



# Genetic Mutation and Injury Initiate Tumorigenesis

CSE 185 Final Project

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# Genetic Mutation and Injury Initiate Tumorigenesis

## Metaplasia

- an adaptive response to tissue injury
- replace with another cell type

An example of acinar-ductal metaplasia (ADM):

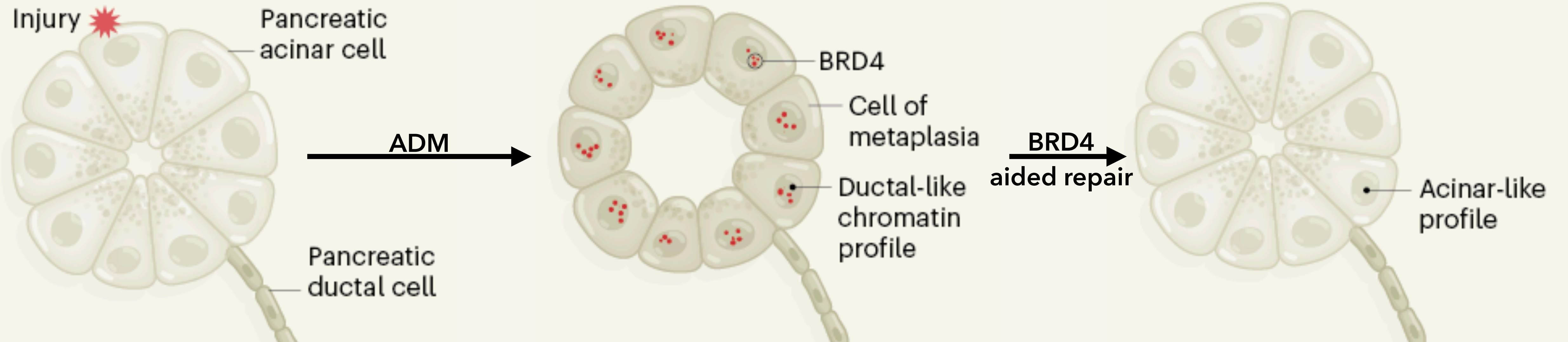


Figure from: <https://www.nature.com/articles/d41586-021-00211-y>

**However**, if metaplasia persists, it becomes a precursor of **carcinoma**

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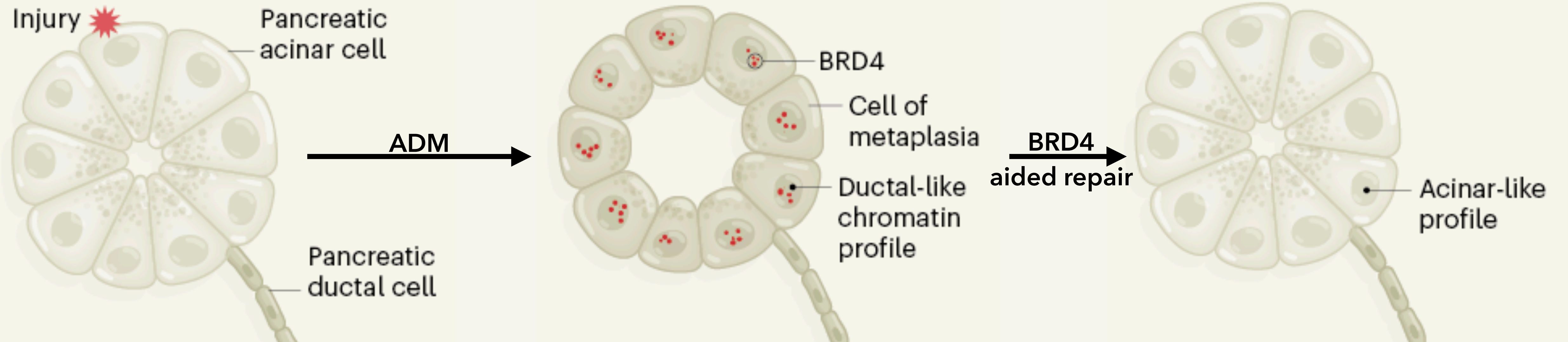


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***Kras* mutation is found to be associated  
with the persistence of ADM**

**However**, if metaplasia **persists**, it becomes a precursor of **carcinoma**



# Genetic Mutation and Injury Initiate Tumorigenesis

## Metaplasia

- an adaptive response to tissue injury
- replace with another cell type

If have **Kras** mutation: an example of **persistent** acinar-ductal metaplasia (ADM):

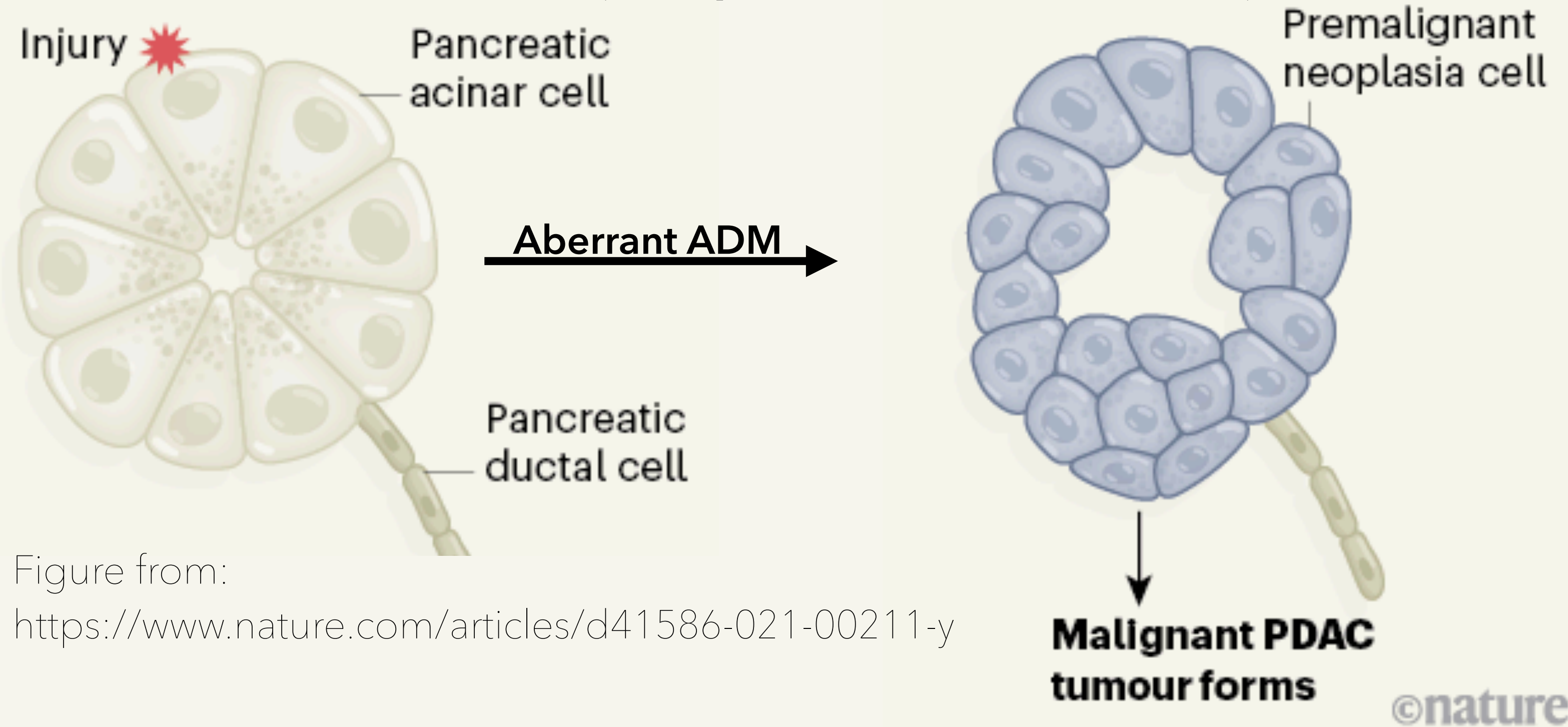


Figure from:

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Essentially,  
**Genetic mutation +  
environment stimuli  
(Injury) => Tumorigenesis**

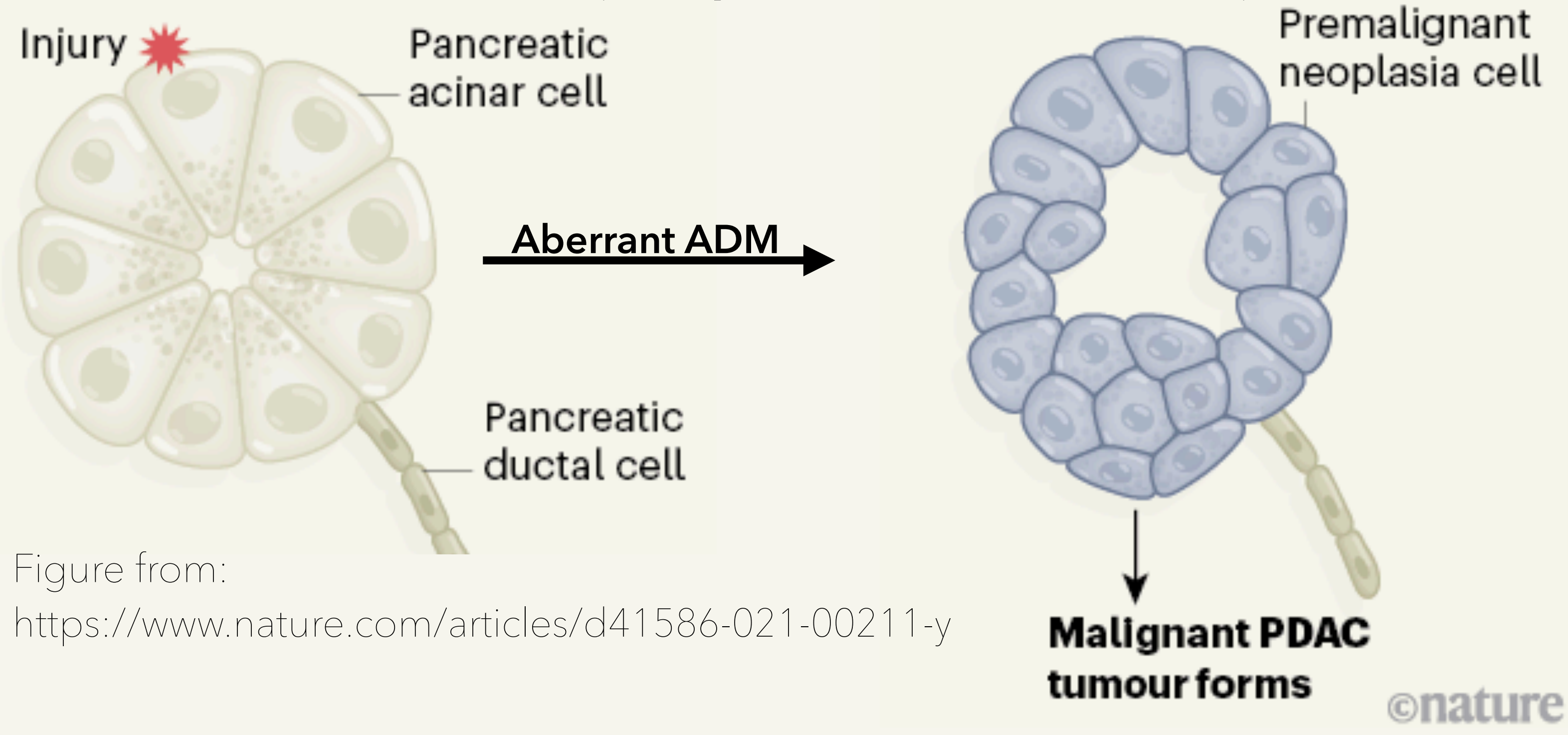
**However**, if metaplasia **persists**, it becomes a precursor of **carcinoma**

# Genetic Mutation and Injury Initiate Tumorigenesis

## Metaplasia

- an adaptive response to tissue injury
- replace with another cell type

If have **Kras** mutation: an example of **persistent** acinar-ductal metaplasia (ADM):



**Goal:** Understand how this equation is applied to this scenario

**However,** if metaplasia **persists**, it becomes a precursor of **carcinoma**

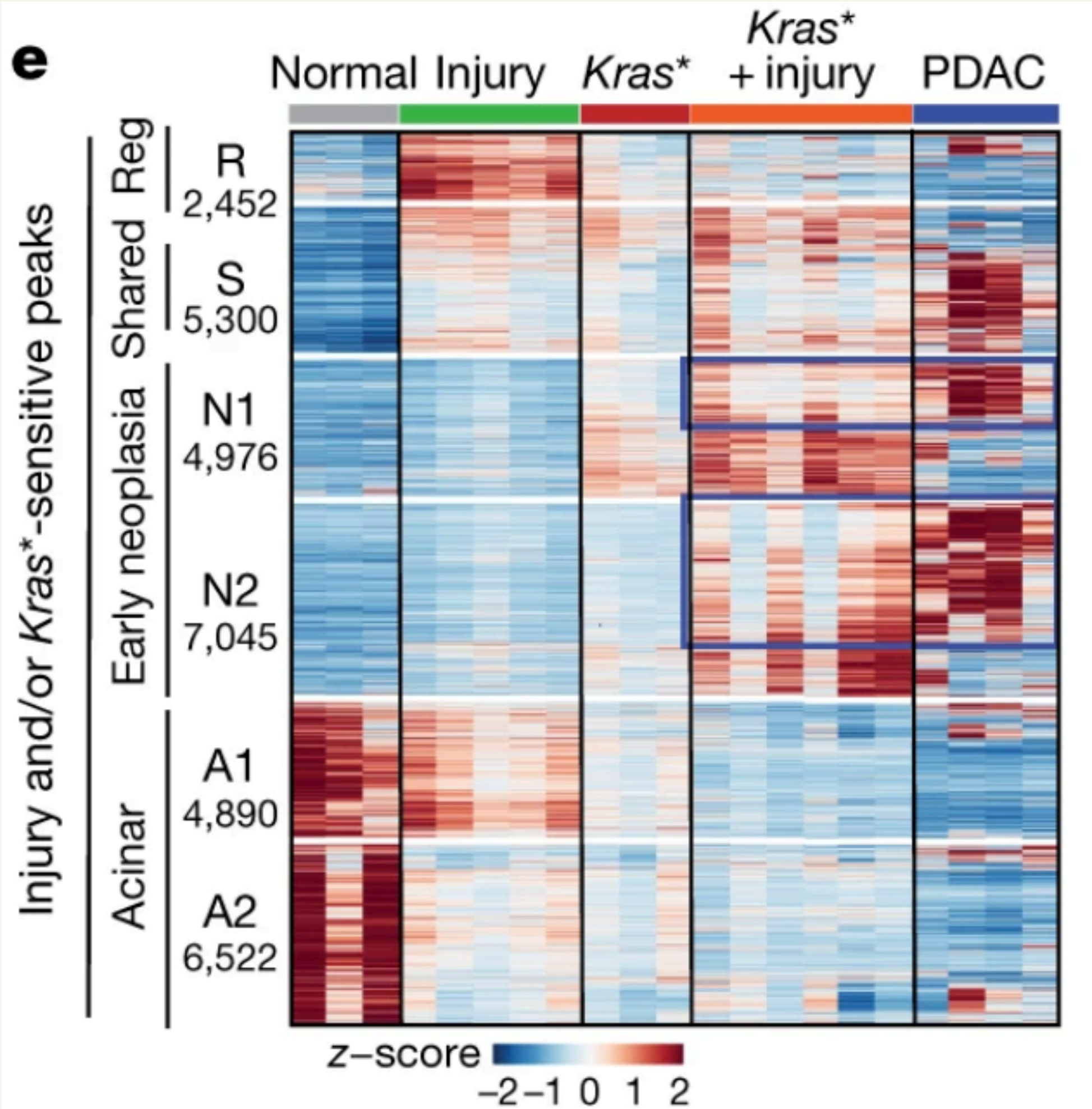


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**Paper:** *A gene-environment-induced epigenetic program initiates tumorigenesis*

**GSE132440**

ATAC-seq



**Check the chromatin accessibility profile**

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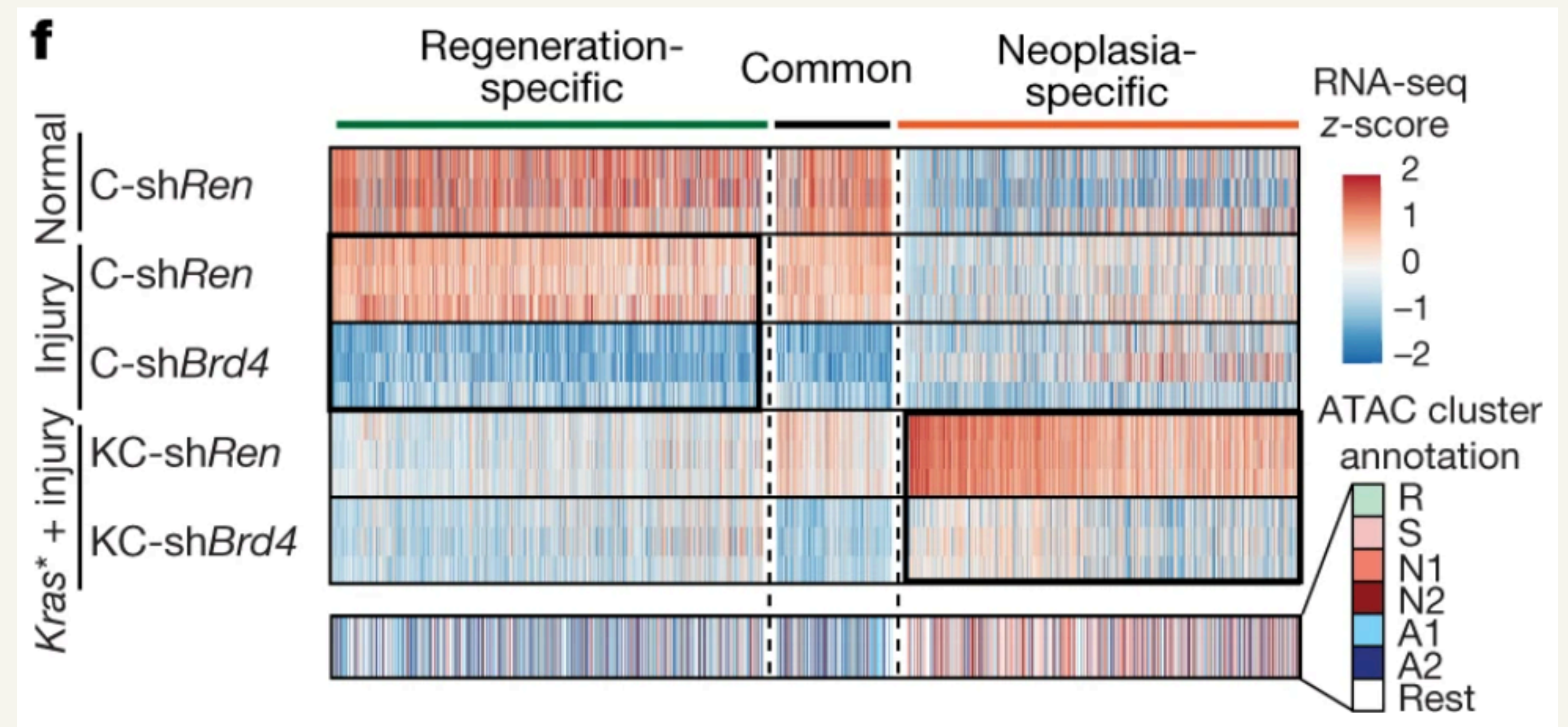
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ATAC-seq

**GSE132329**

RNA-seq



## Differential gene expression analysis after Brd4 perturbation

\*Brd4 is a well-studied chromatin reader that is found to co-occupy ontogenetic driving super-enhancer region with the mediator.



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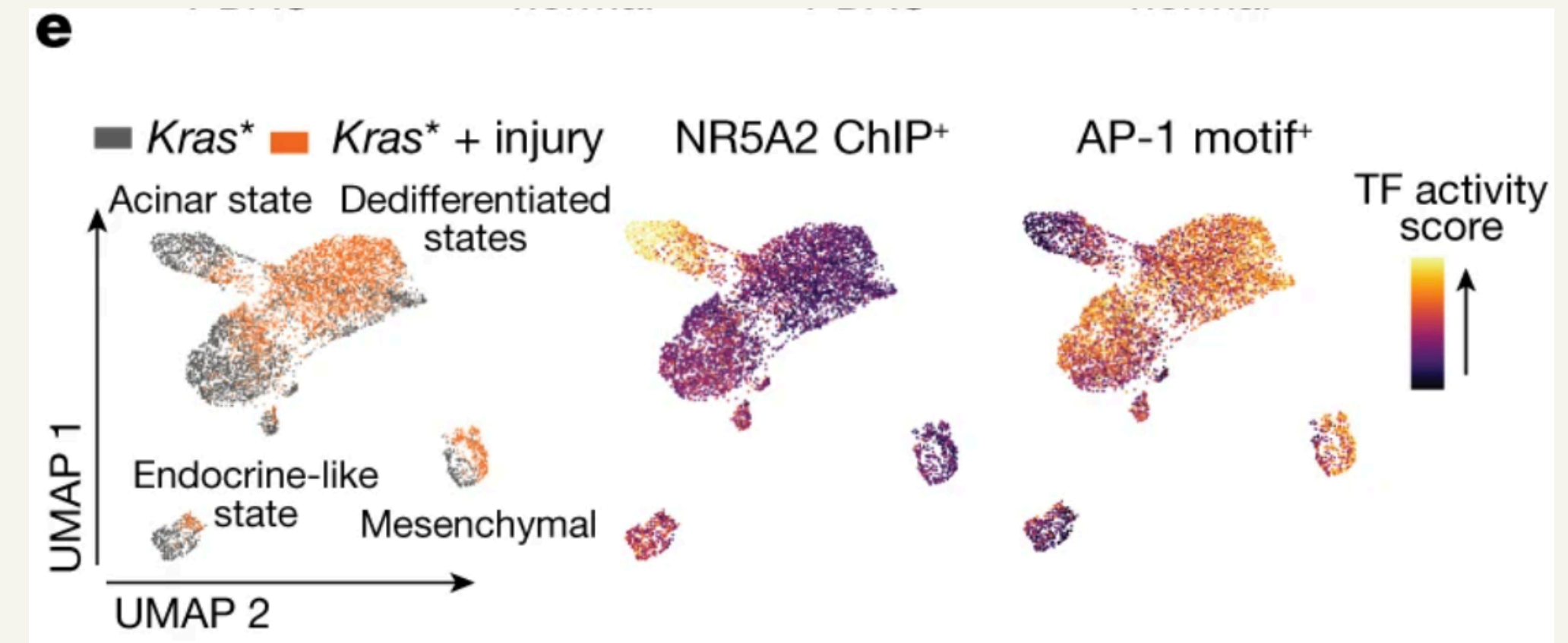
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**Explore transcription factor activity**





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Identify a potential target/effector TF

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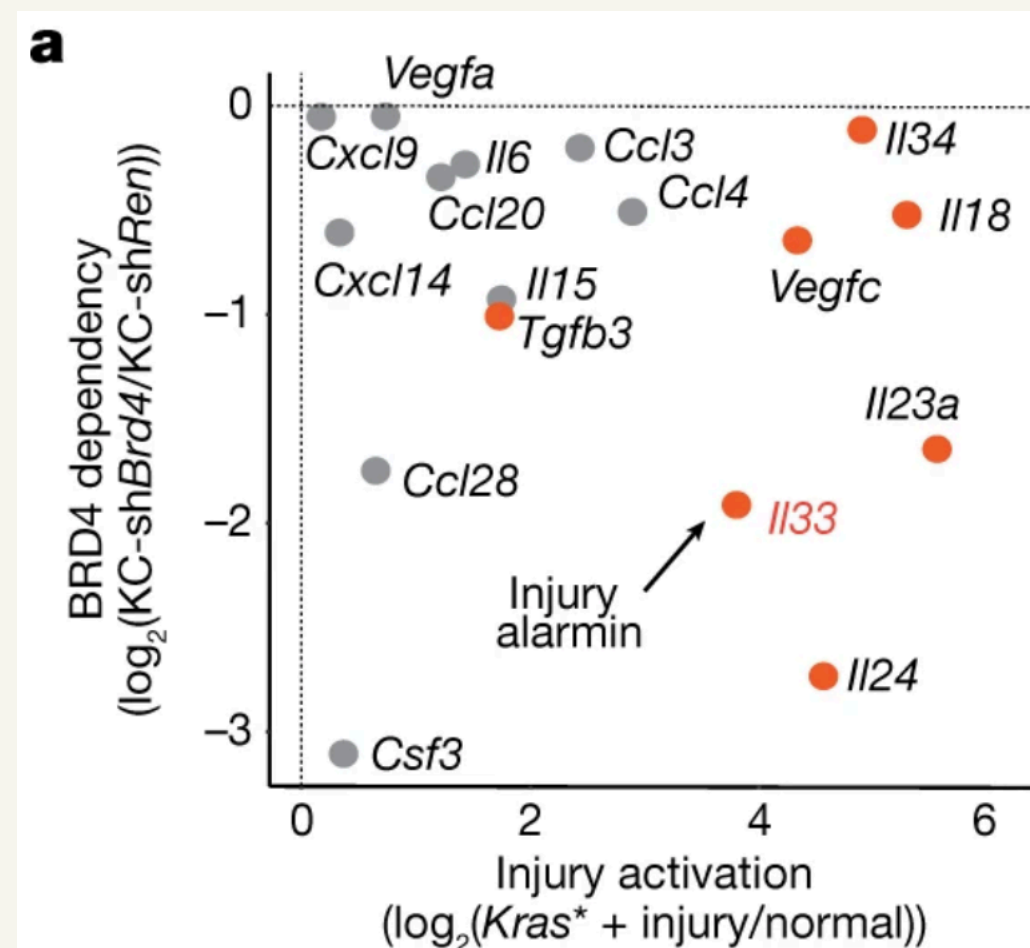
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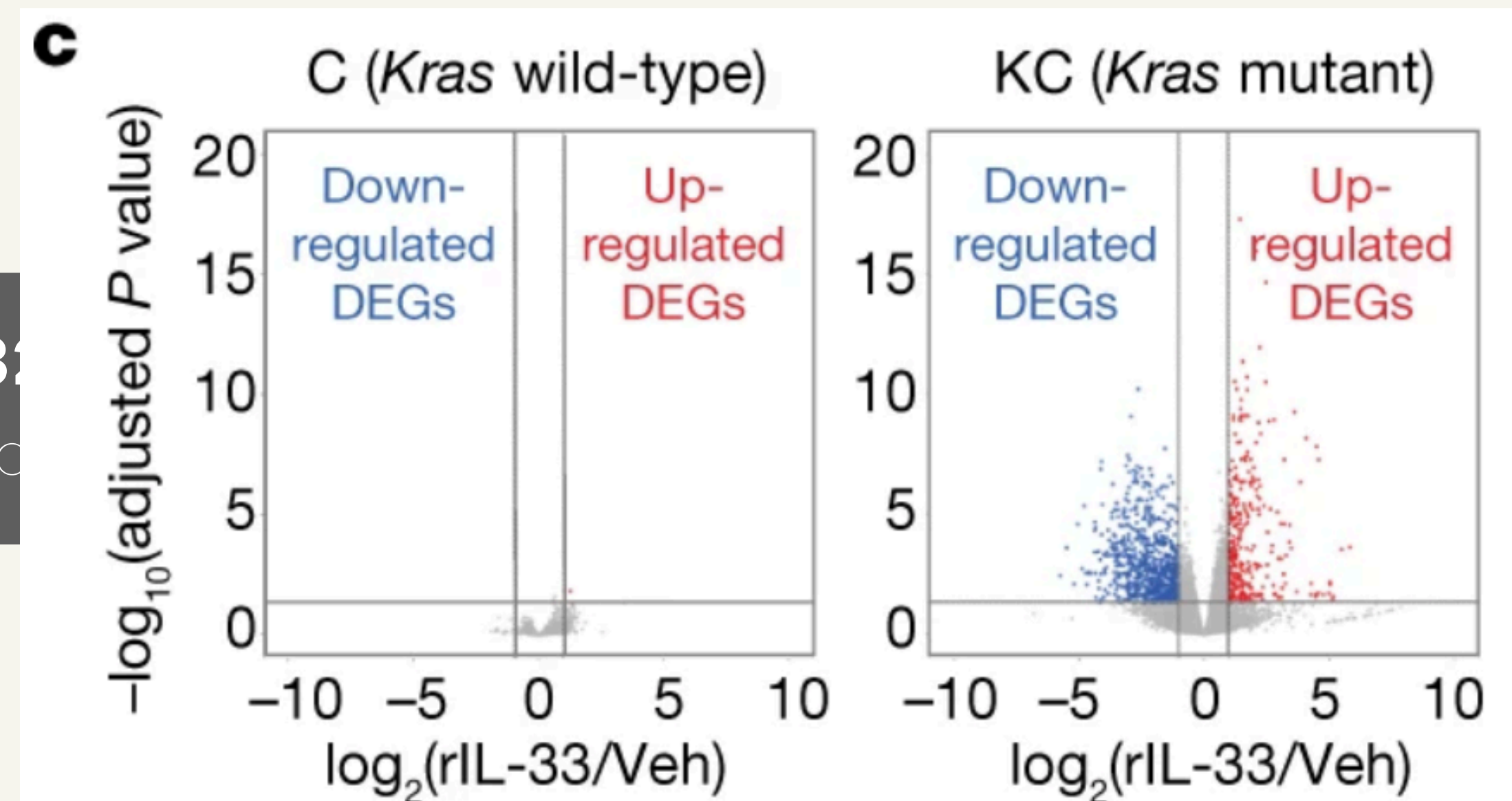
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**GSE13231**

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**GSE154543**

RNA-seq

**Confirm the TF identified previously indeed drives transcriptional reprogramming in a cooperative manner with *Kras*\* mutation**



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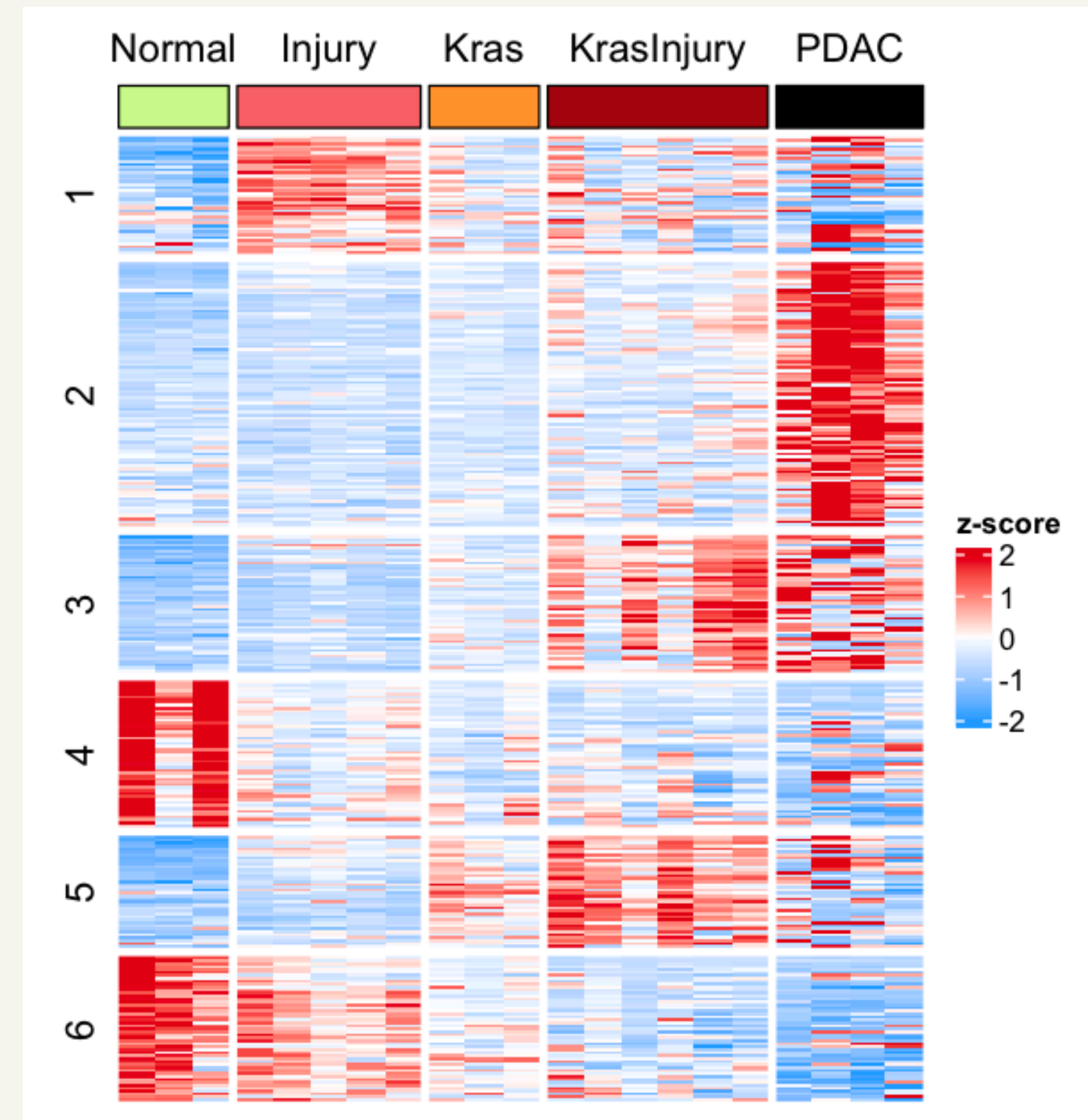
RNA-seq

**GSE154543**

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## Method:

- Start with **normalized peaks**
- Select for **dynamic peaks**  
based on statistics calculated from DESeq2
- **Unsupervised k-means cluster**
- **ComplexHeatmap visualization**





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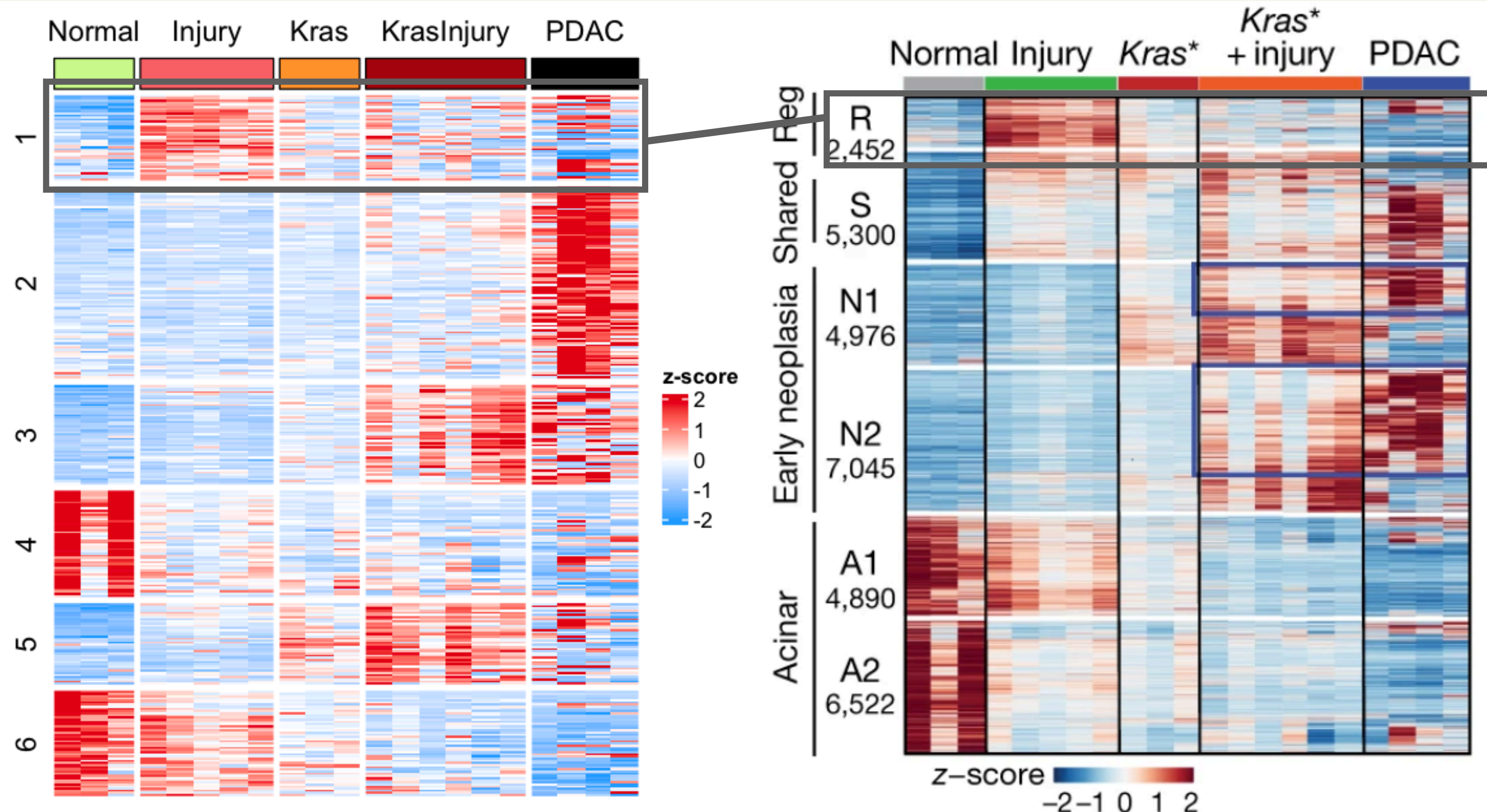
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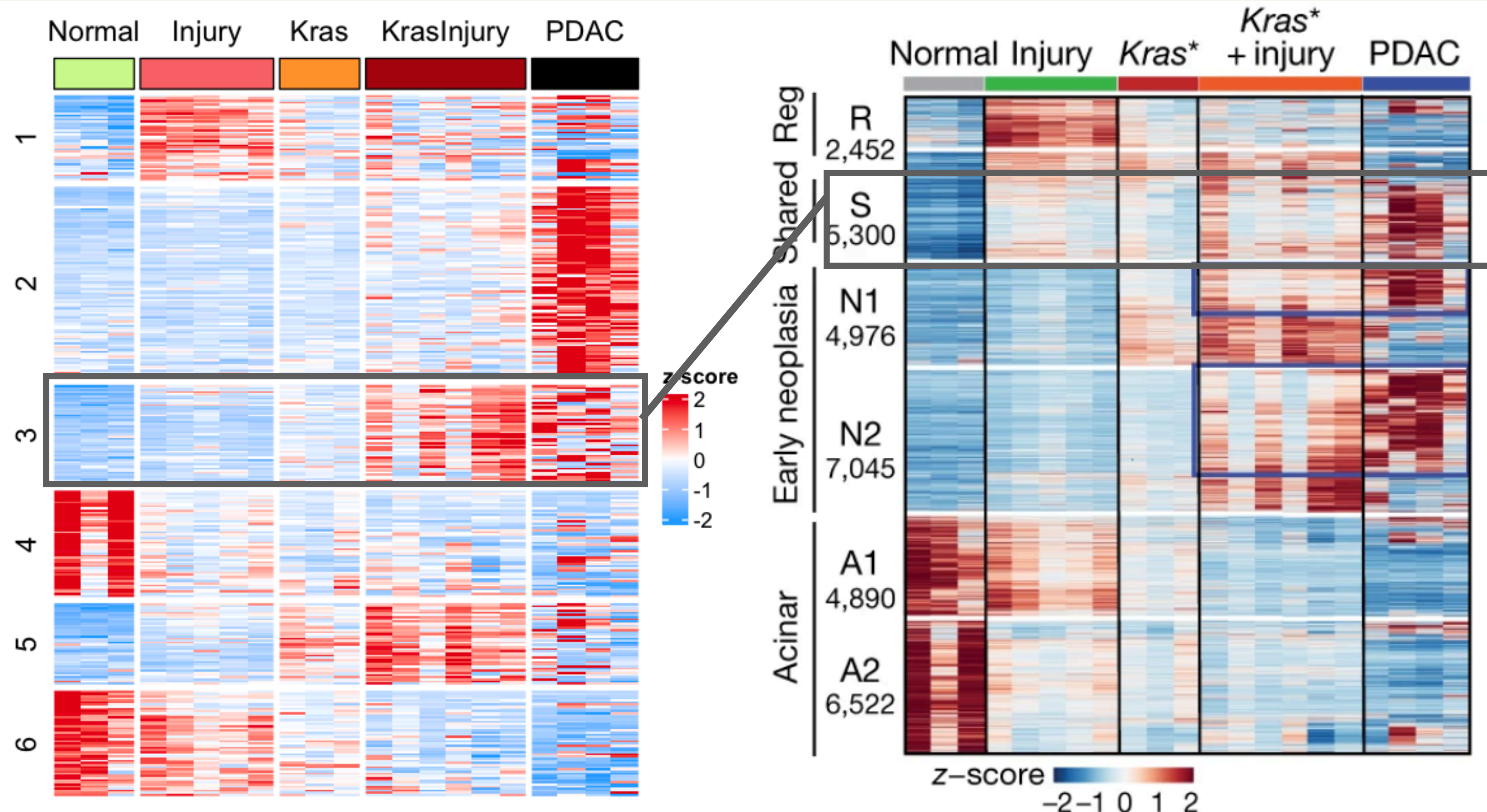
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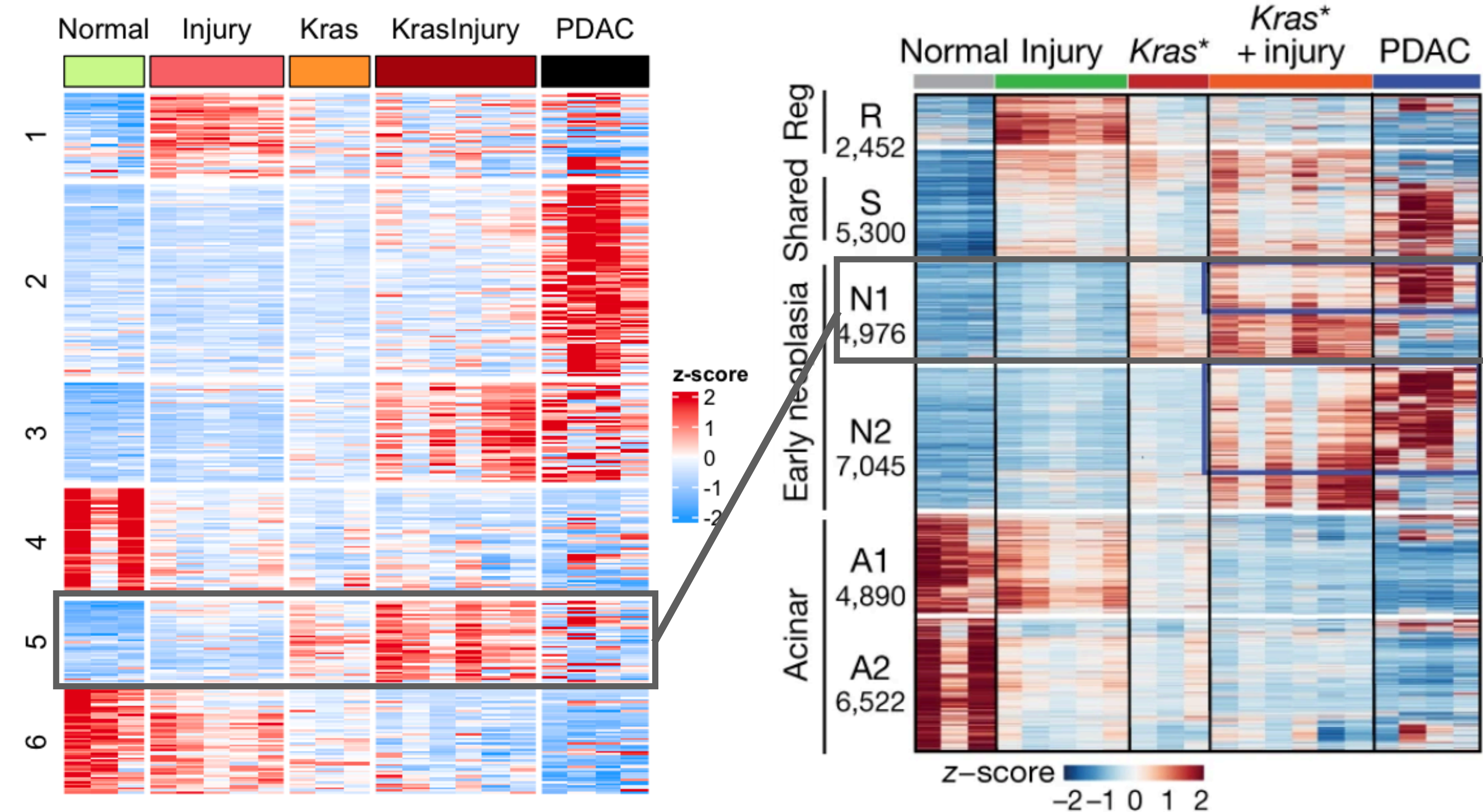
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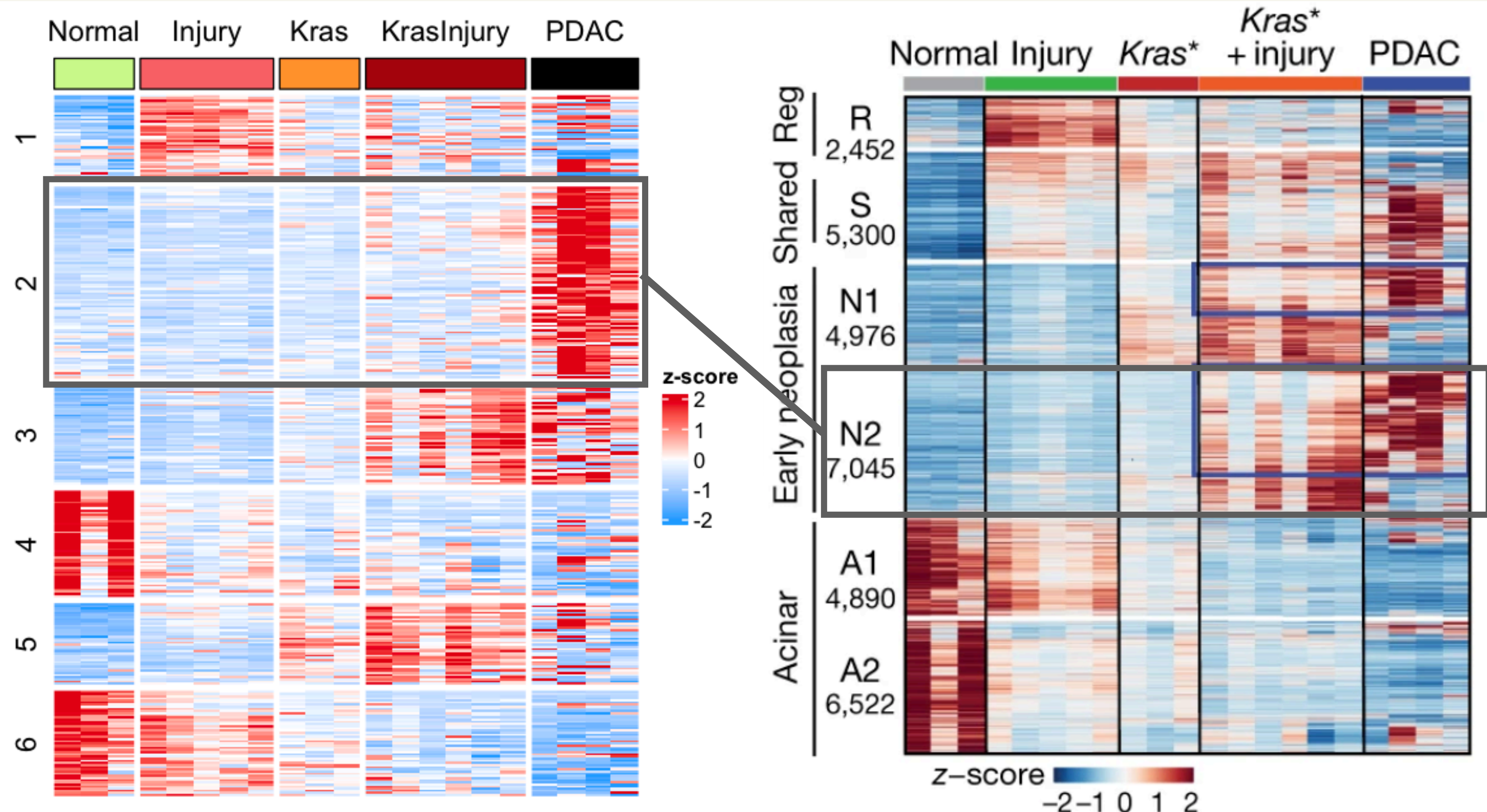
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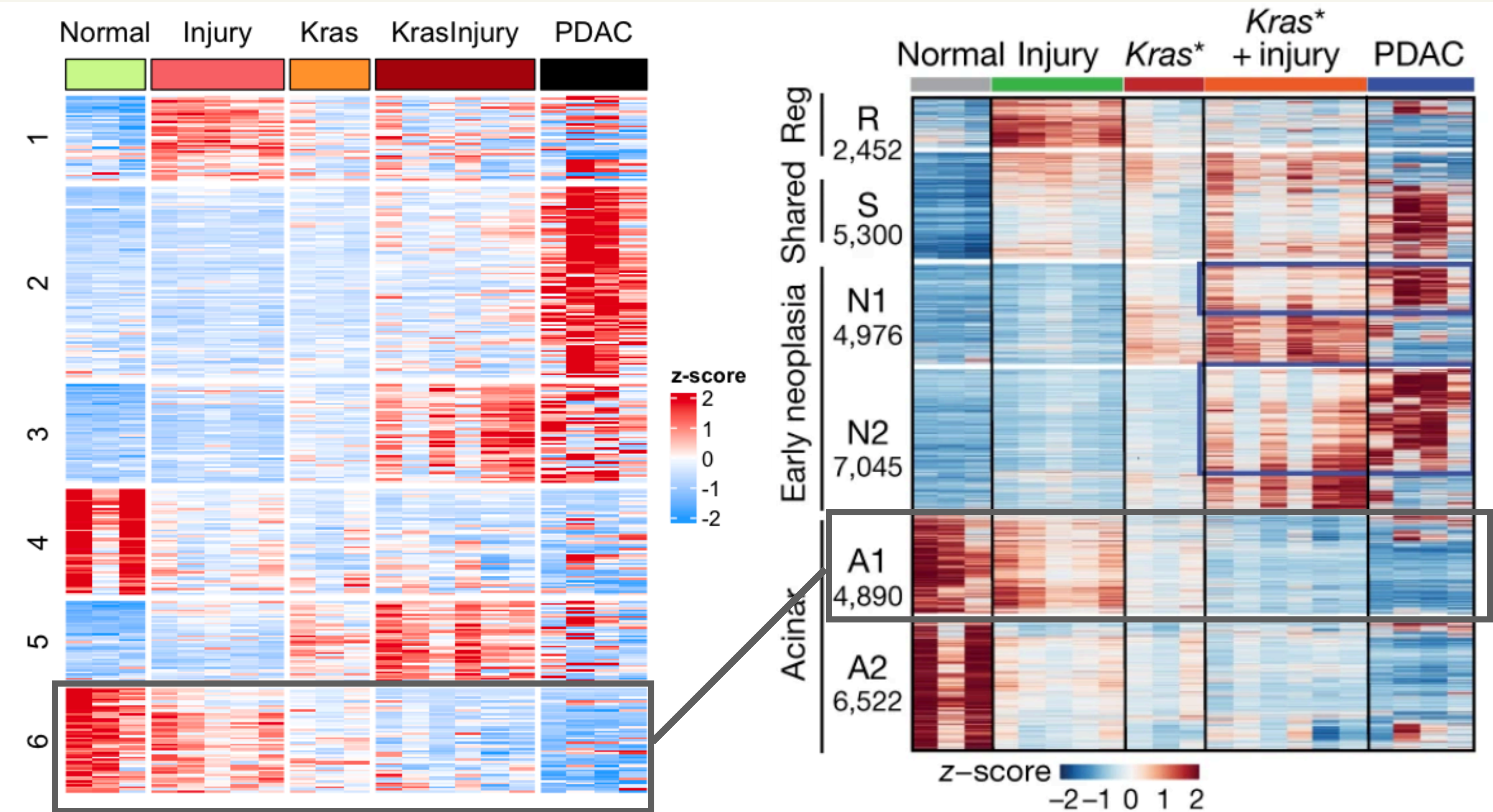
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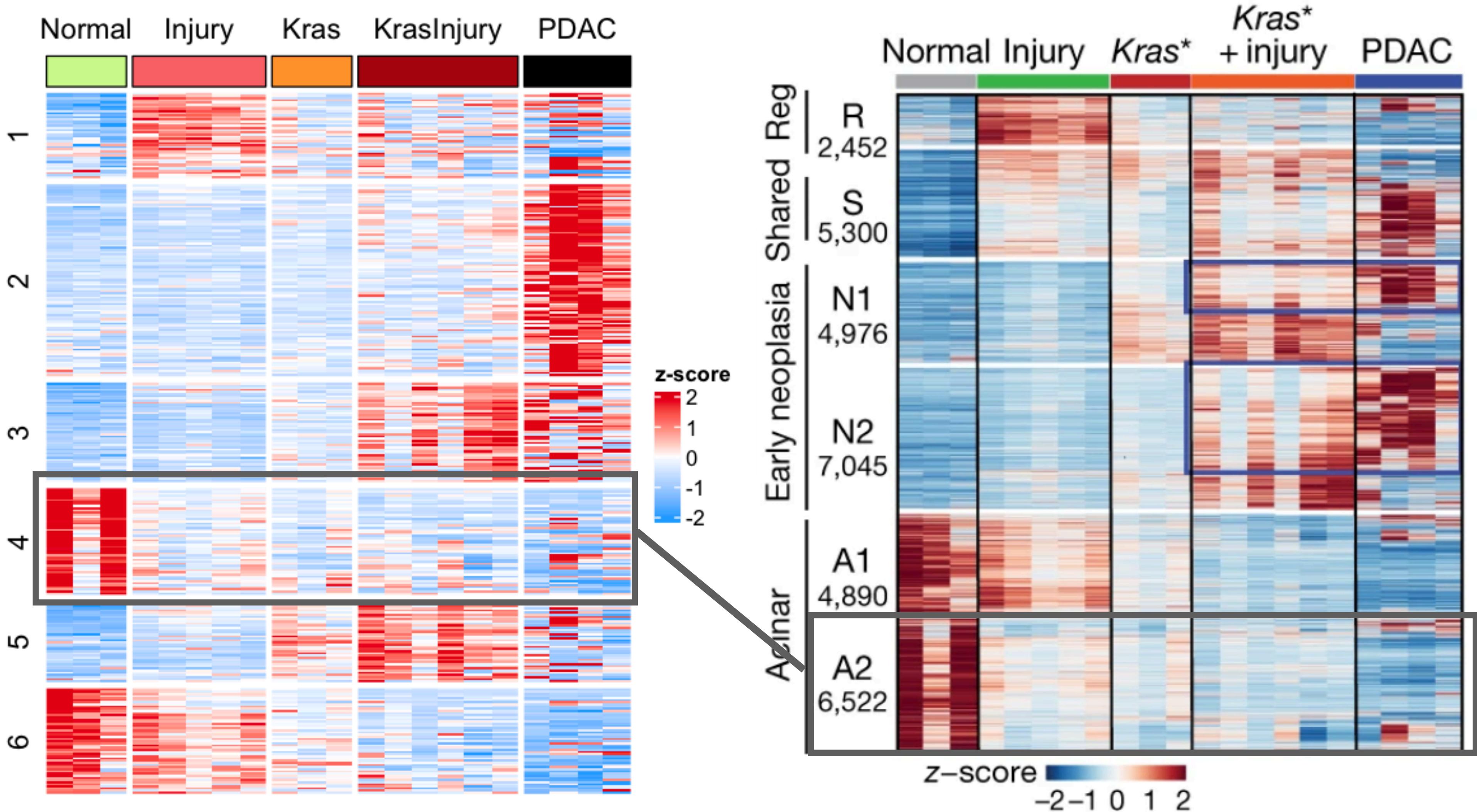
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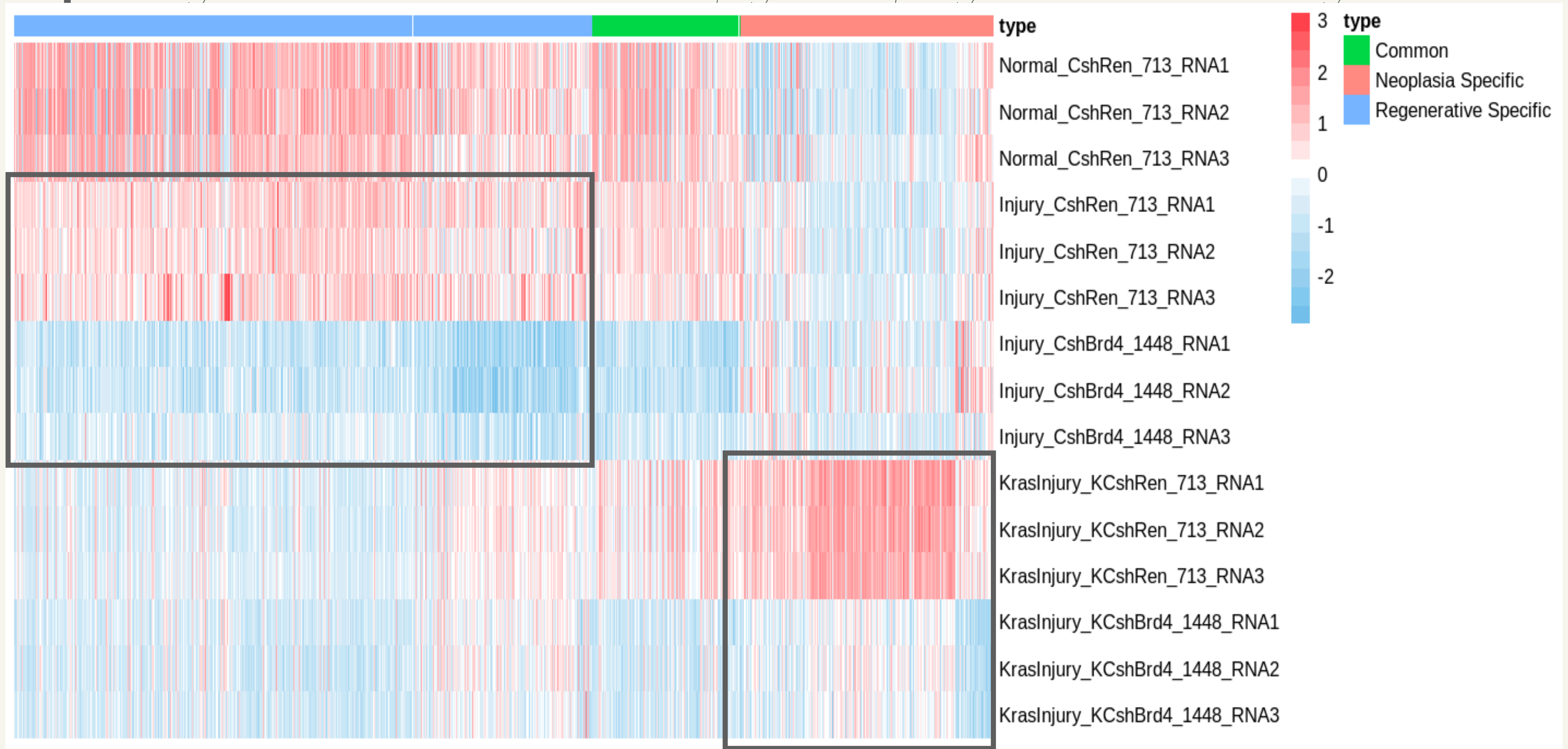
## **Method:**

- Start with **raw RNA count**
- **DEseq2 analysis**
- Select for **significantly differentially expressed genes (DEGs)**
- Among these DEGs, **downregulated ones after the suppression of BRD4** in regenerative metaplasia (Csh: injury) or neoplastic transformation (KCsh:  $\_Kras^*\_$  + injury) settings **are further selected**
- **pheatmap visualization**



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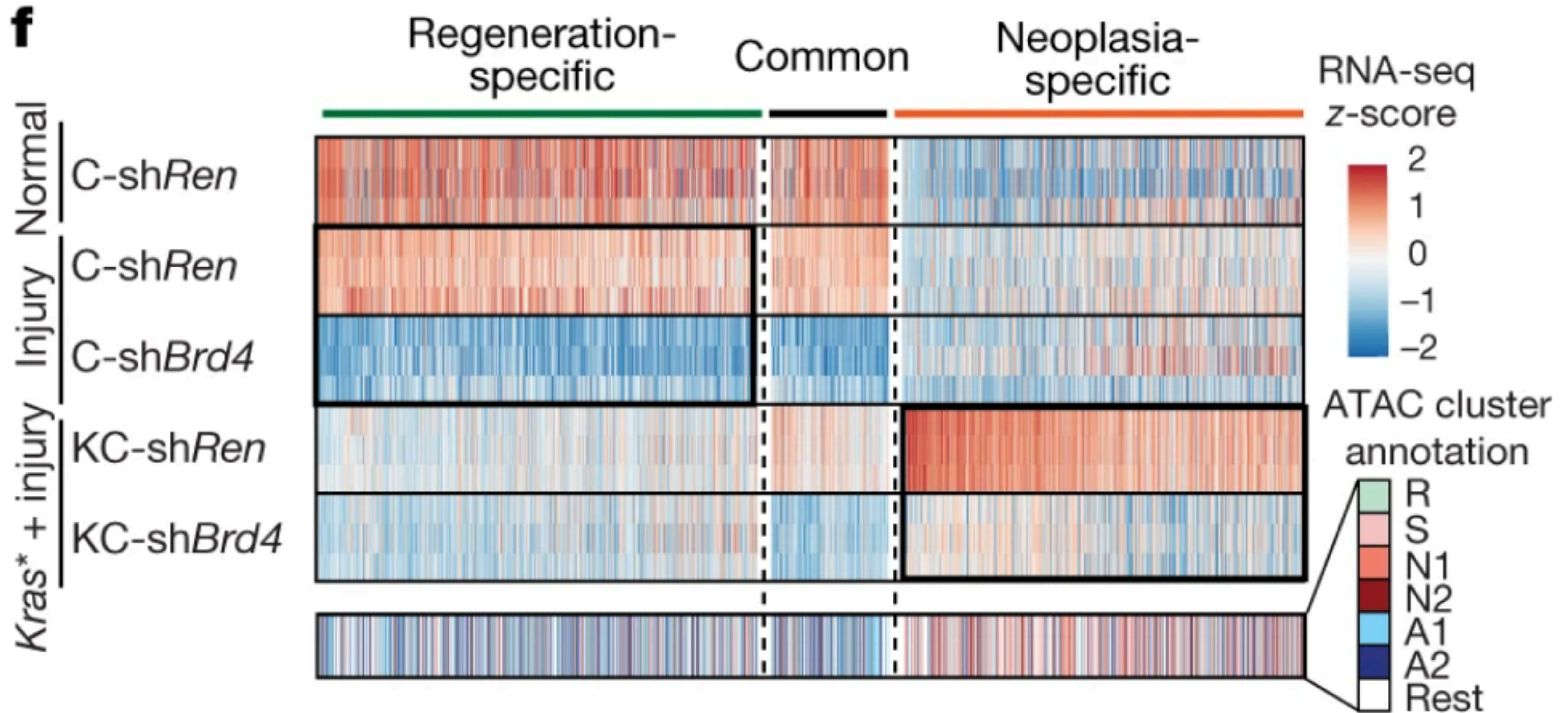
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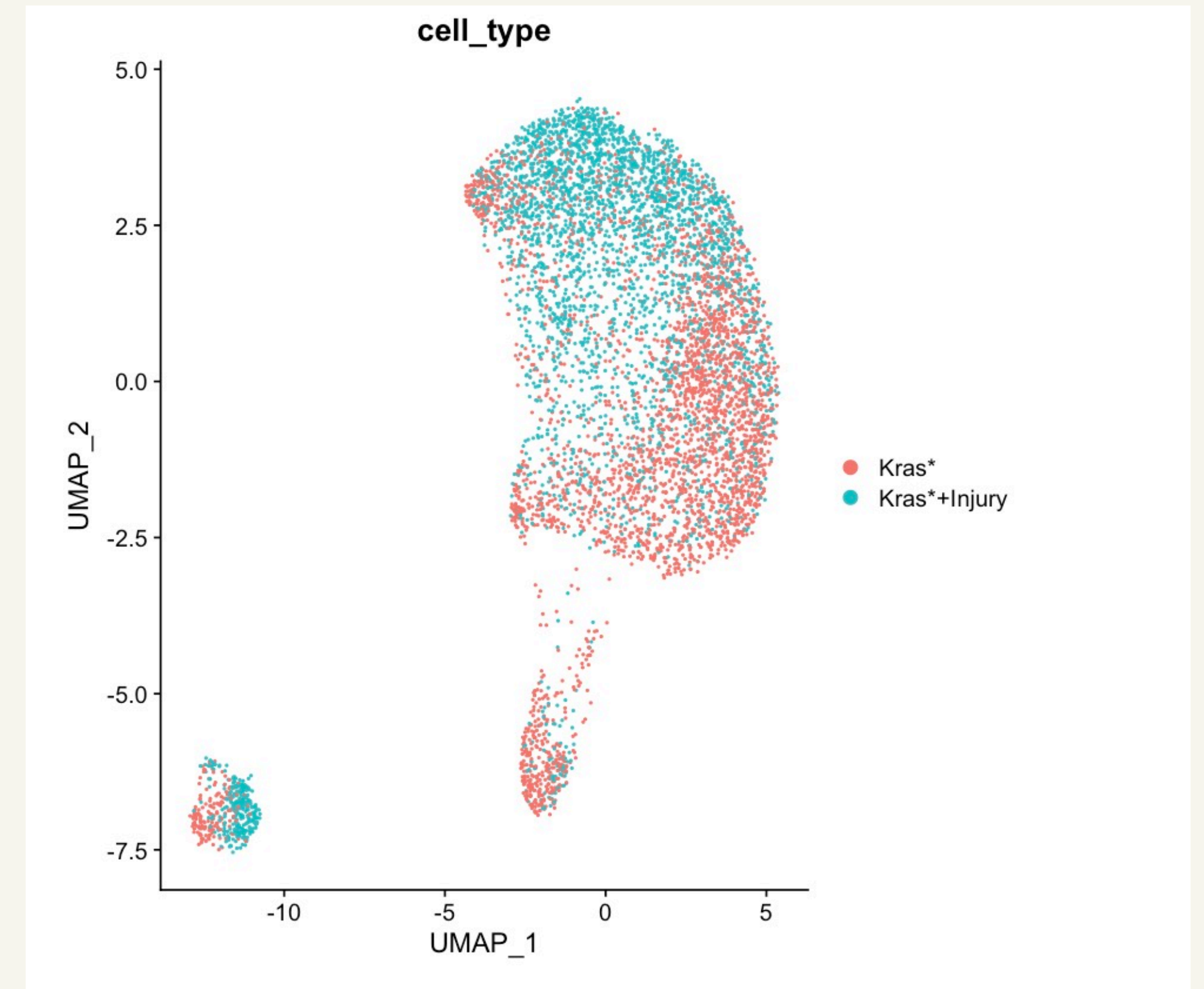
RNA-seq

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RNA-seq

## Method:

- Start with **matrix count**
- **Variable gene finding**
- **Principle component analysis**
- **Clustering & UMAP visualization**



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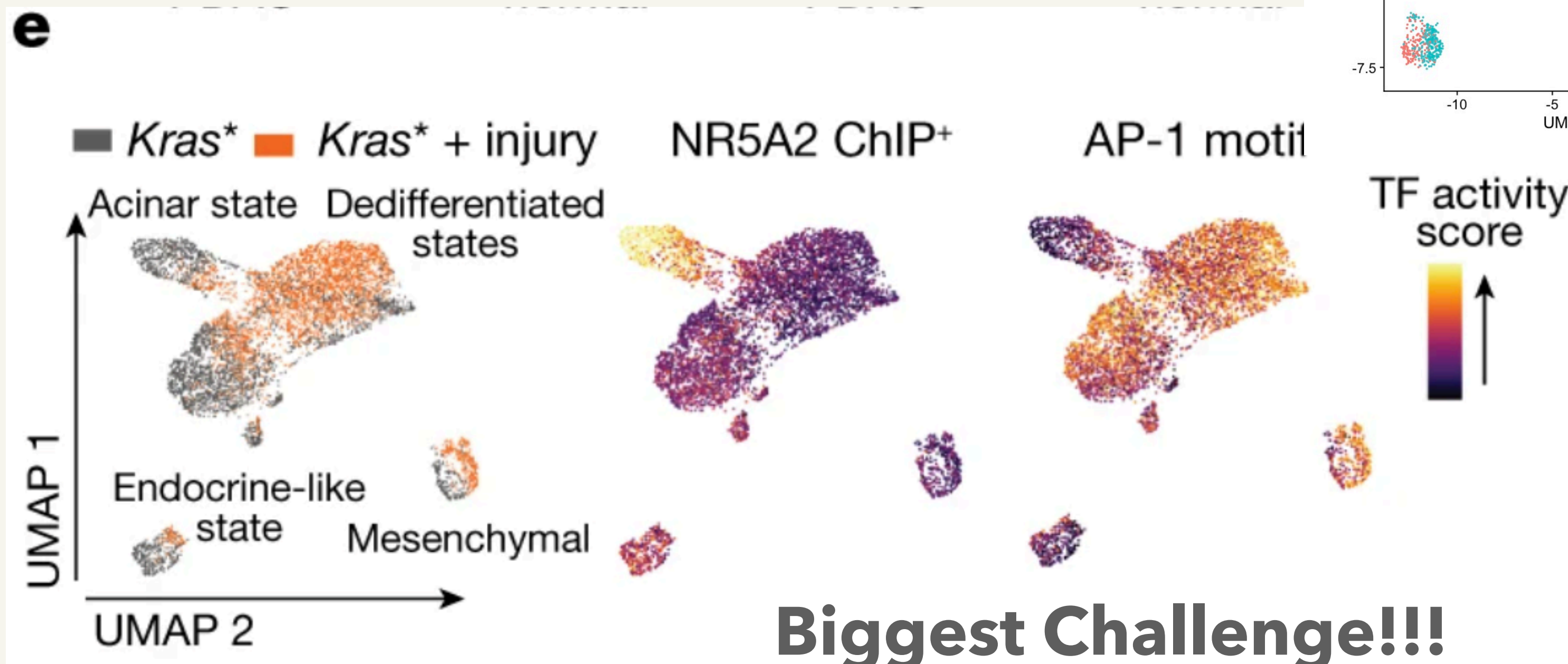
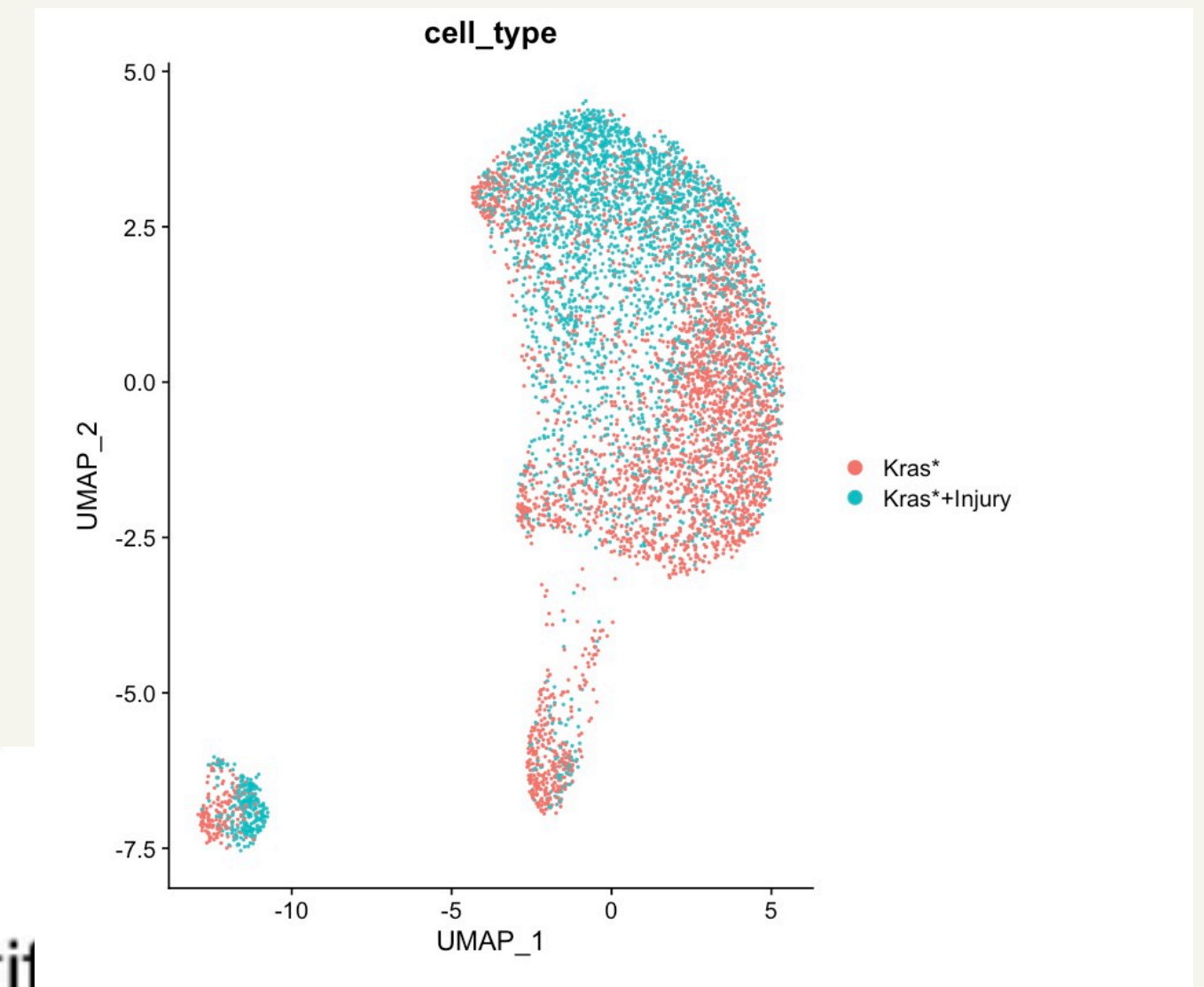
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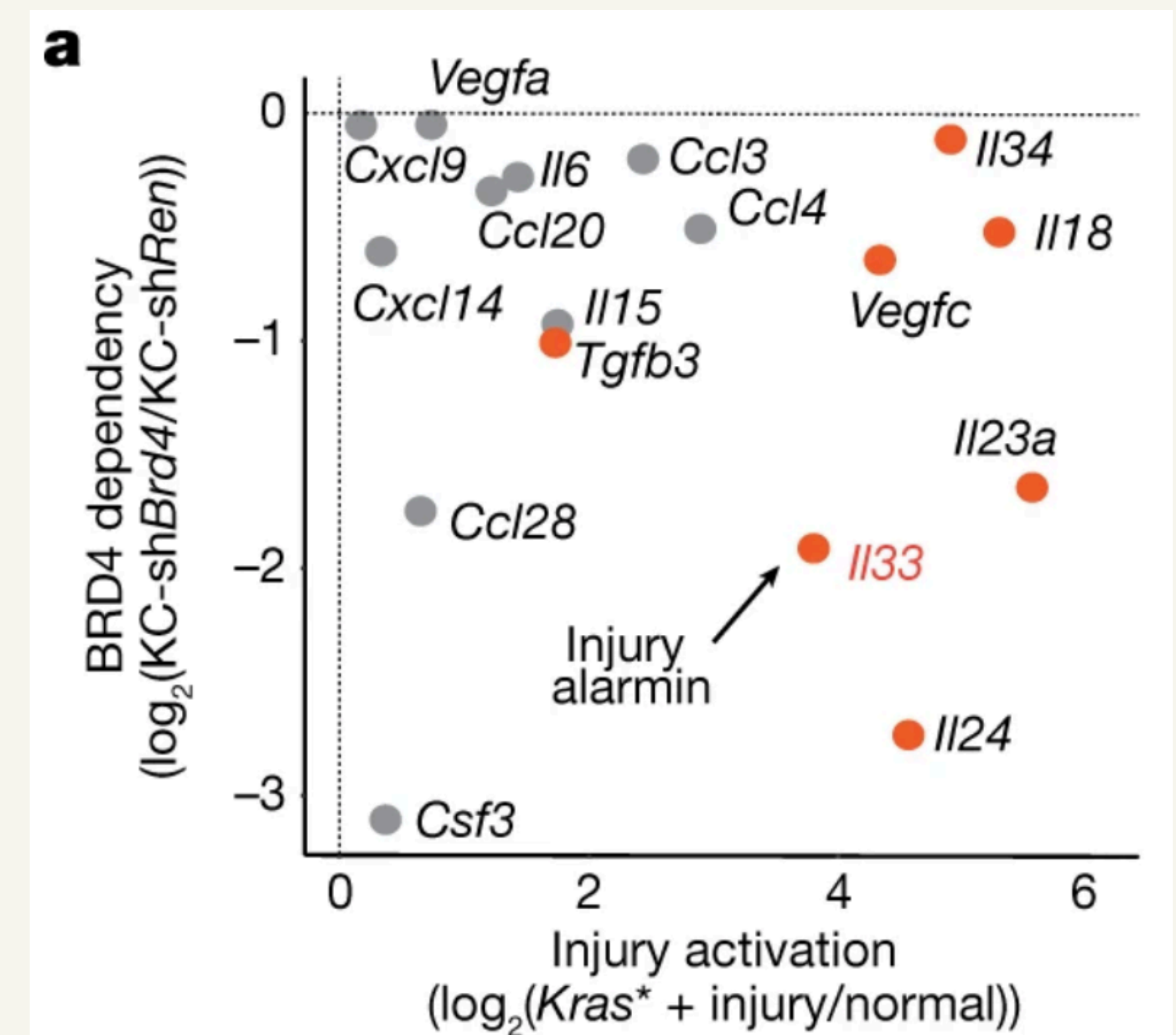
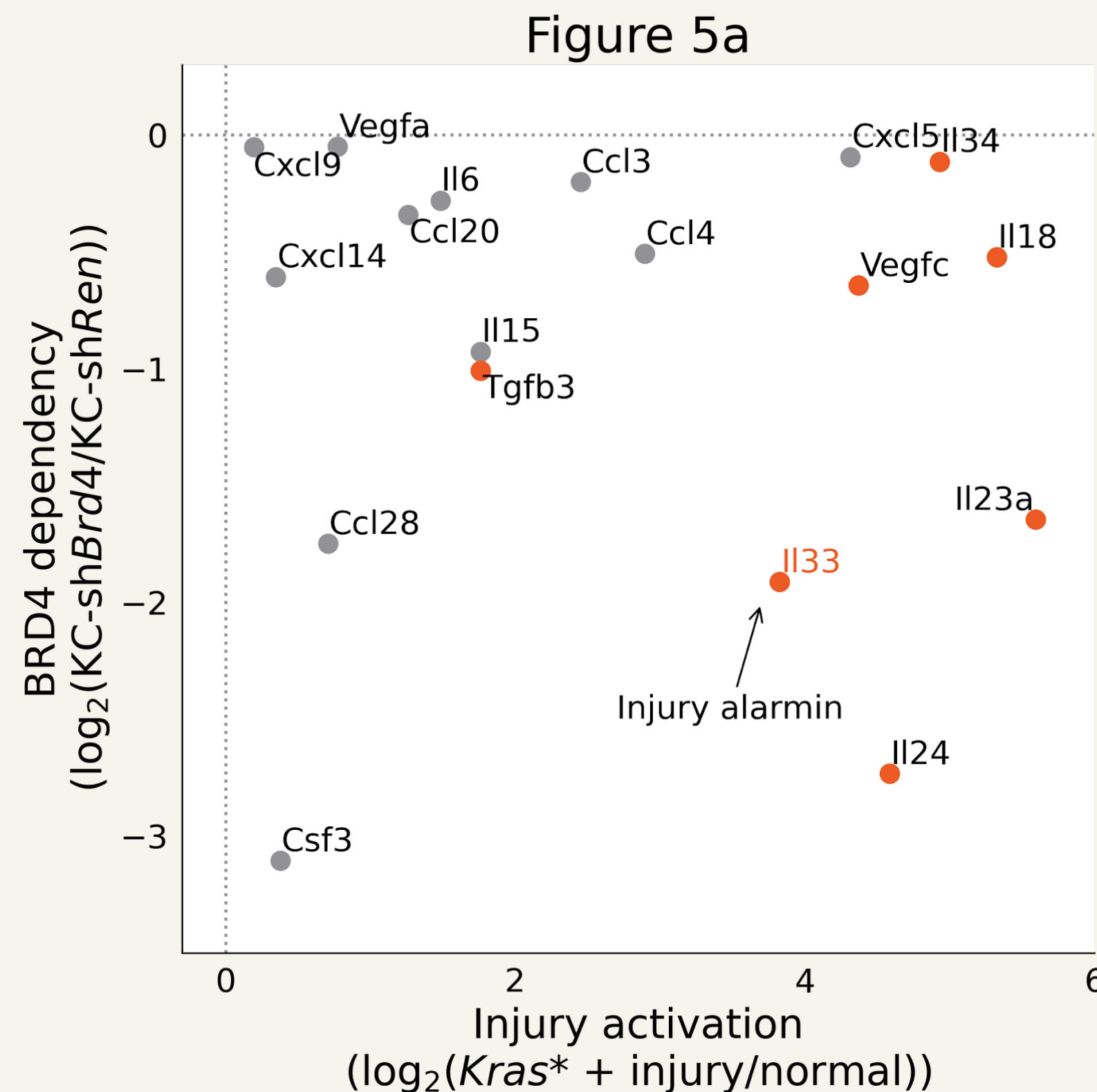
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## Method:

- Differential expression analysis
- Select for **target gene**
- **Matplotlib** visualization



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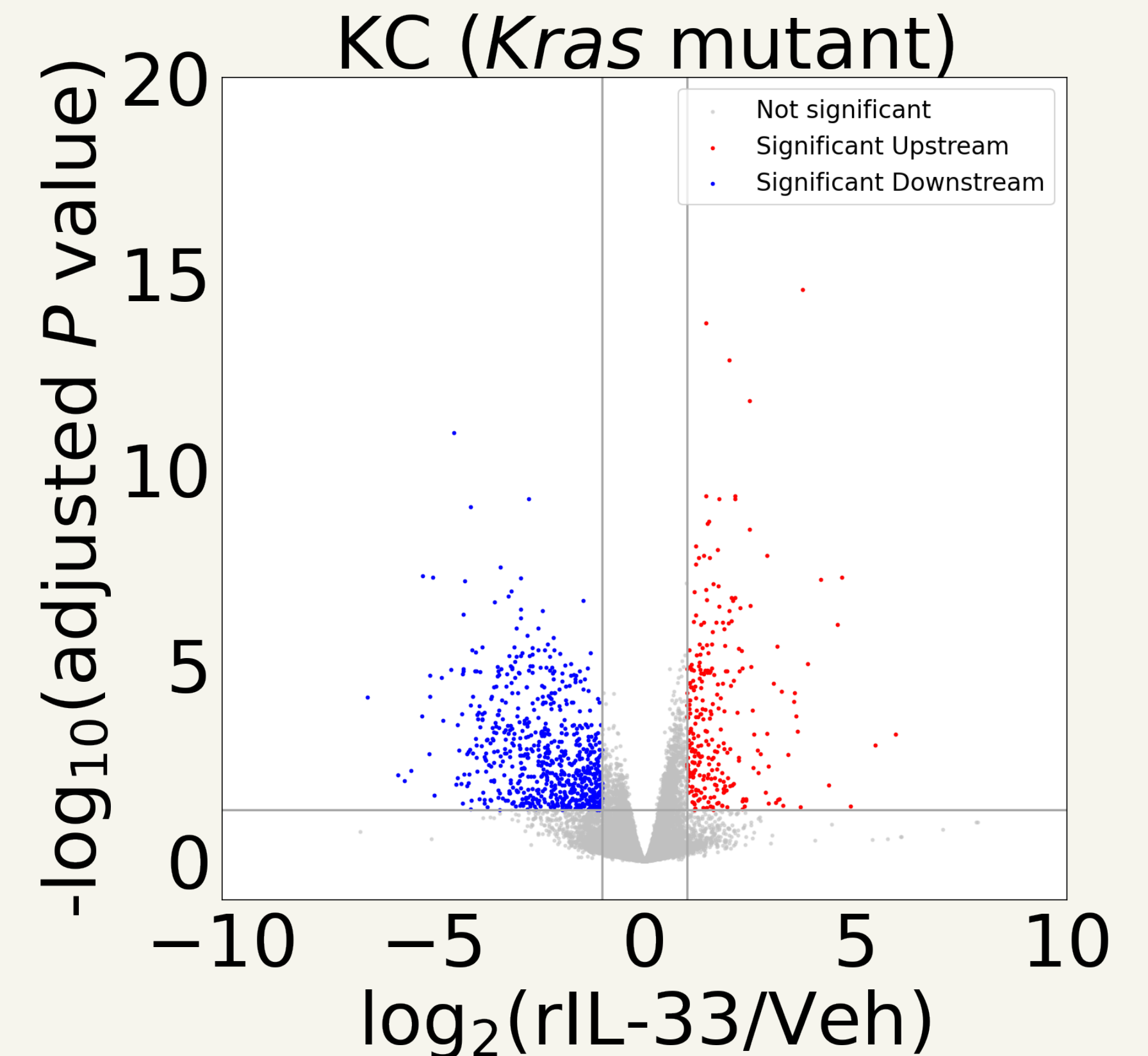
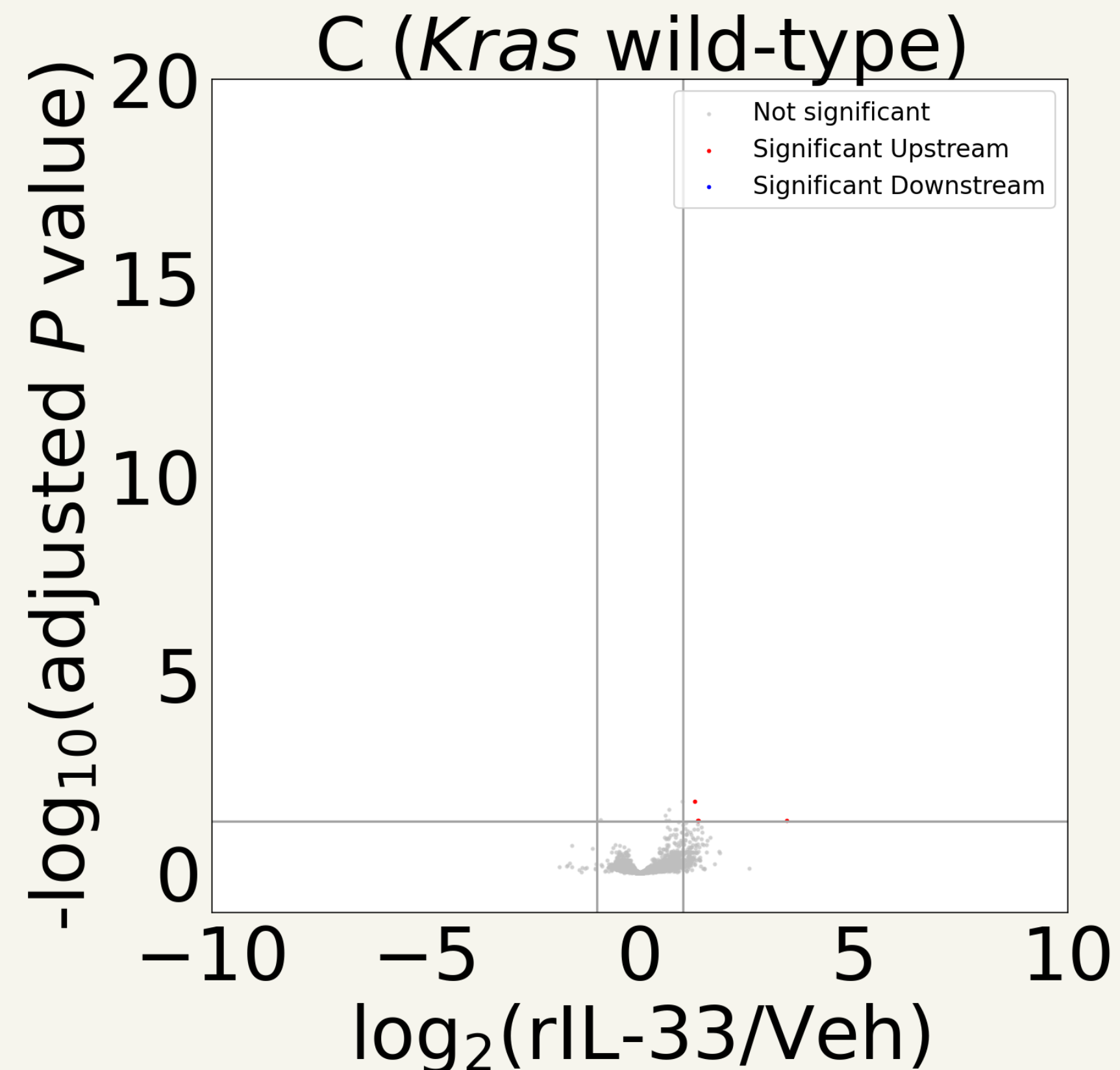
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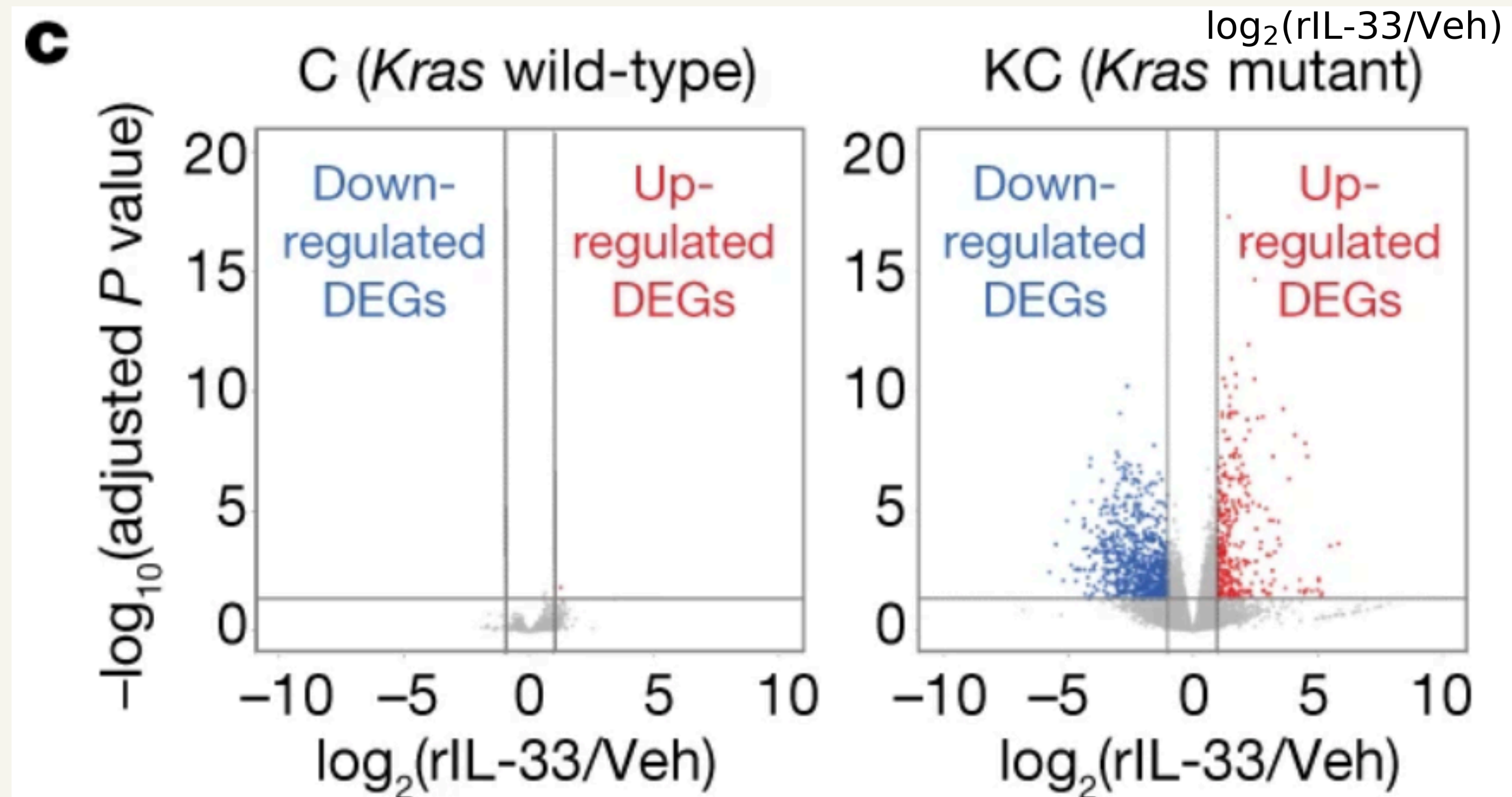
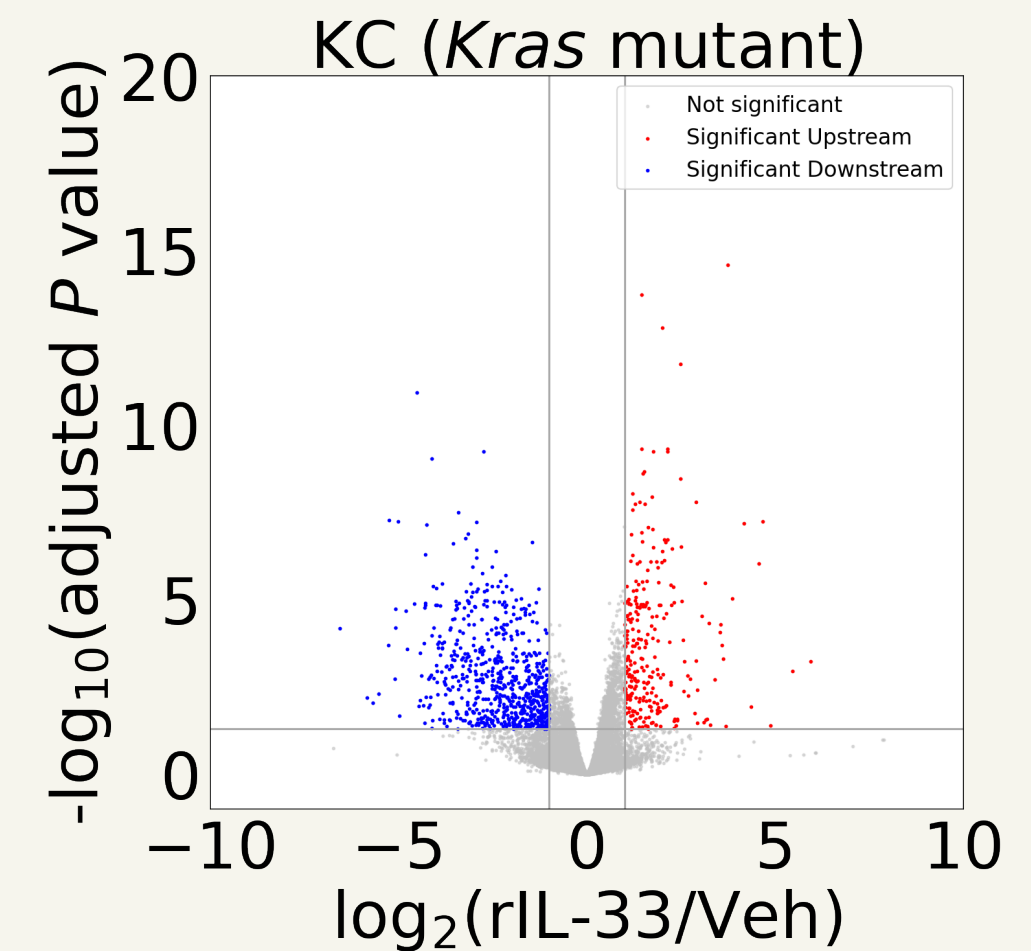
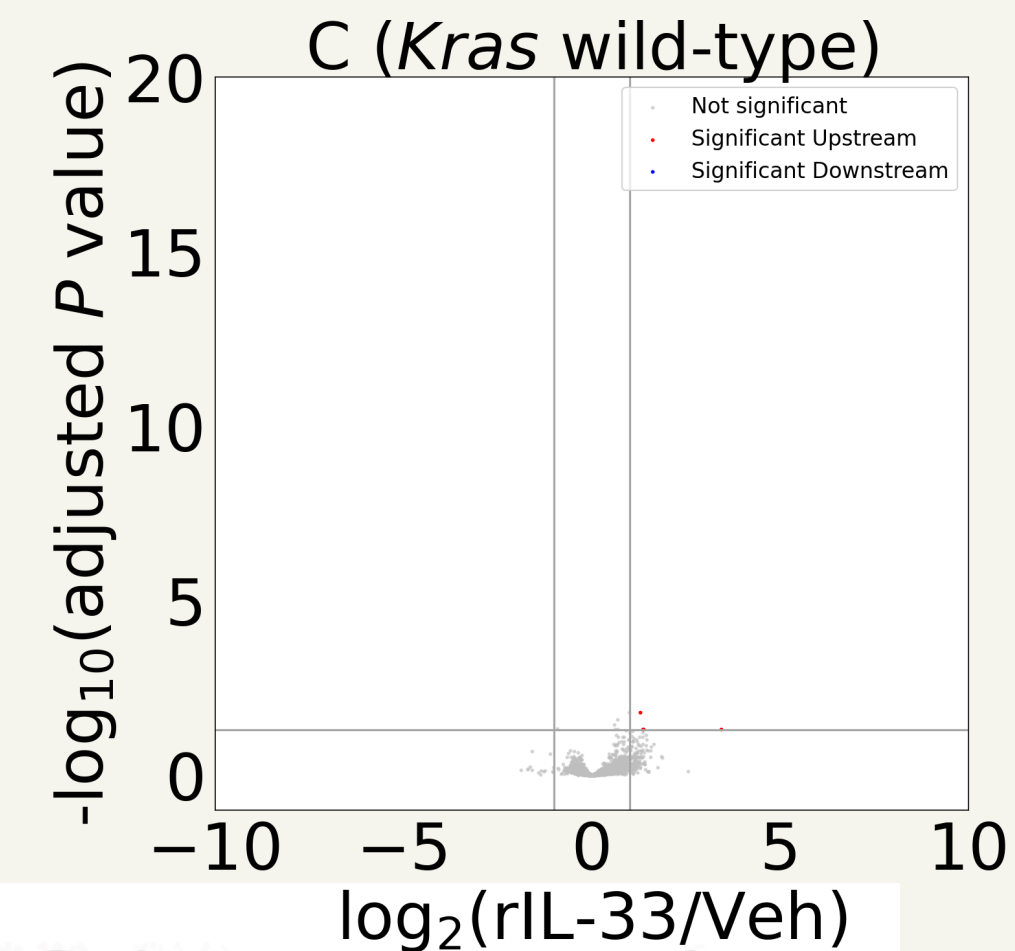
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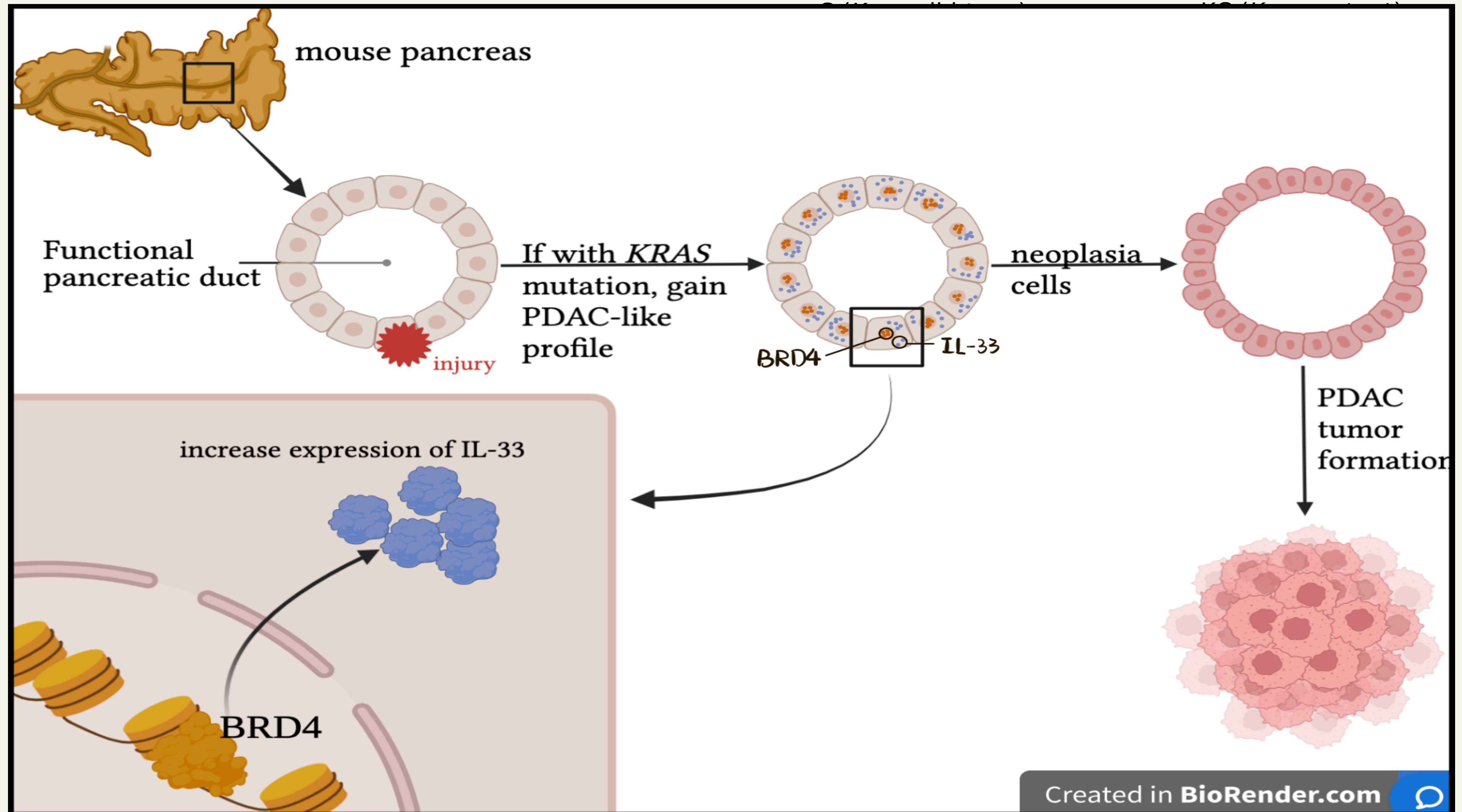
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# Thanks for watching

And special thanks to our amazing CSE185 instructor team for a great quarter