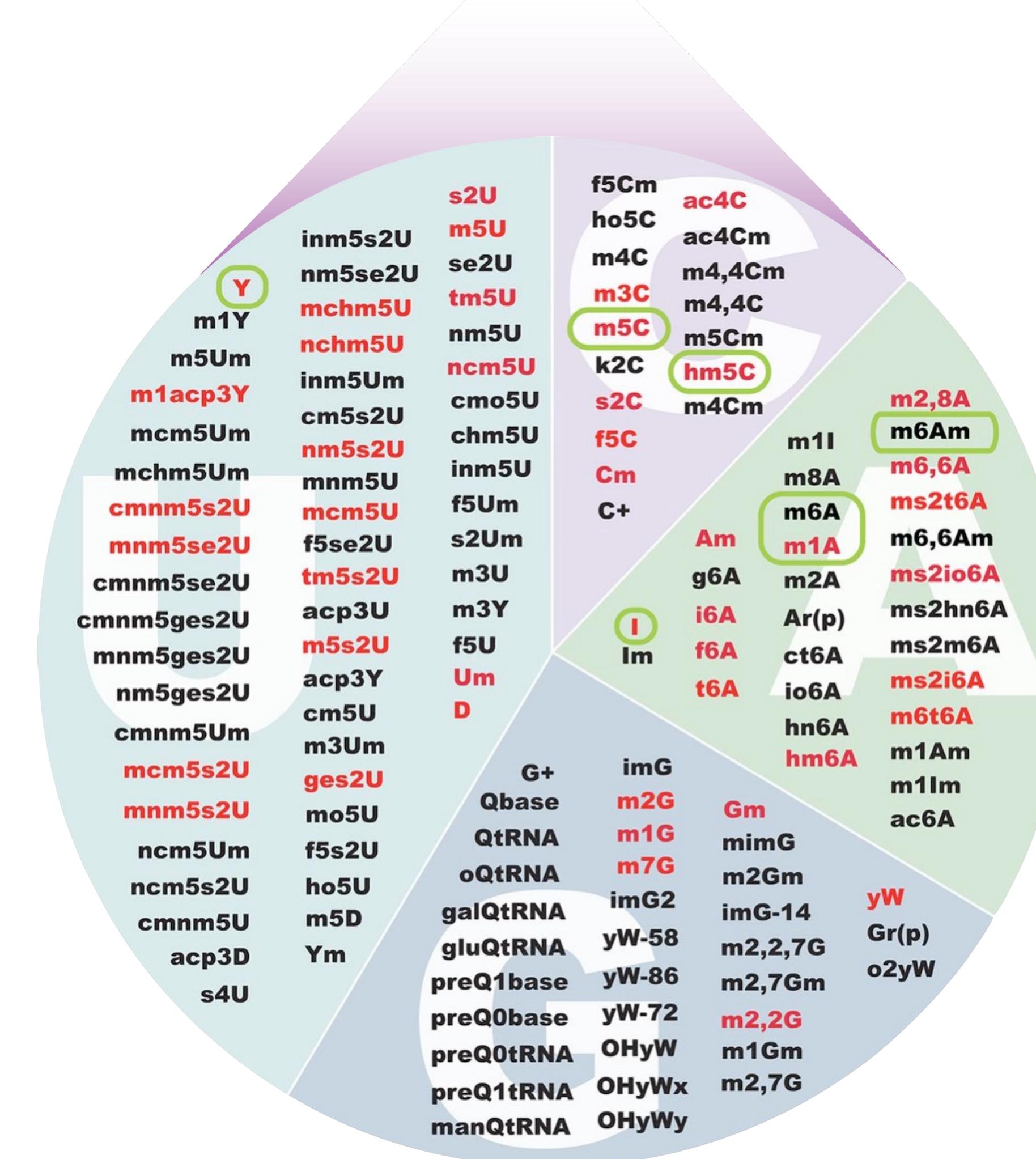
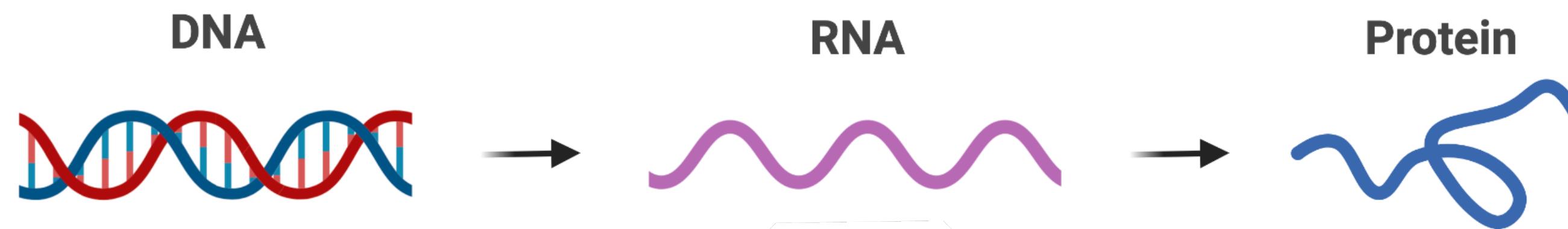


Reduced RNA editing is a major risk factor for inflammatory diseases

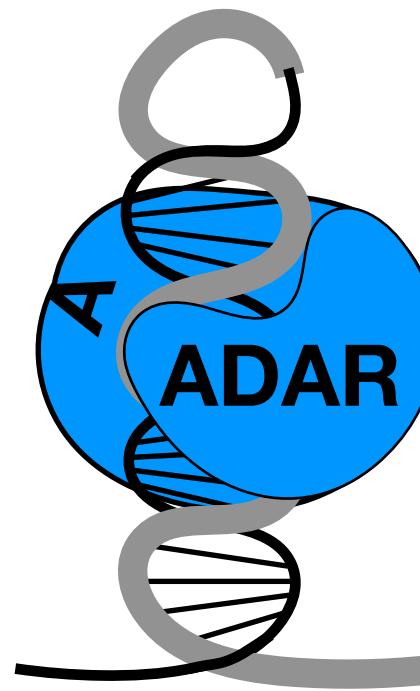
Qin Li

Department of Genetics



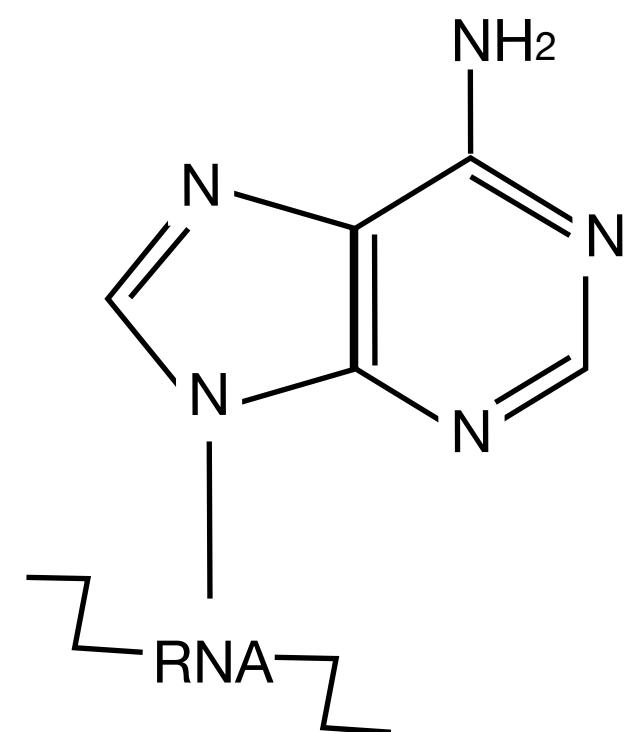
Disease related

Adenosine-to-Inosine (A-to-I) RNA editing is catalyzed by ADAR proteins

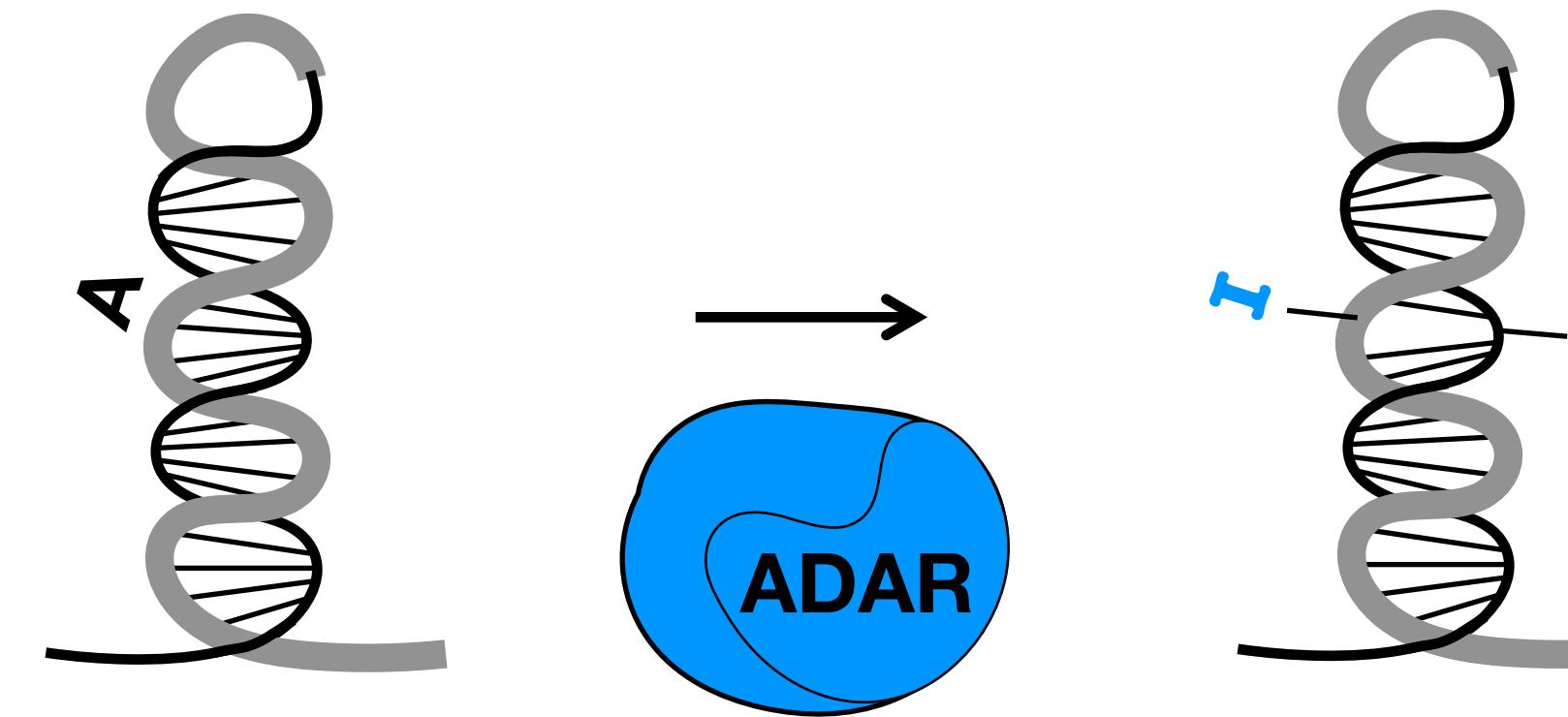


ADAR: Adenosine Deaminase Acting on RNA

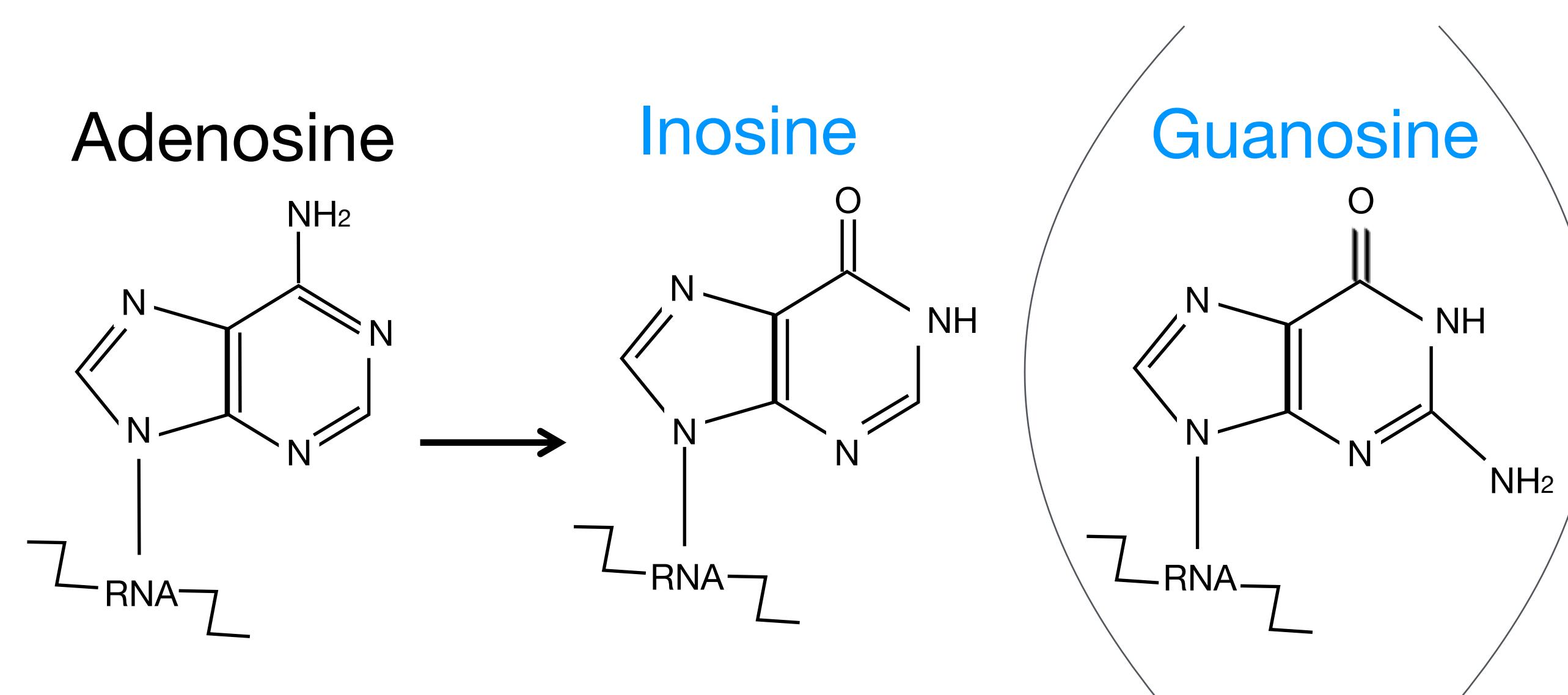
Adenosine



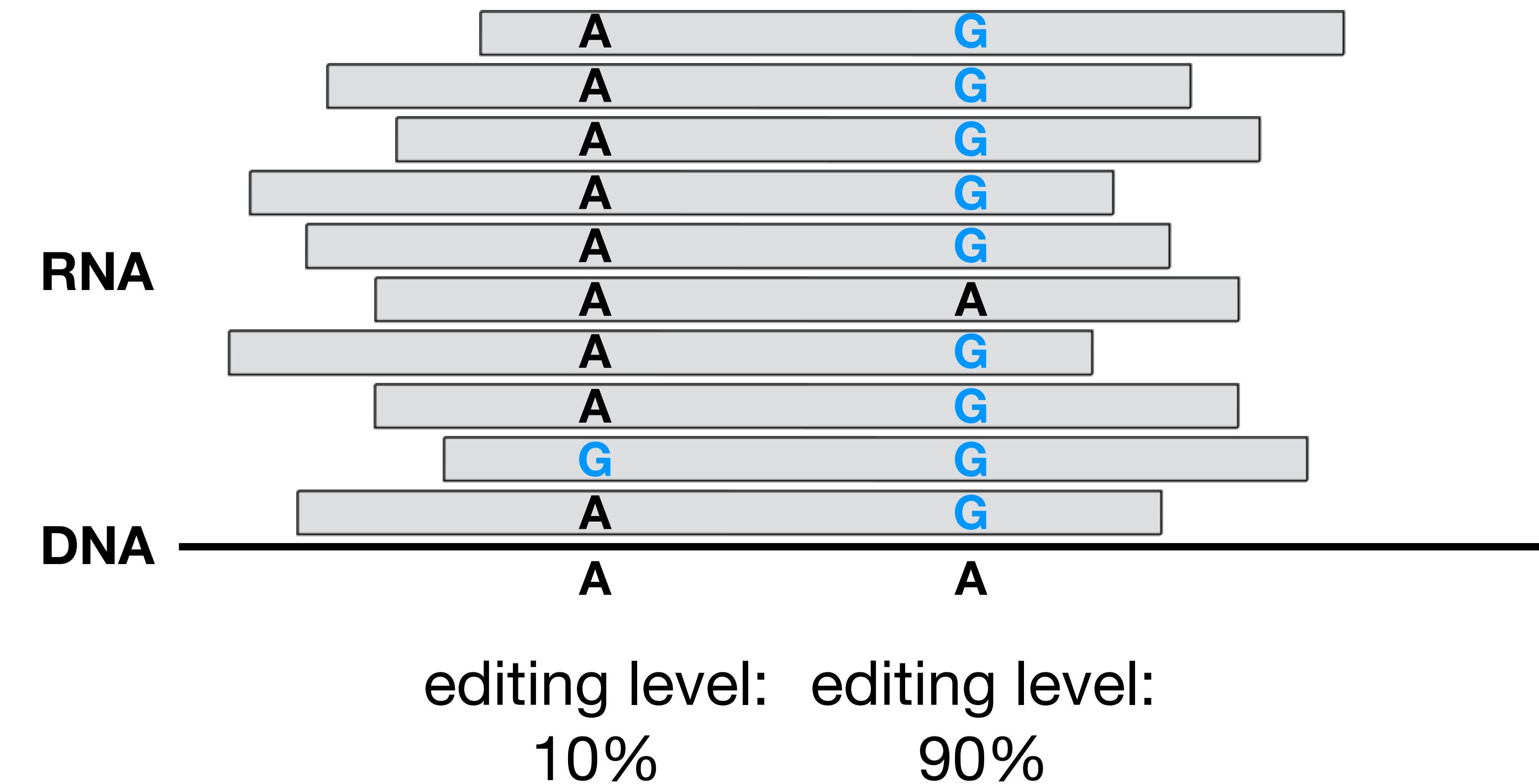
Adenosine-to-Inosine (A-to-I) RNA editing is catalyzed by ADAR proteins



ADAR: Adenosine Deaminase Acting on RNA

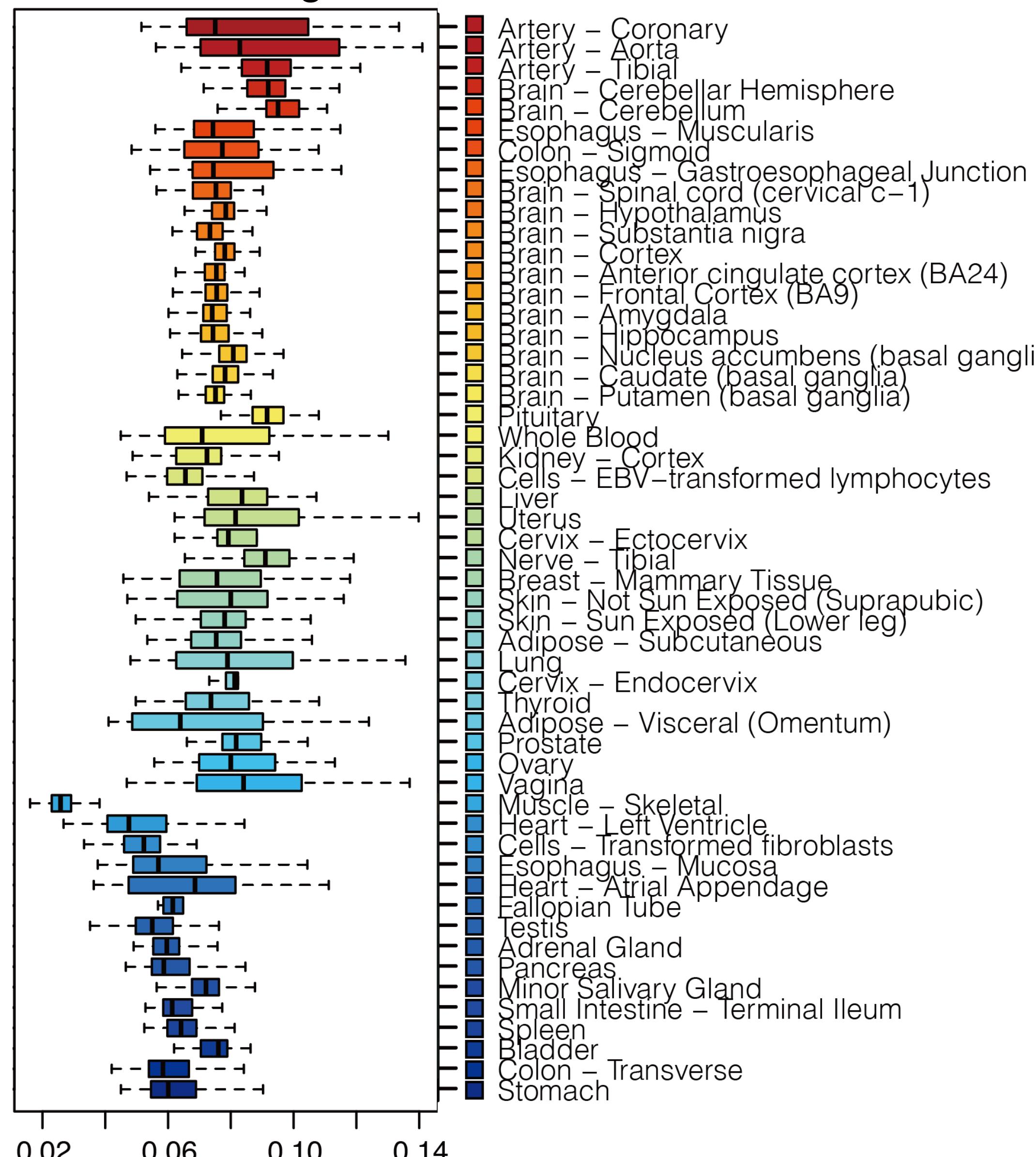


RNA editing can be identified and quantified by RNA-sequencing

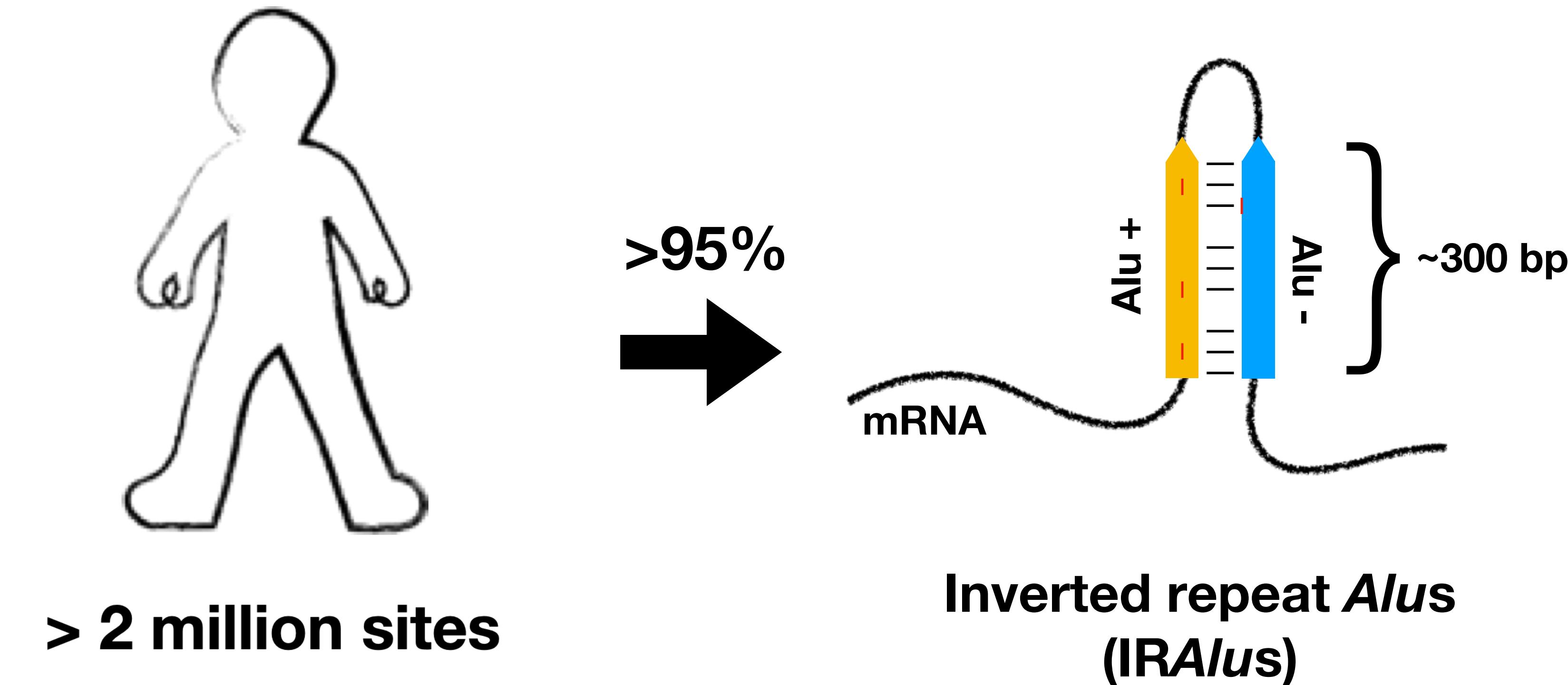


Millions of RNA editing sites are identified in human tissues

Overall editing level



Alu repeats are the main targets of ADAR in human

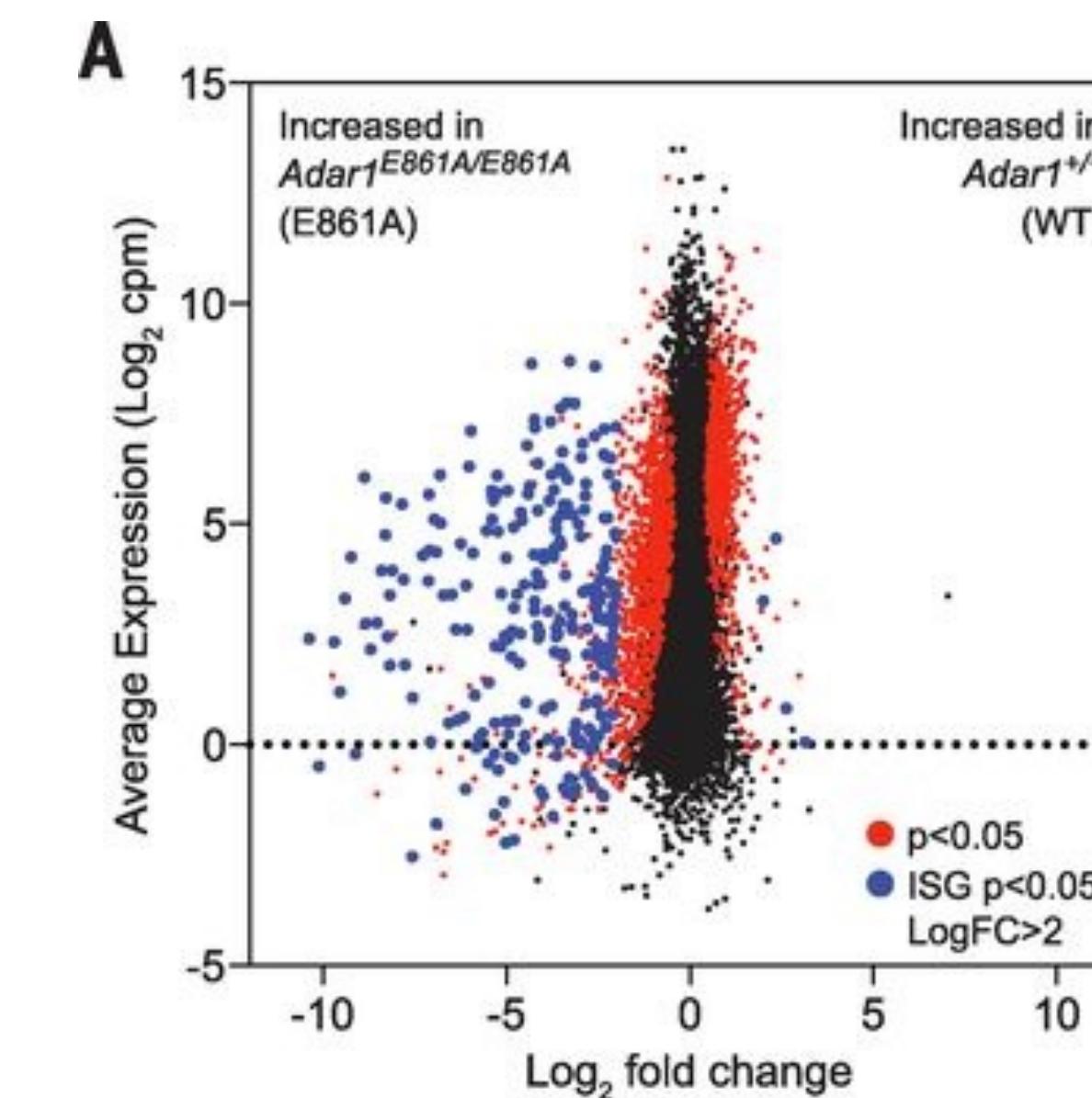


Loss of ADAR editing leads to severe phenotypes in mice

Mice with editing-deficient ADAR die at ~E13.5 due to liver failure



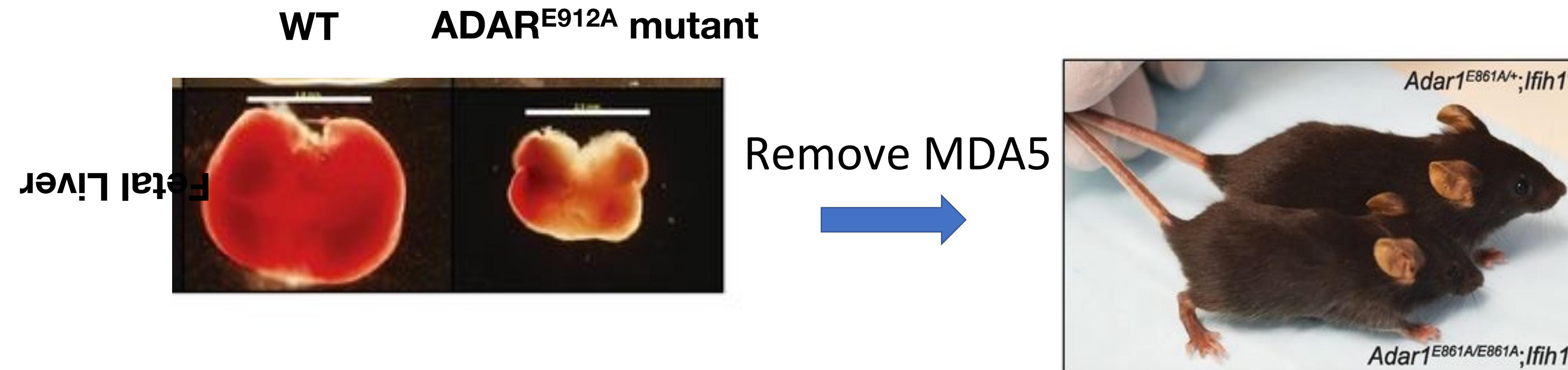
Up-regulation of interferon-stimulated genes (ISGs)



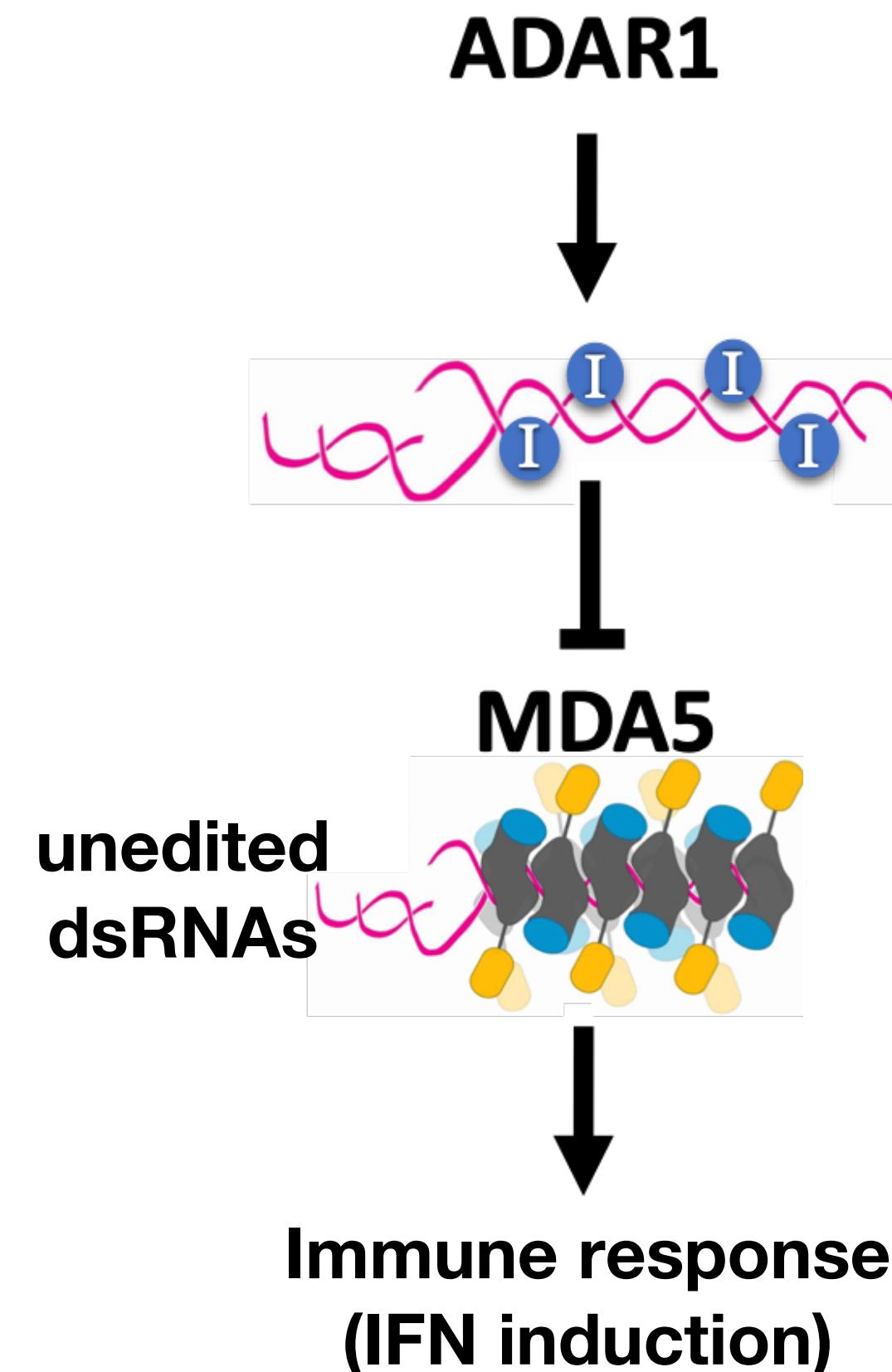
Loss of ADAR editing leads to severe phenotypes in mice

Mice with editing-deficient ADAR die at ~E13.5 due to liver failure

Rescued by concurrent deletion of a cytosolic dsRNA sensor, MDA5/IFIH1

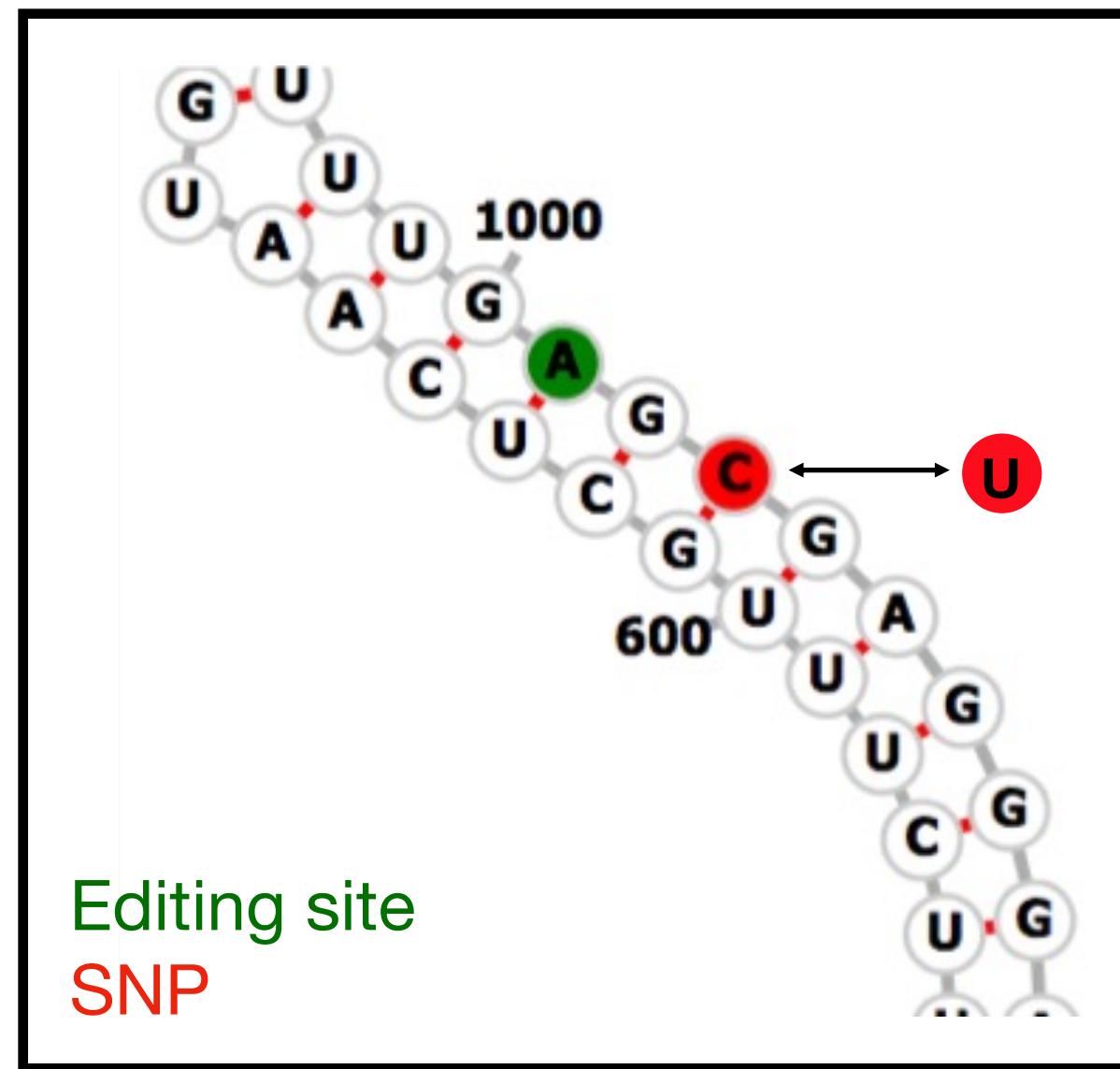


The ADAR-dsRNA-MDA5 axis and diseases

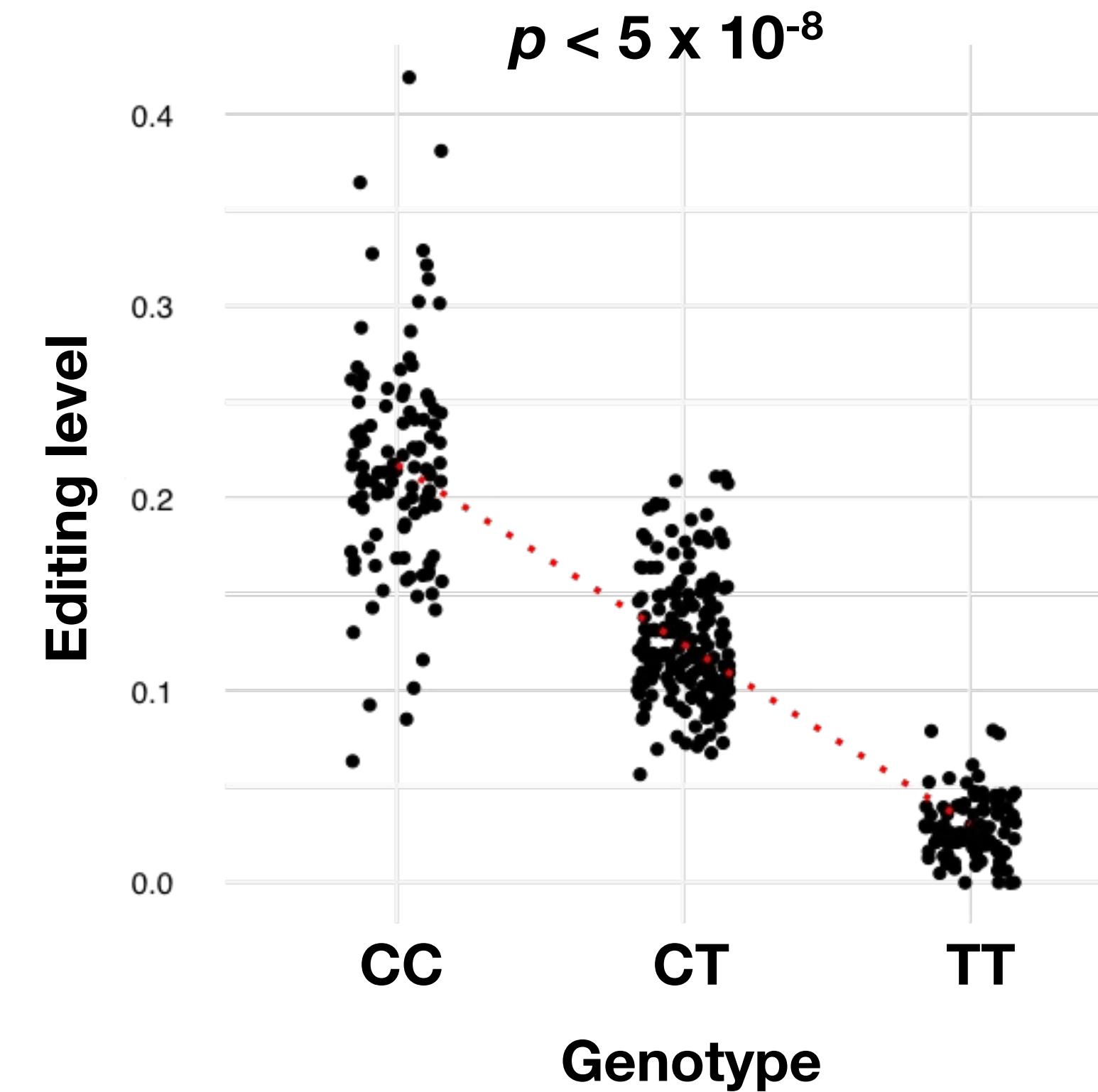


Liddicoat et al., *Science* 2015
Rice et al., *Nat. Genet.* 2012 & 2014
Ahmad et al., *Cell* 2018

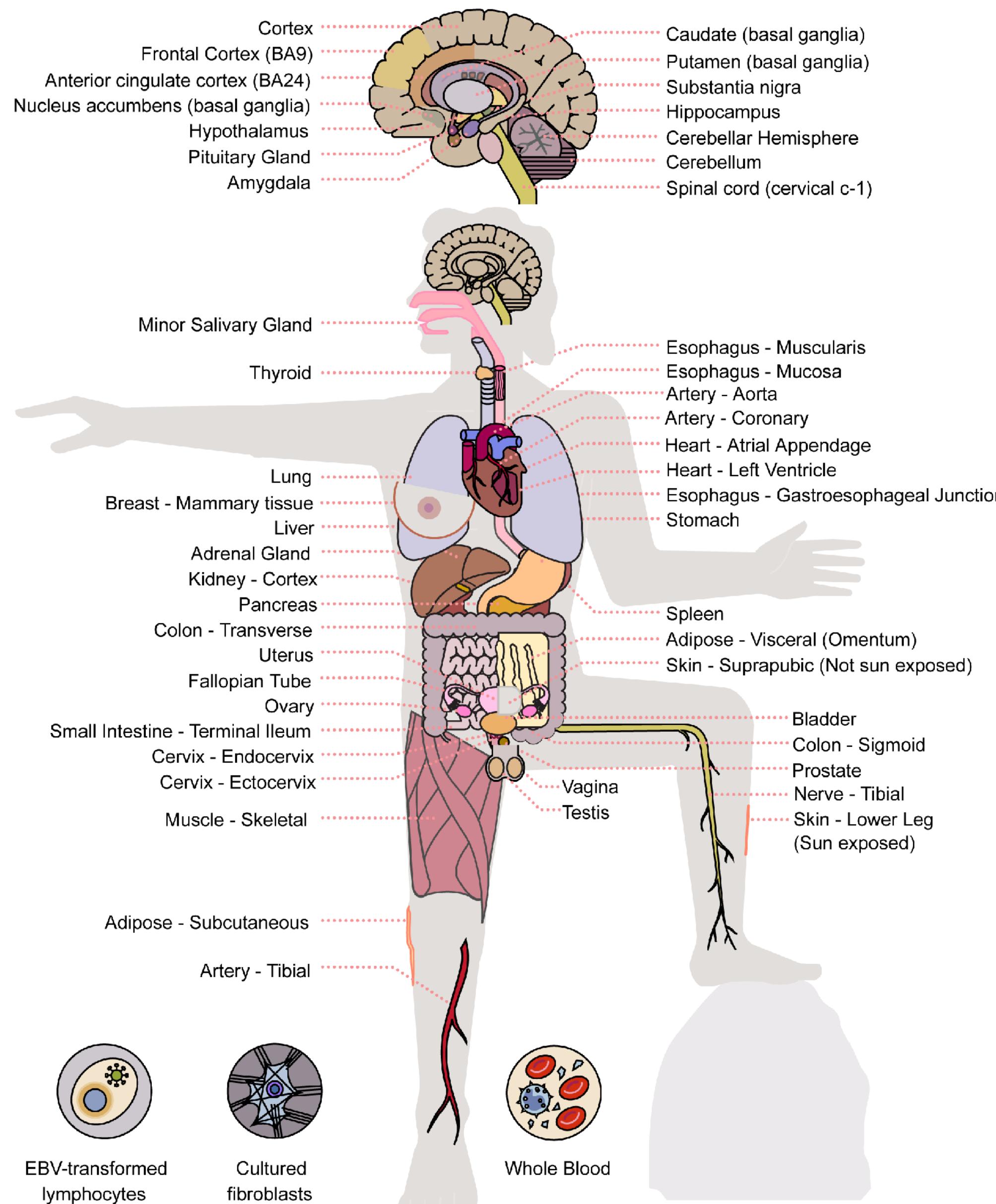
Dissecting genetic basis of RNA editing by mapping editing QTL: Quantitative Trait Locus



Editing level significantly associated with genotype



A large number of genetic loci regulate RNA editing

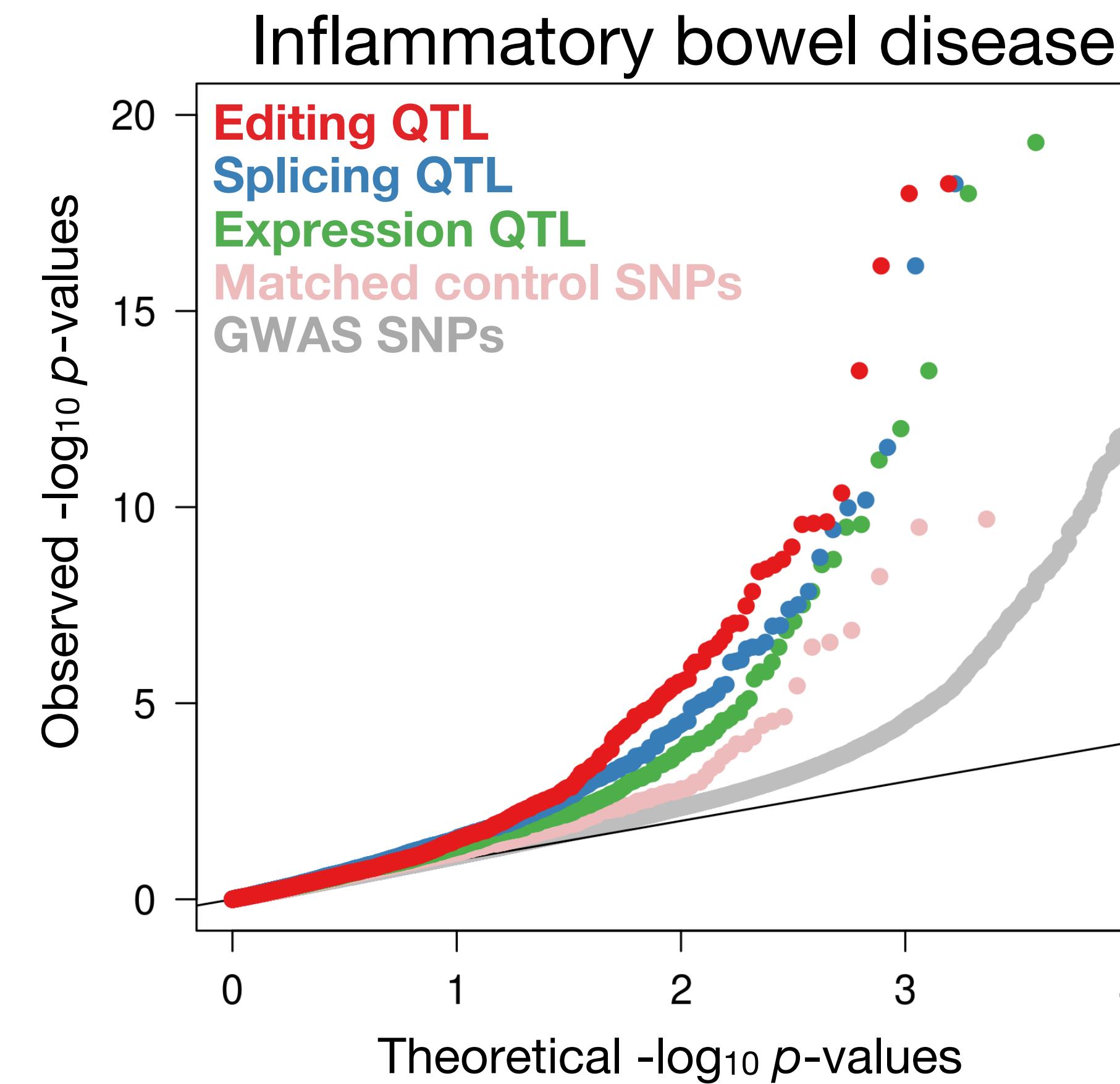


GTEX: Genotype-Tissue Expression project

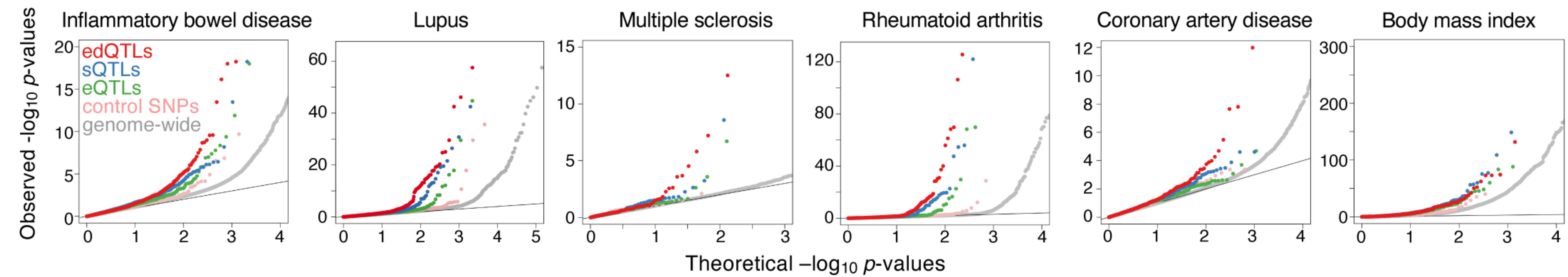
- 903 donors
- 30,319 edQTLs
- 89.6% dysregulated across tissues
- 19368 RNA-seq

How do these edQTLs contribute to genetic diseases?

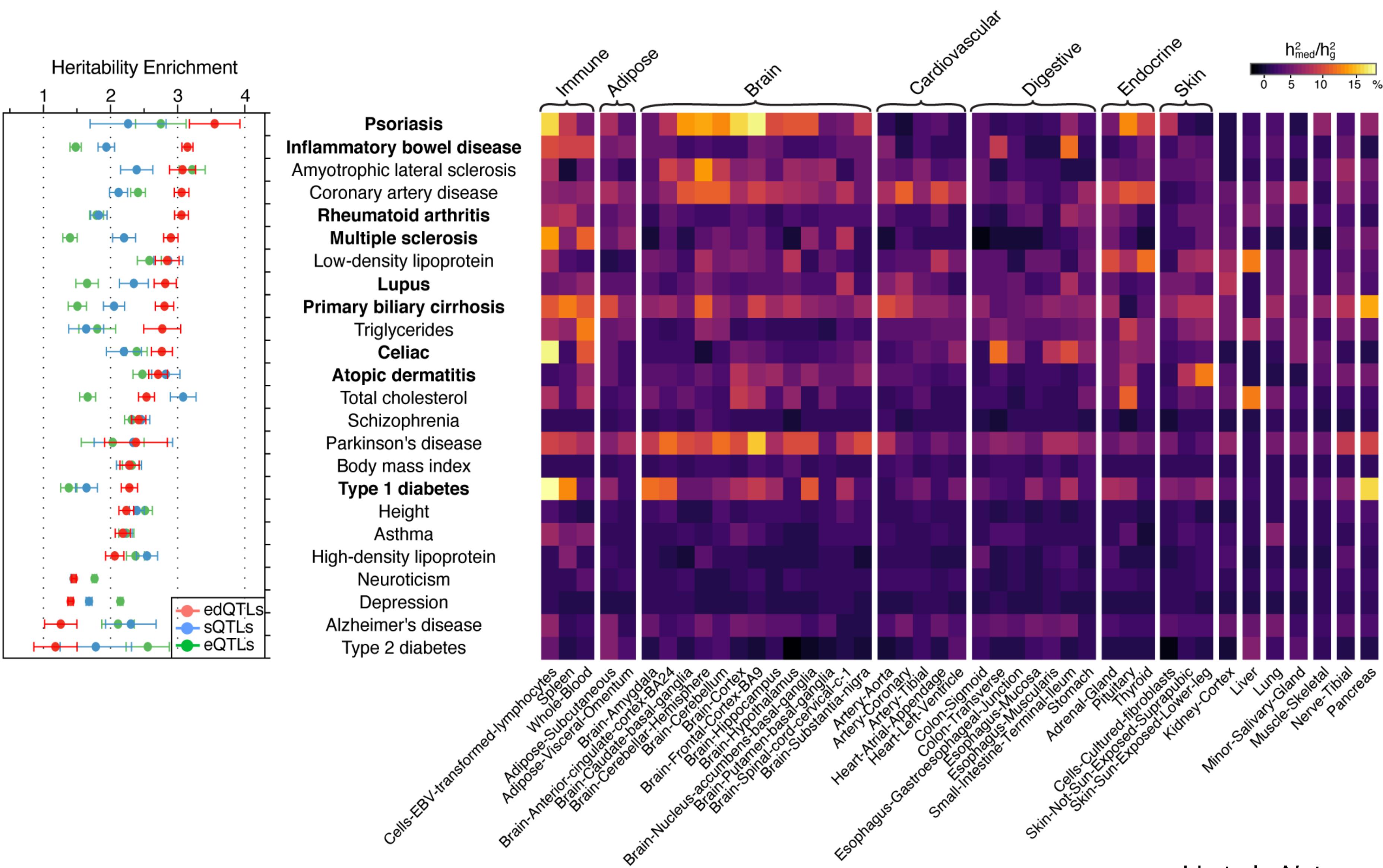
Inflammatory bowel disease GWAS SNPs are enriched in editing QTLs, more than expression and splicing QTLs



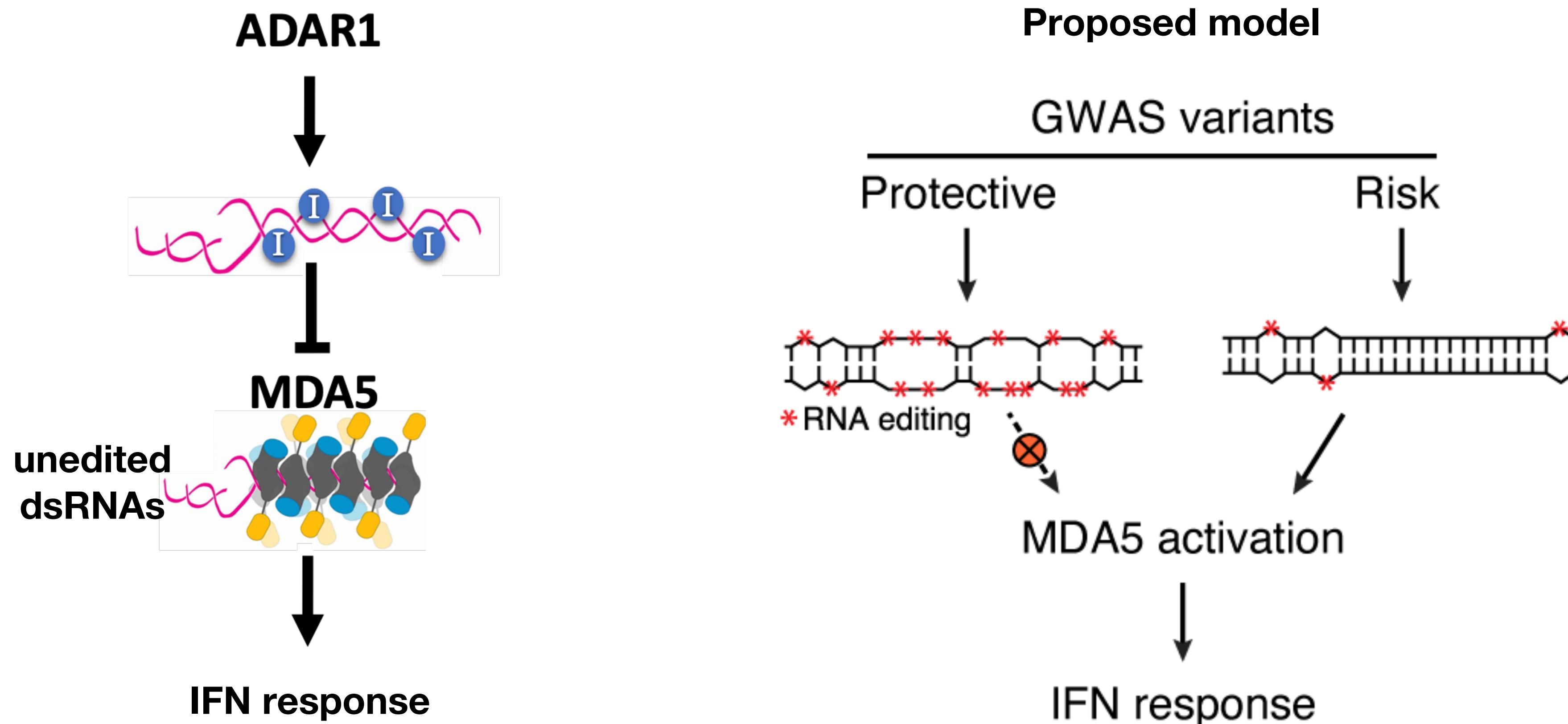
Autoimmune/inflammatory disease GWAS SNPs are often enriched in edQTLs, more than expression and splicing QTLs



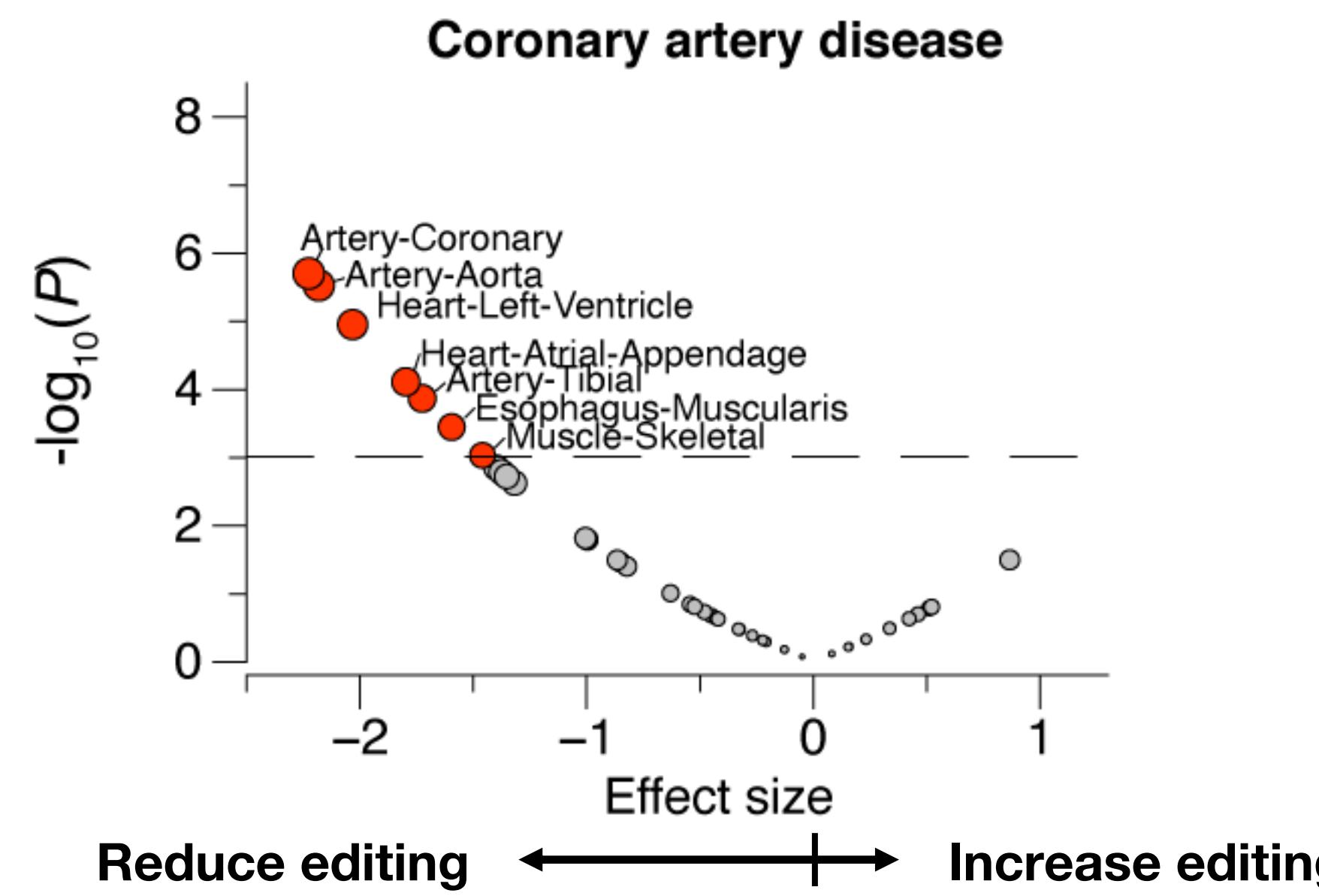
Enrichment of edQTLs-mediated heritability in autoimmune/inflammatory diseases



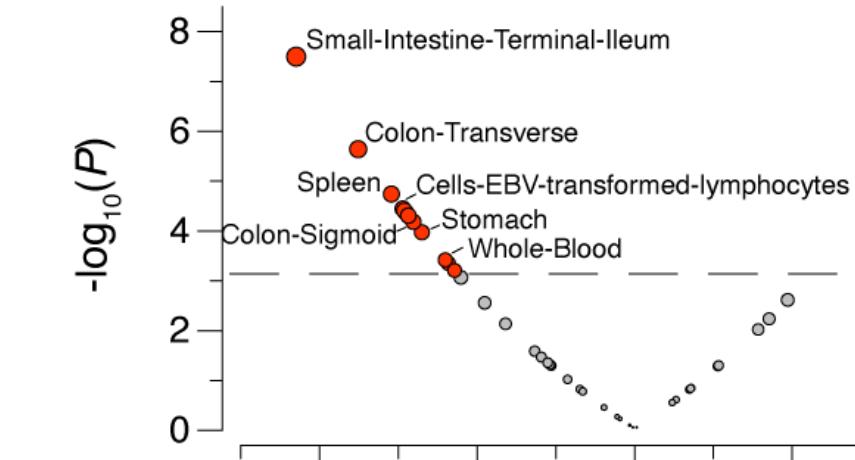
The ADAR1-dsRNA-MDA5 axis



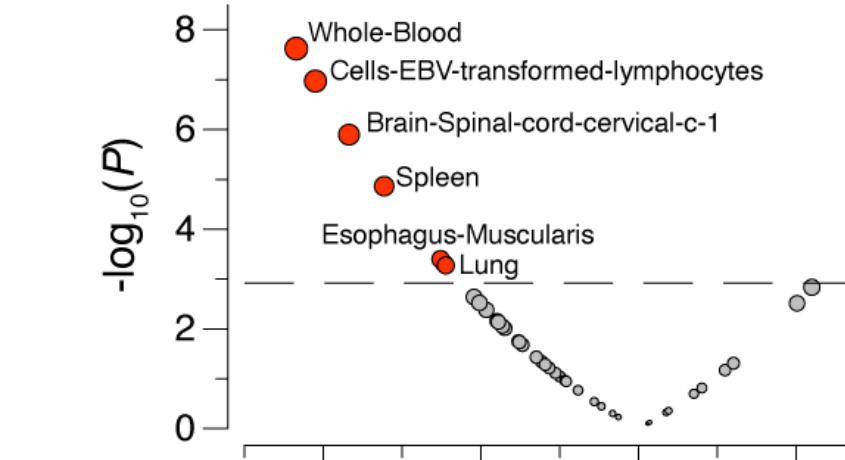
GWAS risk alleles tend to reduce editing levels



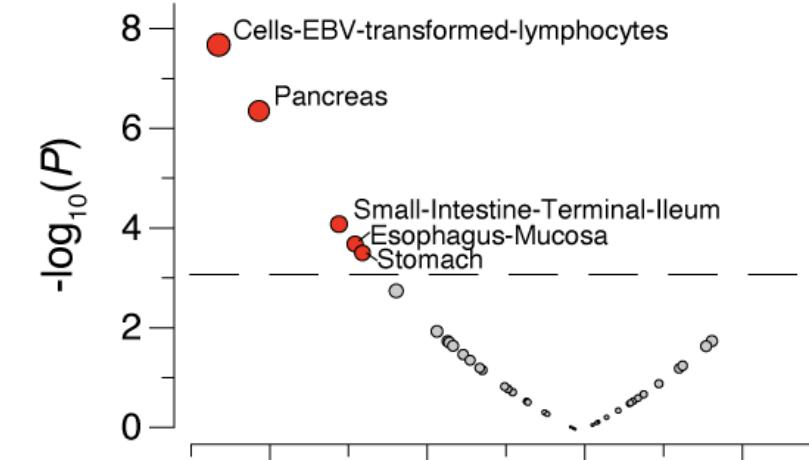
Inflammatory bowel disease



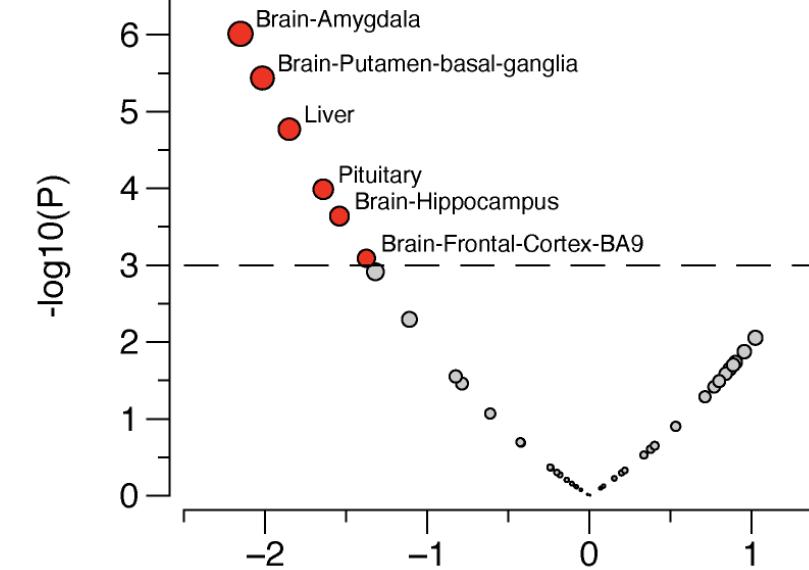
Multiple sclerosis



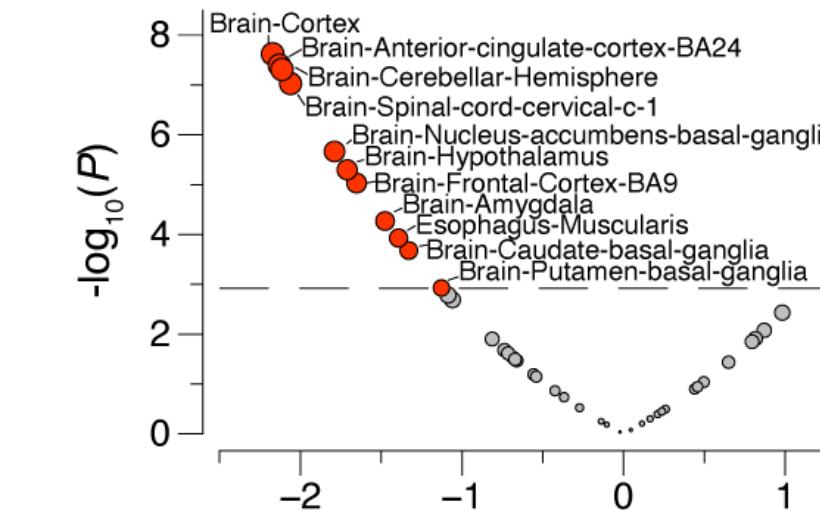
Type 1 diabetes



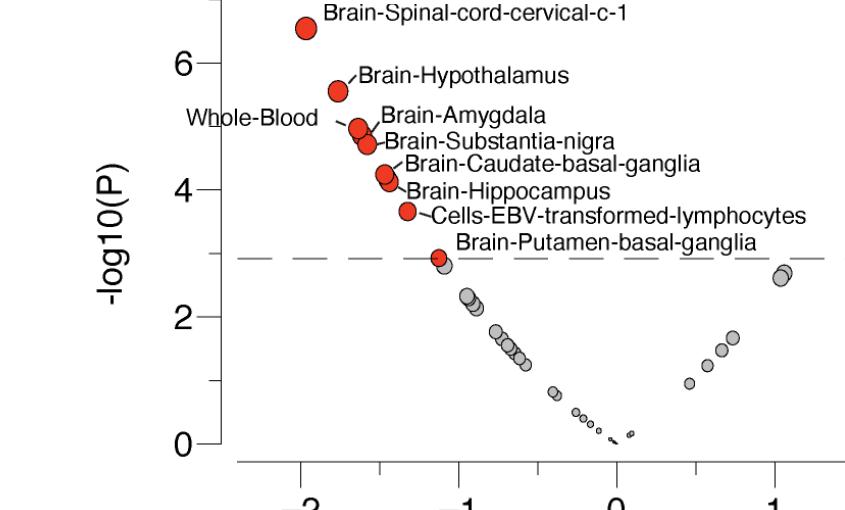
Lupus



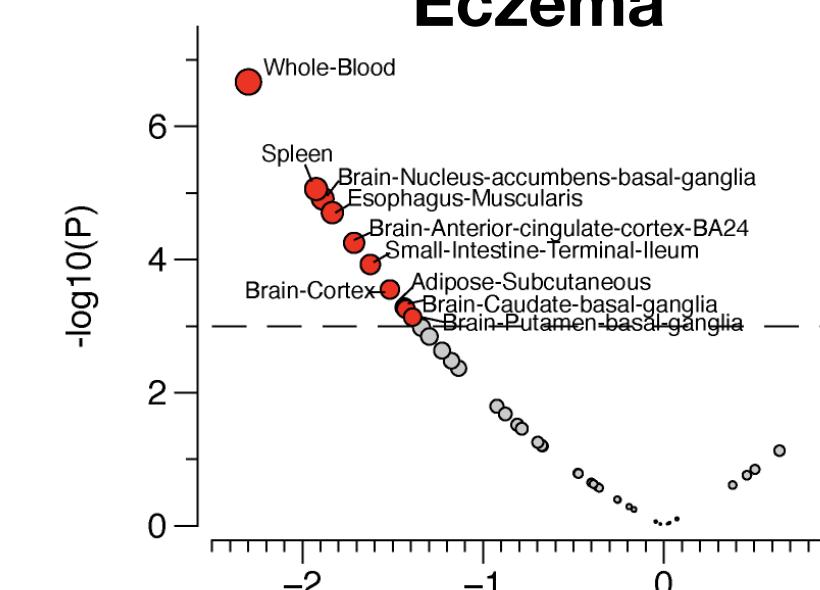
Parkinson's disease



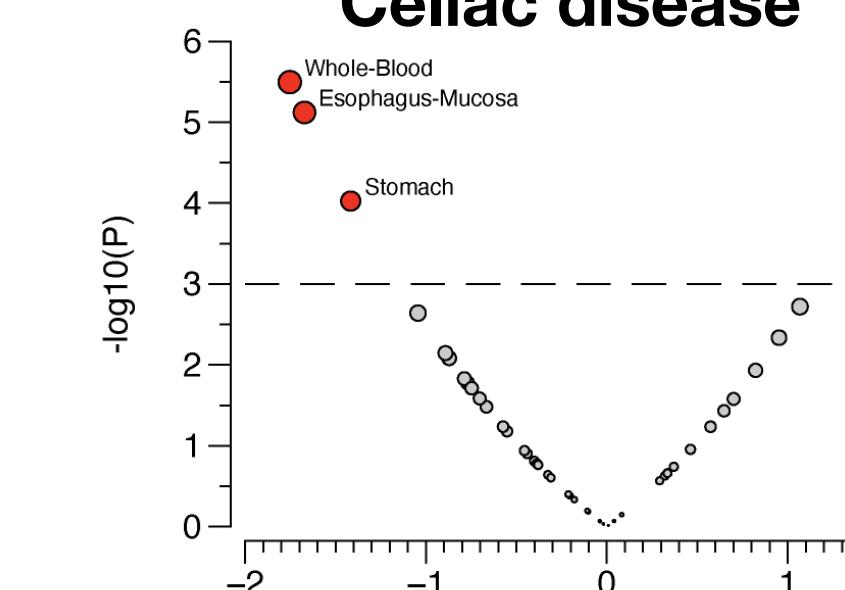
Rheumatoid arthritis



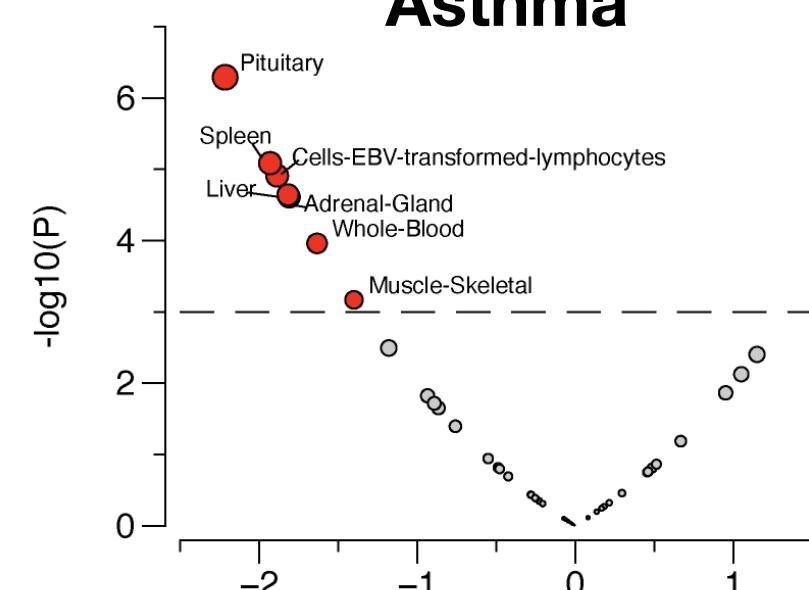
Eczema



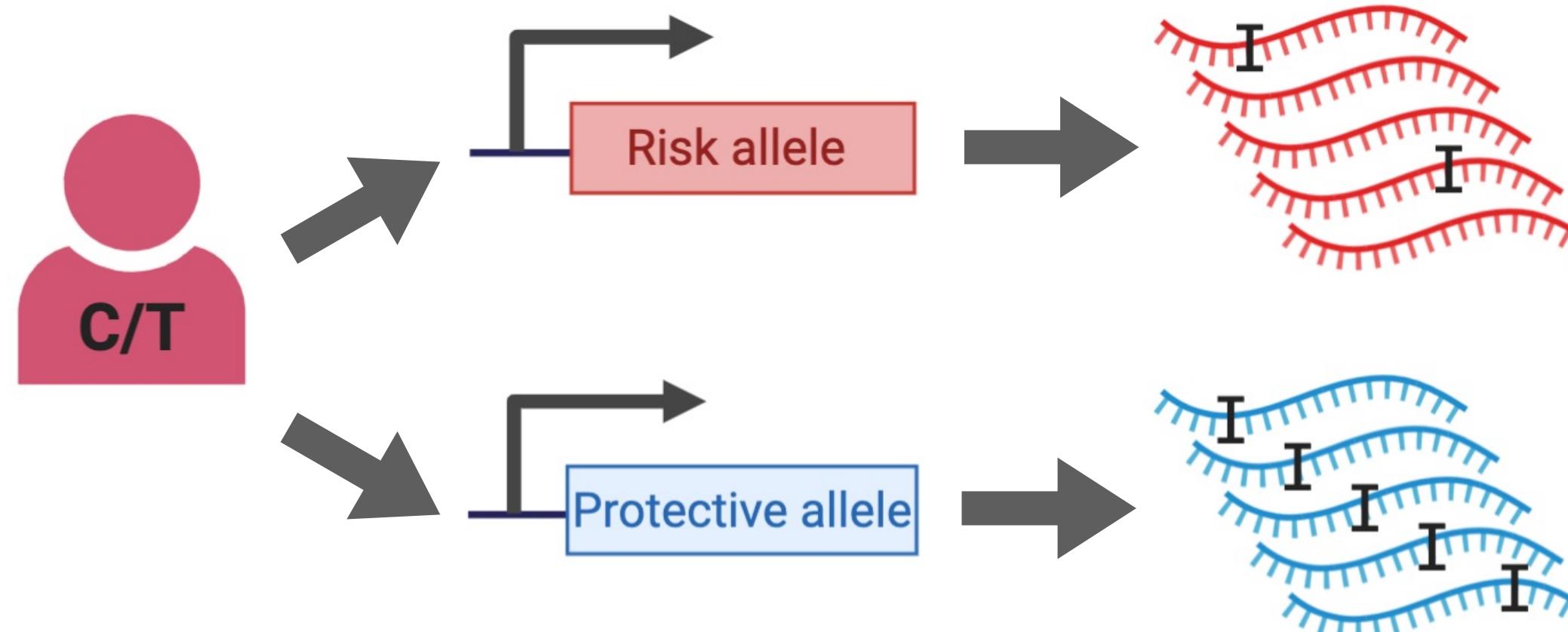
Celiac disease



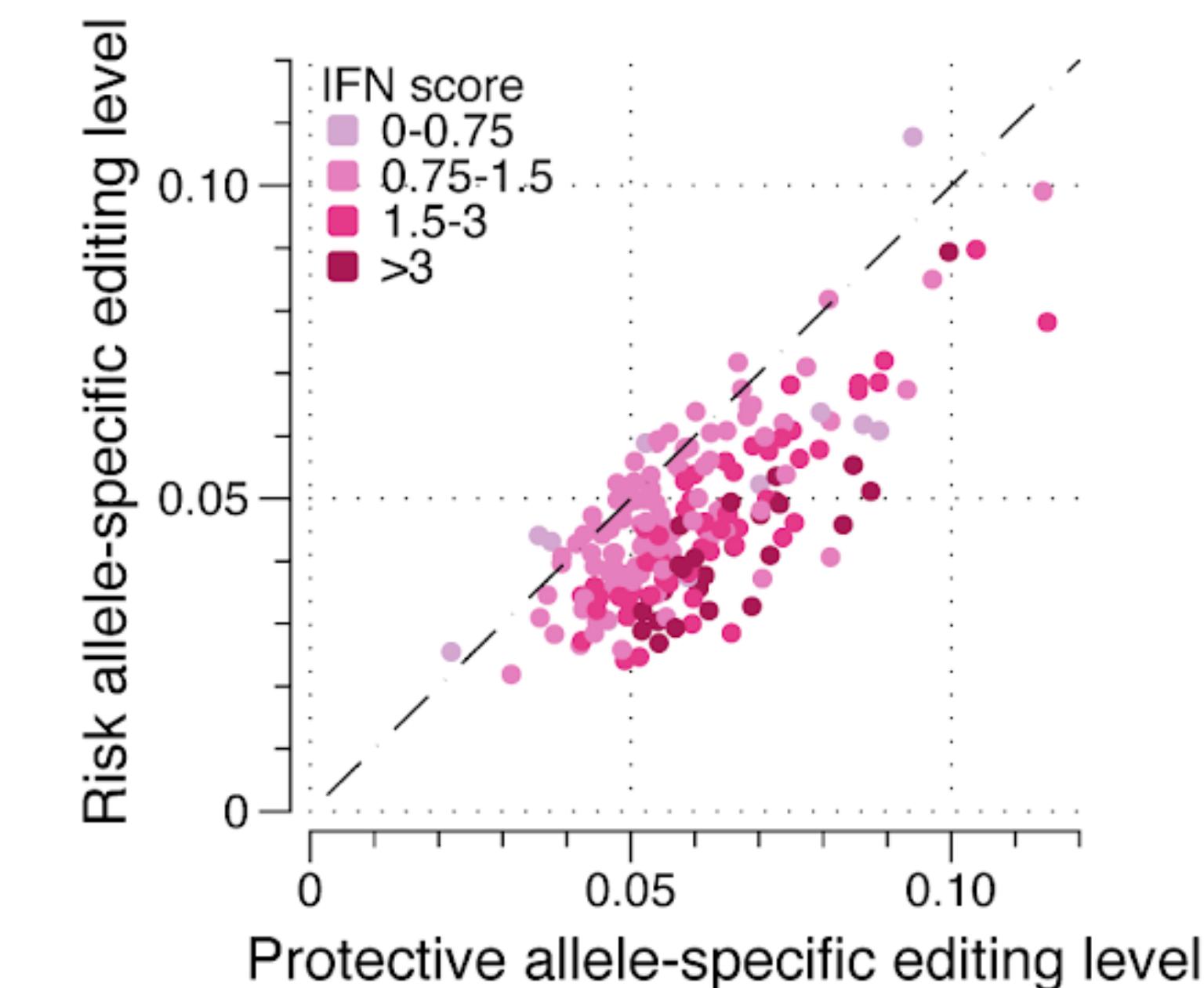
Asthma



Comparing allele-specific RNA editing (ASED) levels in disease samples



Rheumatoid arthritis
(152 synovial tissue samples)

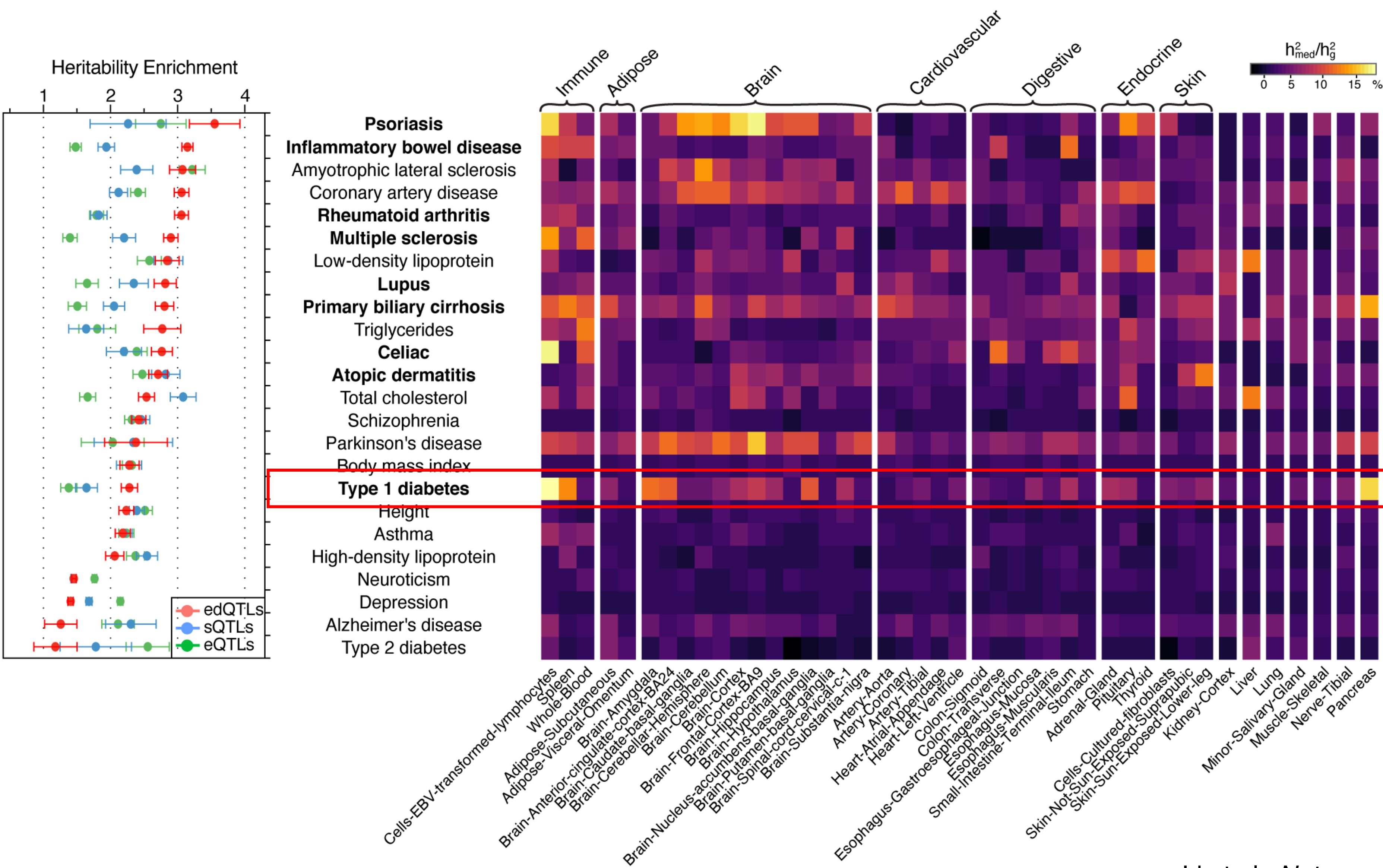


Risk variants → Reduced editing → dsRNA burden → MDA5 activation → IFN response

Questions for next steps:

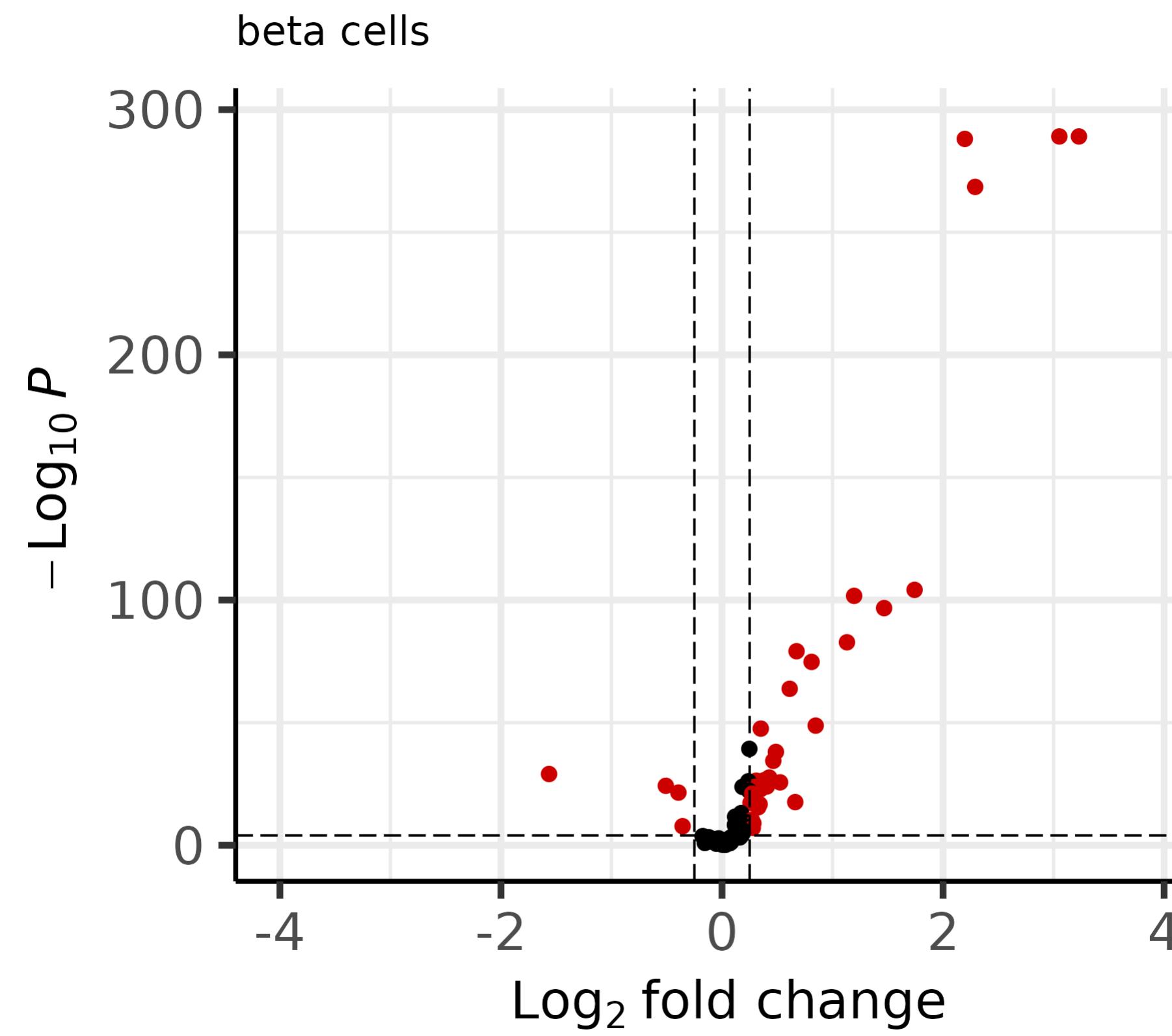
1. Which cell types are responsible for immune response in various inflammatory diseases? (IFN signature, dsRNA expression)
2. Which disease individuals are enriched with risk variants that increase their dsRNA burden? (polygenic risk score)

Enrichment of edQTLs-mediated heritability in autoimmune/inflammatory diseases

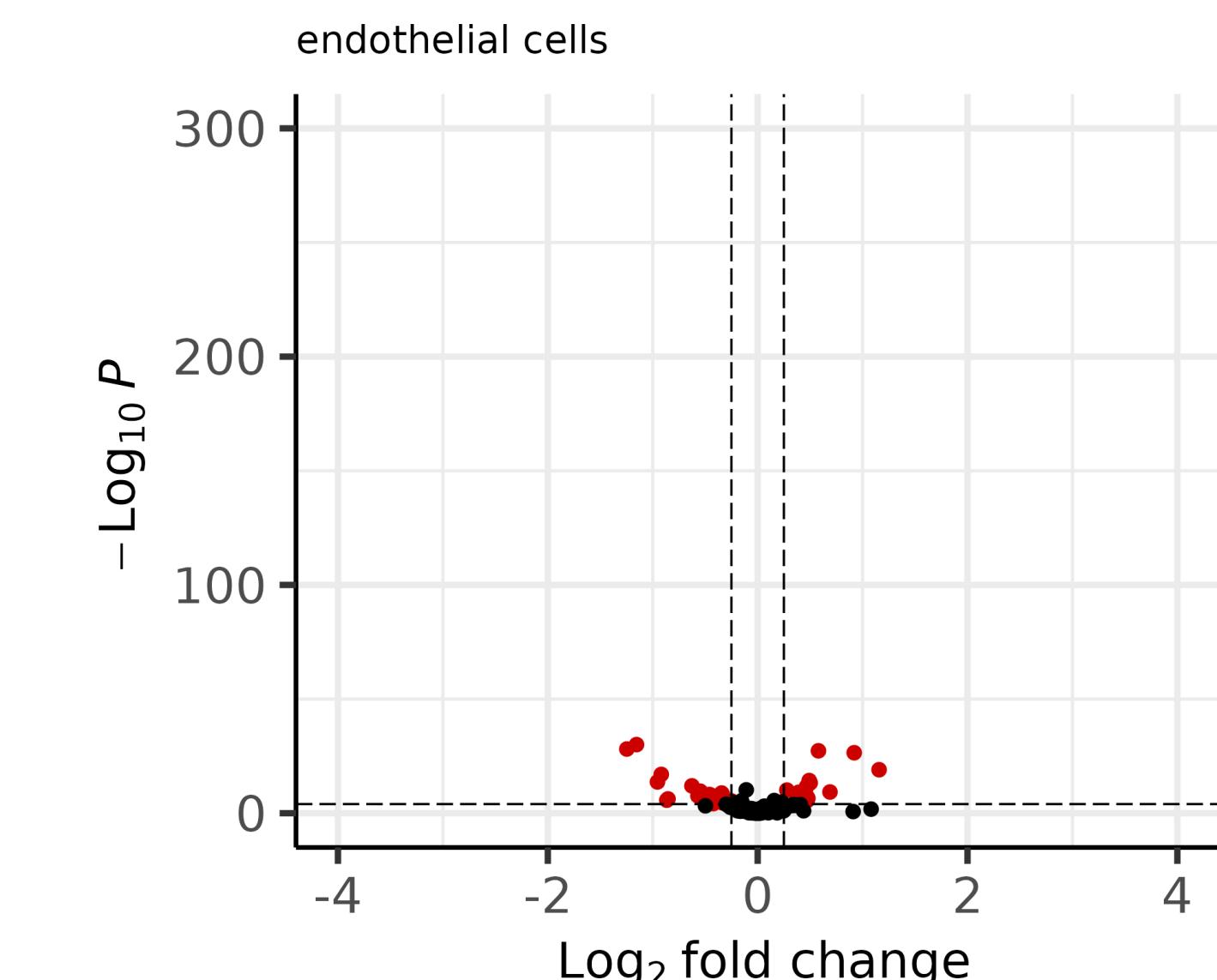
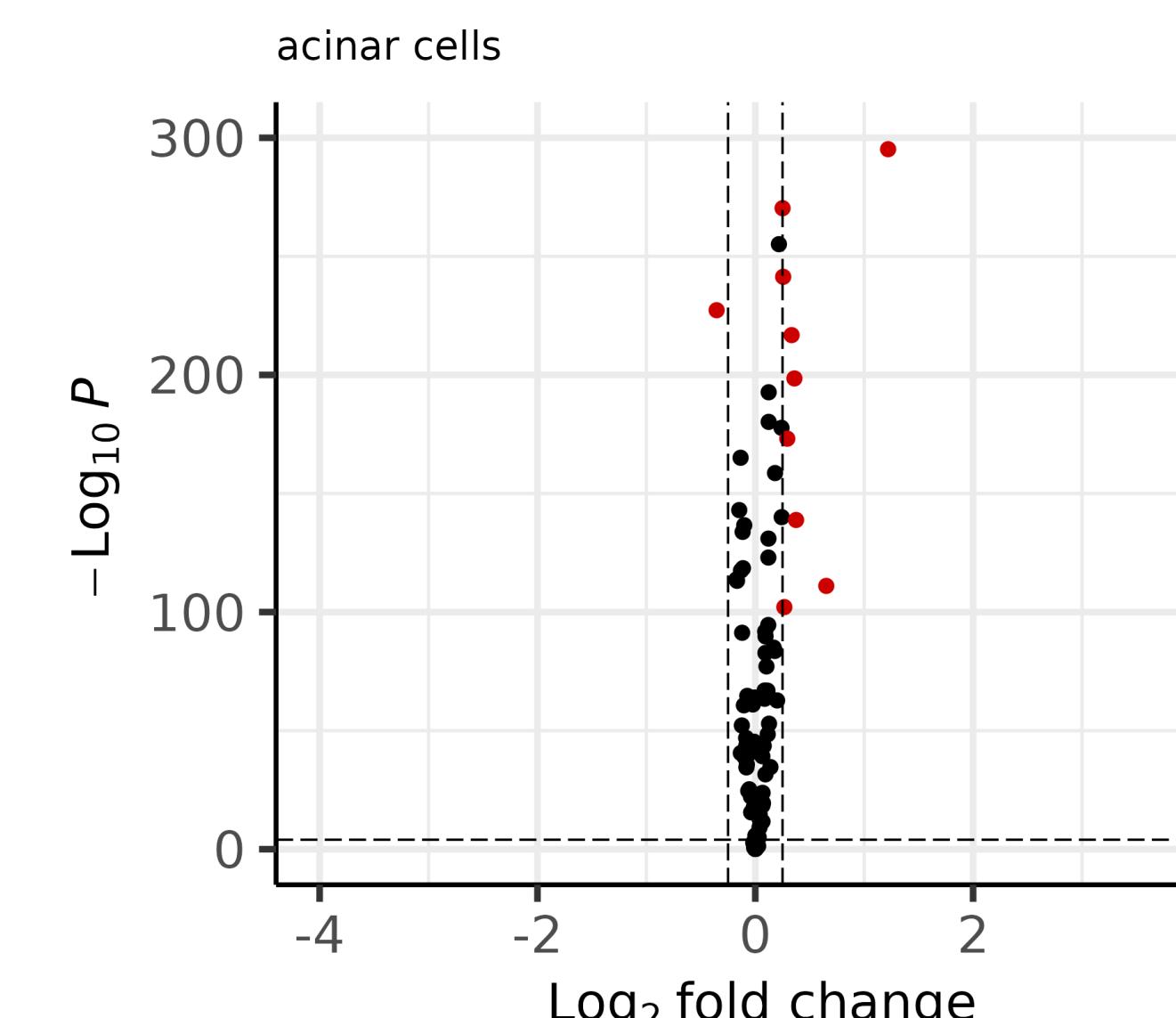
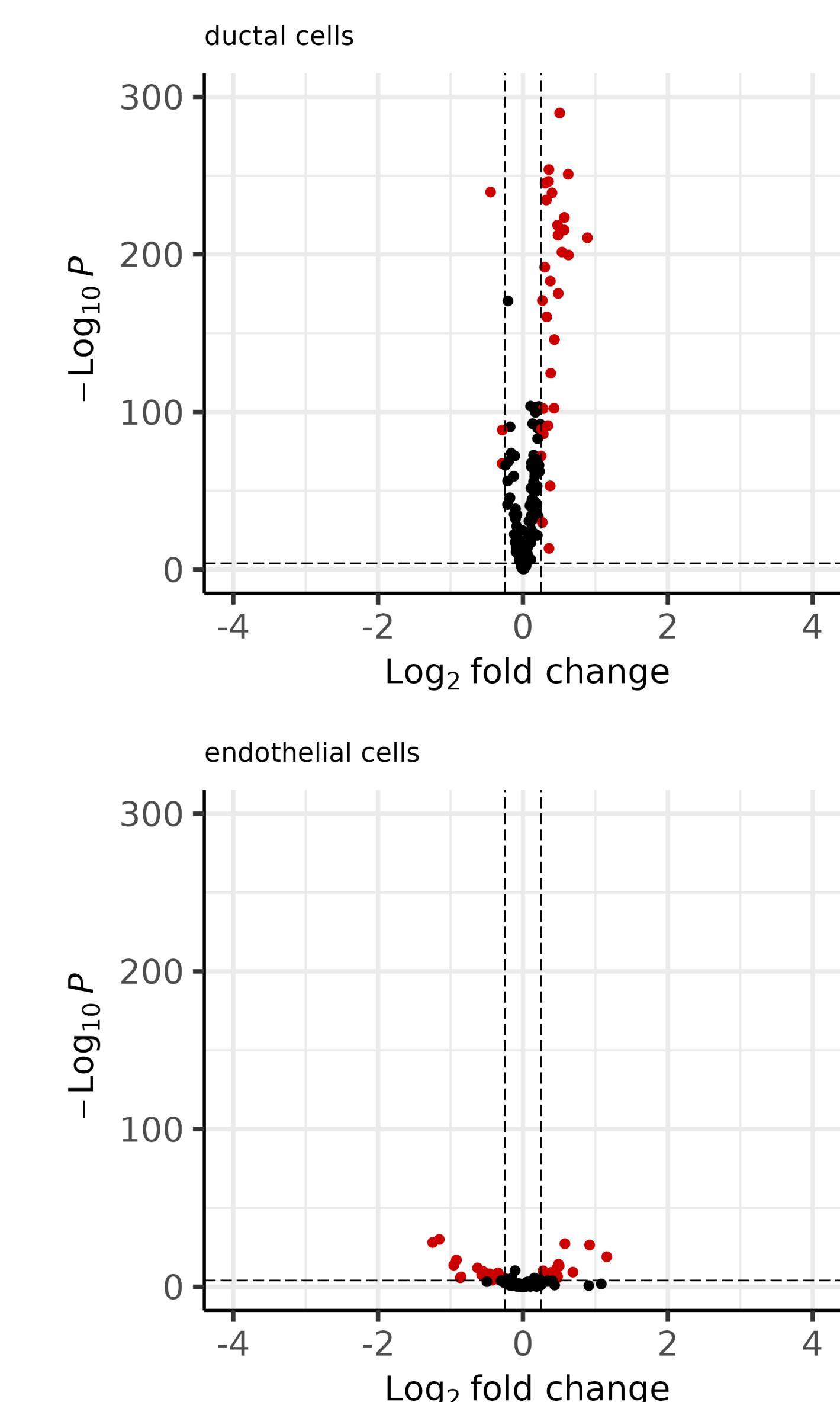
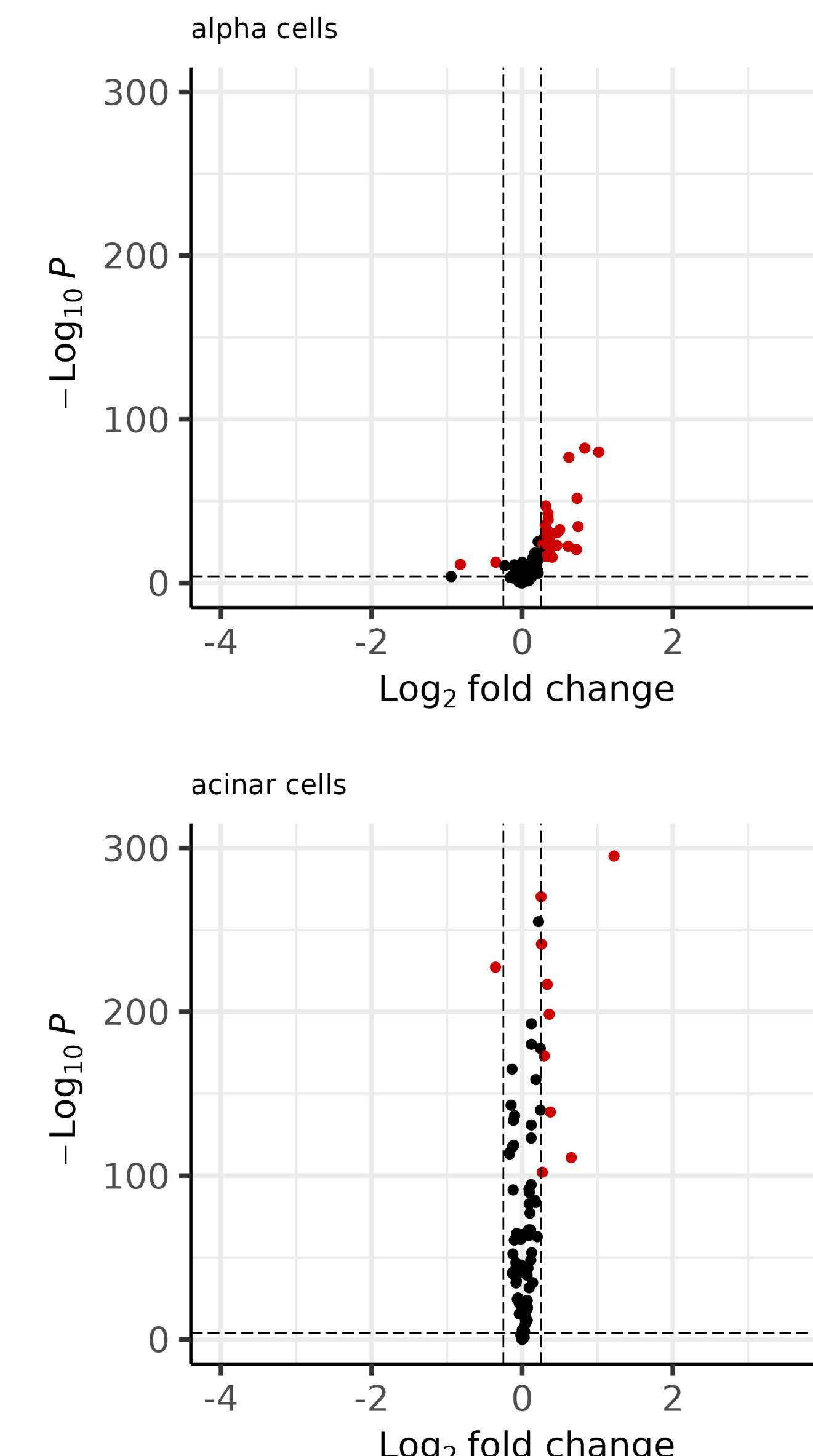


Elevated ISG expression in T1D beta cells

ISG exp in T1DM vs control



Unpublished



Comparison of IFN score across islet cells

