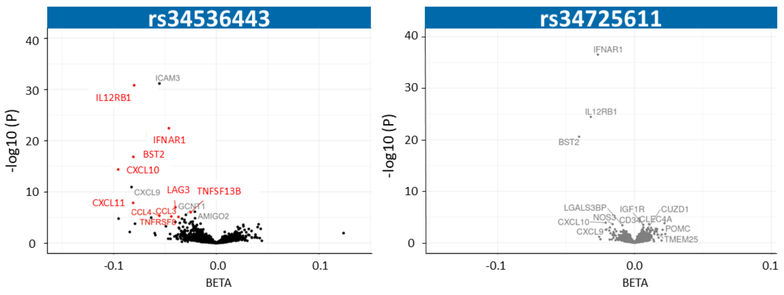
Results

SLE GWAS identified 2 independent variant sets at the *TYK2* locus



- Fine-mapping of GWAS discovered 2 independent single nucleotide polymorphisms (SNPs) at the *TYK2* locus related with SLE.
  - **Rs34536443** (G>C) is a well-characterized pharmacomimetic **TYK2 loss-of-kinase function allele (P1104A)**.
  - Rs34725611 (A>G) is an intronic variant with unknown function.

pQTL pheWAS analysis uncovered unique proteins associated with SLE-related *TYK2* variants



- pQTL PheWAS screen identified >12 proteins that significantly associated with at least one SLE-related TYK2 variant based on a Benjamini-Hochberg correction.
- 10 TYK2-variant associated proteins colocalized with SLE disease susceptibility.

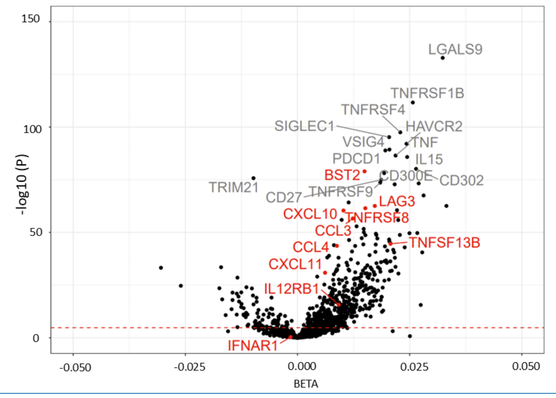
Proteins colocalized with SLE genetic susceptibility, ICAM5 was excluded due to plotting constraints ($p \leq 1.65e^{-497}$)

Colocalized *TYK2* variant-related proteins associated with T-cell and B-cell pathways along with IL-23/12 and type I IFN-signaling

rs34536443

Protein Name	Posterior Probability of Inclusion	Immunological Function
IL12RB1	1	IL-23/12-mediated signaling
IFNAR1	1	Type I IFN-mediated signaling
CXCL10	0.997	T-cell chemotaxis
BST2	0.996	B-cell activation
CXCL11	0.986	T-cell chemotaxis
TNFSF13B	0.986	B-cell and T-cell proliferation
LAG3	0.934	T-cell activation
CCL3	0.861	T-cell chemotaxis
TNFRSF8	0.781	NF-κB-mediated signaling
CCL4	0.45	T-cell chemotaxis

Colocalized *TYK2* variant-related proteins showed increased levels in SLE pathogenesis



- Most colocalized proteins associated with T-cell and B-cell regulation.
- Colocalization of IL12RB1 and IFNAR1 supported TYK2-mediated IL-23/12 and type I IFN-signaling.
- Almost all colocalized proteins were significantly increased in SLE cohorts compared to population controls.
  - IFNAR1 protein levels were not associated with SLE.

Conclusions

Proteogenomic data of this study discovered new TYK2-mediated pathways in SLE pathogenesis in addition to its well-known IL-23/12 and type I IFN-regulation, hence **identified new potential mechanisms that might underlie the protective effects of TYK2 loss-of-function** variants in multiple autoimmune diseases.

- Association of IL12RB1 and IFNAR1 protein levels with TYK2 variants in SLE validated the known TYK2-mediated regulation of IL-23/IL12, and type I IFN pathways in SLE.
- Proteogenomic signatures demonstrated that the **TYK2 loss-of-function allele (P1104A)** also associated with several mediators of **T-cell and B-cell pathways in SLE pathogenesis**, which might contribute to the reported protective effects of TYK2 loss-of-function variants in SLE.

References

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Disclosures

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All authors are employed by Alumis and have no other relationships or conflicts of interest to disclose.

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