The effective number and profile of causative markers in GWAS

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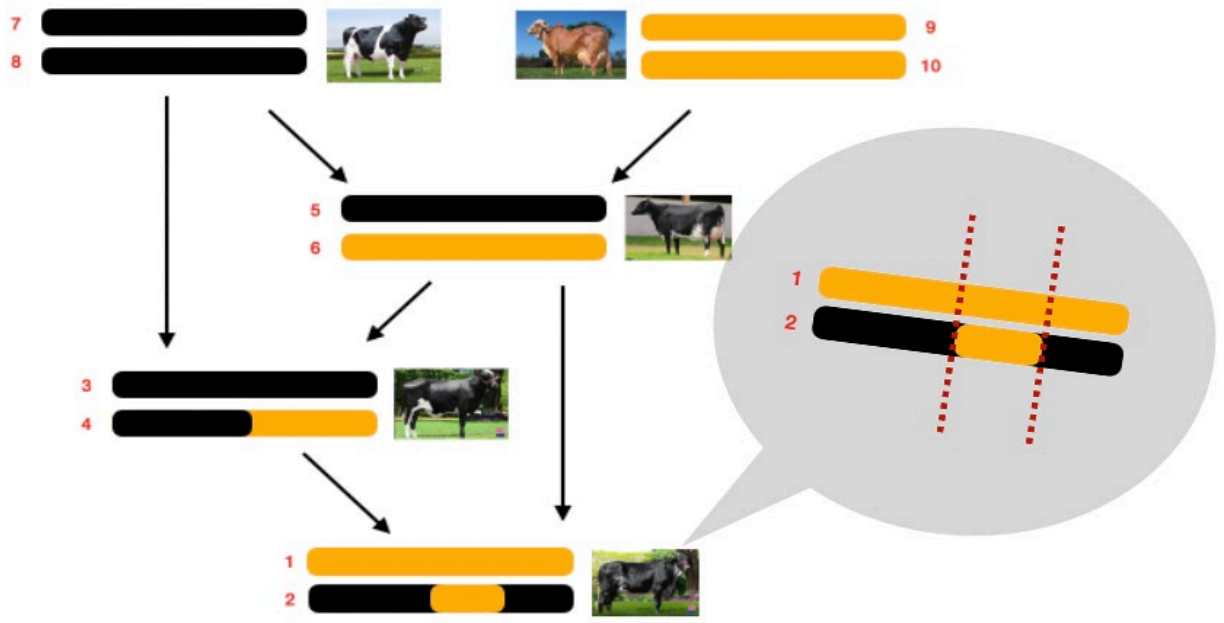
Background

- Inheritance is chunkular



Fortuna (2024)

Background

- Inheritance is chunkular
- Independent chromosome segments (Me)

• Theory of junctions	Fisher (1949)
• E(Me) = 4NeL	Stam (1980)
• 1 / Var(**G**-**A**)	Wientjes et al. (2016)
• Spectral decomposition **G**	Misztal (2016); Pocrnic et al. (2016)

  - Rank ≤ min(#SNP, #ID, #Me)
  - The number that explains 98% of variance in **G**

- … many more exist …

Background

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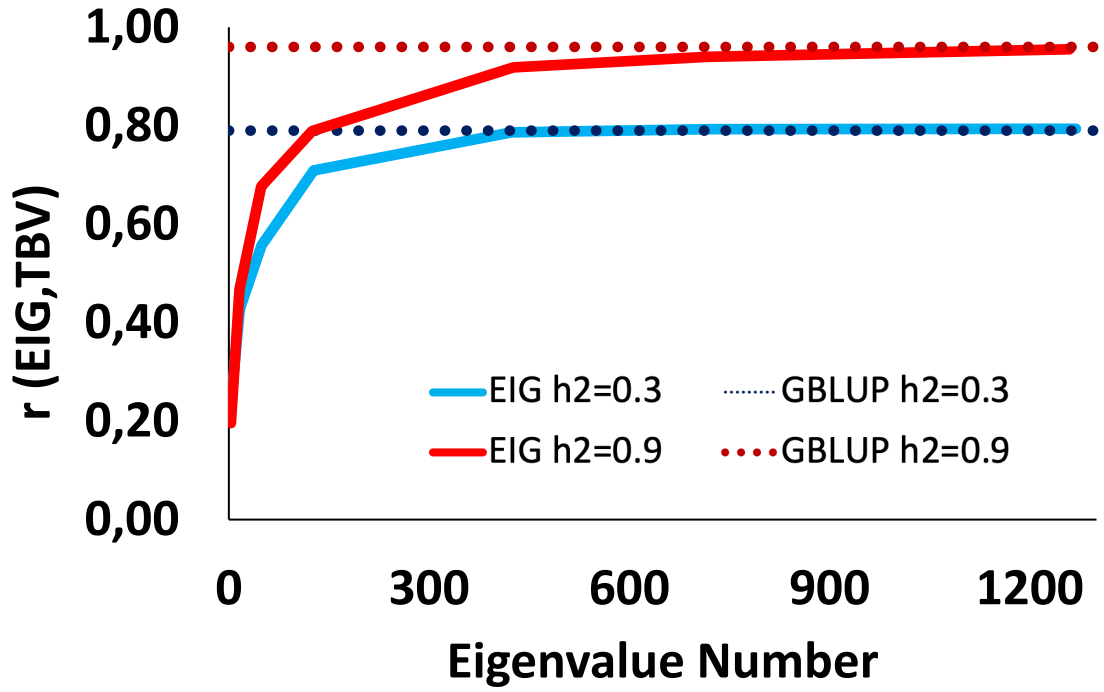
- Independent chromosome segments (Me)
- Genomic dimensionality is limited

Species	Genotyped (x1000)	SNP (x1000)	Dimensionality (x1000)	Ne
Pig	23	37	**4.1**	48
Chicken	16	39	**4.2**	44
Jersey	75	61	**11.5**	101
Angus	81	38	**10.6**	113
Holstein	77	61	**14.0**	149

Pocrnic *et al.* (2016)

Background

- Inheritance is chunkular
- Independent chromosome segments (Me)
- Genomic dimensionality is limited
- Genomic prediction works by estimating chromosome segments (eigenvalues)



Pocrnic *et al.* (2019)

Motivation

- GP works by estimating chromosome segments (eigenvalues)
- How does the effective population size affect GWAS?
- How does the data size affect GWAS?
- What is the profile of a single QTL in Manhattan plots?
- Can the signals on the Manhattan plot be decomposed?

Simulation

- AlphaSimR (Gaynor et al., 2021)

- 10 CHR (100cM / CHR)
- 50,000 equidistant SNP (50/cM)
- 100 equidistant QTL (10/CHR) with equal additive effect
  - 500 SNP (≈10cM)
- Single trait with $h^2 = 0.5$
- 10 generations of random mating

- Populations with Ne 60 (small), Ne 60 (large) and Ne 600 (small)
  - Small; 6k genotyped animals; 24k total (ped + pheno)
  - Large; 18k genotyped animals; 60k total (ped + pheno)

Single-step GWAS

$$\mathbf{y} = \mathbf{1}\mu + \mathbf{Wu} + \mathbf{e}$$
$$\mathrm{Var}(\mathbf{e}) = \mathbf{I}\sigma_e^2$$
$$\mathrm{Var}(\mathbf{u}) = \mathbf{H}\sigma_u^2$$

$$\hat{\mathbf{a}}|\hat{\mathbf{u}} = \lambda\alpha\delta\mathbf{DZ}'\mathbf{G}^{-1}\hat{\mathbf{u}}$$

$$Pvalue_i = 2\left(1 - \Phi\left(\left|\frac{\hat{a}_i}{sd(\hat{a}_i)}\right|\right)\right)$$

BLUPF90 family

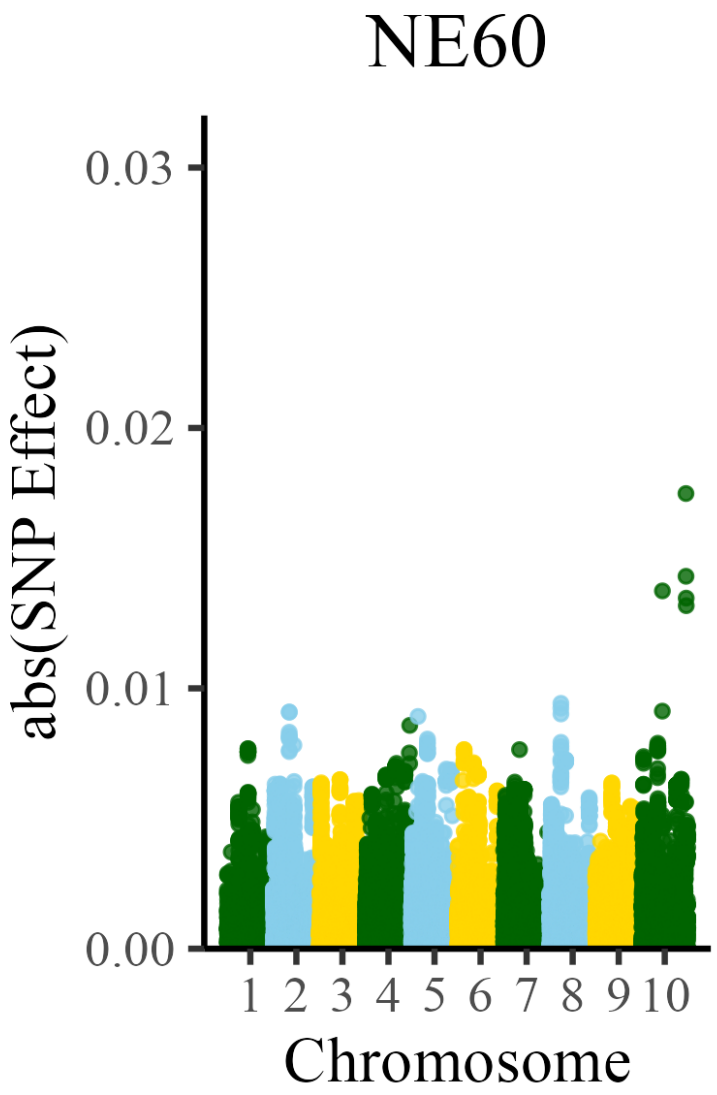
$$\mathbf{H}^{-1} = \mathbf{A}^{-1} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_b^{-1} - \mathbf{A}_{22}^{-1} \end{bmatrix}$$

$$\mathbf{G}_b = \alpha\mathbf{G} + (1-\alpha)\mathbf{A}_{22}$$

$$\mathbf{G} = \frac{\mathbf{ZDZ}'}{2\sum p_j(1-p_j)}$$

Wang *et al.* (2012); Aguilar *et al.* (2019)

Manhattan plots (SNP-effects)



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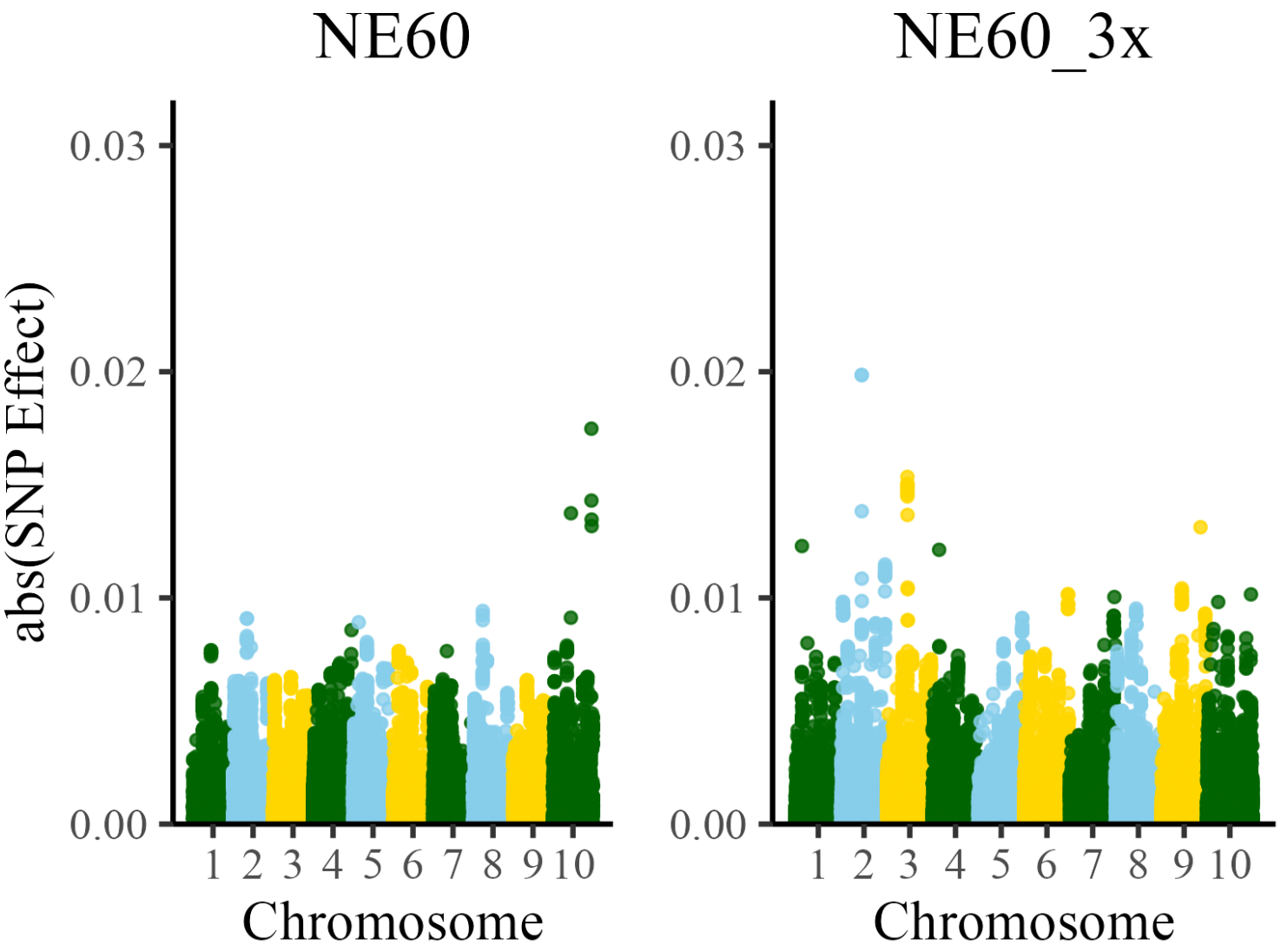
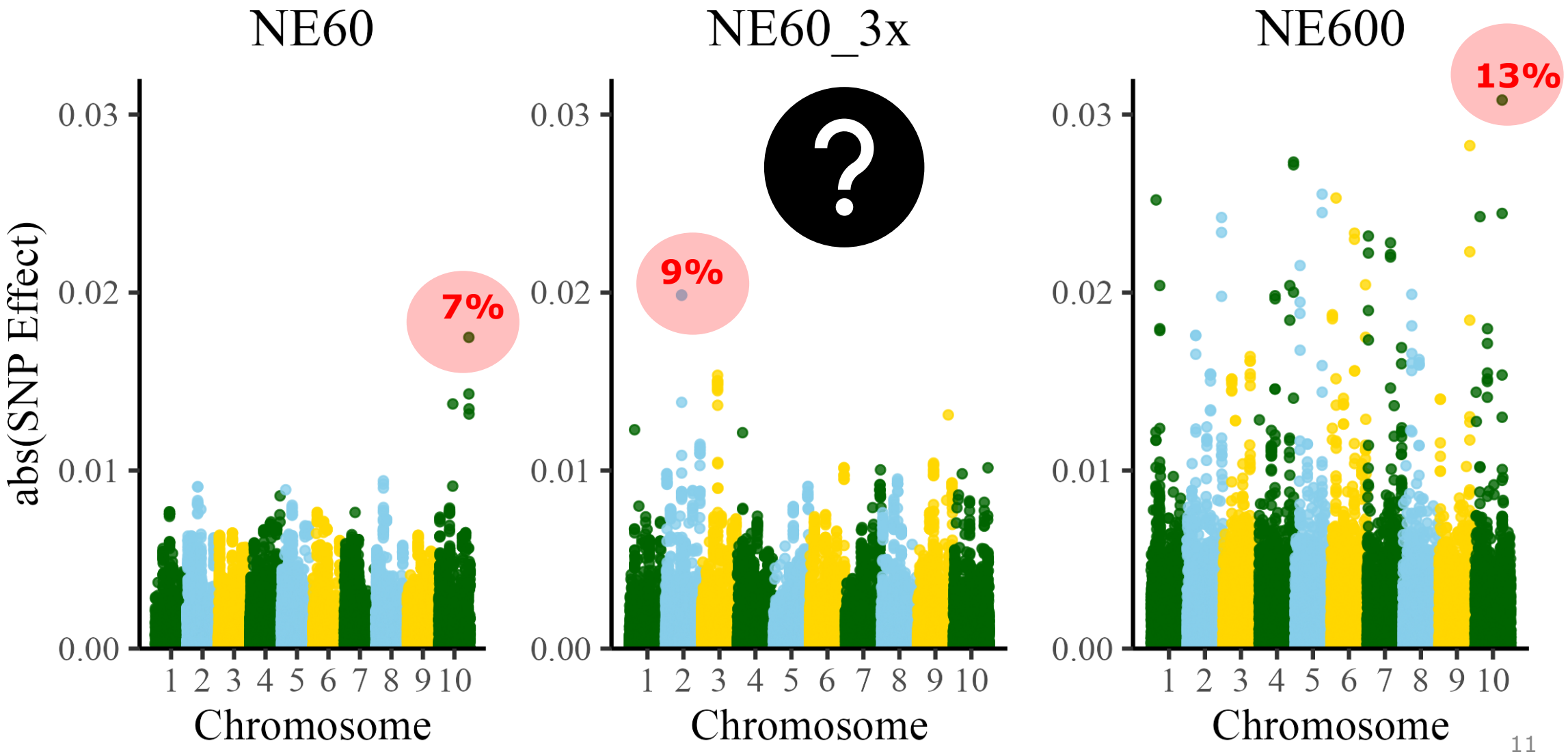
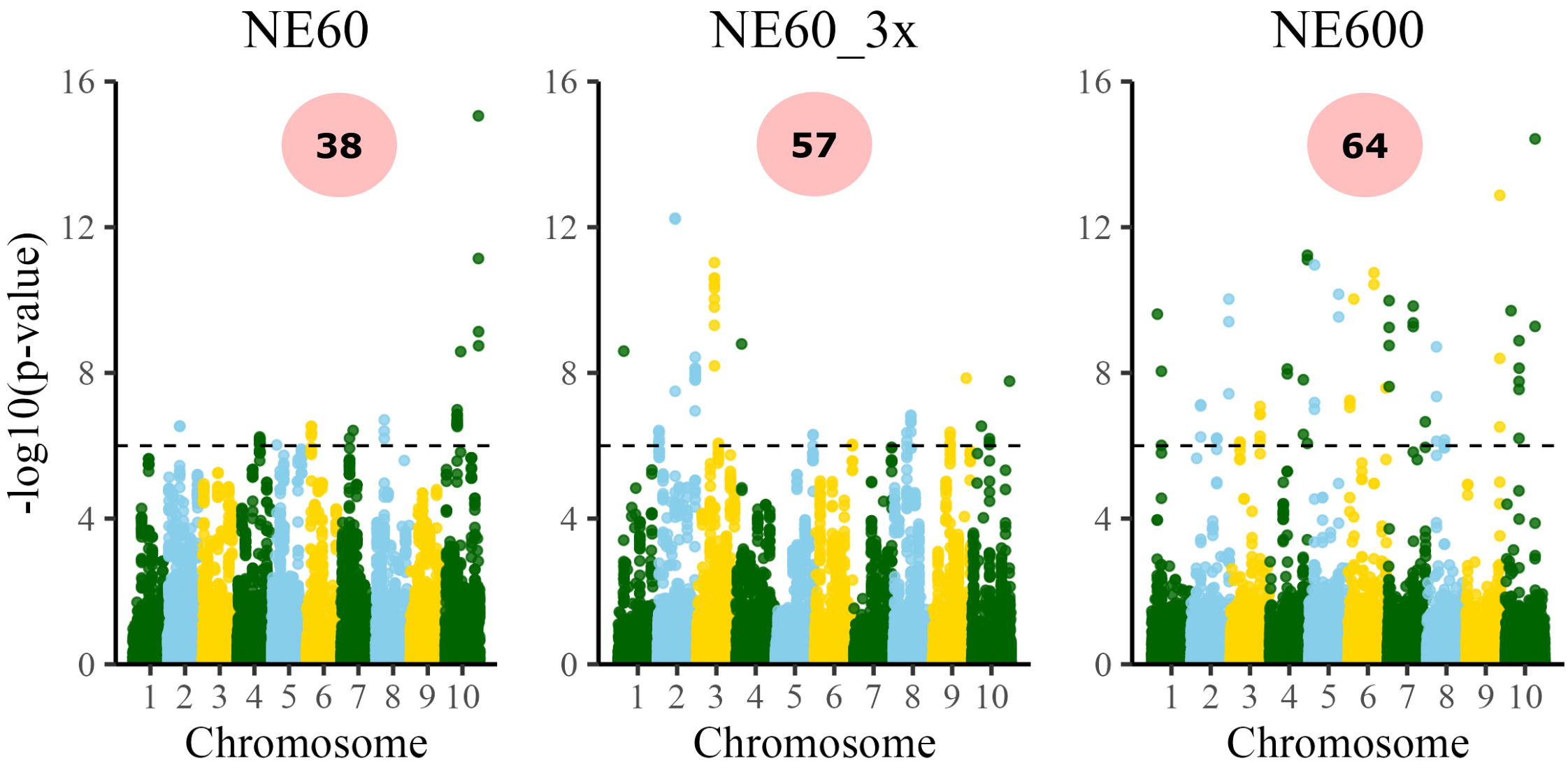


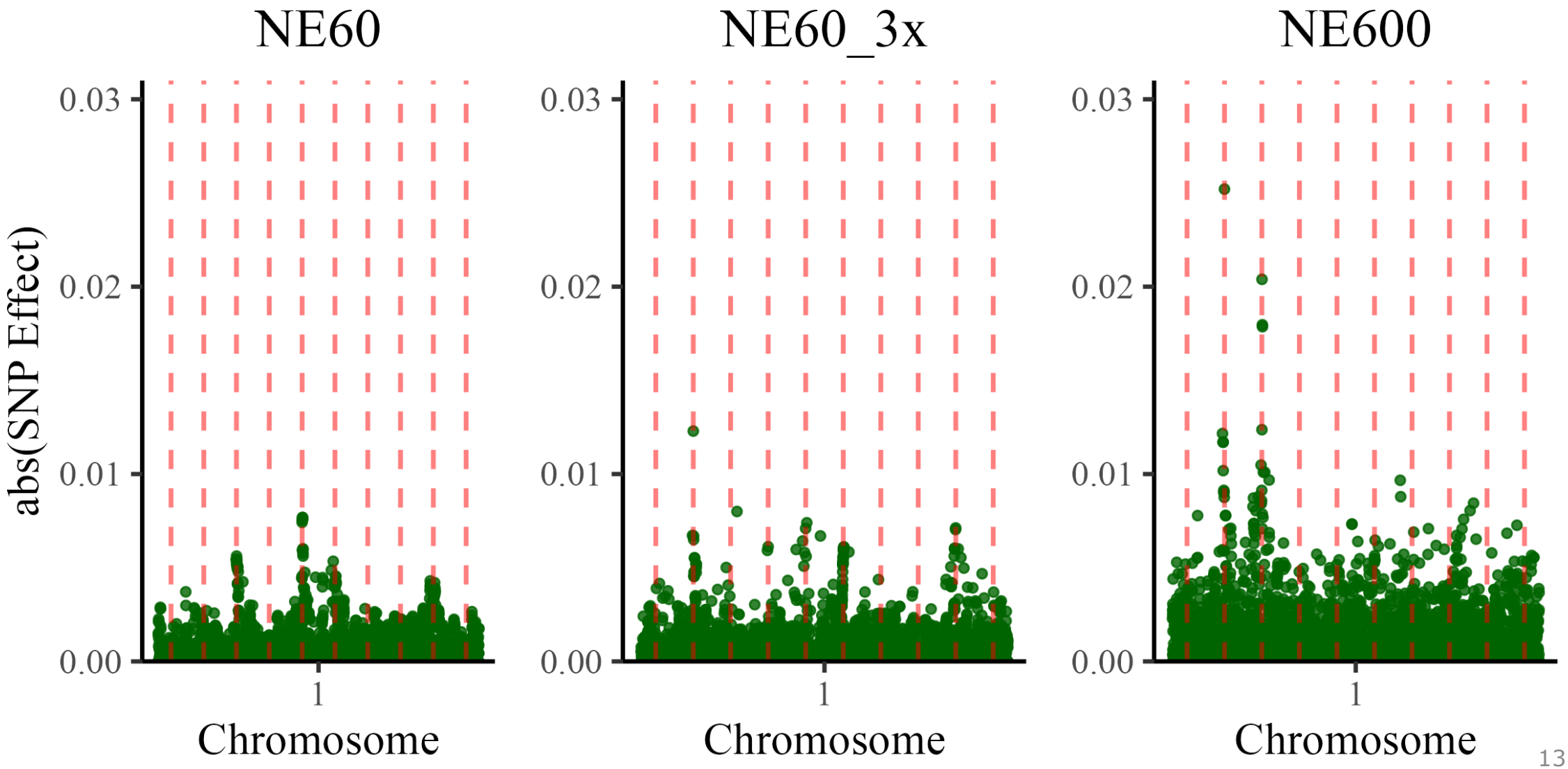
Manhattan plots (SNP-effects)



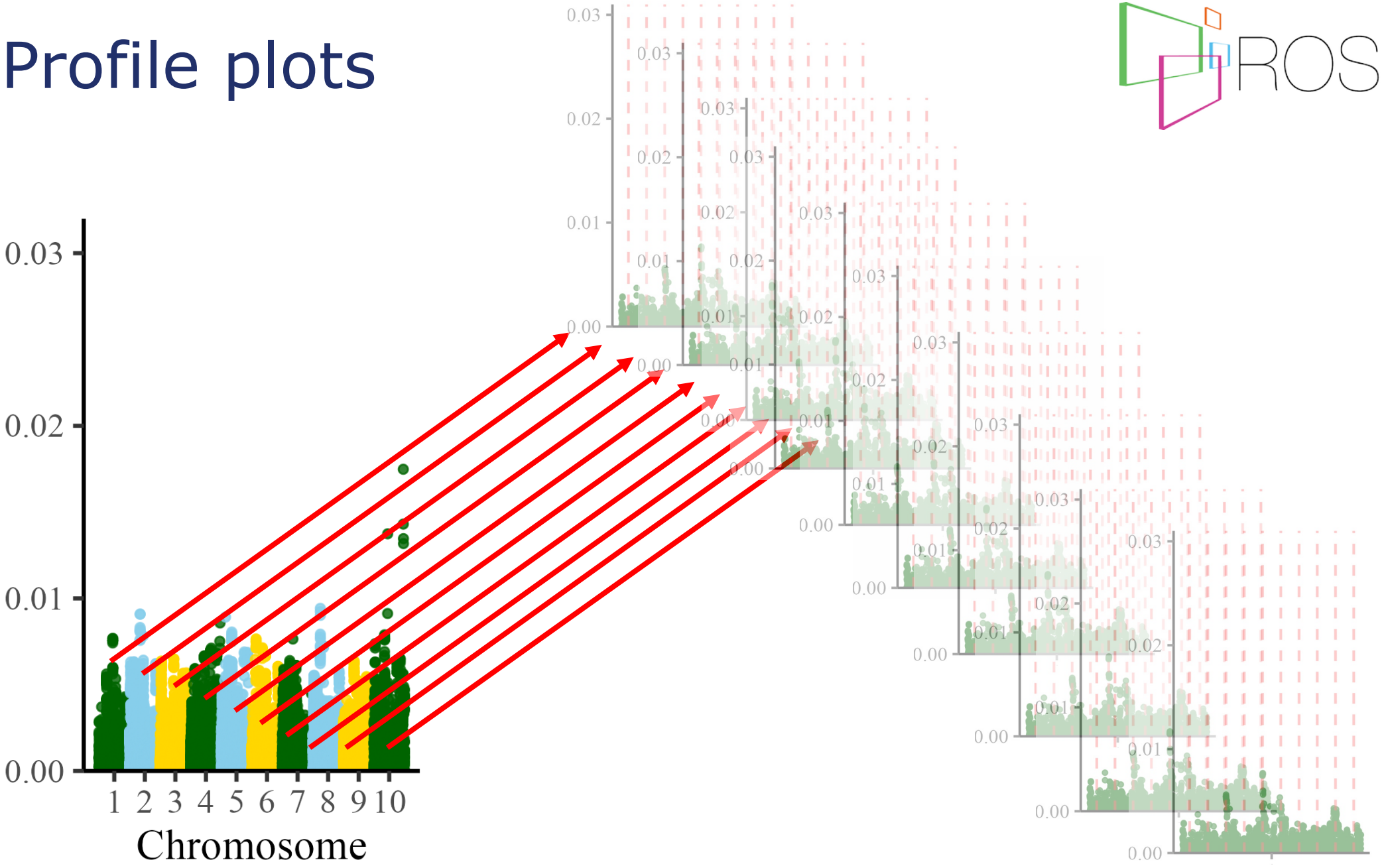
Manhattan plots (p-values)



Zoom-in single chromosome



Profile plots



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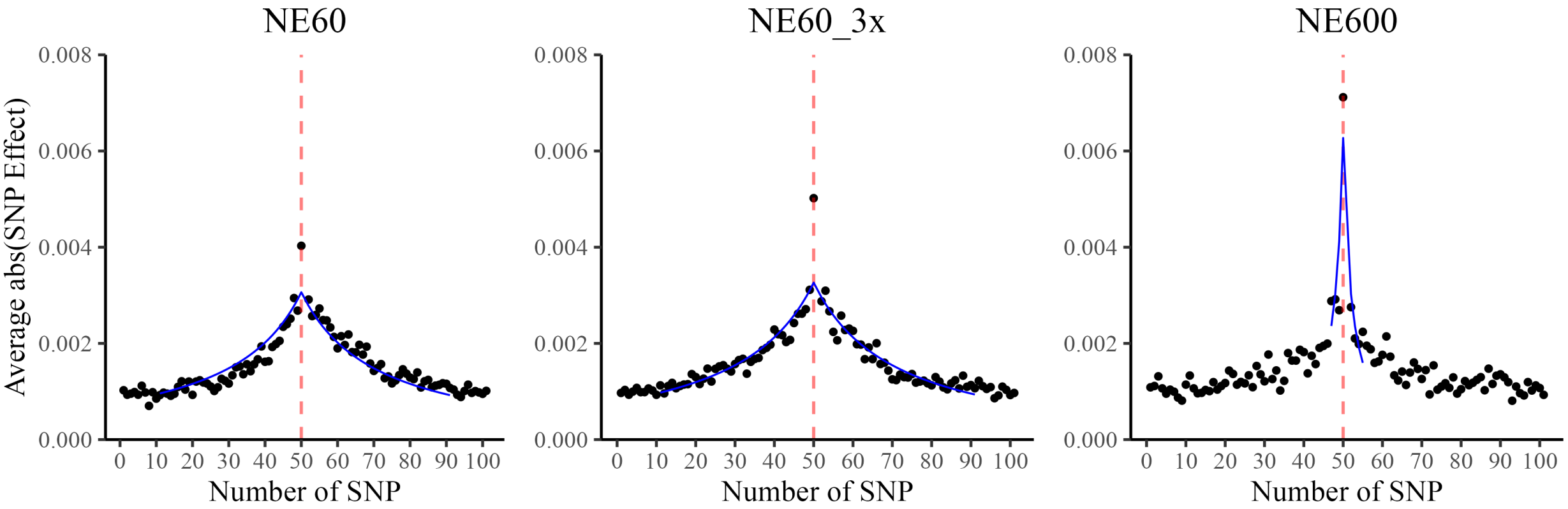


E(Me) = 2,400

E(Me) = 2,400

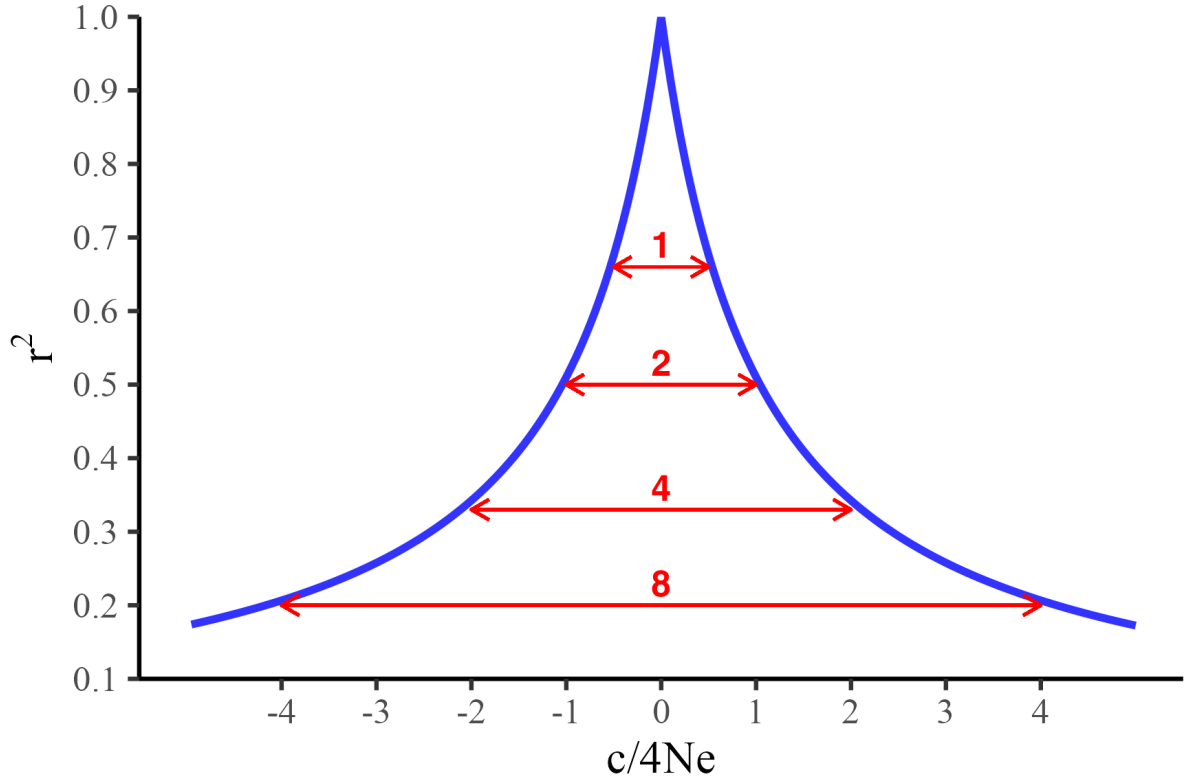
E(Me) = 24,000

What is that profile?

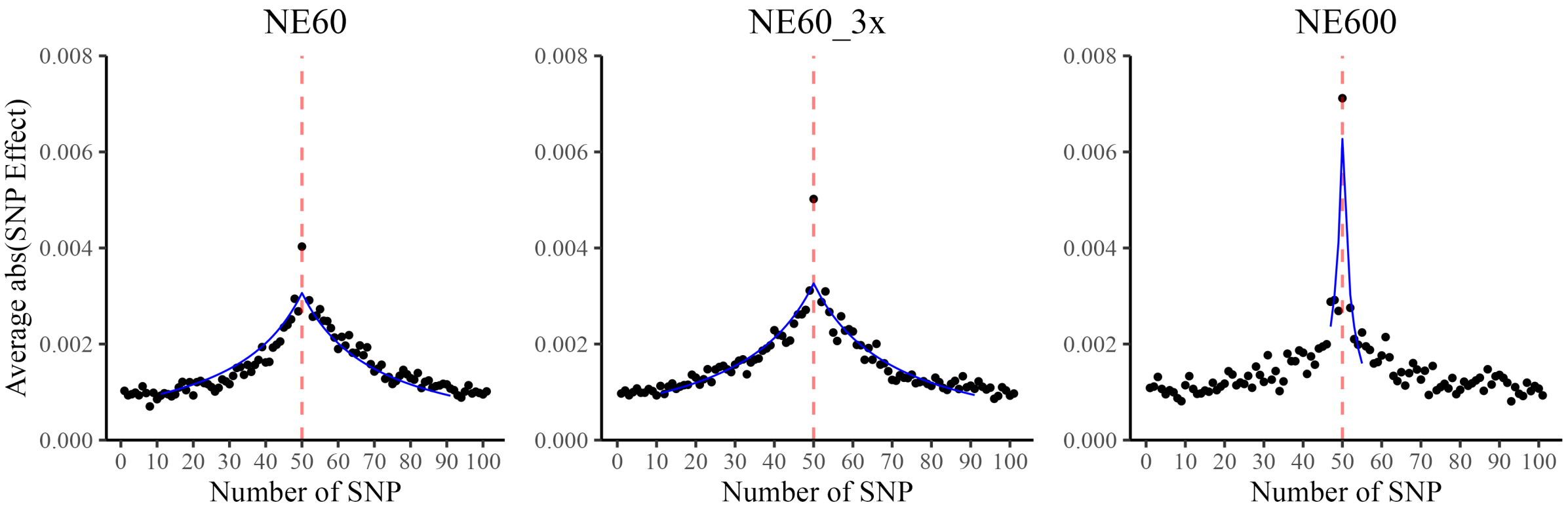
- $E(r^2) = 1/(4cNe + 1)$ Sved(1971)

- Stam segment is 1/4 Ne Morgan

- Optimal size
  - 2Mb (Ne 100)
  - 5Mb (Ne 40)
  - 20kb (Ne 10,000)



Profile plots (fit ± 2 Stam segments)



R^2 = 0.87

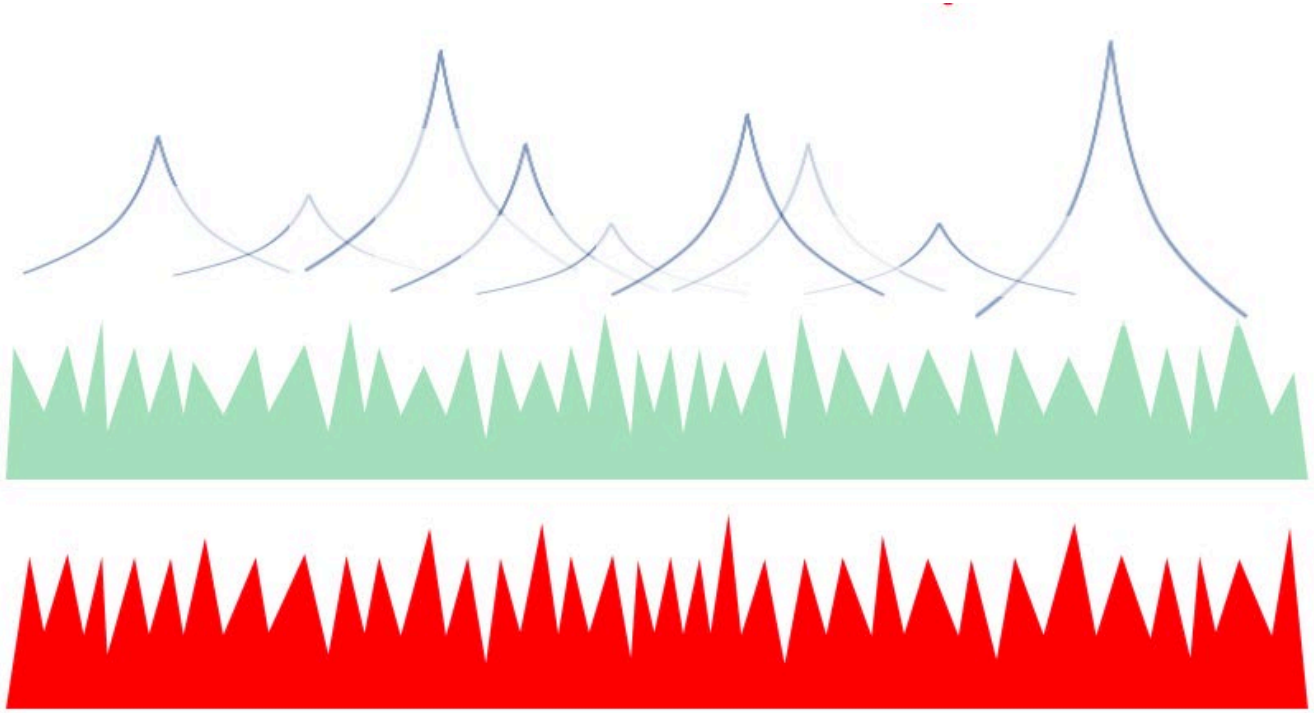
R^2 = 0.85

R^2 = 0.78

Components of Manhattan plot

QTNs

Components of Manhattan plot



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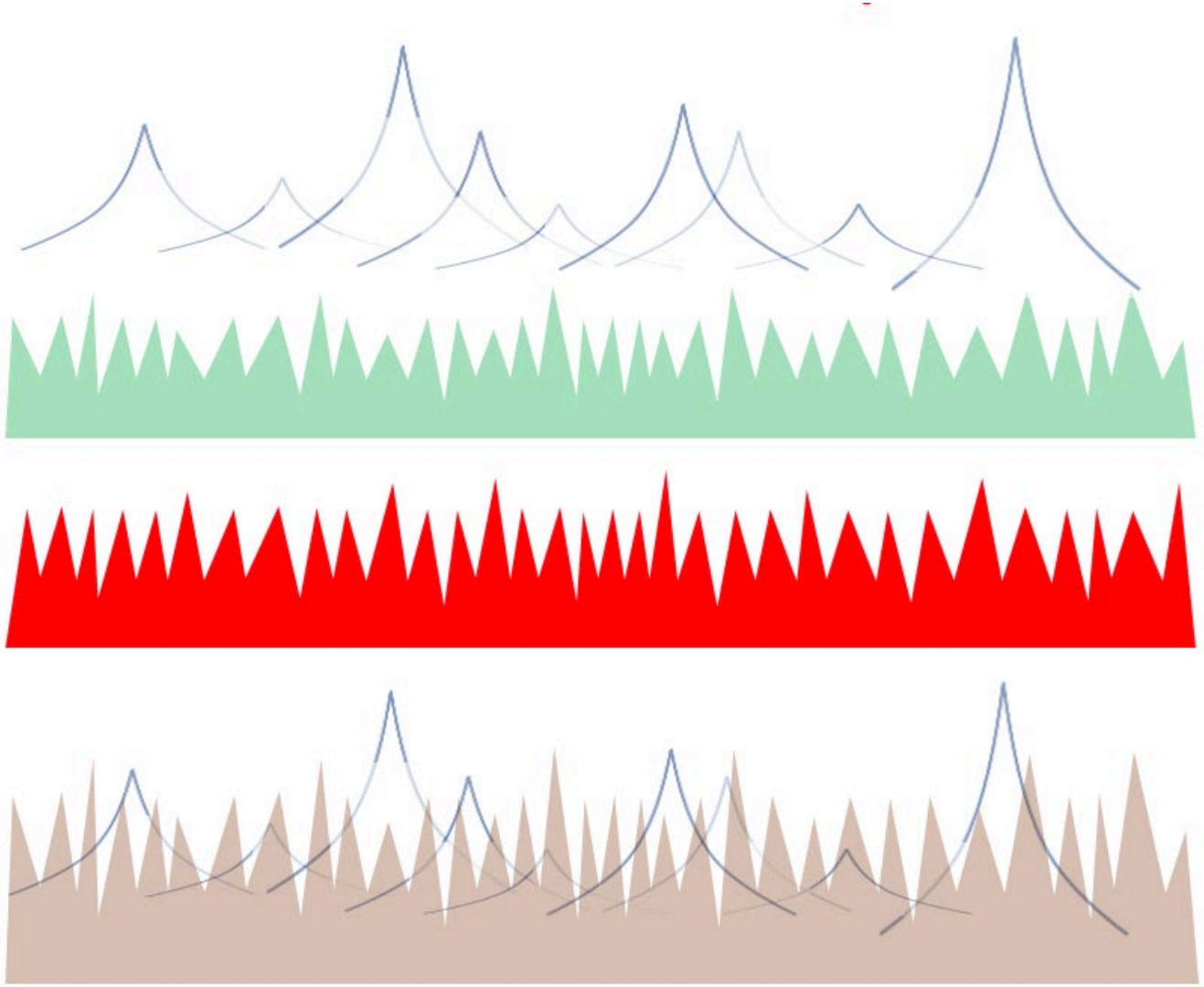


QTNs

Relationships

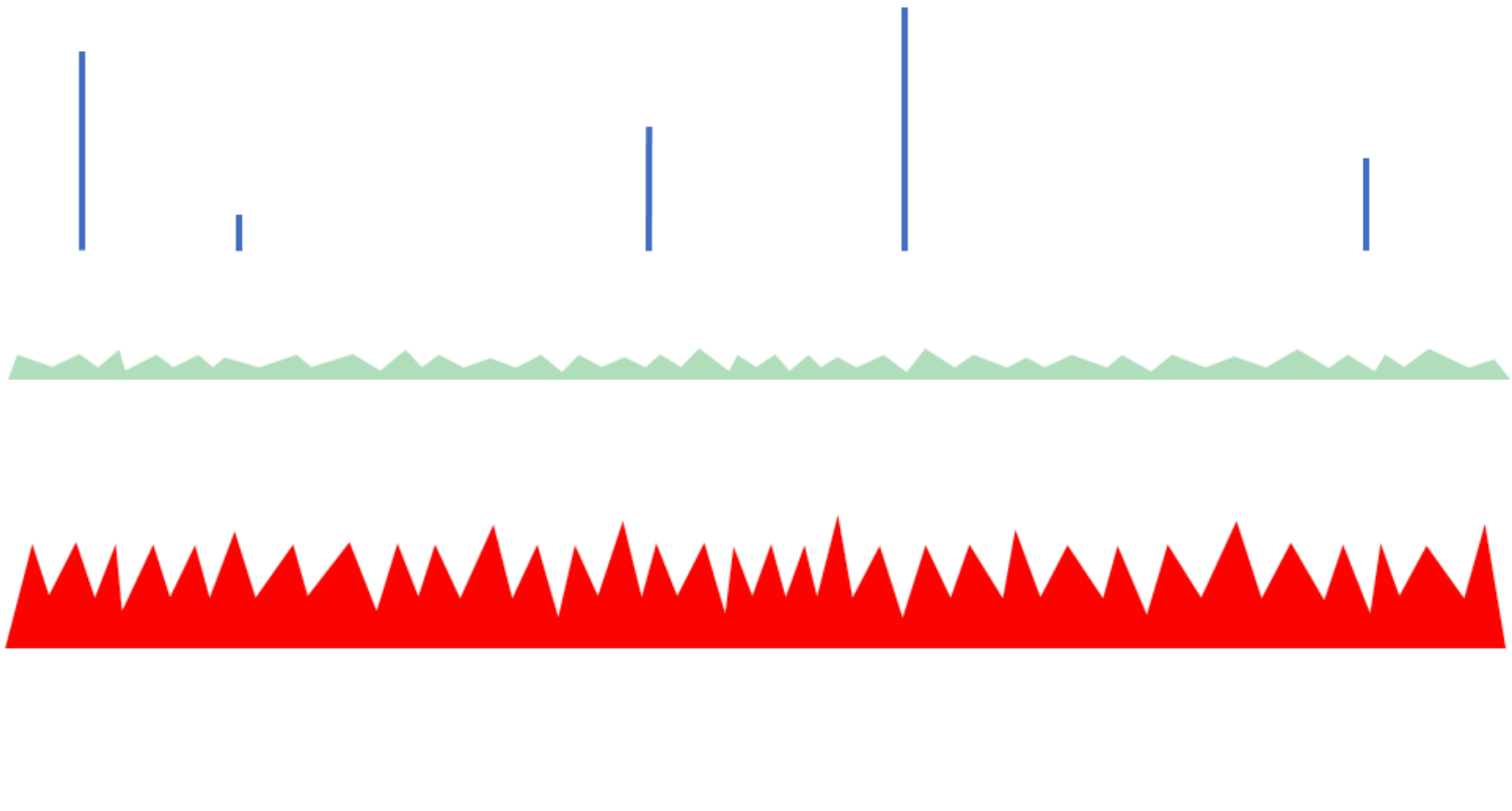
Noise

Combined

Components of Manhattan plot

QTNs

Components of Manhattan plot



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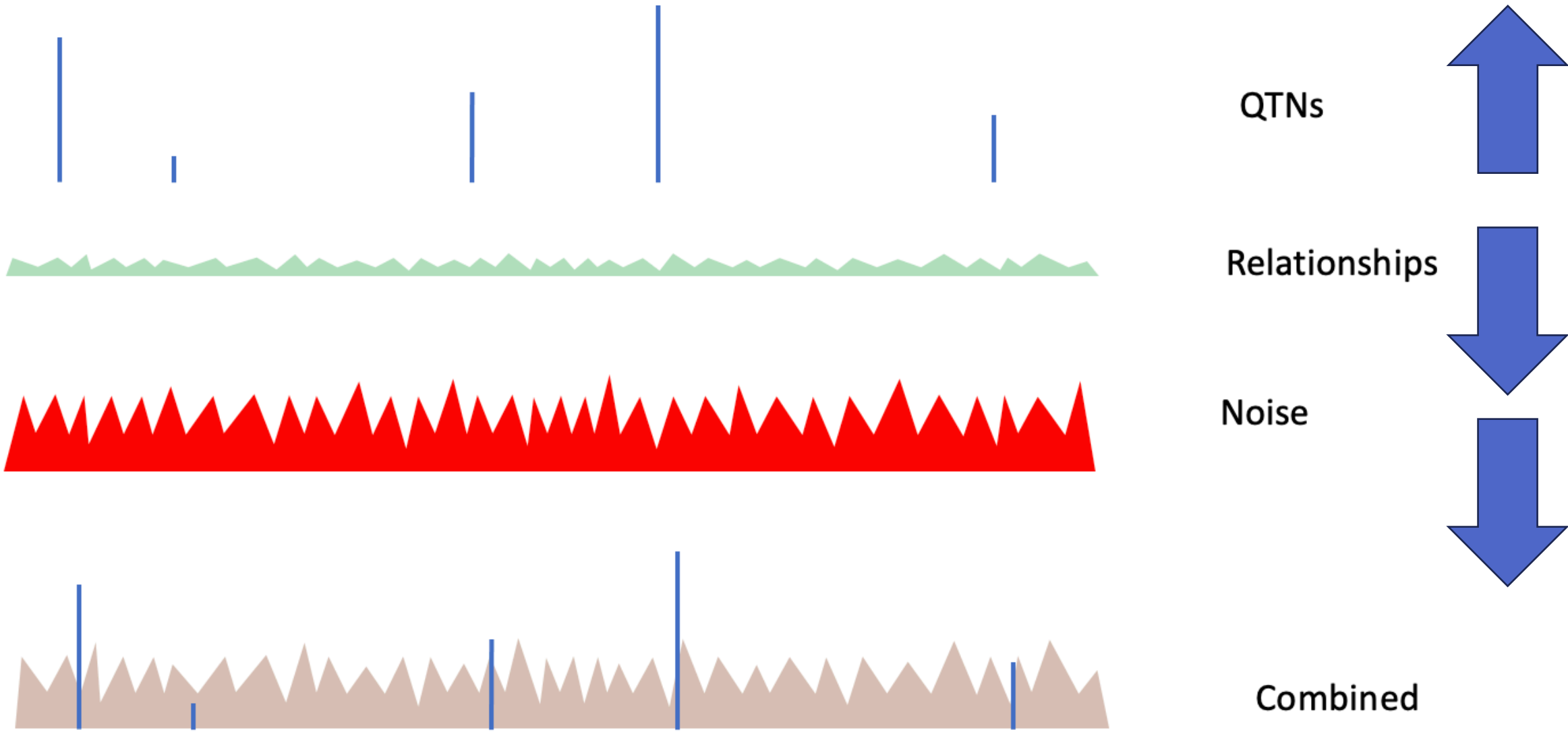
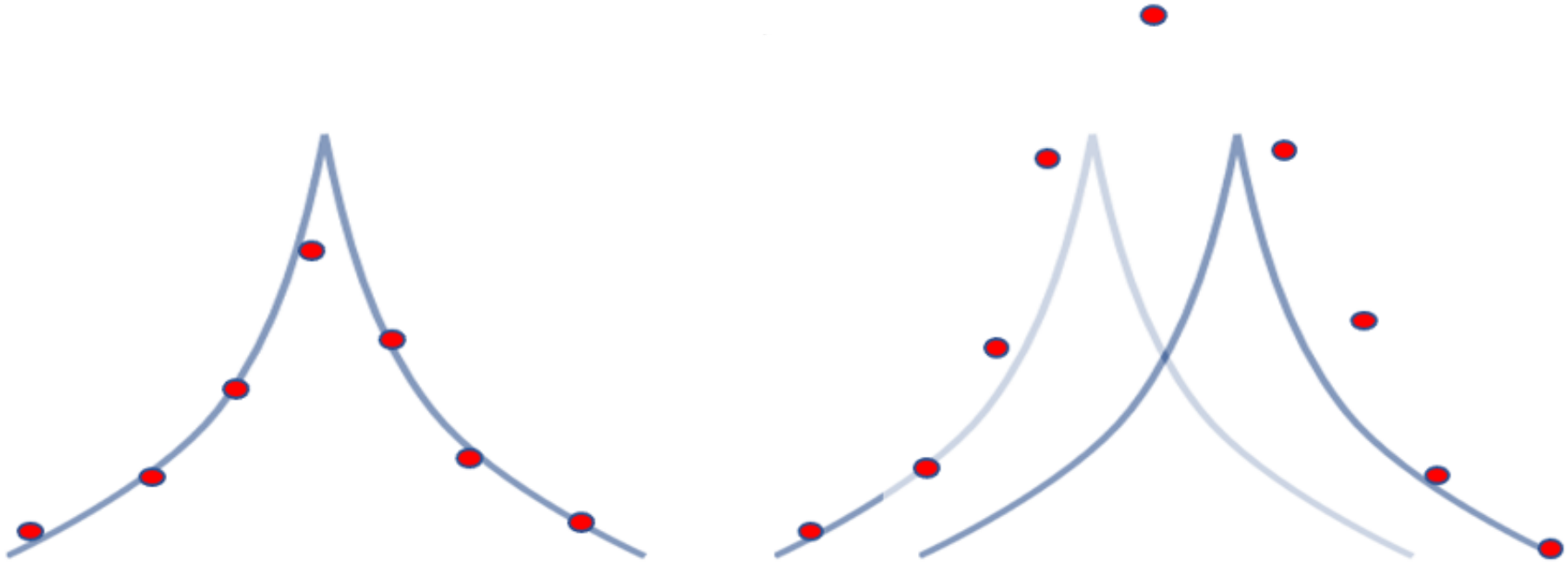


Segments overlap

- Why GP captures QTL?
- Optimal SNP-chip size?



Implications

- Signals due to QTN, QTN profile (LD), relationships and noise
  - Small Ne: QTN profile is wide & confounded with relationships
  - Large Ne: QTN profile is narrow & relationships weaker
- Large data needed
- The shape of pairwise LD curve and function of Ne
- GWAS with windows (segments) is useful
  - ~ 1-2 Mb (Ne 100)
  - ~ 0.1-0.2 Mb (Ne 1000)

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Genomic Prediction

Single nucleotide polymorphism profile for quantitative trait nucleotide in populations with small effective size and its impact on mapping and genomic predictions

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