Fine-mapping of a region on BTA17 associated with milk-fat composition

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SLU

EGS ABG

European Commission
ERASMUS MUNDUS

CRV

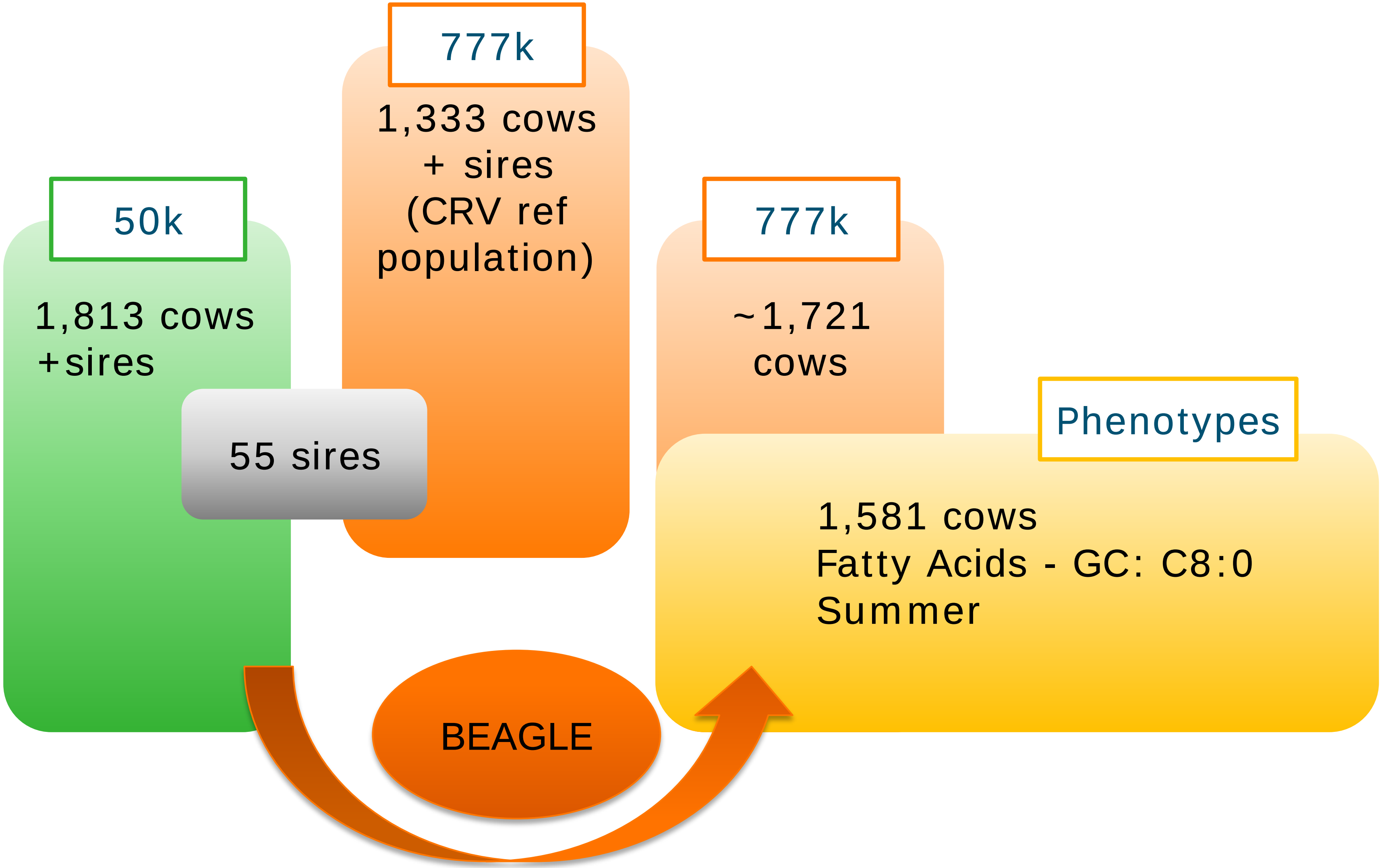
Introduction

- **Besides milk fat% the composition of milk fat might be of interest**
  - Human health
  - Manufacturing properties
  - Indicator for e.g. NEB and methane emission
- **Milk fat composition is heritable and genes have been detected.**
  - e.g. C4:0-C12:0 – $h^2 = 0.60$
  - DGAT1 and SCD1
- **Based on GWAS using 50K SNP we detected a QTL on BTA17 associated with C4:0-C12:0.** Bouwman et al. (2012)

Aims

1. Fine-map a region on BTA17 using imputed 777K SNP genotypes
2. Construct haplotypes that capture genetic variation
3. Analyzing pleiotropic effects on *de novo* synthesized fatty acids

Genotypes and Phenotypes



50k

1,813 cows
+sires

777k

1,333 cows
+ sires
(CRV ref
population)

55 sires

777k

~1,721
cows

Phenotypes

1,581 cows
Fatty Acids - GC: C8:0
Summer

BEAGLE

Statistical analyses

Single-SNP analysis using the following animal model:

$$\boldsymbol{y} = \mu + \boldsymbol{dim} + e^{-0.05*\boldsymbol{dim}} + \boldsymbol{afc} + \boldsymbol{afc}^2 + \boldsymbol{season} + \boldsymbol{scode} + \boldsymbol{SNP} + \boldsymbol{herd} + \boldsymbol{a} + \boldsymbol{e}$$

where:

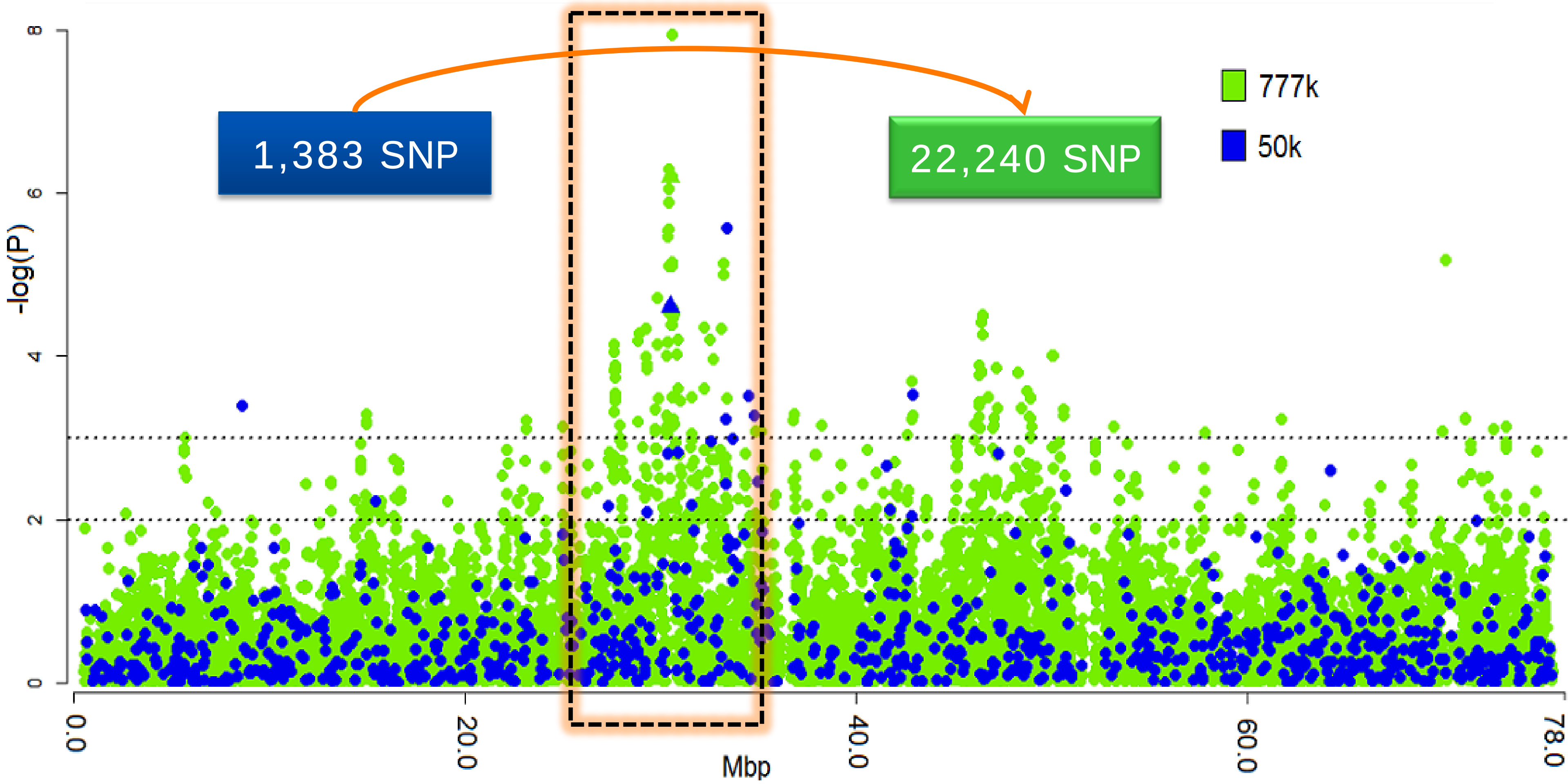
Fixed effects

dim = days in milk
afc = age at first calving
season = calving season
scode = proven vs young bulls
SNP = effect of SNP genotype

Random effects

herd = effect of herd
a = additive genetic effect
e = residual effect

GWAS for C8:0 - BTA17



1,383 SNP

22,240 SNP

Focus on
Region 29.0 to 34.0 Mbp
1,184 SNP

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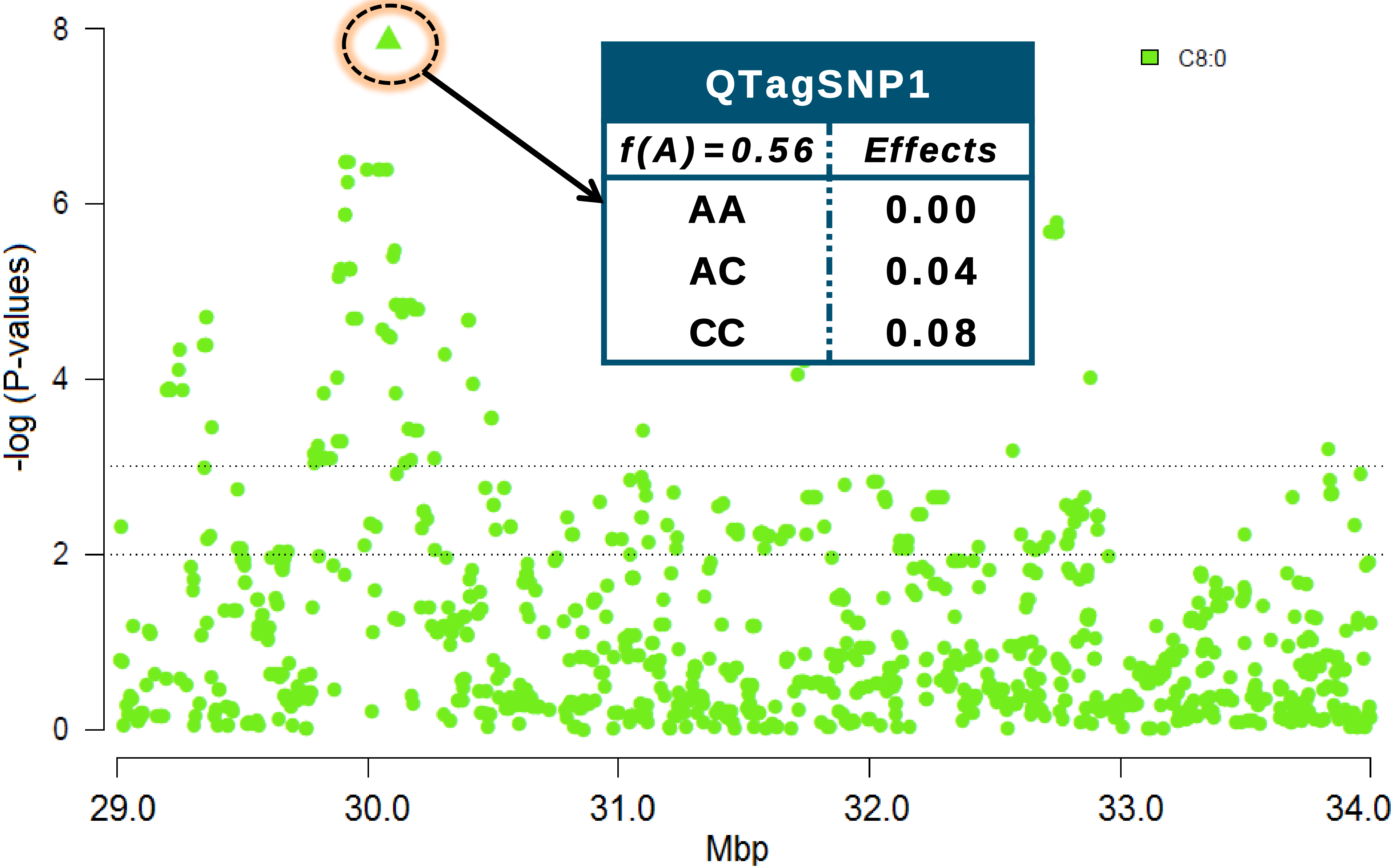
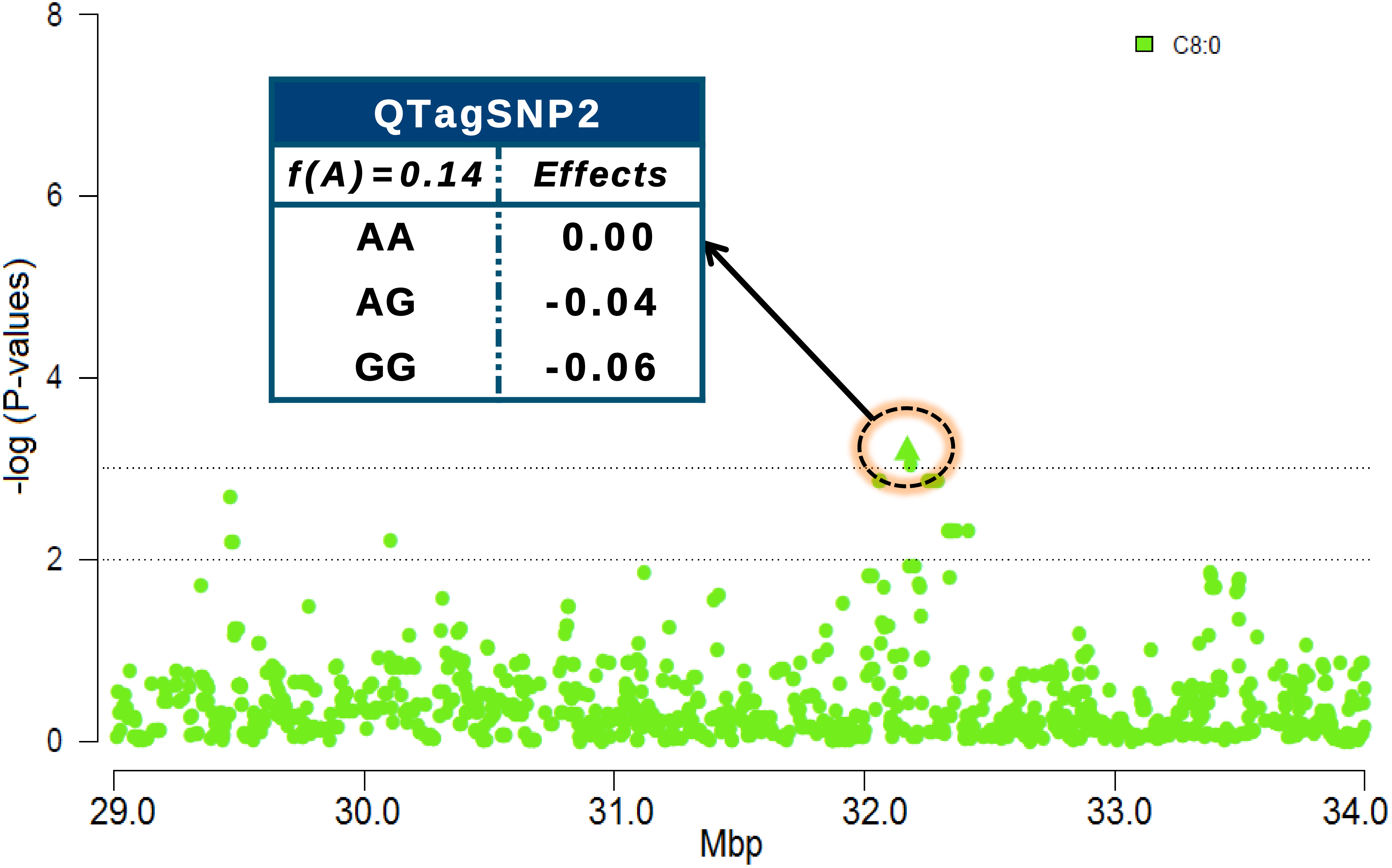
QTagSNP for C8:0 - BTA17



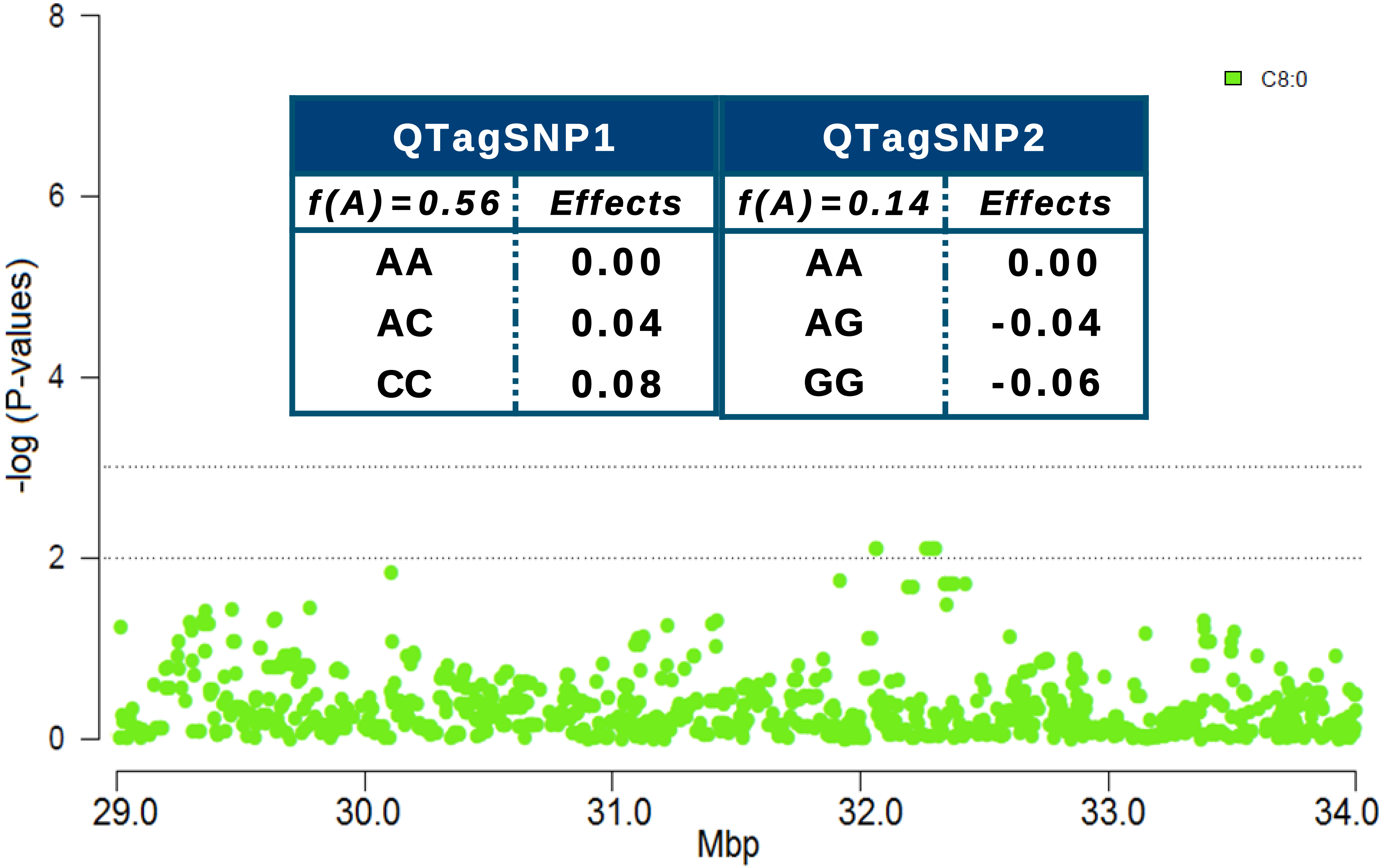
QTagSNP1	
f(A)=0.56	***Effects***
AA	**0.00**
AC	**0.04**
CC	**0.08**

QTagSNP for C8:0 - BTA17



QTagSNP2	
f(A)=0.14	***Effects***
AA	**0.00**
AG	**-0.04**
GG	**-0.06**

QTagSNP for C8:0 - BTA17



QTagSNP1	
f(A)=0.56	***Effects***
AA	**0.00**
AC	**0.04**
CC	**0.08**

QTagSNP2	
f(A)=0.14	***Effects***
AA	**0.00**
AG	**-0.04**
GG	**-0.06**

Building haplotypes

QTagSNP1-QTagSNP2	Frequencies
A-G	0.44
A-A	0.12
C-G	0.42
C-A	0.01

Haplotypes were analyzed as:

- **Covariables** → 0, 1 or 2 copies
- **Random** → estimating haplotype variance

Haplotypes analysed as covariables

A-G
β=-0.04

44%

A-A
β=0.02

12%

C-G
β=0.04

42%

C-A
β=0.06

1%

Two haplotype groups - probably 1 mutation.

Haplotypes analysed as random effects

	Effects	σ^2_{haplo} / σ^2_a
A-A	-0.01	9.9%
A-G	-0.07	
C-A	0.06	
C-G	0.02	

Aims

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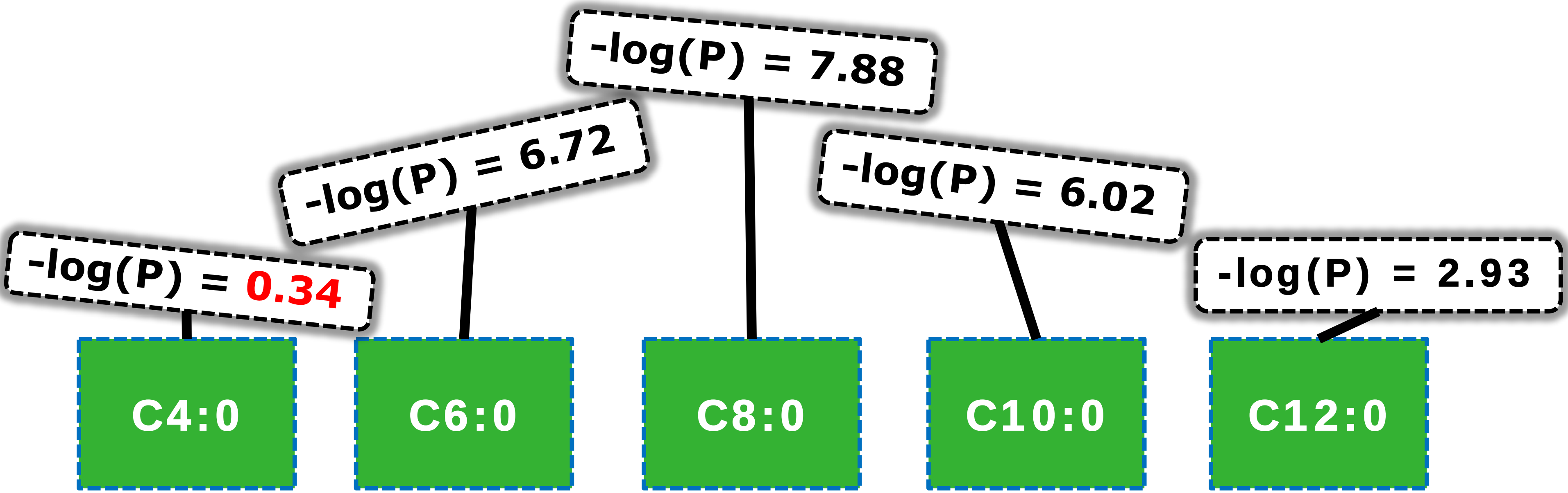
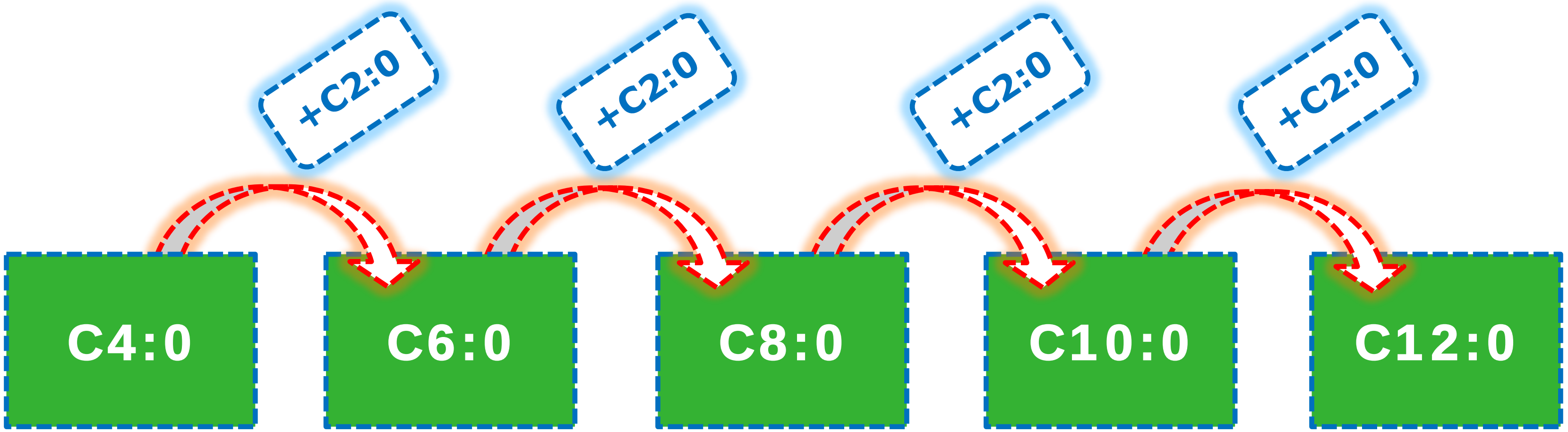
2. Construct haplotypes that capture genetic variation
3. Analyzing pleiotropic effects on *de novo* synthesized fatty acids

Pleiotropic effects on de novo synthesized FA



Pleiotropic effects on de novo synthesized FA



+C2:0

+C2:0

+C2:0

+C2:0

C4:0

C6:0

C8:0

C10:0

C12:0

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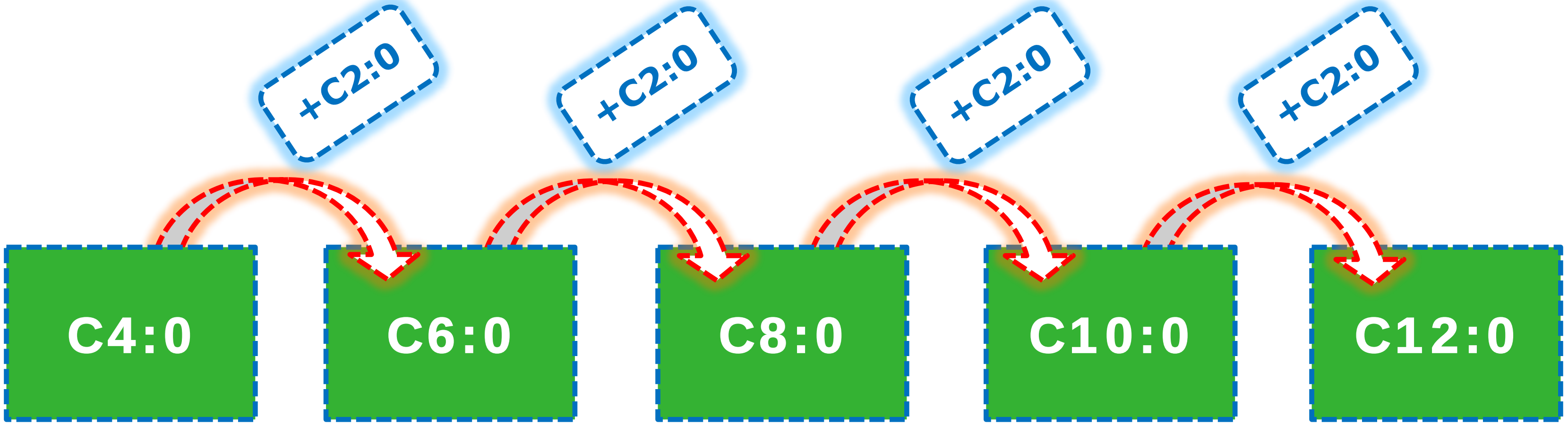
Pleiotropic effects on de novo synthesized FA


+C2:0
+C2:0
+C2:0
+C2:0
C4:0
C6:0
C8:0
C10:0
C12:0

C4:0 = mu + fixed + **QTagSNP1** + random

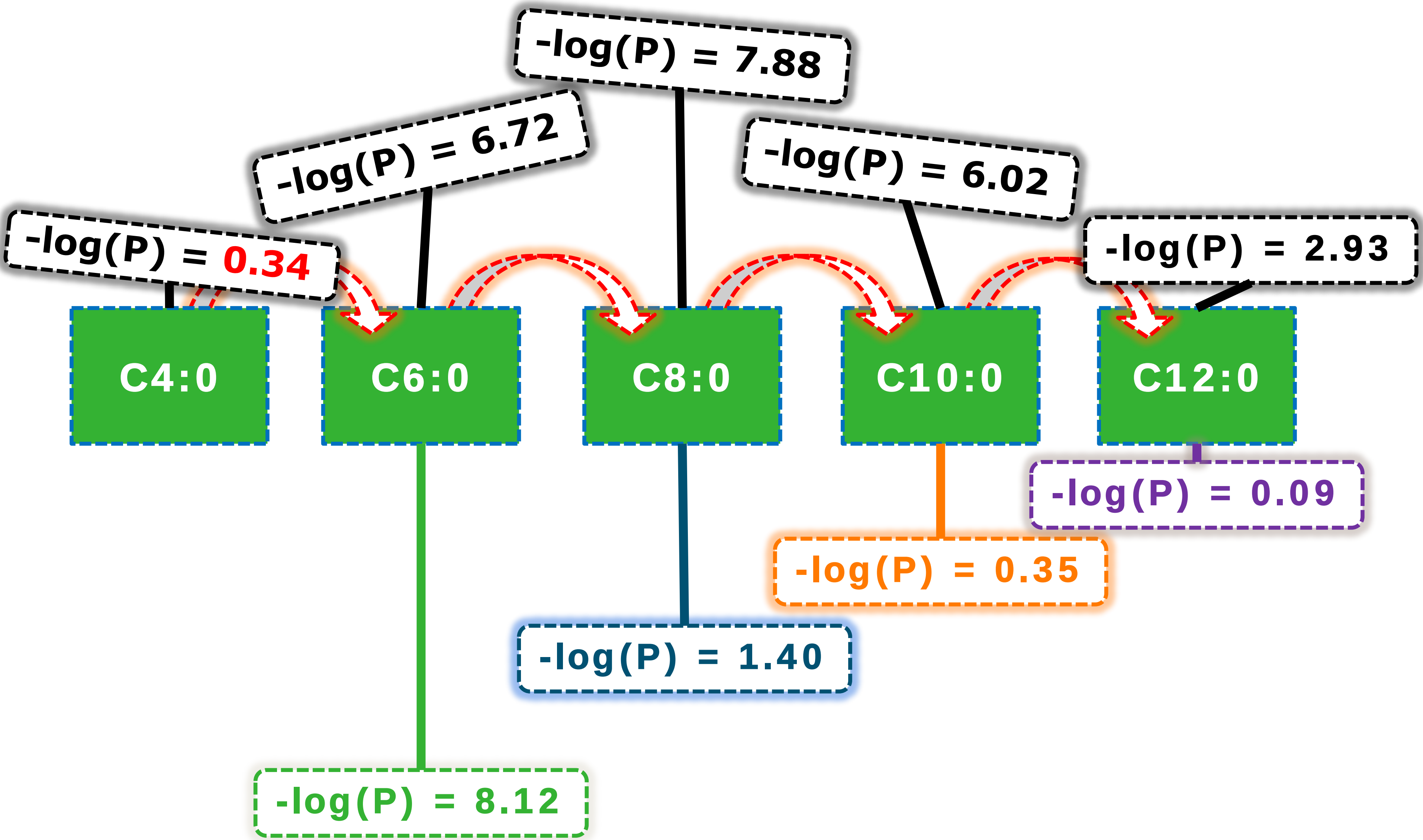
C6:0 = mu + **C4:0** + fixed + **QTagSNP1** + random

C8:0 = mu + **C6:0** + fixed + **QTagSNP1** + random

C10:0 = mu + **C8:0** + fixed + **QTagSNP1** + random

C12:0 = mu + **C10:0** + fixed + **QTagSNP1** + random

Pleiotropic effects on de novo synthesized FA



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Conclusions

- **Improved location** of gene affecting C8:0 on BTA17, using 777K compared to 50K SNP**.**

- Gene explains **~10%** of the genetic variation in C8:0.

- Gene affects **multiple** de novo synthesiszed FA.

- Gene seems to affect **start** of the de novo synthesis: **production/transport** of acetate (C2) or butyrate (C4)