

Diallel analysis reveals *Mx1*-dependent & *Mx1*-independent effects driving the severity of response to influenza

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Advisors: Will Valdar & Mark Heise

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Flu Diallel GitHub Repository: <http://bit.ly/fluDiallel>

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CTC 2017 Organizers

Virus Disease Risk

- Virus outbreaks pose a serious public health challenge.

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- Infection response at first exposure is determined by the:
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- We use influenza A virus (IAV) infections in mice to model genetic effects on host-pathogen interactions.

Questions of Interest

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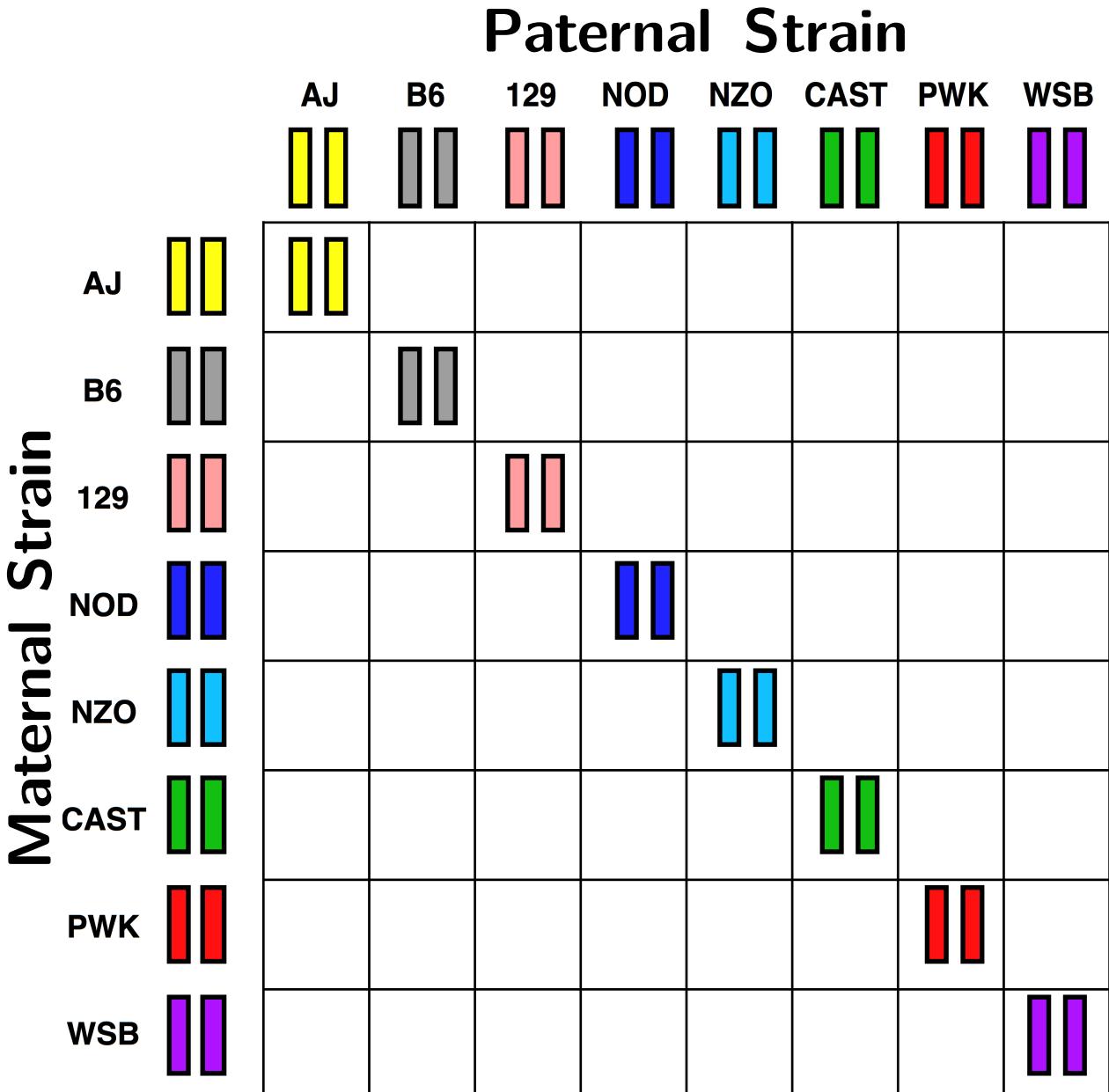
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We can estimate additive & non-additive effects of the host on IAV pathogenesis in a **diallel cross**.

A Diallel Cross



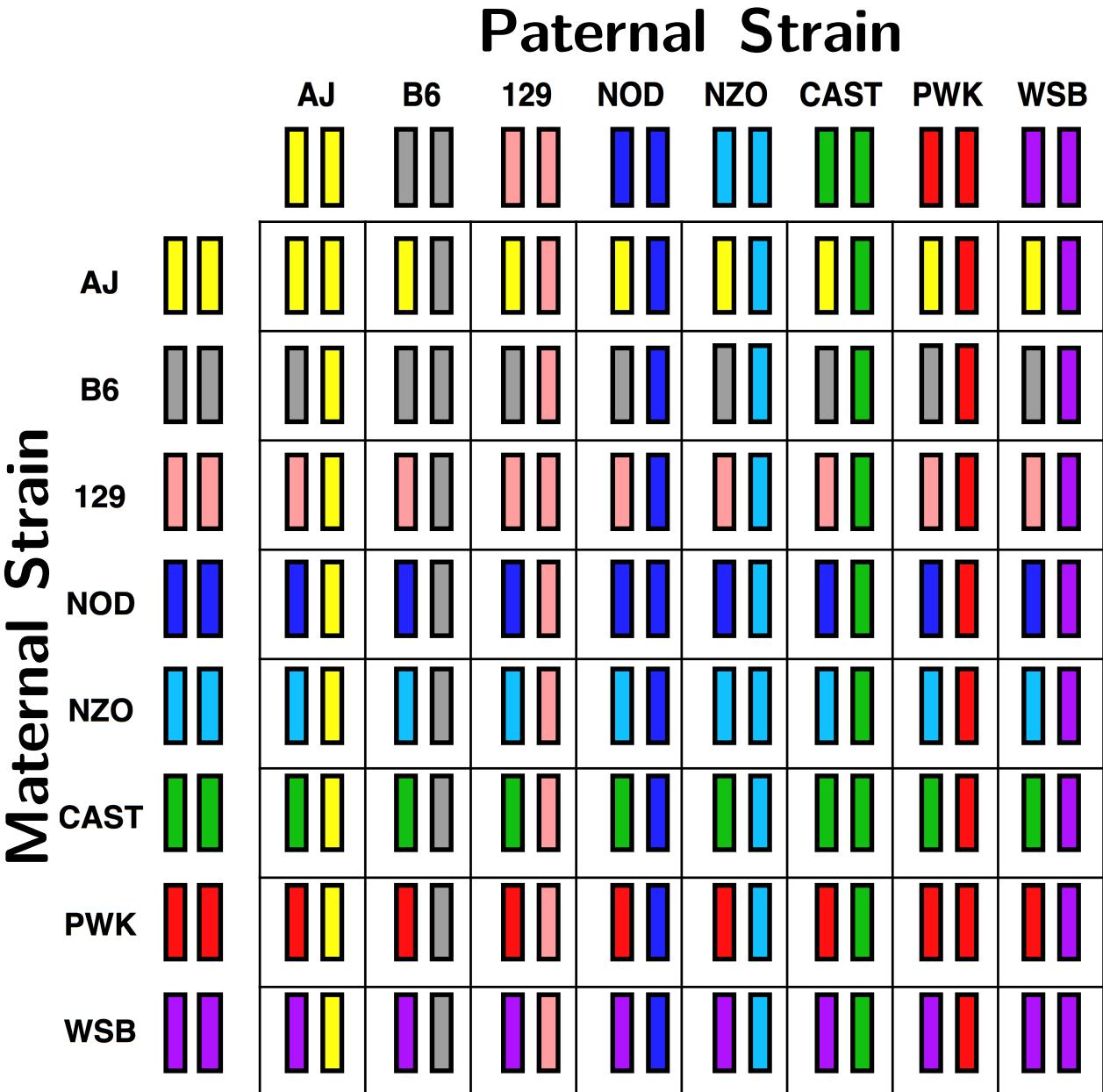
Eight Distinct Inbred Lines
(<http://csbio.unc.edu/CCstatus>)



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Modeling Host Genetic Effects in the Diallel

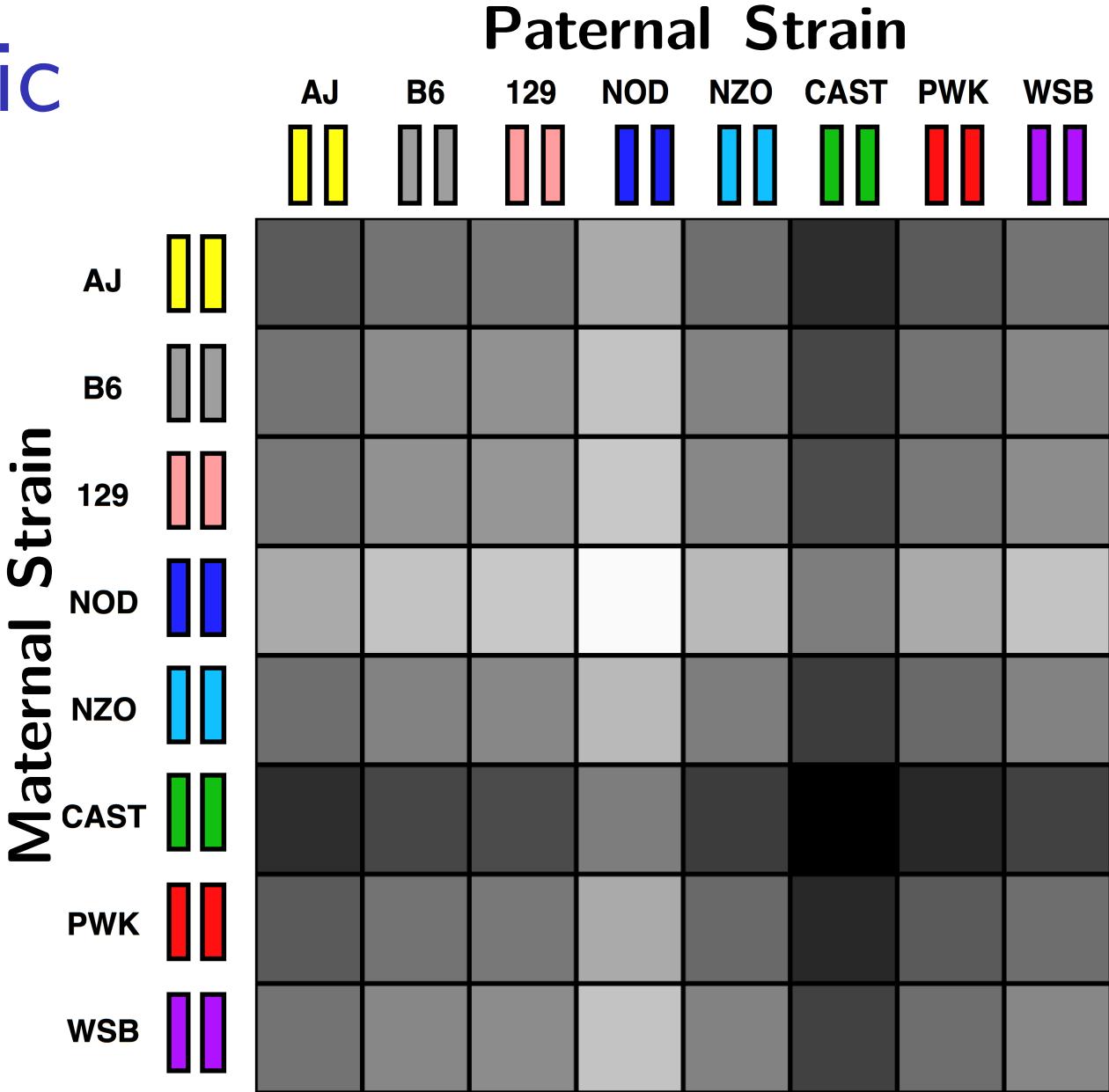
additive

maternal

inbred

epistatic (symmetric)

epistatic (asymmetric)



Modeling Host Genetic Effects in the Diallel

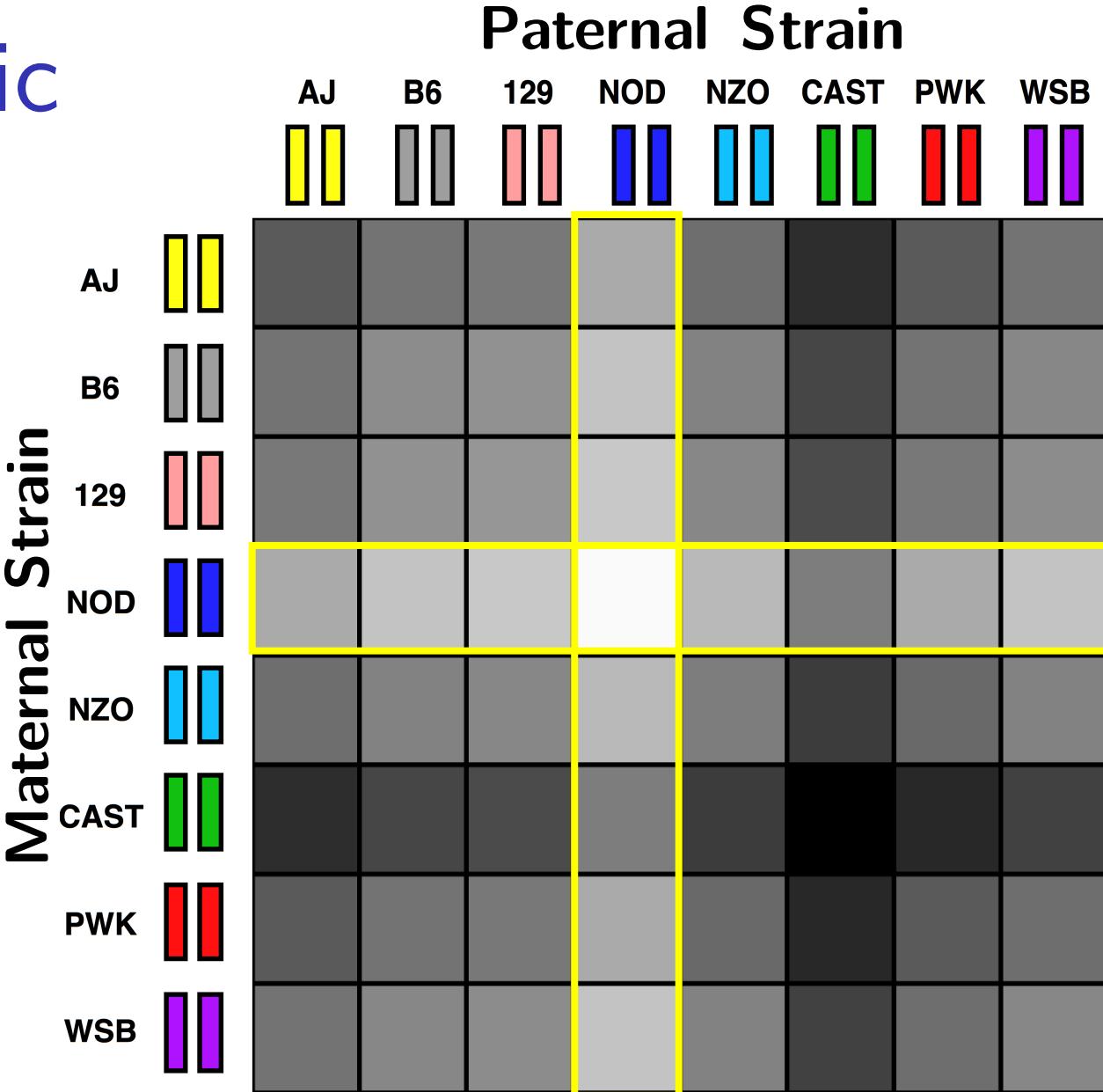
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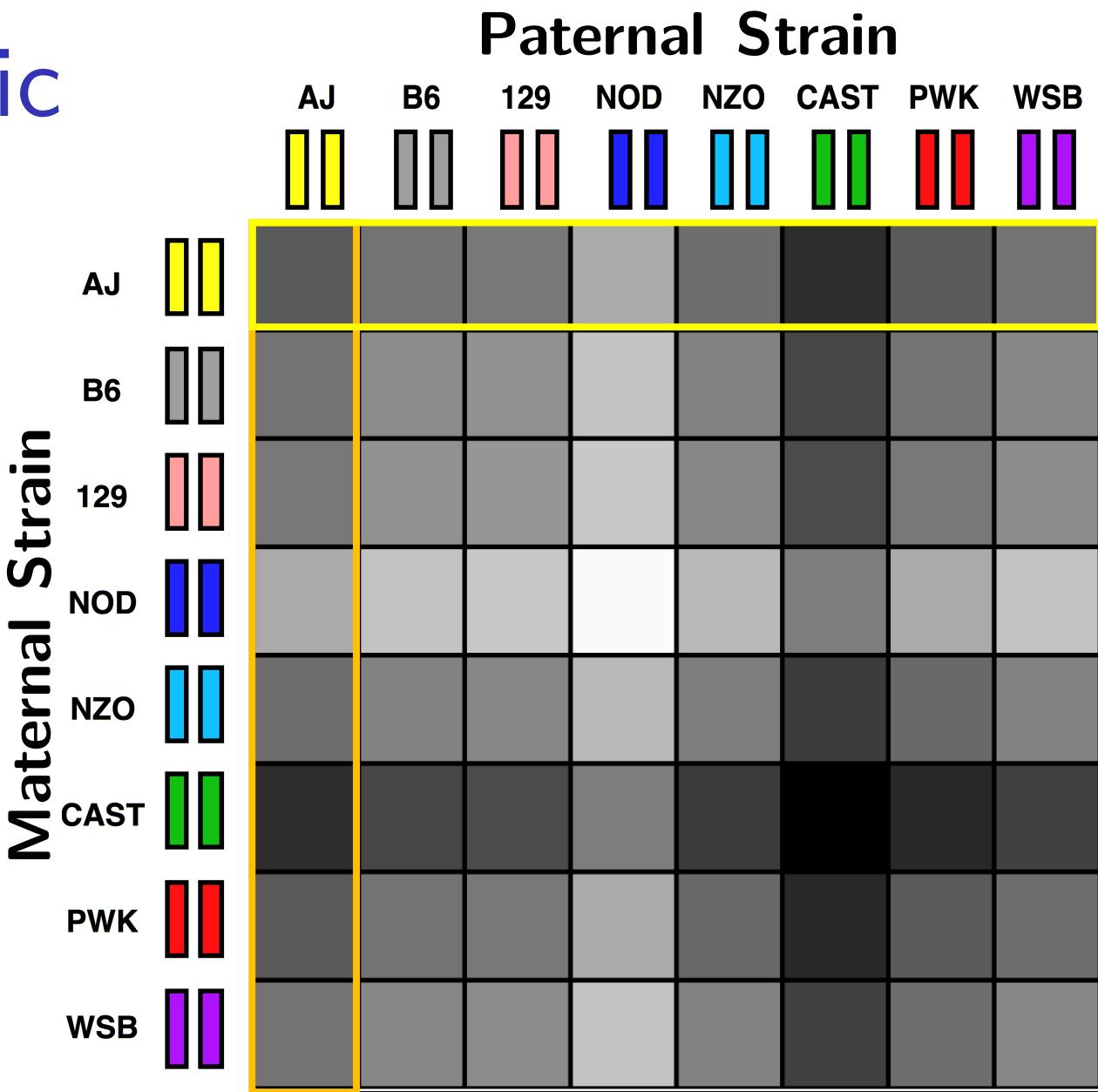
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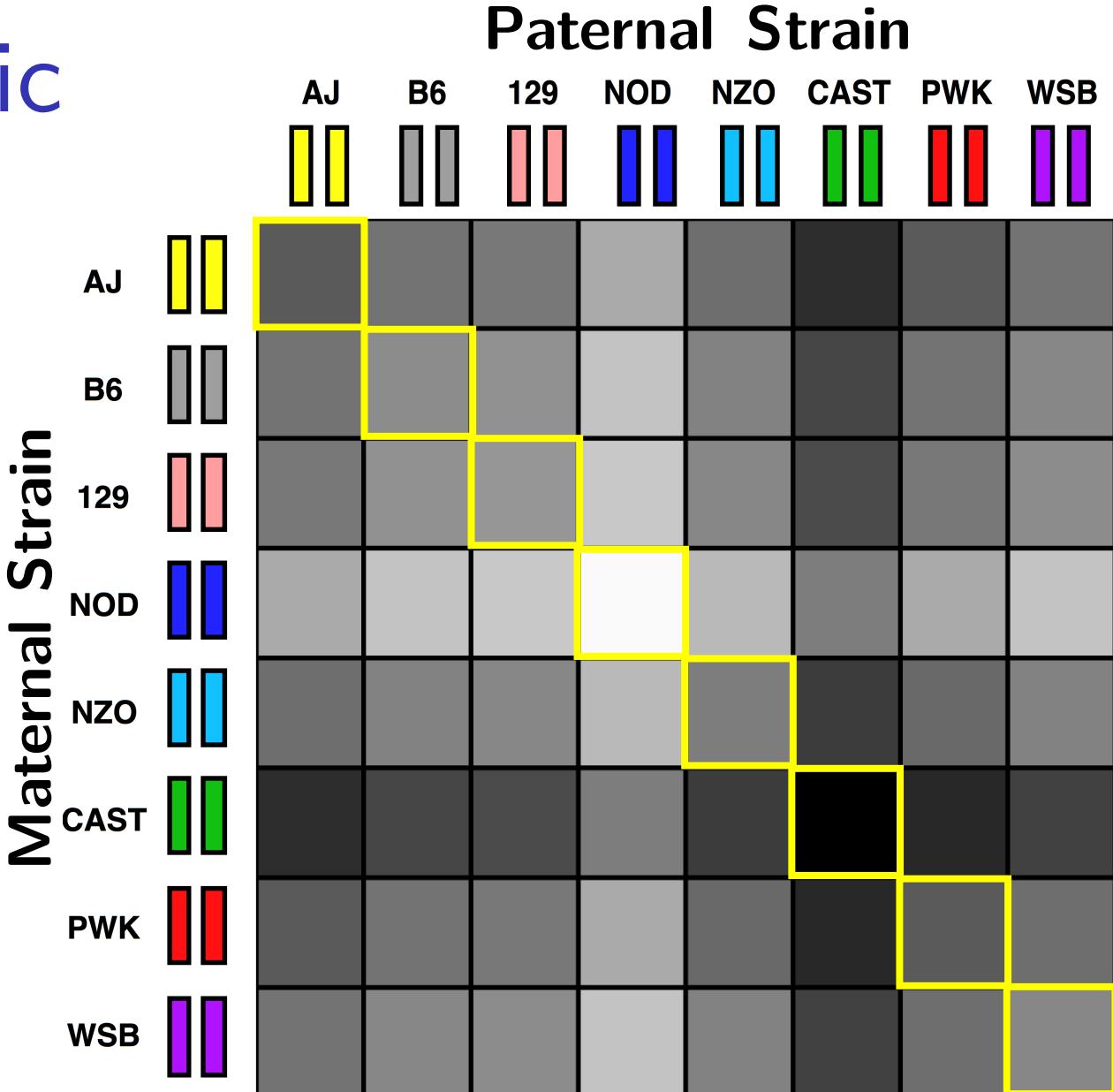
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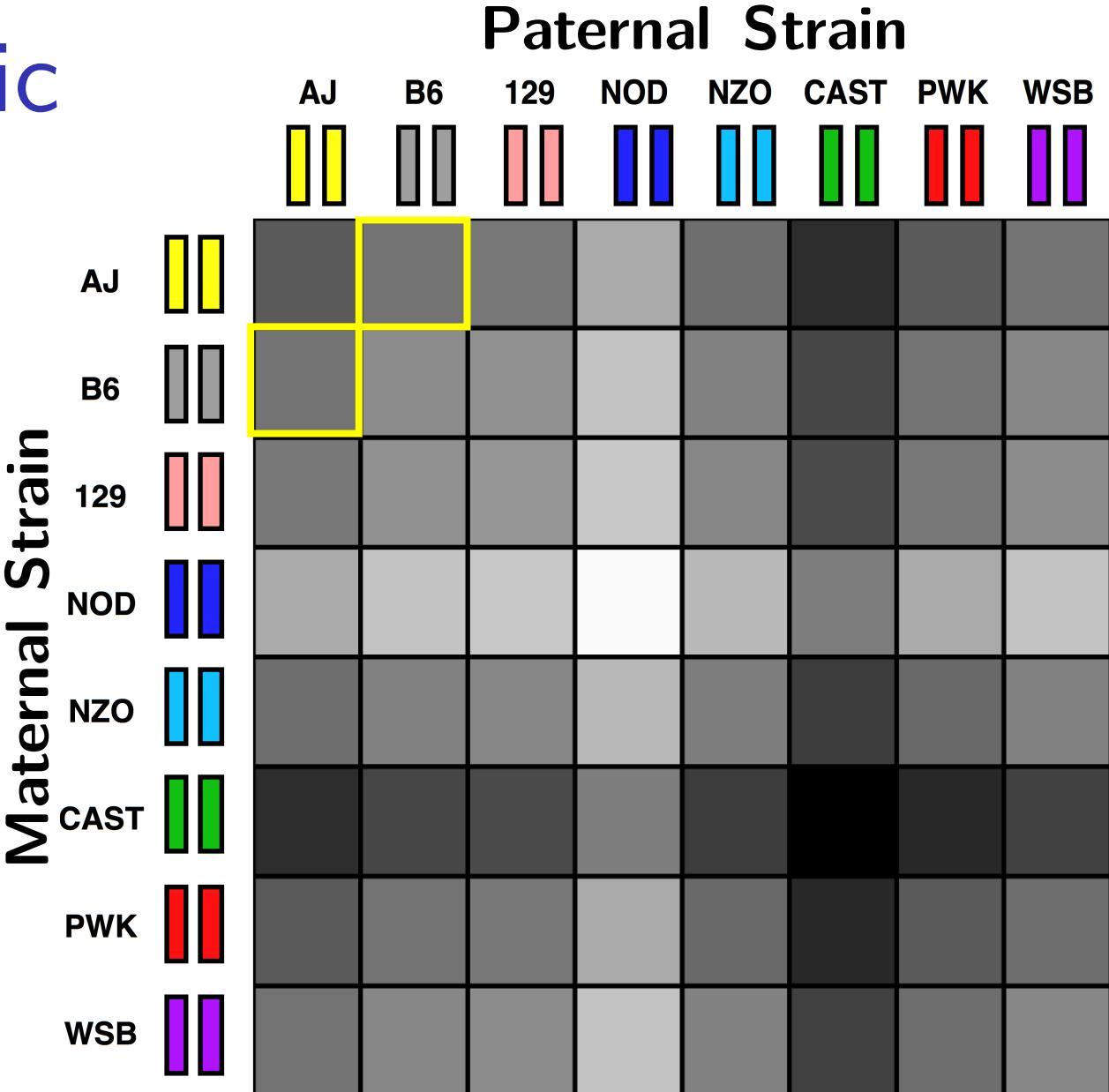
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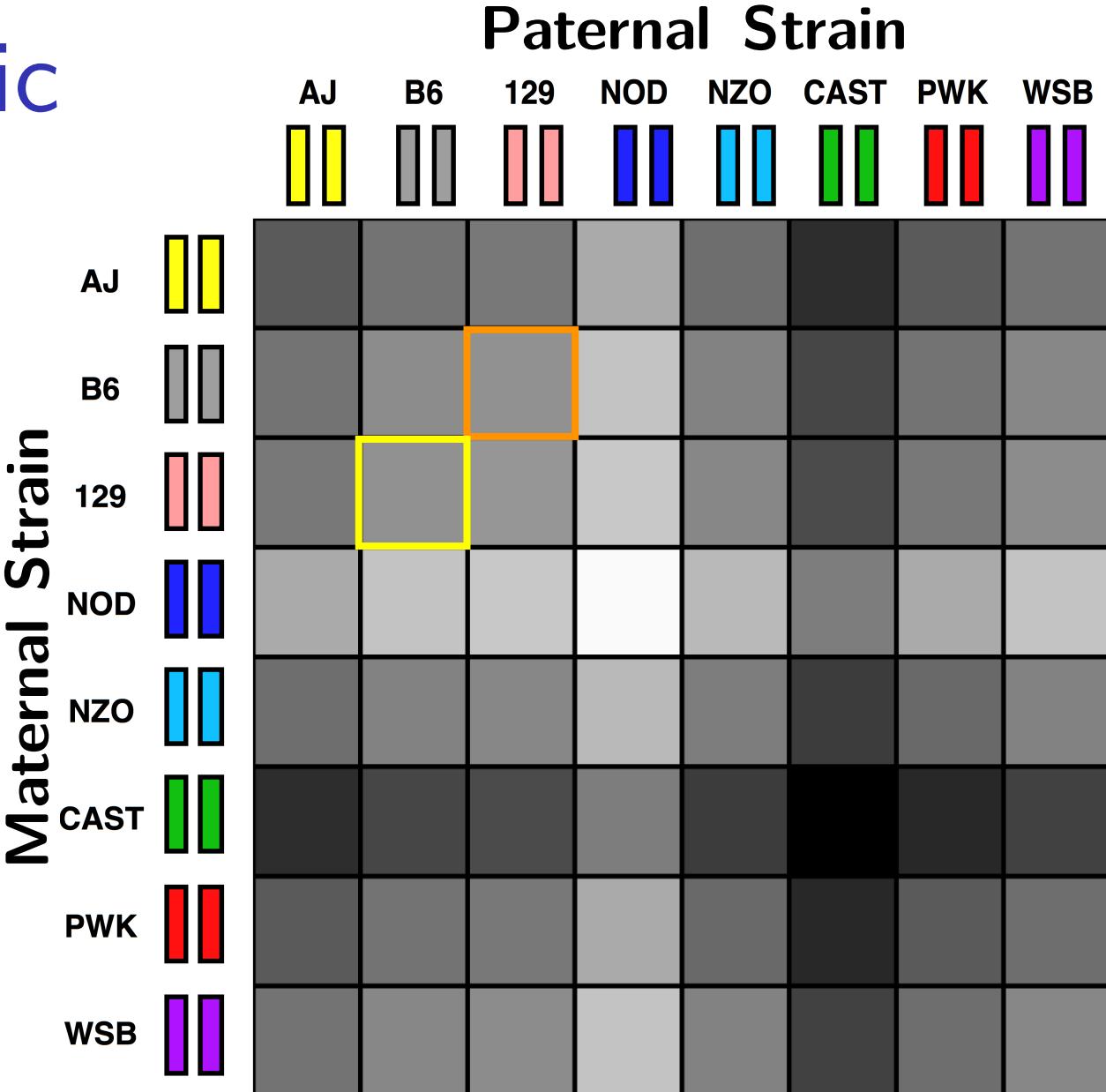
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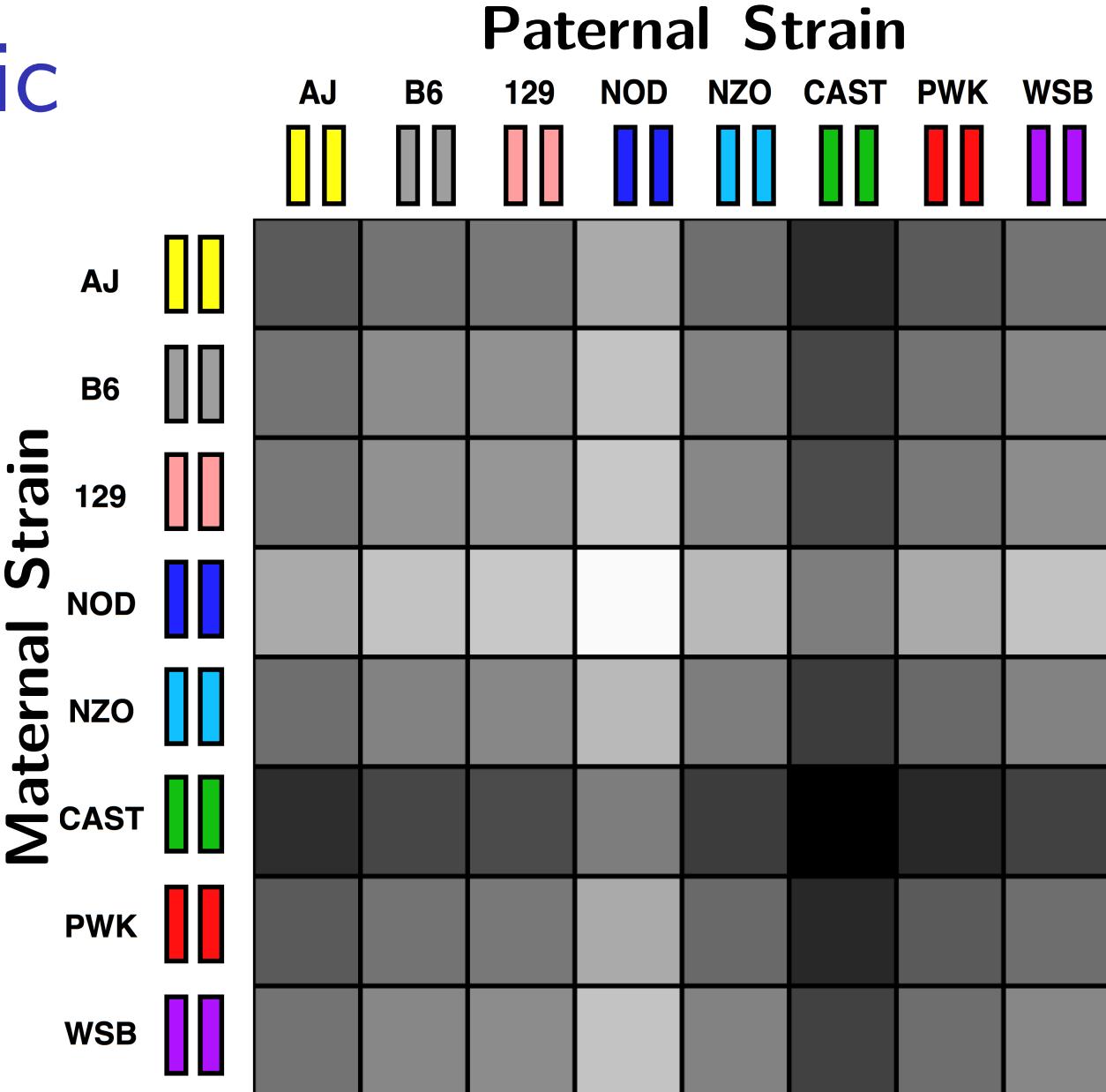
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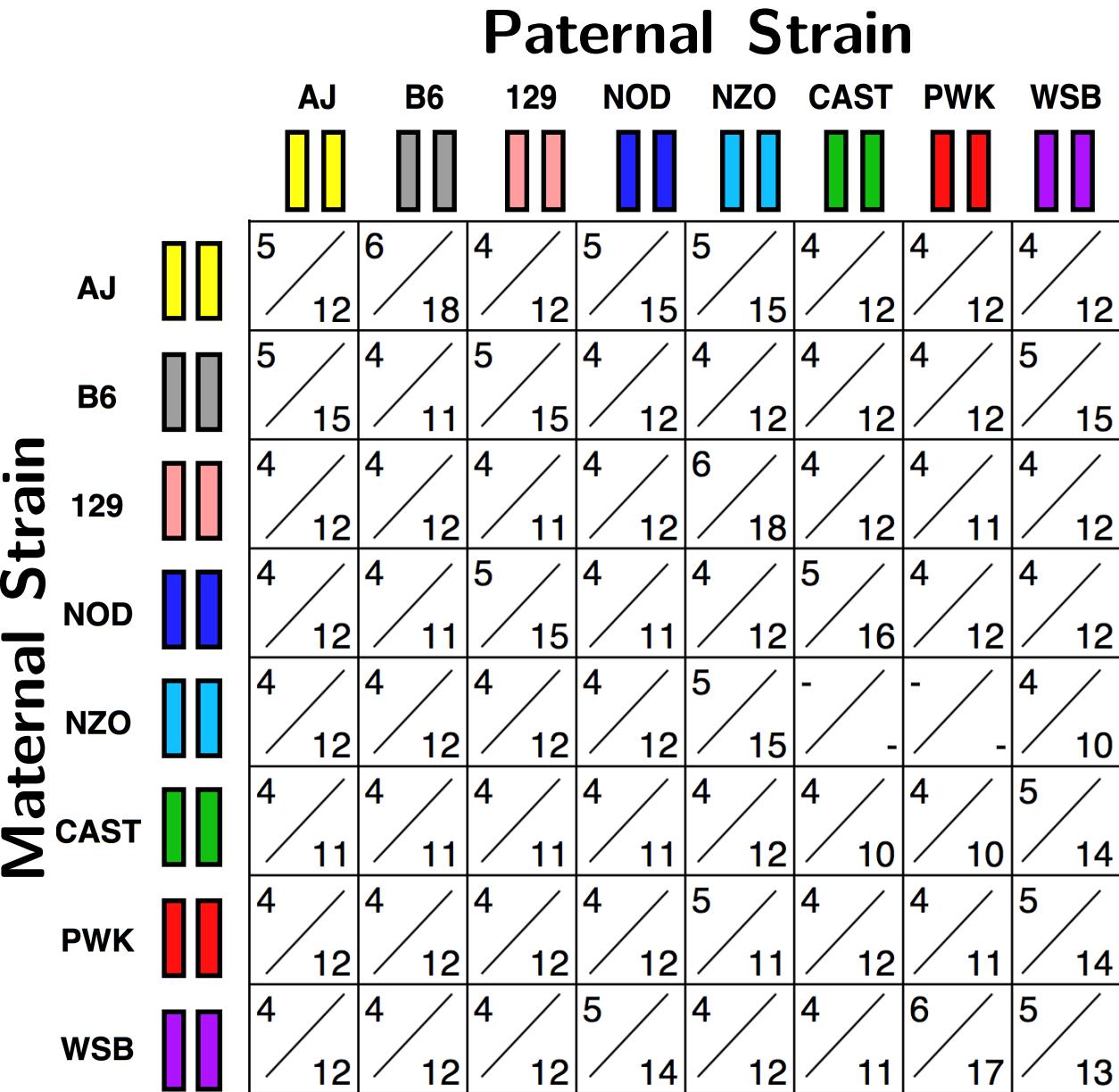
Modeling Host Genetic Effects in the Diallel

$$\begin{aligned}
 y_i &= \underbrace{\mu}_{\text{phenotype overall mean}} + \\
 &\quad \underbrace{a_j + a_k}_{\text{additive}} + \underbrace{m_j - m_k}_{\text{maternal}} + \underbrace{I_{\{j=k\}} (\beta_{\text{inbred}} + b_j)}_{\text{inbreeding}} + \\
 &\quad \underbrace{I_{\{j \neq k\}} (v_{jk} + S_{\{j < k\}} \cdot w_{jk})}_{\text{epistatic}} + S_{\text{sex}} \cdot \left(\sum_{s=1}^S \phi_i^{(s)} \right) + \\
 &\quad \varepsilon_i \quad \text{residual}
 \end{aligned}$$

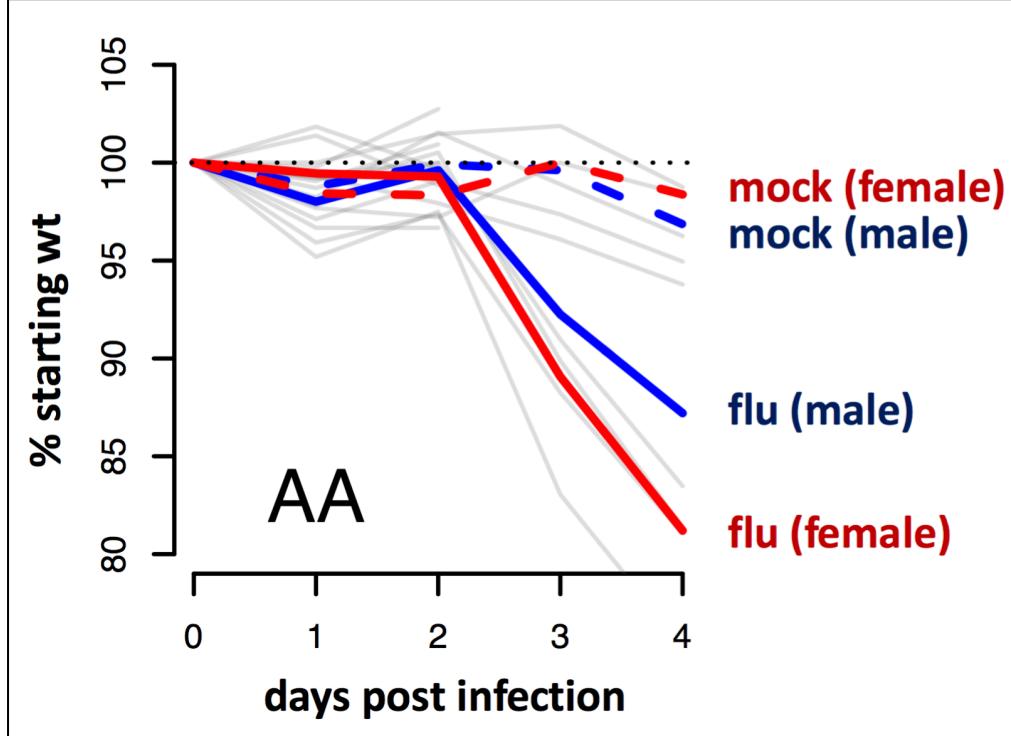
BayesDiallel Model
Adapted from Lenarcic et al., 2012, *Genetics*



Host Genetic Effects on IAV Pathology



Host Genetic Effects on IAV Pathology



$$D4pct_i^{\text{flu}} = 100 \times D4_i^{\text{flu}} / D0_i$$

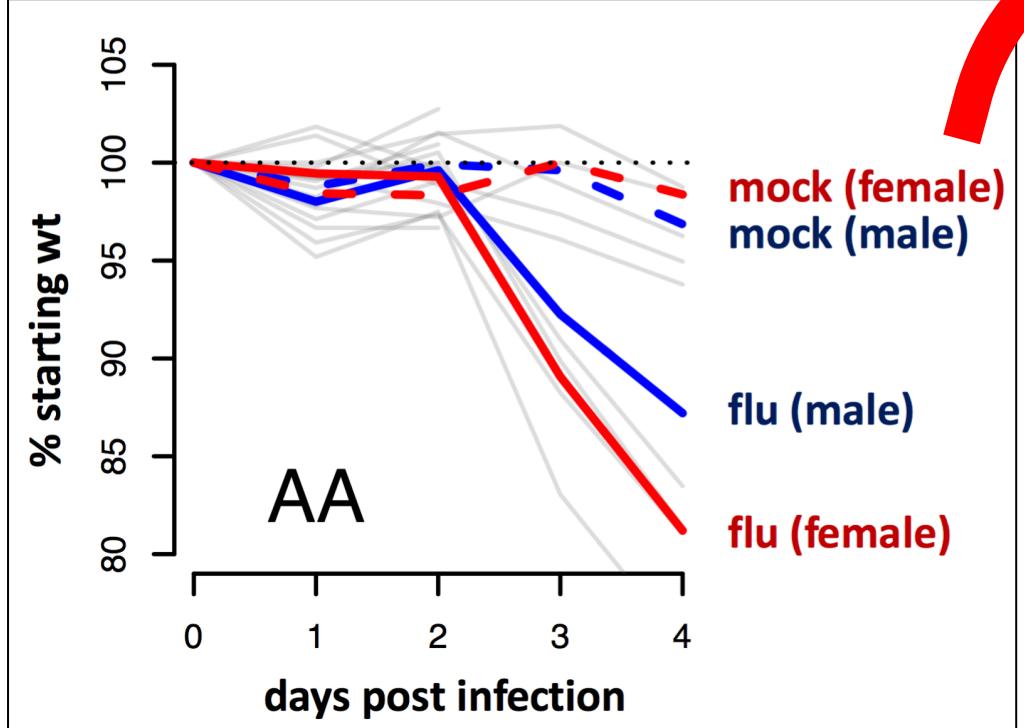
$$D4\delta\alpha_q = \frac{1}{3} \sum_{f=1}^3 D4pct_{q[f]}^{\text{flu}} - D4pct_{q[4]}^{\text{mock}}$$

Paternal Strain

	AJ	B6	129	NOD	NZO	CAST	PWK	WSB
AJ	5 12	6 18	4 12	5 15	5 15	4 12	4 12	4 12
B6	5 15	4 11	5 15	4 12	4 12	4 12	4 12	5 15
129	4 12	4 12	4 11	4 12	6 18	4 12	4 11	4 12
NOD	4 12	4 11	5 15	4 11	4 12	5 16	4 12	4 12
NZO	4 12	4 12	4 12	4 12	5 15	- -	- -	4 10
CAST	4 11	4 11	4 11	4 11	4 12	4 10	4 10	5 14
PWK	4 12	4 12	4 12	4 12	5 11	4 12	4 11	5 14
WSB	4 12	4 12	4 12	5 14	4 12	4 11	6 17	5 13

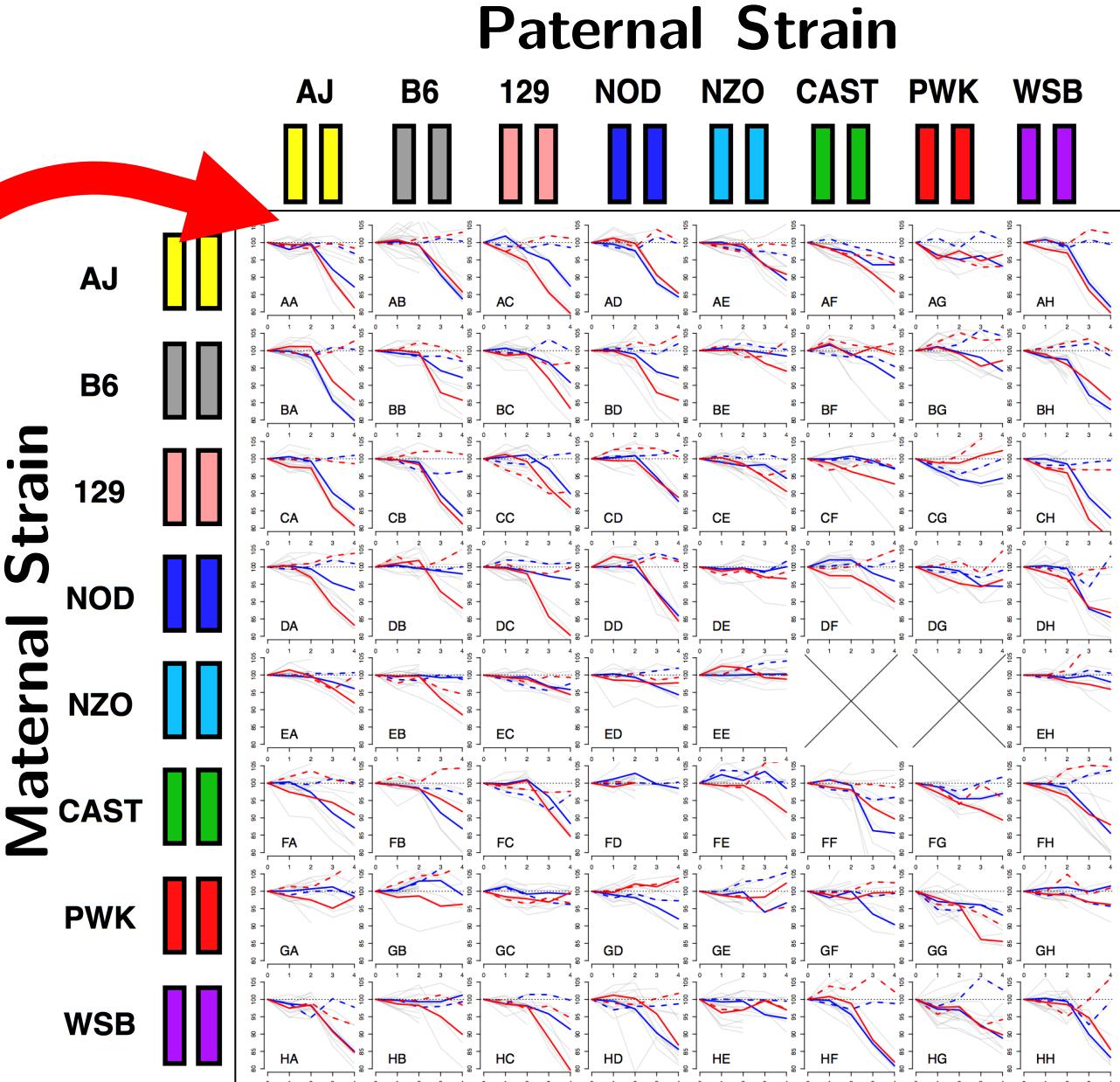
Maternal Strain

Host Genetic Effects on IAV Pathology

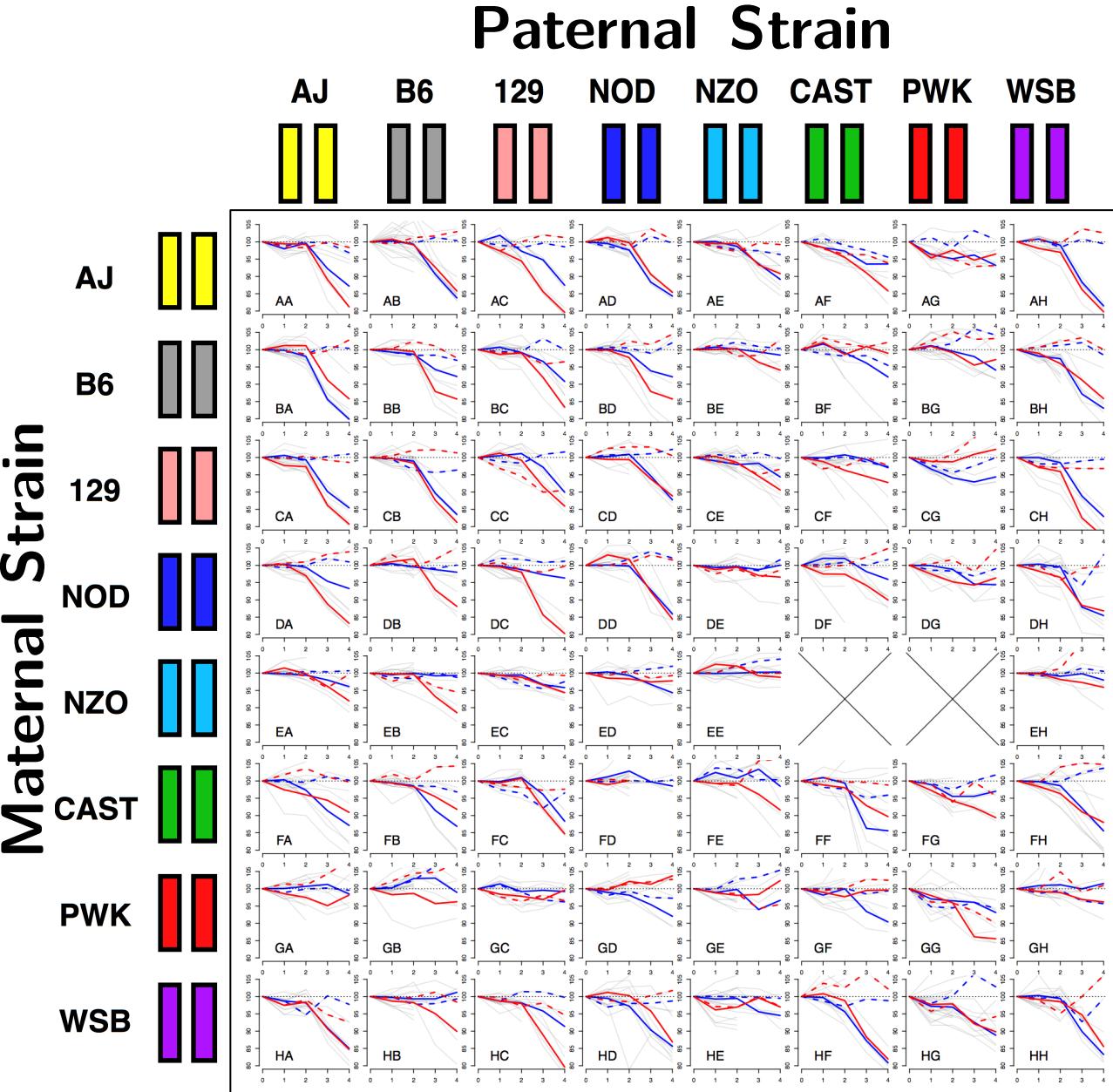
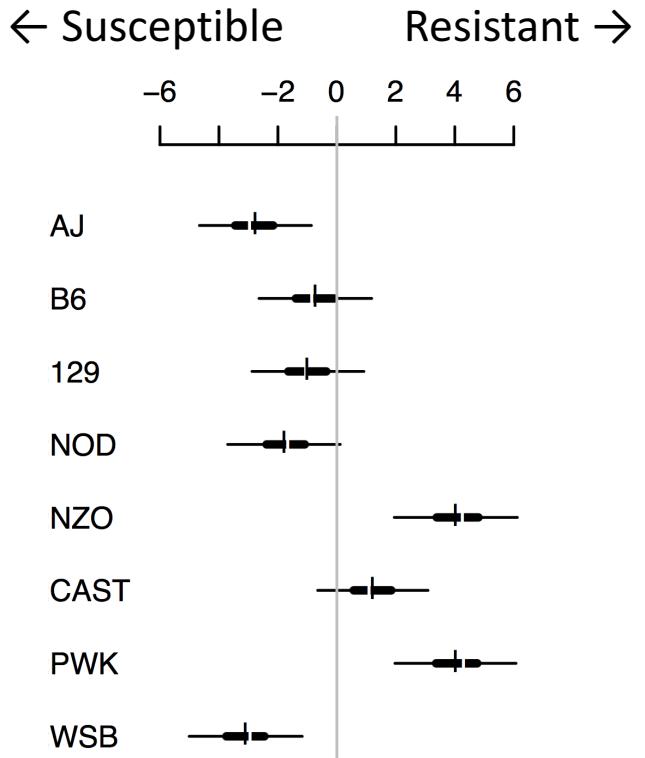


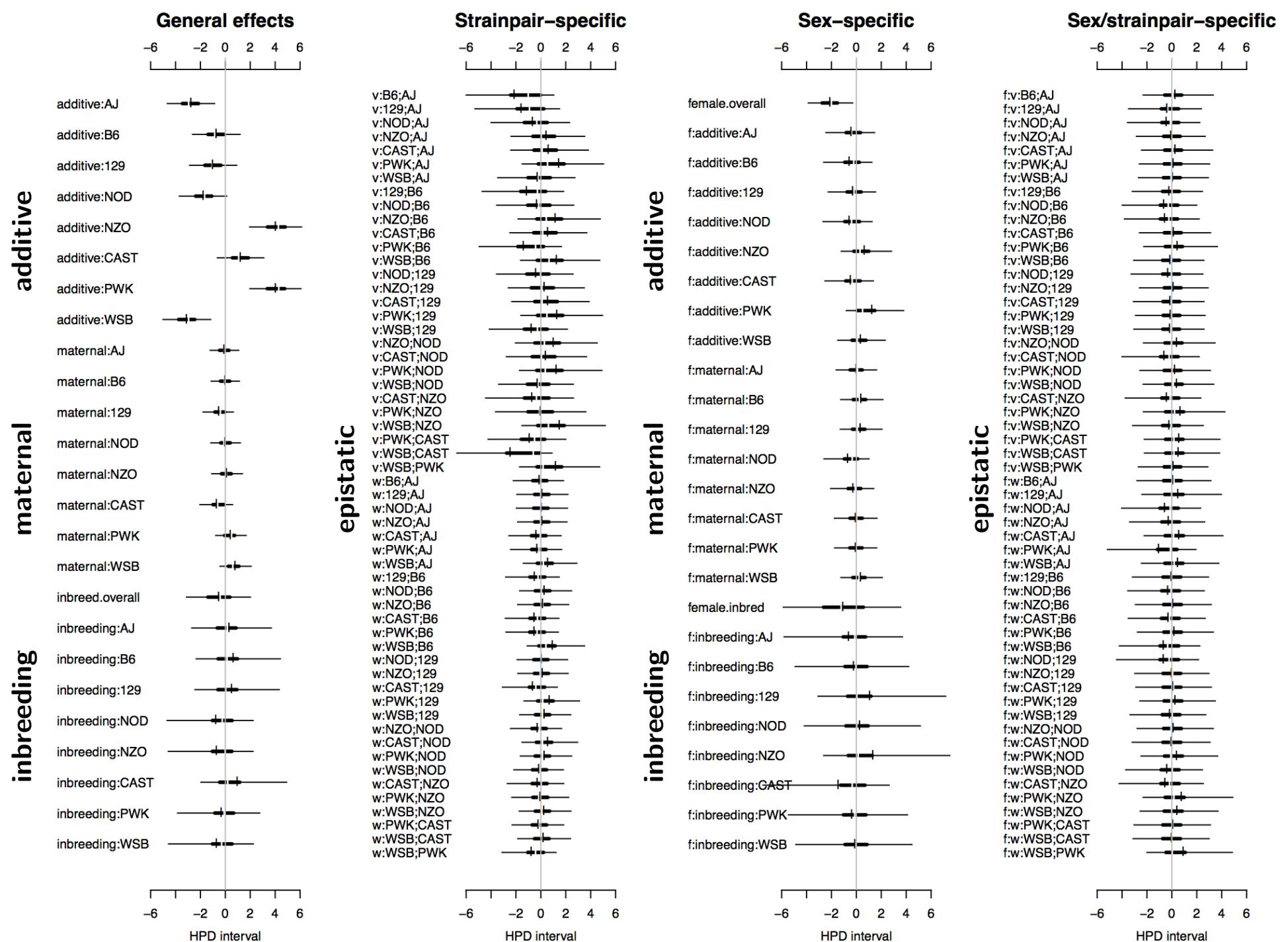
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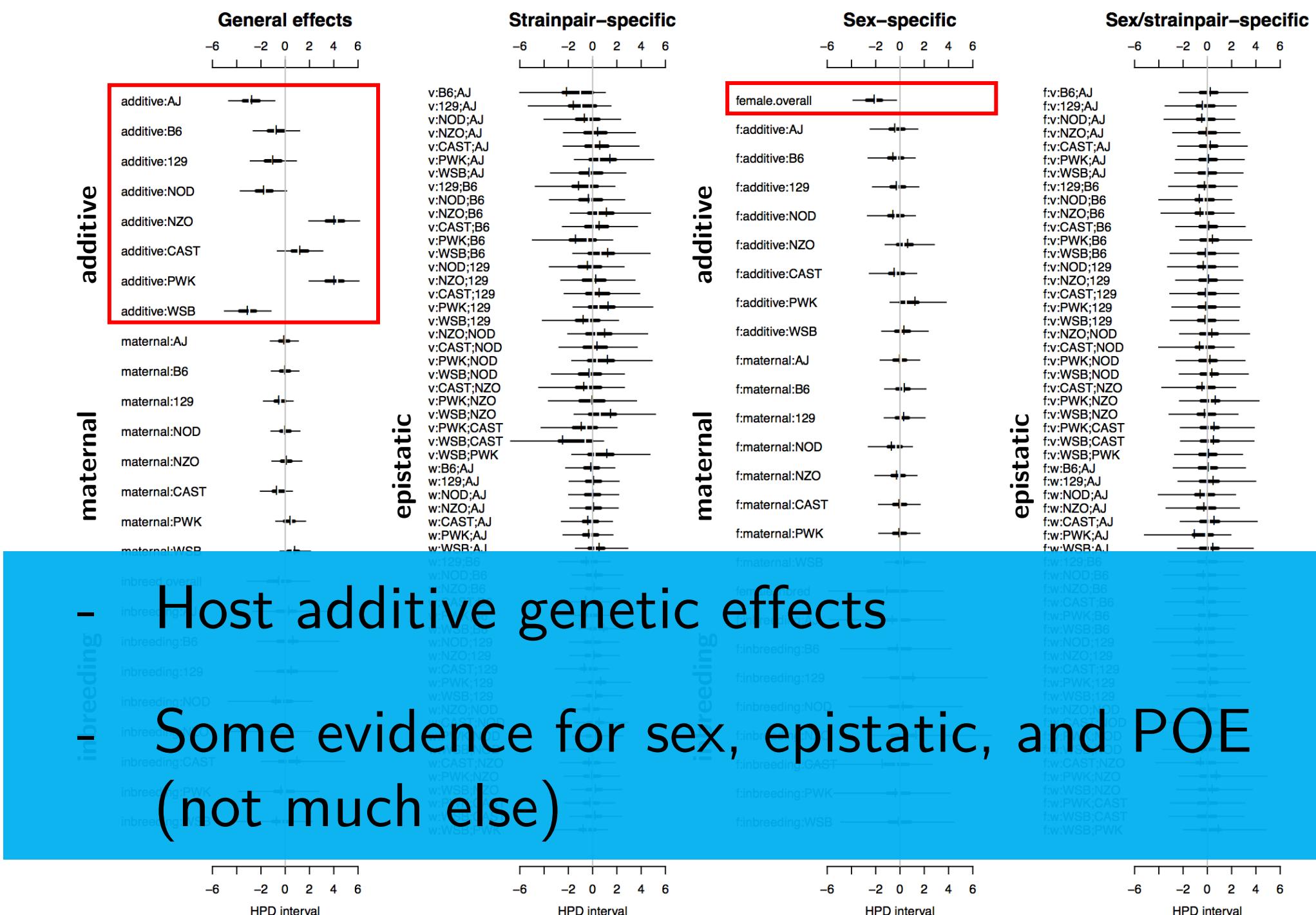
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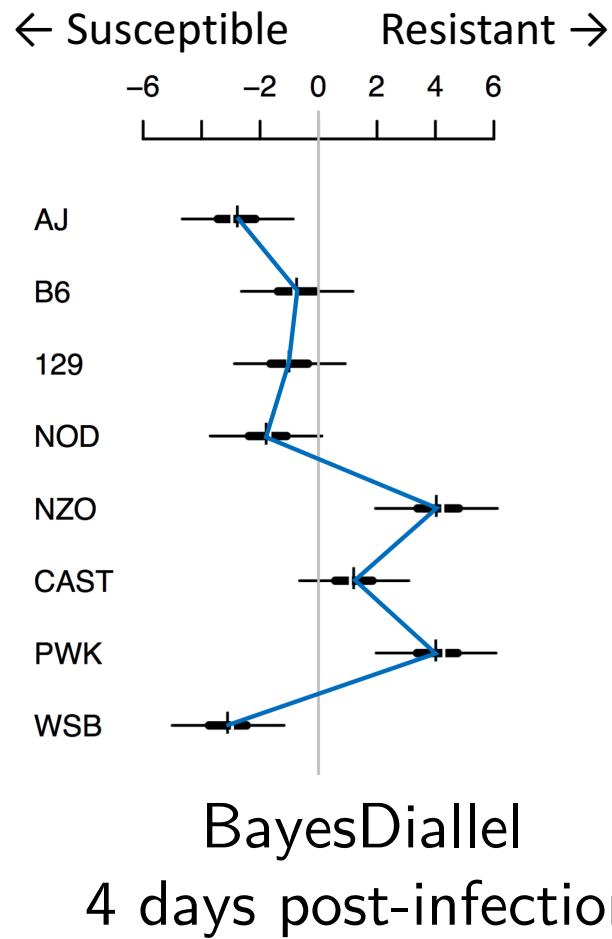






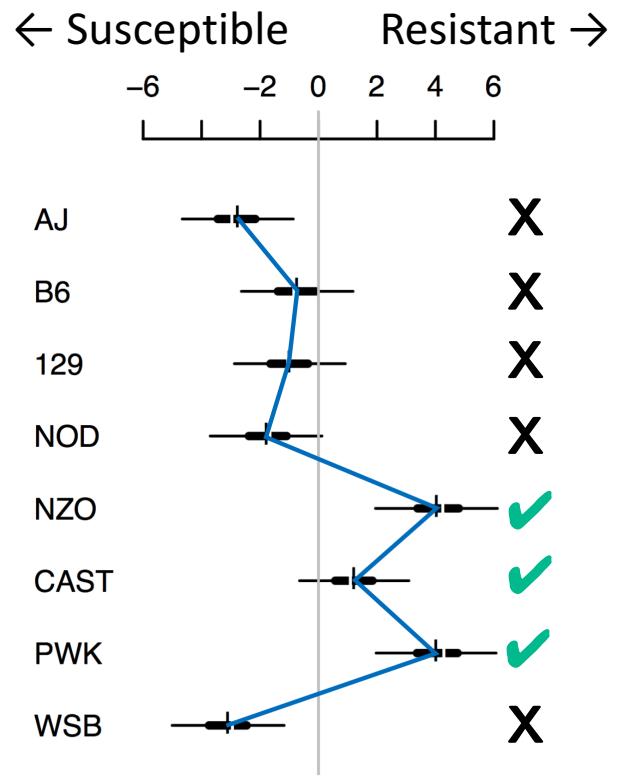
Strain-Specific Genetic Effects Driven by *Mx1* Resistance Gene

Result from Diallel



Strain-Specific Genetic Effects Driven by *Mx1* Resistance Gene

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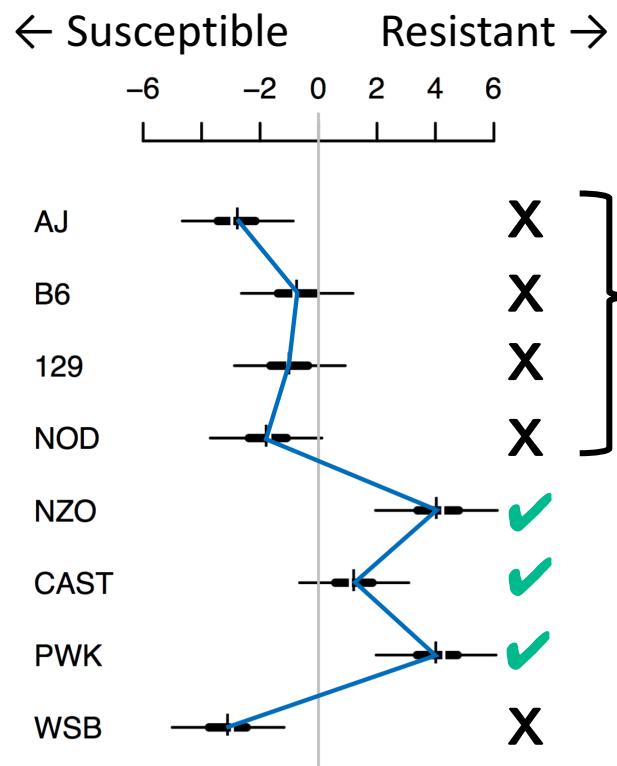


BayesDiallel

4 days post-infection

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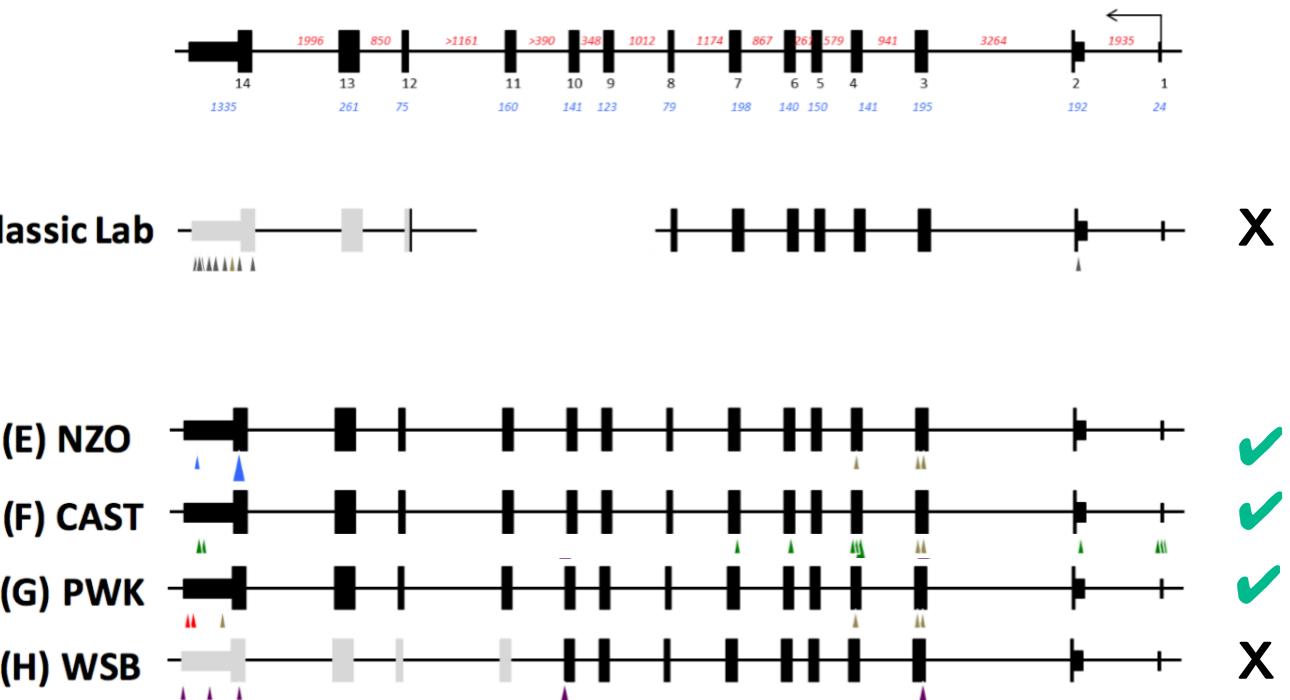
Result from Diallel



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Mx1 Gene

(Ferris et al., 2013, *PLoS Pathogens*)

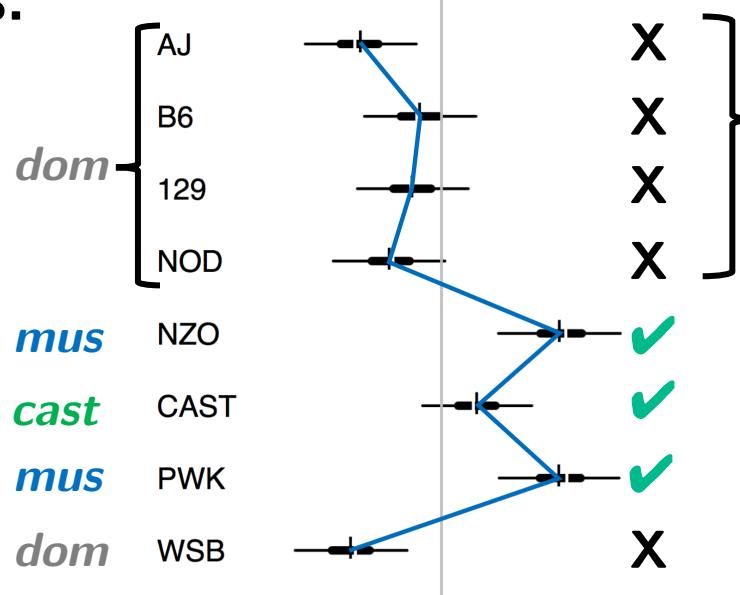


Strain-Specific Genetic Effects Driven by *Mx1* Resistance Gene

Result from Diallel

← Susceptible Resistant →

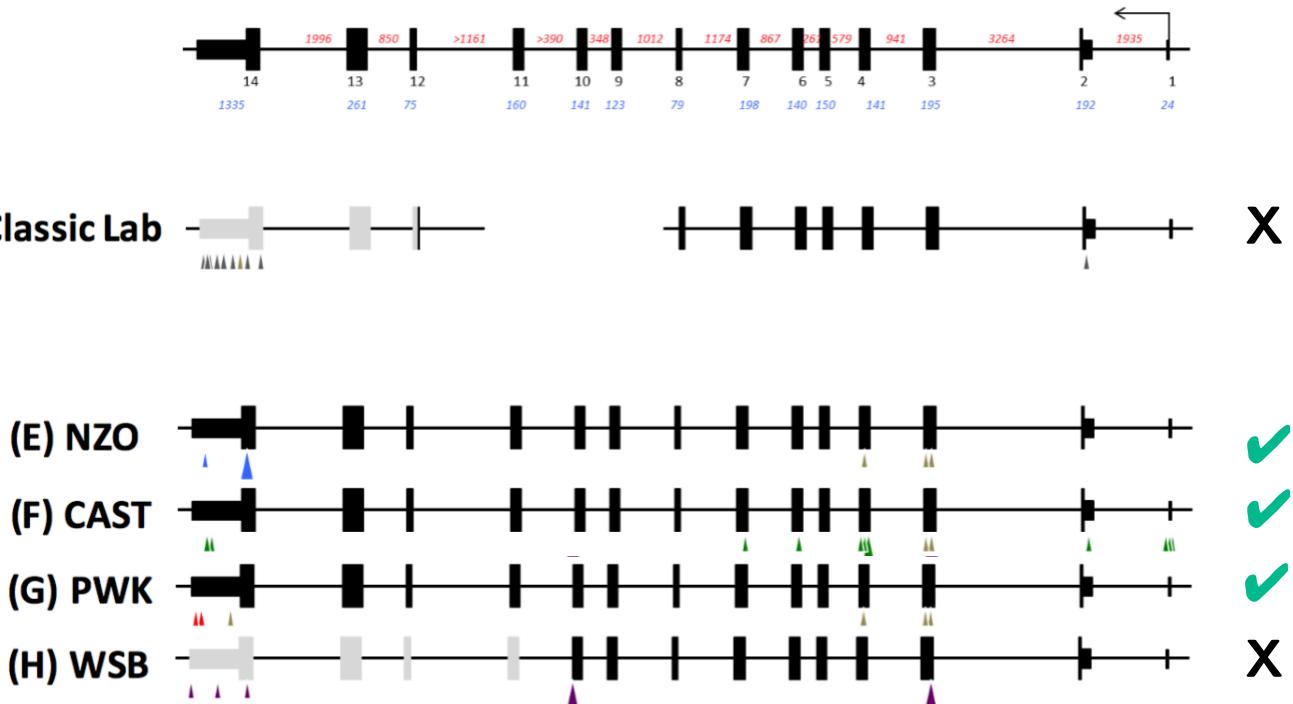
Functional
Class:



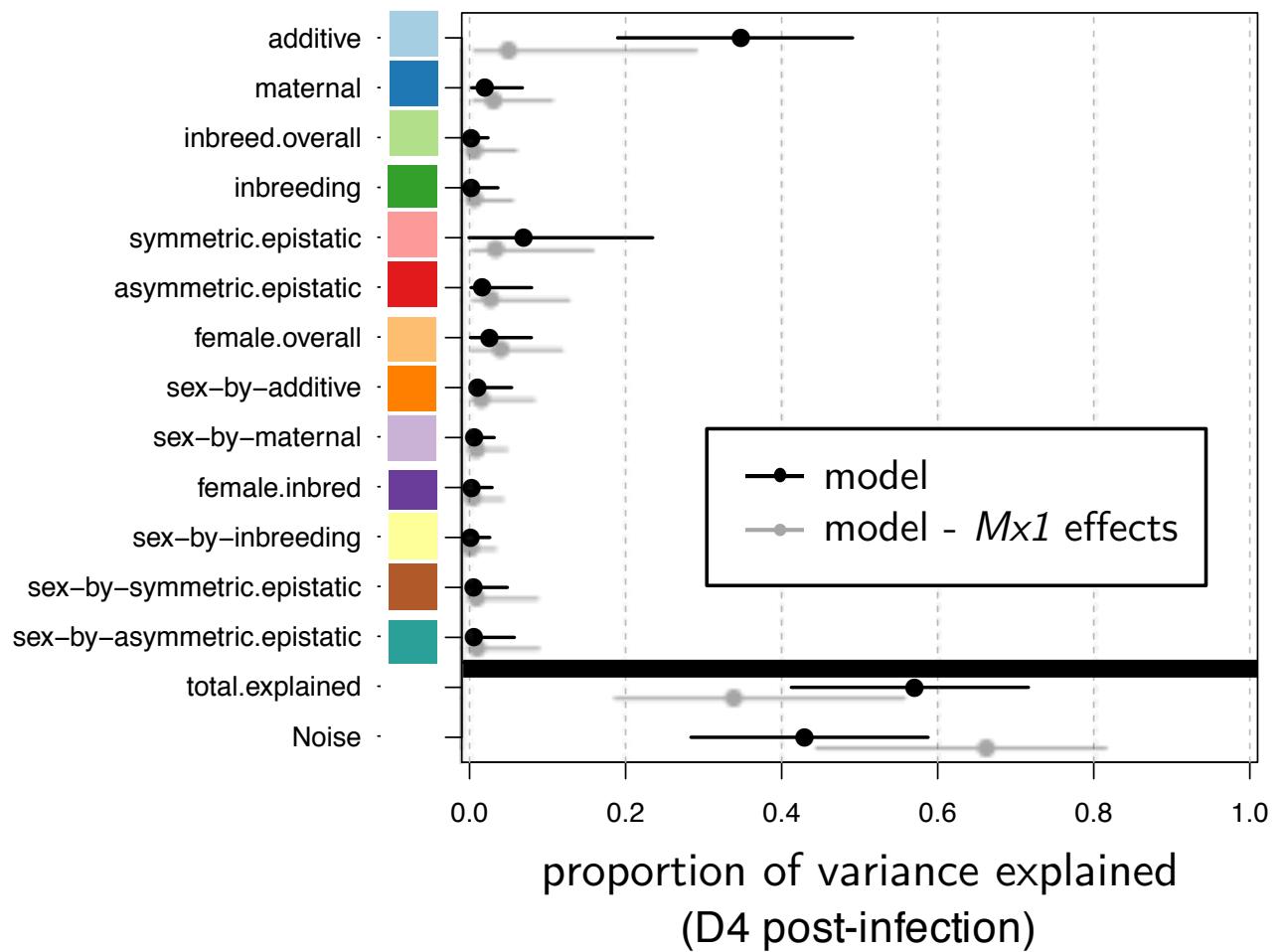
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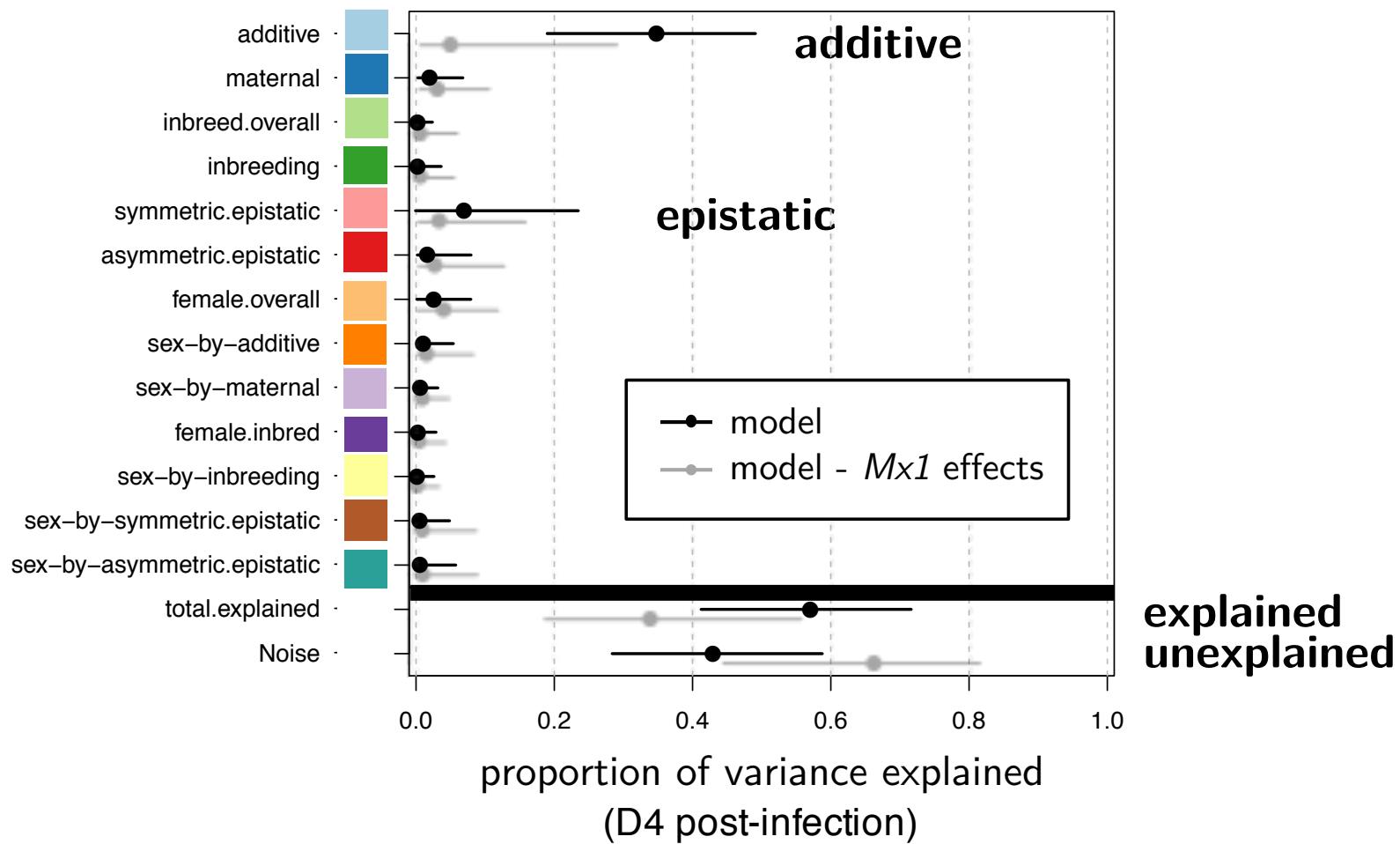
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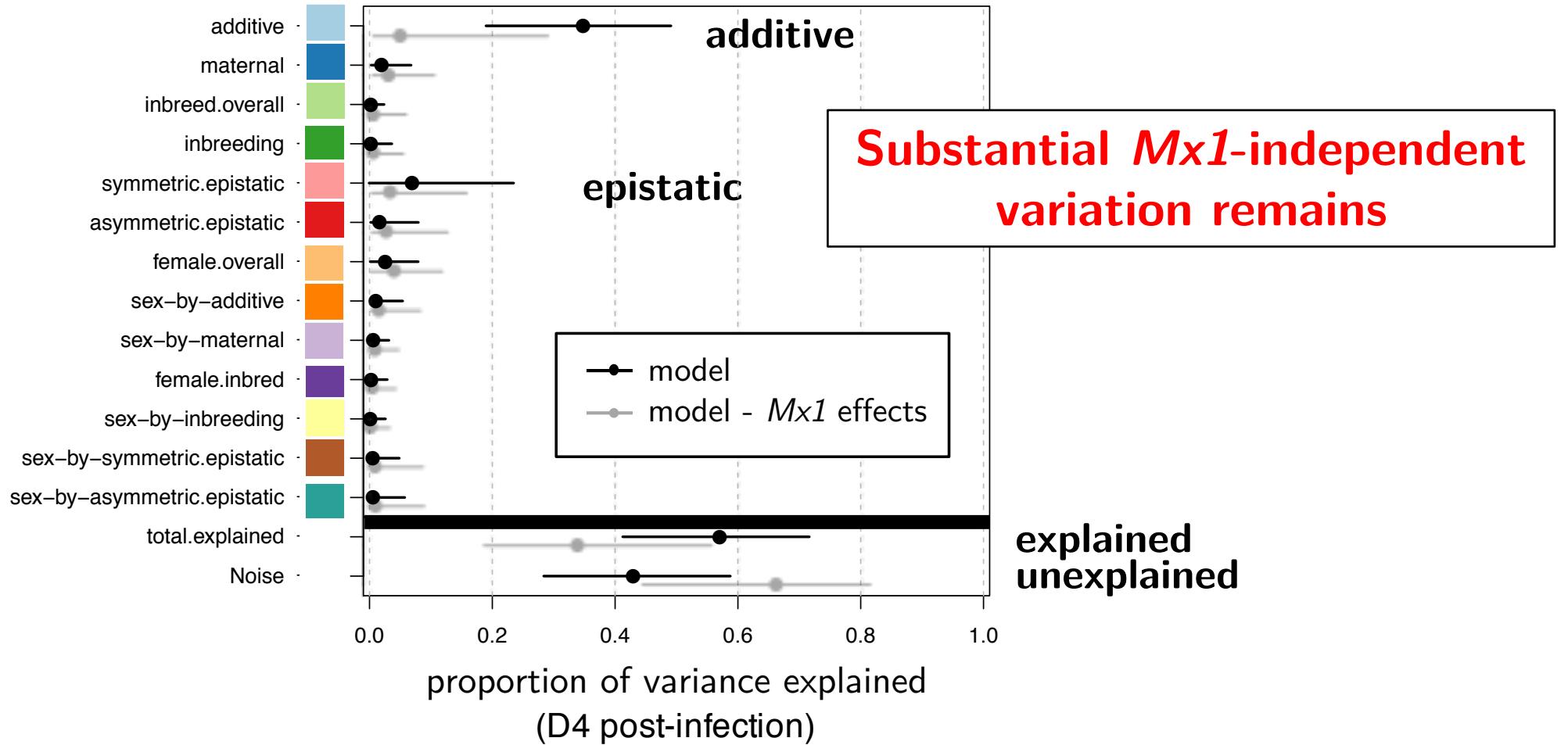
Variance Explained



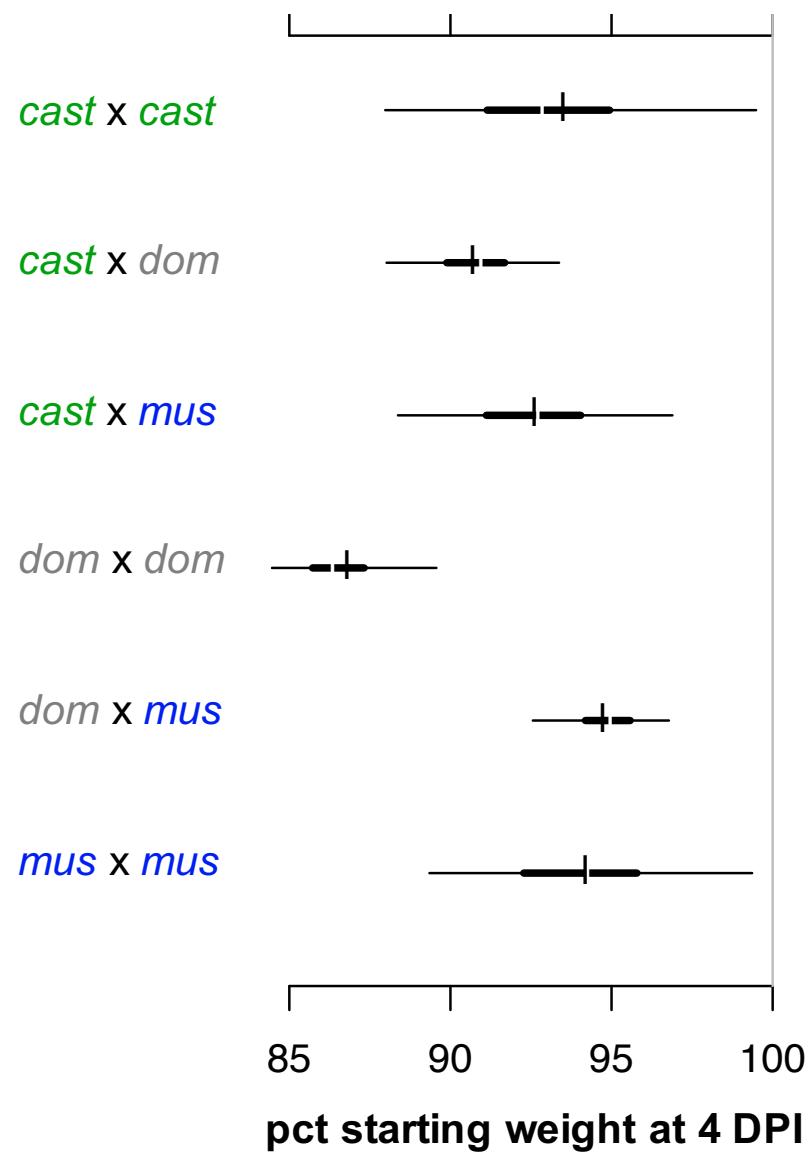
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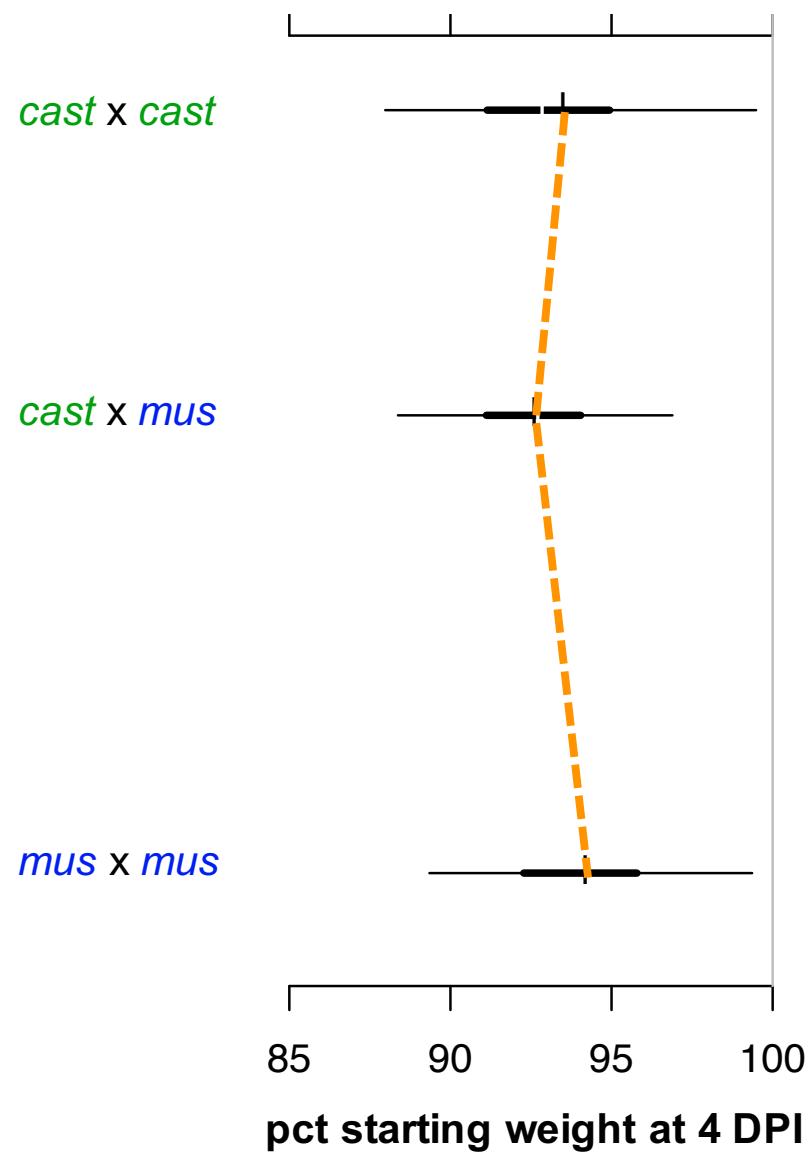
Mx1 Resistance Has Additive and Non-Additive Architecture



Mx1 allele classes

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functional *musculus*: NZO, PWK
functional *castaneous*: CAST

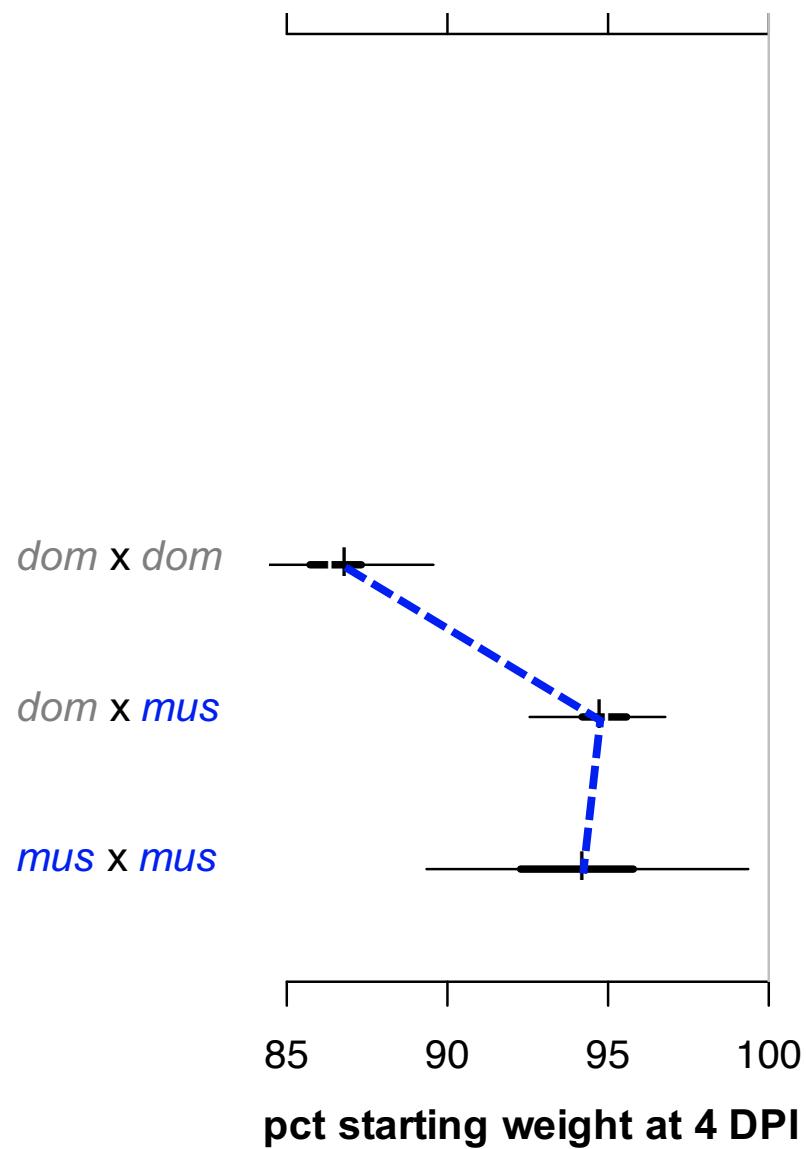
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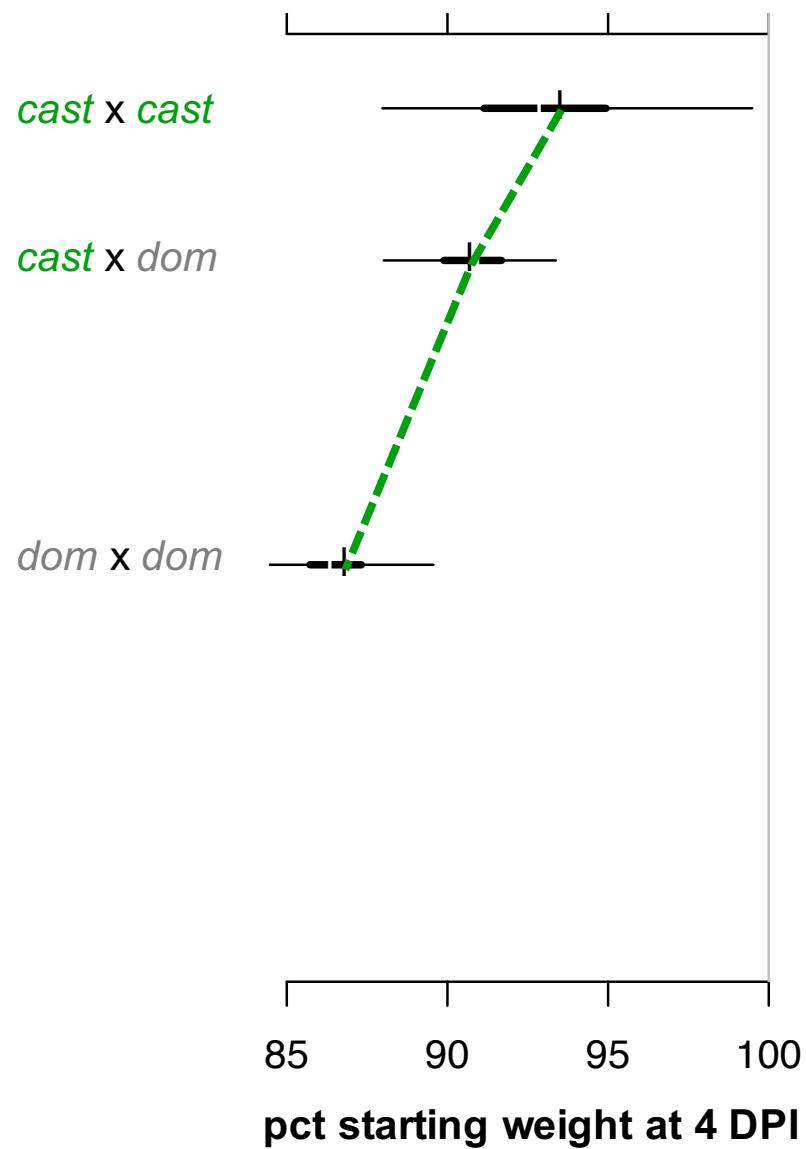


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mus resistance is
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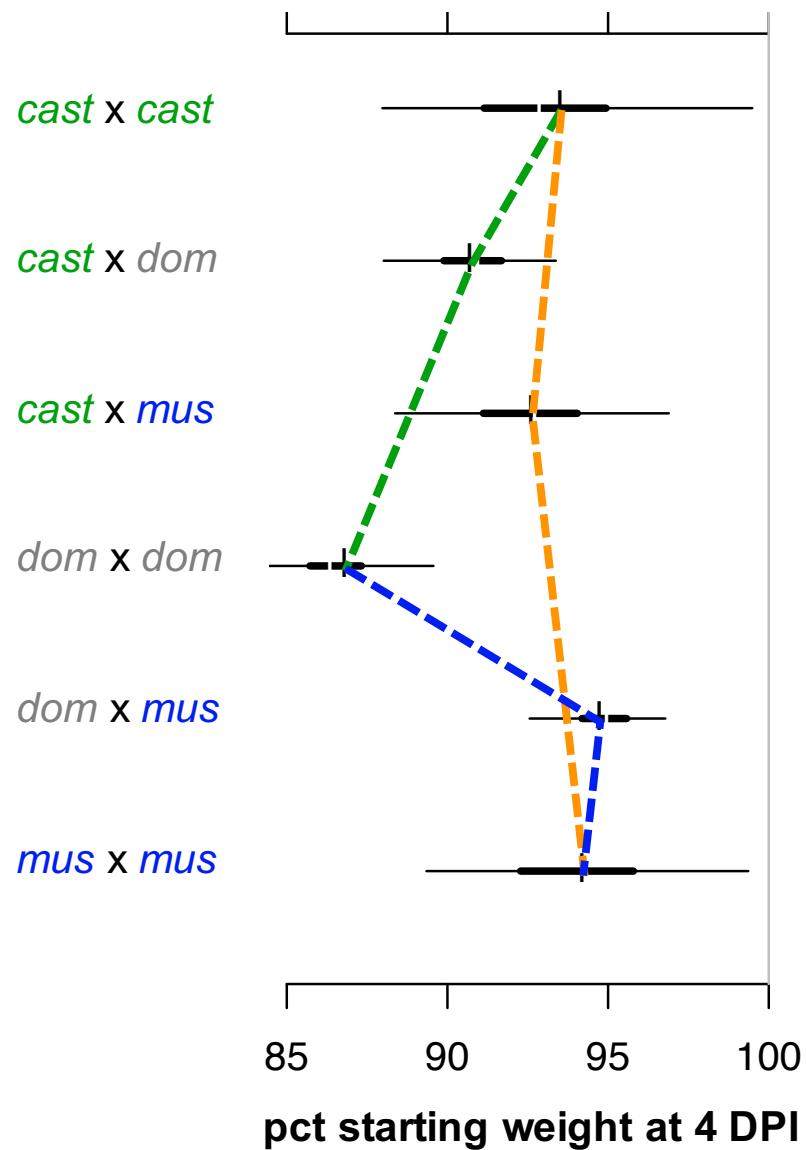


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***cast* resistance is additive**

Mx1 Resistance Has Additive and Non-Additive Architecture



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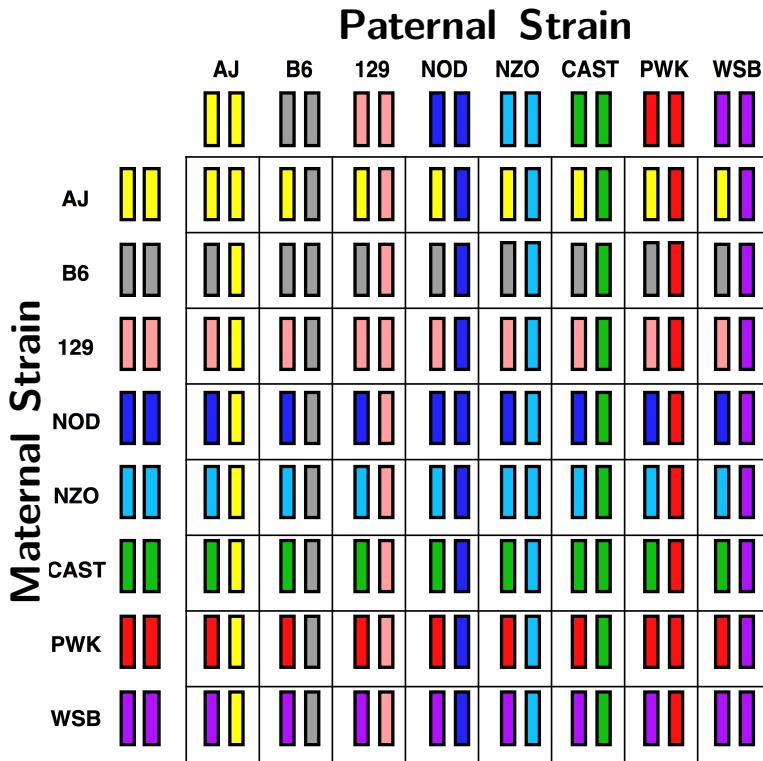
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Are Patterns Consistent Across Populations?

diallel



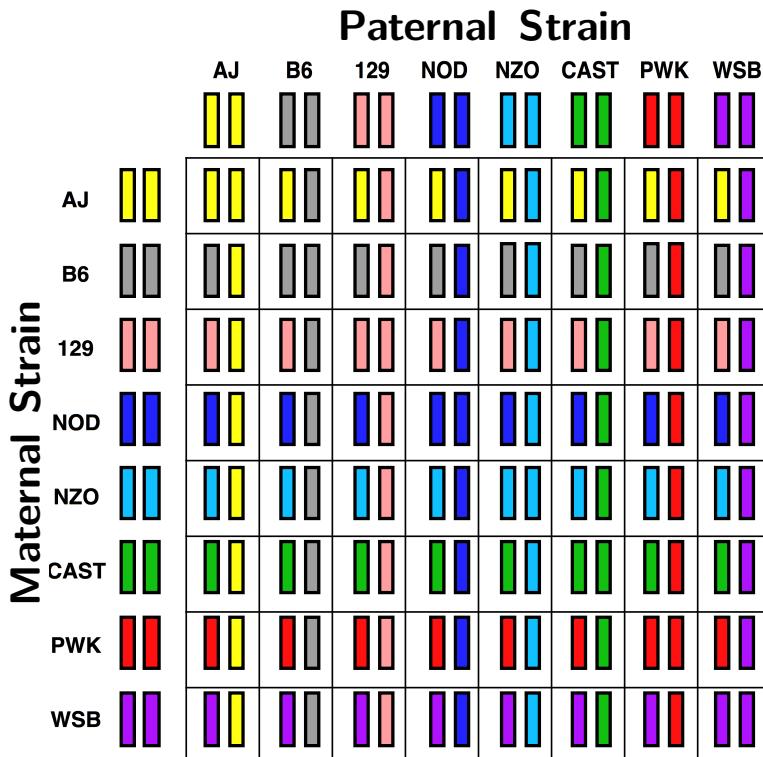
Inbred Strains & F1's
(N=1,043)

Collaborative Cross Consortium. *Genetics* 190: 389-401.
Svenson KL, et al. *Genetics* 190: 437-447.

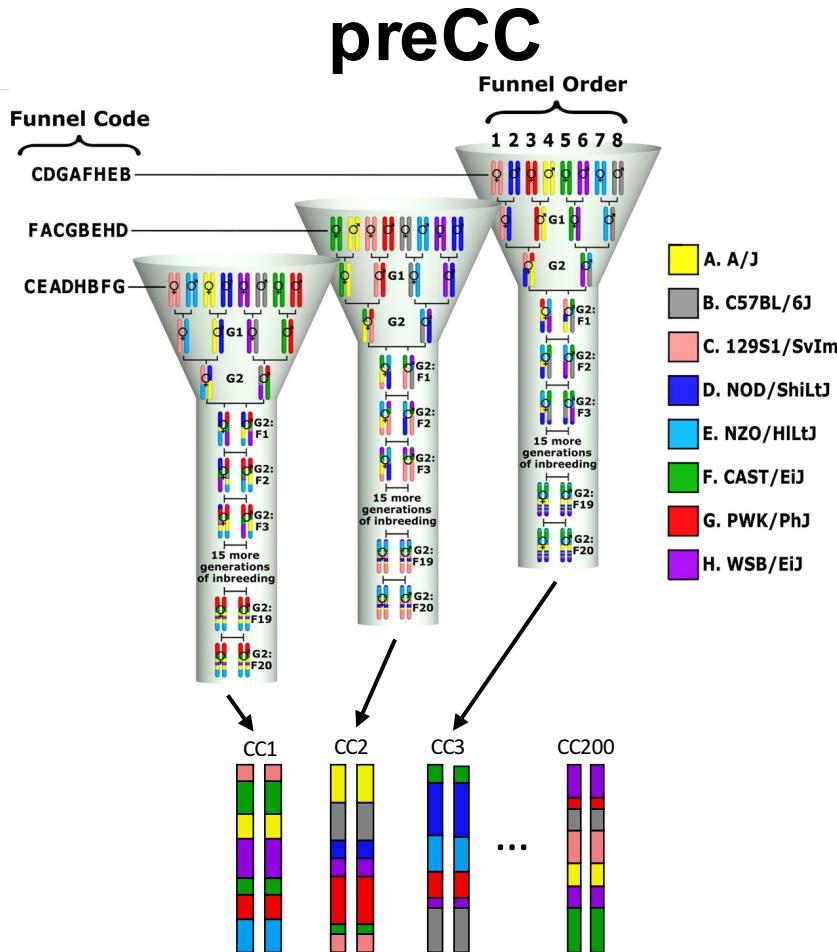
preCC (Ferris et al., 2013, *PLoS Pathogens*)

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diallel



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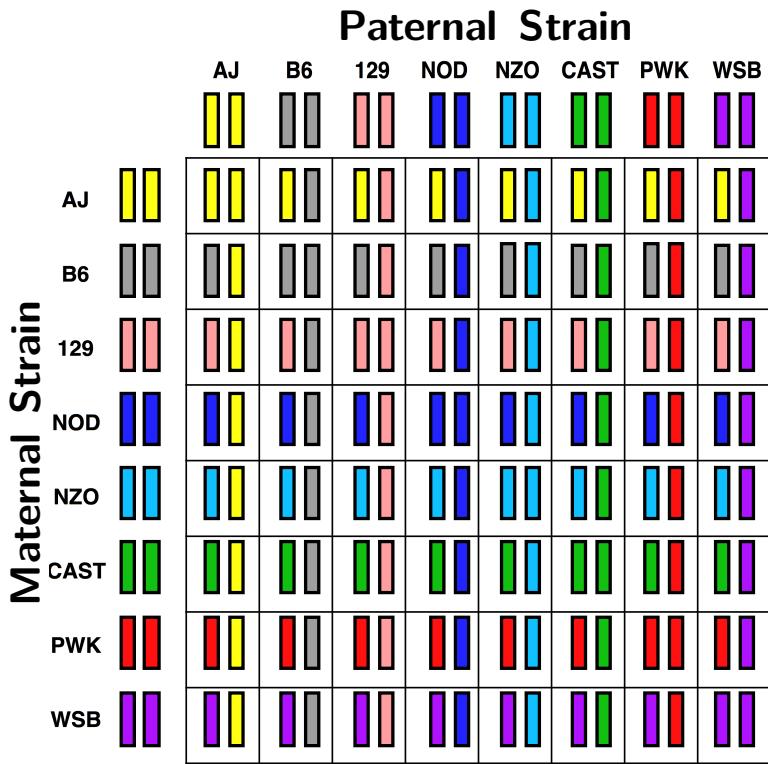
Inbred Lines
(N=155)

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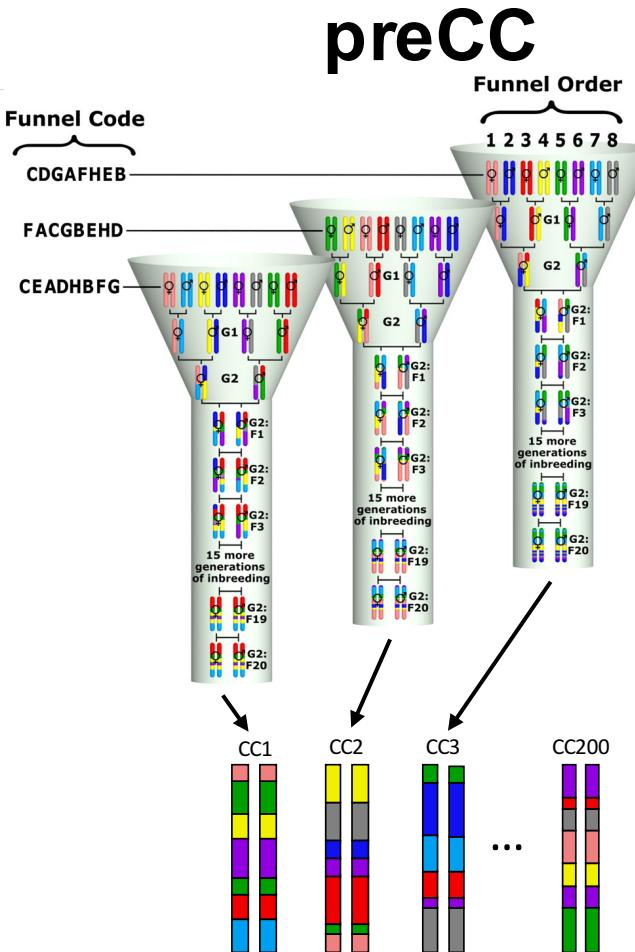
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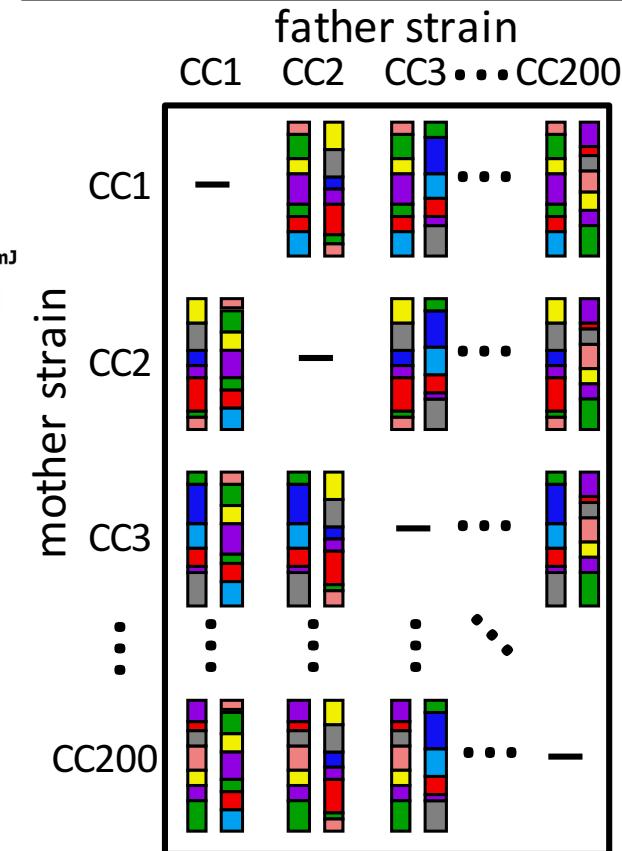
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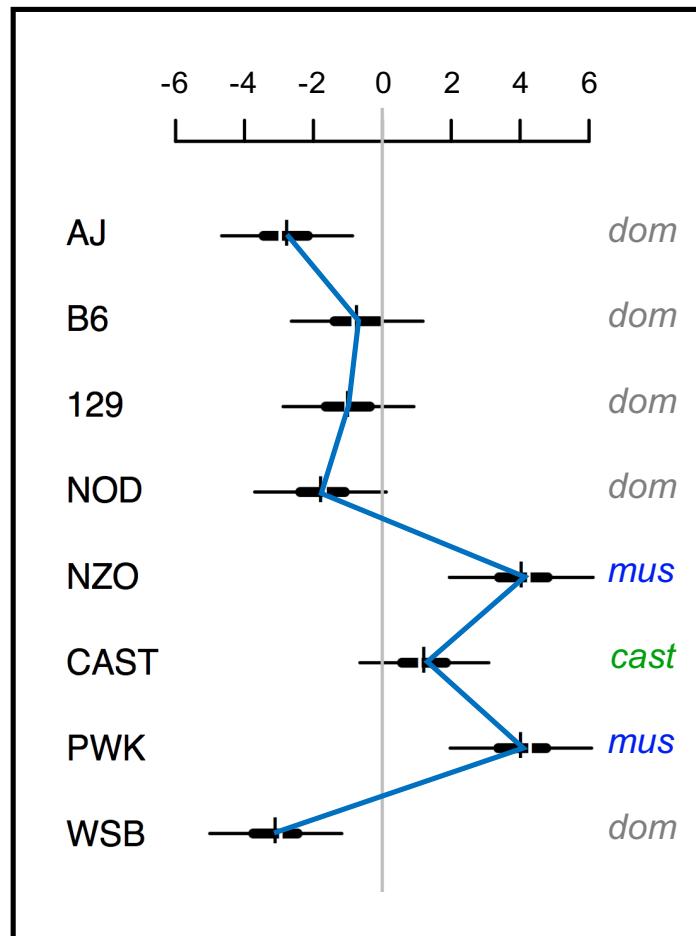
CC-RIX



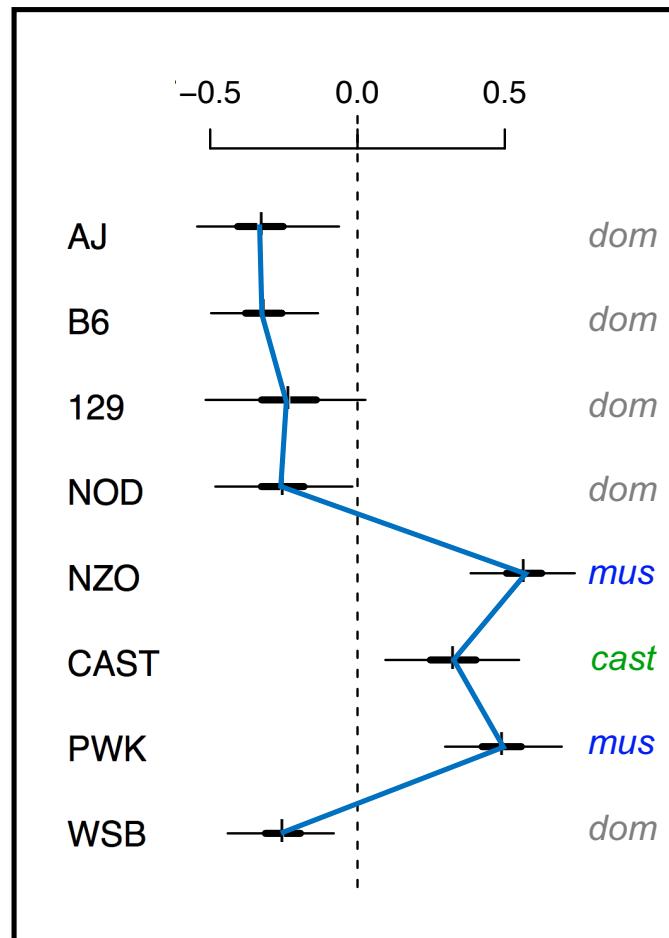
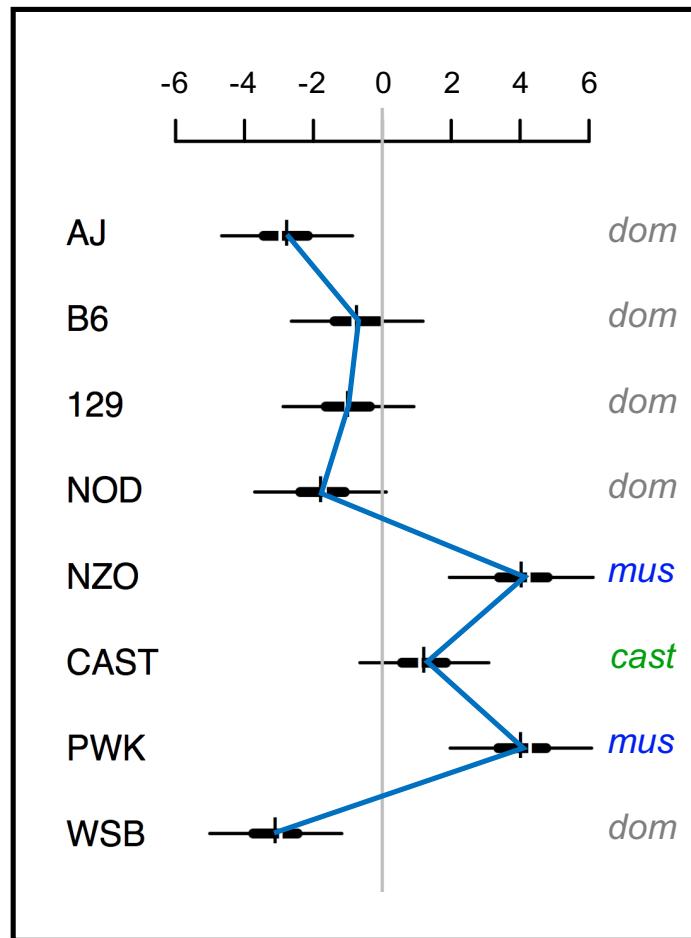
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Strain-Specific Effects Driven by *Mx1* are Consistent diallel preCC CC-RIX

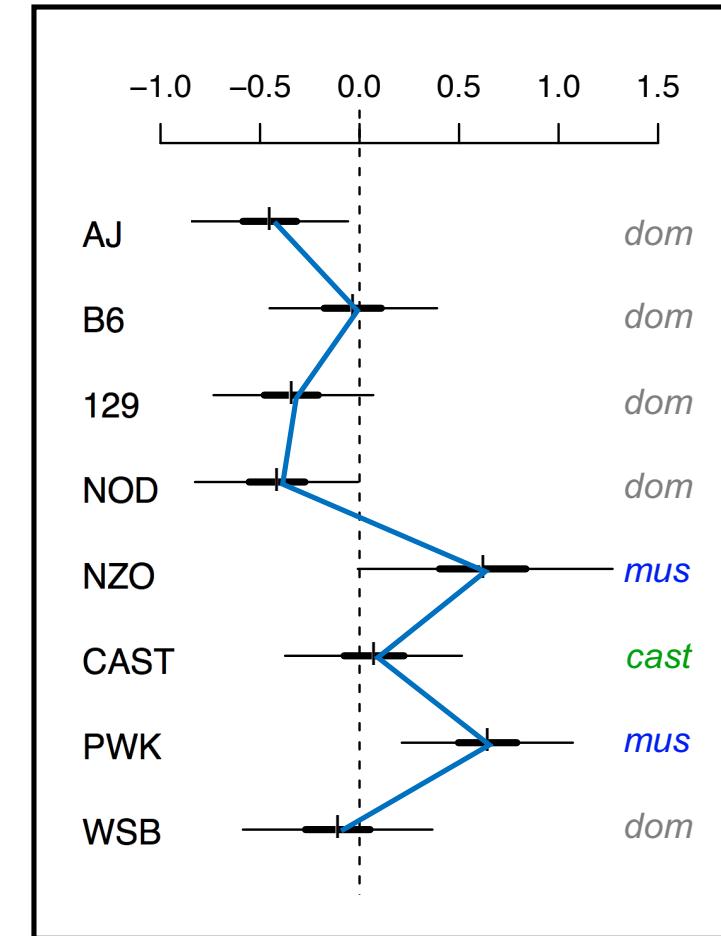
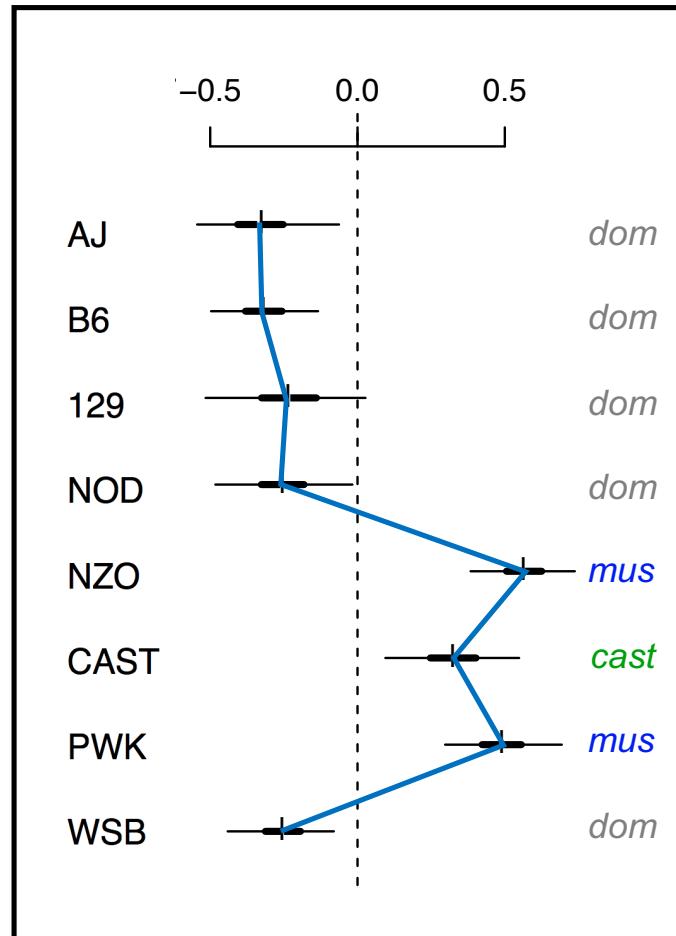
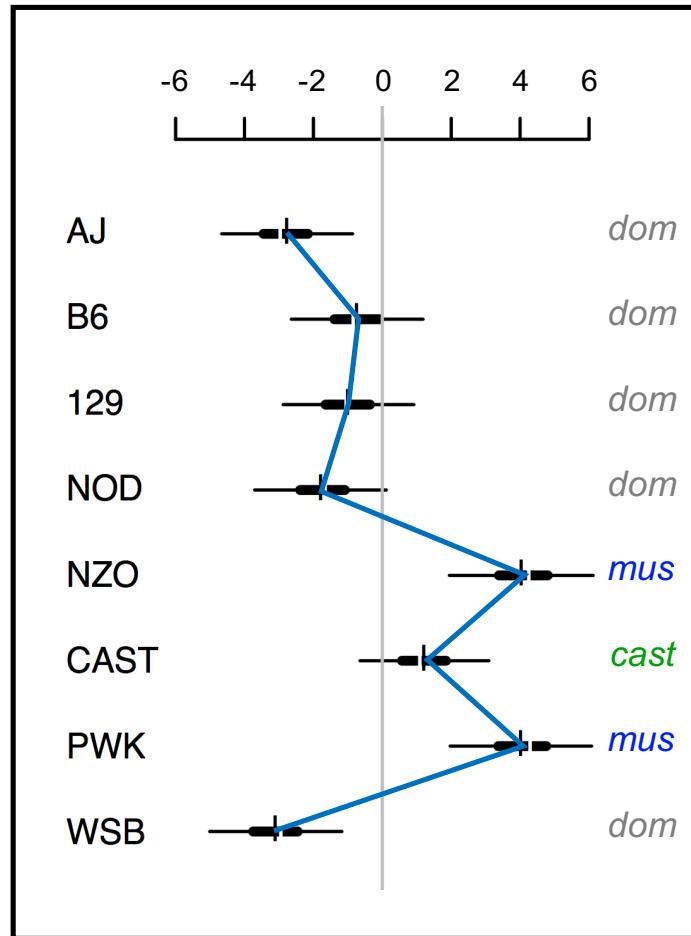


Strain-Specific Effects Driven by *Mx1* are Consistent diallel preCC CC-RIX



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Strain-Specific Effects Driven by *Mx1* are Consistent **diallel** **preCC** **CC-RIX**



Conclusions

- (A) There is substantial ***Mx1-independent*** variation contributing to the host genetic architecture of the response to influenza.

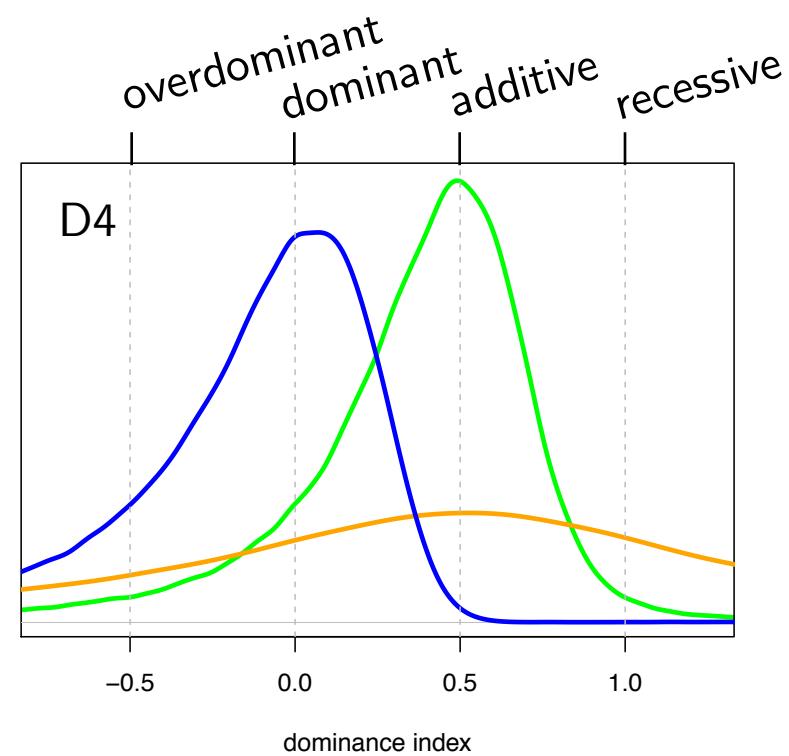
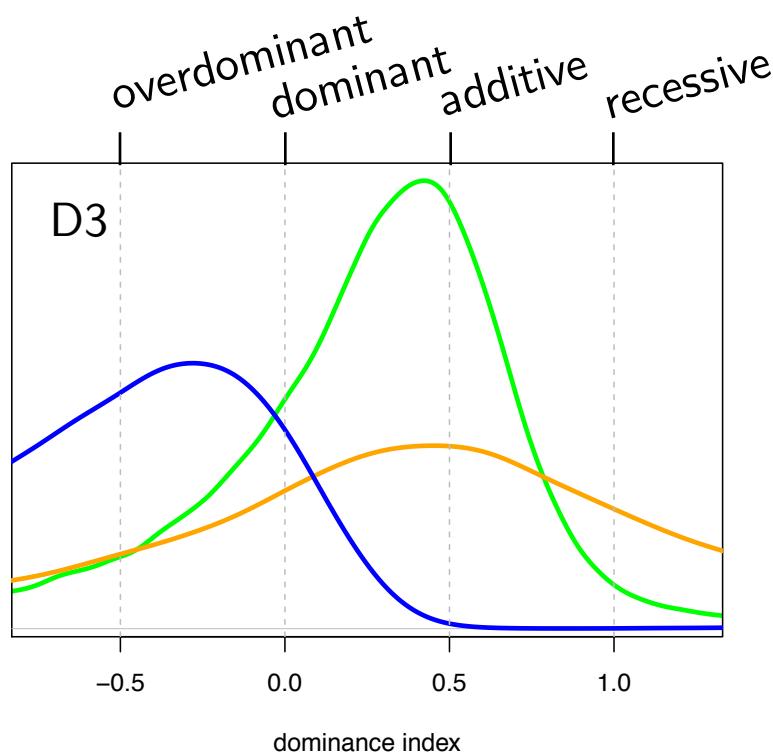
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- (A) There is substantial ***Mx1-independent*** variation contributing to the host genetic architecture of the response to influenza.
- (B) *Mx1*-dependent resistance is driven by functional haplotypes which have distinct **additive and non-additive** architectures.
- (C) The pattern of **strain-specific genetic effects**, driven by *Mx1*, is largely maintained across diallel and CC-related host populations.

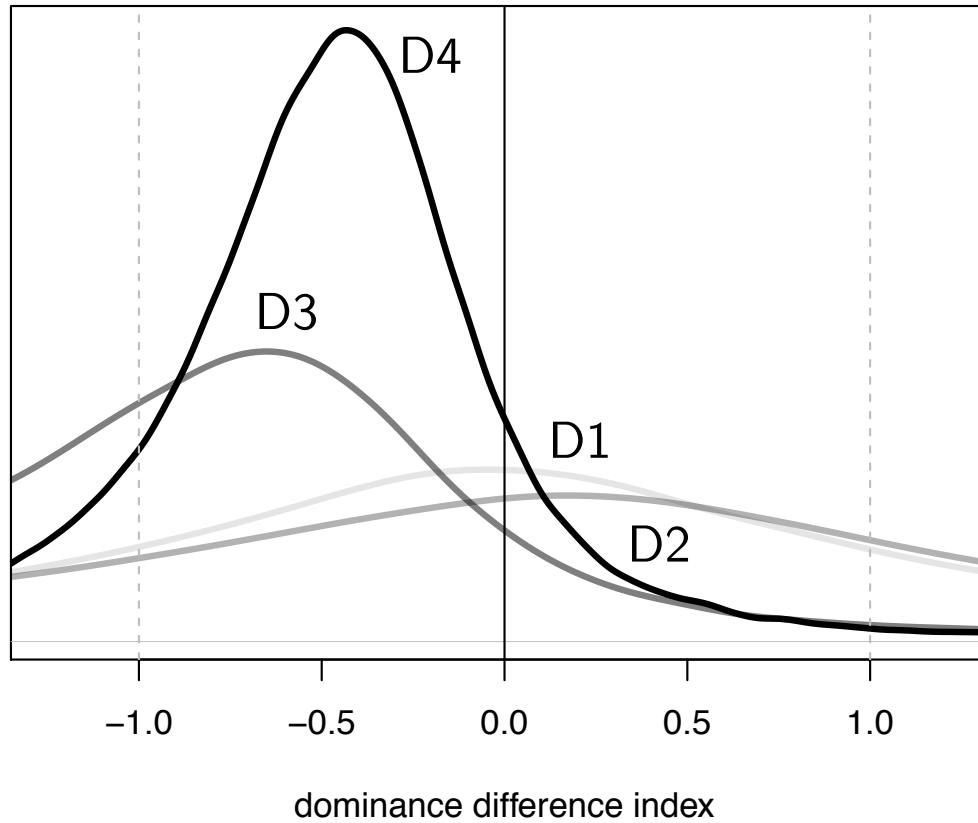
Differences in Degree of Dominance



***Mx1* from *cast* is less dominant (more additive) than *Mx1* from *mus* at D3 and D4 p.i.**

Differences in Degree of Dominance

← *mus* more dominant *cast* more dominant →



**$Mx1$ from *cast* is less dominant (more additive)
than $Mx1$ from *mus* at D3 and D4 p.i.**

Differences in Degree of Dominance

$$\mathcal{D}^{(\text{cast}; \text{dom})} = \frac{u^{(\text{cast cast})} - u^{(\text{cast dom})}}{u^{(\text{cast cast})} - u^{(\text{dom dom})}}$$

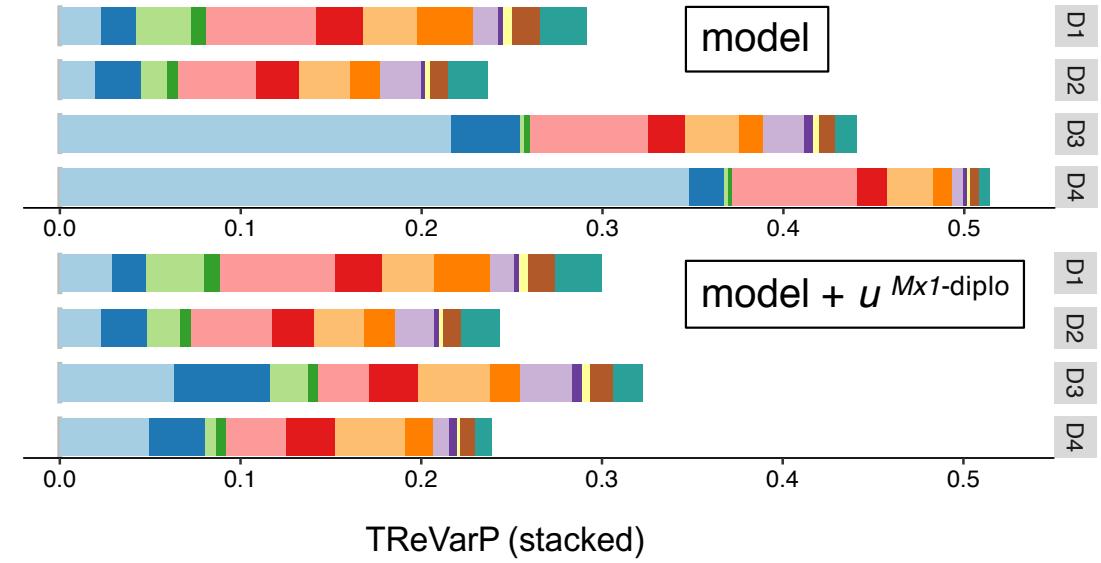
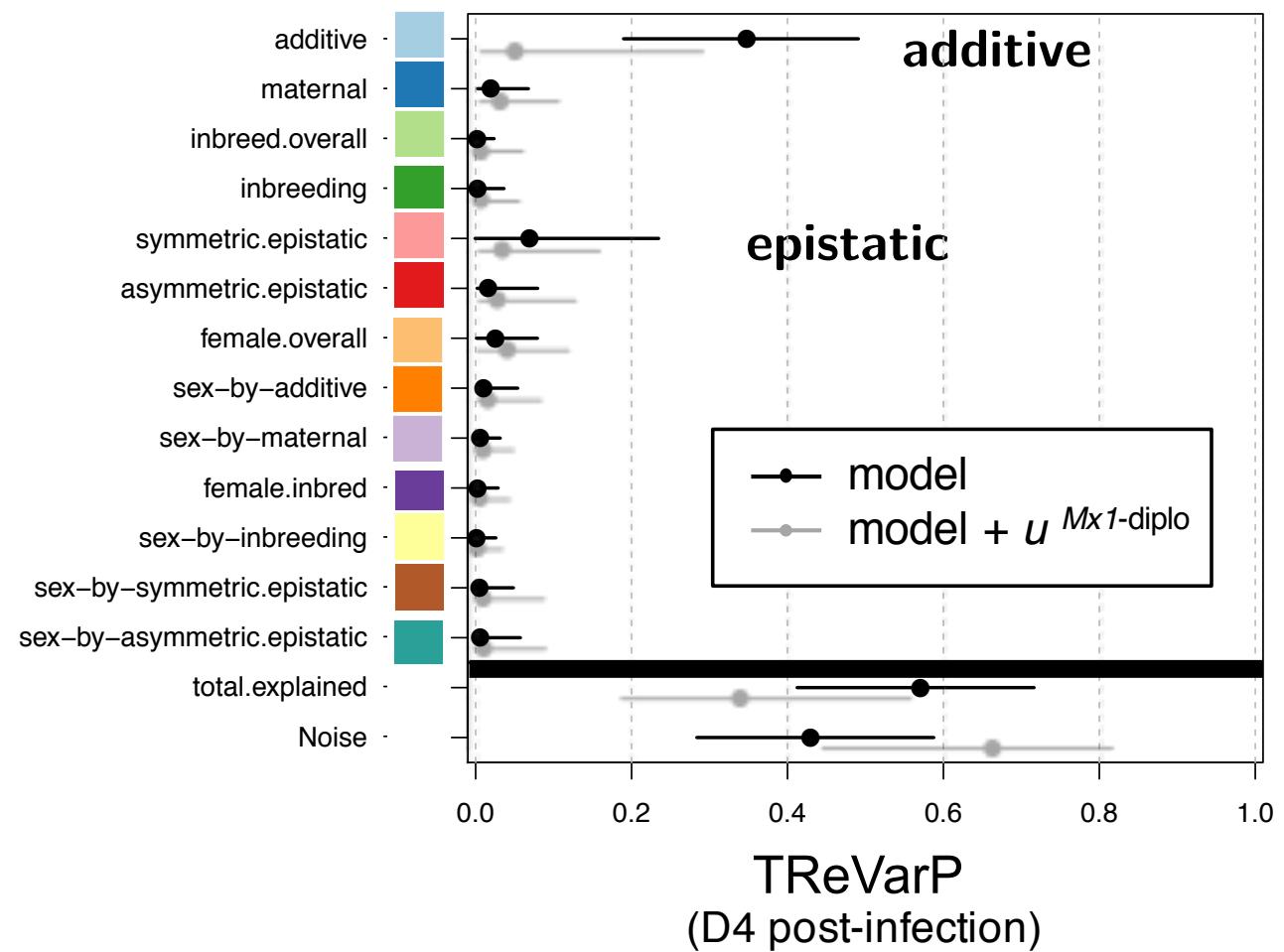
$$\mathcal{D}^{(\text{mus}; \text{dom})} = \frac{u^{(\text{mus mus})} - u^{(\text{dom mus})}}{u^{(\text{mus mus})} - u^{(\text{dom dom})}}$$

$$\mathcal{DD}^{(\text{mus} - \text{cast}; \text{dom})} = \mathcal{D}^{(\text{mus}; \text{dom})} - \mathcal{D}^{(\text{cast}; \text{dom})}$$

overdominant:
D=-0.5
dominant:
D=0.0
additive:
D=0.5
recessive:
D=1.0

Timepoint (p.i.)	D3		D4	
Dominance index	<i>mus</i>	<i>cast</i>	<i>mus</i>	<i>cast</i>
$P(\mathcal{D} \leq 0)$	0.853	0.284	0.594	0.154
$P(\mathcal{D} \geq 0.5)$	0.061	0.295	0.015	0.384
Dominance difference	$(\textit{mus} - \textit{cast})$		$(\textit{mus} - \textit{cast})$	
$P(\mathcal{DD} < 0)$	0.836		0.866	

Variance Explained by Variance Projection of Effects



explained
unexplained

Substantial $Mx1$ -independent variation remains