Epistasis, the Spice of Life (and Evolution)

Lessons from the study of the plant immune system

Detlef Weigel

Max Planck Institute
for Developmental Biology
Tübingen

http://weigelworld.org

@PlantEvolution

Disclaimers

eLIFE

computomics®

KWS

weigelworld
plant biology, developmental genetics
and evolutionary genomics.

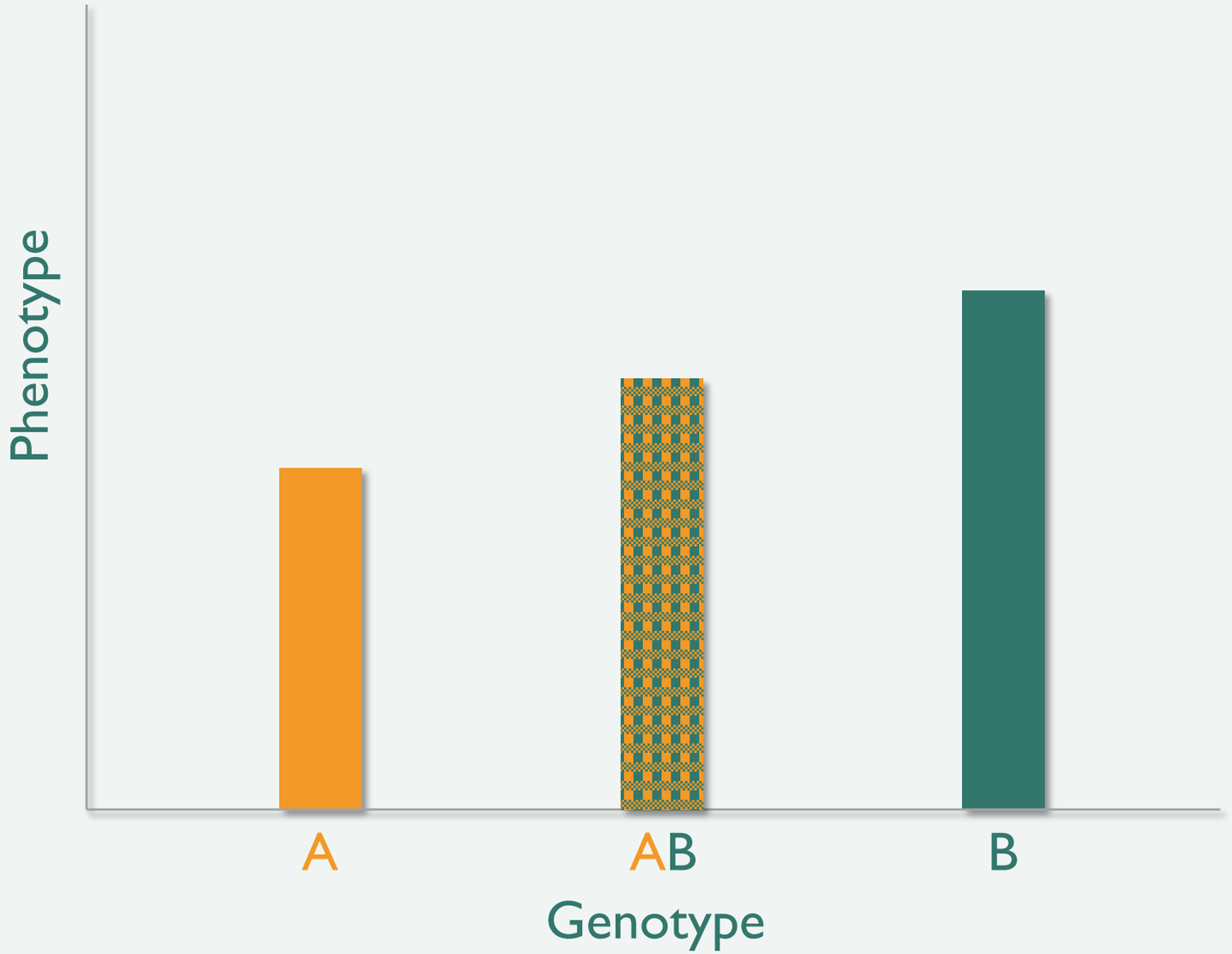
Key Contributors

Cristina Barragan • Lei Li

Eunyoung Chae (now NUS)
Dan Koenig (now UCR)
Diep Tran (now IBENS)

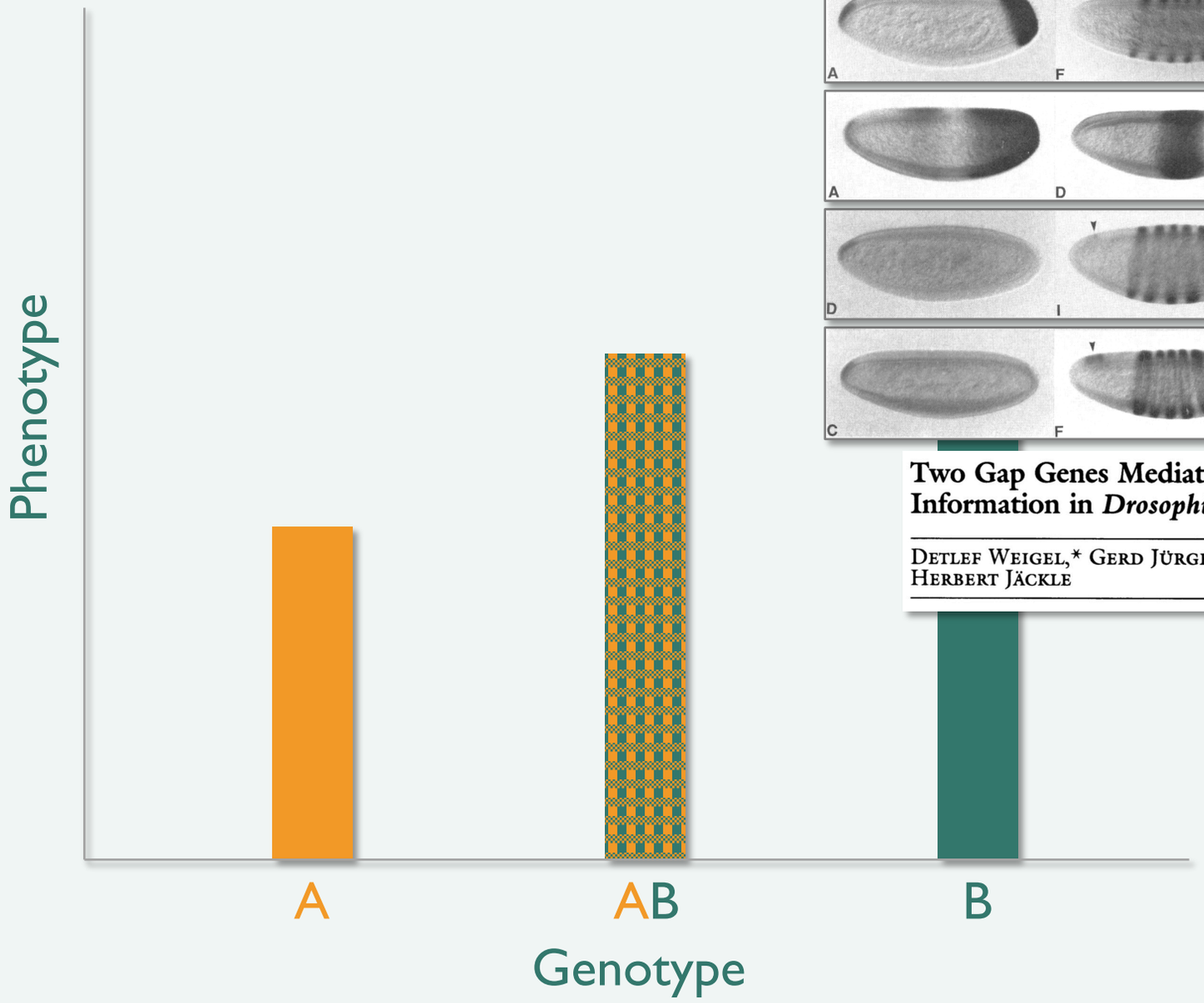
Without Epistasis, Genetics Is Boring

no epistasis:
hybrids are strictly intermediate



Epistasis in Developmental Genetics

One parent (largely) dominant



wild type

tor^{PM}

hkb^{2} tll^{g}

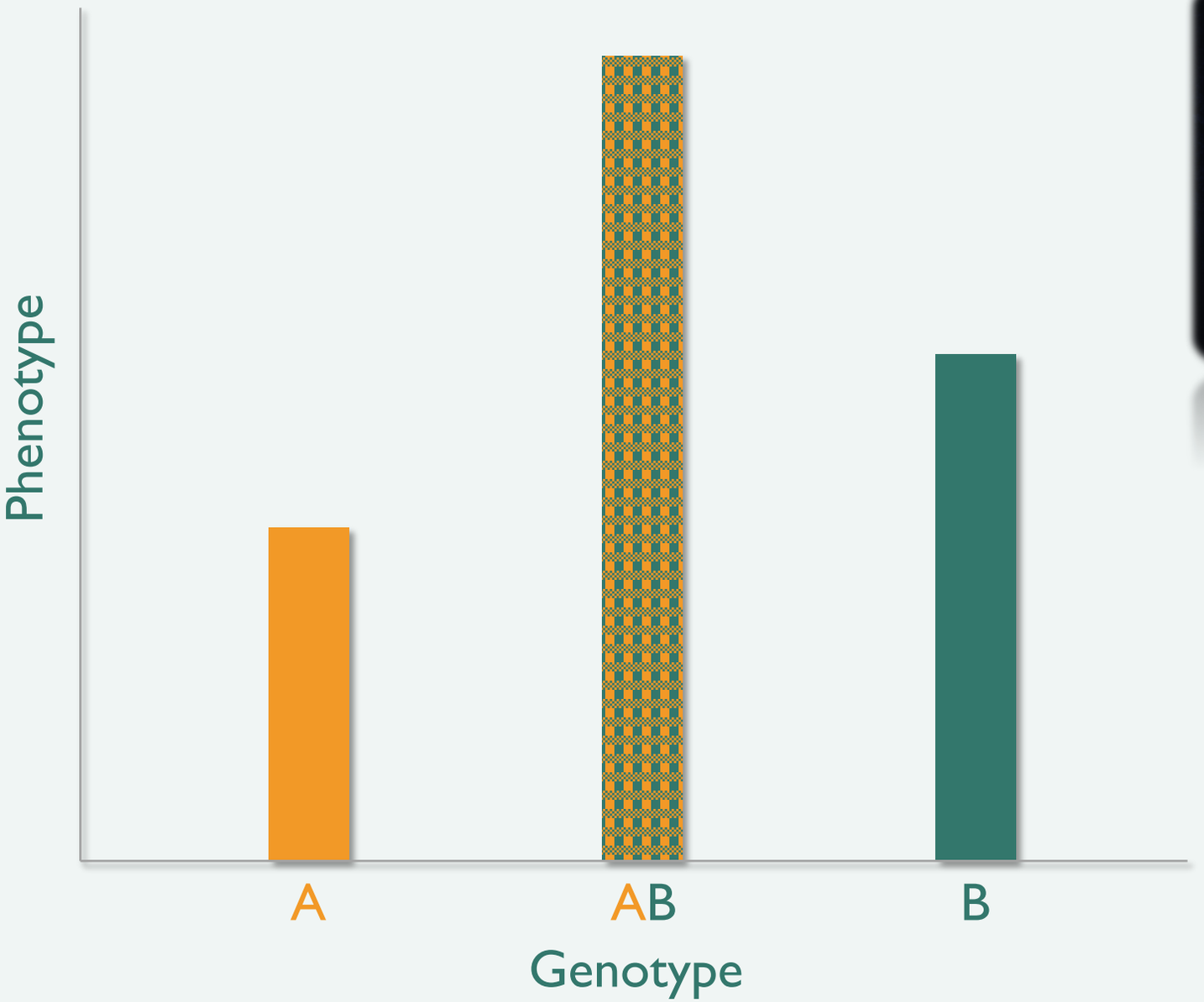
tor^{PM}; hkb^{2} tll^{g}

Two Gap Genes Mediate Maternal Terminal Pattern Information in *Drosophila*

DETLEF WEIGEL,* GERD JÜRGENS, MARTIN KLINGLER,† HERBERT JÄCKLE

Epistasis as Evolutionary Magic

Hybrid vigor – positive heterosis



Bateson's Epistasis (1909)

colour is absent the individual will be devoid of colour. The term is thus used correctly to denote the relation between allelomorphic features belonging to the same pair. But confusion will be introduced if we extend the same term to the relationship between various determining factors which belong to distinct allelomorphic pairs.

Hitherto we have spoken of the determiner for such a colour as grey in rabbits and mice as "dominant" over the colours lower in the scale, such as black or chocolate. Nevertheless we are here dealing with a relationship quite different in order from that subsisting between the coloured and the albino. Pending a more precise knowledge of the nature of this relationship it will be enough to regard those factors which prevent others from manifesting their effects as higher, and the concealed factors as lower. In accordance with this suggestion the terms *epistatic* and *hypostatic* may conveniently be introduced. We shall then speak of the determiner for grey as epistatic to that for black; that for black as epistatic to the determiner for chocolate, and so on.

'09 MENDEL'S

E. L. MARK

PRINCIPLES OF HEREDITY

BY

W. BATESON, M.A., F.R.S., V.M.H.

Fisher's Epistasis (1918)

mean by *d*. The steps from recessive to heterozygote and from heterozygote to dominant are genetically identical, and may change from one to the other in passing from father to son. Somatically the steps are of different importance, and the soma to some extent disguises the true genetic nature. There is in dominance a certain latency. We may say that the somatic effects of identical genetic changes are not additive, and for this reason the genetic similarity of relations is partly obscured in the statistical aggregate. A similar deviation from the addition of superimposed effects may occur between different Mendelian factors. We may use the term Epistacy to describe such deviation, which although potentially more complicated, has similar statistical effects to dominance. If the two sexes are considered as Mendelian alternatives, the fact that other Mendelian factors affect them t

The Correlation between Relatives on the Supposition of Mendelian Inheritance. By **R. A. Fisher**, B.A. *Communicated by* Professor J. Arthur Thomson. (With Four Figures in Text.)

(MS. received June 15, 1918. Read July 8, 1918. Issued separately October 1, 1918.)

Punnett's review points out the earlier, different use by Bateson

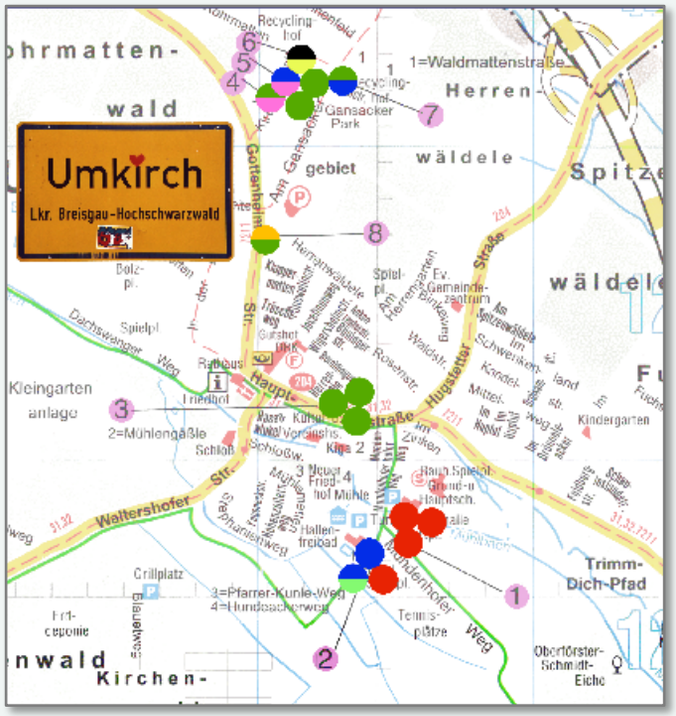
Epistasis as Evolutionary Disaster

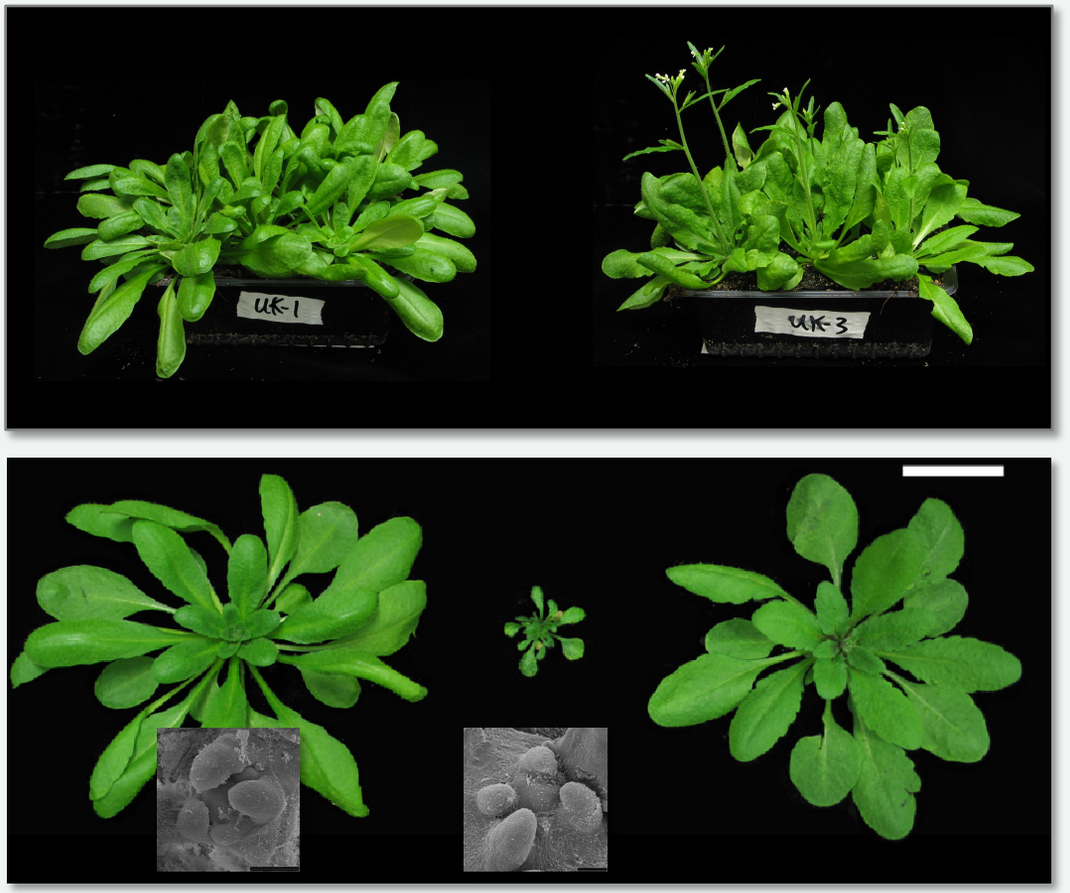
Hybrid weakness – negative heterosis

How We Got Into Hybrid Weakness

Janne Lempe (MPI-PB)

Kirsten Bomblies (ETH)



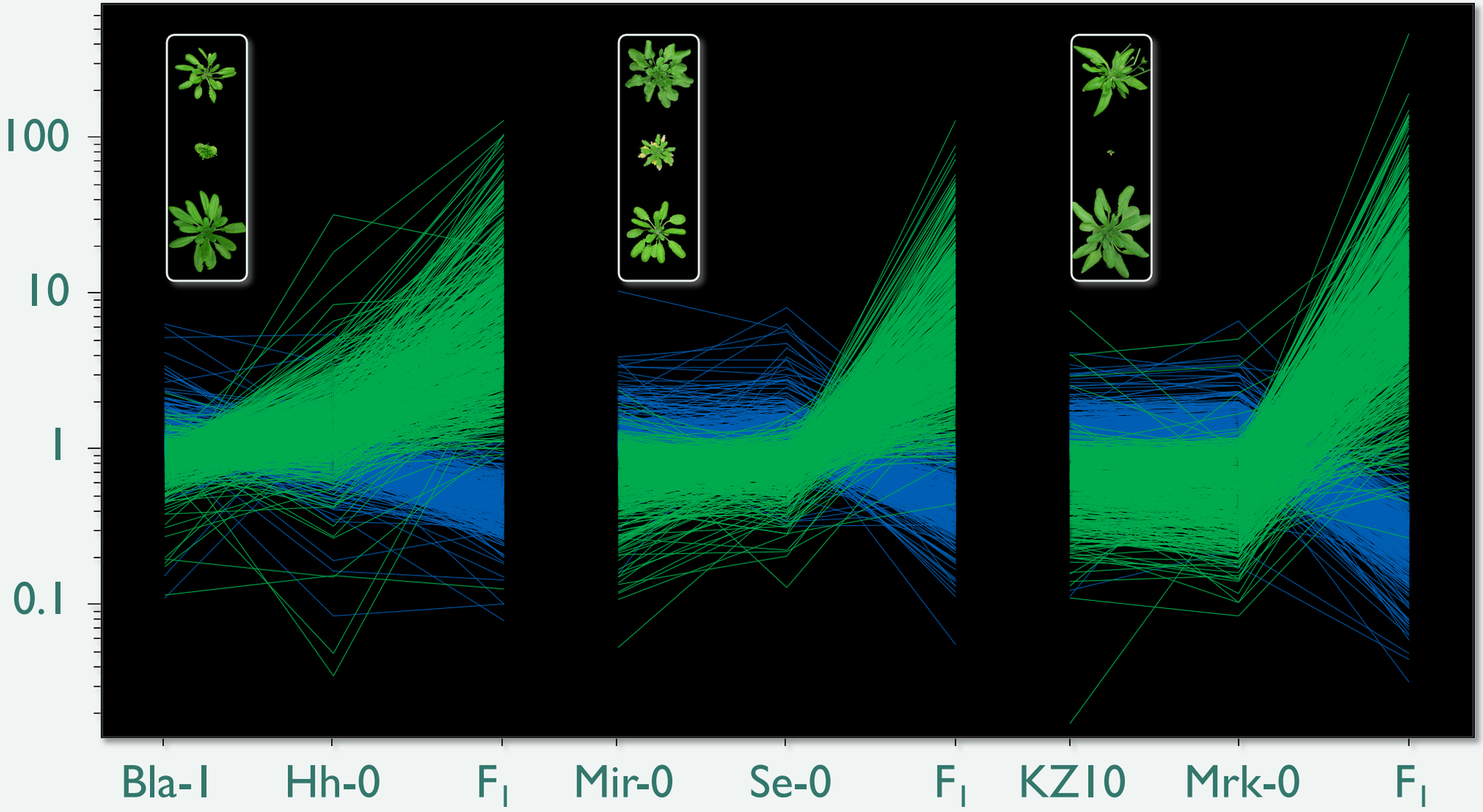


Uk-1 F_1 Uk-3

Several similar cases

Common Gene Expression Profiles in F_1 Hybrids

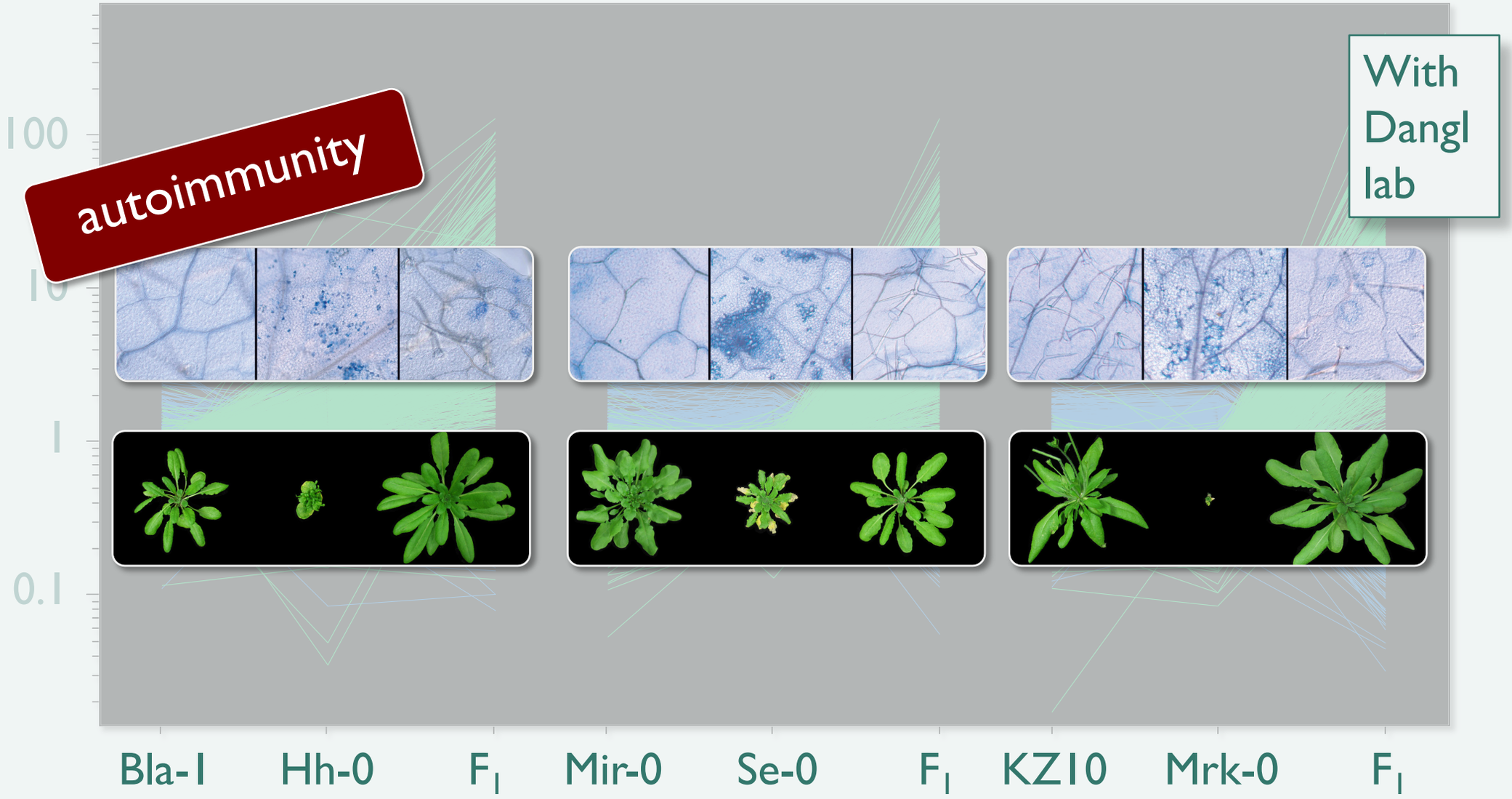
Only overrepresented GO categories relate to **immune response**



Bomblies, Lempe et al. (2007)

Rampant Cell Death as Cause of Growth Defects

Only overrepresented GO categories relate to immune response



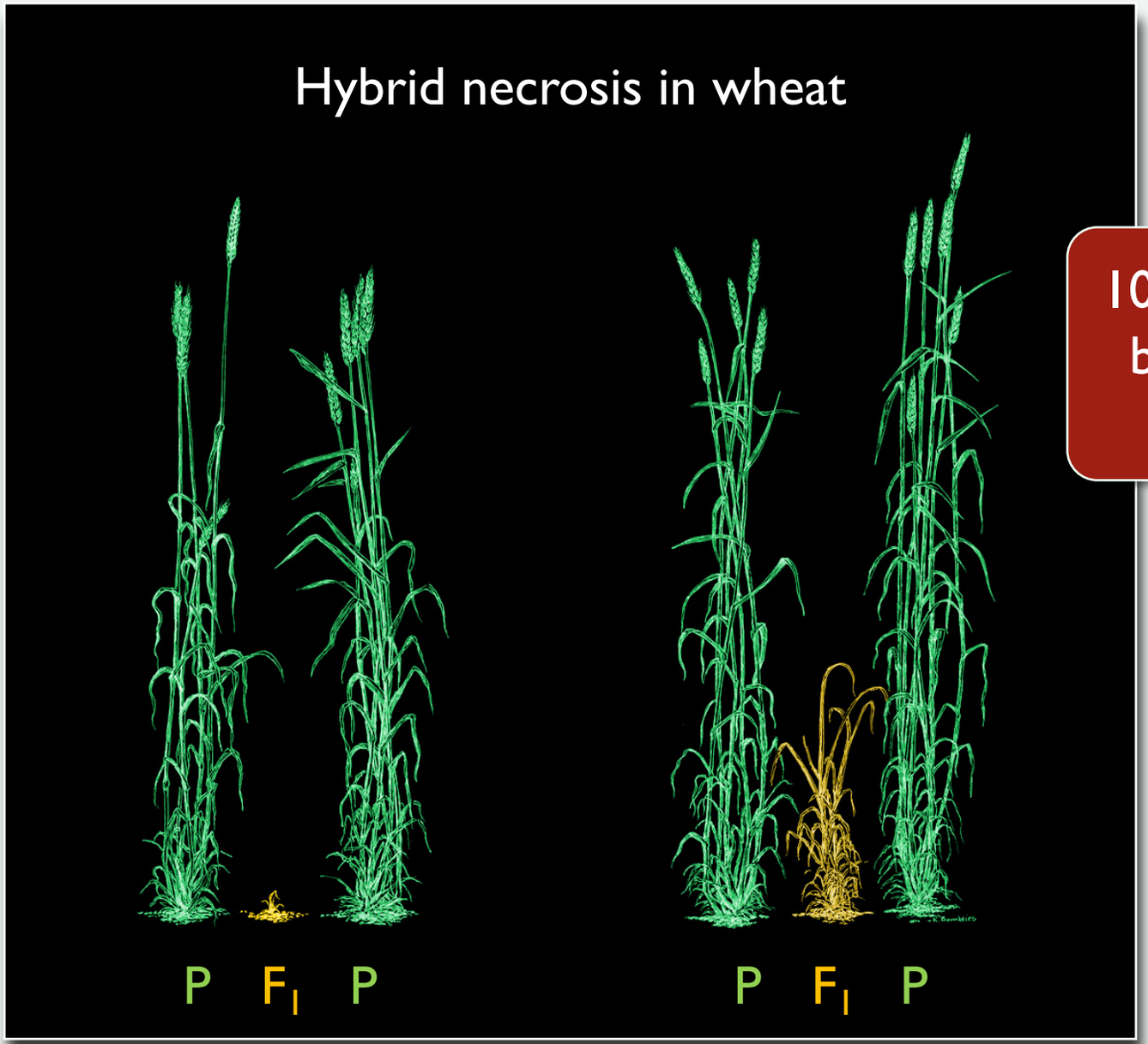
Bomblies, Lempe et al. (2007)

Dangerous Microbes Are Everywhere! (Or Are They?)

Hypothesis:

One genome recognizes something from the other genome as foreign (pathogen derived)

Hybrid Necrosis – A Common Form of Hybrid Weakness

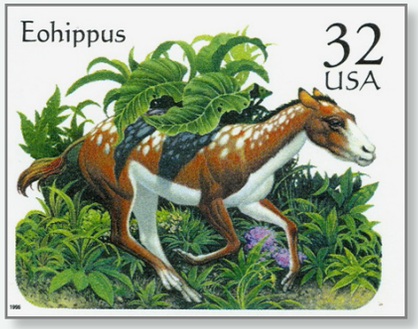


100s of cases described by breeders and naturalists (not in maize?)

Underlying defect: autoimmunity

Extreme Negative Heterosis Can Underlie Speciation

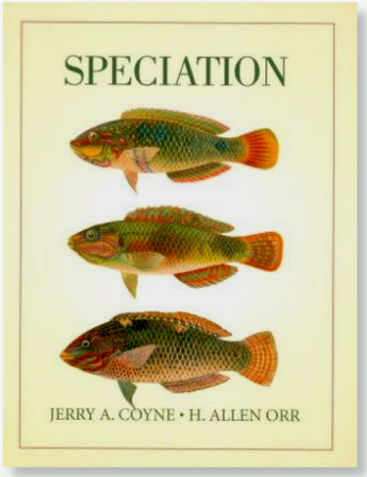
(Bateson) Dobzhansky-Muller model



aa bb

aa bb

AA bb

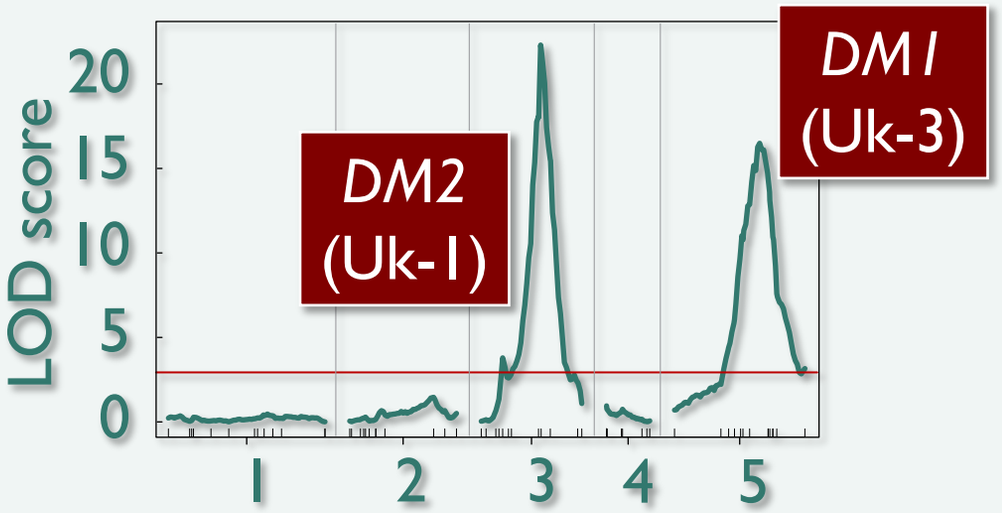


aa bb

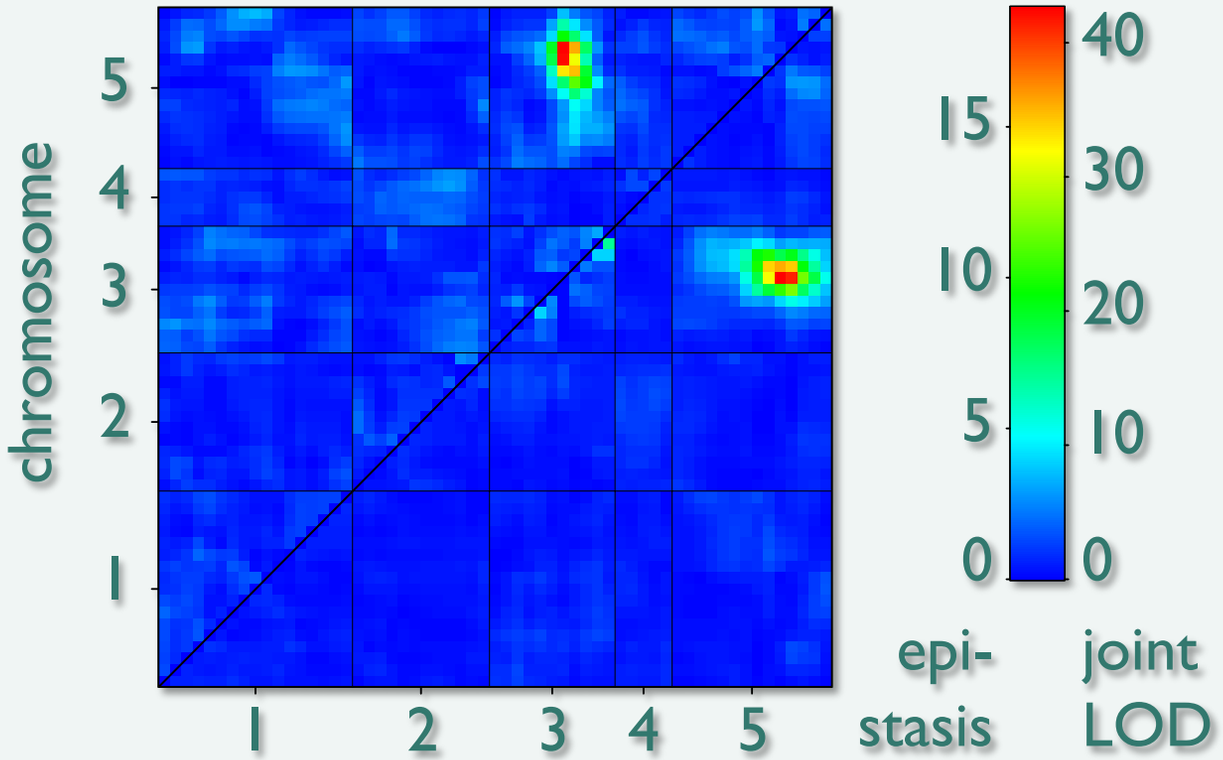
aa BB

Aa Bb

Simple Genetics of Hybrid Necrosis

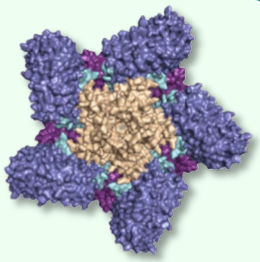


With Dangl lab

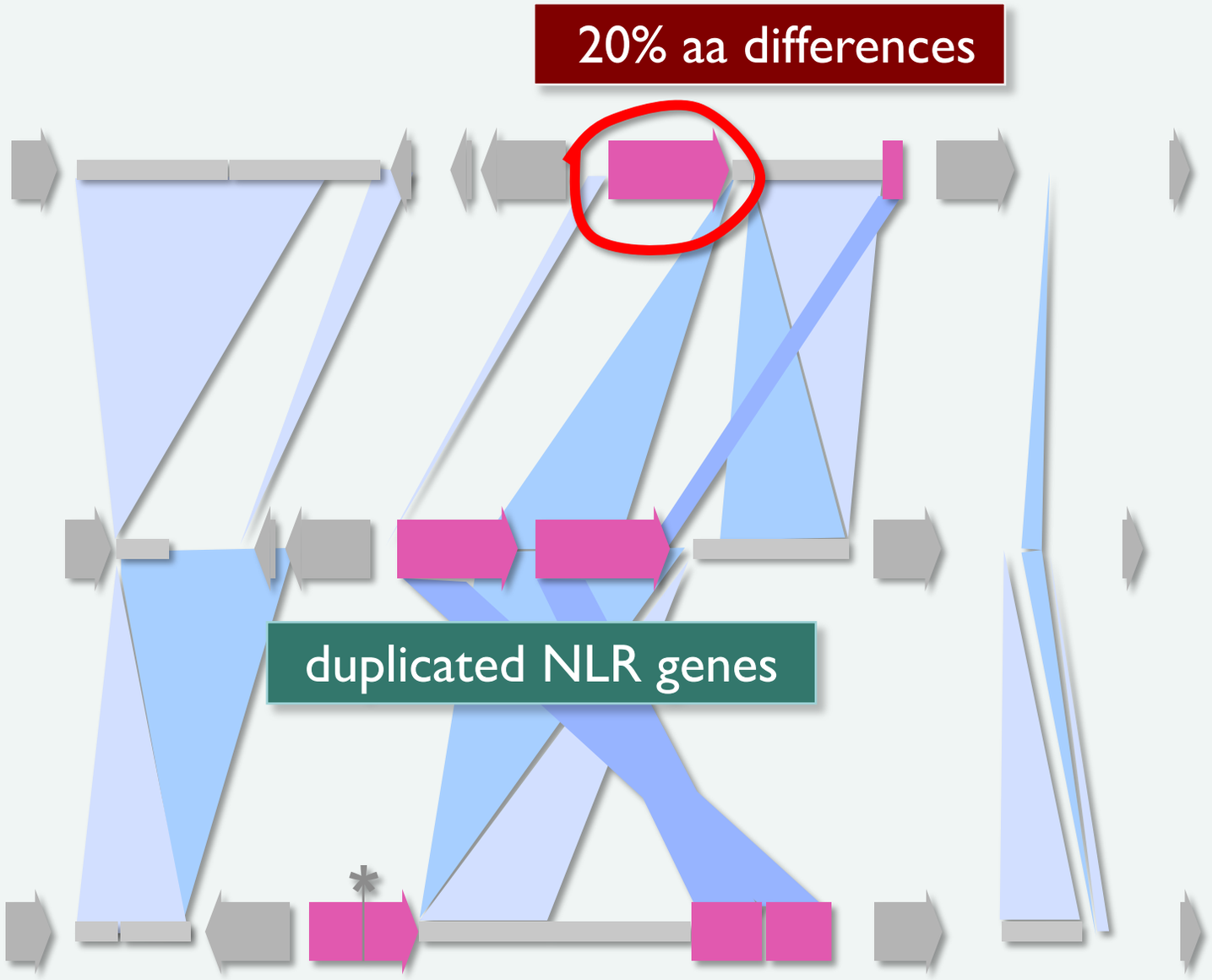


Dangerous Mix (DM)

DM1 Encodes an NLR Immune Receptor

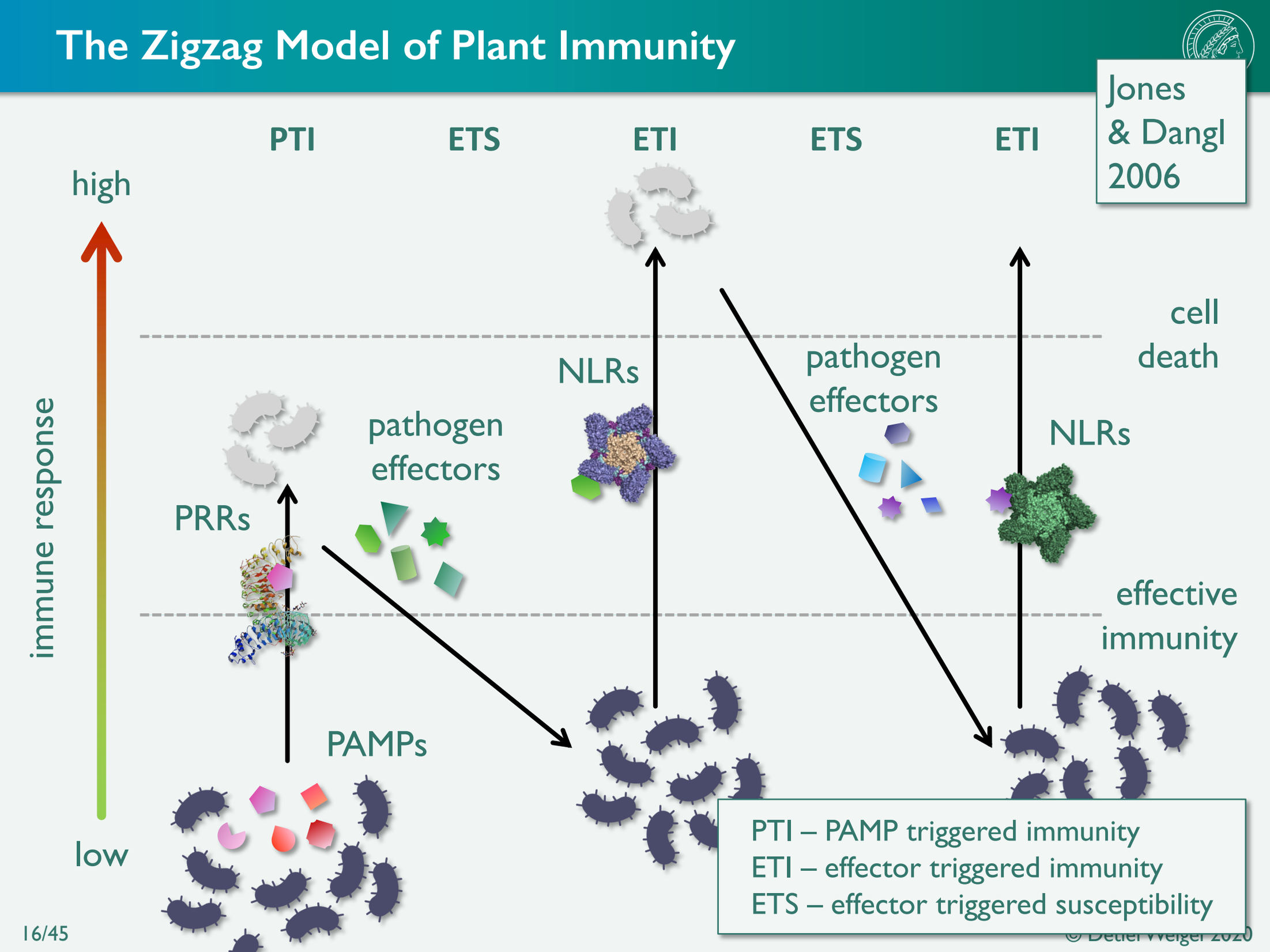


Nucleotide binding site
Leucine rich repeat
Receptor

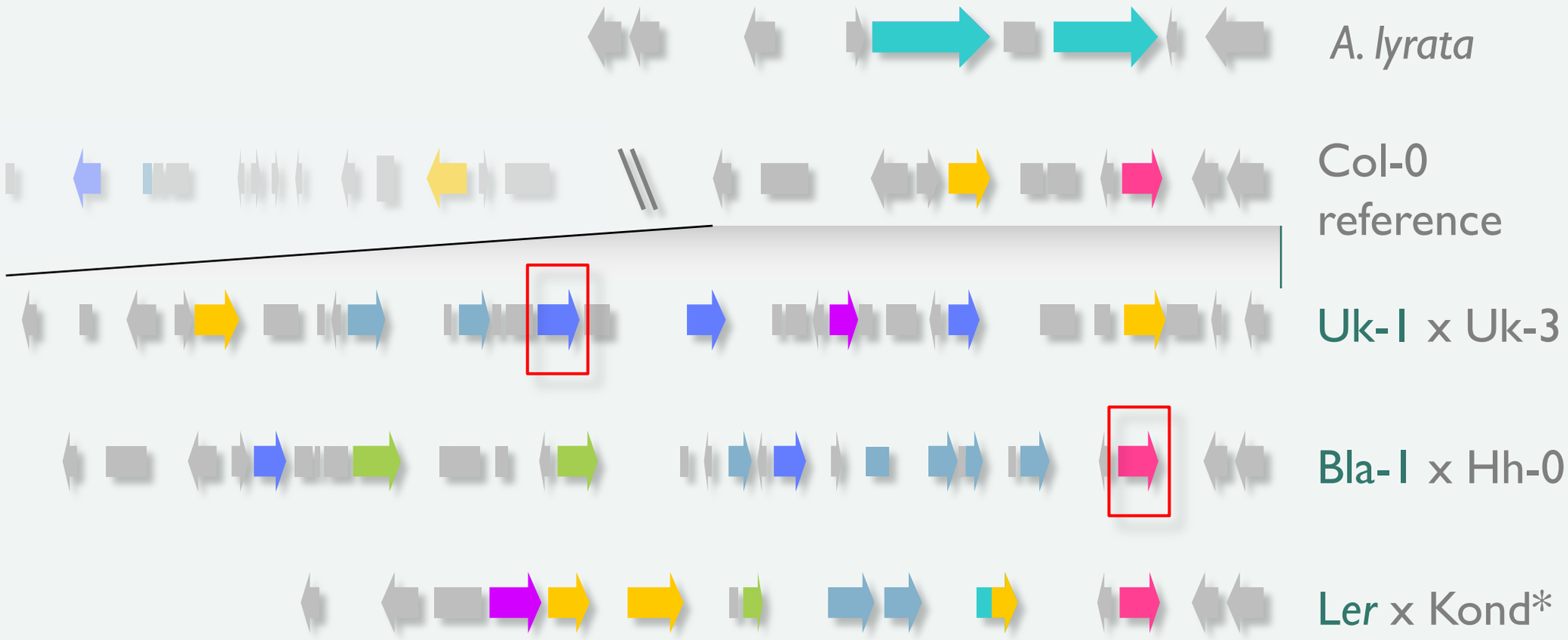


DM1 sufficient & necessary for hybrid necrosis in Uk-1 background

The Zigzag Model of Plant Immunity



But *DM2* Encodes an NLR Immune Receptor as Well



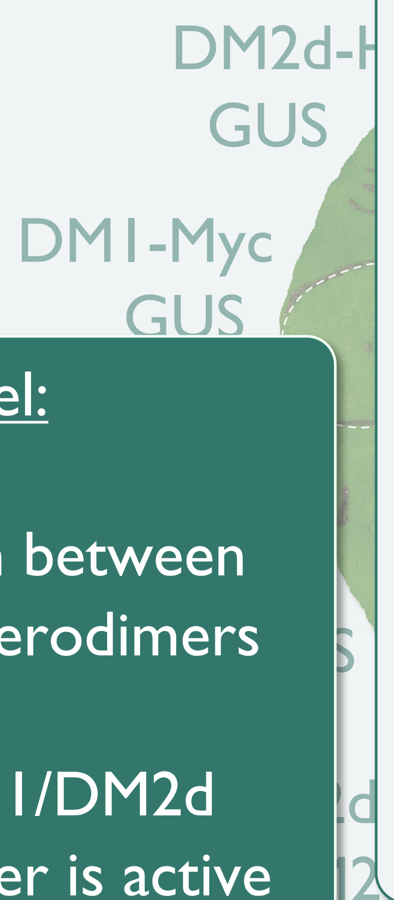
different *NB-LRR* clades

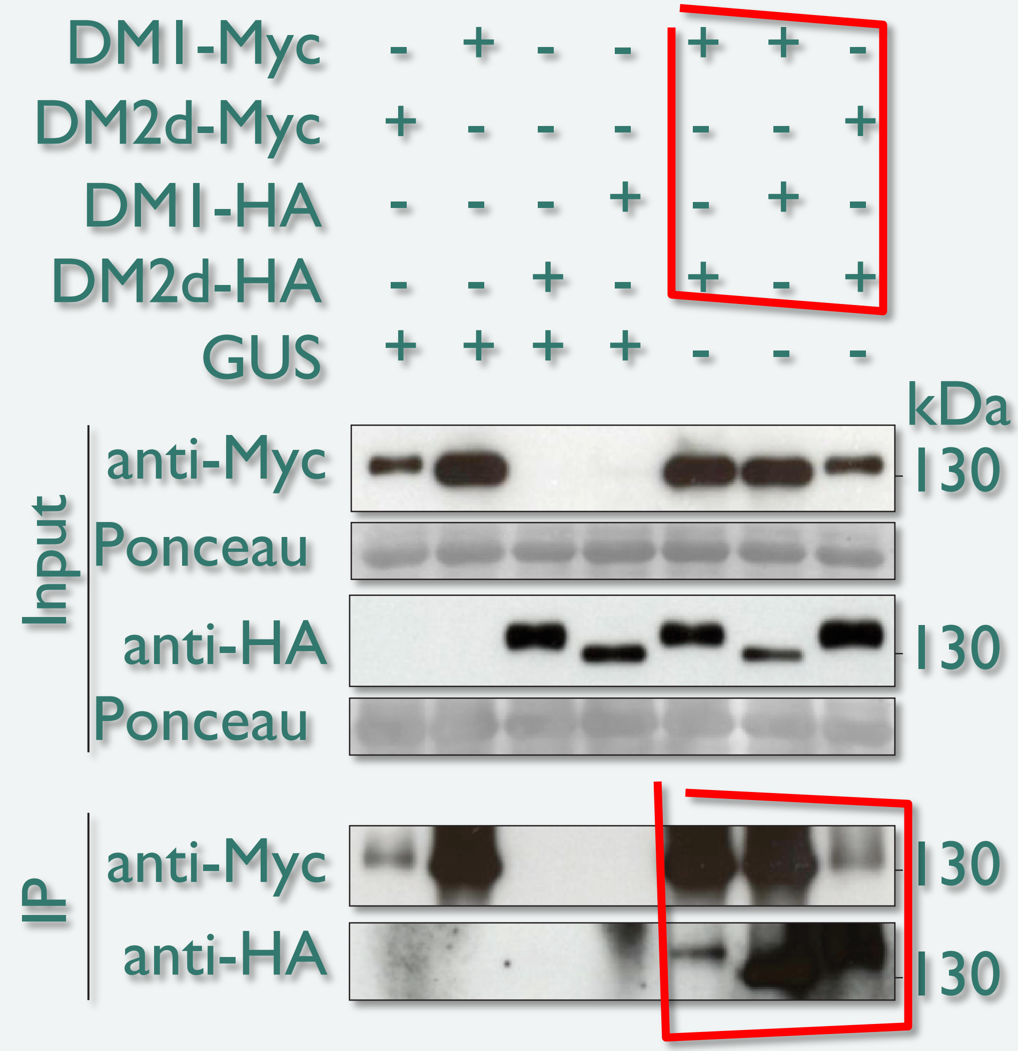
unrelated *NB-LRR* genes

*F_2 incompatibility (Alcázar et al., 2009)

Direct Interaction of DM1 and DM2

Diep Tran
(IP[...]





Model:

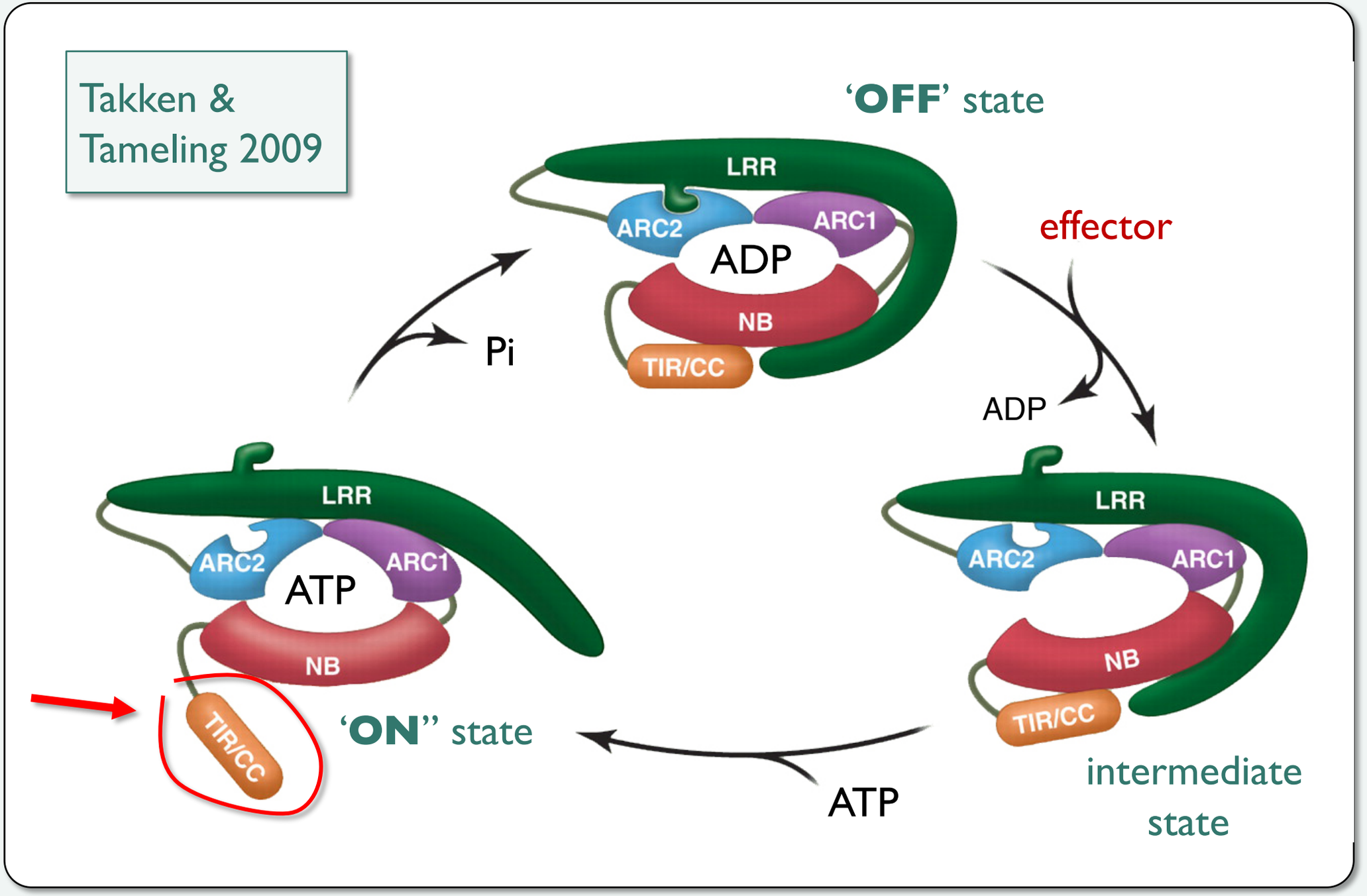
Competition between homo- & heterodimers

→ only DM1/DM2d heterodimer is active

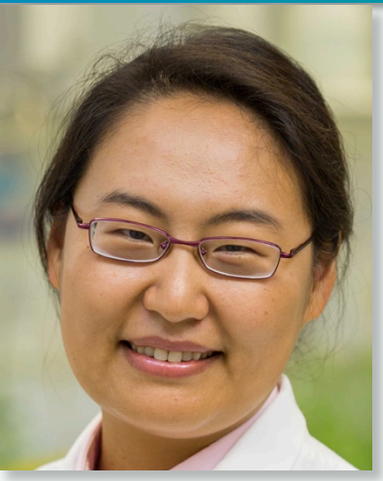
(but interaction not sufficient for signaling)

Tran et al. (2017)

NLRs: Enzymes That Cycle Between 'OFF' and 'ON' States



A Species-wide Survey of Hybrid Necrosis



Eunyoung Chae (NUS)

6,409 crosses (3,330 unique combinations)

~2% of F_1s with hybrid necrosis

♀

♂

not tested

hybrid

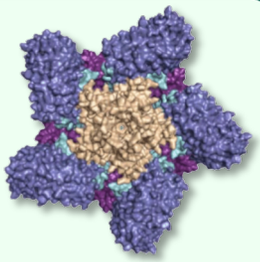
necrosis

classes

geographic origins

Chae et al. (2014)

Almost Always NLR Immune Receptor Genes Causal



Nucleotide binding site
Leucine rich repeat
Receptor

Dangerous Mix (DM)

RPP7
DM6 ICE79
DM6 Lerik1-3
DM6 Mrk-0
DM6 Cdm-0

RPW8/HR
RPP1
DM2 Uk-1
DM2 Bla-1
DM2 Ler
DM2 Dog-4
DM2 S.Tyrol
DM7 Don-0
DM7 Fei-0
DM7 Kz10
DM3 Hh-0

RPP4/5
ACD6
SRF3 Bla-1
DM9 Bla-1
DM9 Hh-0
DM8 Ey1.5-2
DM8 ICE228

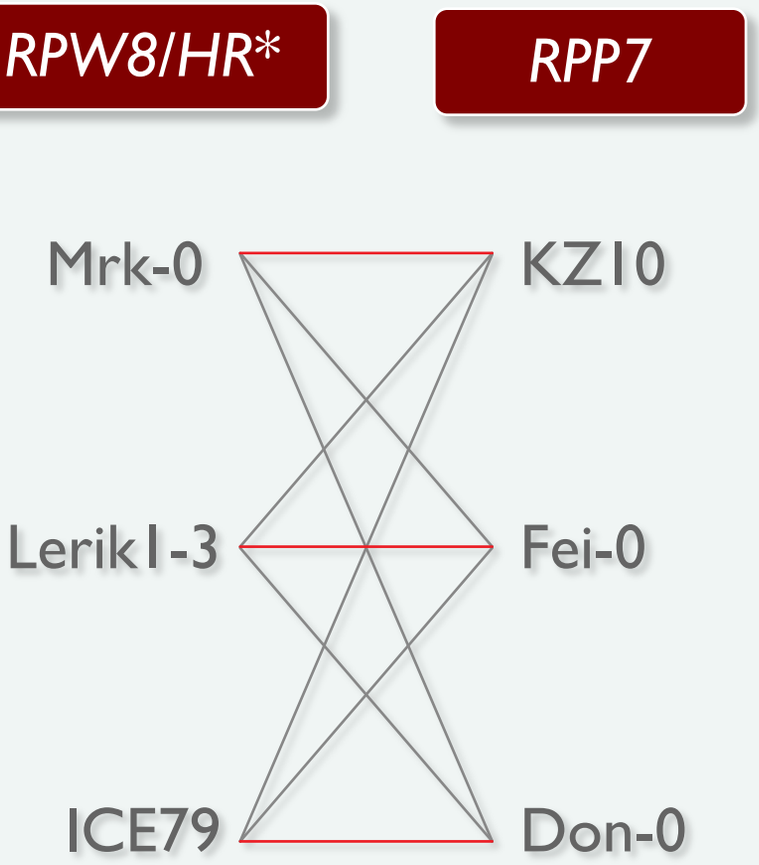
SSI4
RPP8
At5g58120
DM1 Uk-3
DM4 TueWa1-2
DM5 ICE163
DM10 Tuescha9

NLR density

Multiple Pairs of *RPP7* – *RPW8/HR* Interactions

Cristina Barragan

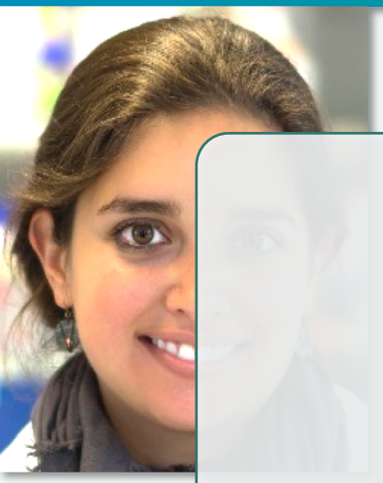
Parent 1 F_1 Parent 2

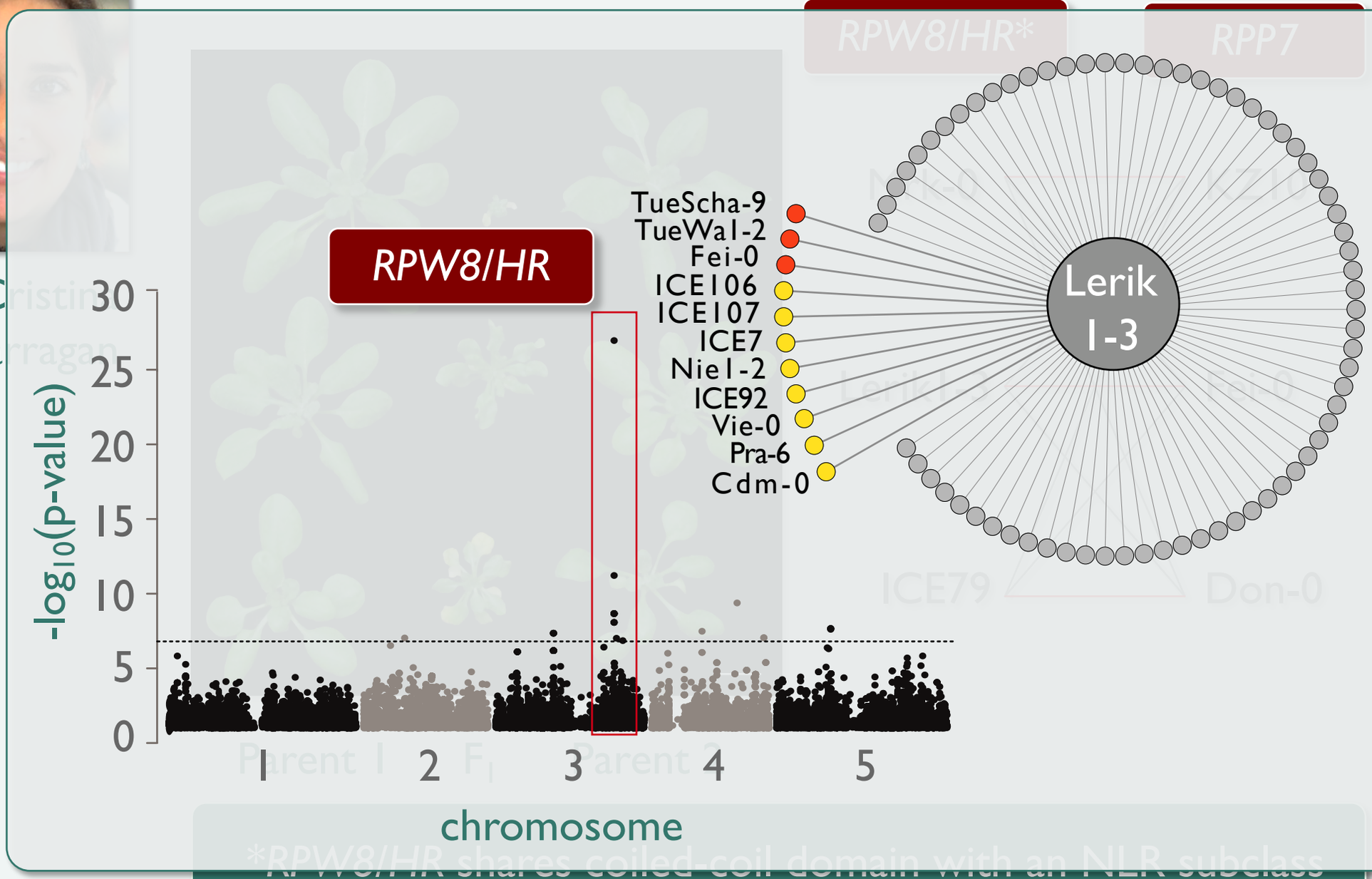


*RPW8/HR shares coiled-coil domain with an NLR subclass

Barragan et al. (2019)

Multiple Pairs of *RPP7* – *RPW8/HR* Interactions

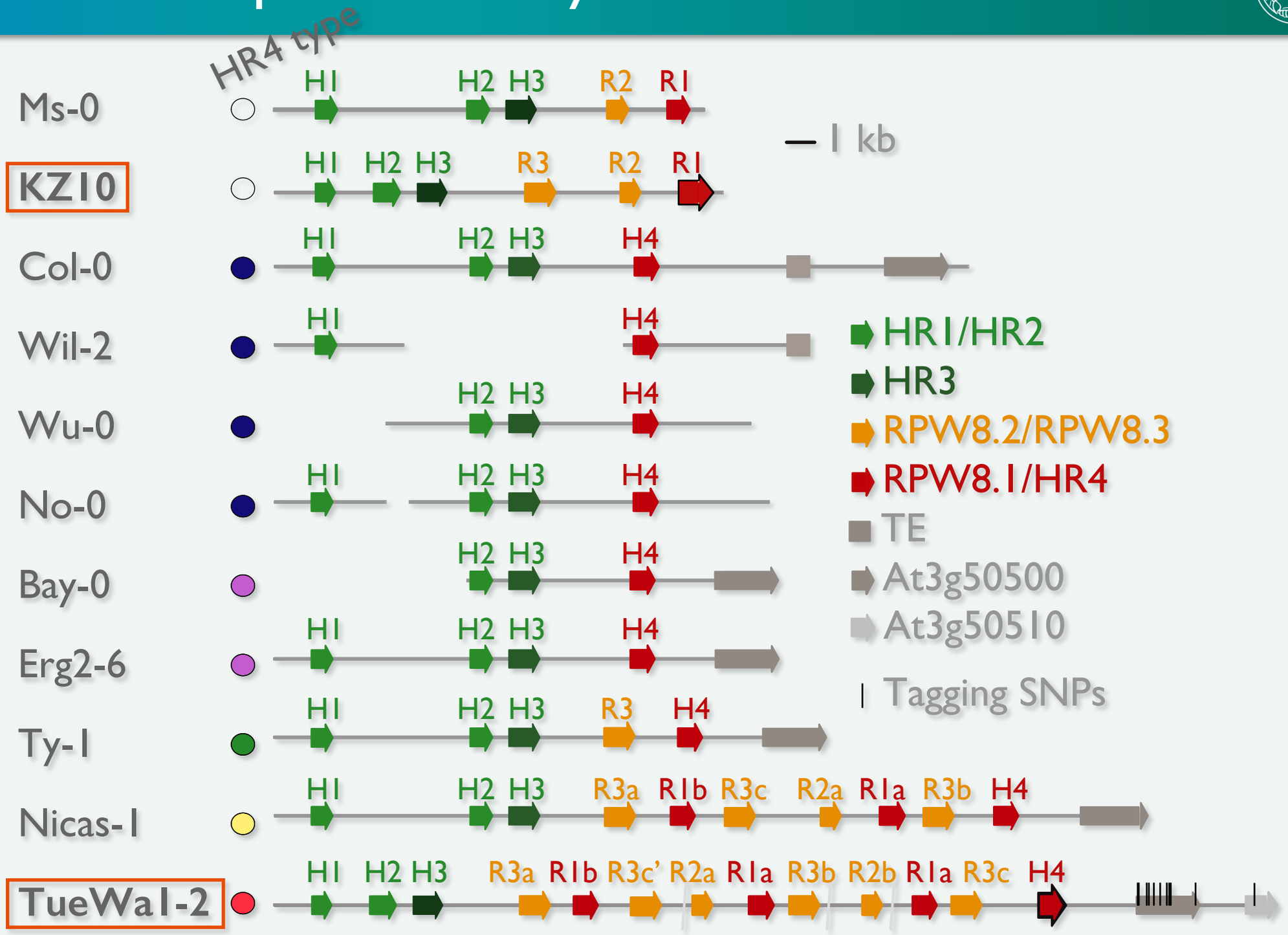




*RPW8/HR shares coiled-coil domain with an NLR subclass

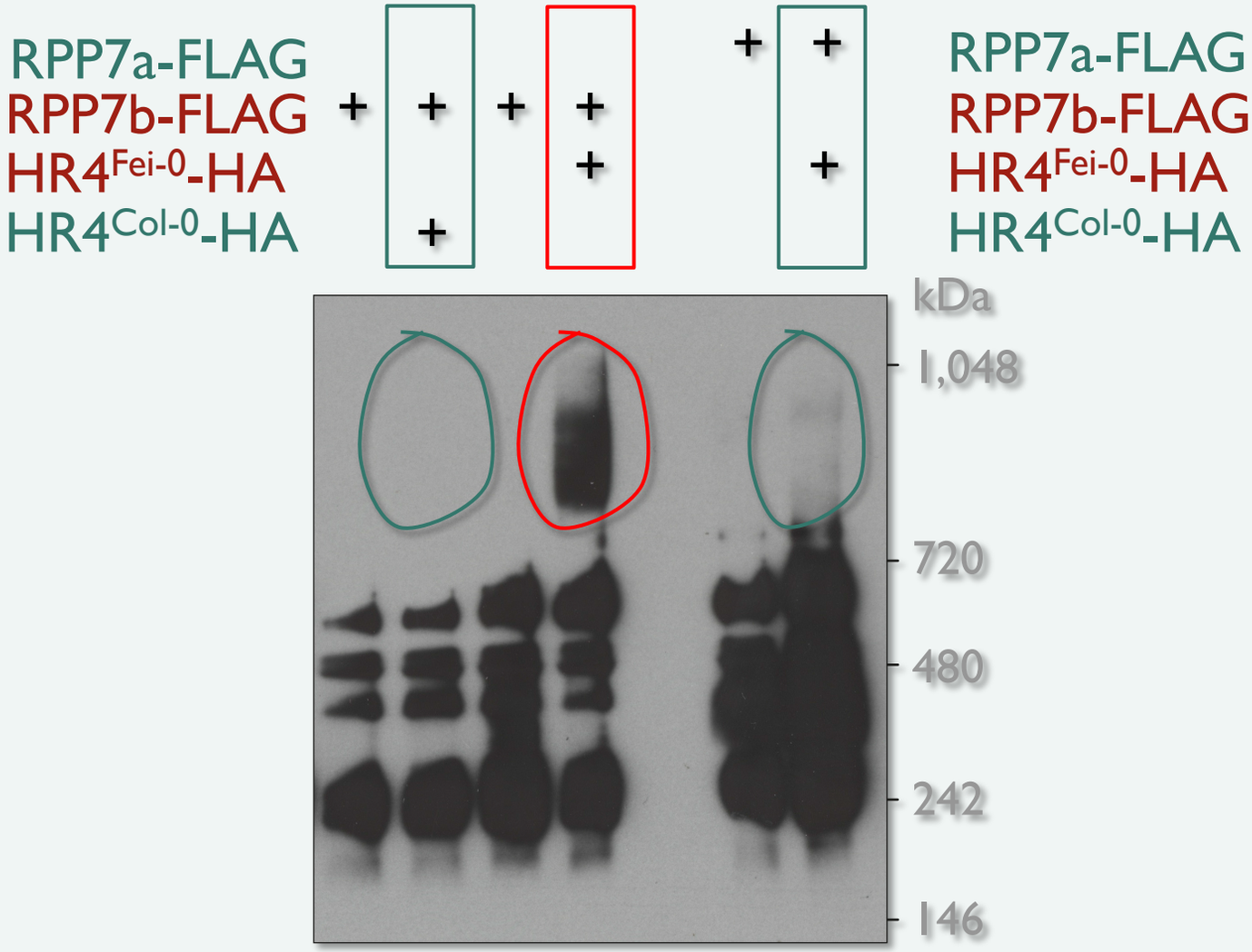
Barragan et al. (2019)

NLR-like Sequence Diversity at *RPW8/HR*



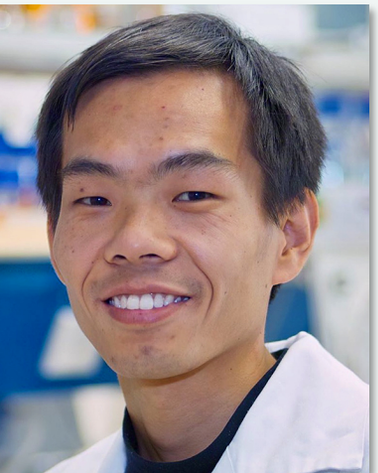
Specific Interactions between RPP7 and RPW8/HR Proteins

Only between proteins encoded by causal alleles of *RPP7* and *RPW8/HR*



3-12% native PAGE

Lei Li



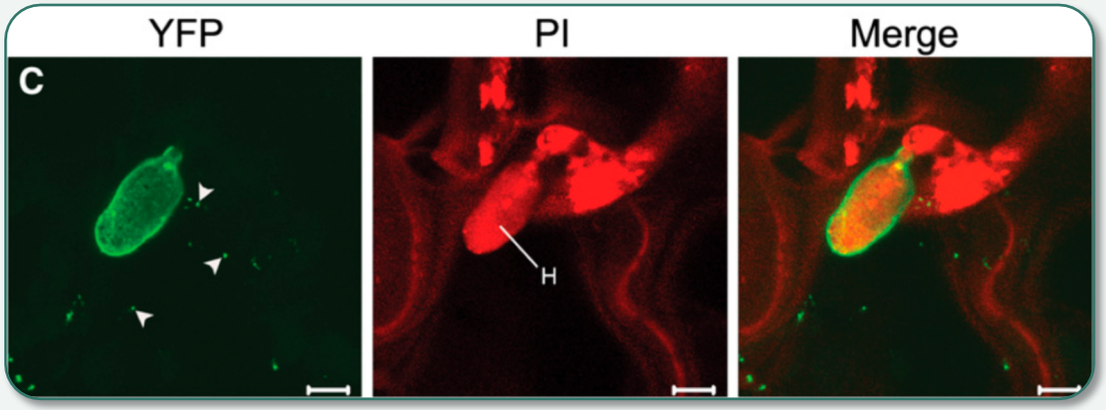
Li et al. (2020)

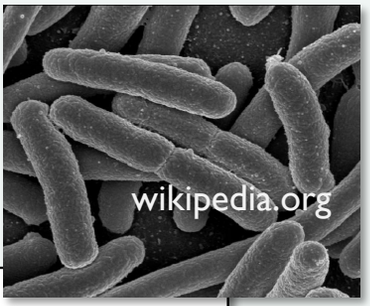
RPW8/HR4 Proteins: Potentially Direct Role in Defense

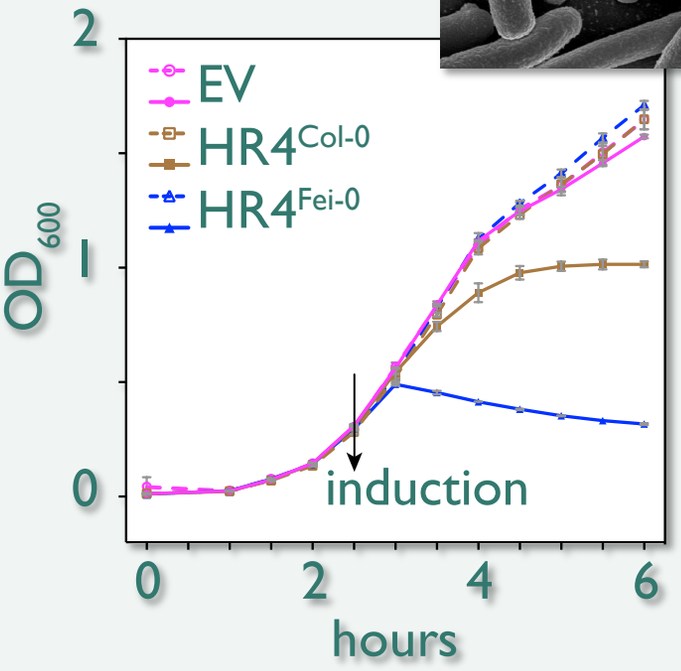
The Plant Cell, Vol. 21: 2898–2913, September 2009, www.plantcell.org © 2009 American Society of Plant Biologists

Specific Targeting of the *Arabidopsis* Resistance Protein RPW8.2 to the Interfacial Membrane Encasing the Fungal Haustorium Renders Broad-Spectrum Resistance to Powdery Mildew [W] [OA]

Wenming Wang, Yingqiang Wen, Robert Berkey, and Shunyuan Xiao[1]

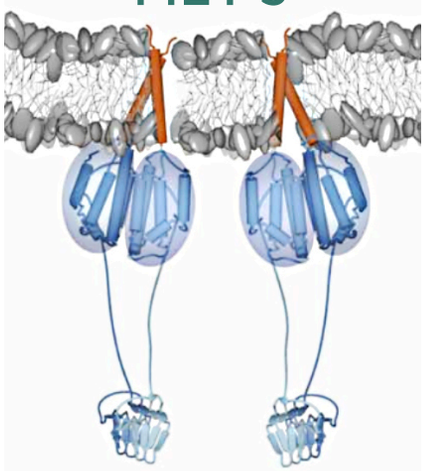




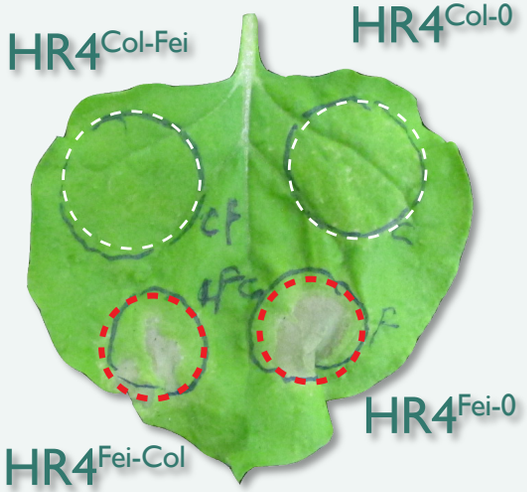


HR4 kills cells on its own

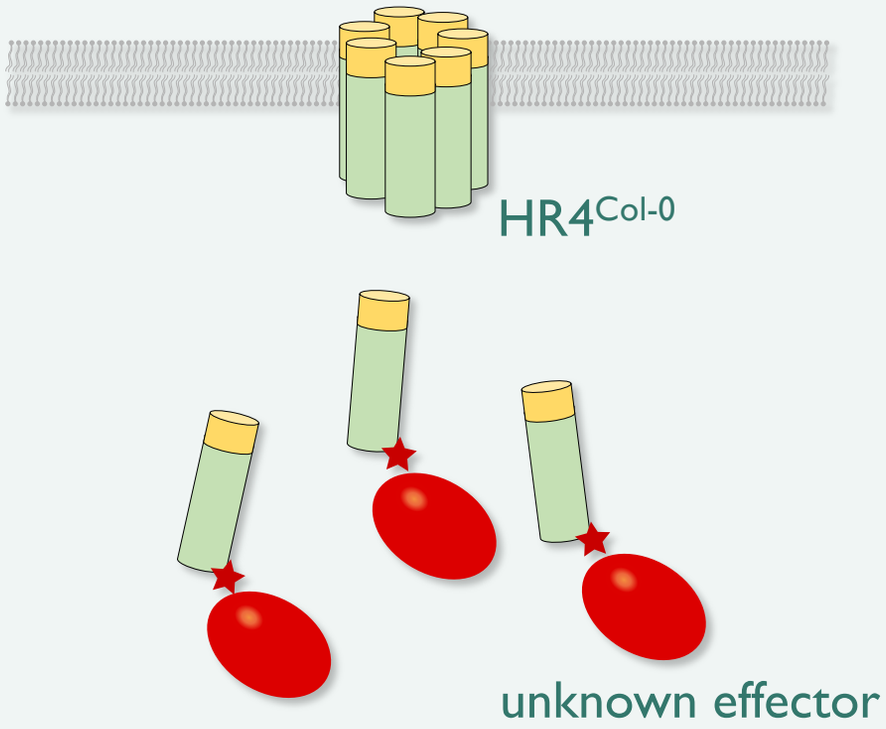
HR4 homolog HET-S

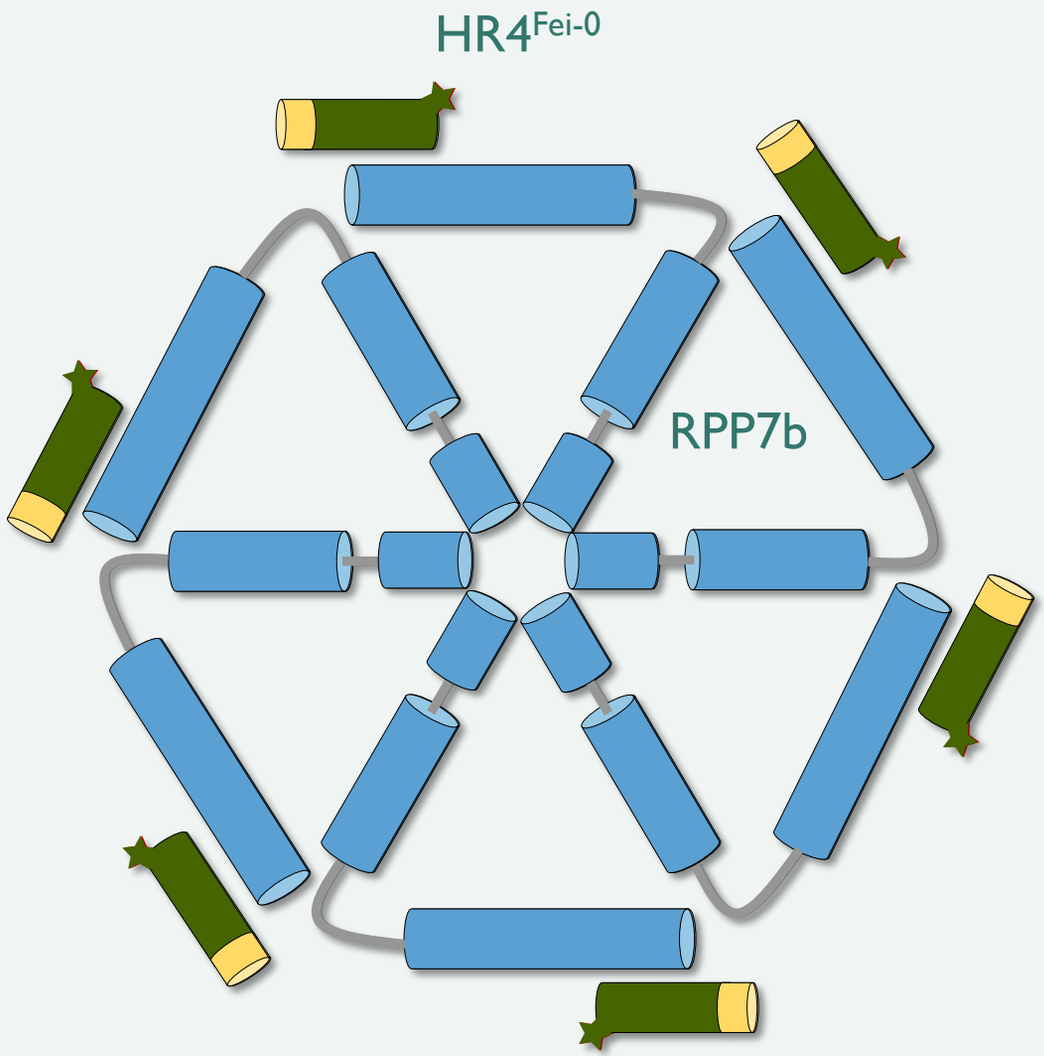


Seuring et al., *PLoS Biol.* 2012



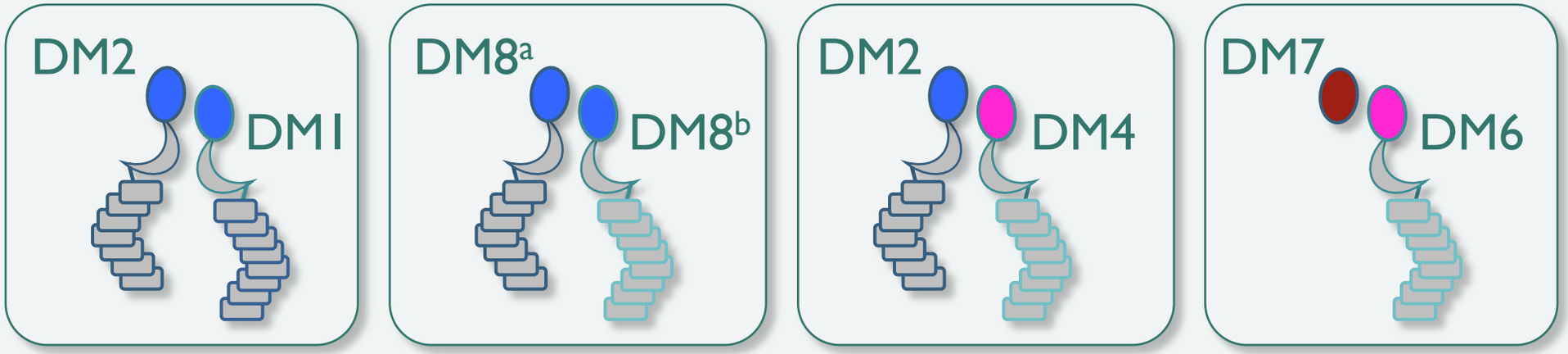
Hypothesis: HR4^{Fei-0} Mimics an Effector-modified HR4^{Col-0}





A Wide Range of (Direct?) NLR Interactions

Potentially promiscuous NLR interactions limit possible immune receptor combinations in single genotype



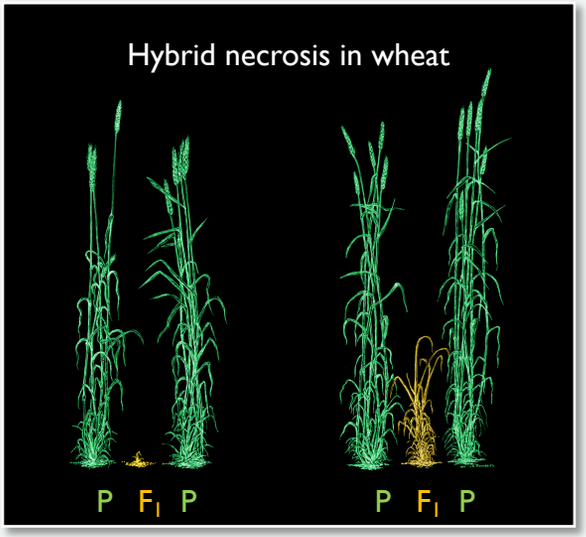
Genome-wide functional analyses of plant coiled–coil NLR-type pathogen receptors reveal essential roles of their N-terminal domain in oligomerization, networking, and immunity

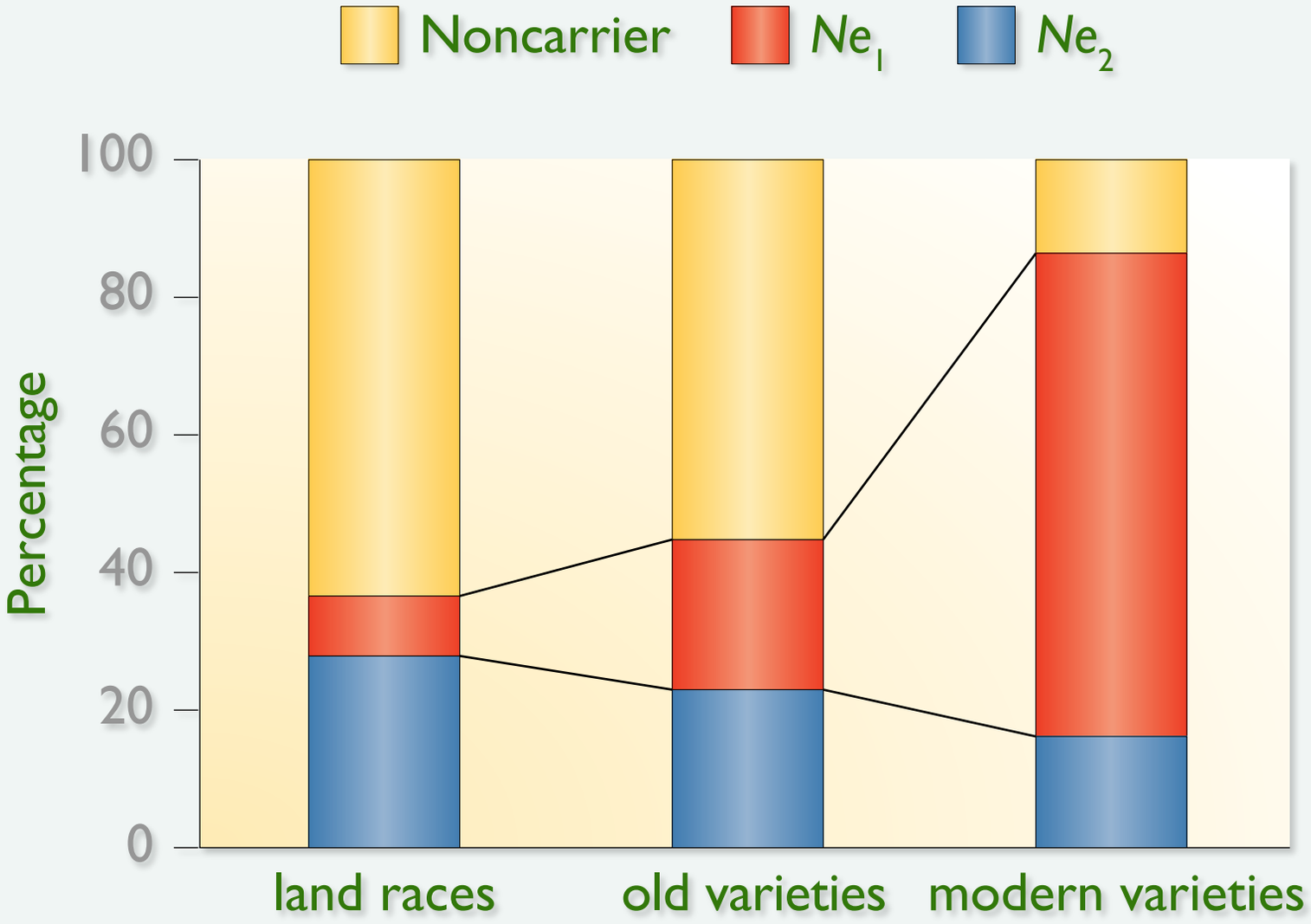
Tadeusz Wróblewski[1]*, Laurentiu Spiridon[2], Eliza Cristina Martin[2], Andrei-Jose Petrescu[2], Keri Cavanaugh[1], Maria José Truco[1], Huaqin Xu[1], Dariusz Gozdowski[3], Krzysztof Pawłowski[3], Richard W. Michelmore[1,4,5], Frank L.W. Takken[6]*

NLR network mediates immunity to diverse plant pathogens

Chih-Hang Wu[a], Ahmed Abd-El-Haliem[b], Tolga O. Bozkurt[a,c], Khaoula Belhaj[a], Ryohei Terauchi[d,e], Jack H. Vossen[b], and Sophien Kamoun[a,1]

Historical Selection Affected Frequency of *Ne* Genes



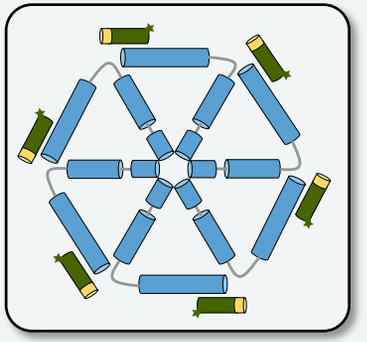


This could eventually lead to speciation

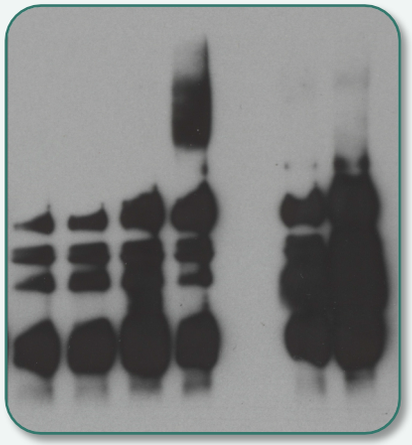
Lessons

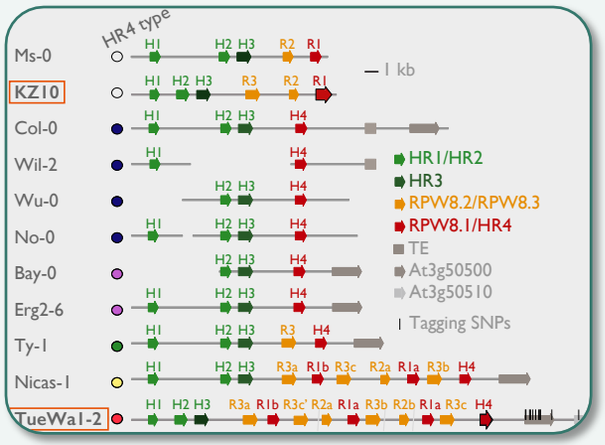
- Epistatic interactions in immune system are common

- Many translate into direct protein-protein interactions



- Too much diversity at NLR & other immune loci can backfire
- Natural autoimmunity reveals new aspects of plant immune system



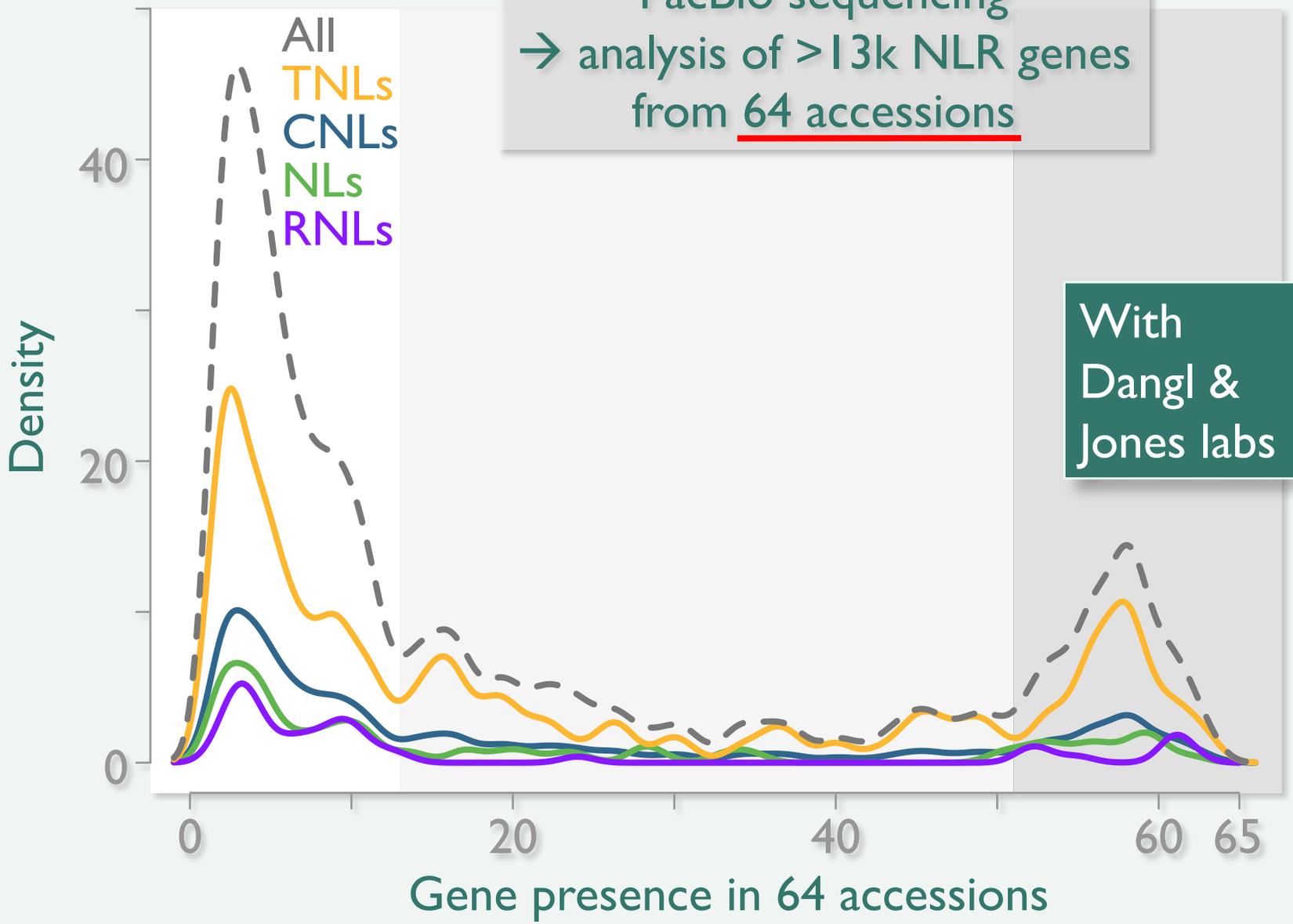


NLR Immune Receptor Genes Very Polymorphic

Anna-Lena Van de Weyer (LaboKlin)

Felix Bemm (KWS)

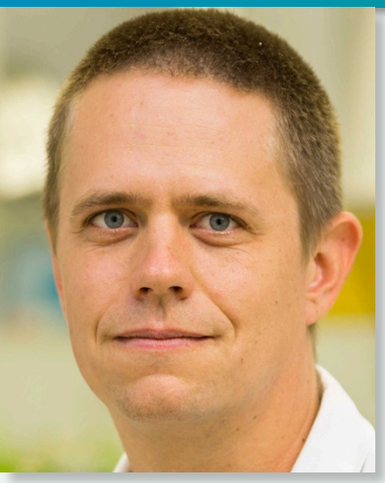
NLR sequence enrichment & PacBio sequencing
→ analysis of >13k NLR genes from 64 accessions



With Dangl & Jones labs

Van de Weyer et al. (2019)

Why Are NLRs so Diverse?

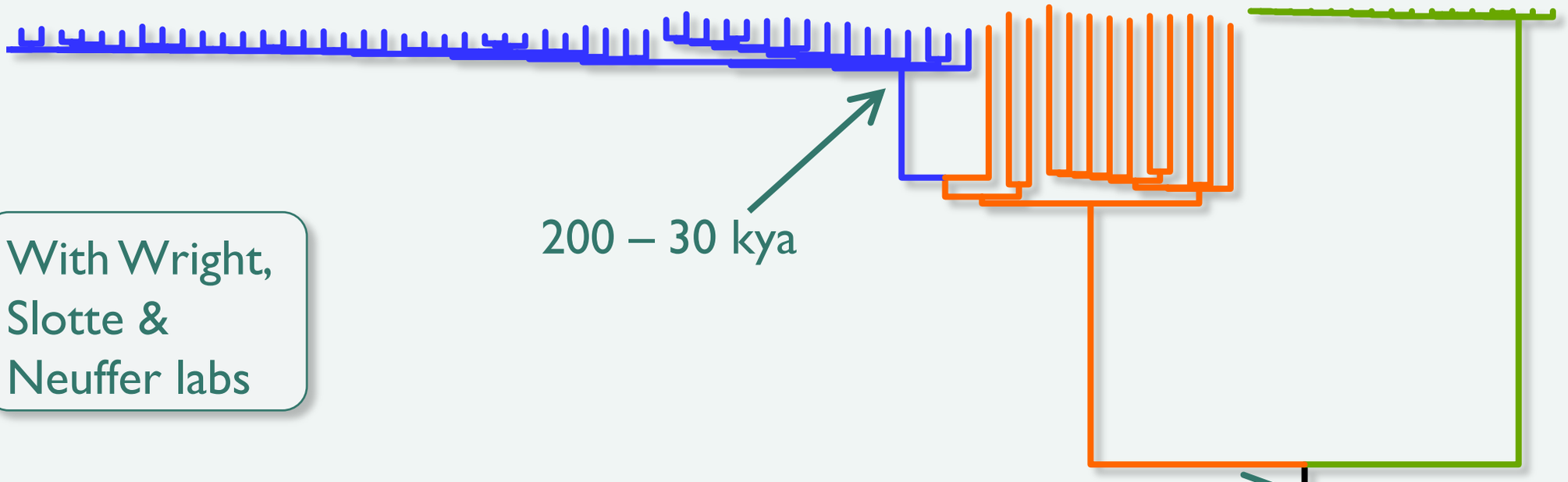


Daniel Koenig
(UCR)

Distance trees from whole-genome sequences

Capsella rubella *C. grandiflora* *C. orientalis*

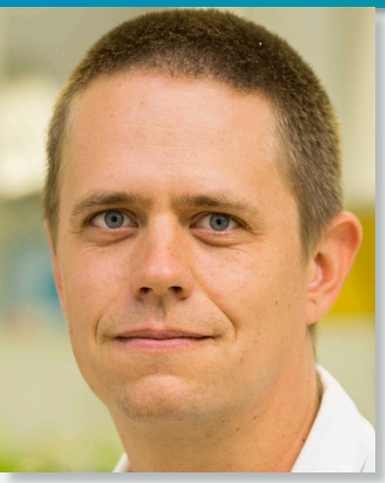




With Wright, Slotte & Neuffer labs

Koenig et al. (2019)

Why Are NLRs so Diverse?

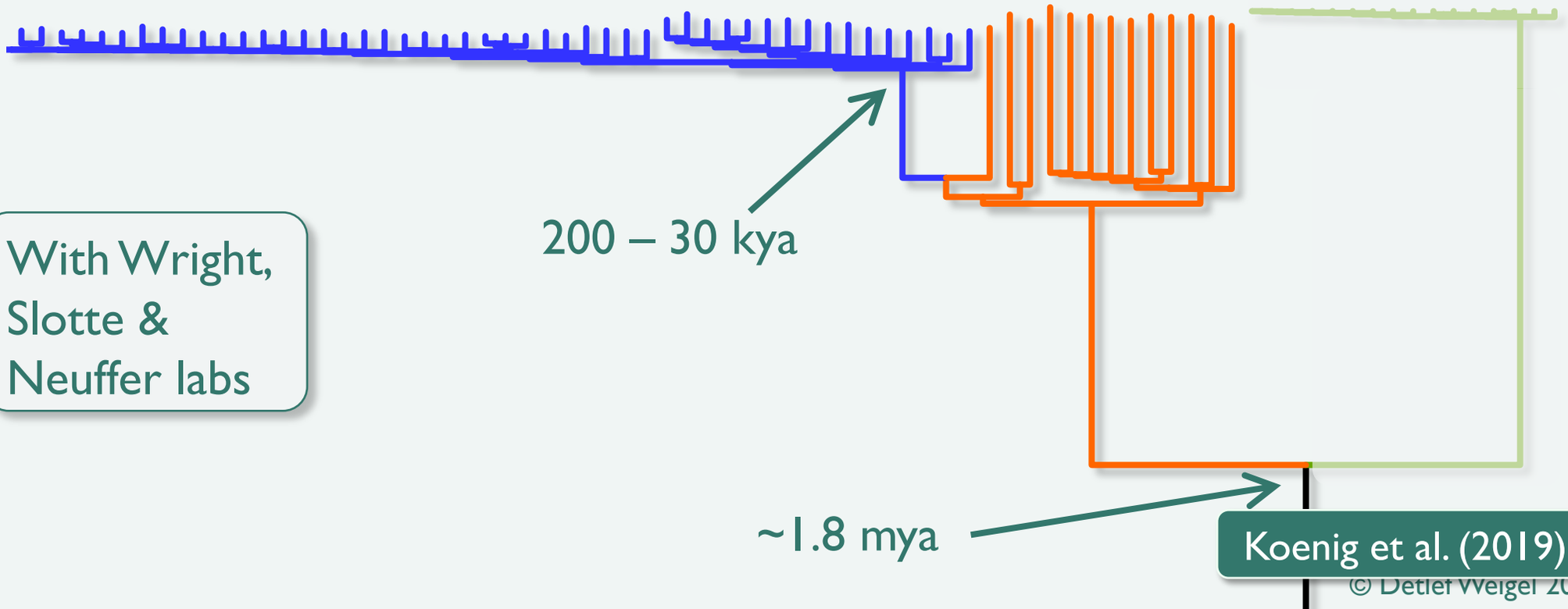


Daniel Koenig
(UCR)

Many trans-specific alleles

Capsella rubella *C. grandiflora* *C. orientalis*



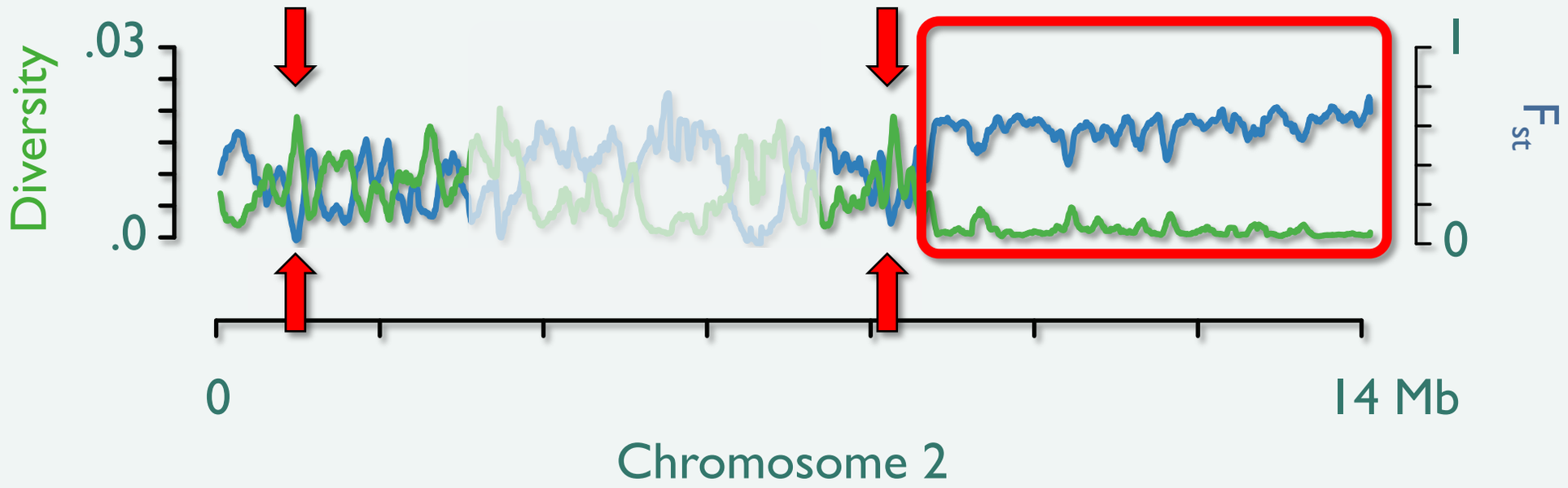


With Wright, Slotte & Neuffer labs

Koenig et al. (2019)

Nonrandom Distribution of Trans-Specific Alleles

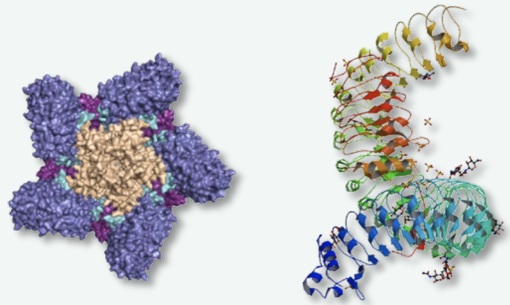
- **Diversity** within *C. rubella*
- **Differentiation** between *C. rubella* & *C. grandiflora*



Nonrandom Distribution of Trans-Specific Alleles

- **Diversity** within *C. rubella*
- **Differentiation** between *C. rubella* & *C. grandiflora*

~2% of total genome



21 regions
9 overlap with NLR immune receptor genes
5 overlap with other immune genes incl. Pattern Recognition Receptors
Several of these with known function in *A. thaliana*

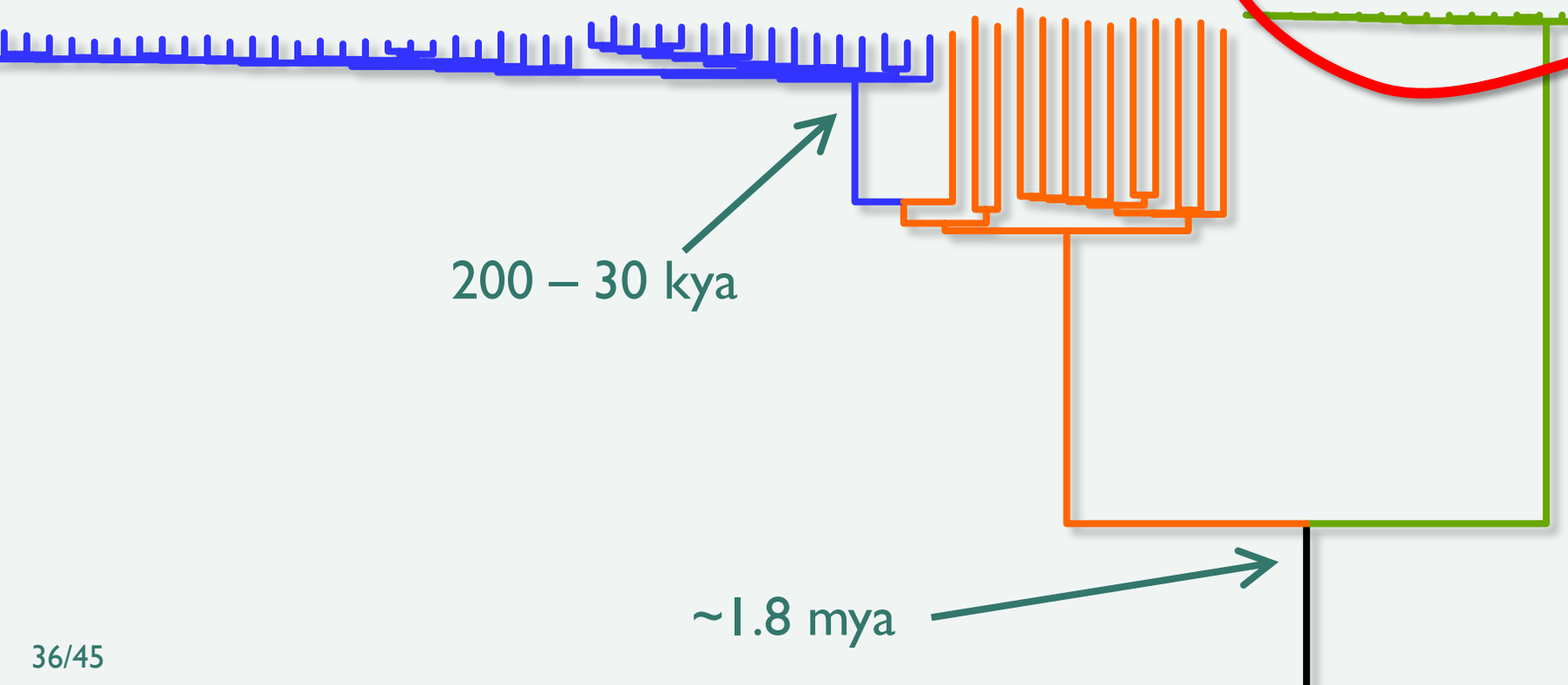
0 14 Mb

Chromosome 2

Supported by Analysis of a Much More Diverged Species?

Distance trees from whole-genome sequences

Capsella rubella *C. grandiflora* *C. orientalis*



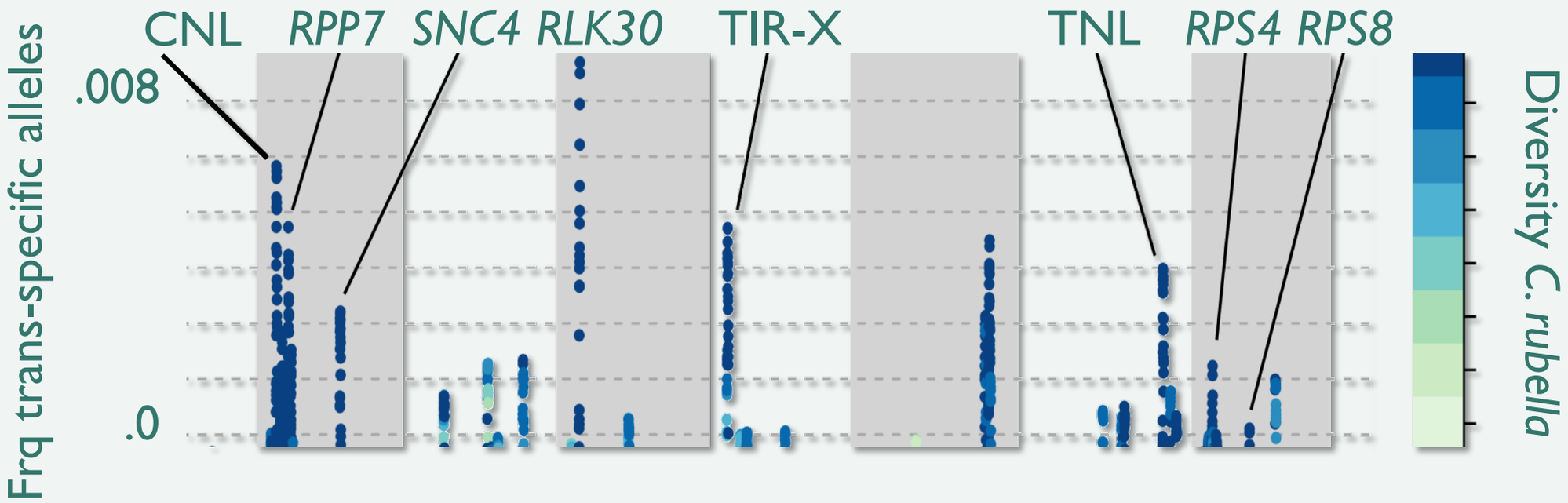
Many Trans-Specific Alleles in *C. orientalis* as Well

Shared with *C. grandiflora*

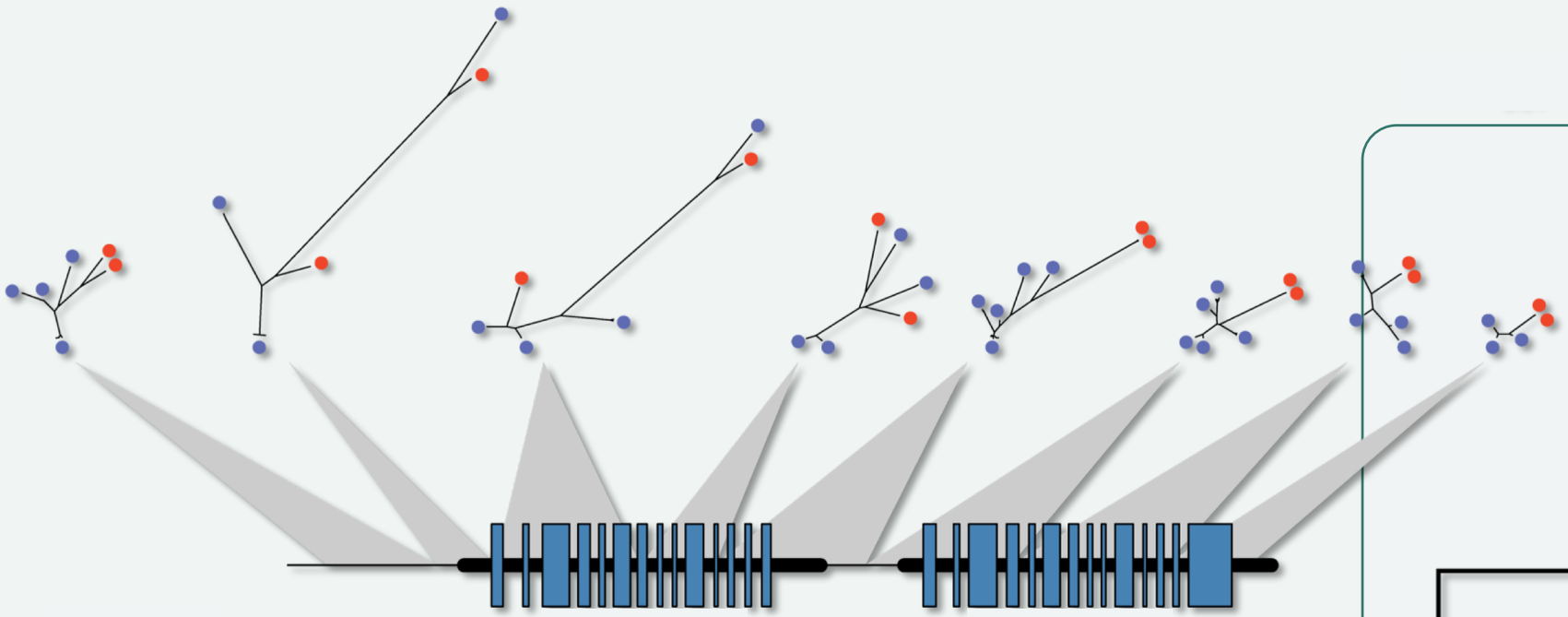
Shared with *C. rubella*

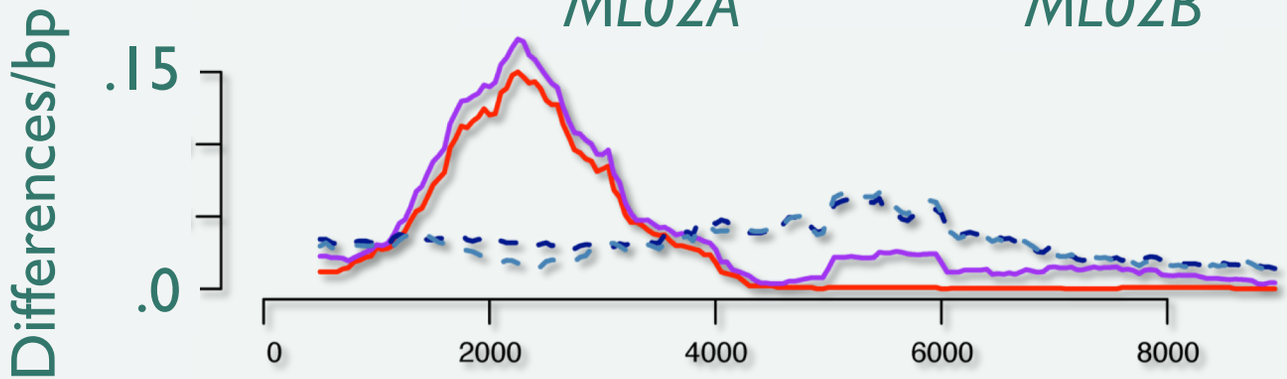
Shared with both species

Maintenance of Same Immune Receptor Alleles



Ancient Balanced Polymorphism at *MLO2*

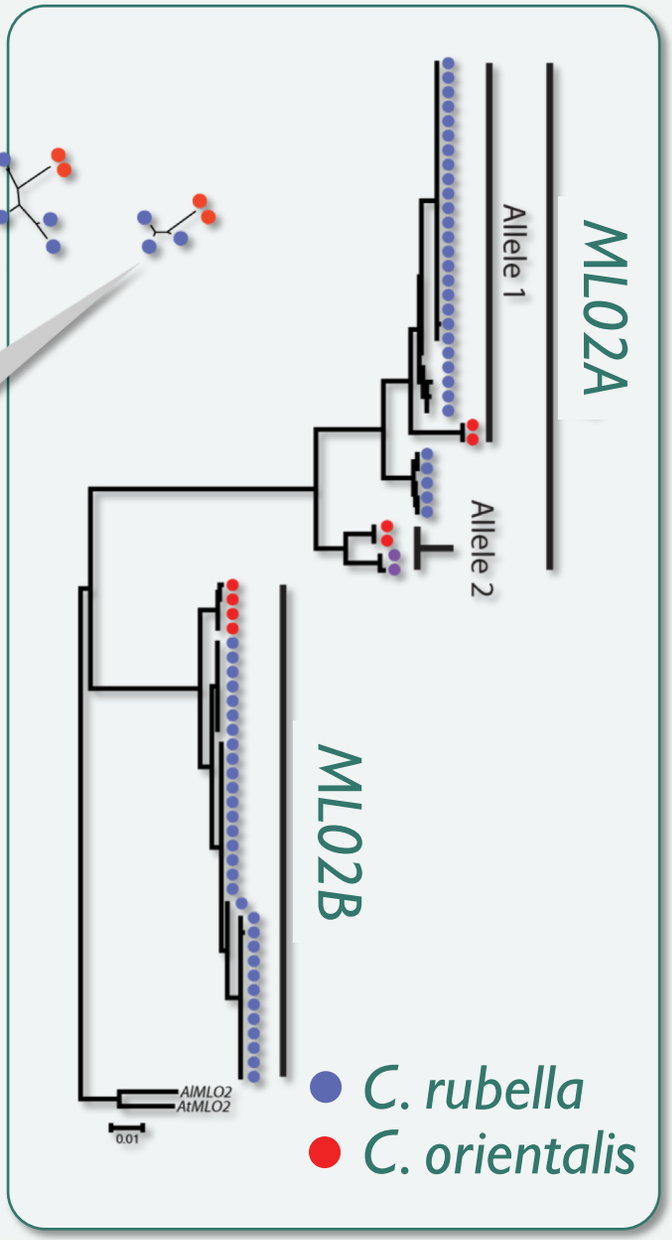




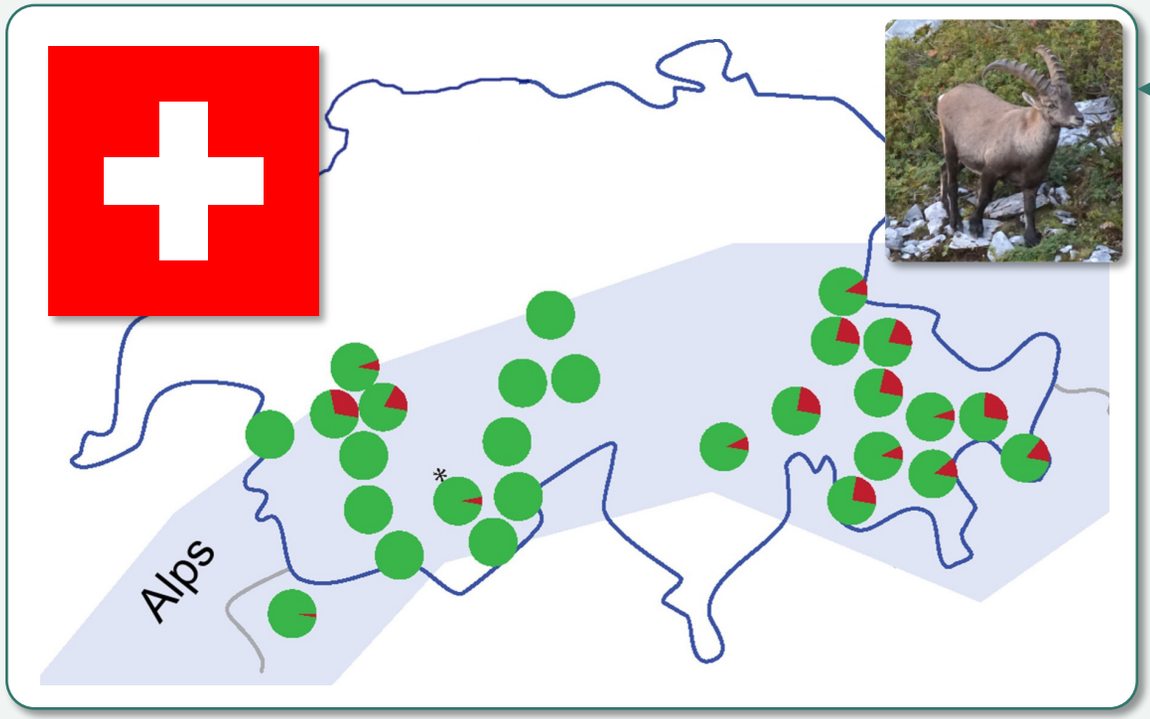
Between different alleles in *C. orientalis*

Between different alleles in *C. rubella*

Between same allele in two species

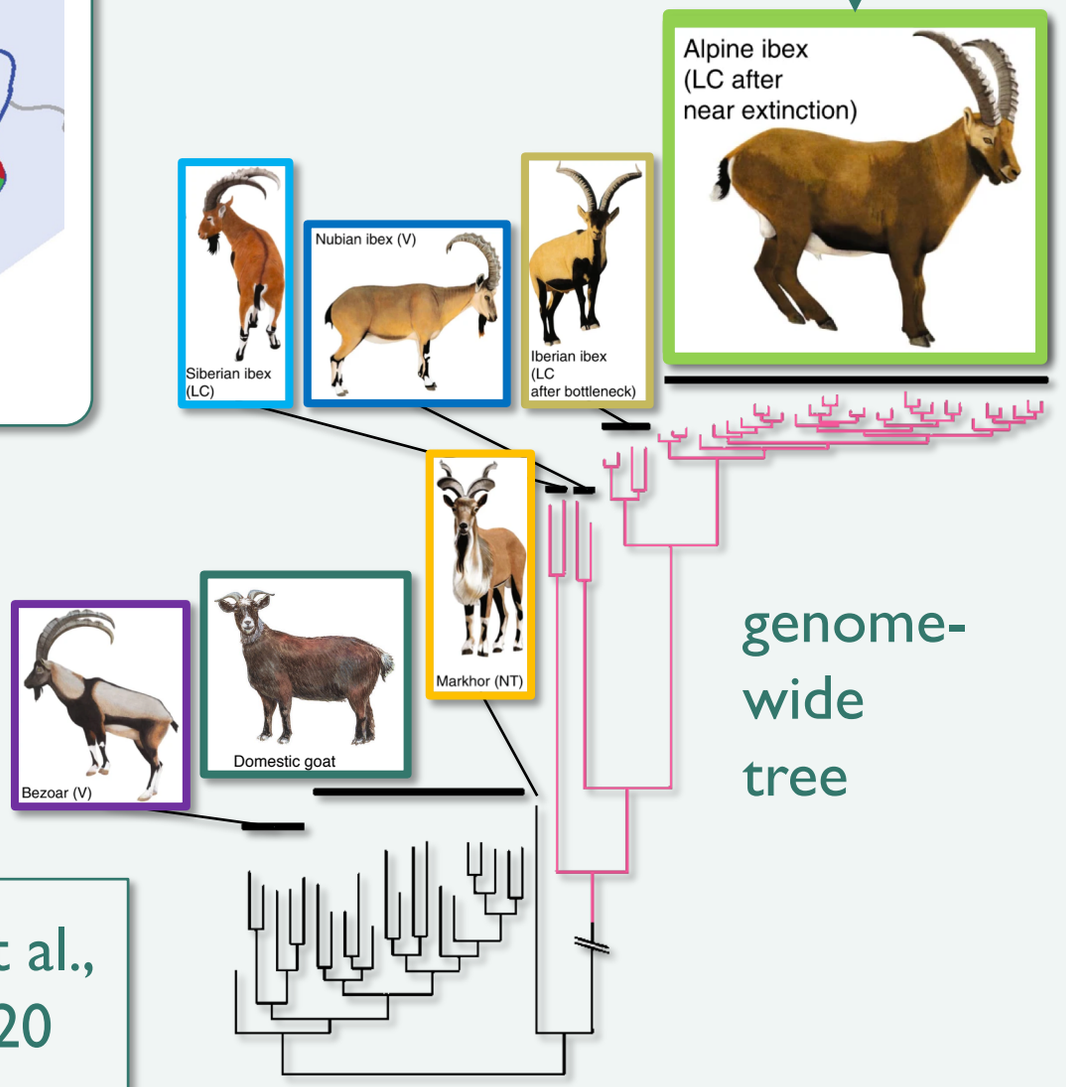


Only One Locus With Diversity in Alpine Ibex: MHC



ibex MHC allele

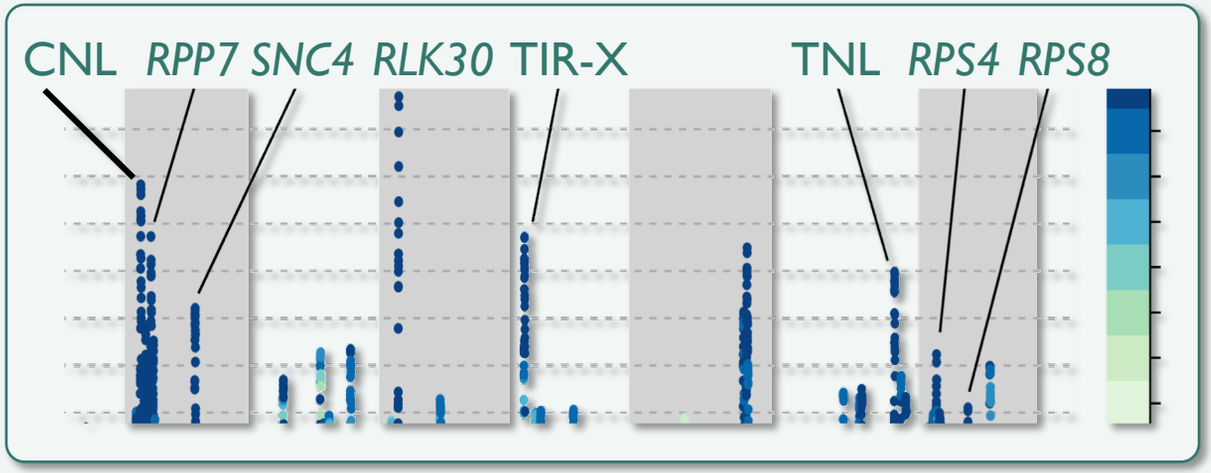
goat MHC allele

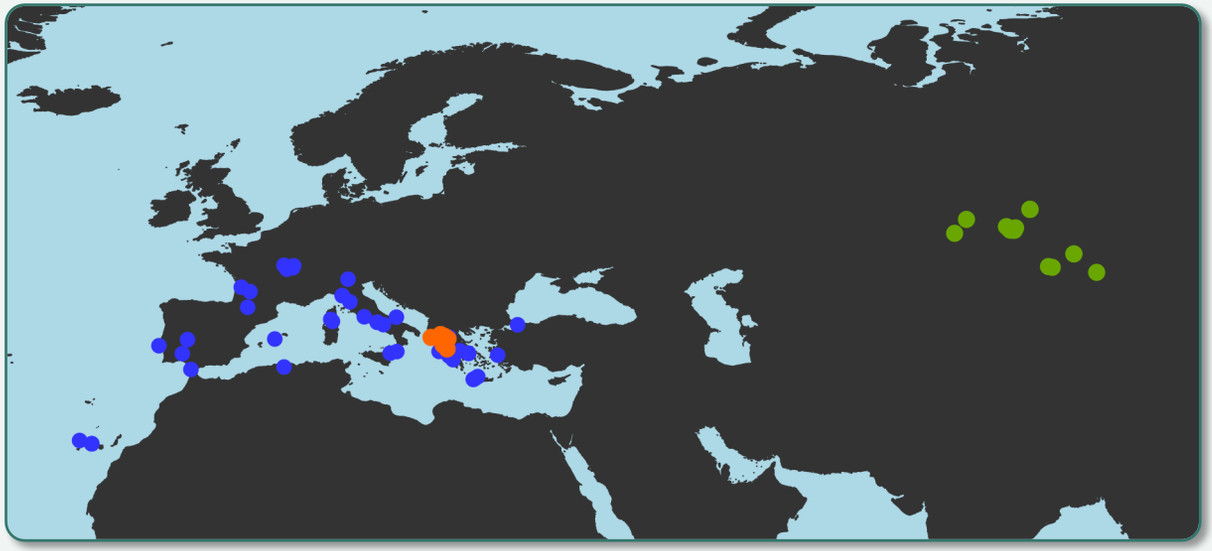


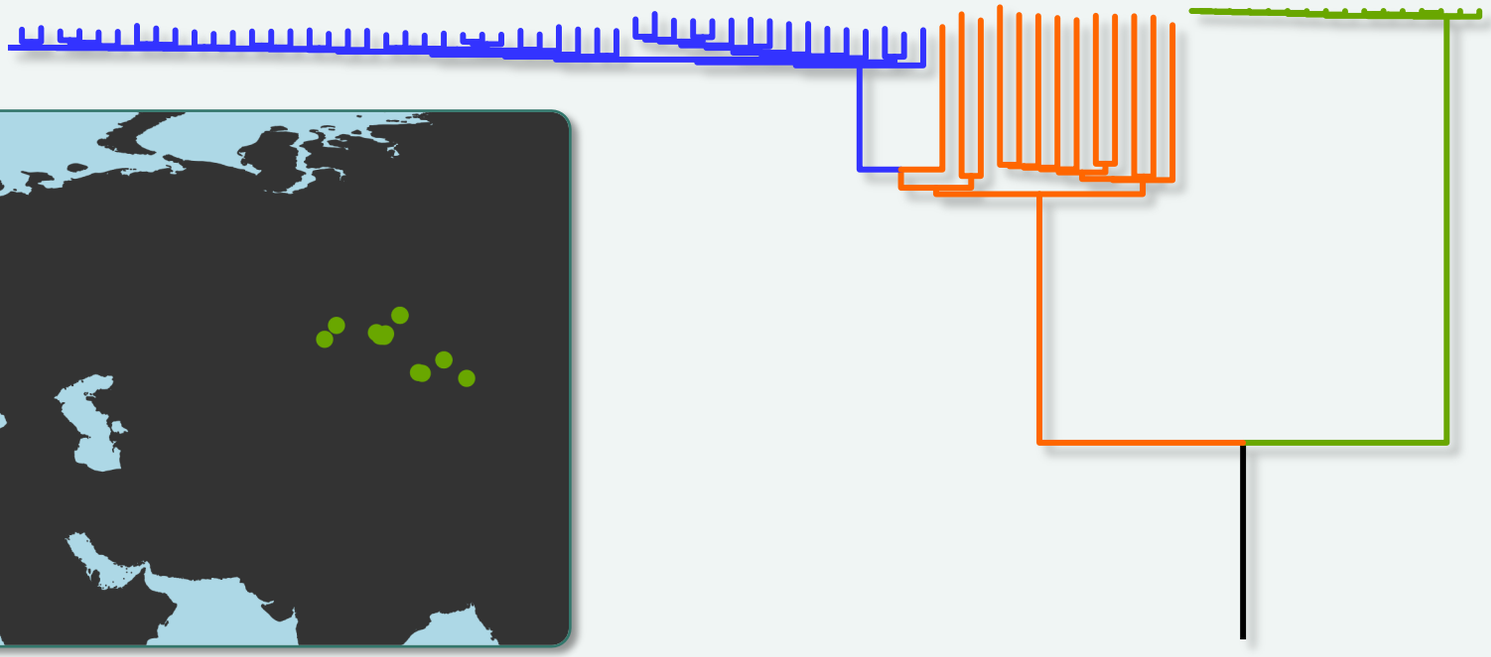
genome-wide tree

Grossen et al., 2014 & 2020

But Why The Same Loci and Often Same Alleles?



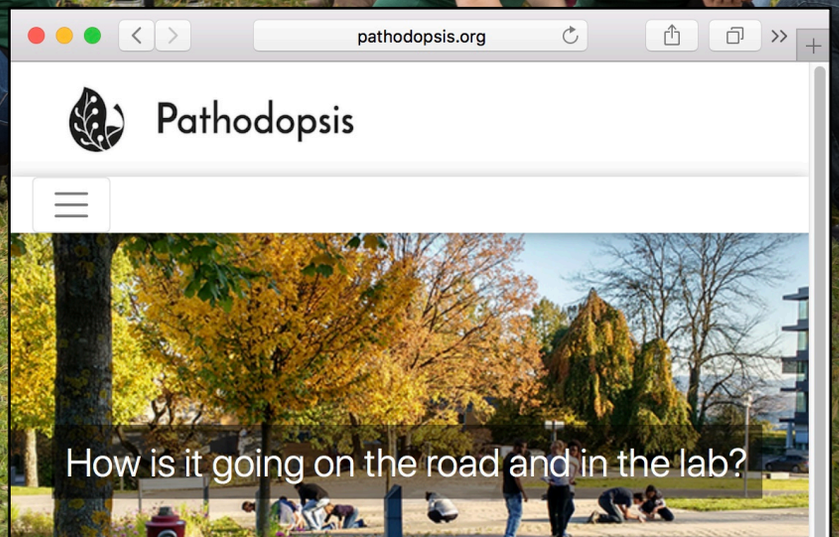




What drives immune system diversification in the wild?

Project Pathodopsis

Patho(gens on Arabi)*dopsis*

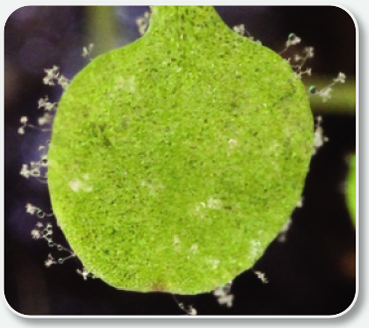


Flor's Gene-for-Gene Model: Interspecific Epistasis

Rebecca Schwab

host	pathogen: Avr^+	pathogen: Avr^-
R^+	defense	disease
R^-	disease	disease

defense



disease

Gautam Shirsekar

Where are the Resistance genes of the host?
Where are the effector (*Avr*) genes of the pathogen?