

**Structural and rare variants underlying psoriasis susceptibility identified by whole-genome sequencing: discovery of *CERCAM* as a novel risk gene**

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# Financial Disclosure

I do not have any relationships to report within the last 24 months with ACCME defined ineligible companies.

# Unlabeled/Investigational Uses

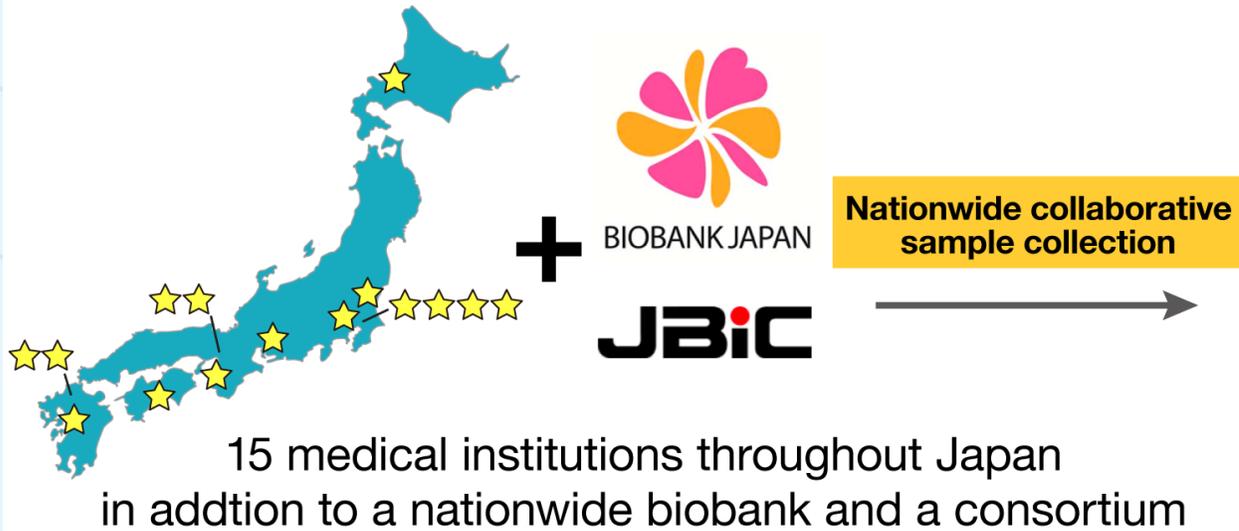
I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals during this presentation.

# Psoriasis genetics

- A common, chronic immune-mediated inflammatory skin disorder with high heritability (~70%).
- Previous GWAS have mainly targeted **common small variants** in **Europeans**.
- The contribution of **rare variants** and **structural variants** remains largely unexplored.
- Studying non-European populations can help uncover novel genetic determinants.



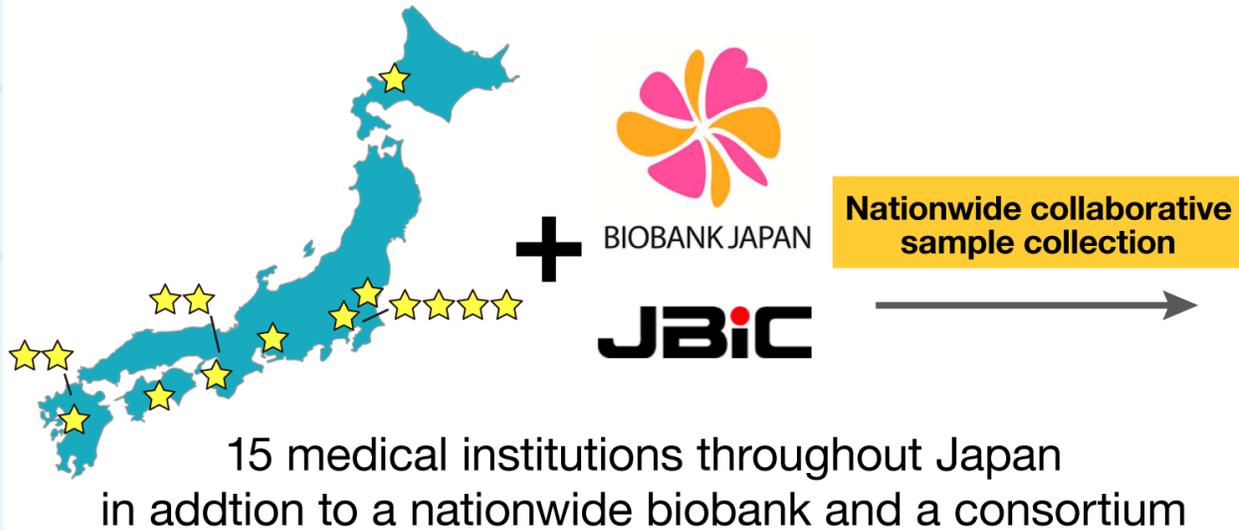
# WGS dataset



## Whole-genome sequence of $N = 5,383$ Japanese

Psoriasis patients $N = 1,415$		Control participants $N = 3,968$		
				<b>WGS Dataset 1</b>
$N = 957$		$N = 2,764$		
				<b>WGS Dataset 2</b>
$N = 458$		$N = 1,204$		

# WGS dataset



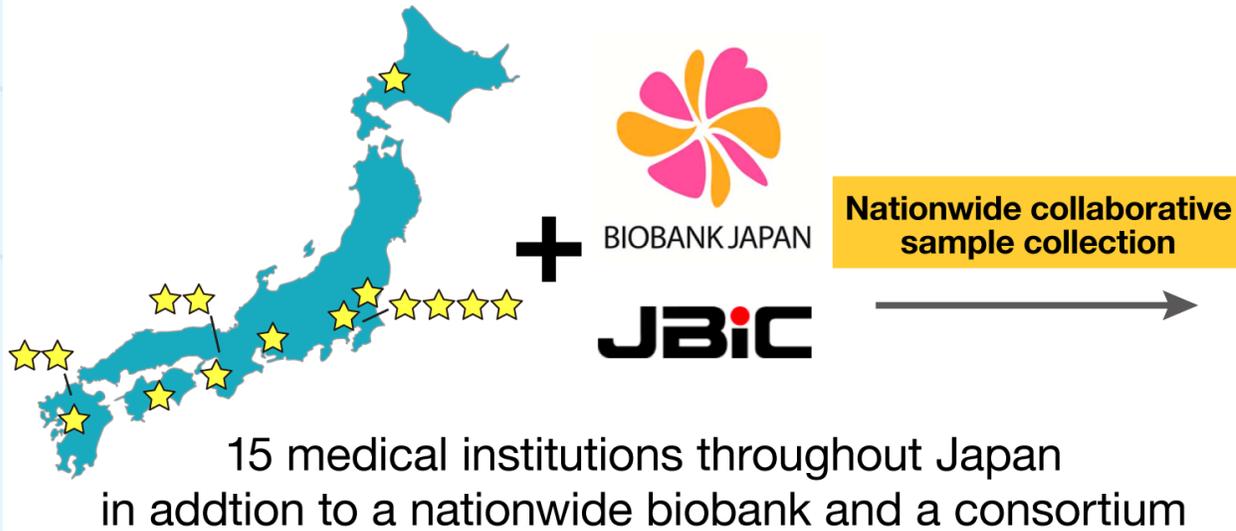
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**Structural variant GWAS and statistical fine-mapping**

**Rare variant gene-based analysis and functional analysis in a mouse model**

# WGS dataset



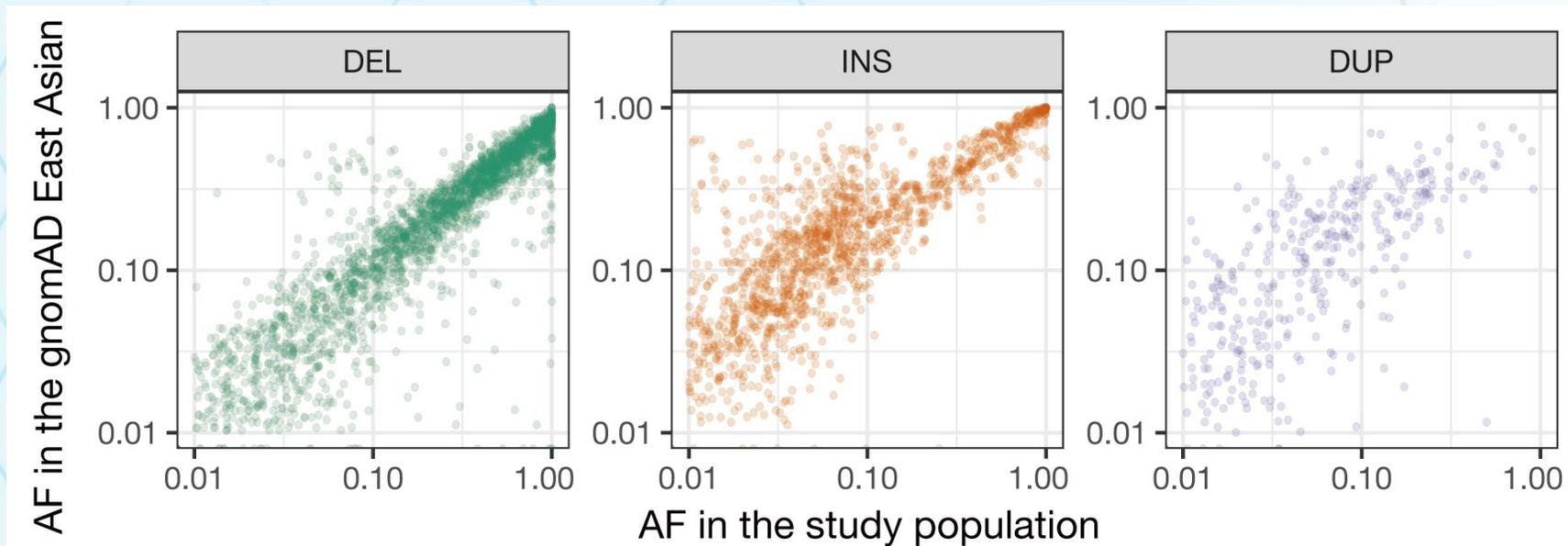
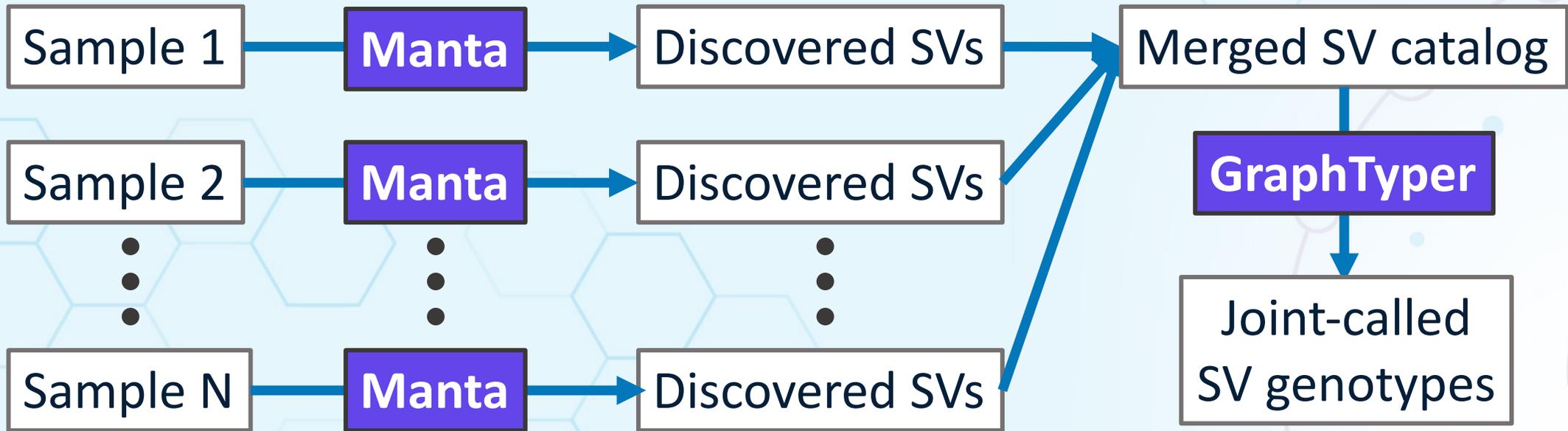
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**Structural variant GWAS and statistical fine-mapping**

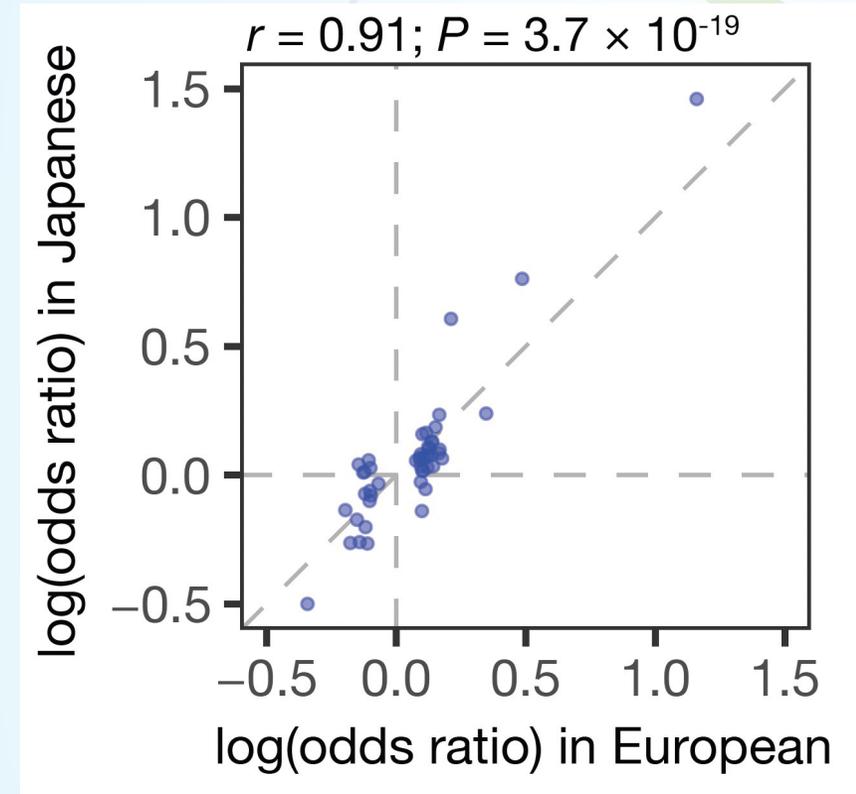
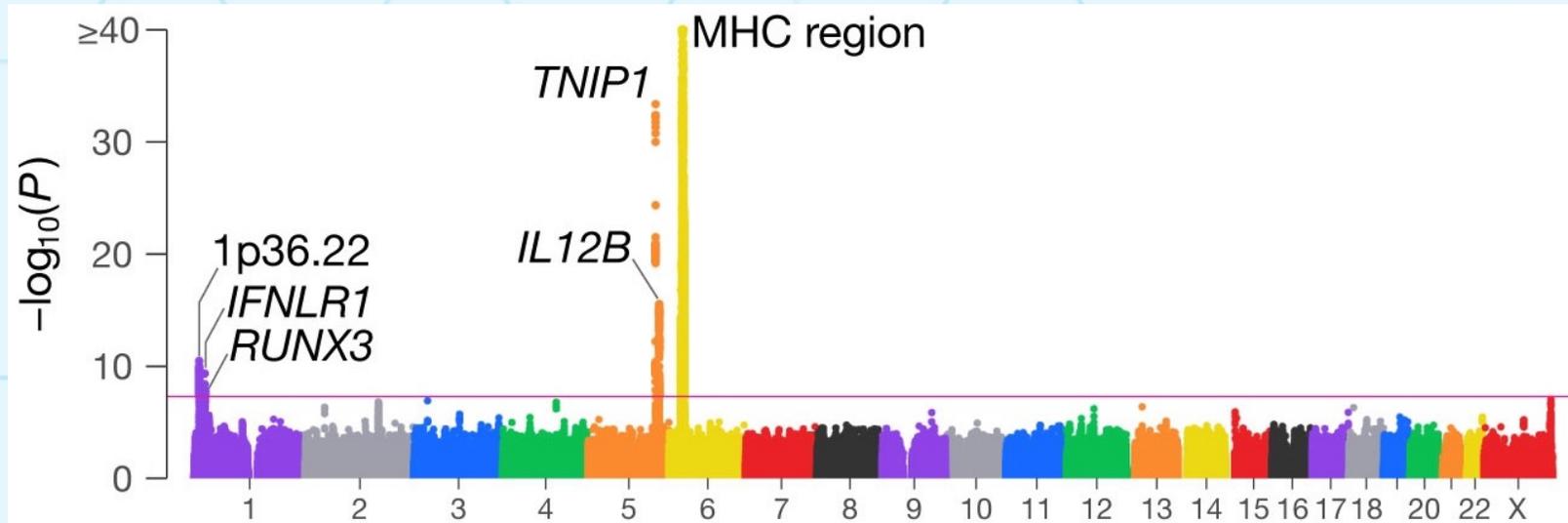
**Rare variant gene-based analysis and functional analysis in a mouse model**

# Structural variant calling



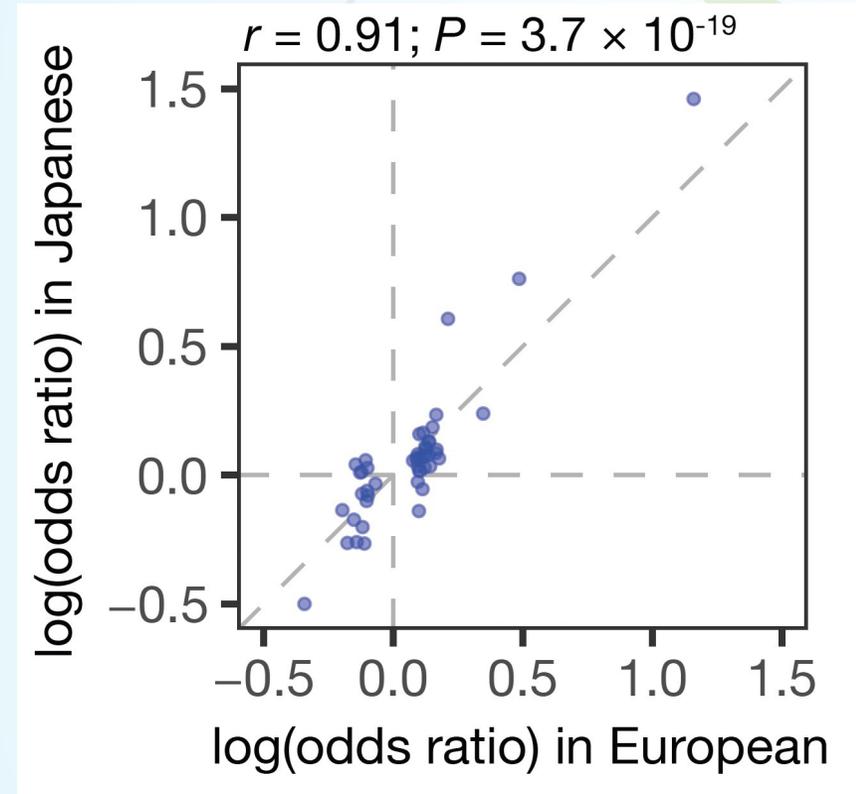
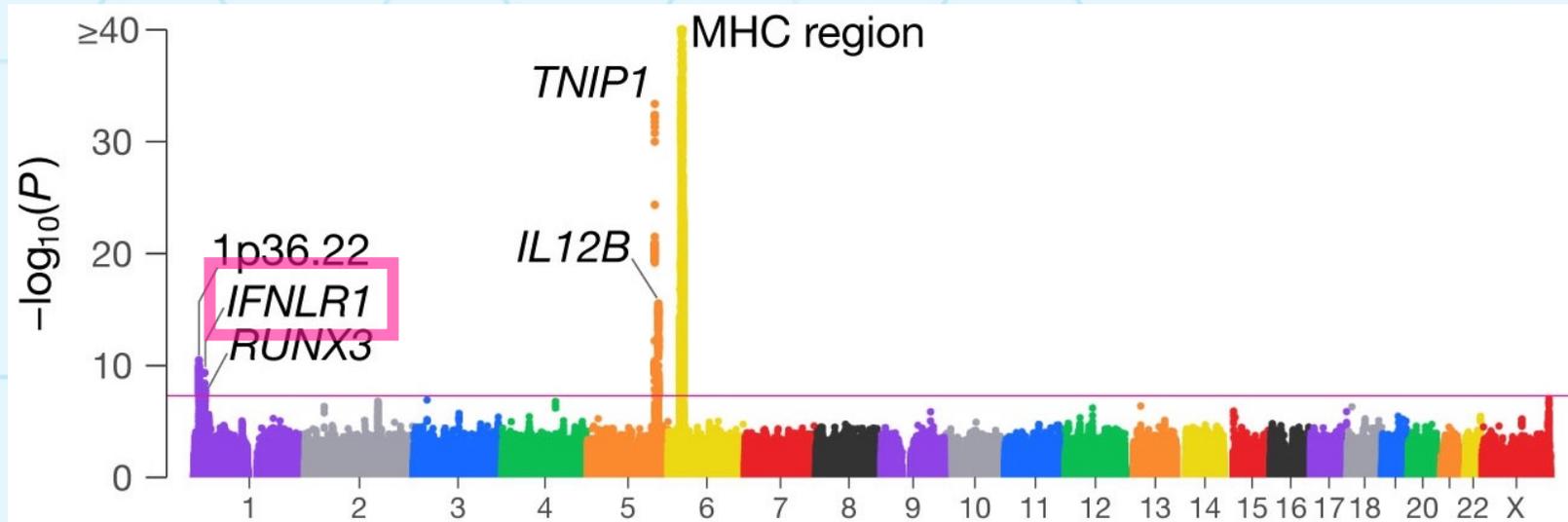
# Common variant GWAS (SV + SNP)

9/24

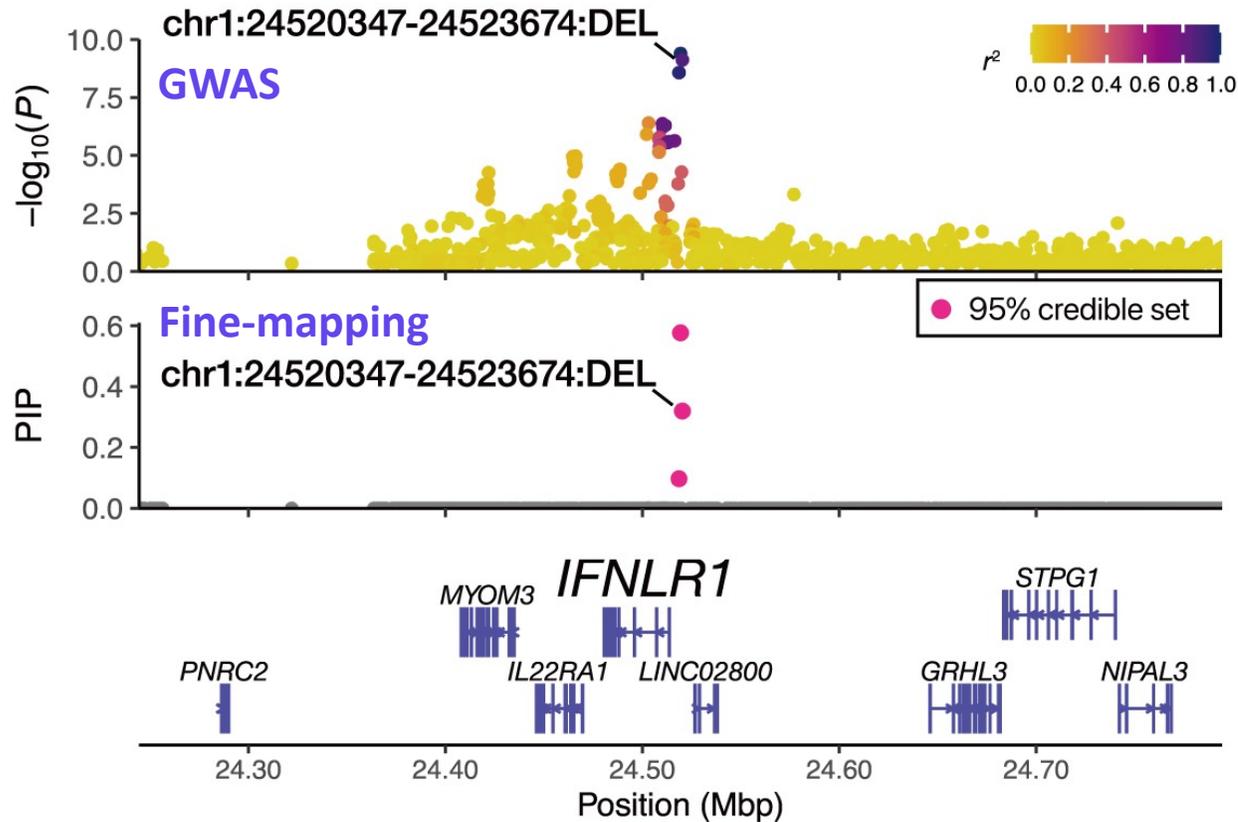
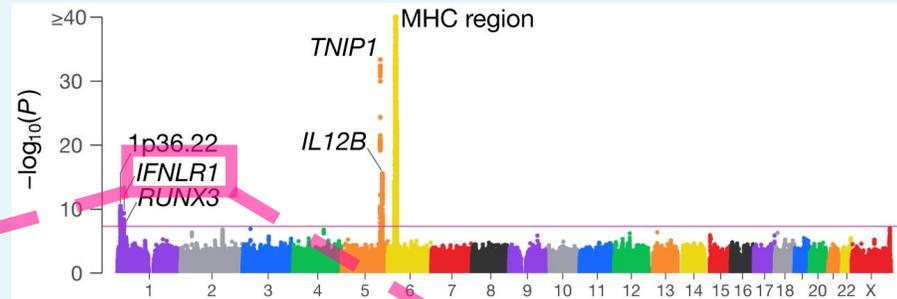


# Common variant GWAS (SV + SNP)

10/24

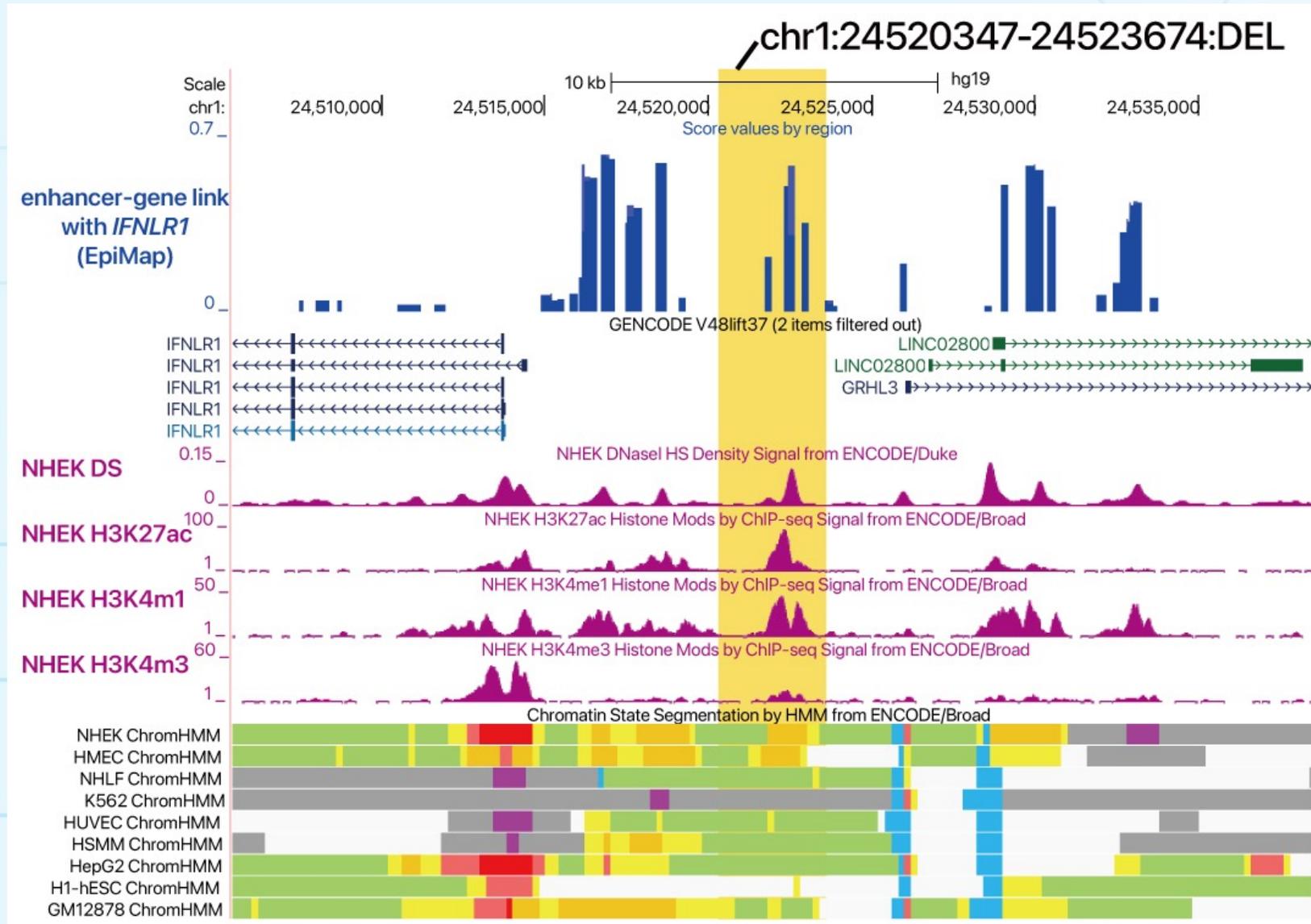


# Fine-mapping at *IFNL1* nominates 3.3kb deletion



Analysis	Allele frequency		$P$	Odds ratio (95% CI)
	PsV	Control		
WGS1	0.135	0.198	$8.3 \times 10^{-8}$	0.64 (0.54–0.75)
WGS2	0.157	0.204	0.0024	0.72 (0.58–0.89)
meta-analysis	0.143	0.200	$1.1 \times 10^{-9}$	0.67 (0.58–0.76)

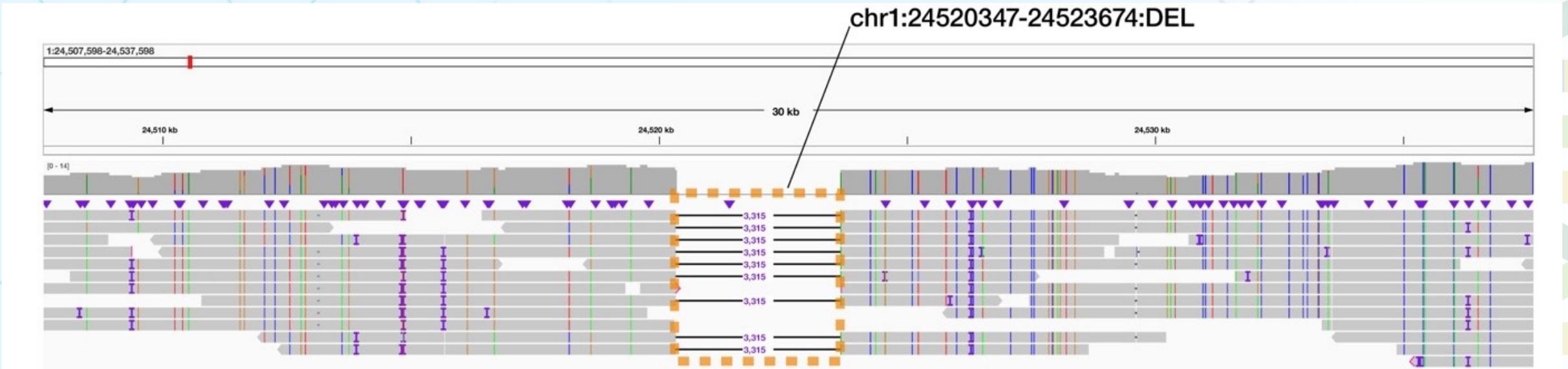
# Fine-mapping at *IFNLR1* nominates 3.3kb deletion



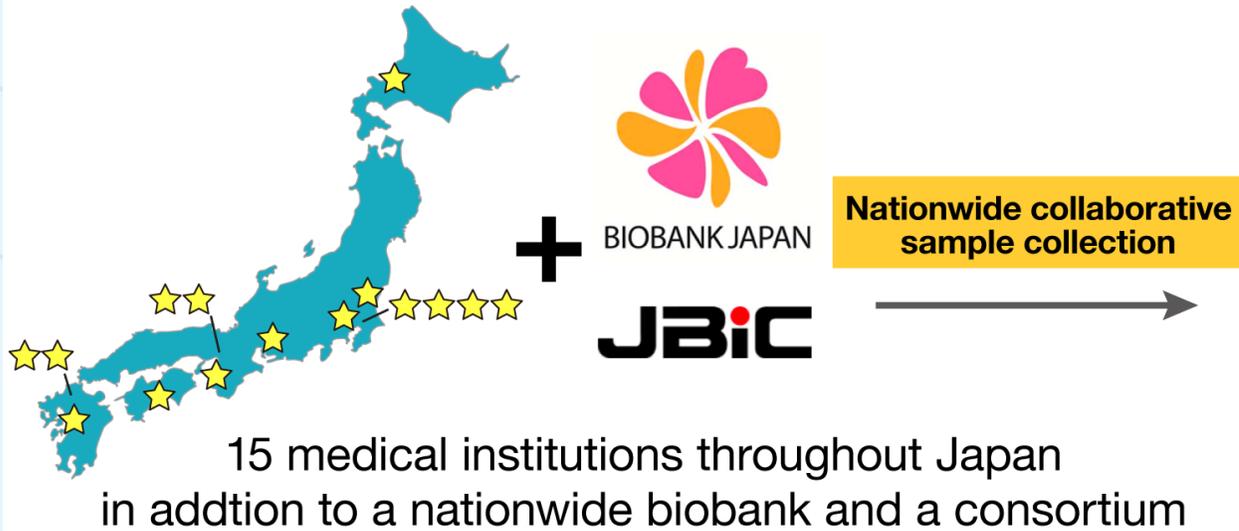
NHEK:  
Normal Human Epidermal Keratinocytes

# Fine-mapping at *IFNLR1* nominates 3.3kb deletion

PacBio HiFi long-read sequencing



# WGS dataset



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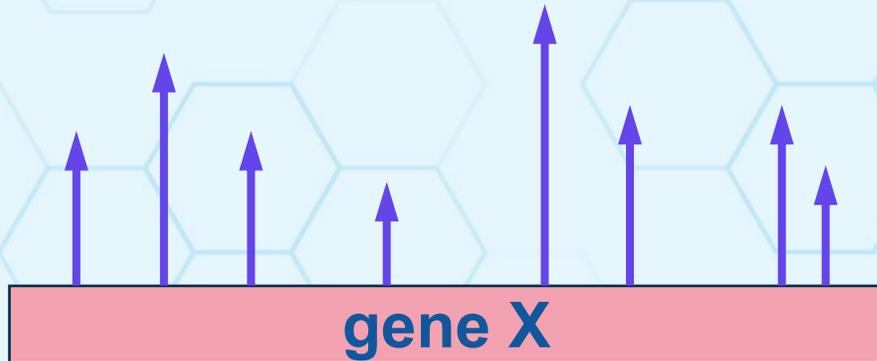
**Structural variant GWAS and statistical fine-mapping**

**Rare variant gene-based analysis and functional analysis in a mouse model**

# Gene-based rare variant test

- Due to its low AF, a single rare variant has low statistical power.
- Aggregating rare variants helps gain power.
- To aggregate the rare variants, we need an assumption on the correlation in the variants' effect sizes.

Burden test: same effect directions



SKAT: varied effect directions



# Gene-based rare variant test

Methods

Burden

SKAT

×

Functional annotation

pLoF by LOFTEE  
+  
HIGH or MODERATE by VEP

pLoF by LOFTEE  
+  
HIGH or MODERATE by VEP  
+  
SpliceAI delta score  $\geq 0.2$

Allele frequency filter

AF  $\leq 1\%$

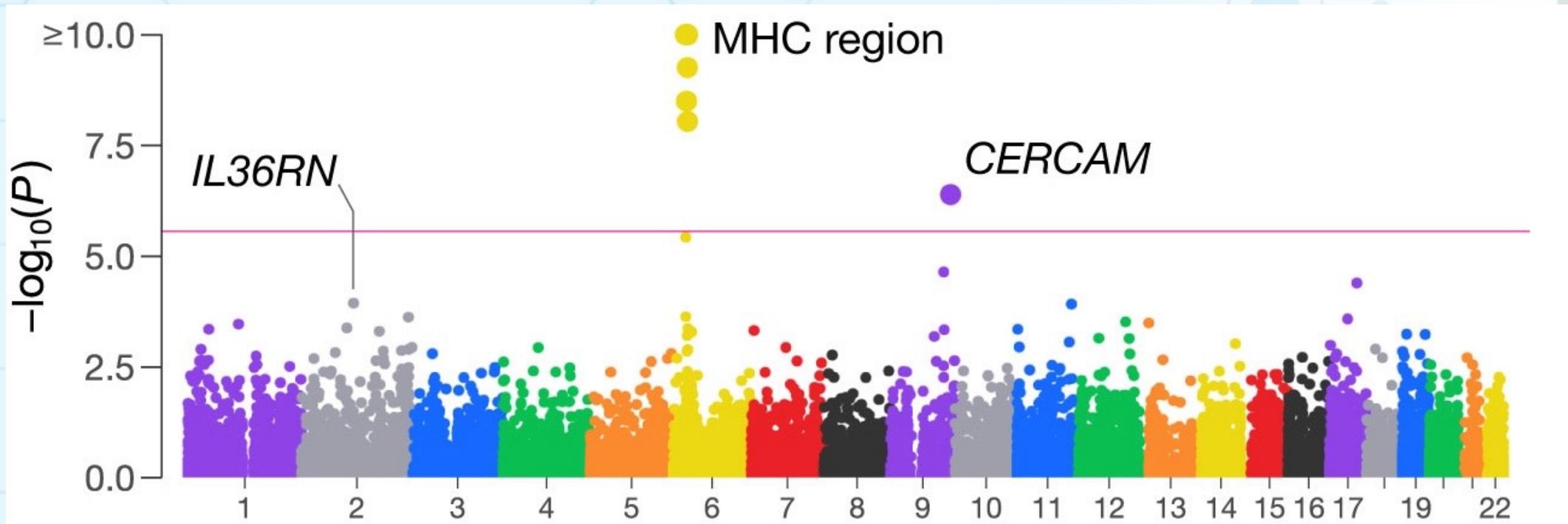
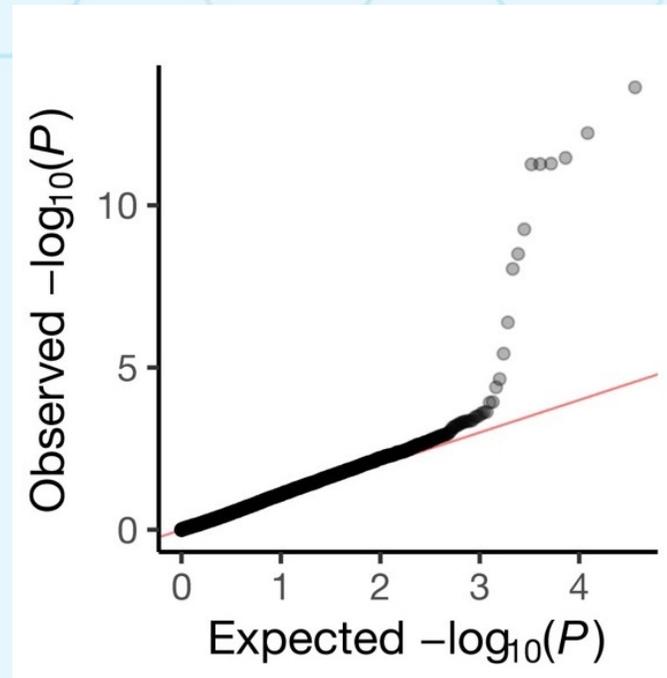
AF  $\leq 0.5\%$

AF  $\leq 0.1\%$

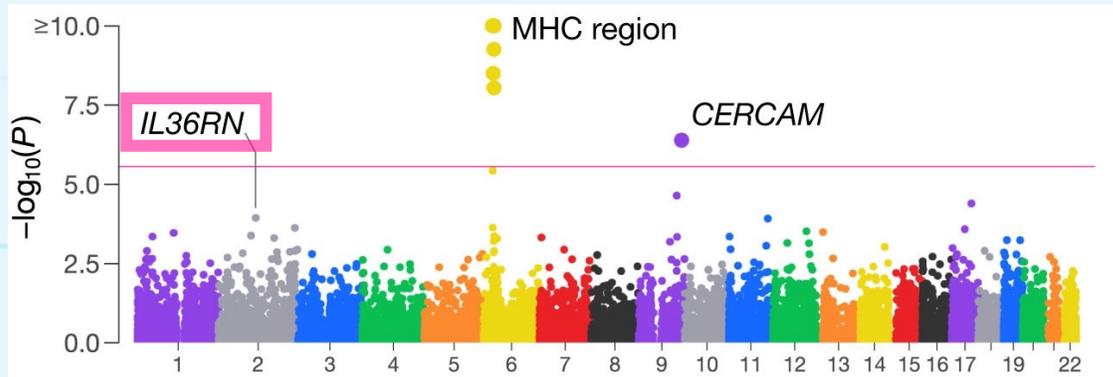
×

Combining results using the aggregated Cauchy association test (ACAT)

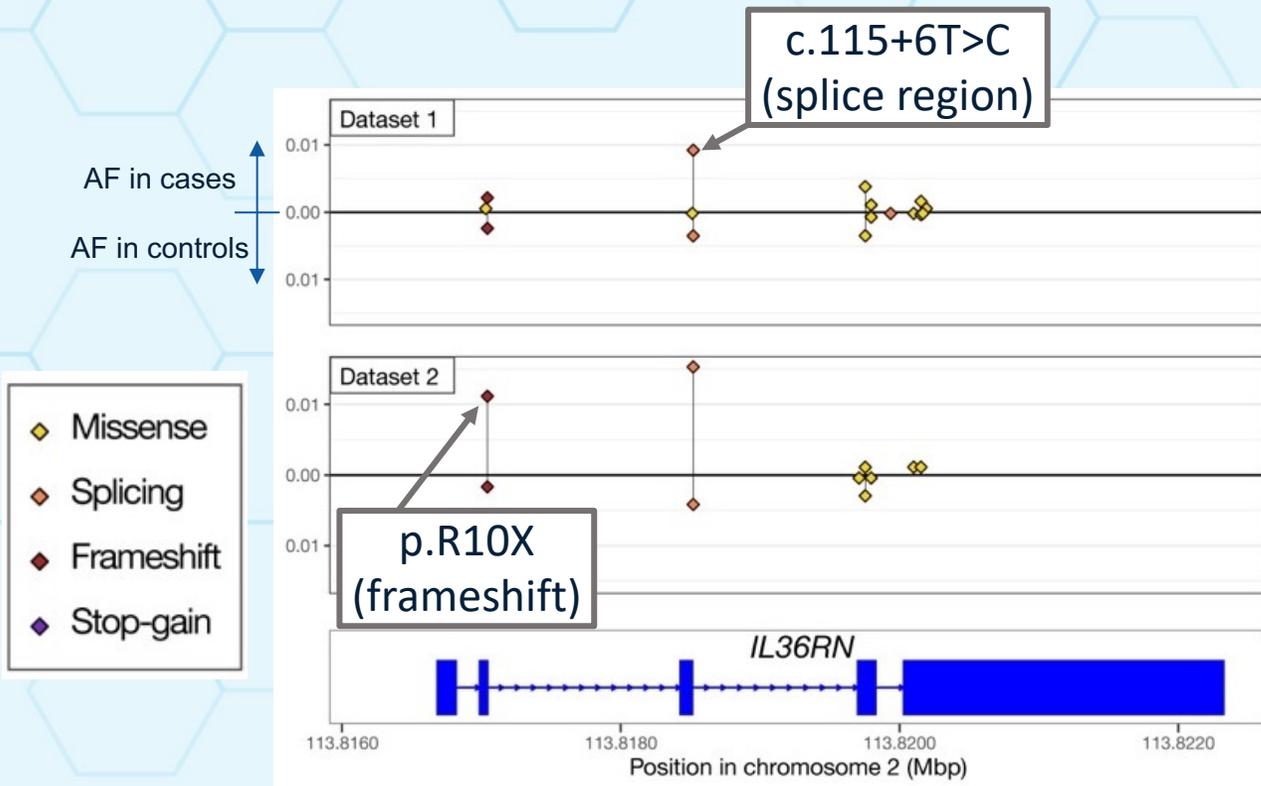
# Gene-based rare variant test



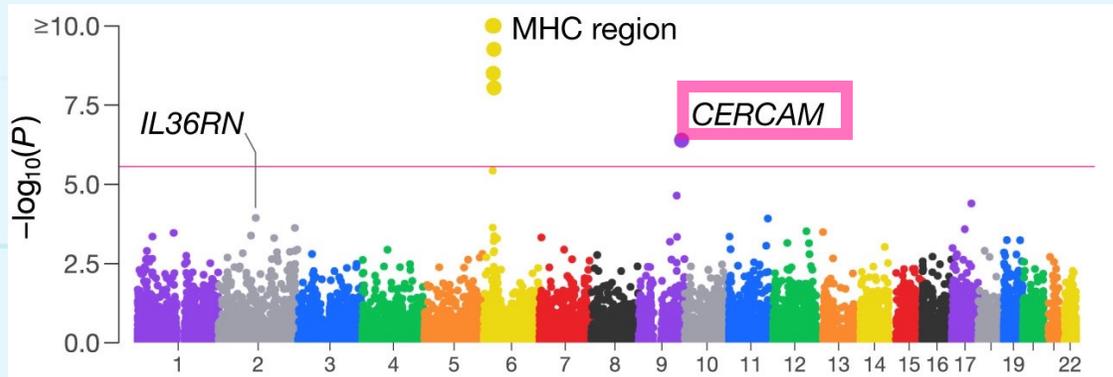
# Rare-variant gene-based test identified *IL36RN* <sup>18/24</sup>



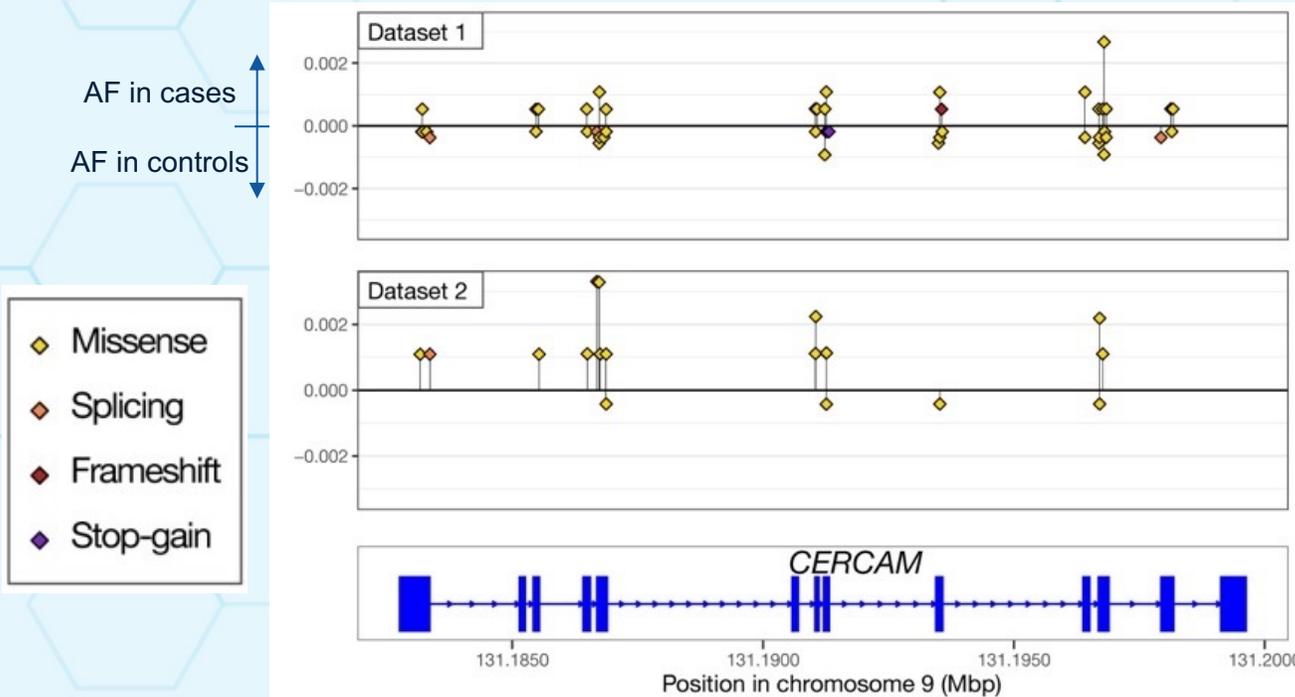
- Causal gene for generalized pustular psoriasis (GPP), a rare and lethal systemic inflammation disease (~7 cases per million).
- The association was driven by known pathogenic mutations for GPP.



# Rare-variant gene-based test identified *CERCAM*



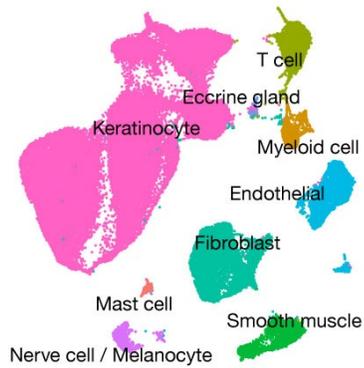
- *CERCAM* encodes cerebral endothelial cell adhesion molecule, whose role in the skin was unknown.
- The association was replicated in the UK Biobank with the same directional effect ( $P_{\text{burden}} = 0.021$ ).



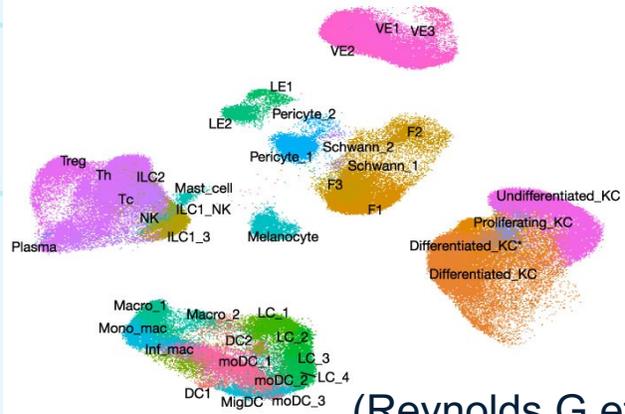
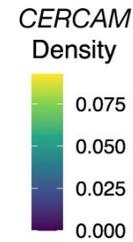
# CERCAM in skin tissue

Single-cell RNA-seq  
(10X)

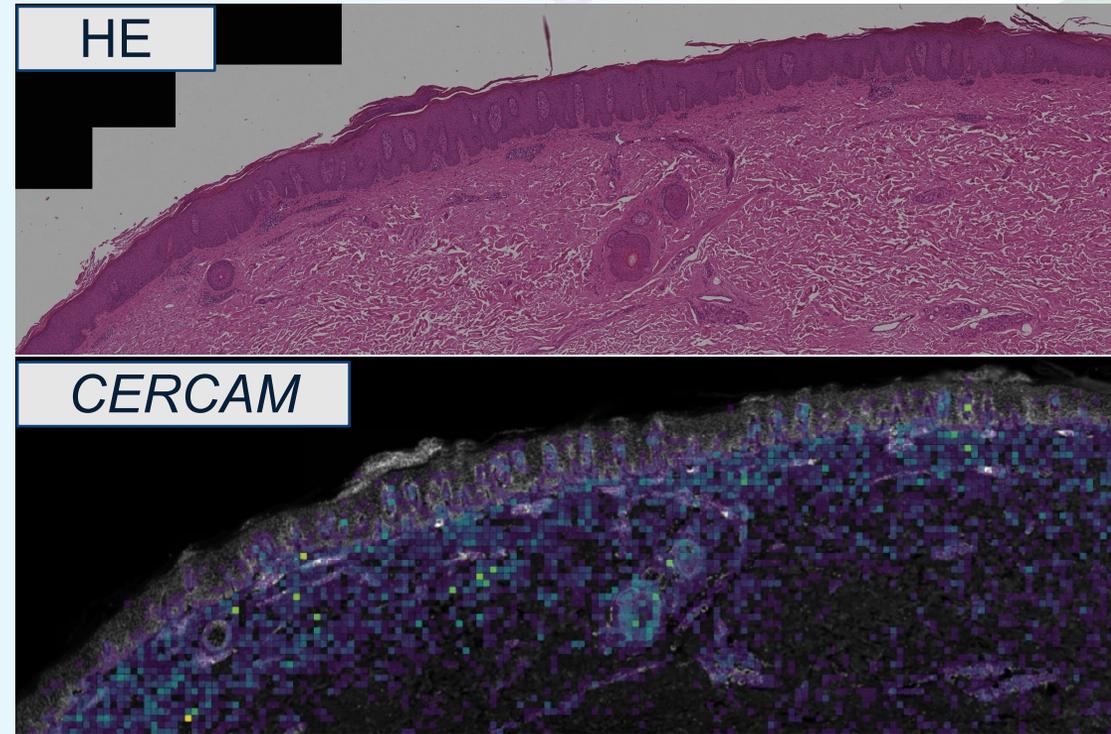
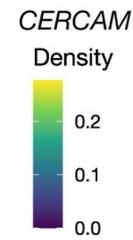
Spatial transcriptome  
(Xenium)



(Ma F et al. 2023)

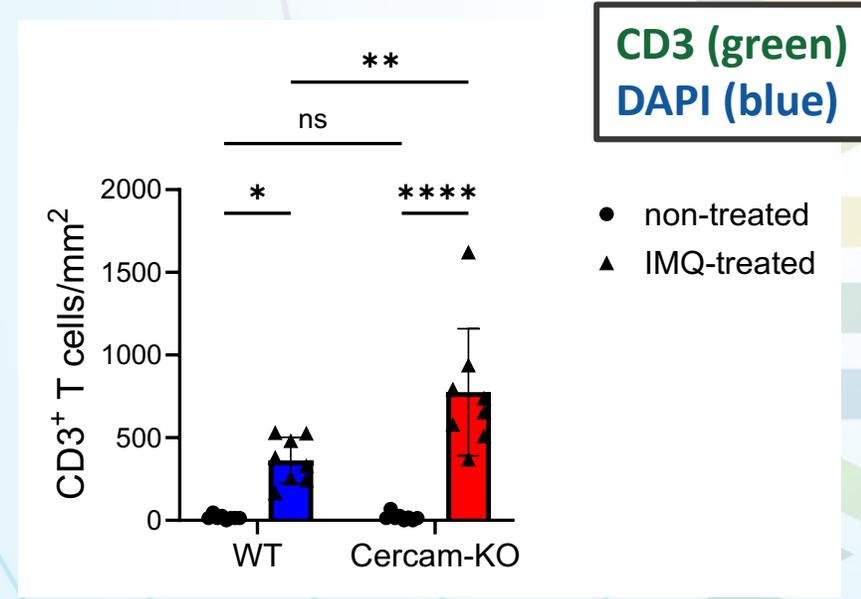
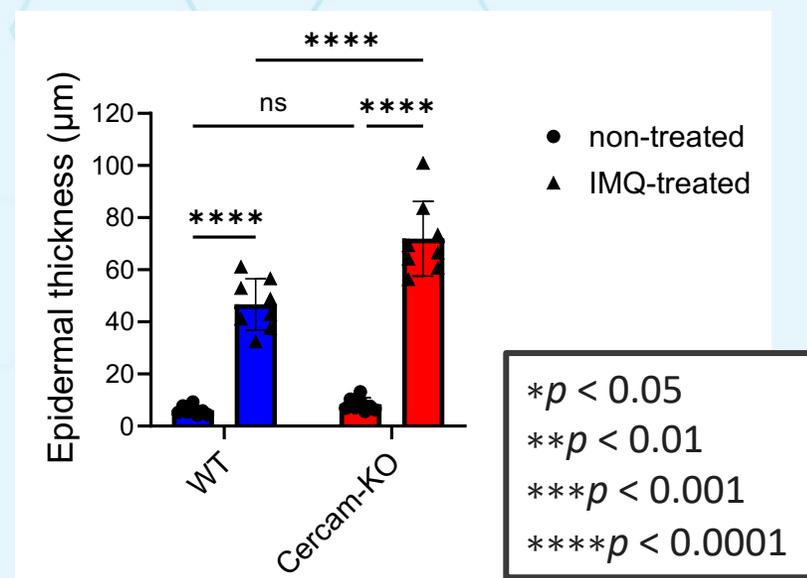
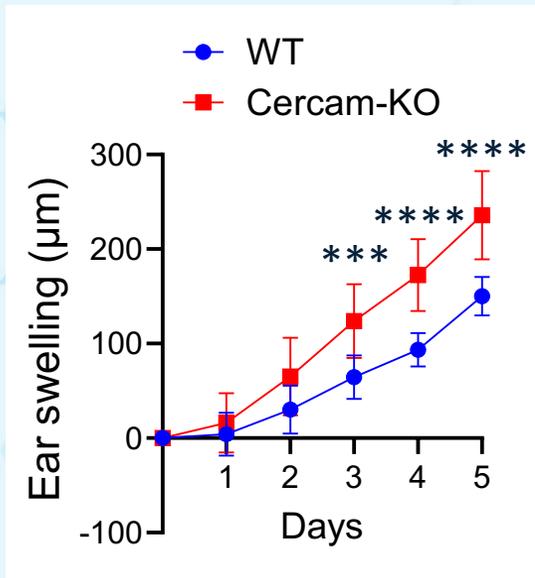
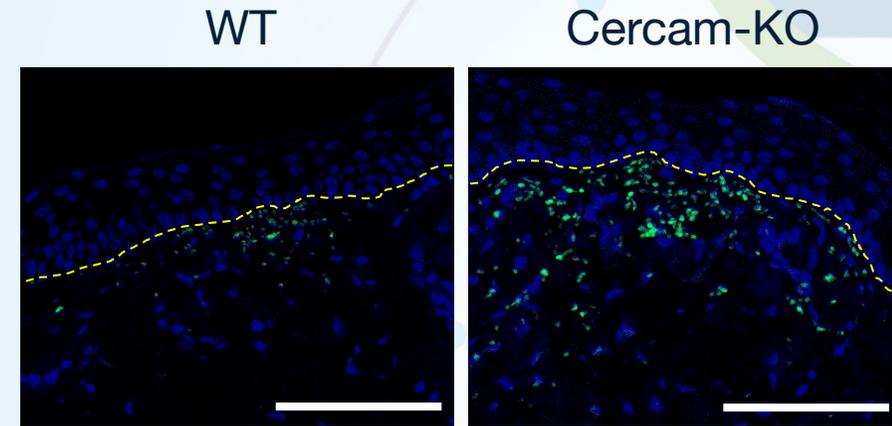
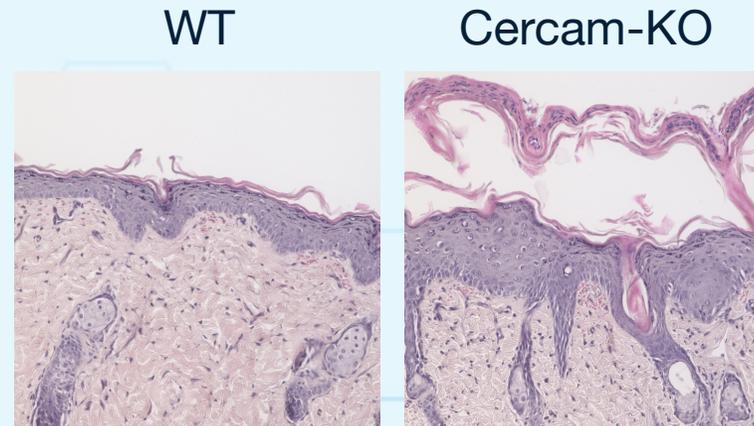


(Reynolds G et al. 2021)



# Cercam knock-out in psoriasis mouse model

- *Cercam*<sup>-/-</sup> mice showed more severe dermatitis induced by imiquimod.

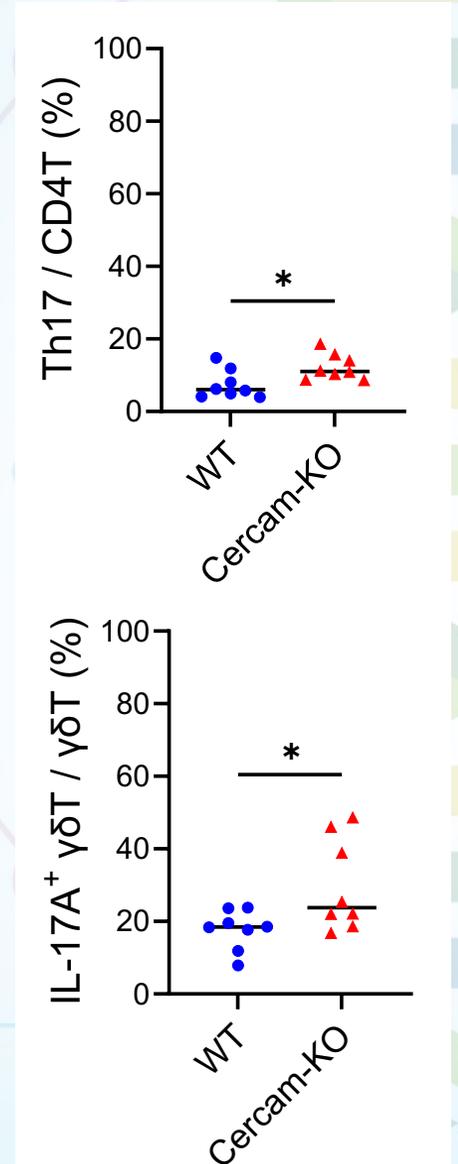
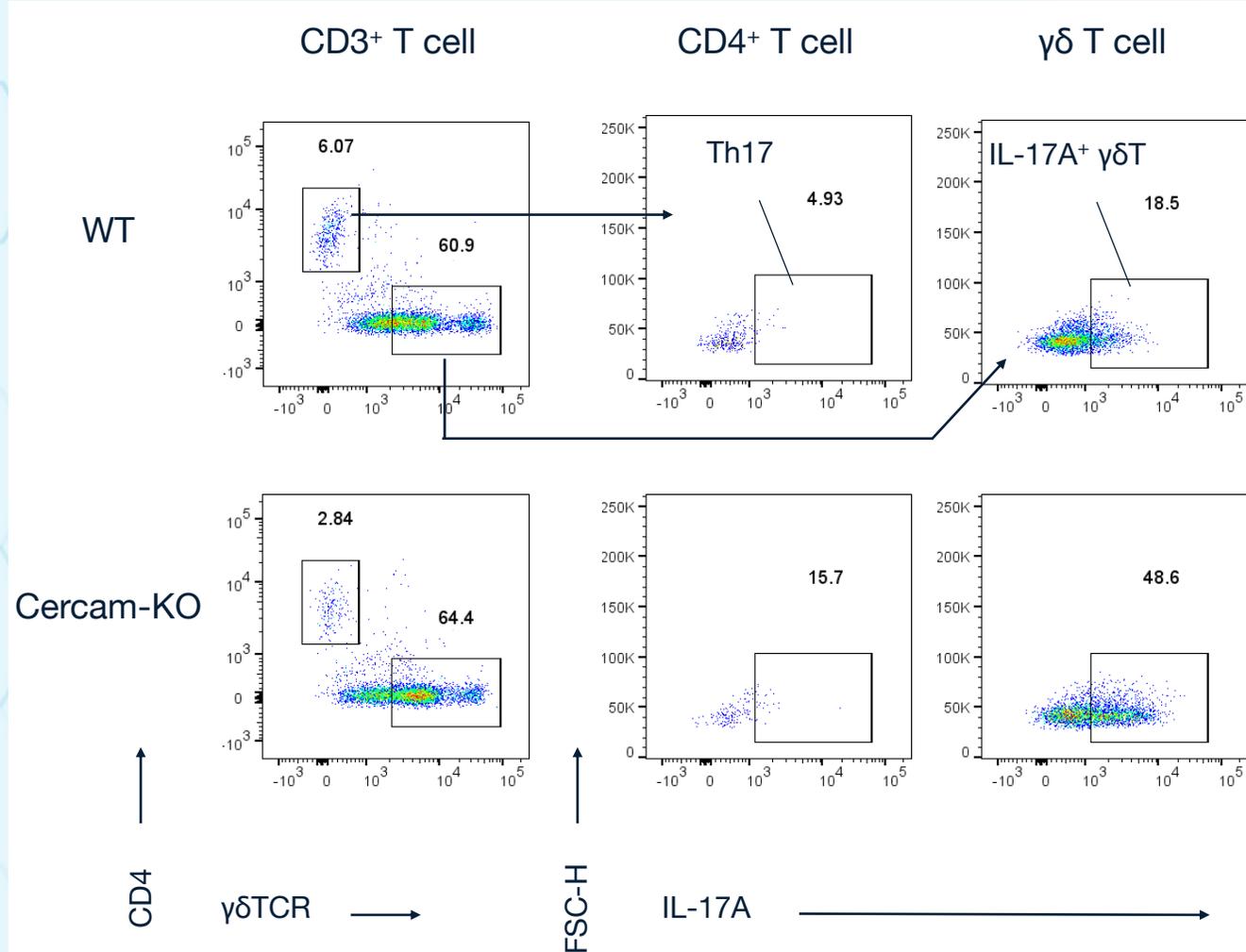
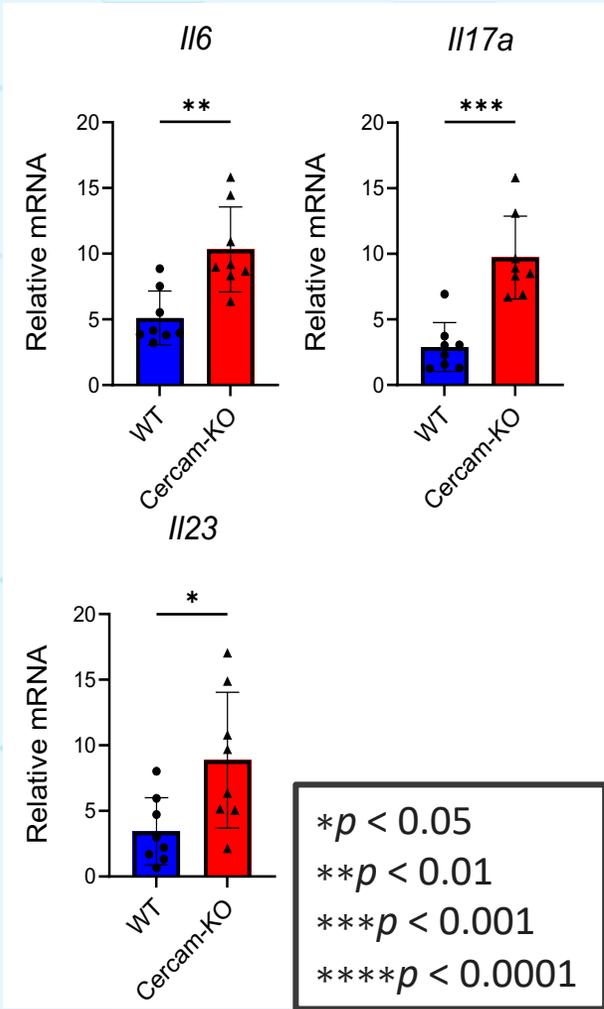


CD3 (green)  
DAPI (blue)

\*p < 0.05  
\*\*p < 0.01  
\*\*\*p < 0.001  
\*\*\*\*p < 0.0001

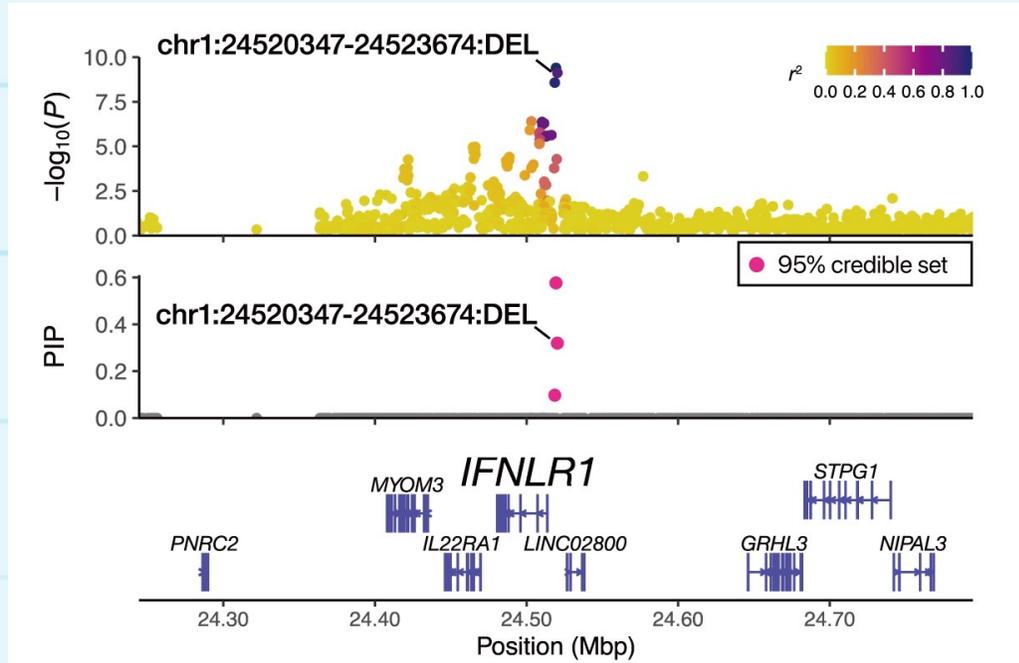
# Cercam knock-out in psoriasis mouse model

- CD4<sup>+</sup> T cells and  $\gamma\delta$  T cells producing IL-17 were increased.

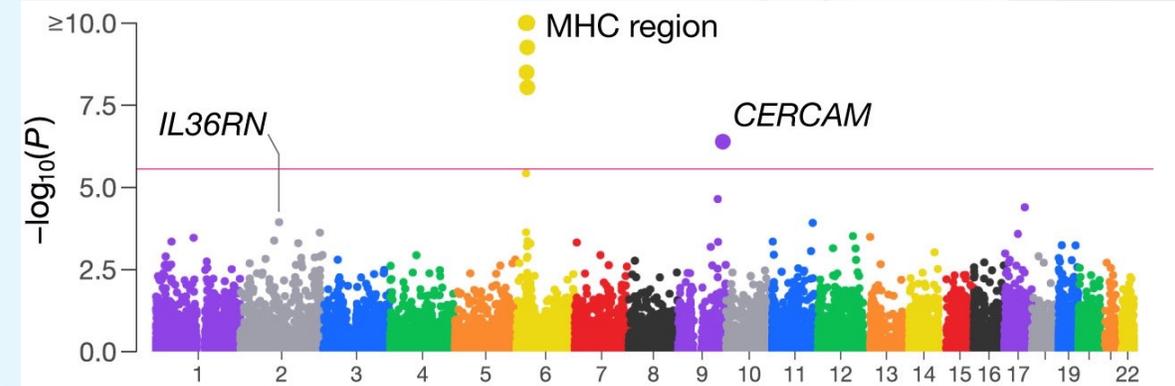


# Conclusions

## Structural variant

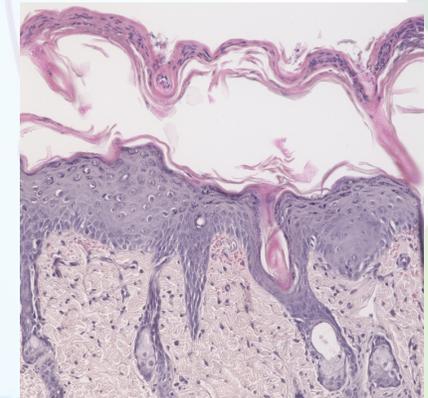
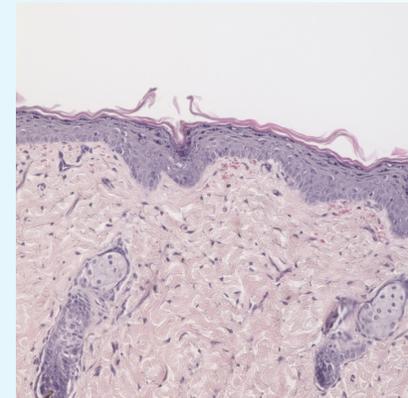


## Rare variant



WT

Cercam-KO



← More details are available in our recently published paper (Sonehara K et al. *Cell Genomics* published on Aug 19, 2025)



# Acknowledgments

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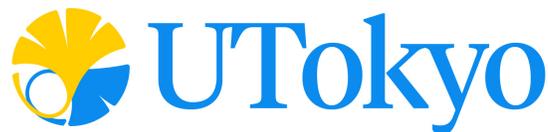
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Akimichi Morita

**Biobank Japan**

Koichi Matsuda



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