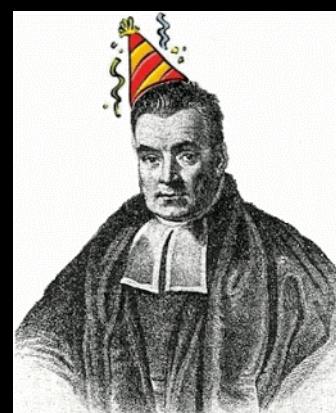
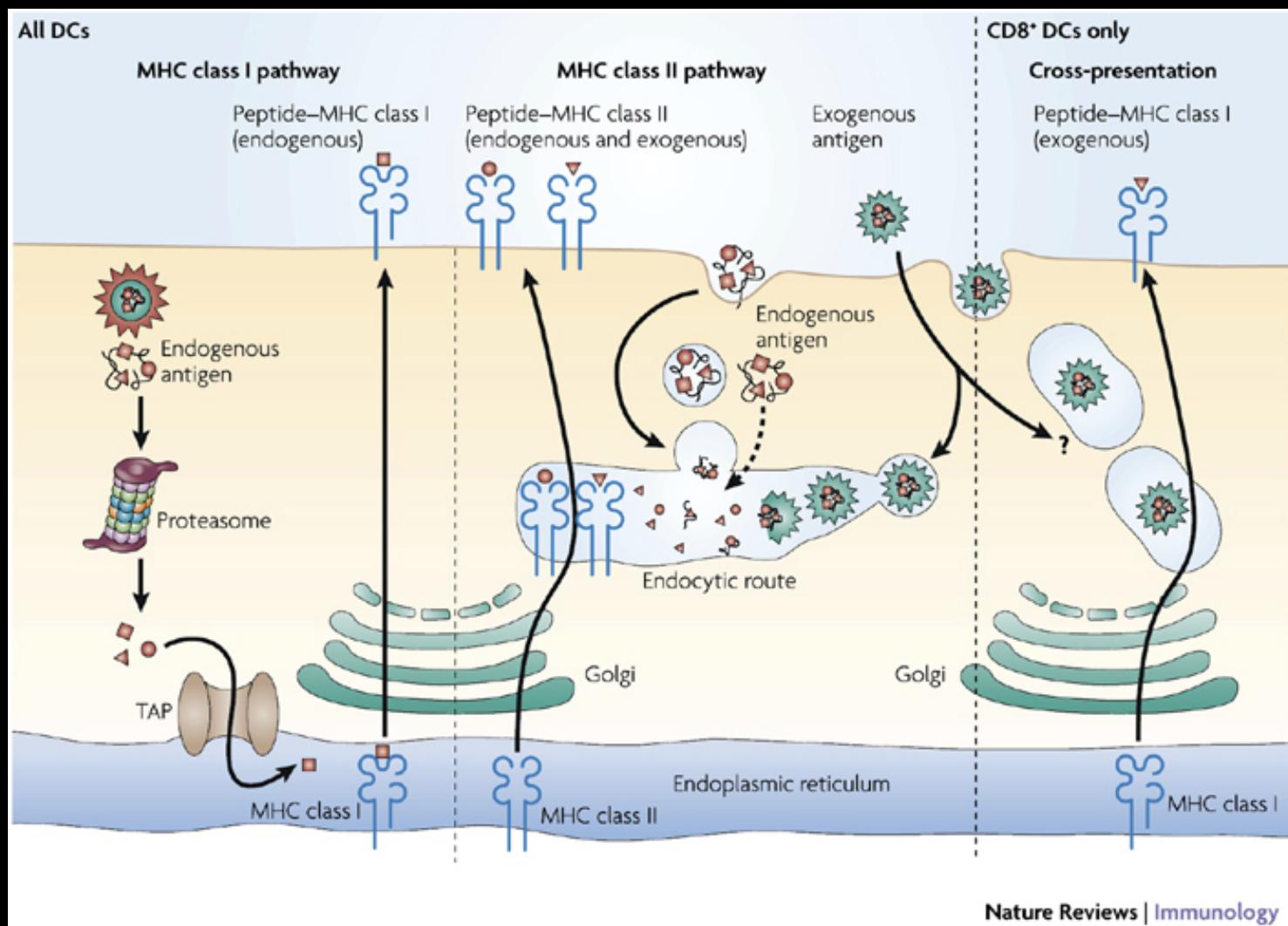


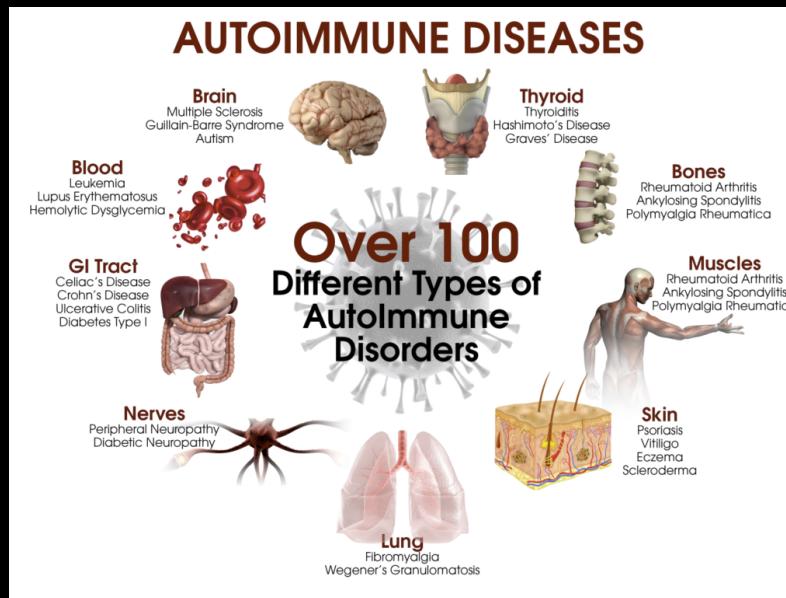
# Identifying novel MHC pathway candidates with a naive Bayesian classifier



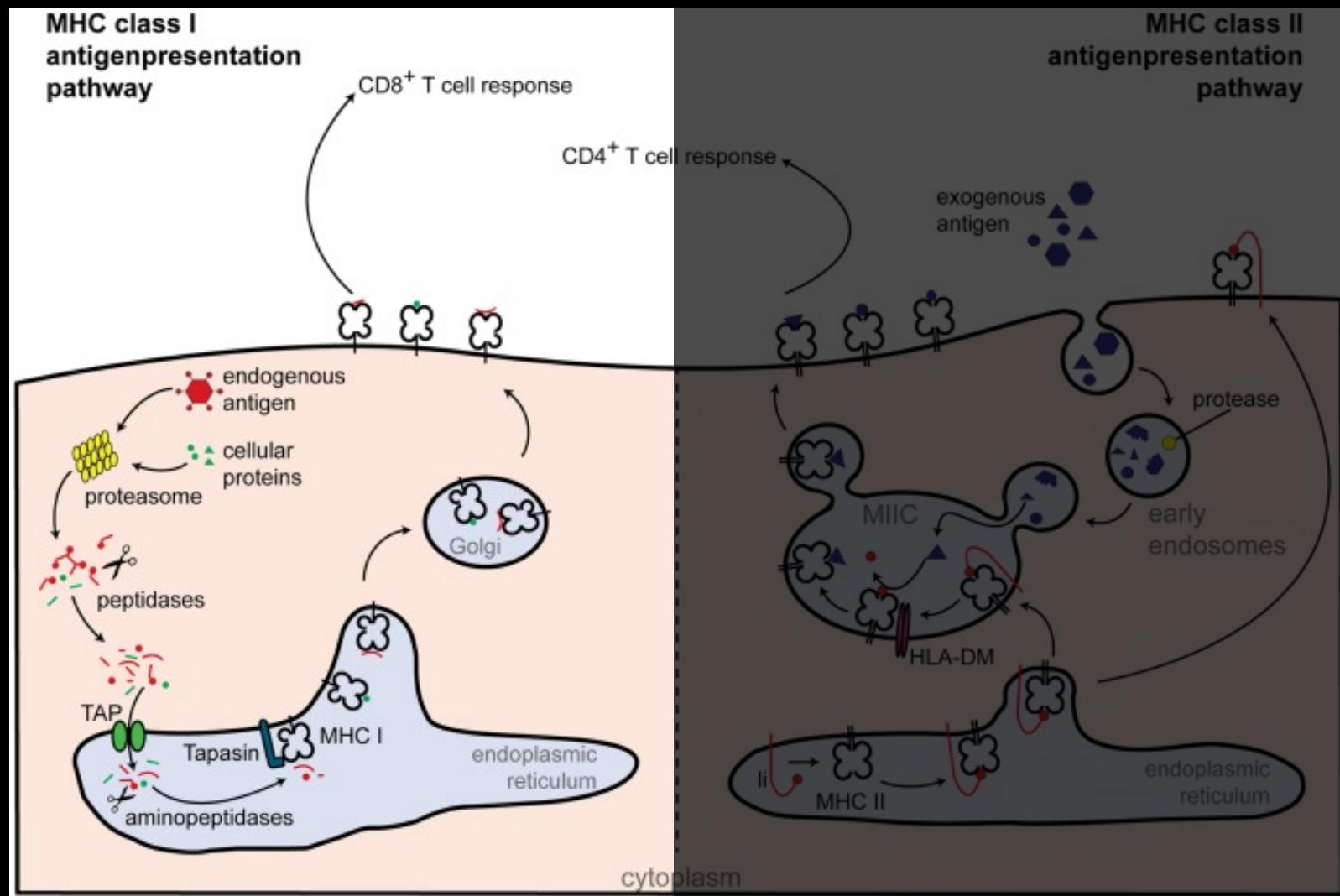
# What I want to do

---

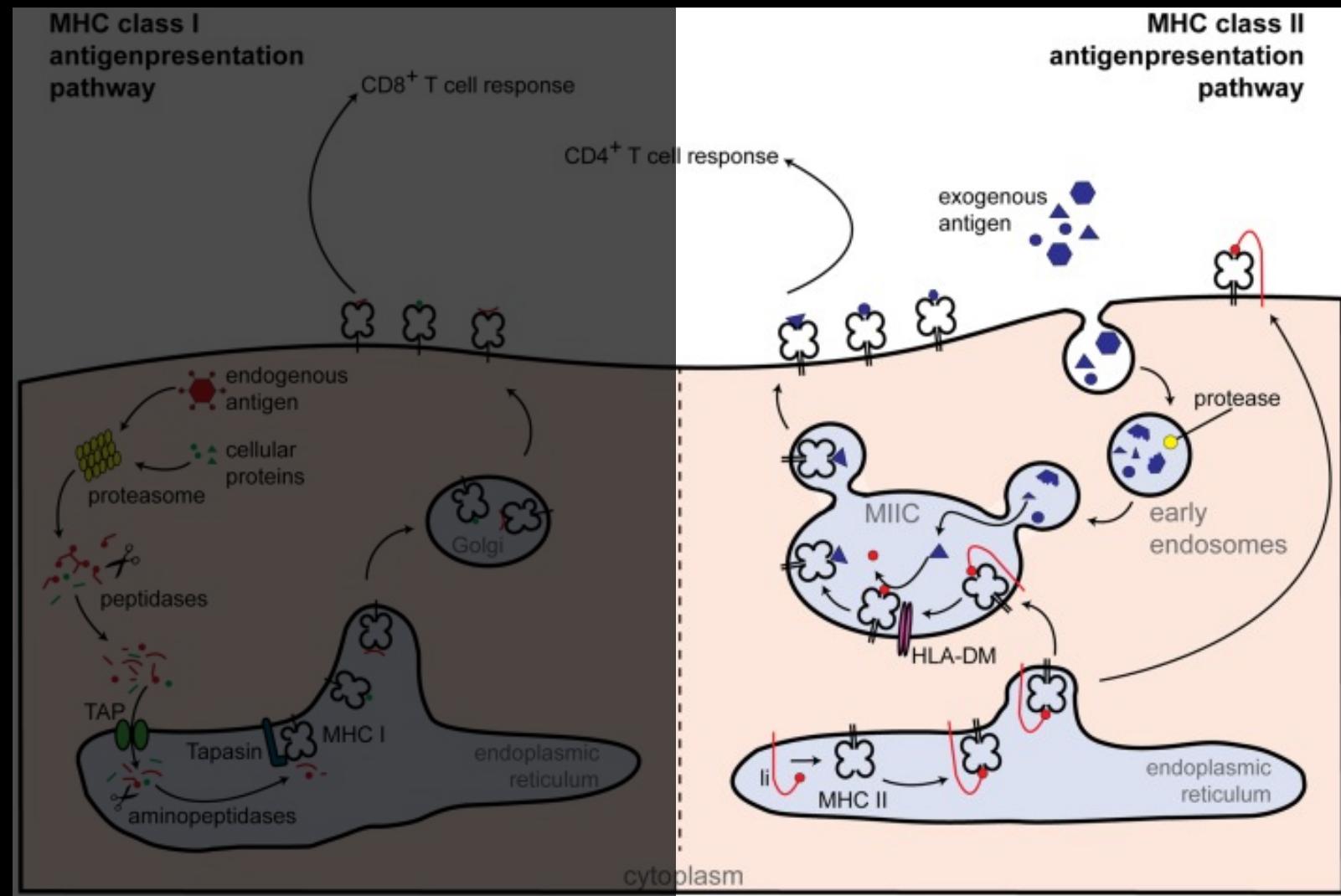
- Use features of known MHC pathway genes to identify novel candidate genes in all human protein-coding genes



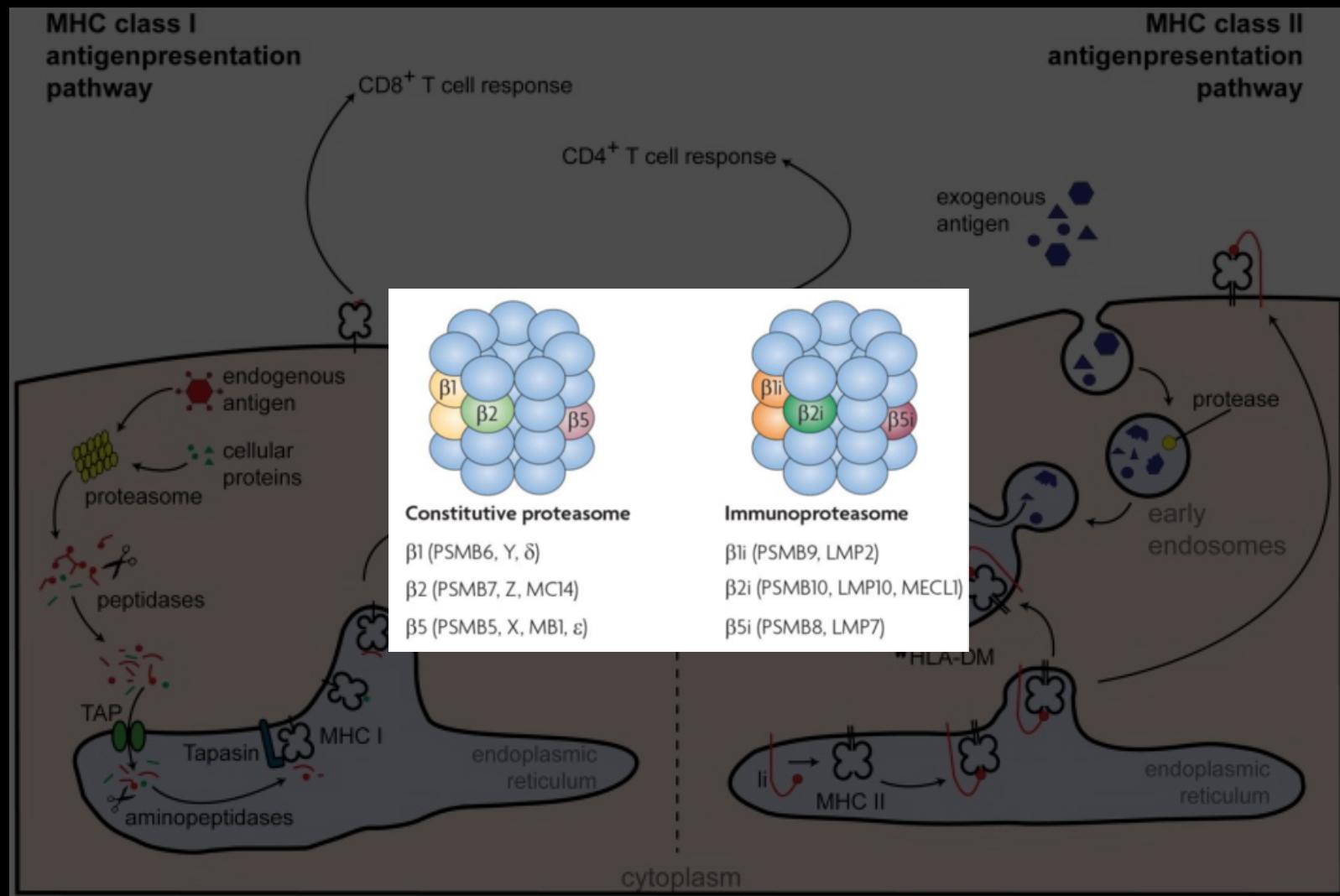
# The MHC pathway



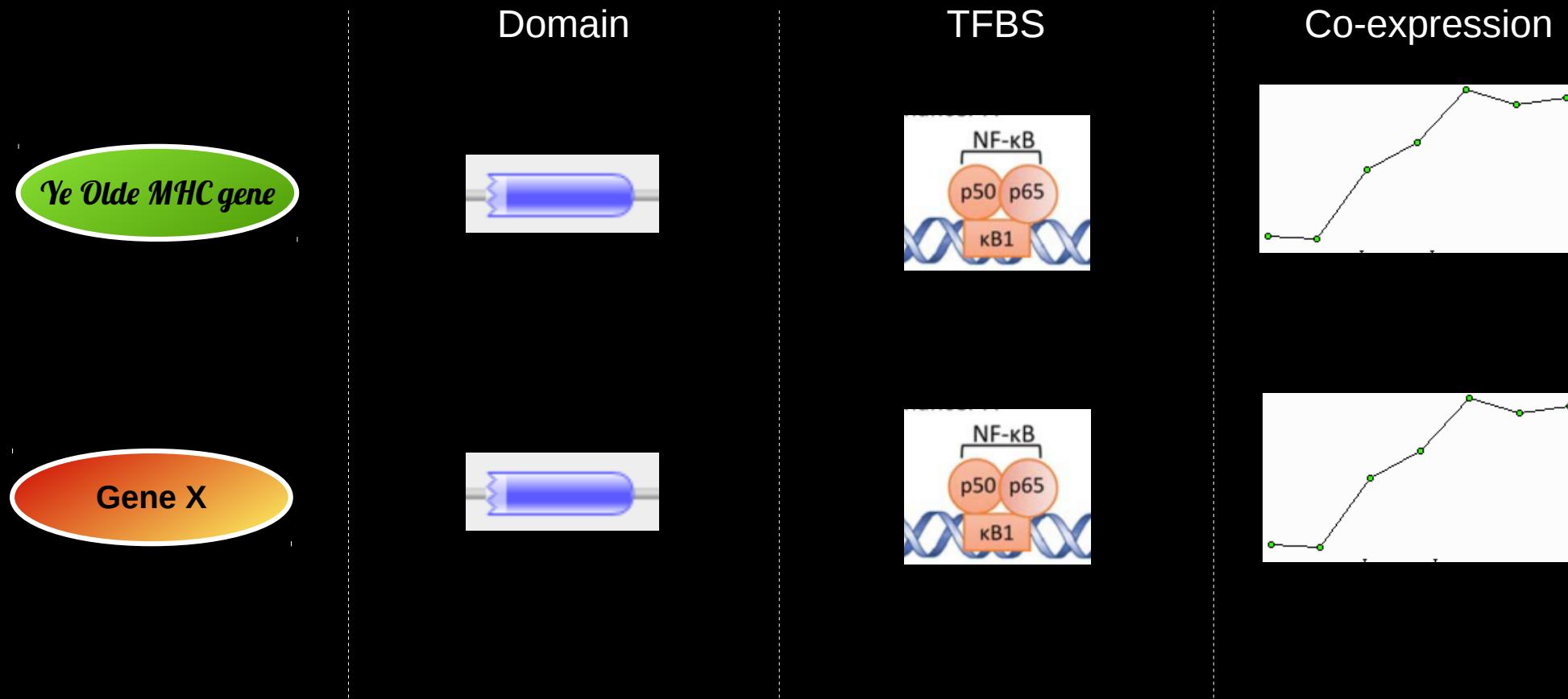
# The MHC pathway



# The MHC pathway



# Why integration?



# Why a Bayesian classifier?

*(Why not \*INSERT MY FAVOURITE CLASSIFIER.TXT\*?)*

---

# Why a Bayesian classifier?

(*Why not \*INSERT MY FAVOURITE CLASSIFIER.TXT\*?*)

---

- Brutal honesty:
  - Student project and supervisor had affinity  
→ other classifiers will be future work

# Why a Bayesian classifier?

(*Why not \*INSERT MY FAVOURITE CLASSIFIER.TXT\*?*)

---

- Brutal honesty:
  - Student project and supervisor had affinity  
→ other classifiers will be future work
- Advantages:
  - Can show the information value per dataset
  - Can deal well with missing data

# What's a naive Bayesian?

---

- Different type of statistics:  
Objective measure of belief

# What's a naive Bayesian?

---

- Different type of statistics:  
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- Intuition:

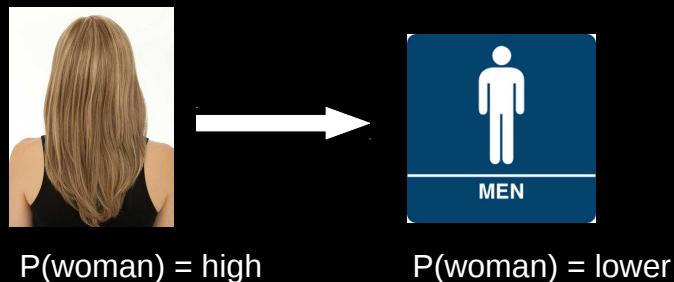


$P(\text{woman}) = \text{high}$

# What's a naive Bayesian?

---

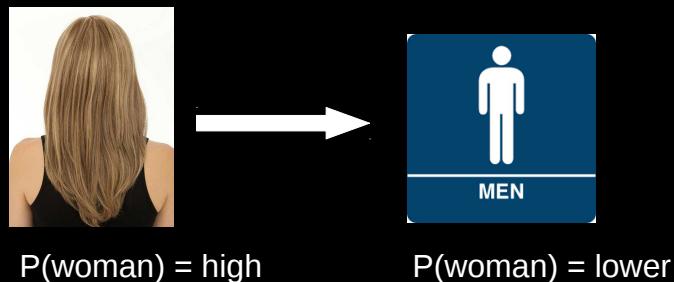
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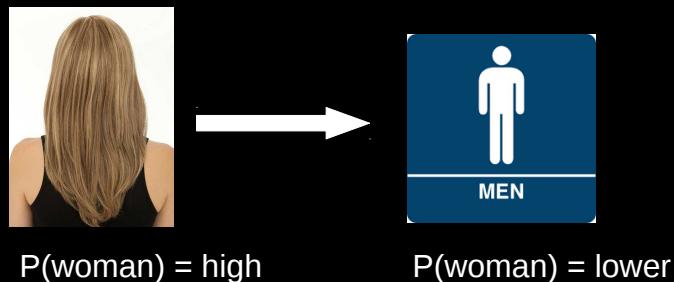


- ***Update your beliefs*** based on data

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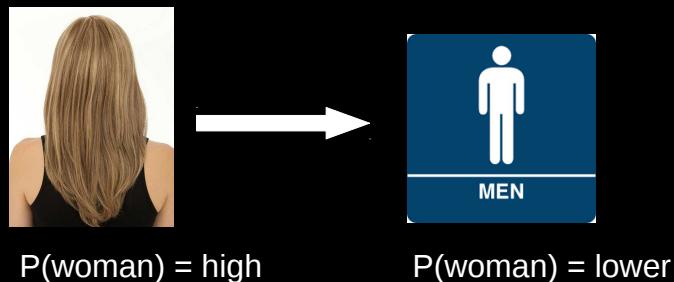


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# What's a *naive* Bayesian?

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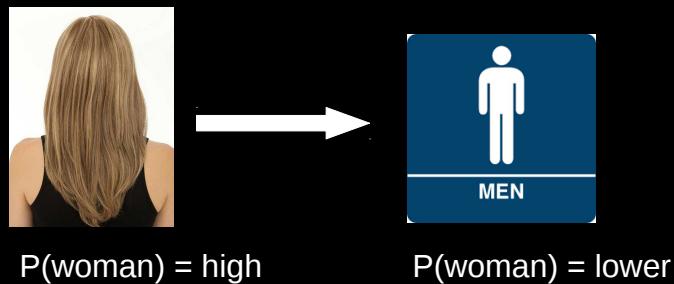


- ***Update your beliefs*** based on data
  - Assume all evidence is independent → *naive*

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# How does it work?

---

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$$\frac{P(MHC\ gene|data)}{P(not\ MHC\ gene|data)} = \frac{P(MHC\ gene)}{P(not\ MHC\ gene)} * \frac{P(data|MHC\ gene)}{P(data|not\ MHC\ gene)}$$

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Odds of being  
an MHC gene



Prior odds



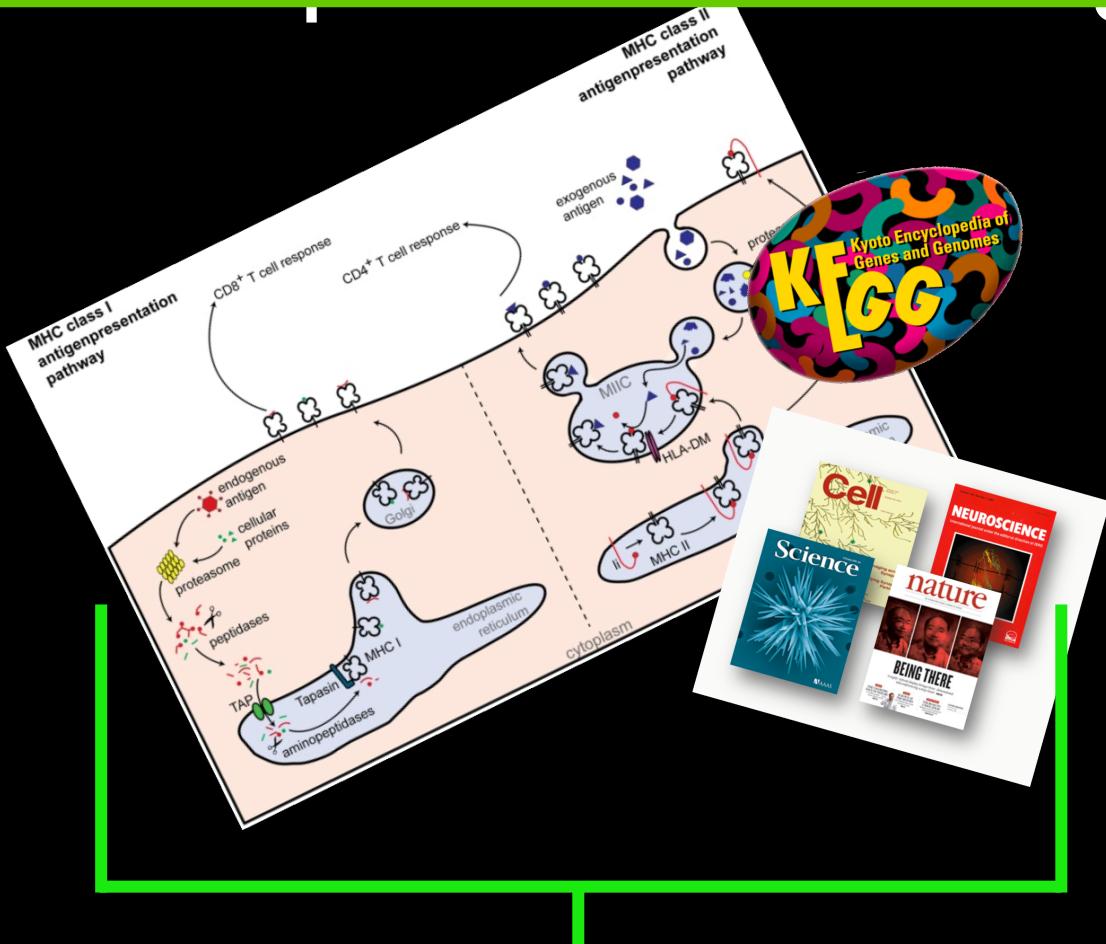
Updating  
based on data

# Applying the bayesian to MHC: positive and negative set

---

- Need to compare what MHC pathway genes do relative to non-MHC pathway genes
- Gives you enrichments of MHC pathway genes, relative to non-MHC pathway genes

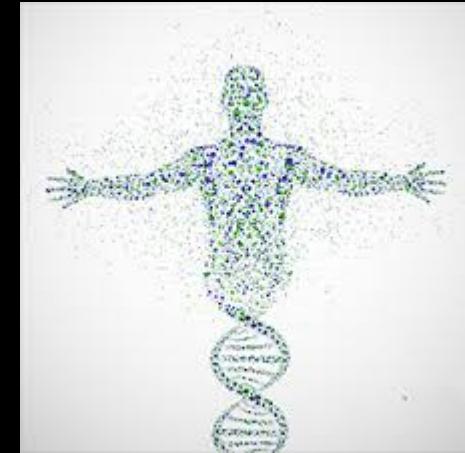
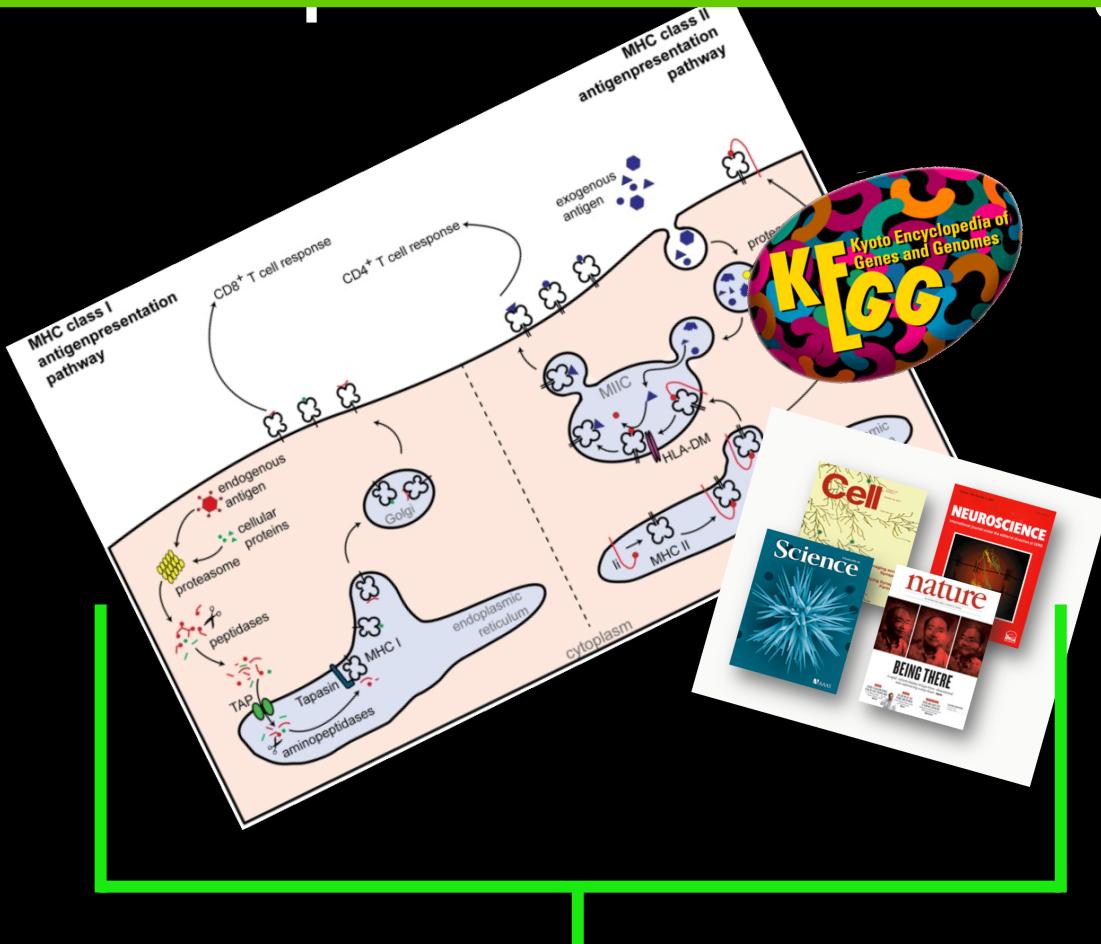
# Applying the bayesian to MHC: positive and negative set



86 positive set genes

Paul et al., 2011;  
Kanehisa, Furumichi,  
Tanabe, Sato, &  
Morishima, 2017

# Applying the bayesian to MHC: positive and negative set

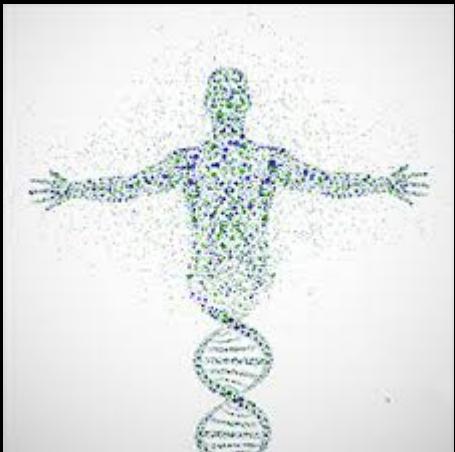


(all human genes - 86)  
negative set genes

Paul et al., 2011;  
Kanehisa, Furumichi,  
Tanabe, Sato, &  
Morishima, 2017

# Applying the bayesian to MHC: positive and negative set

---



- Feasible for a student project
- Gives a conservative score:
  - We expect some negative set genes to actually be involved in the MHC pathway!

(all human genes-86)  
**negative set** genes

# Applying that to MHC: prior

---

$$Prior = \frac{P(MHC \text{ pathway gene})}{P(\text{not } MHC \text{ pathway gene})}$$

# Applying that to MHC: prior

---

$$Prior = \frac{P(MHC \text{ pathway gene})}{P(\text{not } MHC \text{ pathway gene})}$$

$$Prior = \frac{\frac{200}{22,357}}{\frac{(22,357 - 200)}{22,357}} \approx 0.009$$

# Applying that to MHC: prior

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$$Prior = \frac{\frac{200}{22,357}}{\frac{(22,357 - 200)}{22,357}} \approx 0.009$$

- Your prior belief that a gene is MHC-related relative to not MHC-related is *very low*

# Applying that to MHC: viral PPI data

---

# Applying that to MHC: viral PPI data

[Database \(Oxford\)](#). 2016; 2016: baw103.

Published online 2016 Jul 2. doi: [10.1093/database/baw103](https://doi.org/10.1093/database/baw103)

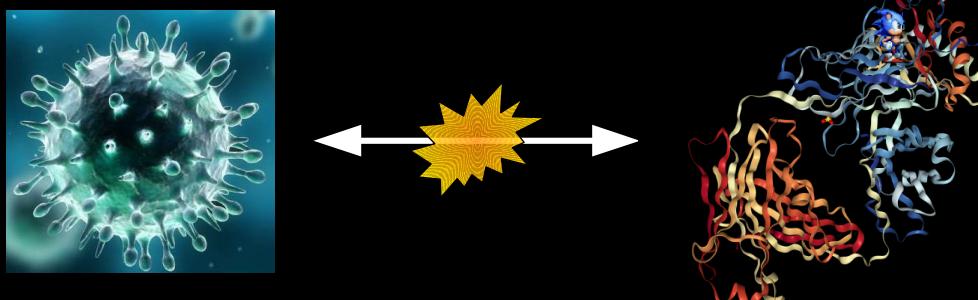
PMCID: PMC4930832

## HPIDB 2.0: a curated database for host–pathogen interactions

Mais G. Ammari,<sup>1</sup> Cathy R. Gresham,<sup>2</sup> Fiona M. McCarthy,<sup>1</sup> and Bindu Nanduri<sup>2,\*</sup>

The screenshot shows the PHISTO website interface. At the top, there is a header with the text "Database (Oxford). 2016; 2016: baw103." and "Published online 2016 Jul 2. doi: 10.1093/database/baw103" on the left, and "PMCID: PMC4930832" on the right. Below the header, the title "HPIDB 2.0: a curated database for host–pathogen interactions" is displayed. The main content area features the "PHISTO" logo, a search bar labeled "QUICK SEARCH", and navigation links for "Home", "Search", "Browse", "BLAST", and "Compare". A circular icon with a virus-like structure and the text "0101102010" is also present. The "VirHostNet 2.0" section is highlighted, showing its own navigation links for "Home", "Help", "Cite", "Contact", and "Download". Below this, there are buttons for "Search", "BLAST", and "Browse".

Ammari, Gresham, McCarthy, & Nanduri,  
2016;  
Durmuş Tekir et al., 2013;  
Guirimand, Delmotte, & Navratil, 2015



# Applying that to MHC: viral PPI data

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**PHISTO** [QUICK SEARCH](#) [Home](#) [Search](#) [Browse](#) [BLAST](#) [Compare](#)

 **VirHostNet 2.0**

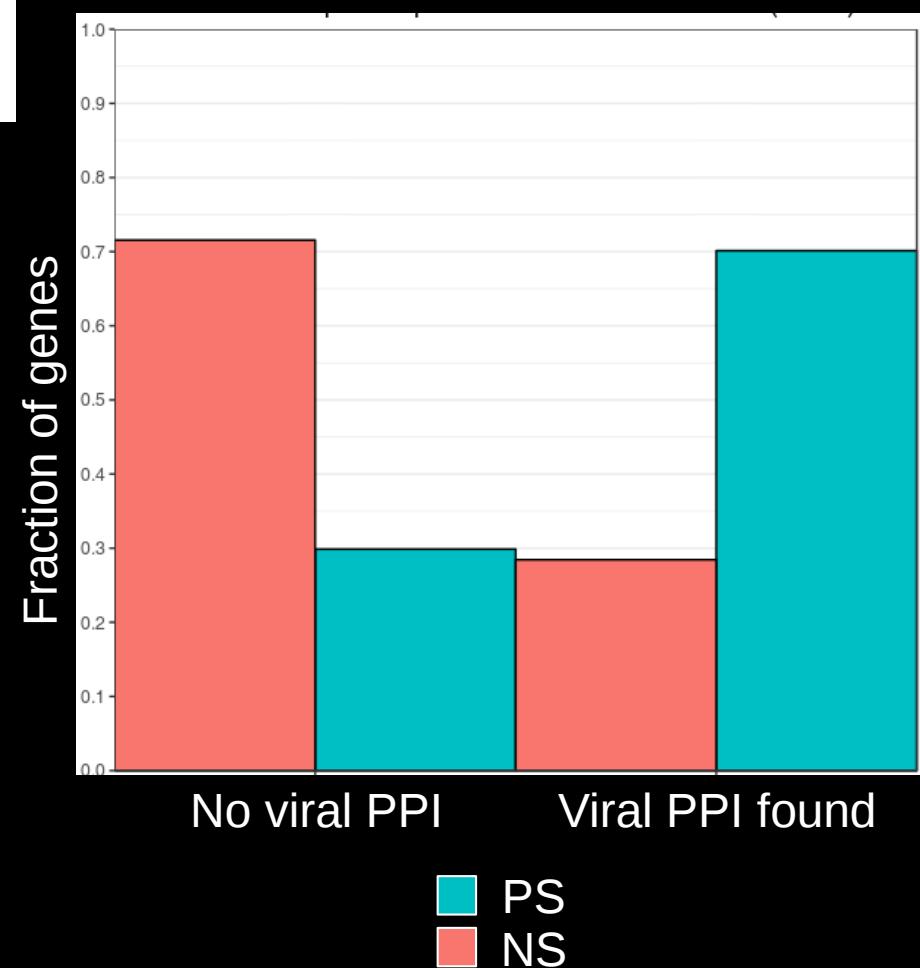
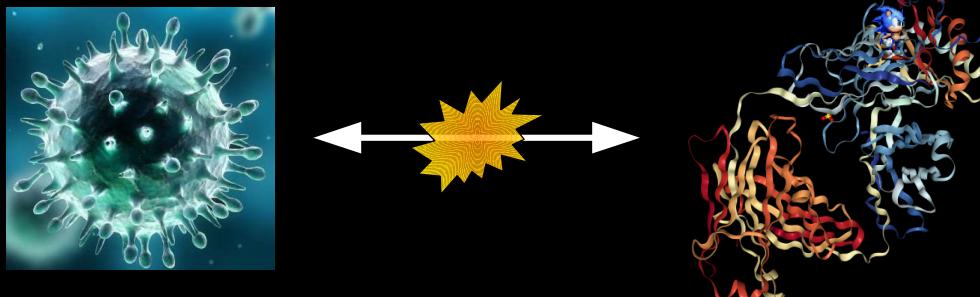
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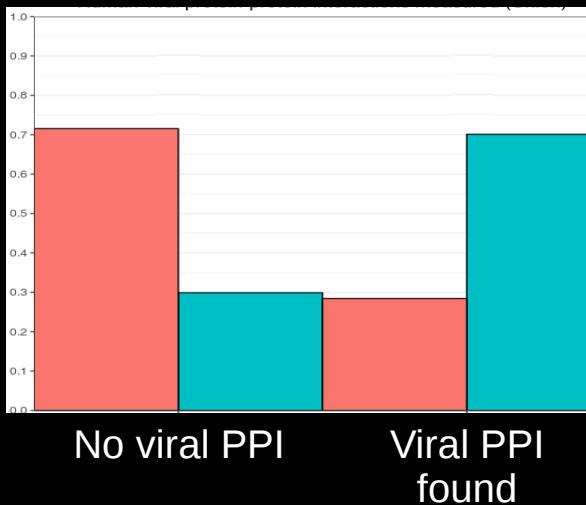
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# Applying that to MHC: viral PPI data

Fraction of genes



$$0.009 * \frac{P(\text{viral PPI} | \text{MHC pathway gene})}{P(\text{viral PPI} | \text{not MHC pathway gene})}$$

# Applying that to MHC: viral PPI data

Fraction of genes



PS  
NS

$$0.009 * \frac{P(\text{viral PPI} | \text{MHC pathway gene})}{P(\text{viral PPI} | \text{not MHC pathway gene})}$$

No viral PPI      Viral PPI  
found

$$\longrightarrow 0.009 * \frac{0.7}{0.3} \approx 0.021 \quad P(\text{MHC pathway gene})$$

# Applying that to MHC: viral PPI data

Fraction of genes



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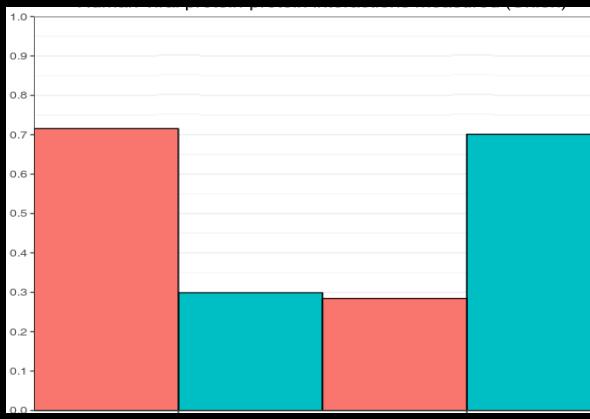
No viral PPI      Viral PPI found

$$0.009 * \frac{0.7}{0.3} \approx 0.021 \quad P(\text{MHC pathway gene})$$

$$0.009 * \frac{0.3}{0.7} \approx 0.004 \quad P(\text{MHC pathway gene})$$

# Applying that to MHC: viral PPI data

Fraction of genes



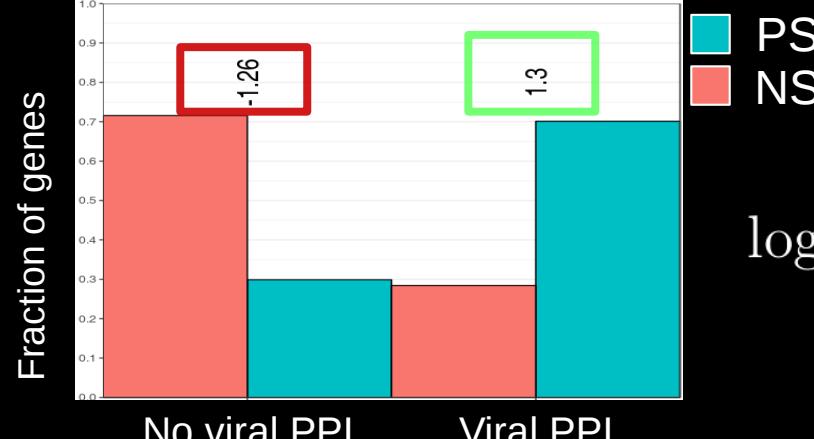
$$0.009 * \frac{P(\text{viral PPI} | \text{MHC pathway gene})}{P(\text{viral PPI} | \text{not MHC pathway gene})}$$

$$0.009 * \frac{0.7}{0.3} \approx 0.021 \quad P(\text{MHC pathway gene})$$

$$0.009 * \frac{0.3}{0.7} \approx 0.004 \quad P(\text{MHC pathway gene})$$

Prior **the same** for every gene:  
does not contribute to eventual rank!

# Applying that to MHC: viral PPI data



$$\log 2(0.009) + \log 2\left(\frac{P(\text{Viral PPI} | \text{MHC pathway gene})}{P(\text{Viral PPI} | \text{not MHC pathway gene})}\right)$$

→  $\log 2(0.009) + \log 2\left(\frac{0.7}{0.3}\right) \approx -6.8 + 1.22 \approx -5.58$   $P(\text{MHC pathway gene})$  ↑

→  $\log 2(0.009) + \log 2\left(\frac{0.3}{0.7}\right) \approx -6.8 - 1.22 \approx -8$   $P(\text{MHC pathway gene})$  ↓



# Overview of datasets

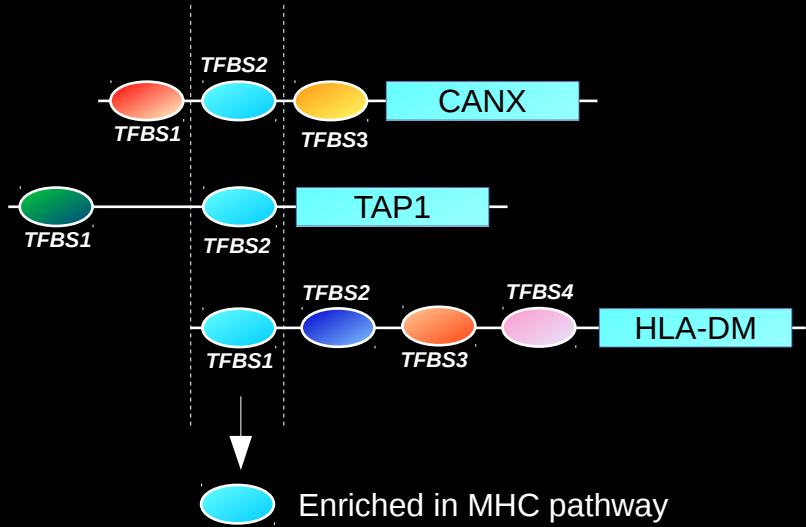
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- Viral Protein-Protein Interaction (PPI) data  
Ammari, Gresham, McCarthy, & Nanduri, 2016;  
Durmuş Tekir et al., 2013;  
Guirimand, Delmotte, & Navratil, 2015
- Transcription Factor Binding Site (TFBS) data  
Kheradpour & Kellis, 2014
- Human Tissue Atlas data
  - information about immune tissue enrichment

Uhlen et al., 2015
- Genome-wide siRNA screen for MHC II surface perturbation  
Paul et al., 2011
- Gene expression time series data in activated human macrophages  
Derlindati et al., 2015;  
Ernst & Bar-Joseph, 2006



# Applying that to MHC: TFBS



Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS

The diagram illustrates the presence of transcription factor binding sites (TFBS) in three genes: CANX, TAP1, and HLA-DM. CANX has TFBS1 (red), TFBS2 (cyan), and TFBS3 (yellow). TAP1 has TFBS1 (green) and TFBS2 (cyan). HLA-DM has TFBS1 (blue), TFBS2 (cyan), TFBS3 (orange), and TFBS4 (pink). A vertical dashed line separates the genes. An arrow points from the bottom right to the text "Enriched in MHC pathway".

2976–2987 *Nucleic Acids Research*, 2014, Vol. 42, No. 5  
doi:10.1093/nar/gkt1249 Published online 13 December 2013

**Systematic discovery and characterization of regulatory motifs in ENCODE TF binding experiments**

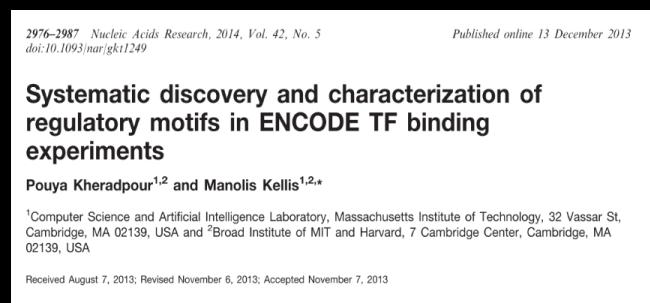
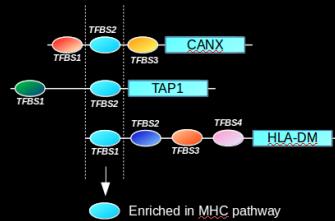
Pouya Kheradpour<sup>1,2</sup> and Manolis Kellis<sup>1,2,\*</sup>

<sup>1</sup>Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, 32 Vassar St, Cambridge, MA 02139, USA and <sup>2</sup>Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, MA 02139, USA

Received August 7, 2013; Revised November 6, 2013; Accepted November 7, 2013

Kheradpour & Kellis, 2014;  
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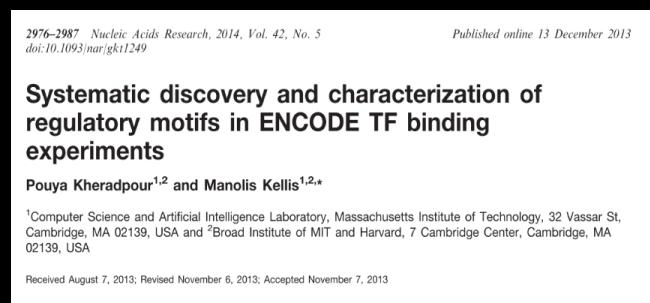
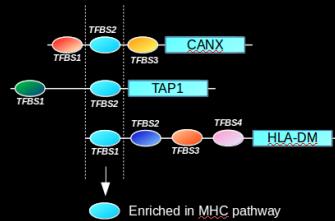
# Applying that to MHC: TFBS



Ensembl ID	TFBS
ENSG00002π	FOXA_known4-3 FOXA_known2-3 FOX_1-2 HDAC2_disc2-2 FOXD3_3-1 FOXA_disc2-1
ENSG0000τ	RUNX1_8-1 RUNX1_3-1 DLX3_1-1 POU3F2_2-1 EBF1_known2-1 TAL1_known1-1 TAL1_known5-2 TCF21_1-1 MYF6_2-1
ENSG000042	RXRA_disc4-3 AP1_disc8-1 FOXA_disc4-1 STAT_disc5-1 ZBTB33_known1-2 CEBPB_known1-1 EGR4_2-1 STAT_disc6-1

Kheradpour & Kellis, 2014;  
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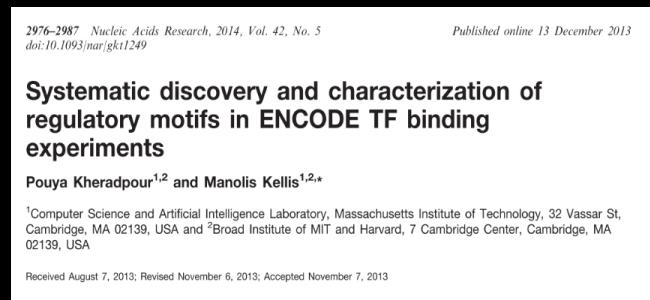
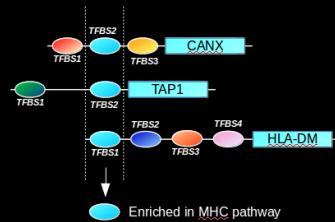


Broader TFBS groups

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ENSG00002π	FOXA-3 FOXA-3 FOX-2 HDAC2-2 FOXD3-1 FOXA-1
ENSG0000τ	RUNX1-1 RUNX1-1 DLX3-1 POU3F2-1 EBF1-1 TAL1-1 TAL1-2 TCF21-1 MYF6-1
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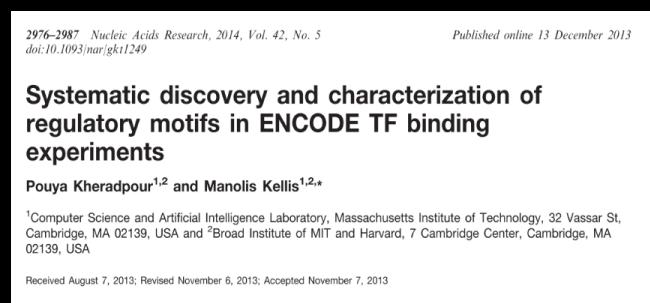
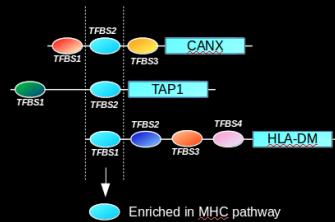


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ENSG000042	RXRA_disc4-3 AP1_disc8-1 FOXA_disc4-1 STAT_disc5-1 ZBTB33_known1-2 CEBPB_known1-1 EGR4_2-1 STAT_disc6-1

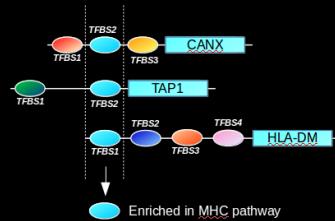


Broader TFBS groups

Ensembl ID	TFBS
ENSG00002π	FOXA-7 FOX-2 HDAC2-2 FOXD3-1
ENSG0000τ	RUNX1-2 DLX3-1 POU3F2-1 EBF1-1 TAL1-3 TCF21-1 MYF6-1
ENSG000042	RXRA-3 AP1-1 FOXA-1 STAT-2 ZBTB33-2 CEBPB-1 EGR4-1

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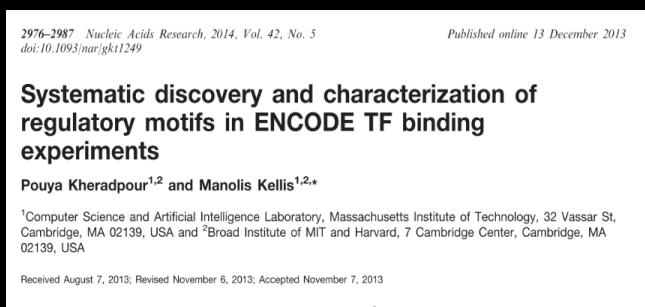
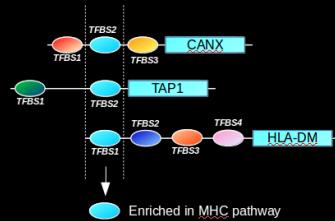
<sup>1</sup>Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, 32 Vassar St, Cambridge, MA 02139, USA and <sup>2</sup>Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, MA 02139, USA

Received August 7, 2013; Revised November 6, 2013; Accepted November 7, 2013

↓ Calculate for every TFBS group whether it is informative for the positive set

Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS

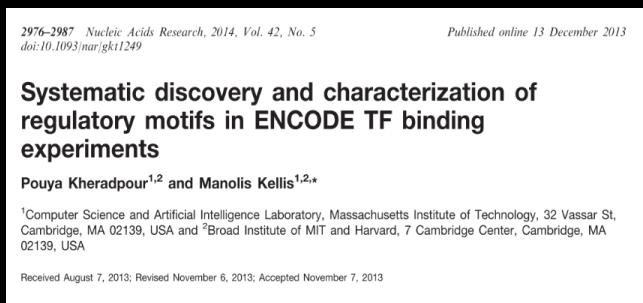
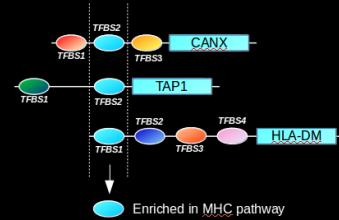


↓ Calculate for every TFBS group whether it is informative for the positive set

Gene	TIE::PHITER TFBS Count	Total TFBS Count
Positive Set	30	5000
Negative Set	900	4,585,588

Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS



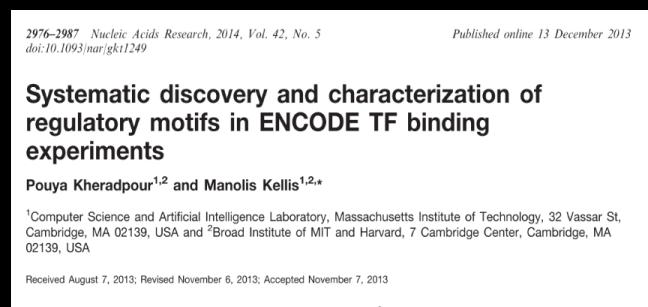
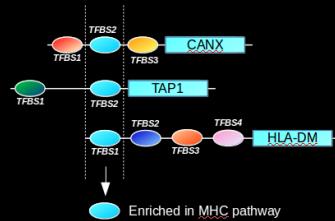
Gene	TIE::PHITER TFBS Count	Total Count
Positive Set	30	5000
Negative Set	900	4,585,588

↓ Calculate for every T it is informative



Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS



↓ Calculate for every TFBS group whether it is informative for the positive set

Gene	TIE::PHITER TFBS Count	Total TFBS Count
Positive Set	30	5000
Negative Set	900	4,585,588

↓ Fisher's exact test

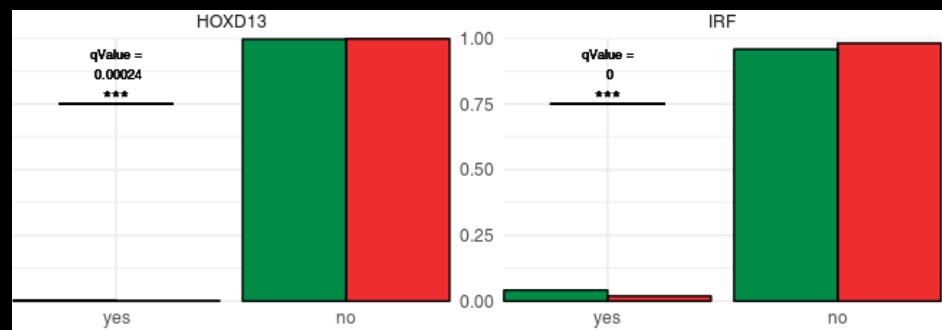
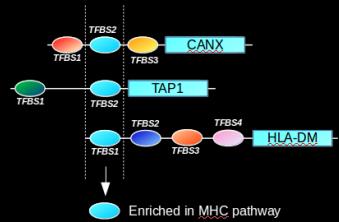


Enrichment TFBS TIE::PHITER in Positive Set

p value	sample estimate odds ratio	lower CI odds ratio	higher CI odds ratio
1.23359108837992E-33	30.749318256	20.5958483043	44.2724949603

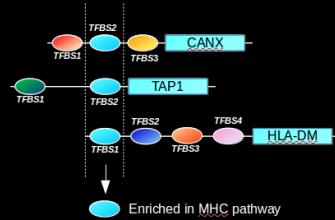
Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS



Kheradpour & Kellis, 2014;  
Yates et al., 2016

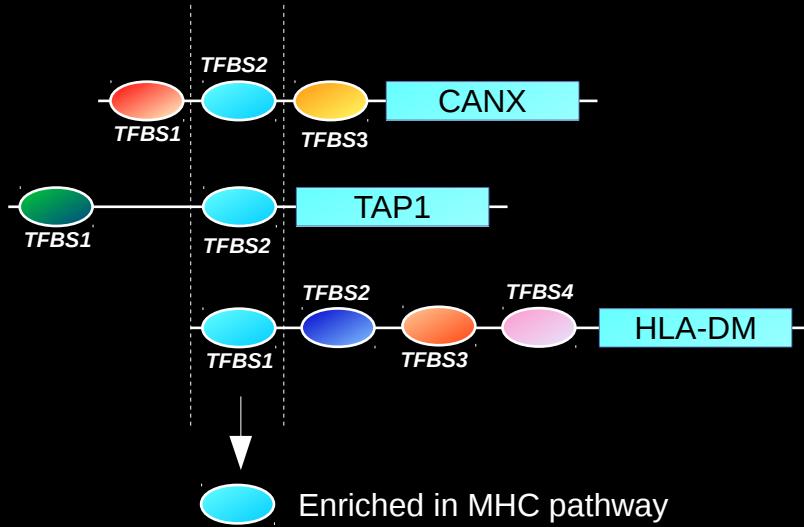
# Applying that to MHC: TFBS



Name	# crossVals in which informative	Known from literature?
IRF	10	YES
NFKB	10	YES
NFY	10	YES
IRF4	10	YES
PRDM1	10	YES
RAD21	10	YES
LMX1B	10	YES
HOXD13	10	NO!
REL	10	YES
TFAP2	10	YES
FOXD2	10	NO!
ZSCAN16	9	NO!
HOXB13	9	NO!
MYC	9	YES

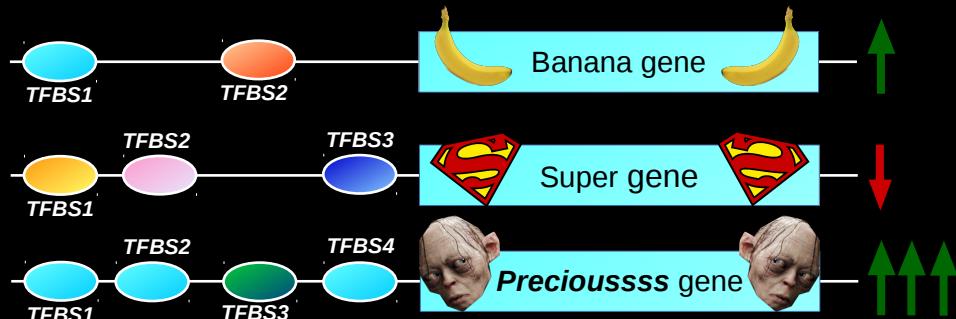
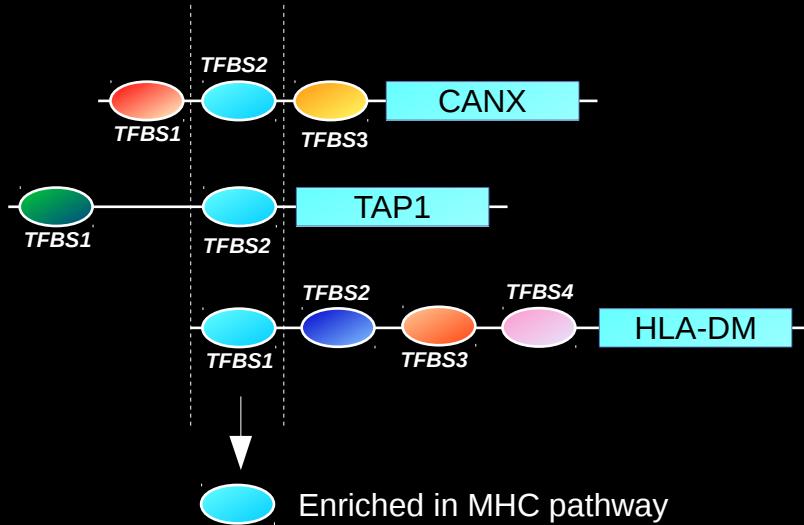
Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS



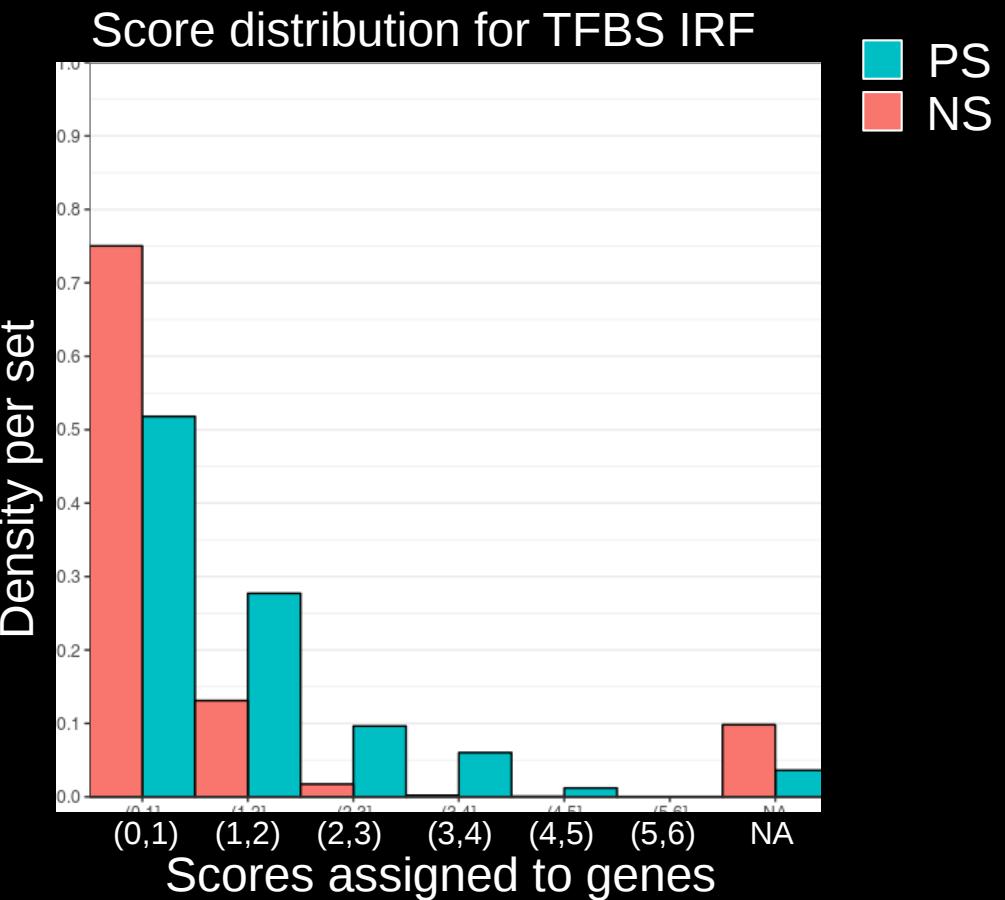
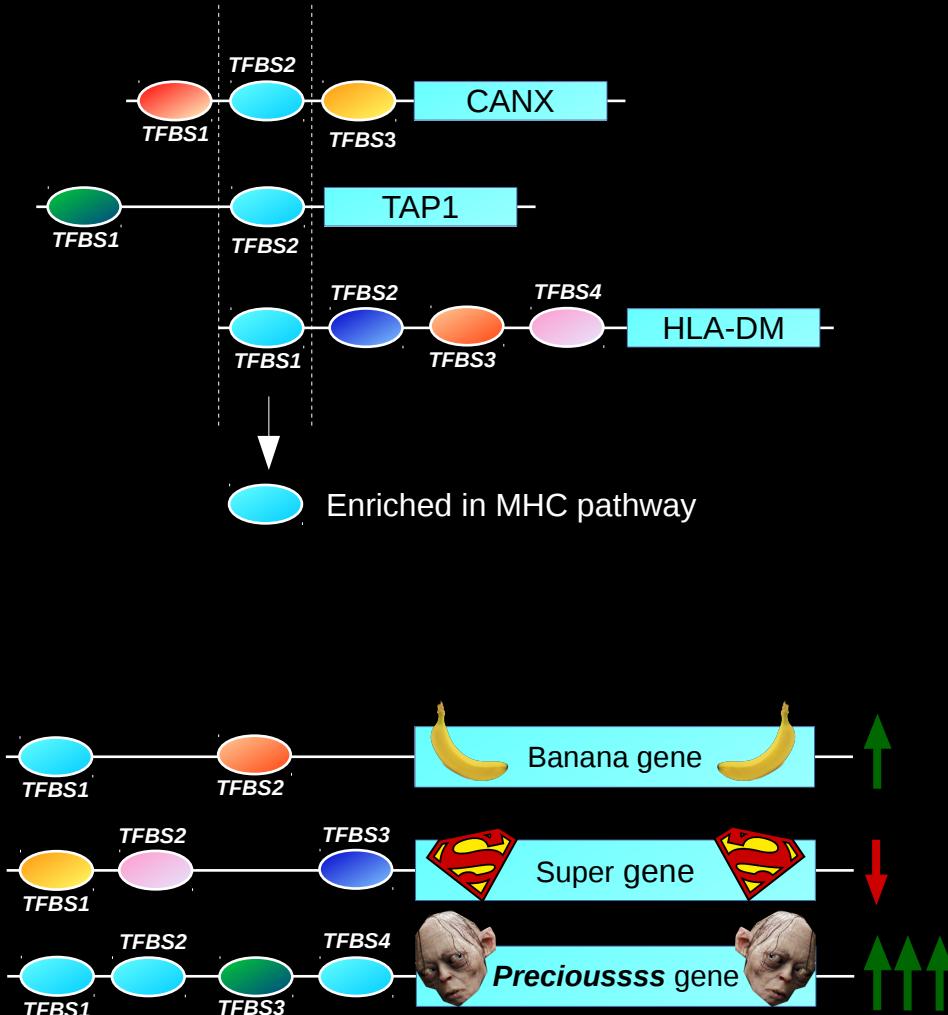
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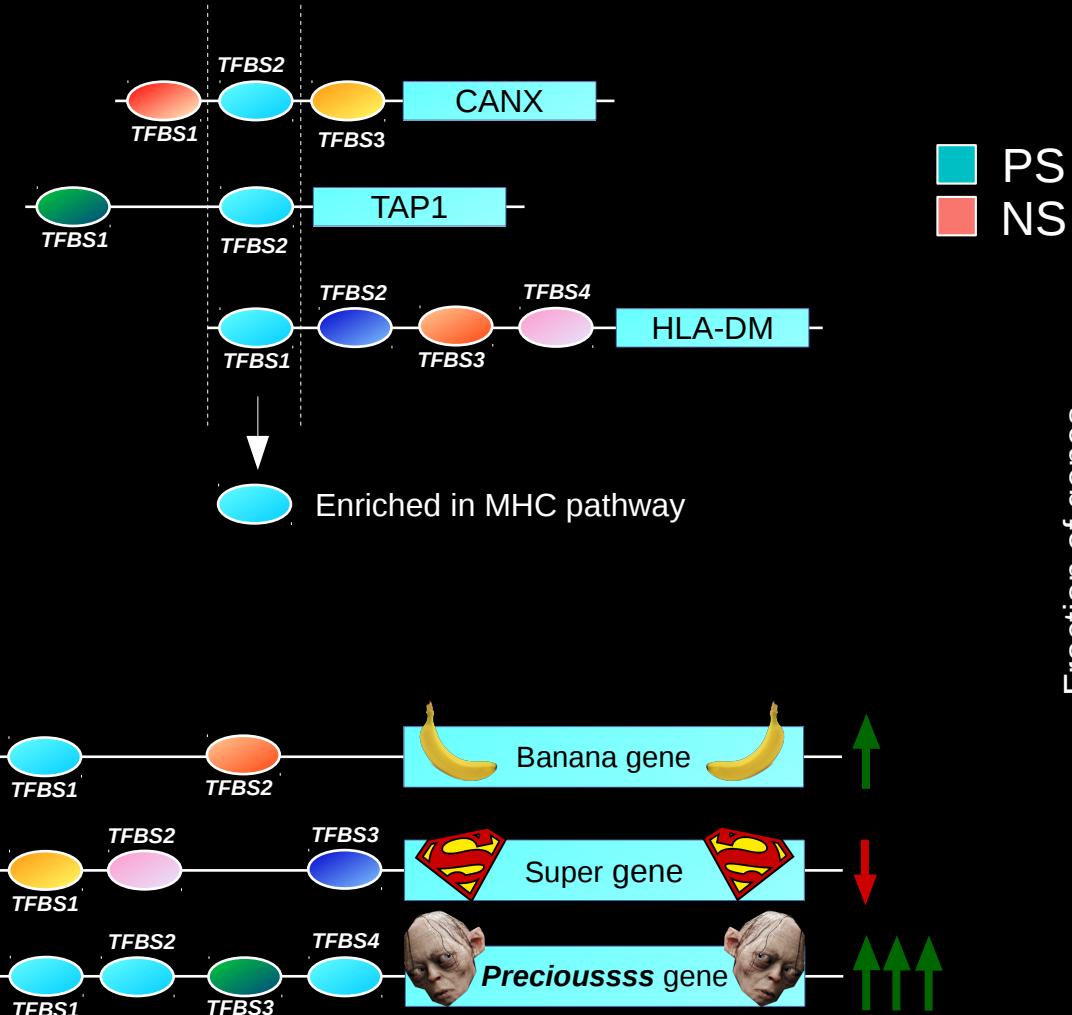
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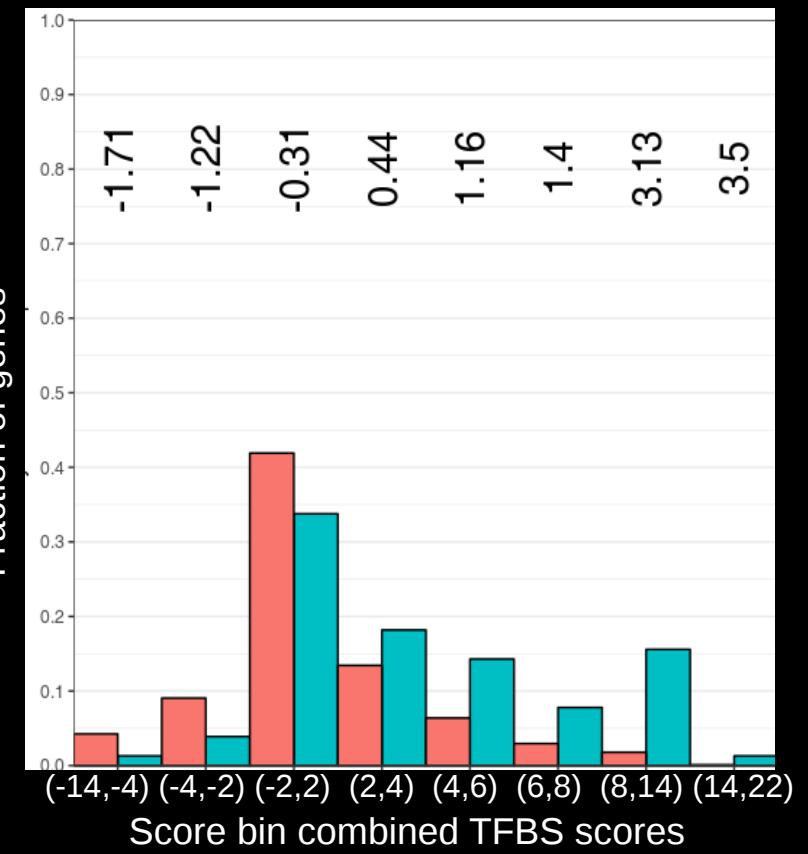


Kheradpour & Kellis, 2014;  
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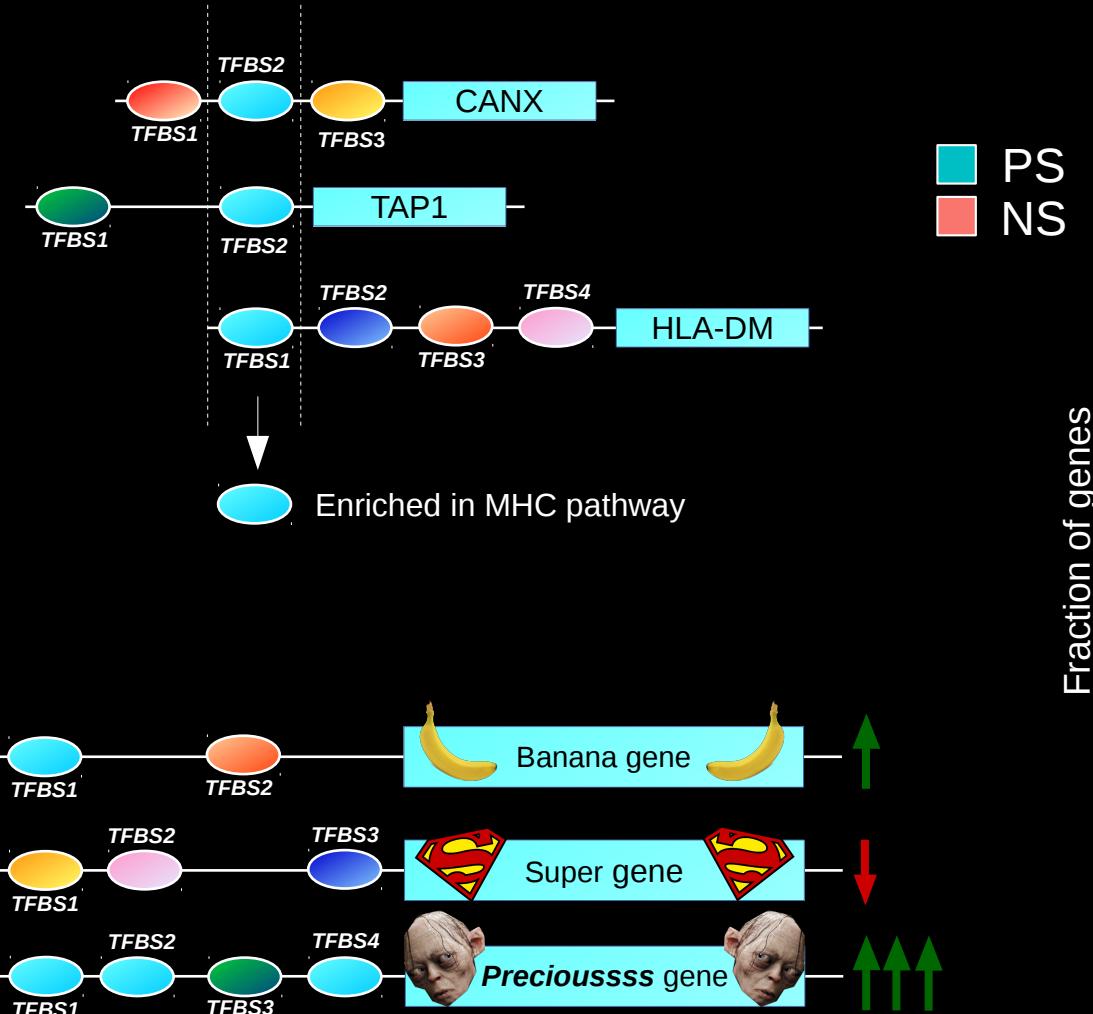


Total TFBS score distribution

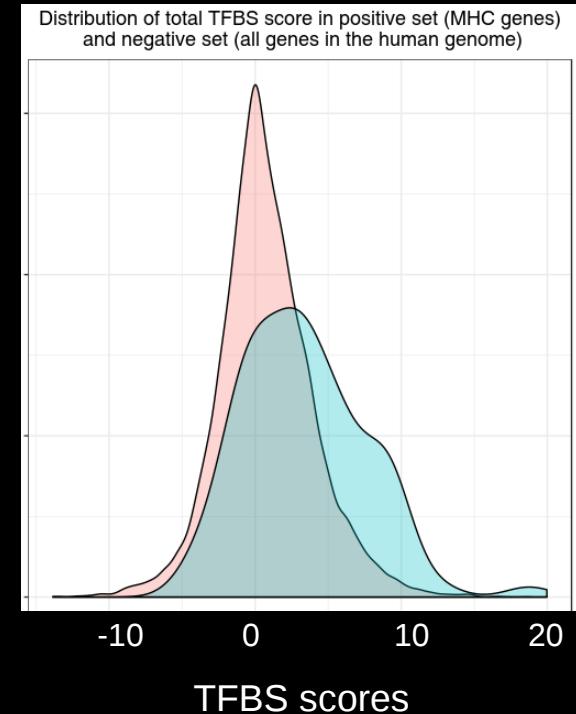


Kheradpour & Kellis, 2014;  
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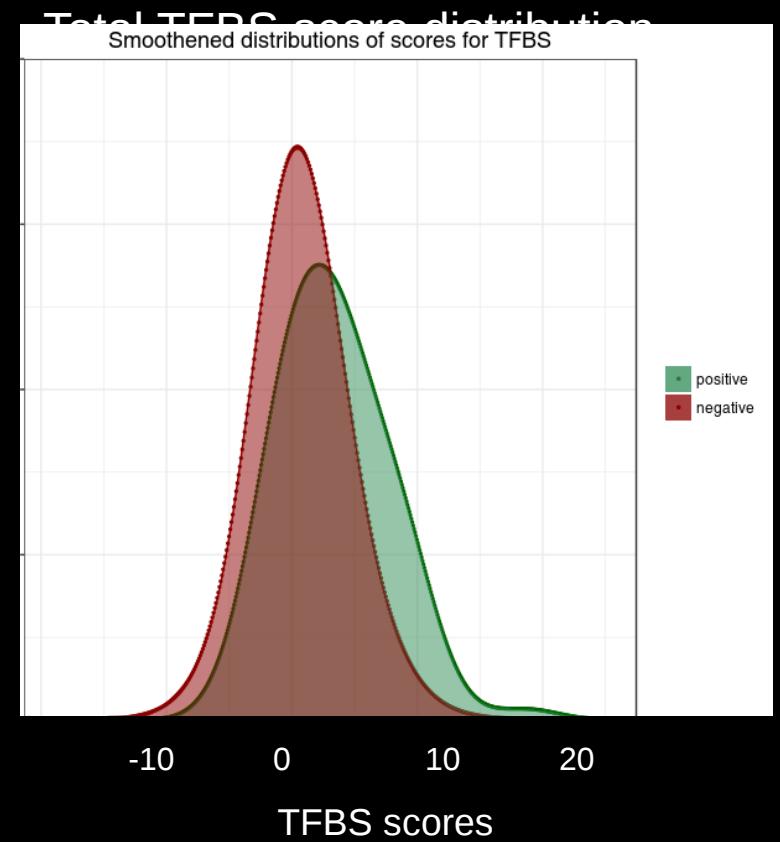
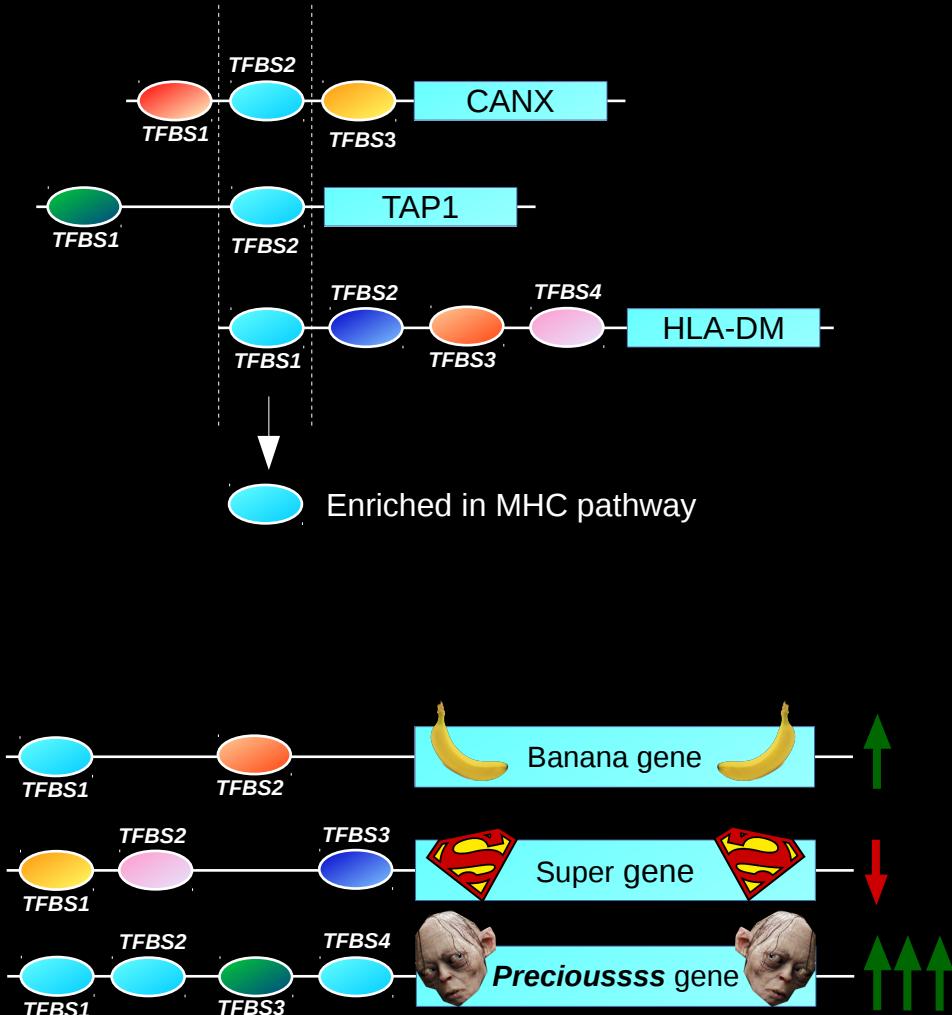


Total TFBS score distribution



Kheradpour & Kellis, 2014;  
Yates et al., 2016

# Applying that to MHC: TFBS



Kheradpour & Kellis, 2014;  
Yates et al., 2016

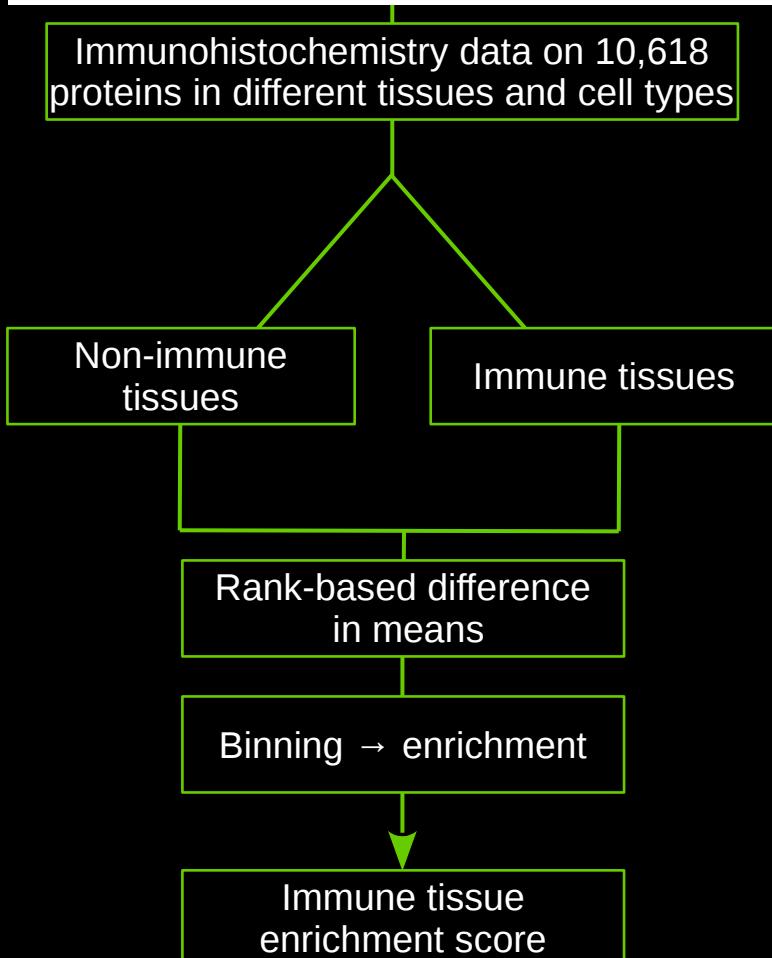
# Applying that to MHC: Immune tissue overrepresentation

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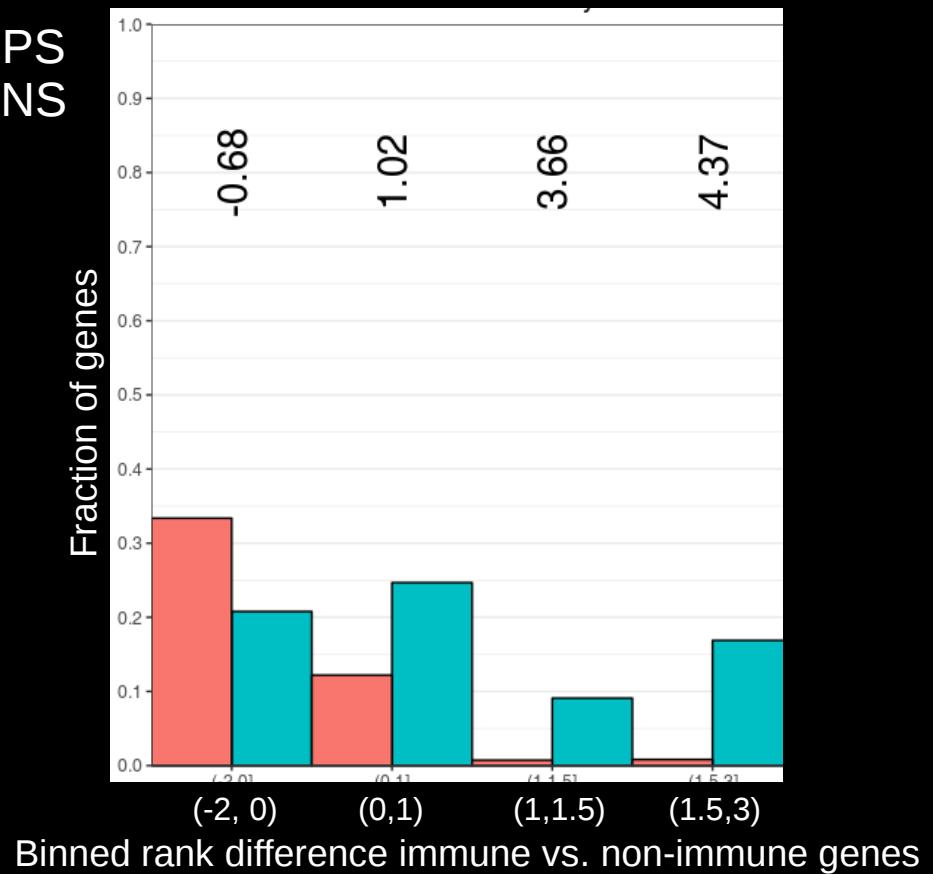
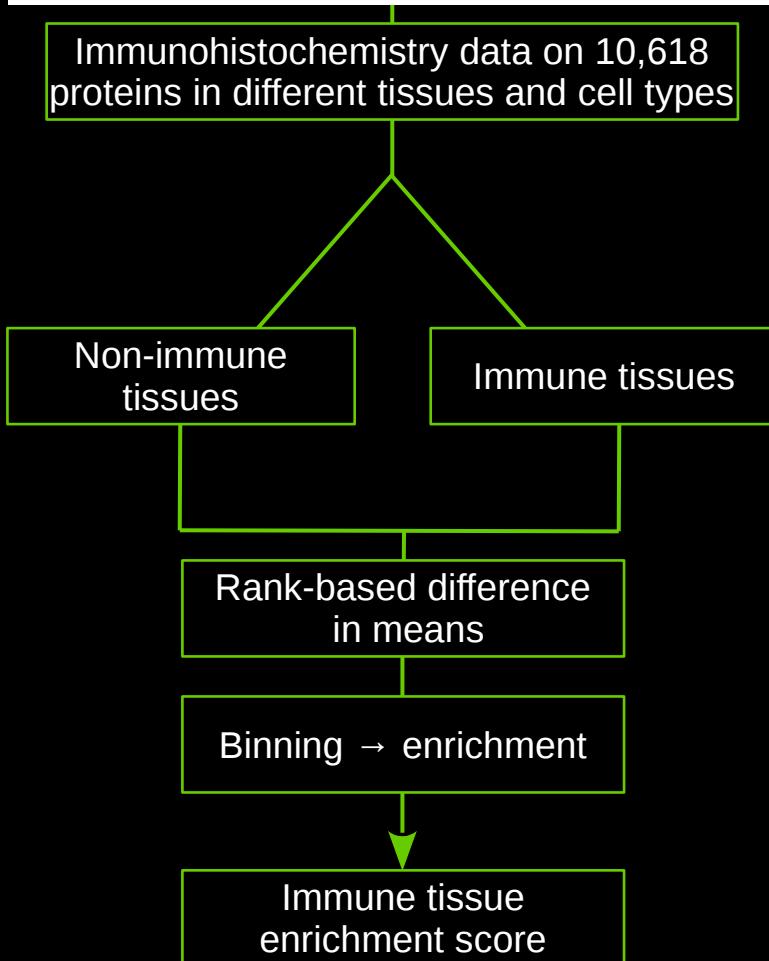
Uhlen et al., 2015

# Applying that to MHC: Immune tissue overrepresentation



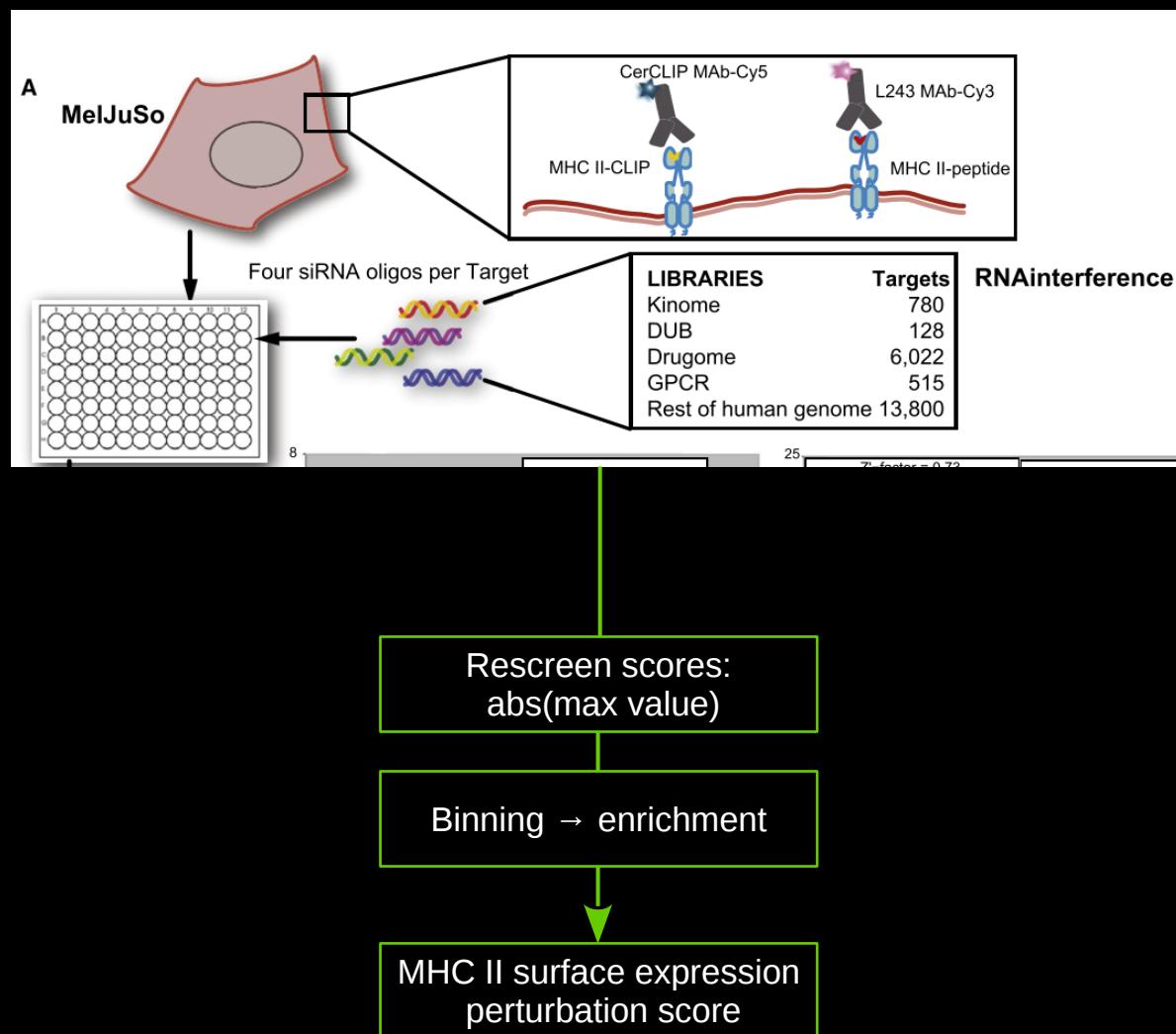
Uhlen et al., 2015

# Applying that to MHC: Immune tissue overrepresentation

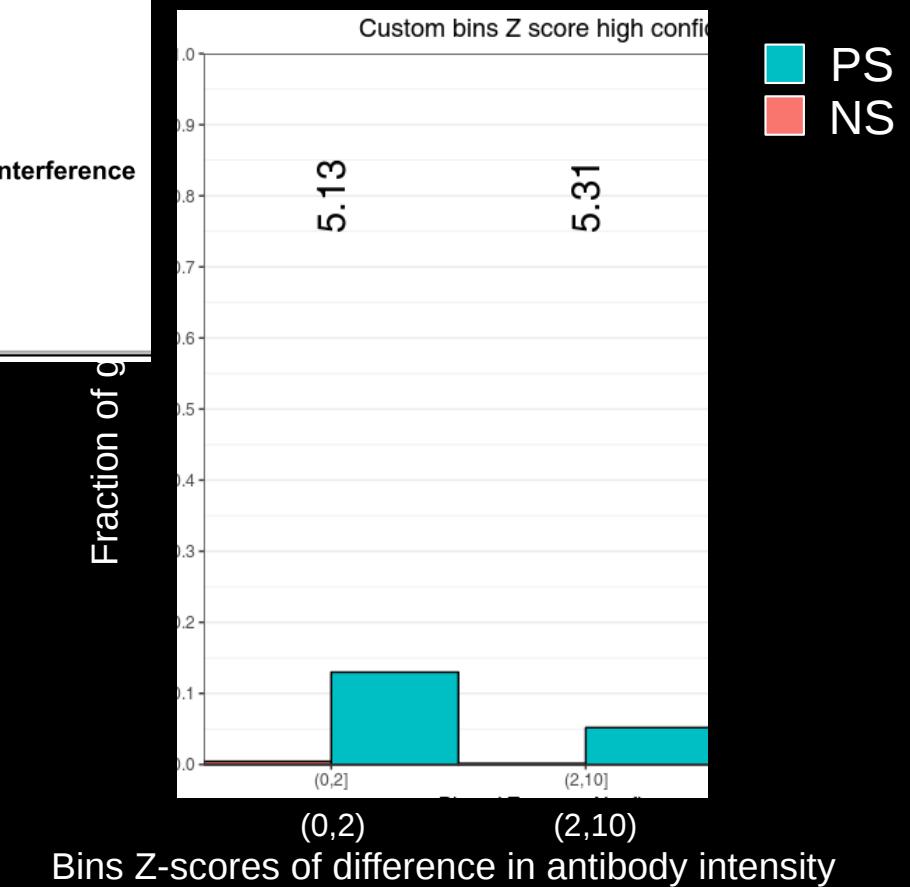
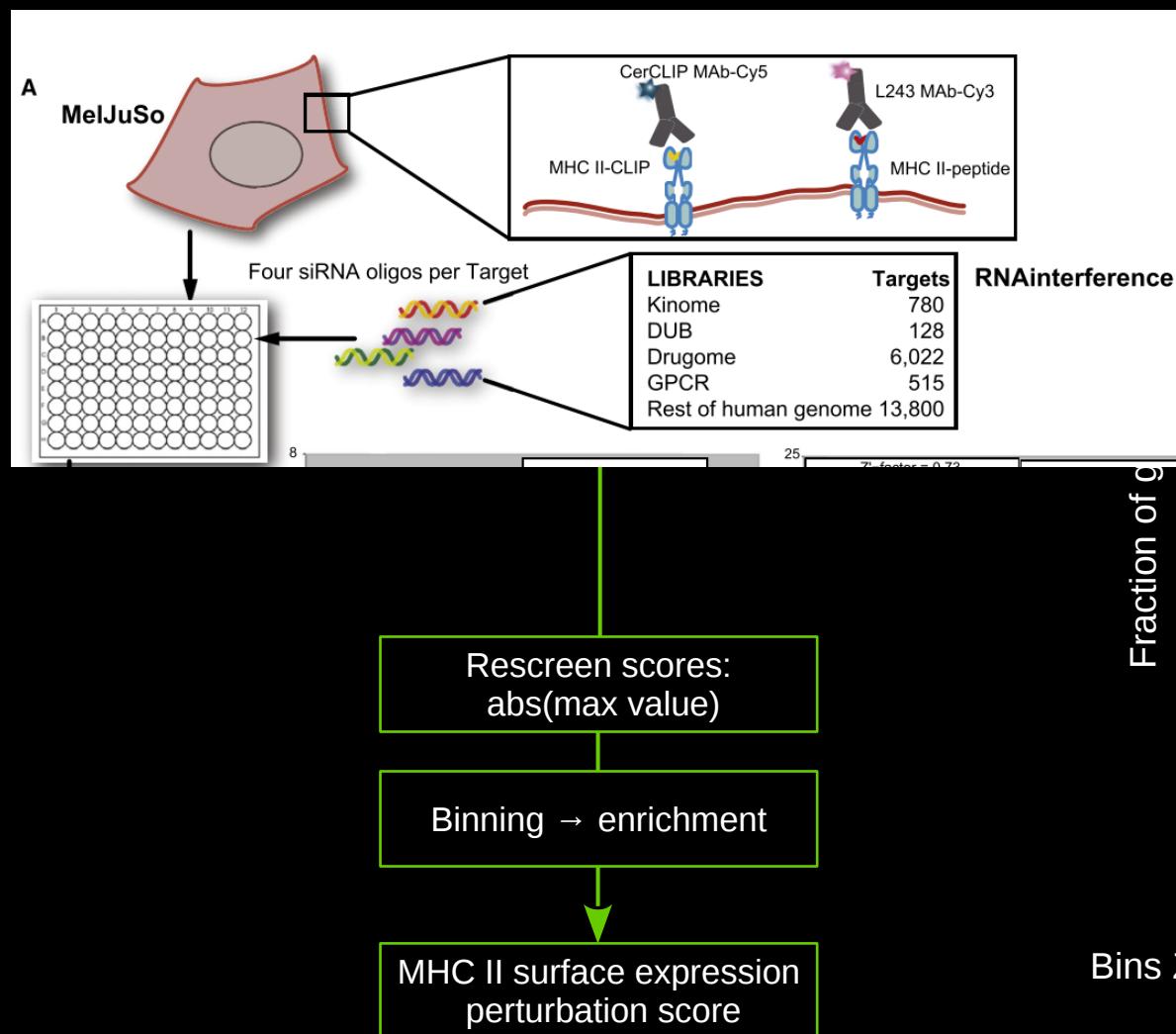


Uhlen et al., 2015

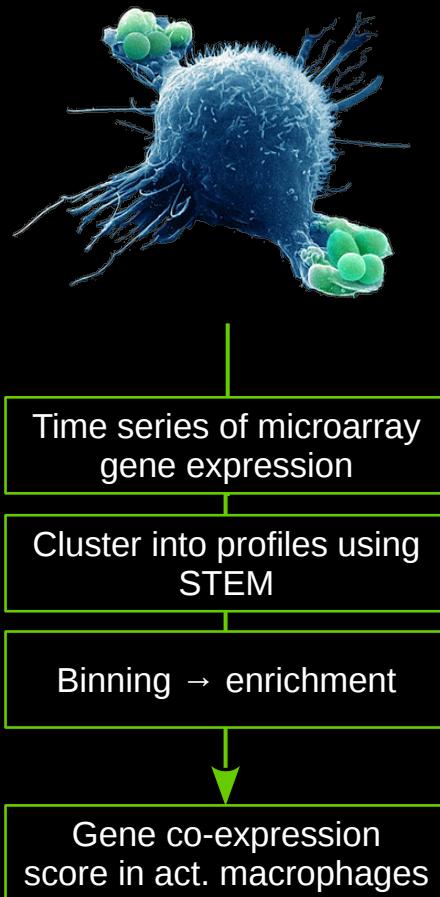
# Applying that to MHC: siRNA screen on MHC II surface expression



# Applying that to MHC: siRNA screen on MHC II surface expression

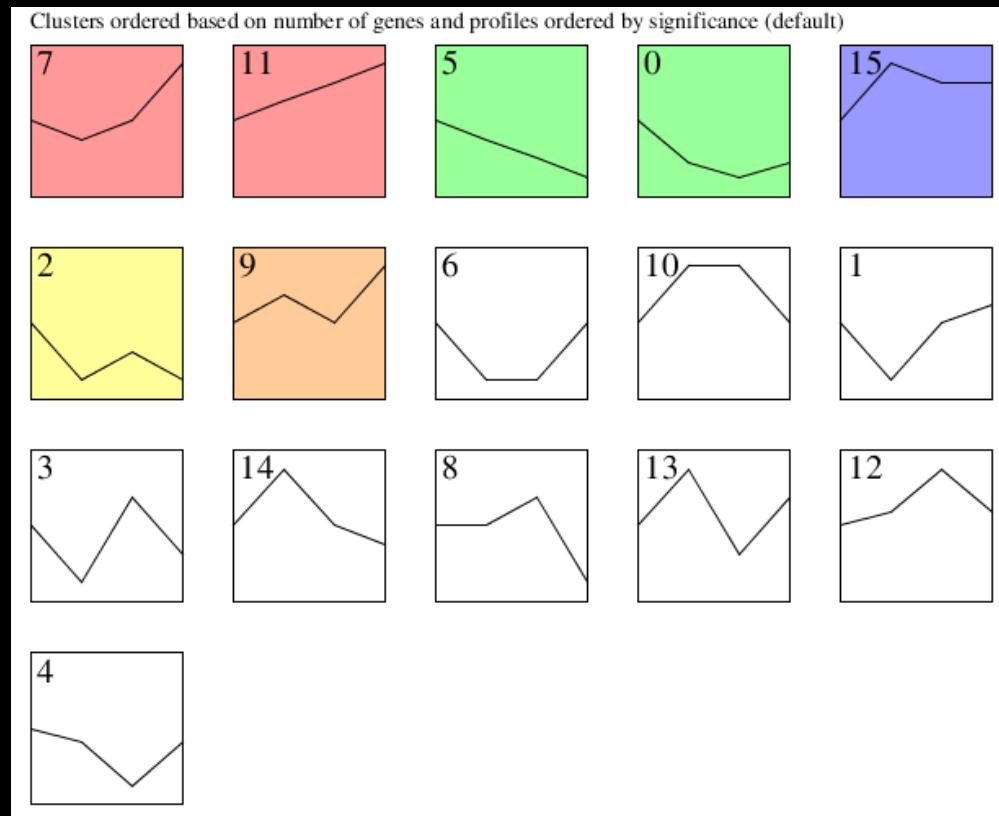
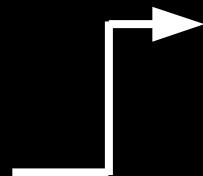
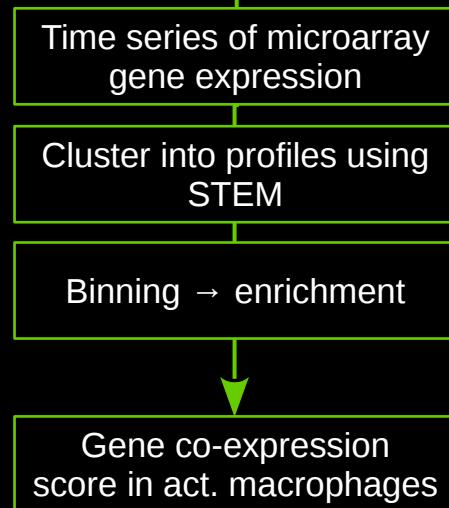


# Applying that to MHC: co-expression in activated human macrophages



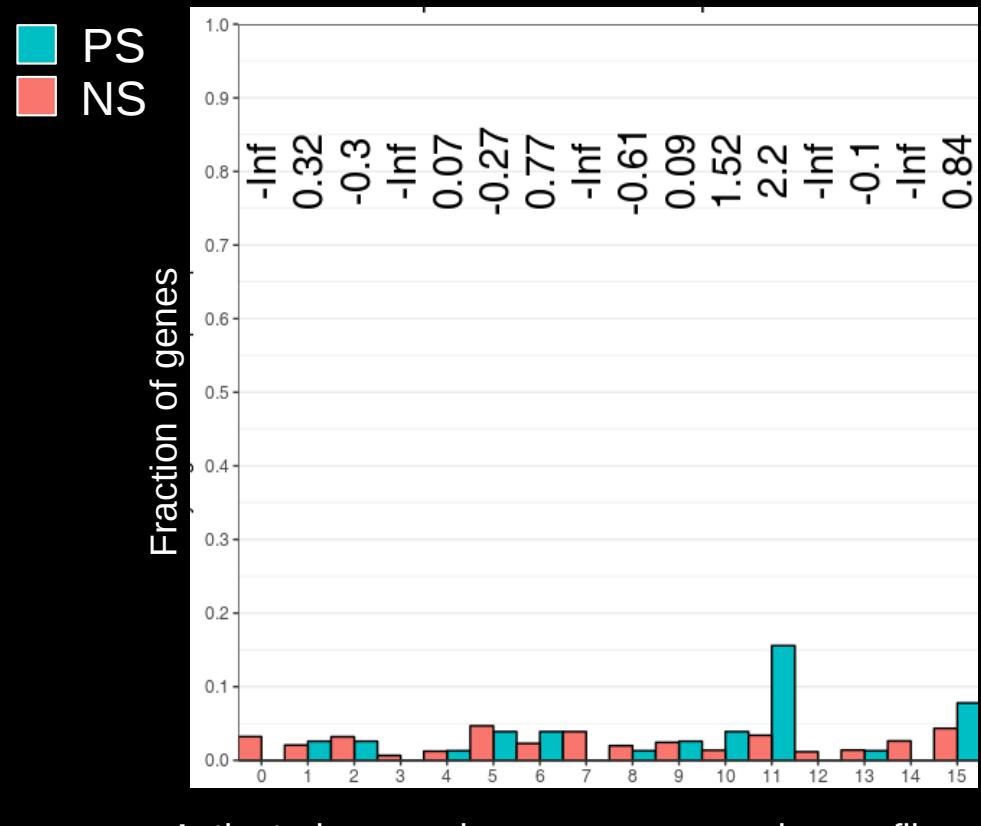
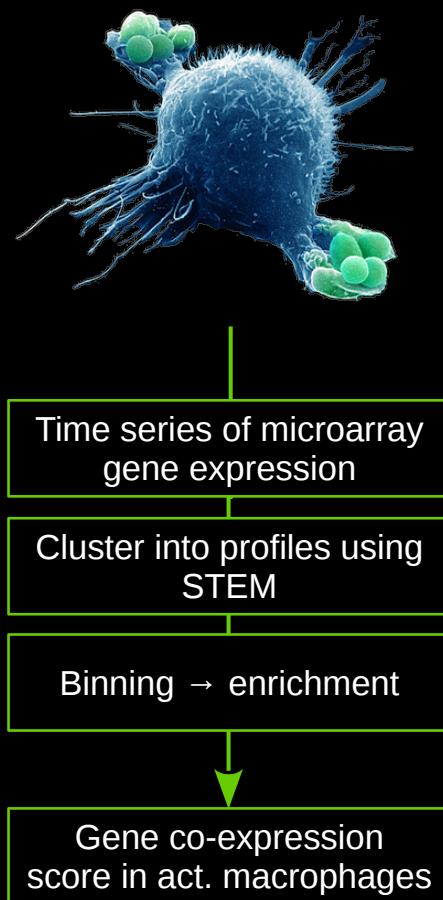
Derlindati et al., 2015;  
Ernst & Bar-Joseph, 2006

# Applying that to MHC: co-expression in activated human macrophages



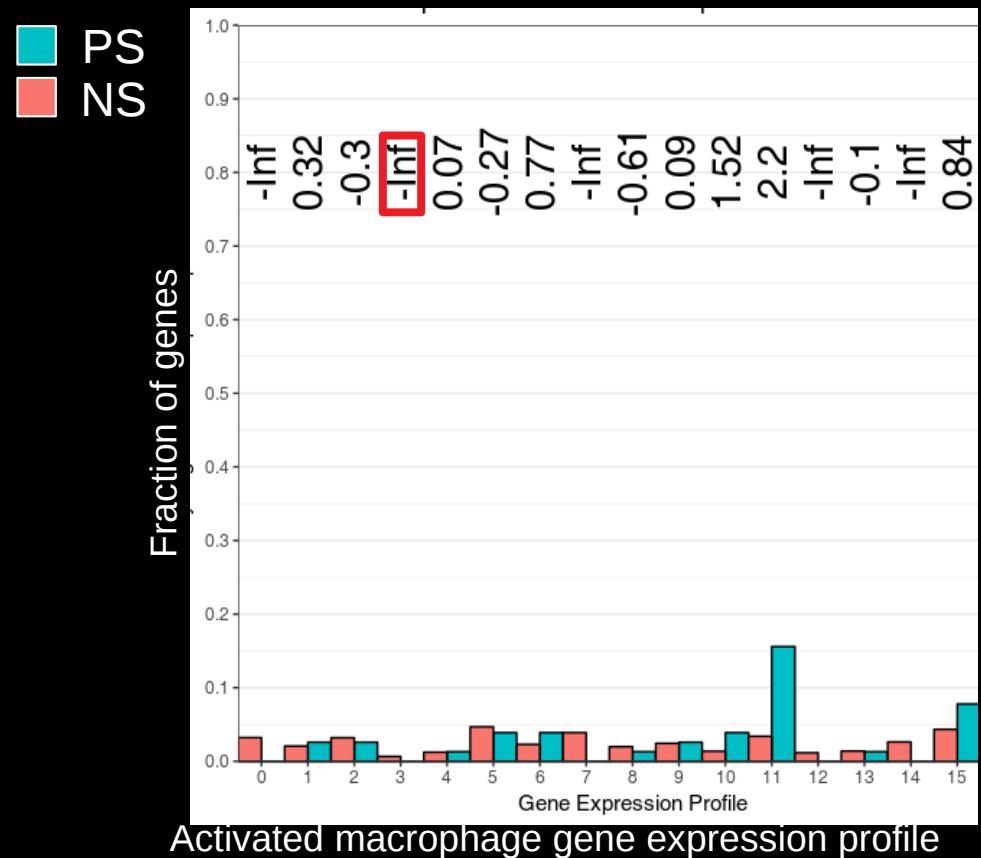
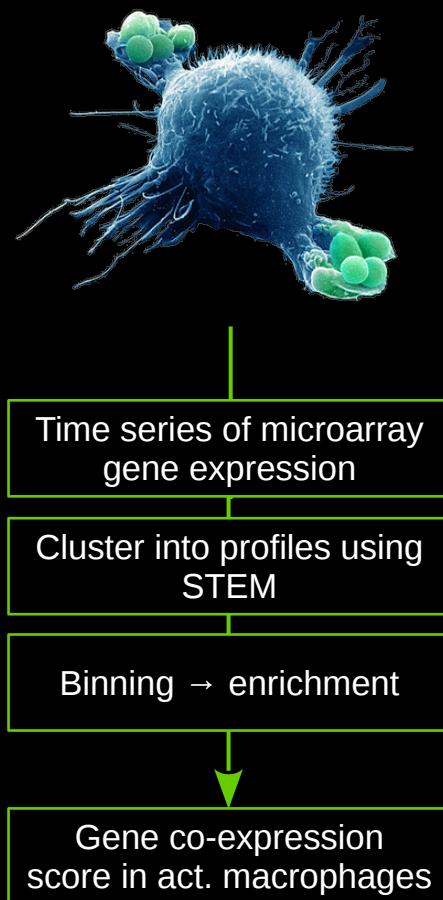
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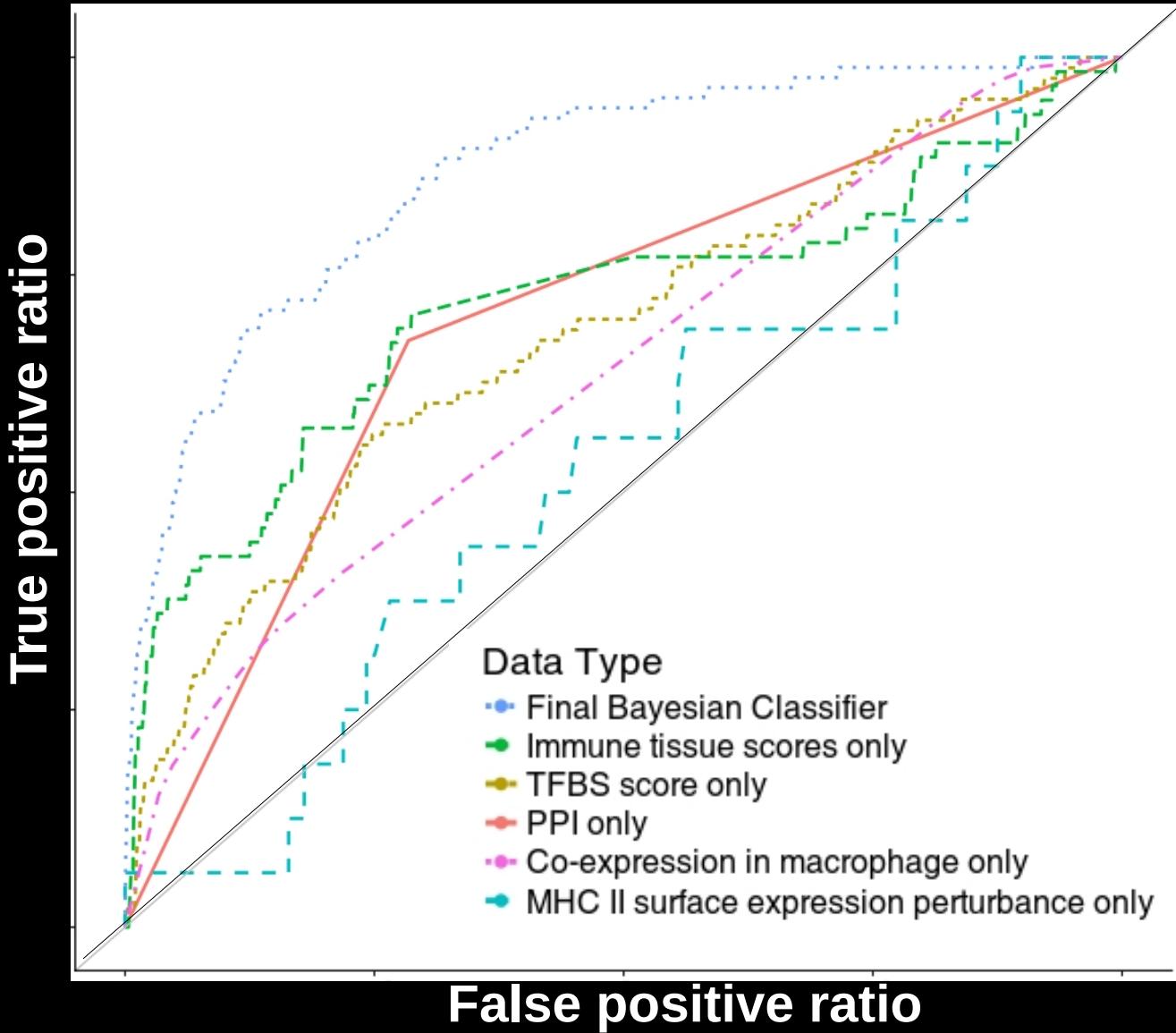
Derlindati et al., 2015;  
Ernst & Bar-Joseph, 2006

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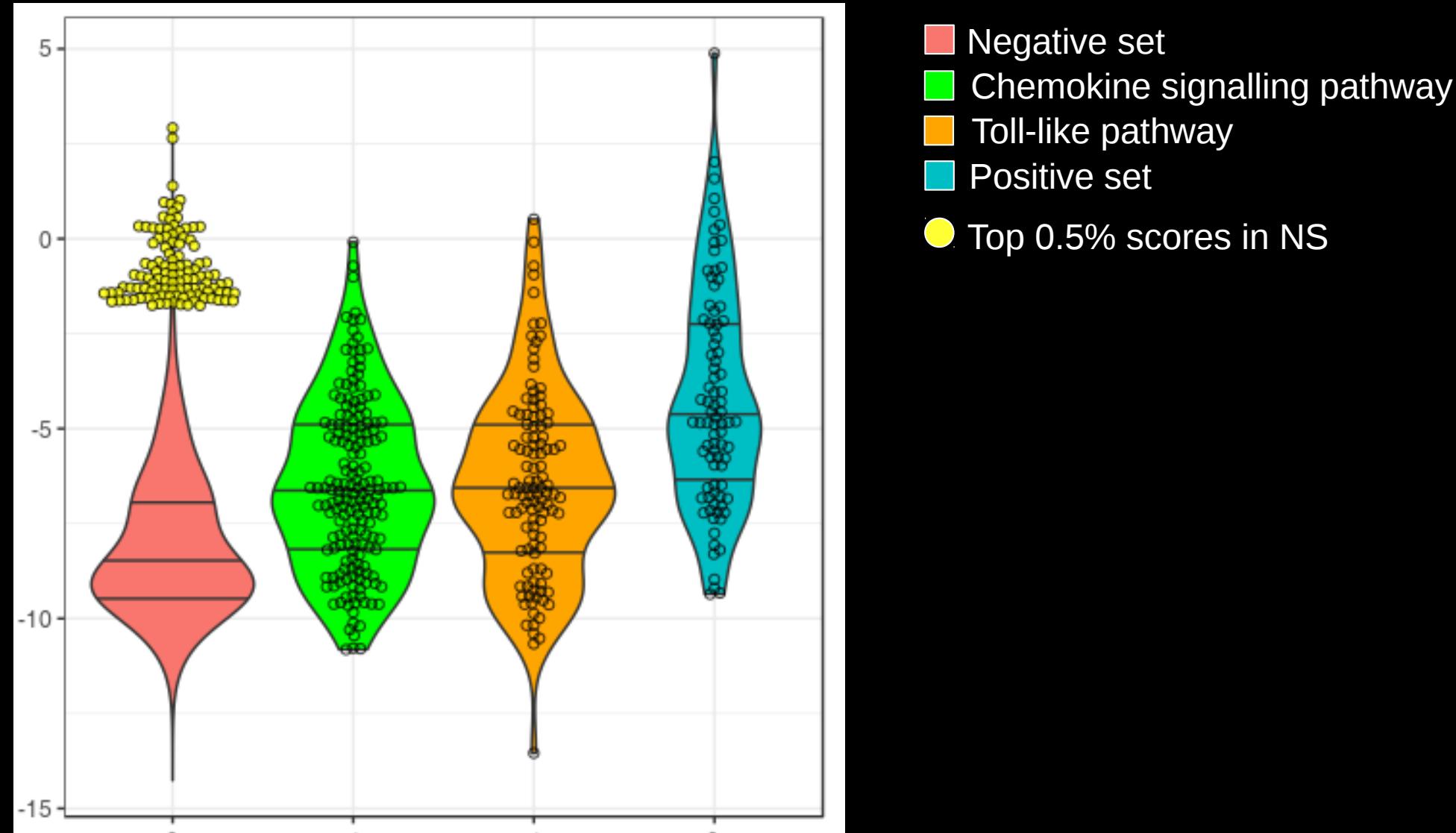


Derlindati et al., 2015;  
Ernst & Bar-Joseph, 2006

# Results



# Results



# Preliminary look at top candidates

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Gene	Comment
CD38	Generates ADP-ribose, expressed in thymocytes, T cells, B cells, plasma cells and Dcs. Function unknown.
BAK1	Regulator of apoptosis. Deletion causes accumulation of B and T cells in lymphoid organs. Might play critical role in autoimmune disease development
TRAF1	Forms heterodimer with TRAF2, found as TFBS important in MHC genes. Regulates NF-κB.
SP100	Subnuclear organelle, upregulated by IFN, plays a role in autoimmunity, oncogenesis and virus-host interaction
NFKB2	NF-κB
CAD	Pyrimidine biosynthesis?
DPYSL2	Neuronal functions, promotes microtubule assembly. But found to interact with immune system components. “CRMP2 was highly expressed in peripheral T cells during virus-induced neuroinflammation, and may regulate T-cell migration”
SRP54	Translocation into ER. Probably high score because when missing, stops MHC II from getting to the cell surface
LPXN	Leupaxin negatively regulates B cell receptor signaling.

# Future work

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- More in-depth literature analysis of top candidates
- Classifier voting: using neural nets, tree-based methods on the same data, pool classifications
- Experimental verification of top candidates

# Acknowledgments

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- Dr. T.J.P. van Dam
- Dr. Can Kesmir
- Jan Kees van Amerongen
- Rutger Hermsen
- Pouya Kheradpour
- Dr. Derlindati
- Marlieke Jongsma
- My mother for my mitochondrial DNA



# Questions?



# Data with NA

