Understanding how non-coding mutations cause Juvenile Idiopathic Arthritis (JIA)

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INTRODUCTION

- More than 73 genetic loci associated with JIA have been identified, meaning mutations (or SNPs) in these loci increases the risk of JIA. However, the biological impact of these SNPs remains unknown, mainly because most are located outside of protein coding regions.
- Recent evidence has found that elements in the non-coding regions can regulate the expression of distant target genes, one way is through physical interactions
- Identifying the expression of which genes in which tissues are affected by these non-coding SNPs may enable us to understand the biological mechanism behind the development of JIA.

METHODS

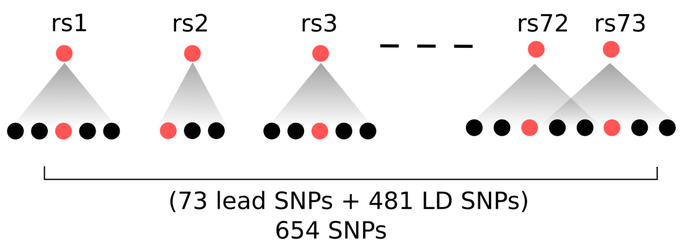
We identified the genes regulated by JIA-associated SNPs using a computational pipeline

Step 1

73 JIA-associated risk loci / lead SNPs

Retrieved from **GWAS catalog**[1]

Step 2



Other SNPs in high LD and within 10kb of the lead SNPs are identified using data from **1000 Genomes Project**[2]

(73 lead SNPs + 481 LD SNPs)
654 SNPs

Step 3 CoDeS3D pipeline[3]

(i) Identification of SNP - gene physical interactions pairs

Chromatin interaction data from **76 Hi-C cell lines**

(ii) Identification of SNPs that alter the expression of their target genes (eQTL - target gene pairs)

eg.,Skeletal muscle (GTEx) Naive B-cell (DICE)

eQTL data from :

- **GTEx** (49 human tissues)[4]
- **DICE** (15 immune cells)[5]

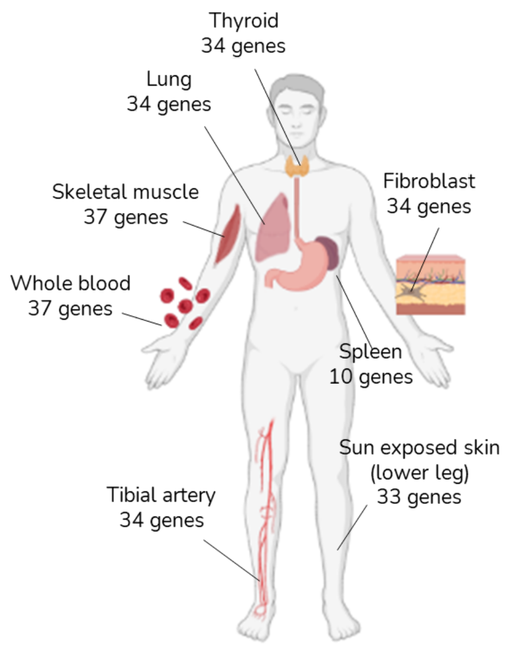
Legend

- Lead SNP
- LD SNP
- LD r2 ≥ 0.8 and and within 10kb
- Gene

Tissue-specific target genes regulated by JIA-associated SNPs

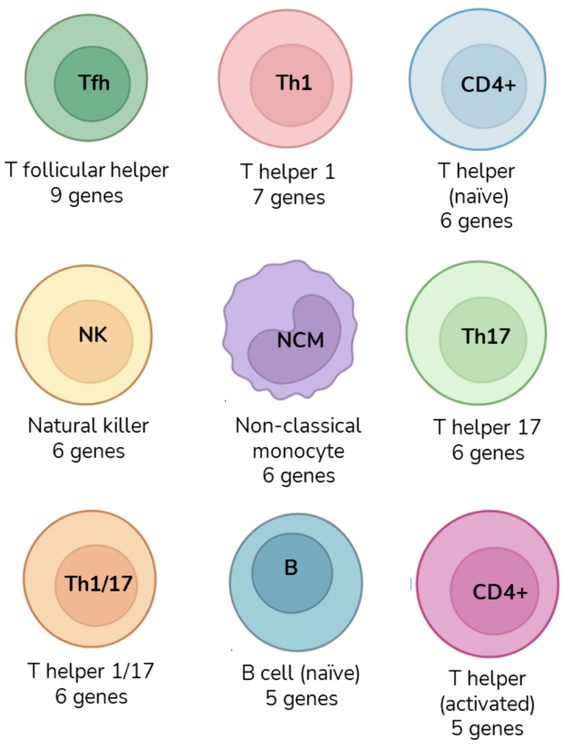
RESULTS

JIA SNPs have regulatory effects across the body



***Total : 194 target genes in 49 tissues**

Regulatory effects of JIA SNPs differ between immune cell types



***Total : 31 target genes in 15 immune cells**

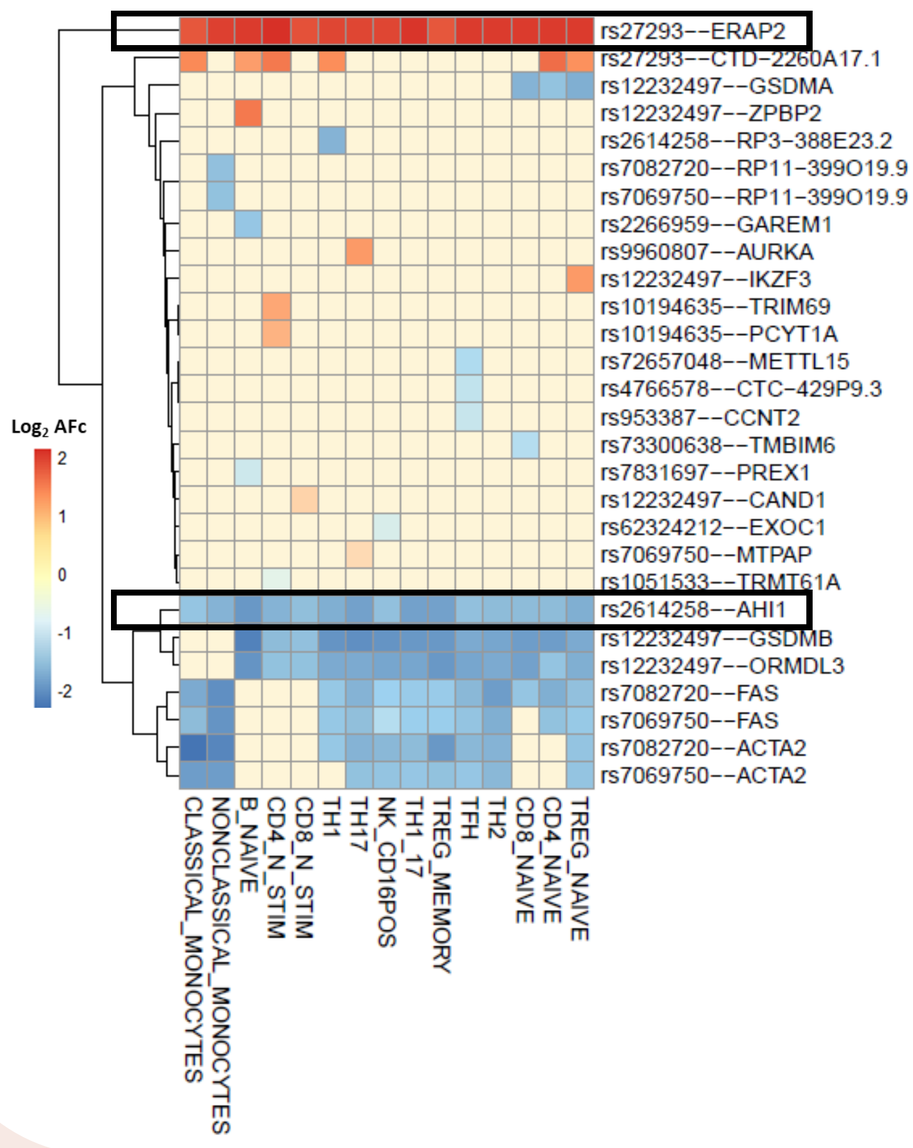
GENEONTOLOGY Unifying Biology

Biological Process enrichment

	No. genes	*P*-val
Antigen processing and presentation	13	9.6×10^{-9}
MHC class II protein complex assembly	5	5.2×10^{-5}
Immune system response	41	1.0×10^{-3}
Regulation of lymphocyte cell activation	14	7.7×10^{-3}
Regulation of T cell activation	11	8.9×10^{-3}
Cellular response to interleukin-2	3	1.1×10^{-2}
MAPK cascade	18	1.6×10^{-2}

JIA target genes are enriched for immune-related functions

Two genes (ERAP2 and AHI1) are regulated across all cell types, while other genes are regulated in a cell type-specific manner



CONCLUSION

- We have integrated multiple levels of biological information to decipher the mechanism that links genetic risk to the development of JIA.
- These results may contribute to the development of improved therapies by identifying tissue-specific therapeutic targets that play a role in the development of JIA.

REFERENCES

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