Altered Prior Mean Allelic Effects:

An approach for adequately considering Gene Edited Variants within Genomic Predictions

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Rumigen
TOWARDS IMPROVEMENT OF RUMINANT BREEDING THROUGH GENOMIC AND EPIGENOMIC APPROACHES

WAGENINGEN UNIVERSITY & RESEARCH

gene edited variants

Targeted modification of DNA

uses tools such CRISPR-Cas9, TALENs, or zinc-finger nucleases

Regulatory status open

e.g. PRLR gene for ‘SLICK’ trait for improved heat tolerance

a. SLICK b. wild-type

(Littlejohn et al., 2014)

gene edited variants
genomic prediction

Assists conventional breeding on polygenic traits

calculation of genomic estimated breeding values (GEBVs)

Like polygenic risk scores, in it's simplest form is the sum of allelic effects for the selection candidates

$$\hat{u} = X\hat{\alpha}$$

Considering gene edited variants in genomic prediction methods

Why do this?

Keep the gene edited variant in the population

Introduce additional selection rules

Integrate into the gEBVs for traits of interest

↳ Challenge: initially i) Extremely rare allele ii) No phenotypes

Considering gene edited variants in genomic prediction methods

Why do this?

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↳ Challenge: initially i) Extremely rare allele ii) No phenotypes

Idea: use altered priors of allele effects in SNPBLUP

Prior variances → eq. to reweighting of effects

Prior means → instead of shrinking effects to 0, relatively unexplored

Comparison of 4 different genomic prediction methods

In a simulated population with recurrent genomic selection

Strategies with different priors for the effect of the edited variant
Pr0: conventional prior (treated as any marker)
PrV: altered prior variance
PrM: altered prior mean
PrVM: both altered pior variance and prior mean

Simulated population under genomic selection

Historical generations with population bottleneck

To achieve mutation-drift equilibrium & long-distance LD

Recent generations: 200 selected from 1000 individuals each generation

10 generations of genomic selection

⇓ gene edit on 5 selected sires

20 generation of genomic selection ← Methods compared here

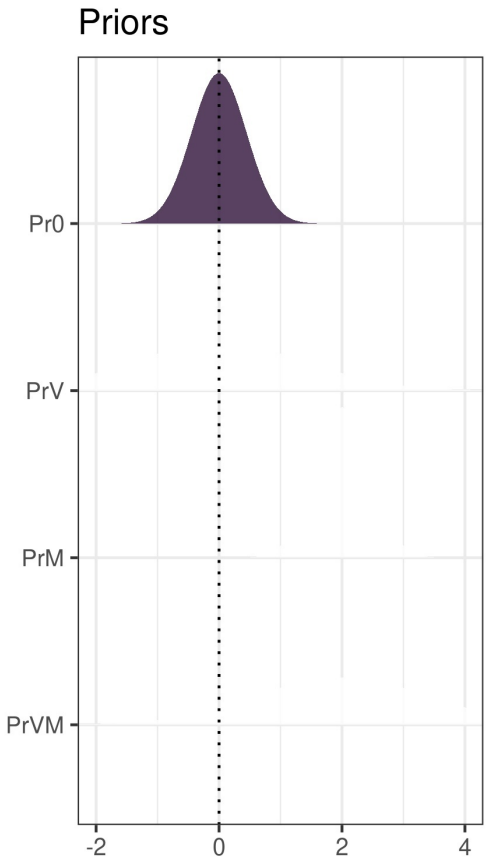
Gene edited variant

Introduced at the 10^{th} generation of selection
On a previously monomorphic locus
Set 5 selected sires to be homozygote on the introduced variant

Has a positive effect on the selected trait
Half the genetic standard deviation: **$0.5\sigma_a$**

Created one marker in full linkage with the edited locus

Conventional prior for allele effects



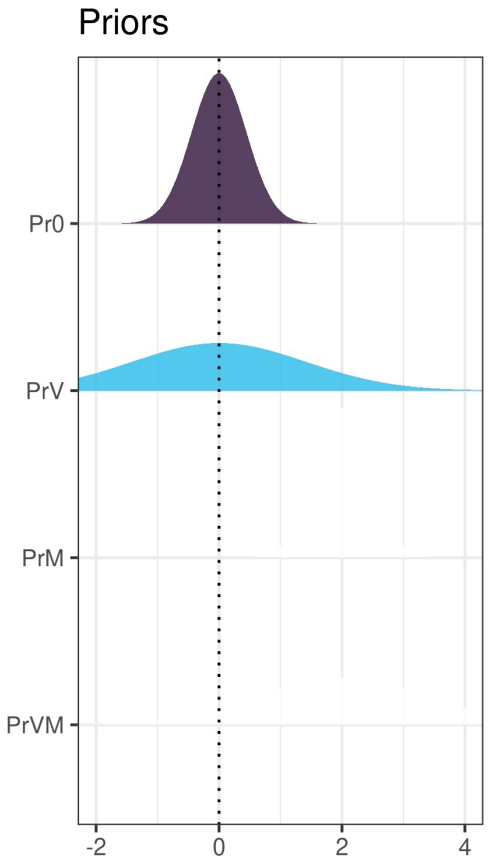
Prior mean equals zero $E[\alpha_j] = 0$

Prior variance equals (σ^2_a / # markers) $V[\alpha_j] = \sigma^2_a / m$

This results in BVs, $u = X\alpha$, with the usual prior:

$$\mathbf{E[u] = 0, V[u] = G\sigma^2_a}$$

Altered prior variance for edited variant



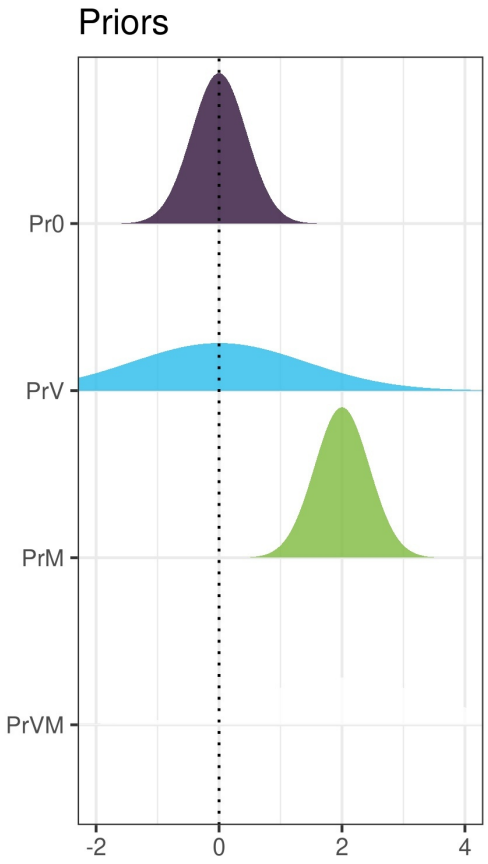
Modify variance

Set equal to the contribution to the variance of the true breeding values in the first generation after introduction

$$V[\beta_e] = 2 \cdot p_e \cdot (1-p_e) \cdot \alpha_e^2 \Rightarrow \sim 1.2\% \ \sigma^2_a$$

$$V[\beta_e] \simeq 300 \cdot V[\beta_j]$$

Altered prior mean for edited variant

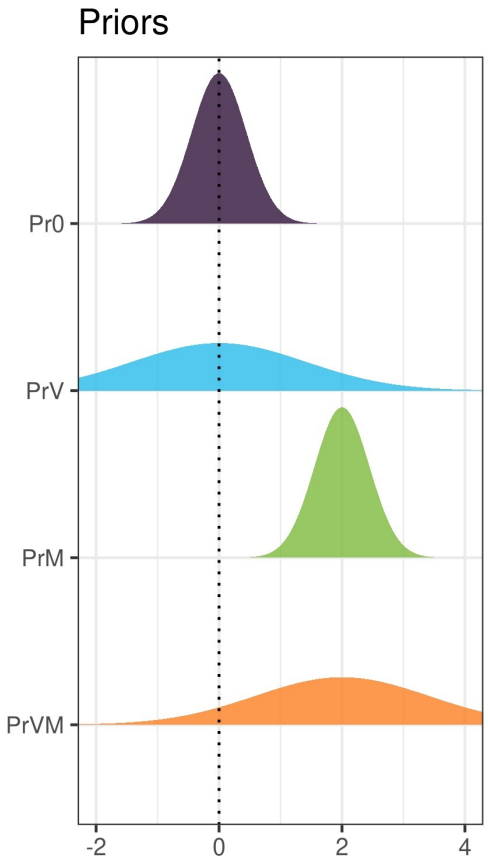


Modify mean

Set to the true effect of the gene edited variant

$$E[\beta_e] = \alpha_e \Rightarrow 0.5\sigma_a$$

Altered prior variance & mean for edited variant



Modified both variance and mean

Altered prior mean & variance, implementation in SNPBLUP

$$\begin{bmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + I\sigma_{\alpha}^{-2} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{\alpha} \end{bmatrix} = \begin{bmatrix} X'R^{-1}y \\ Z'R^{-1}y \end{bmatrix}$$

Altered prior mean & variance, implementation in SNPBLUP

$$\begin{bmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + I\sigma_{\alpha}^{-2} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{\alpha} \end{bmatrix} = \begin{bmatrix} X'R^{-1}y \\ Z'R^{-1}y + (I\sigma_{\alpha}^{-2})0 \end{bmatrix}$$

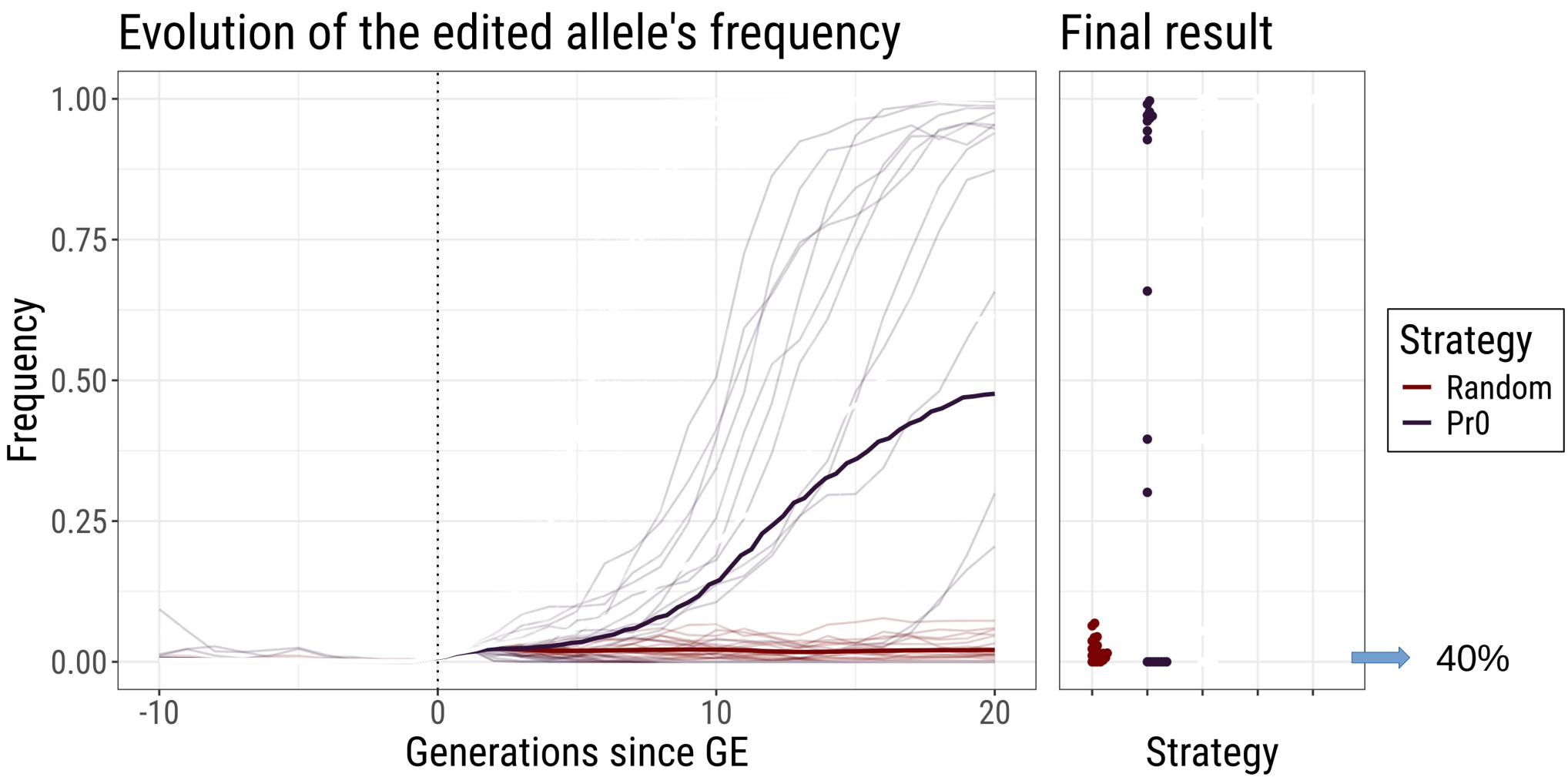
Altered prior mean & variance, implementation in SNPBLUP

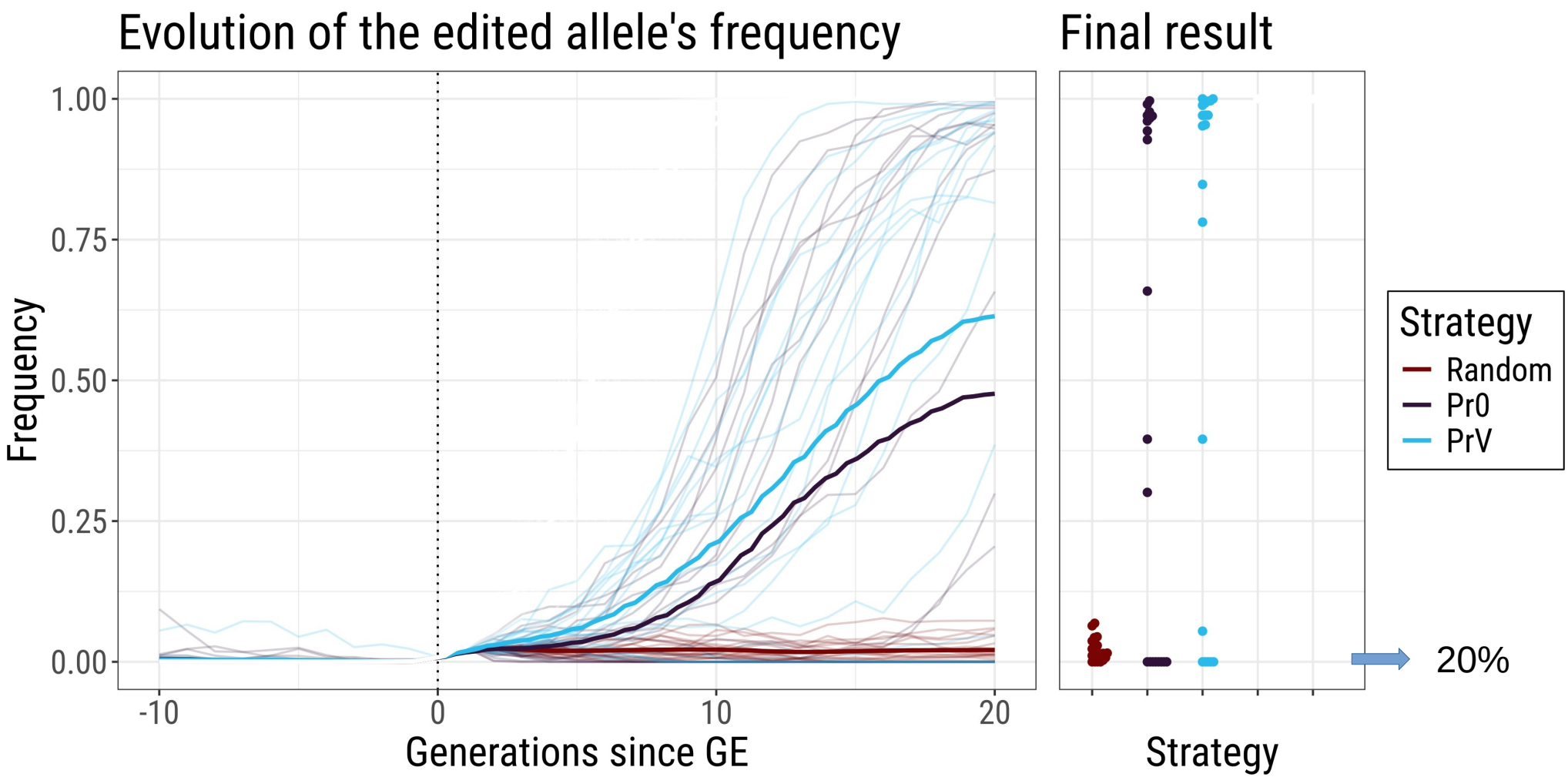
$$\begin{bmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + I\sigma_{\alpha}^{-2} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{\alpha} \end{bmatrix} = \begin{bmatrix} X'R^{-1}y \\ Z'R^{-1}y + (I\sigma_{\alpha}^{-2})\mu \end{bmatrix}$$

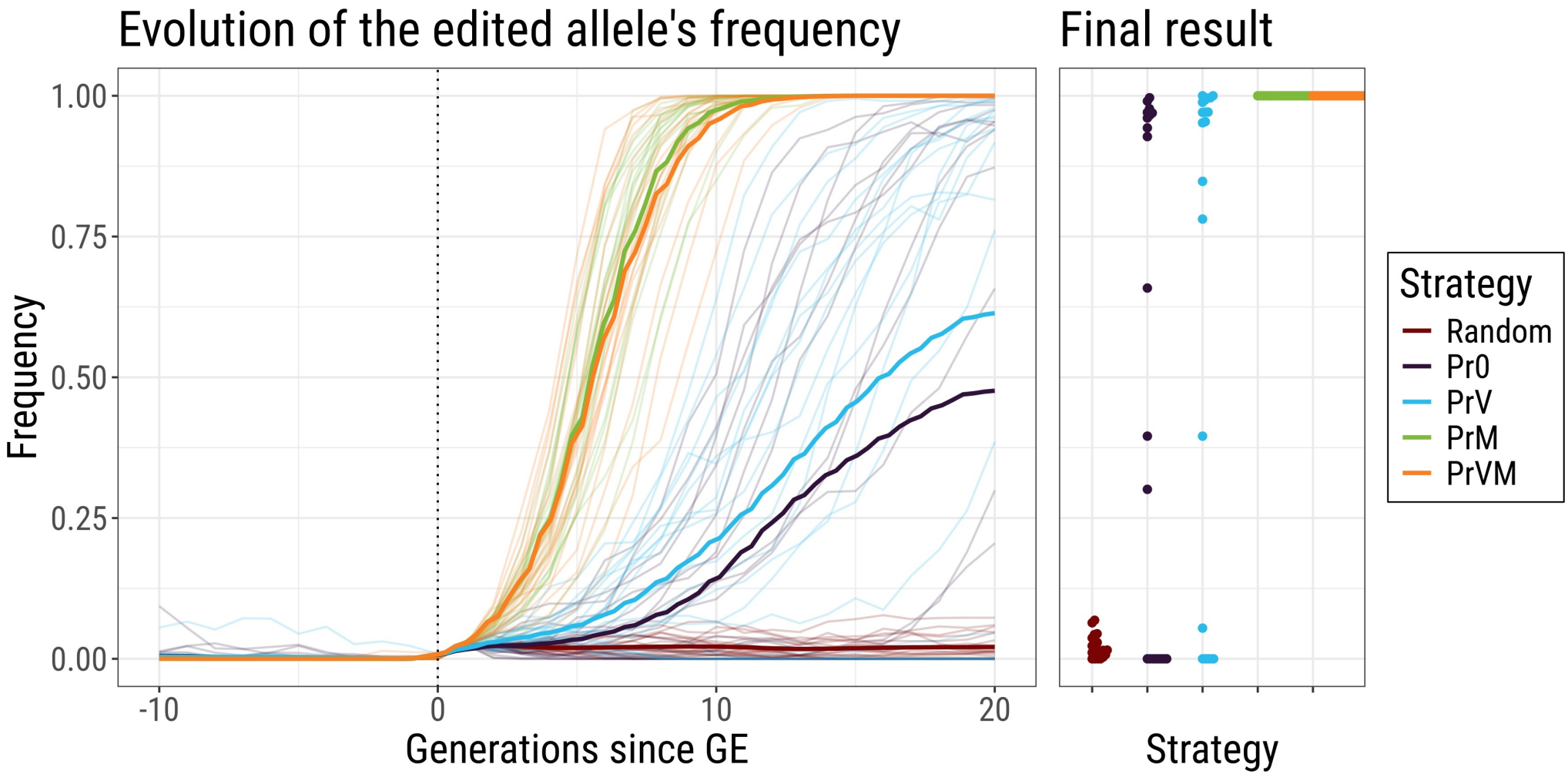
Altered prior mean & variance, implementation in SNPBLUP

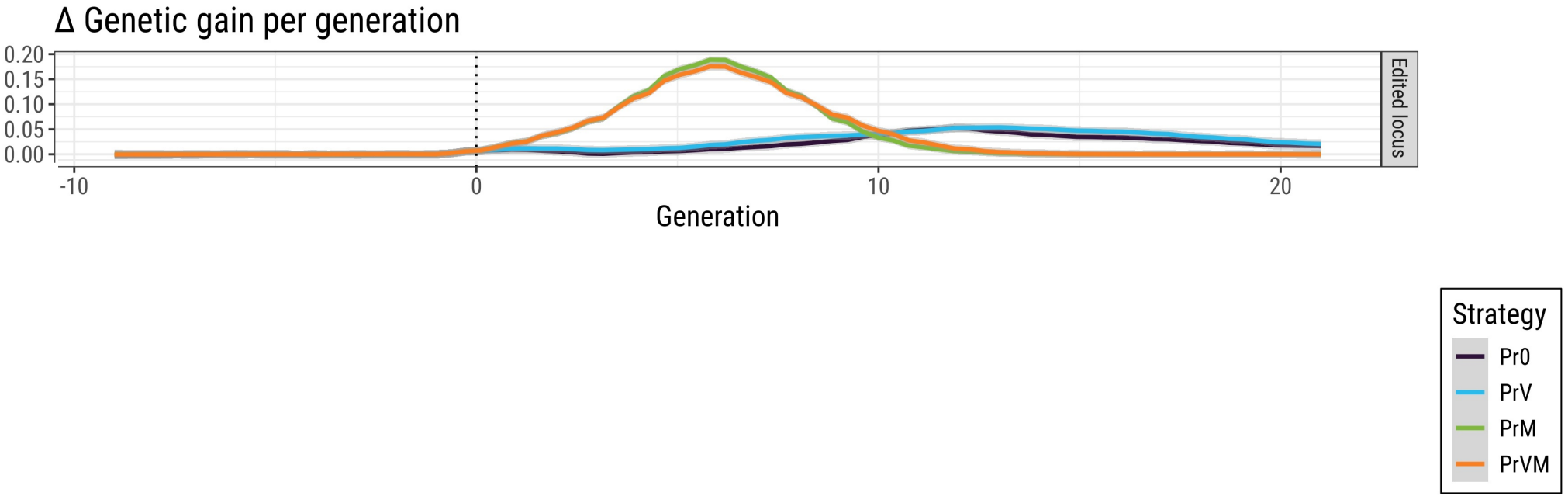
$$\begin{bmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + \Sigma^{-1} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{\alpha} \end{bmatrix} = \begin{bmatrix} X'R^{-1}y \\ Z'R^{-1}y + (\Sigma^{-1})\mu \end{bmatrix}$$

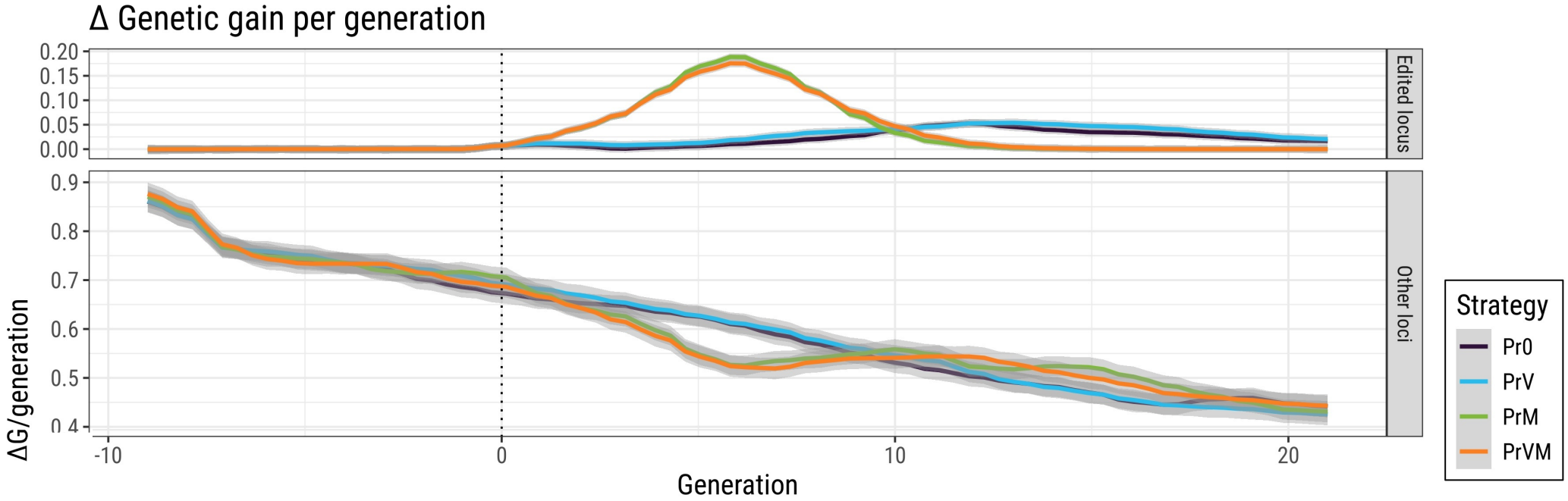
Results

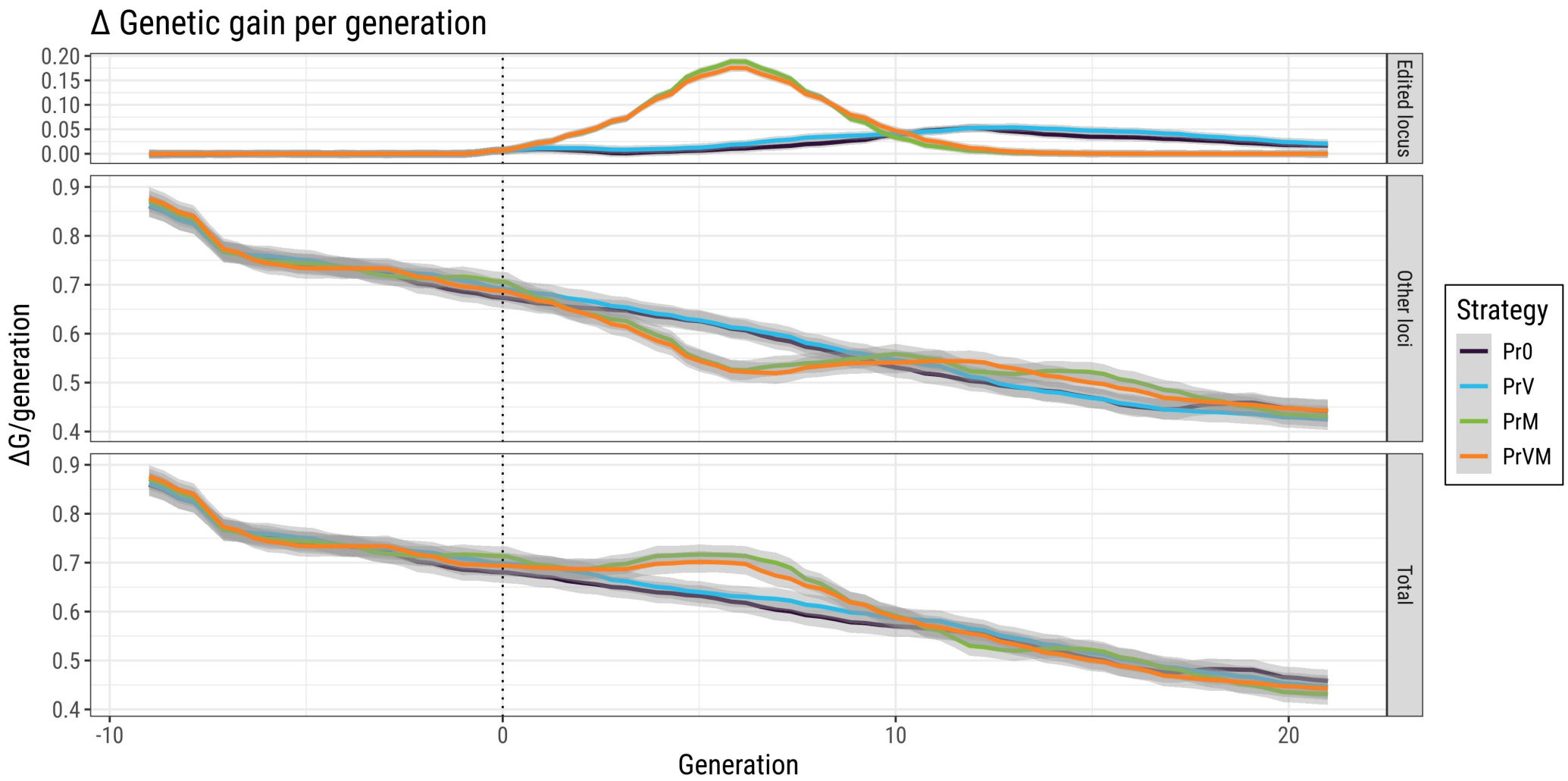

Evolution of the edited allele's frequency
Final result
1.00
0.75
0.50
0.25
0.00
Frequency
-10
0
10
20
Generations since GE
Strategy
Random
Pr0
40%
Strategy


Evolution of the edited allele's frequency
Final result
1.00
0.75
0.50
0.25
0.00
Frequency
-10
0
10
20
Generations since GE
Strategy
Random
Pr0
PrV
20%
Strategy


Evolution of the edited allele's frequency
Final result
1.00
0.75
0.50
0.25
0.00
Frequency
-10
0
10
20
Generations since GE
Strategy
Strategy
Random
Pr0
PrV
PrM
PrVM


Δ Genetic gain per generation
0.20
0.15
0.10
0.05
0.00
-10
0
10
20
Generation
Edited locus
Strategy
Pr0
PrV
PrM
PrVM


Δ Genetic gain per generation
0.20
0.15
0.10
0.05
0.00
Edited locus
0.9
0.8
0.7
0.6
0.5
0.4
Other loci
ΔG/generation
-10
0
10
20
Generation
Strategy
Pr0
PrV
PrM
PrVM


Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
0.20
0.15
0.10
0.05
0.00
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0.8
0.7
0.6
0.5
0.4
-10
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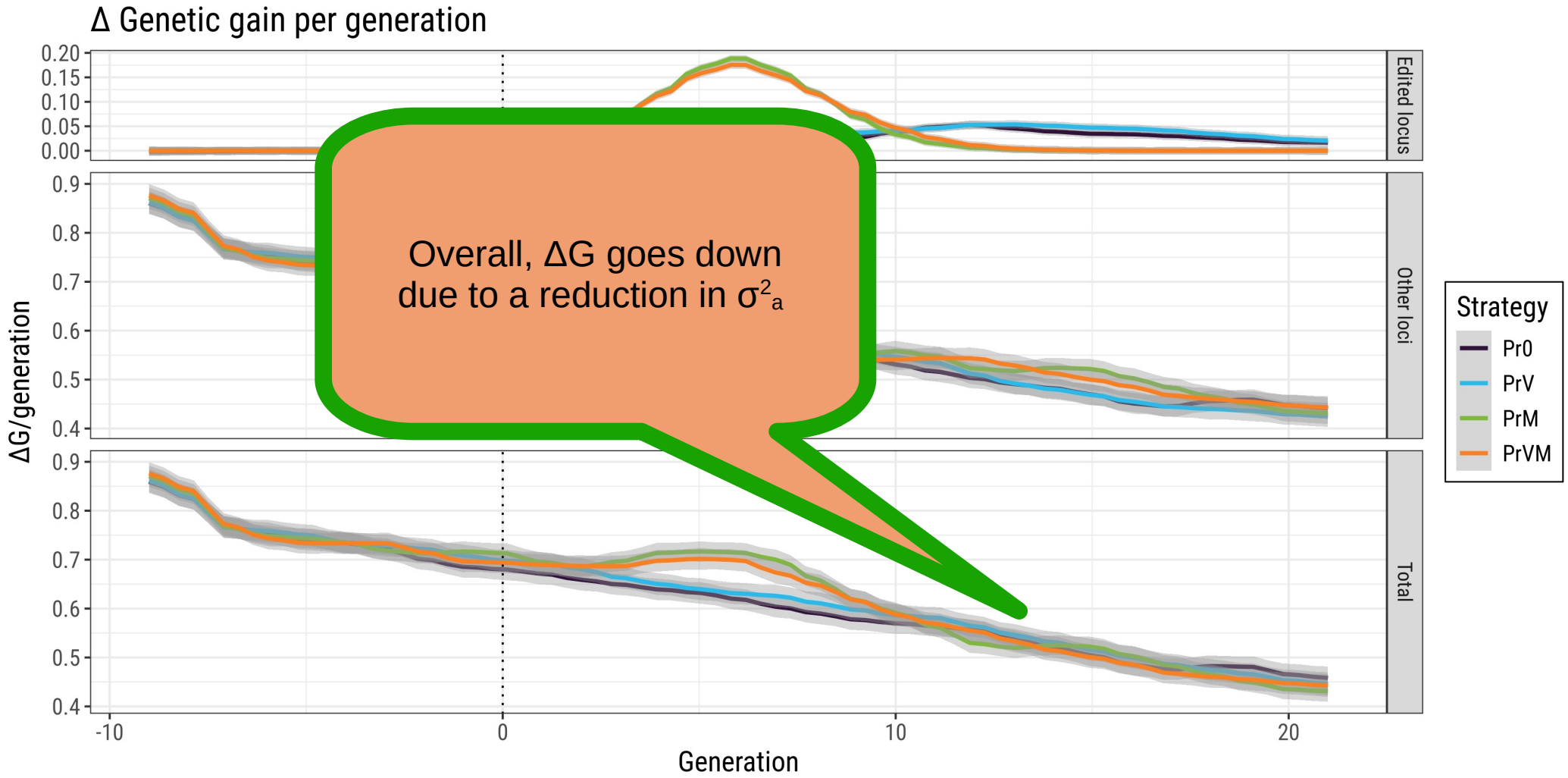
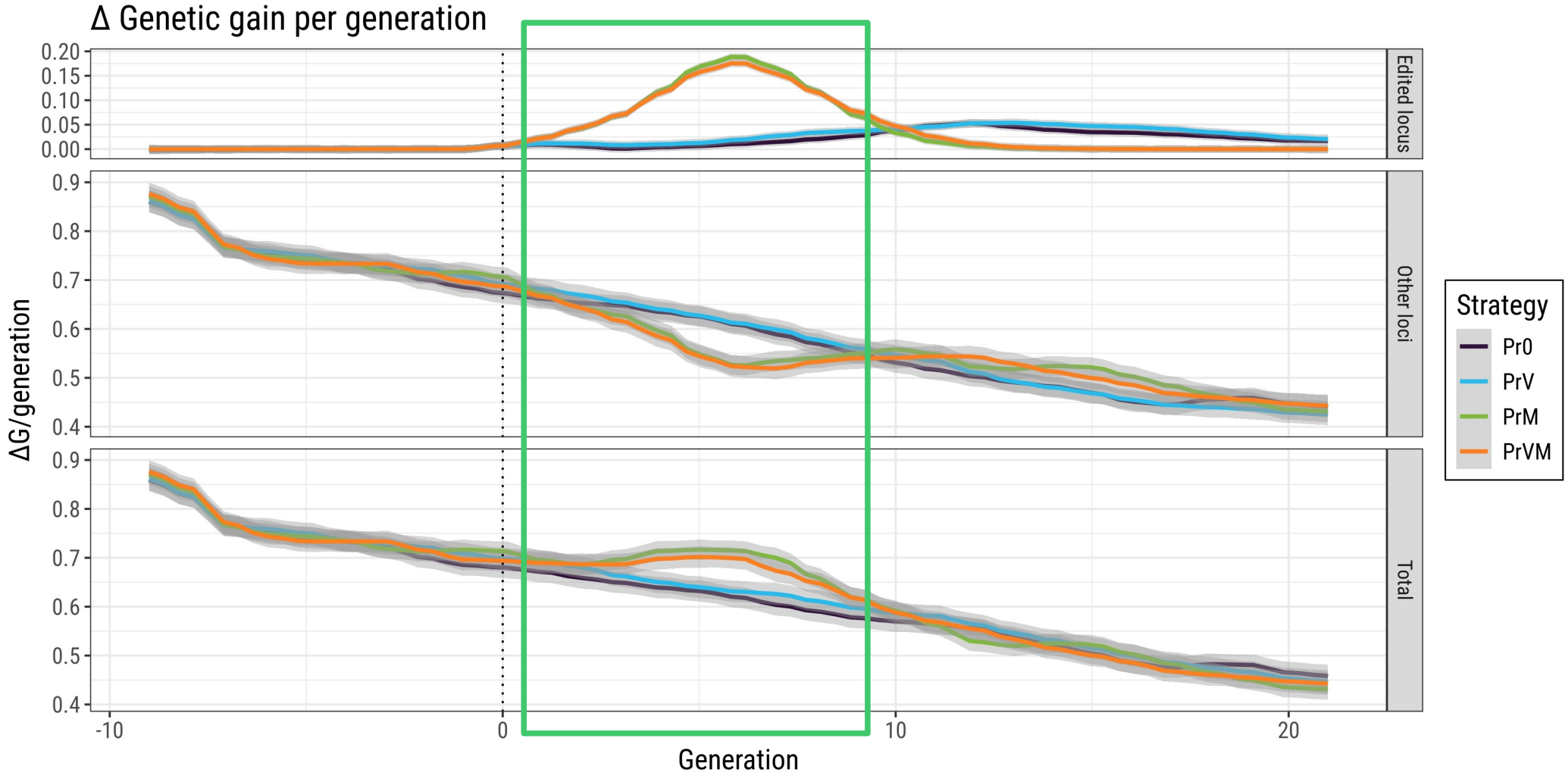
10
20


Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
Overall, ΔG goes down due to a reduction in σ^2_a


Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
0.20
0.15
0.10
0.05
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0.4
-10
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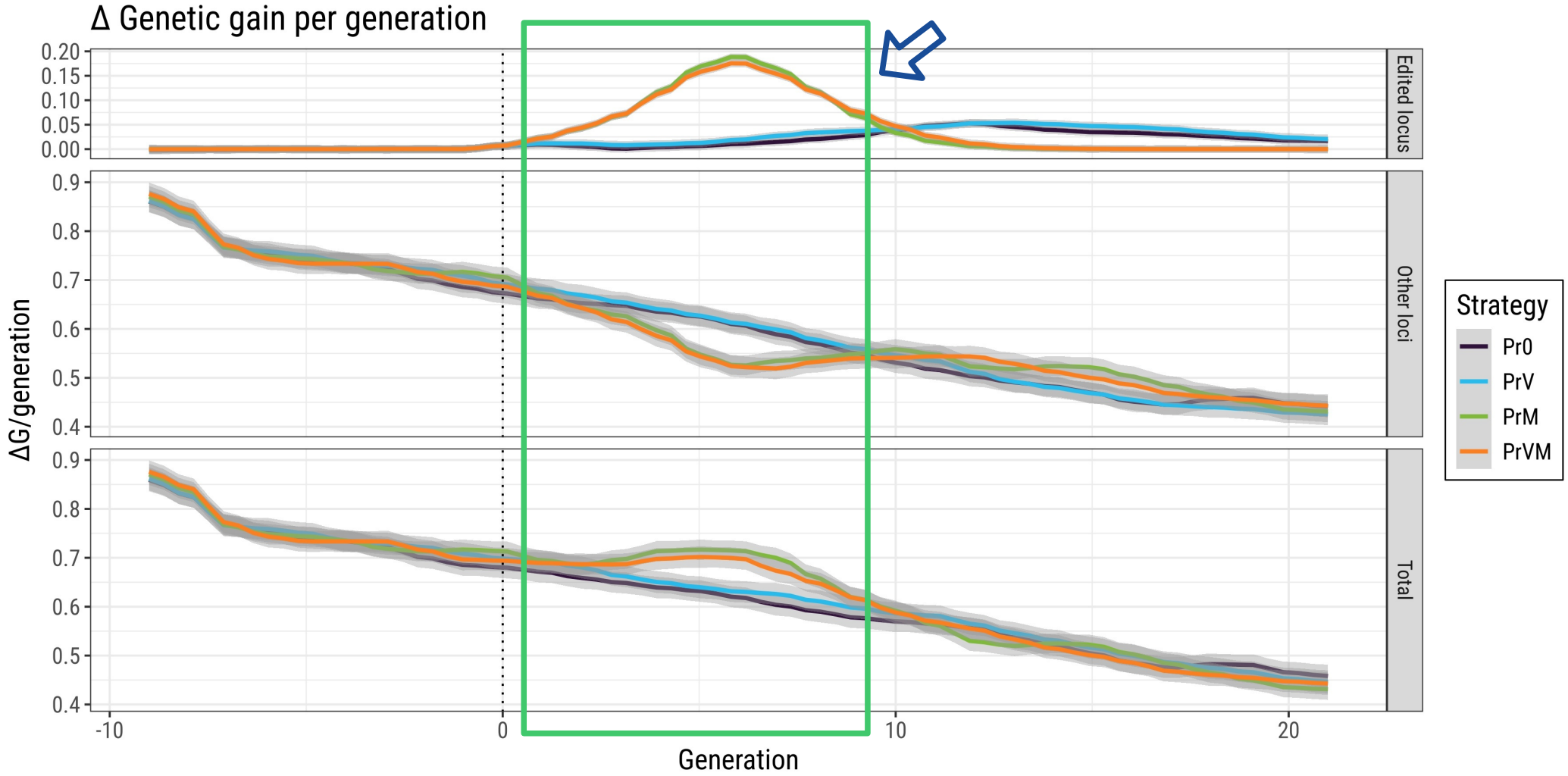
20


Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
0.20
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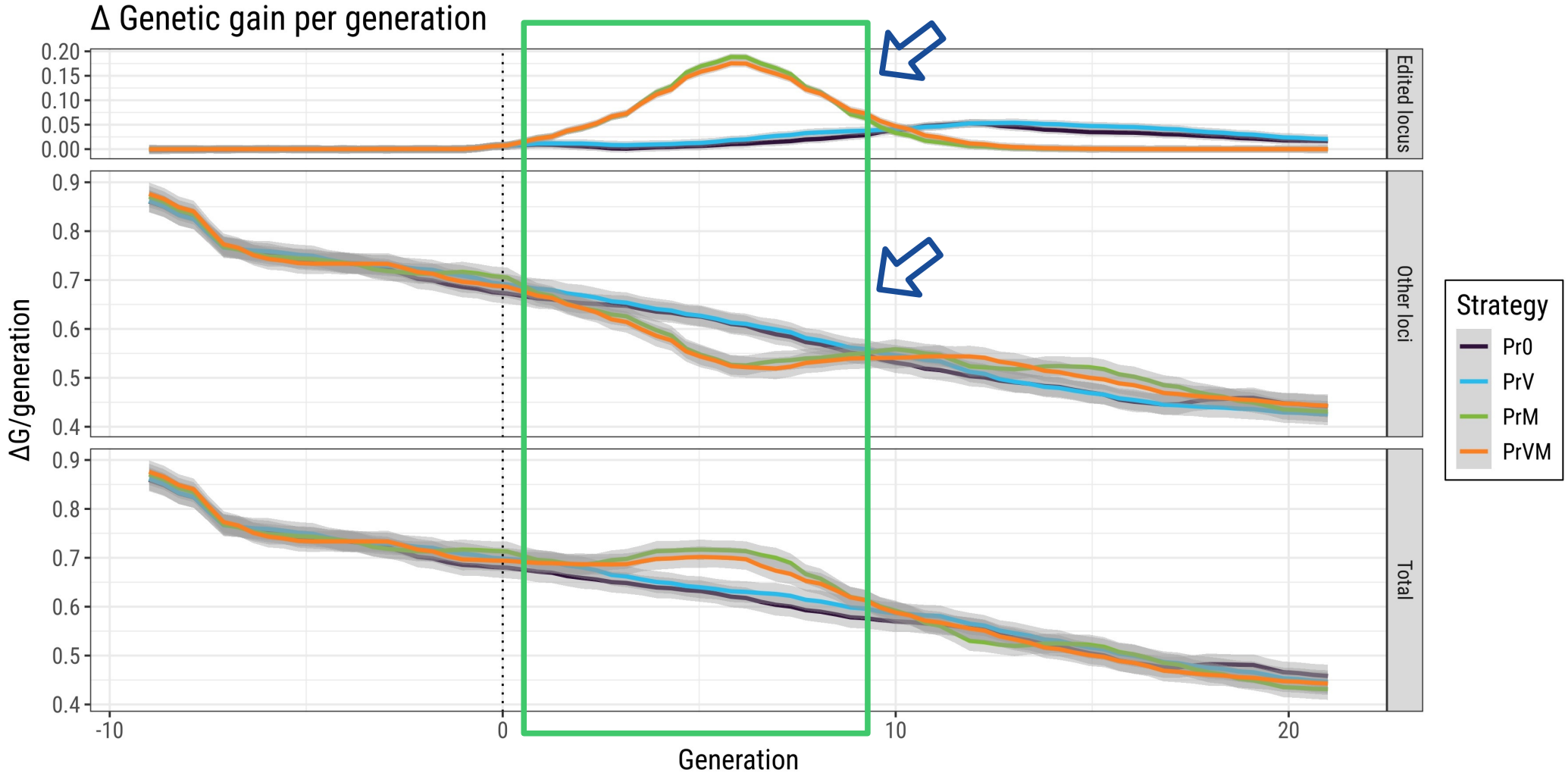
Δ Genetic gain per generation
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Generation
Edited locus
Other loci
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Pr0
PrV
PrM
PrVM
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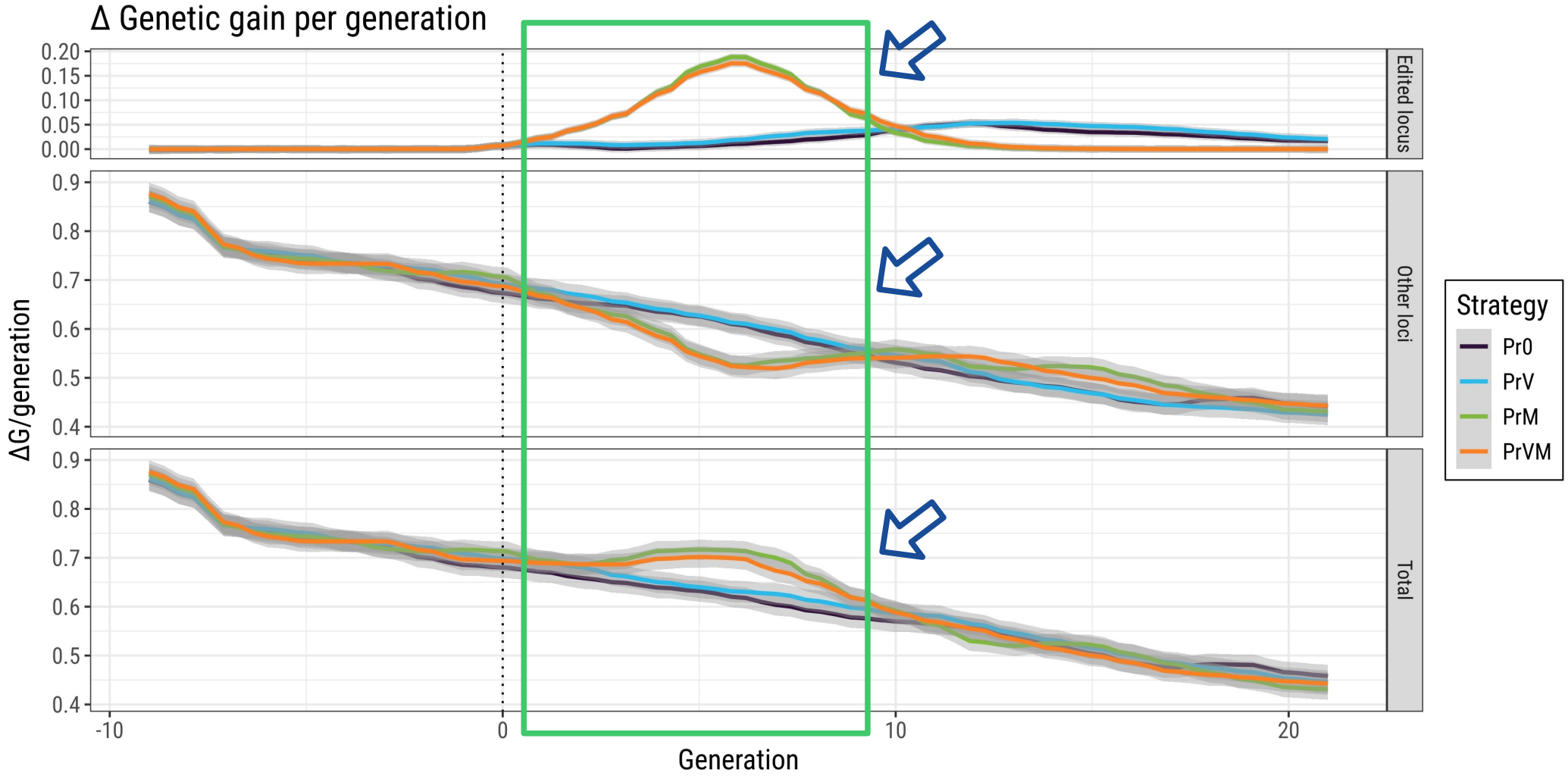
Δ Genetic gain per generation
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0.20
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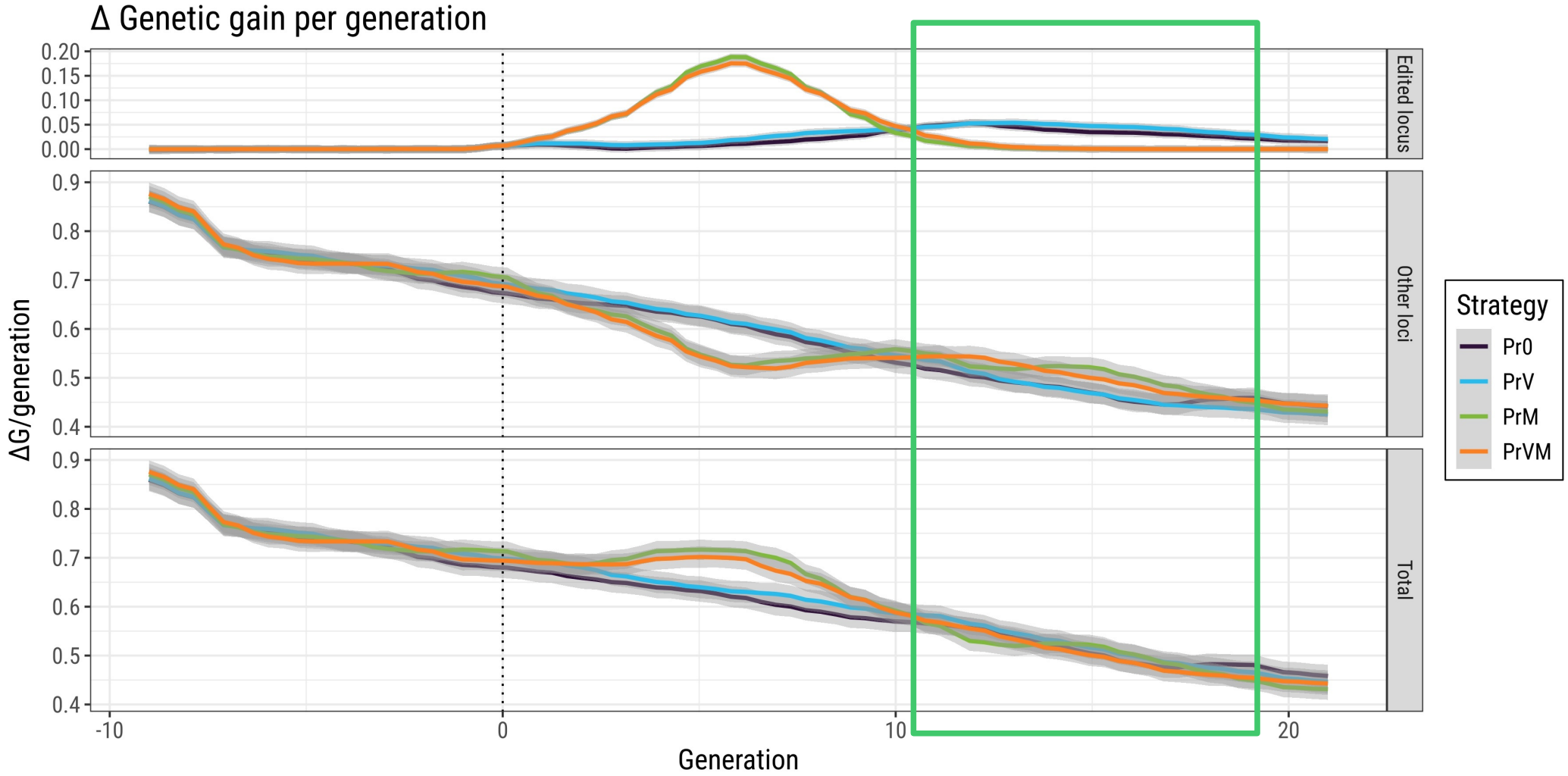
Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
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Pr0
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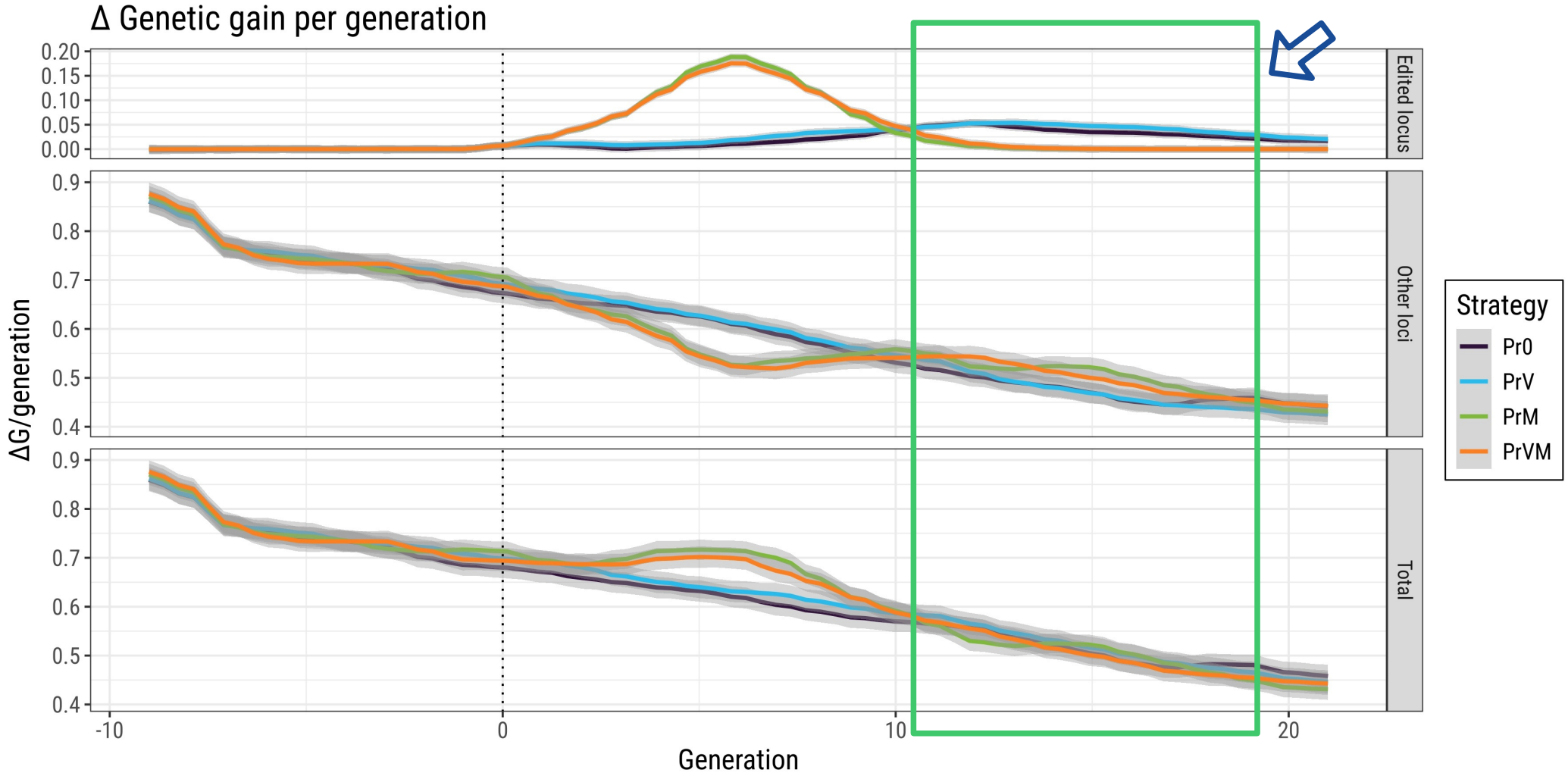
Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
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Strategy
Pr0
PrV
PrM
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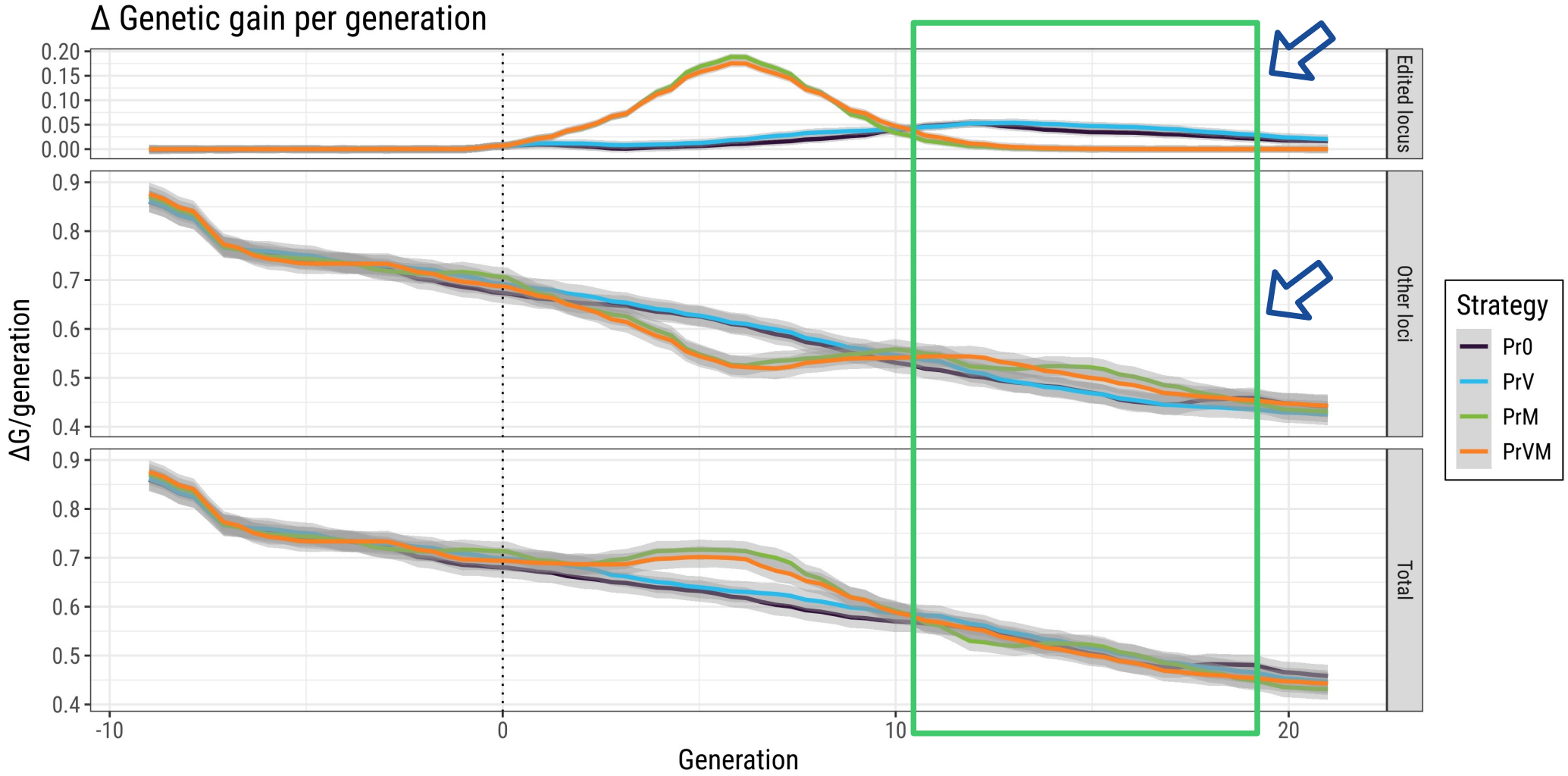
Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
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0.15
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0.00
0.9
0.8
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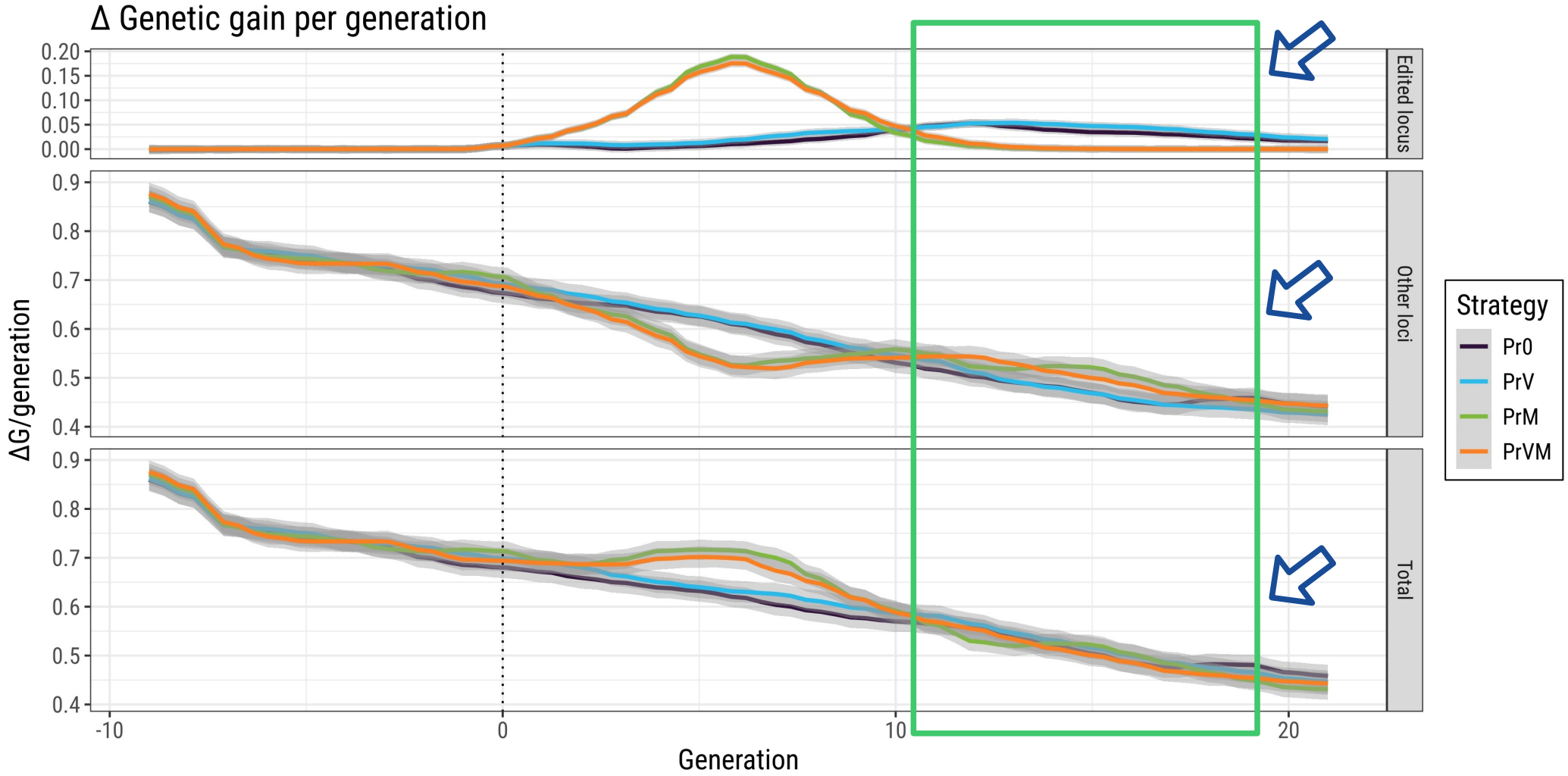
0.5
0.4
-10
0
10
20


Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
0.20
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-10
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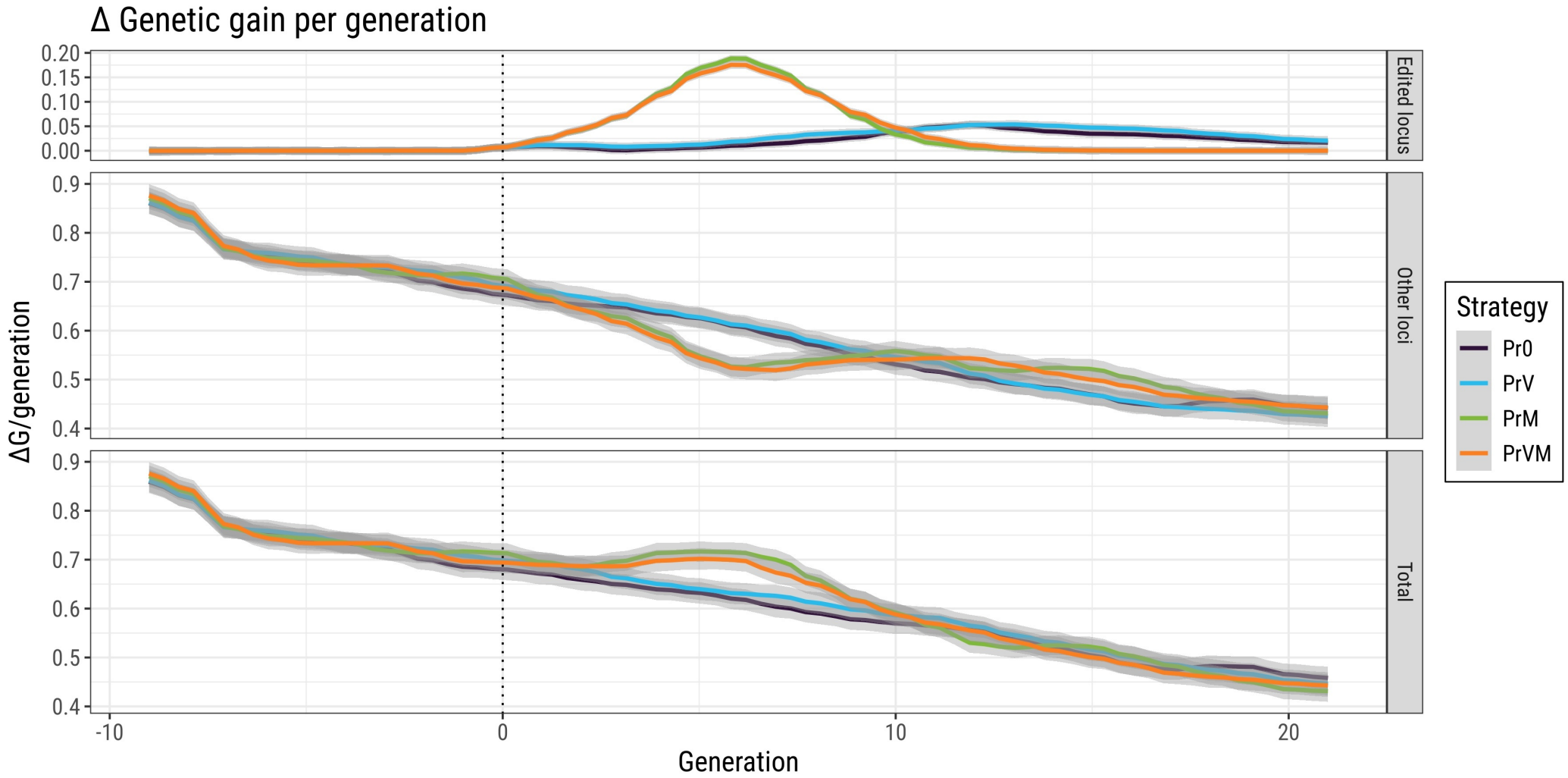
20


Δ Genetic gain per generation
ΔG/generation
Generation
Edited locus
Other loci
Total
Strategy
Pr0
PrV
PrM
PrVM
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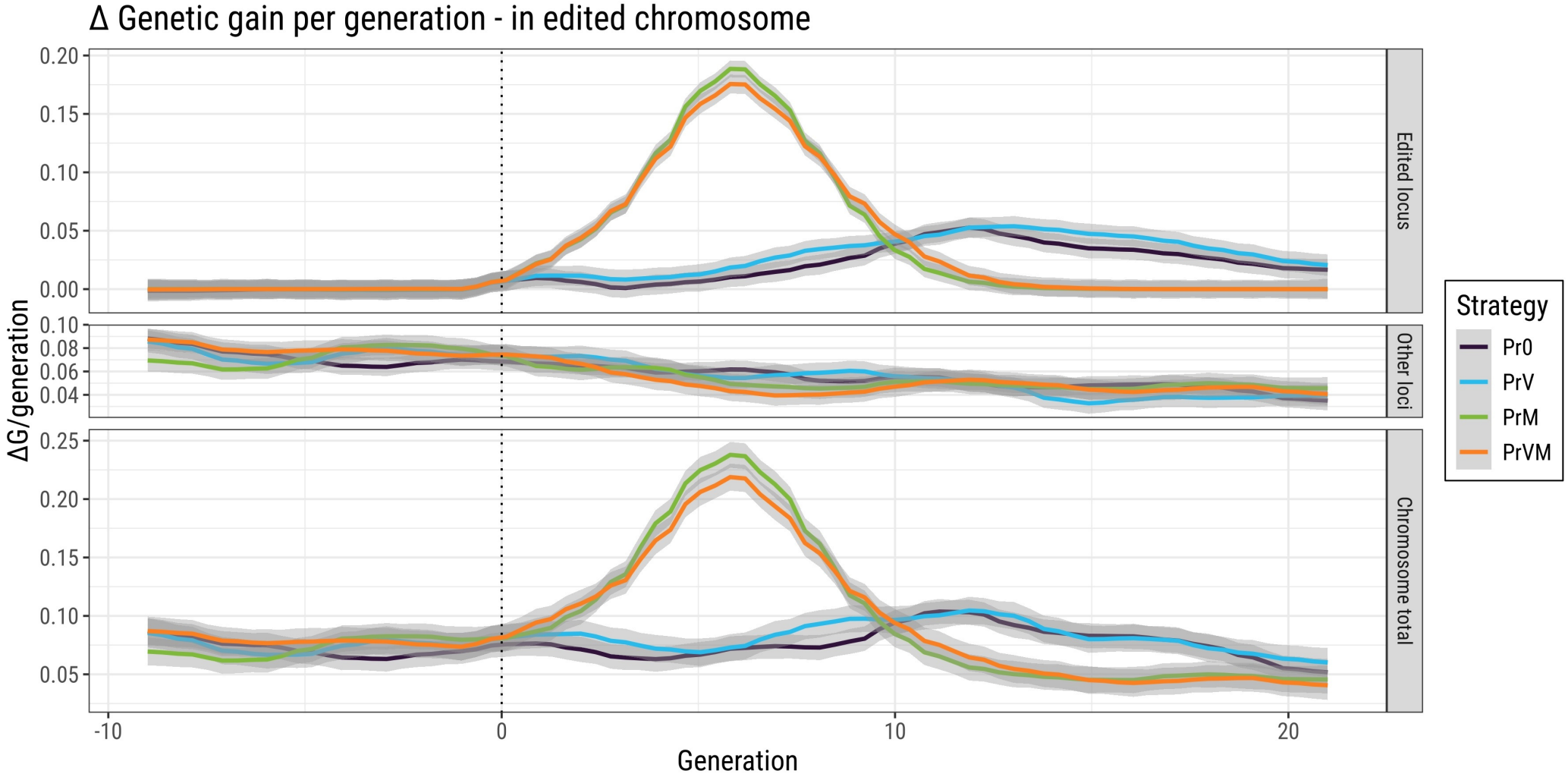
Δ Genetic gain per generation - in edited chromosome
ΔG/generation
Generation
Edited locus
Other loci
Chromosome total
Strategy
Pr0
PrV
PrM
PrVM
0.20
0.15
0.10
0.05
0.00
0.10
0.08
0.06
0.04
0.25
0.20
0.15
0.10
0.05
-10
0
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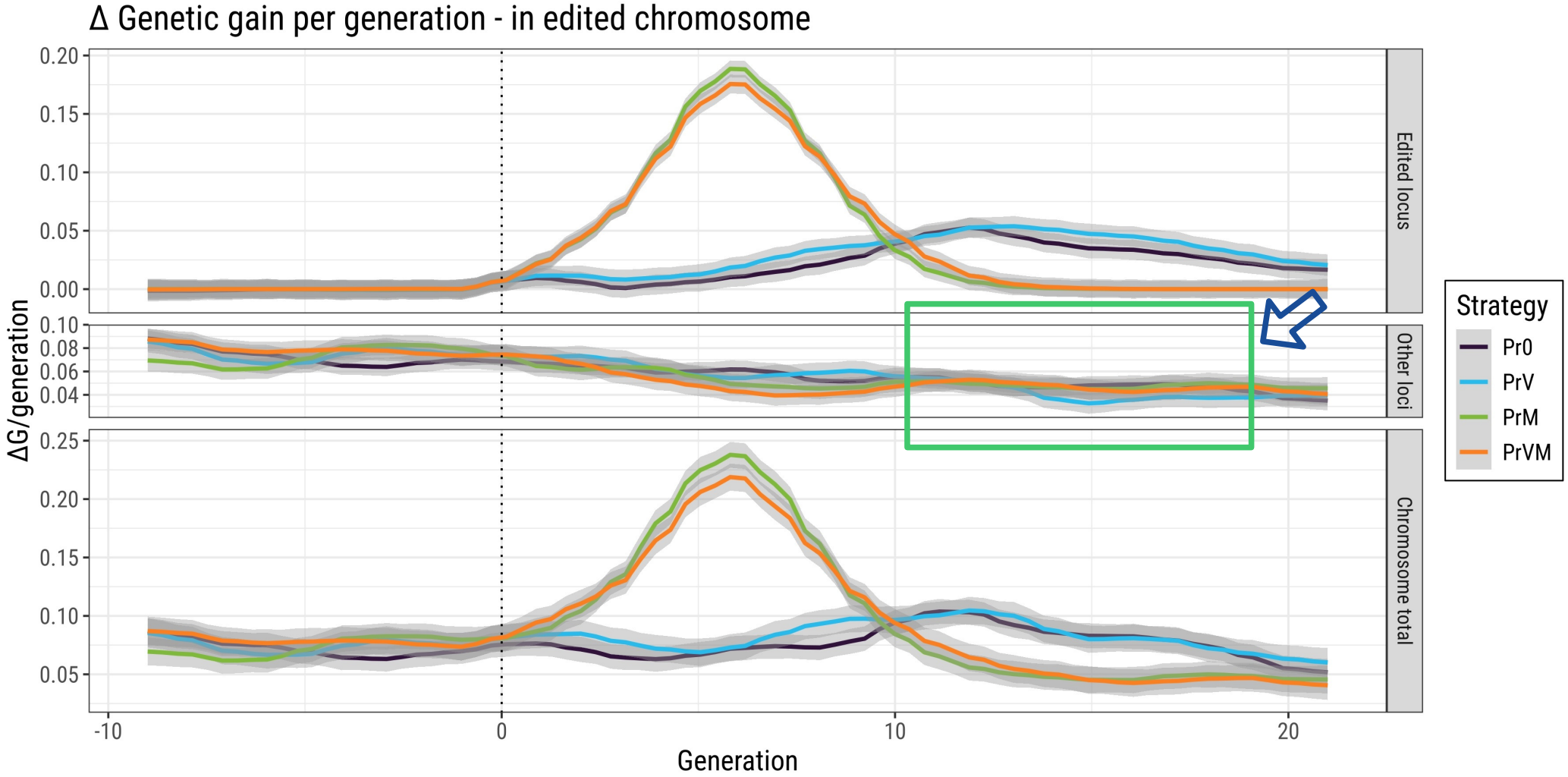
20


Δ Genetic gain per generation - in edited chromosome
ΔG/generation
Generation
Edited locus
Other loci
Chromosome total
Strategy
Pr0
PrV
PrM
PrVM
0.20
0.15
0.10
0.05
0.00
0.10
0.08
0.06
0.04
0.25
0.20
0.15
0.10
0.05
-10
0
10
20

Discussion

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Selection on conventional GEBVs is at high risk of losing the gene edited (GE) alleles,

- altering **prior variances** improves the situation marginally
- both methods would need an extra measure to keep the GE.

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Selection on conventional GEBVs is at high risk of losing the gene edited (GE) alleles,

- altering **prior variances** improves the situation marginally
- both methods would need an extra measure to keep the GE.

Altering **Prior Means** effectively preserves the GE alleles,

- allows a fast increase of their frequency within the selected population, integrated in the selection criteria,
- seemingly without great loss of variation in the edited chromosome.

Next Steps

We are further exploring the use of altered **Prior Means**,

- in similar but more challenging scenarios than presented here,
- e.g., with incorrect prior effects for the gene edited variant.

as a general tool to modify **selection pressure** on specific **rare alleles** in the context genomic selection

- e.g., to purge rare recessive deleterious mutations,
- or share information from alleles common in other breeds.

Thank you for your attention

www.rumigen.eu

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Extra

Edited allele 5 generations after introduction

strategy	lost	over50	over90	fixed
Random	0.0	0.00	0	0
Pr0	0.2	0.00	0	0
PrV	0.0	0.00	0	0
PrM	0.0	0.25	0	0
PrVM	0.0	0.25	0	0

Edited allele 10 generations after introduction

strategy	lost	over50	over90	fixed
Random	0.05	0.00	0.00	0.00
Pr0	0.40	0.05	0.00	0.00
PrV	0.20	0.10	0.00	0.00
PrM	0.00	1.00	0.95	0.30
PrVM	0.00	1.00	0.90	0.15

Edited allele 20 generations after introduction

strategy	lost	over50	over90	fixed
Random	0.2	0.00	0.00	0
Pr0	0.4	0.35	0.15	0
PrV	0.2	0.55	0.10	0
PrM	0.0	1.00	1.00	1
PrVM	0.0	1.00	1.00	1