Determining the effect of Hepatitis C genotype on infection outcome

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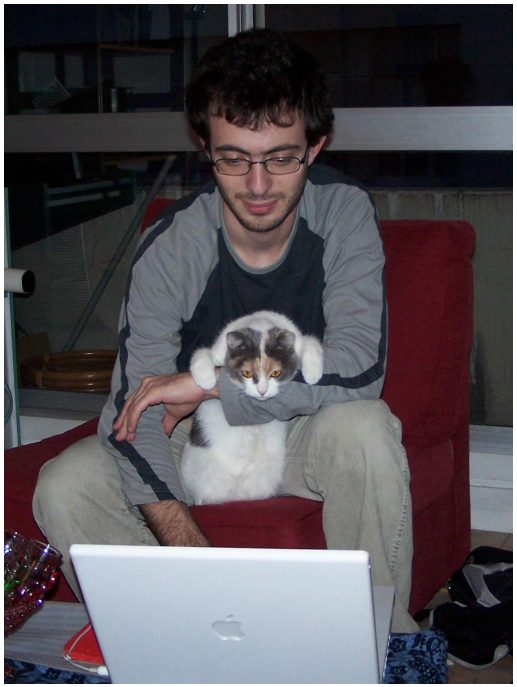
Acknowledgements



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Rowena Bull
Peter White

Heritability

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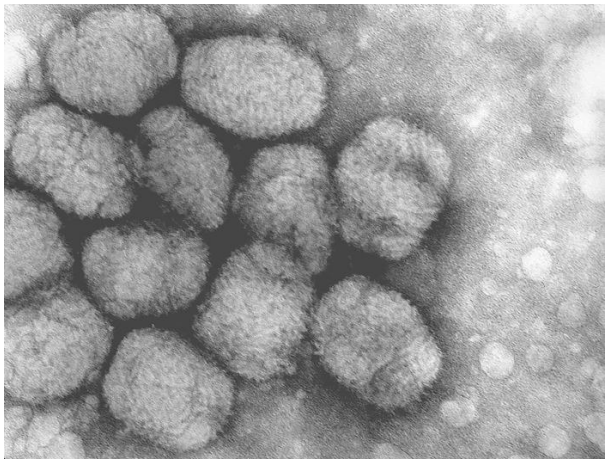
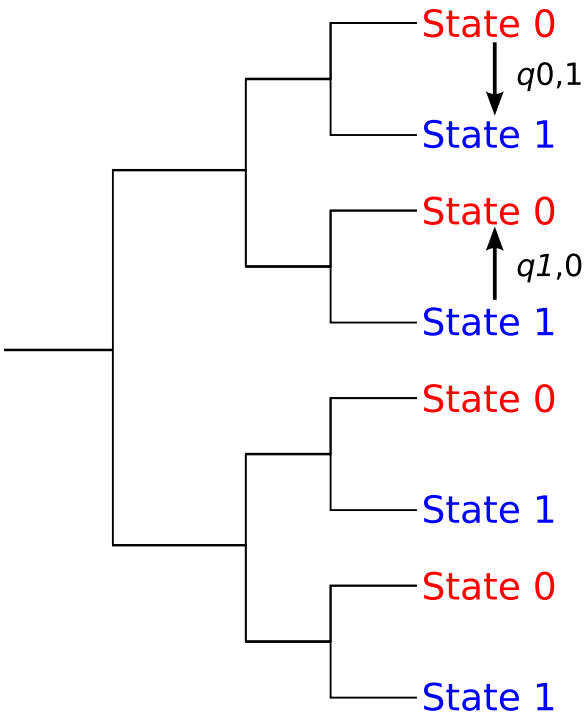


Virus control in Hepatitis C

- Traditional viewpoint is that host genetics mostly controls infection outcome in HCV.
- Alizon *et al.* (2010) used a method to detect virus genetic effect without knowing direct contact structure for HIV.
- Hepatitis C shows two main infection outcomes:
  - Virus infection can either clear naturally within a few months
  - Or it can be chronic if untreated (persist for many years)
- It is known that several SNPs in humans correlate with infection outcome.
- What is the effect of HCV virus genome on the infection?

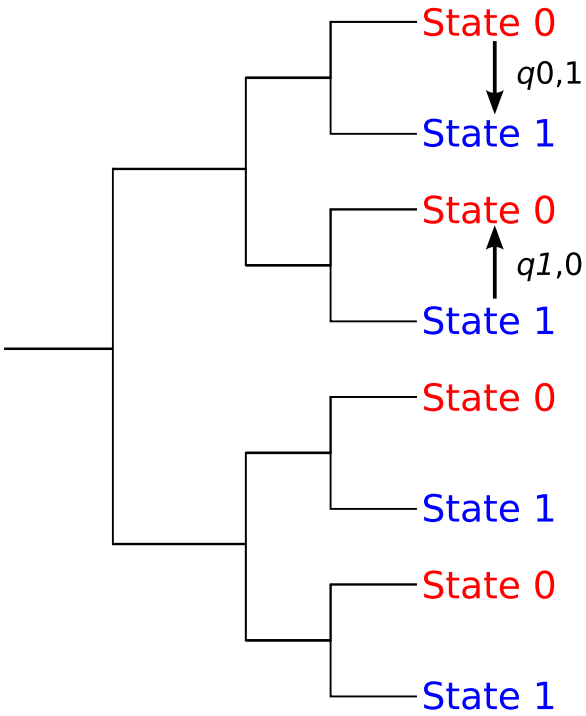
Estimating trait correlation



Low virus control,
Little clustering,
High switching rates

We use a maximum-likelihood method to estimate rate of trait-changing.

Estimating trait correlation



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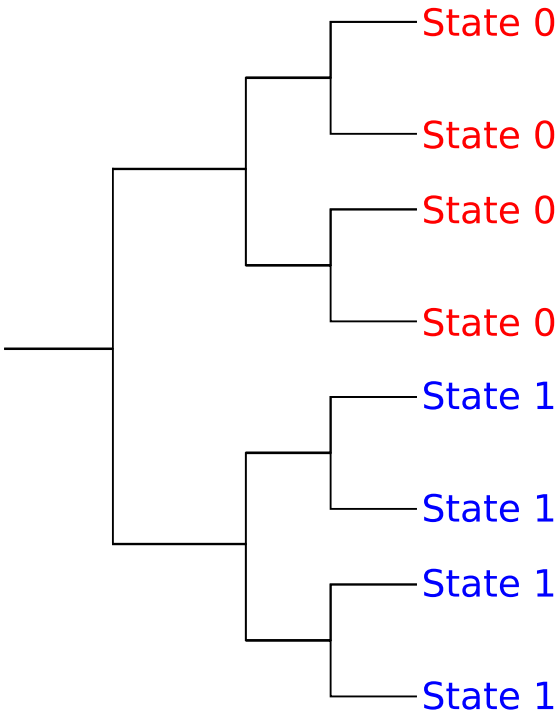

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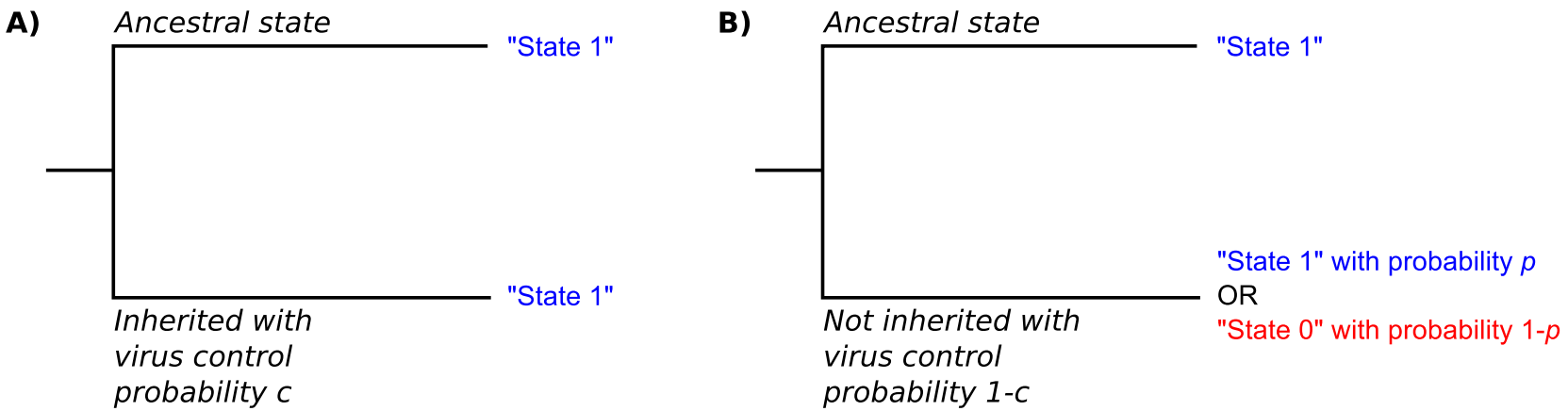
Simulating virus control on trait

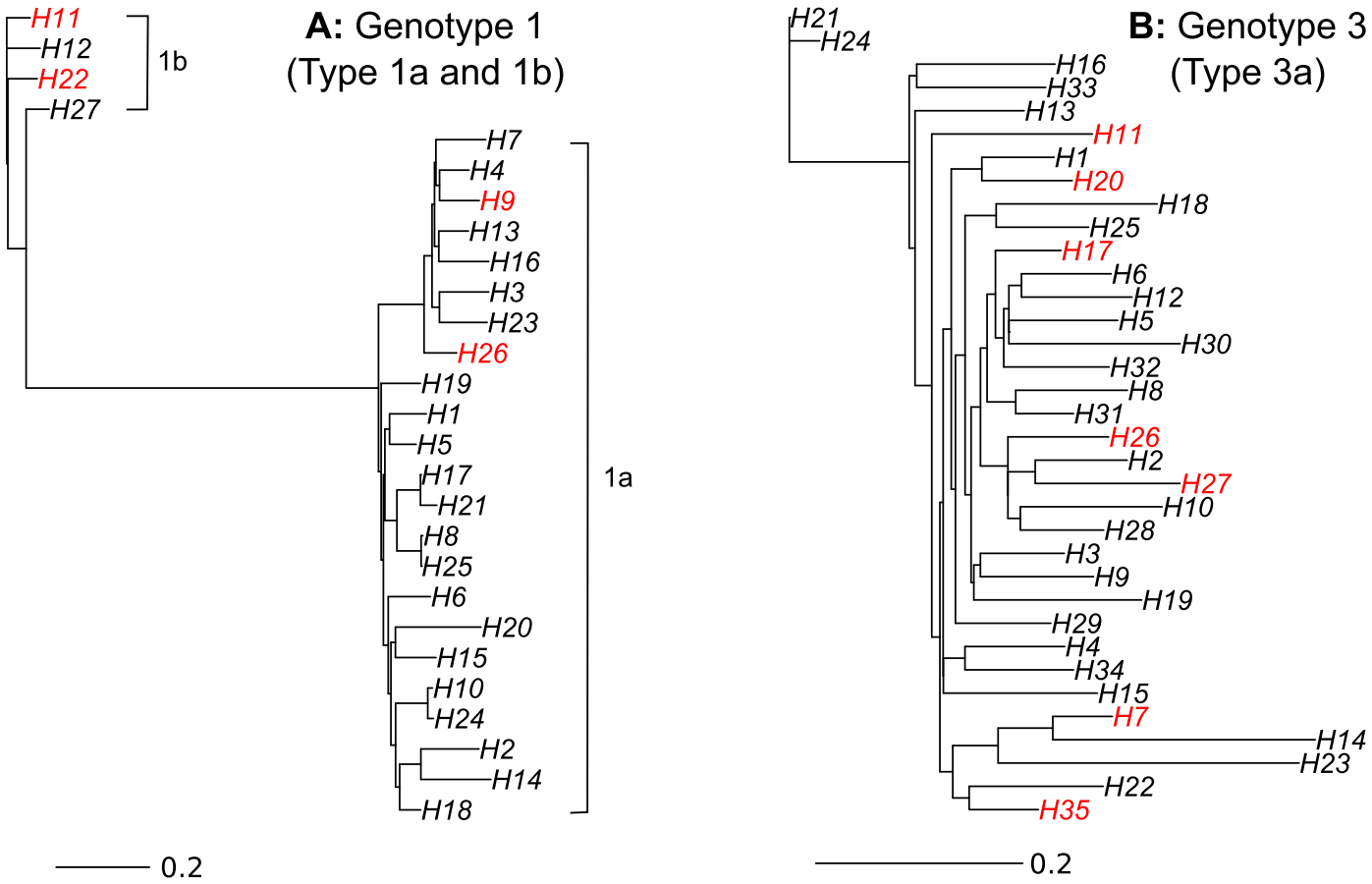


- We simulate virus control of infection outcomes along a posterior distribution of trees (produced with BEAST).
- Use switching rates from real data to estimate virus control based on simulations.
- Confidence intervals based on 1000 randomised tipsets.

Datasets used

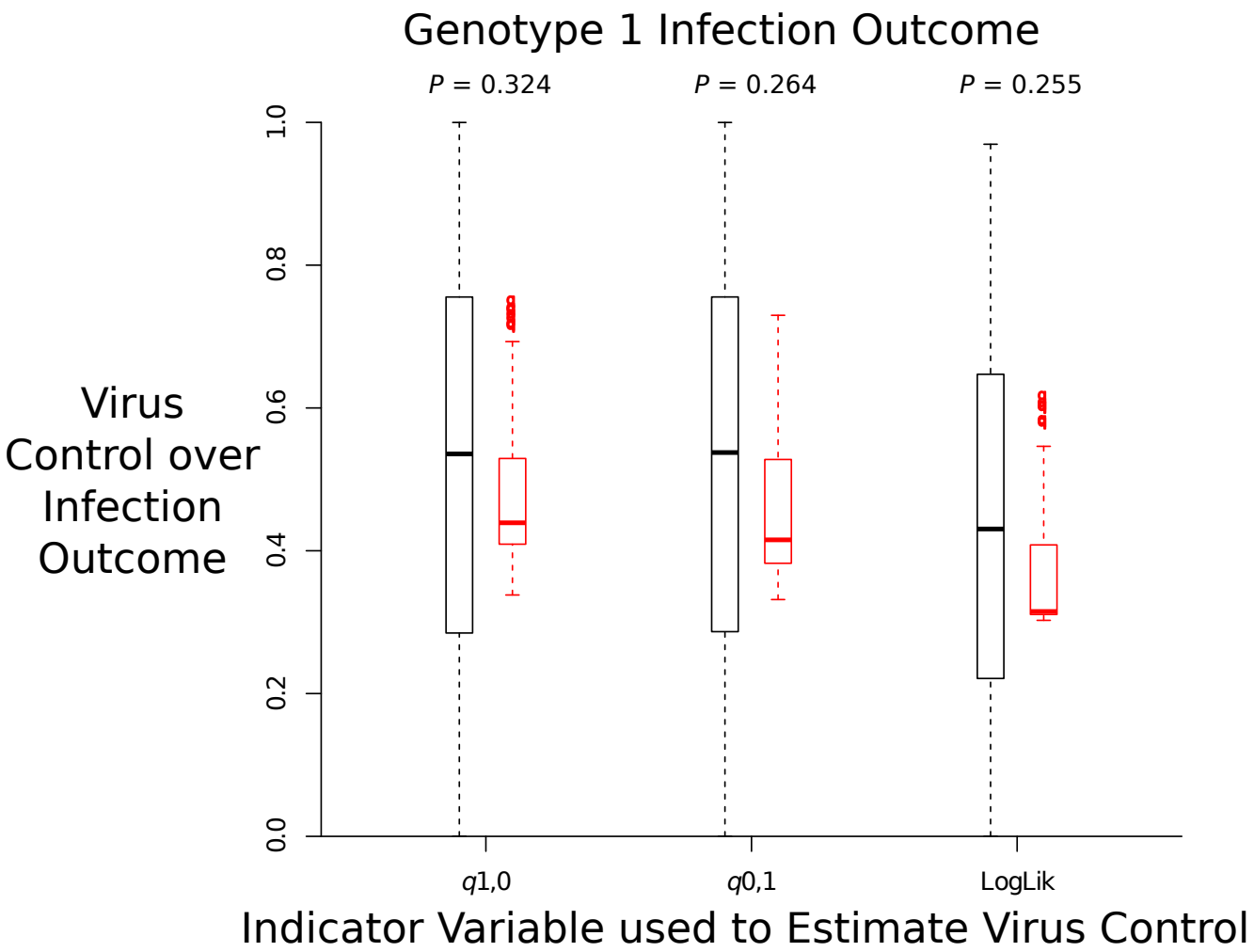
- Tested with data from Hepatitis C Incidence and Transmission in Prisons Study (HITS)
- Ability to detect clearing infections quickly.
- Data resolved into one of two clades; analysed each separately to prevent confounding signal with genotype.

Datasets used



(Red = Clearers; Black = Chronic)

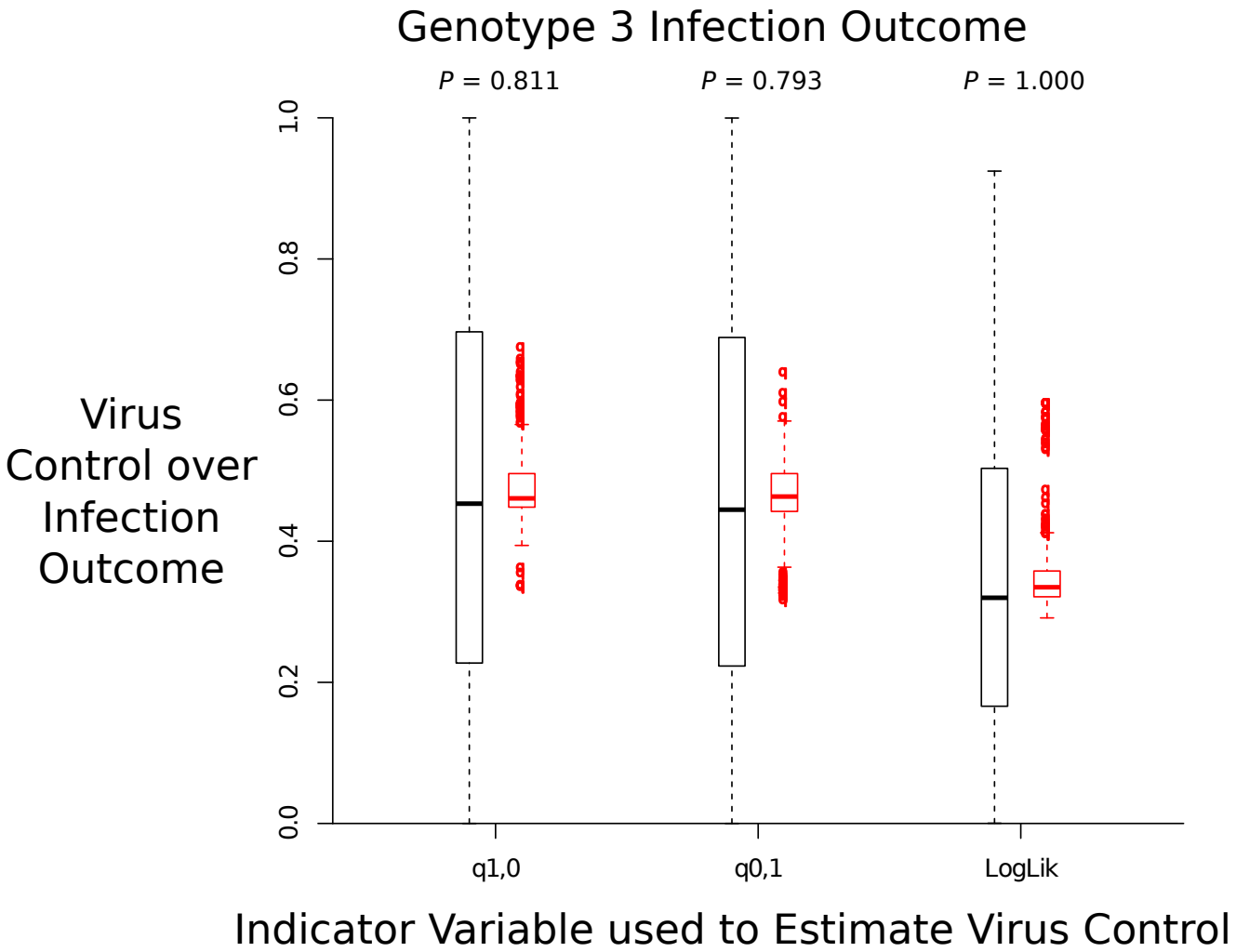
Genotype 1 Results



Black = True Dataset

Red = Medians of Randomised Tips

Genotype 3 Results



IL28B SNPs and their effects

- Variation in *IL28B* locus in humans known to correlate with virus clearance.

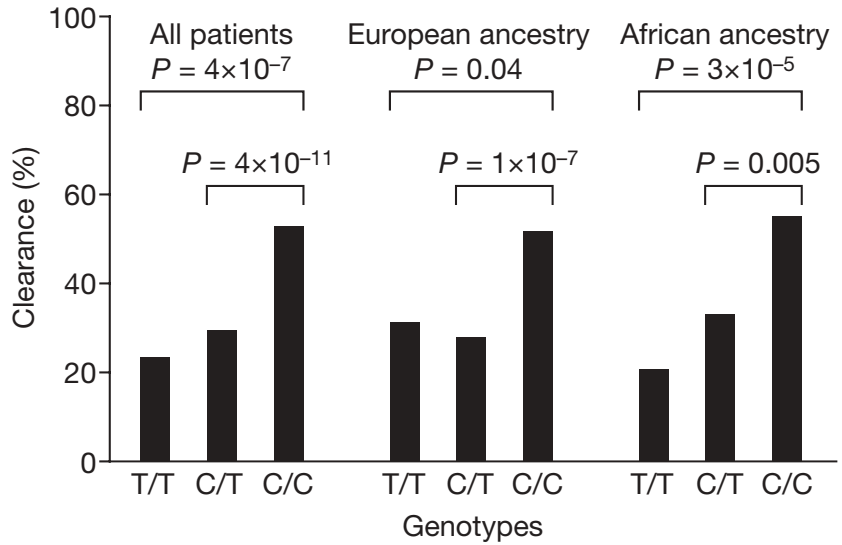
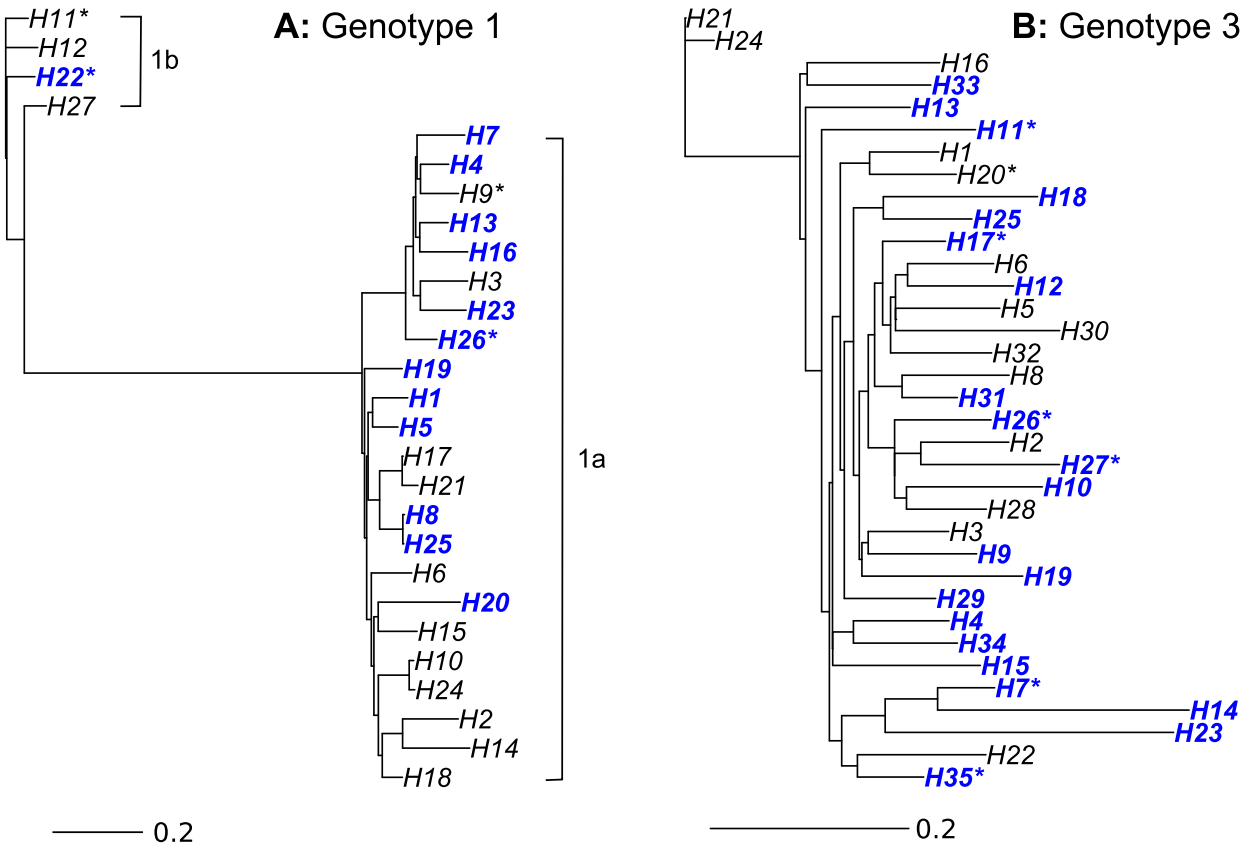


Figure 1 | Percentage of HCV clearance by rs12979860 genotype. Data are shown for all patients, as well as individuals of European ancestry and African ancestry separately.

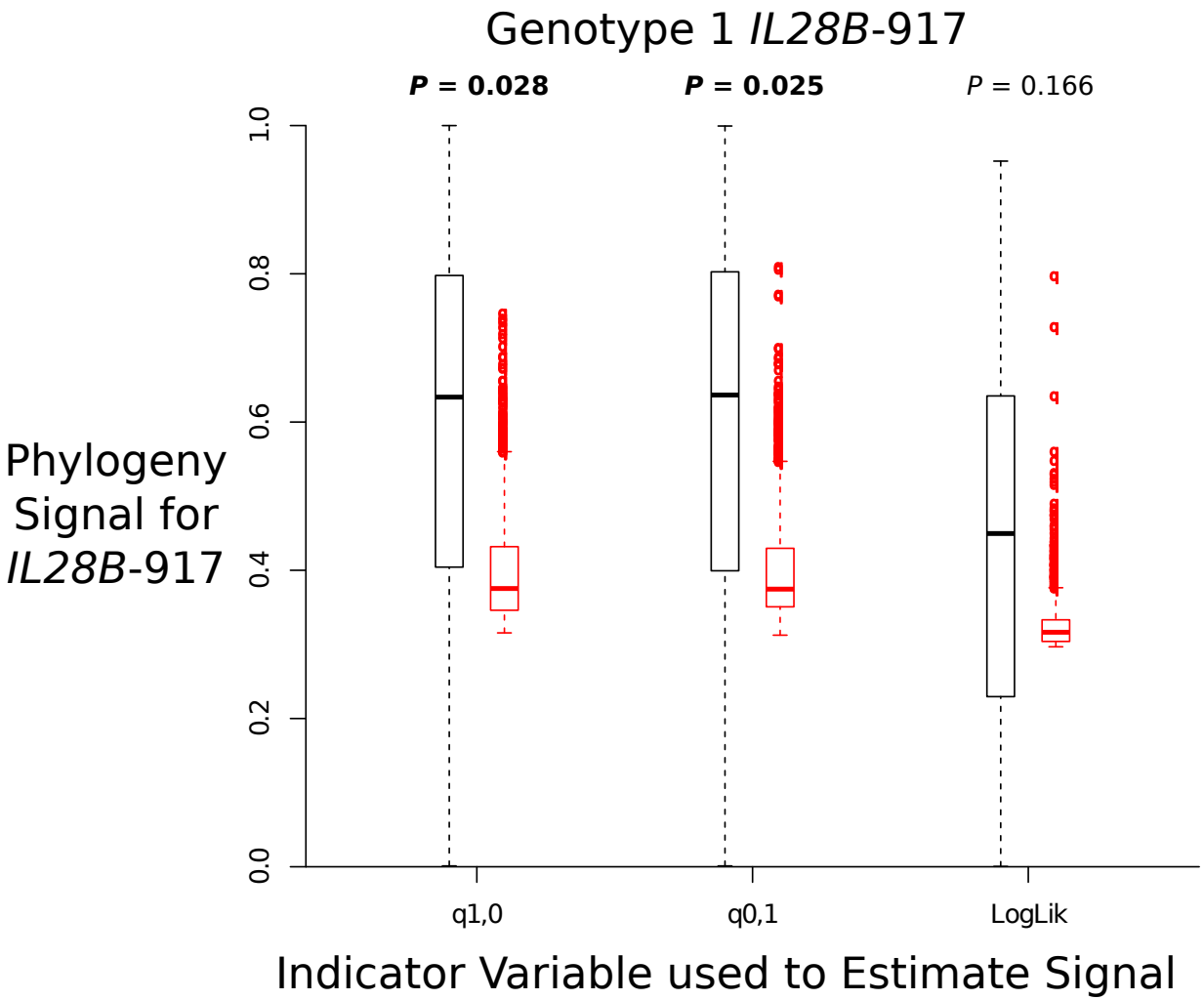
Figure from Thomas *et al.* 2009

IL28B SNPs clustering



Repeated the above analysis for SNP location in hosts known to increase clearance rate of HCV (labelled *IL28B*-917).

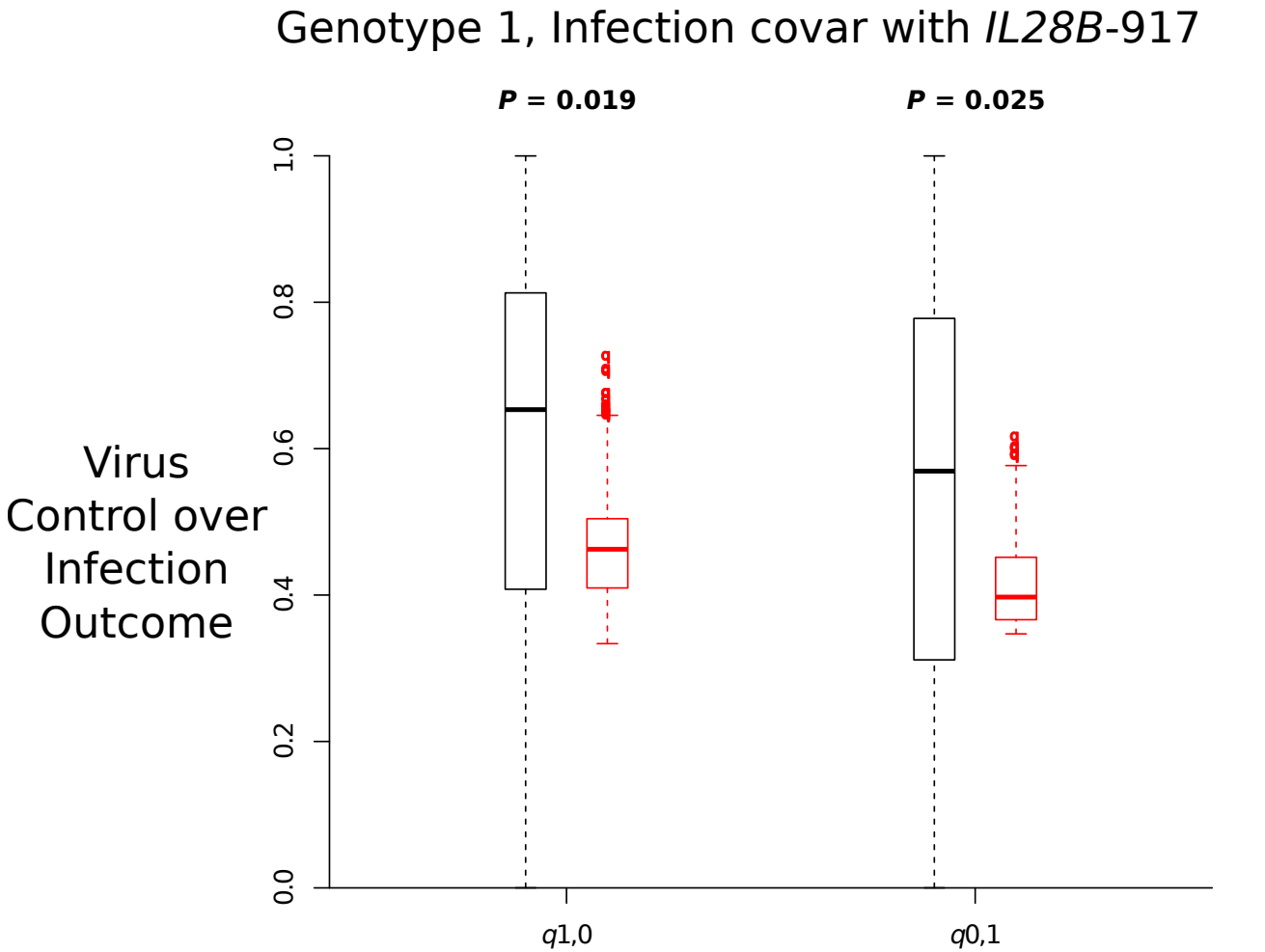
Genotype 1 *IL28B*



Second Analysis

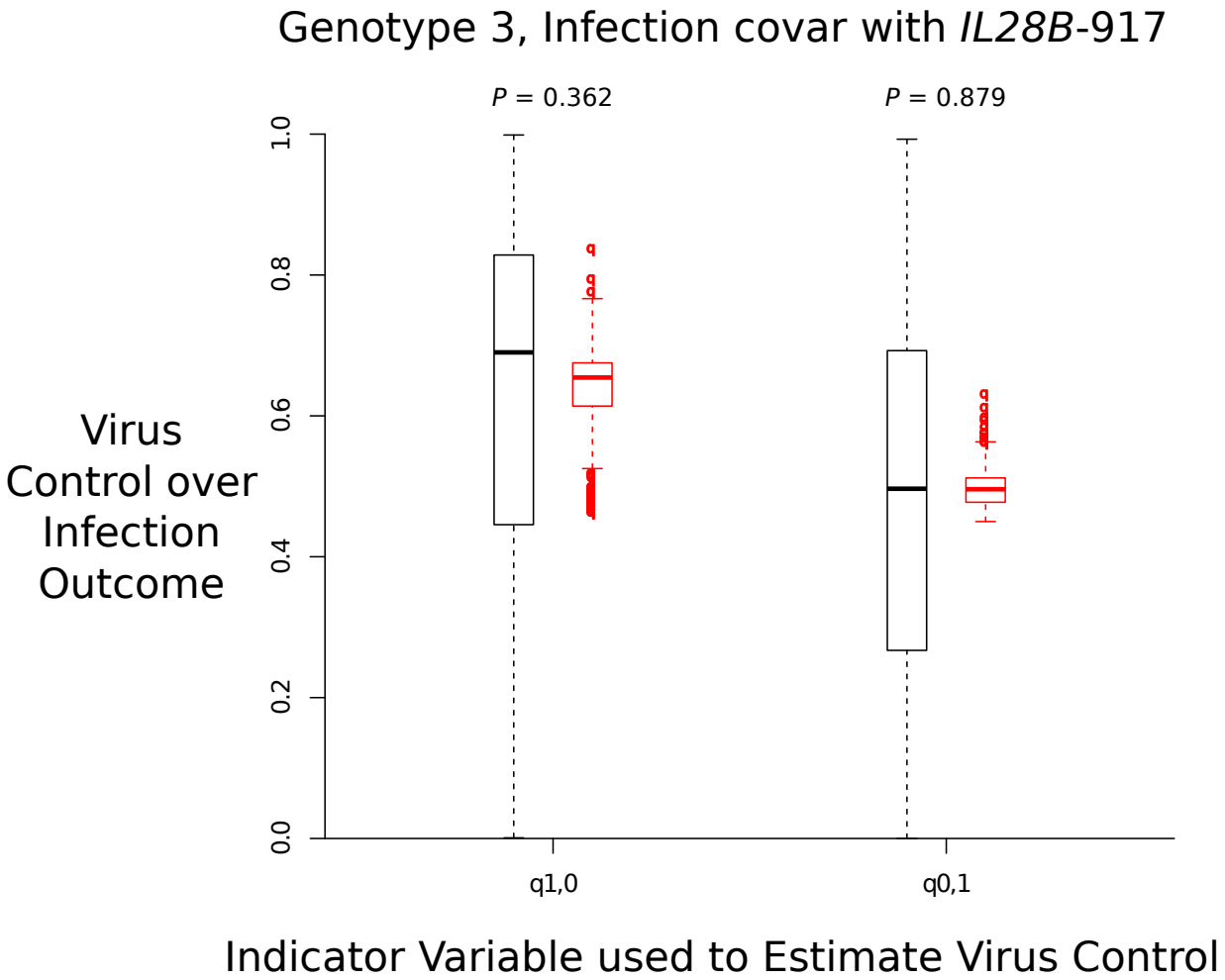
- There is evidence of a non-random clustering of hosts on the phylogeny, particularly for *IL28B*-917 in Genotype 1.
- This host clustering effect is likely to have affected our previous analysis on infection outcome status.
- We therefore decided to re-estimate rates of infection outcome evolution whilst accounting for *IL28B* status.
- We used the *BayesTraits* package (available from `www.evolution.rdg.ac.uk`) to achieve this.

Genotype 1 with *IL28B* covar



True tipset median is around
30% higher than random median

Genotype 3 with *IL28B* covar



Lack of significance possibly due to larger effective population size.

Conclusions (*Messages à emporter à votre maison*)

- We have found significant virus control over infection outcome in the genotype 1a and 1b clade, after correcting for host's *IL28B* status.
- Estimates of virus control lie at around 30% after accounting for non-zero value of randomised tips.
- We found no significant control in genotype 3a clade.
- This discrepancy is probably due to larger rates of evolution so genomes are more homogenised.