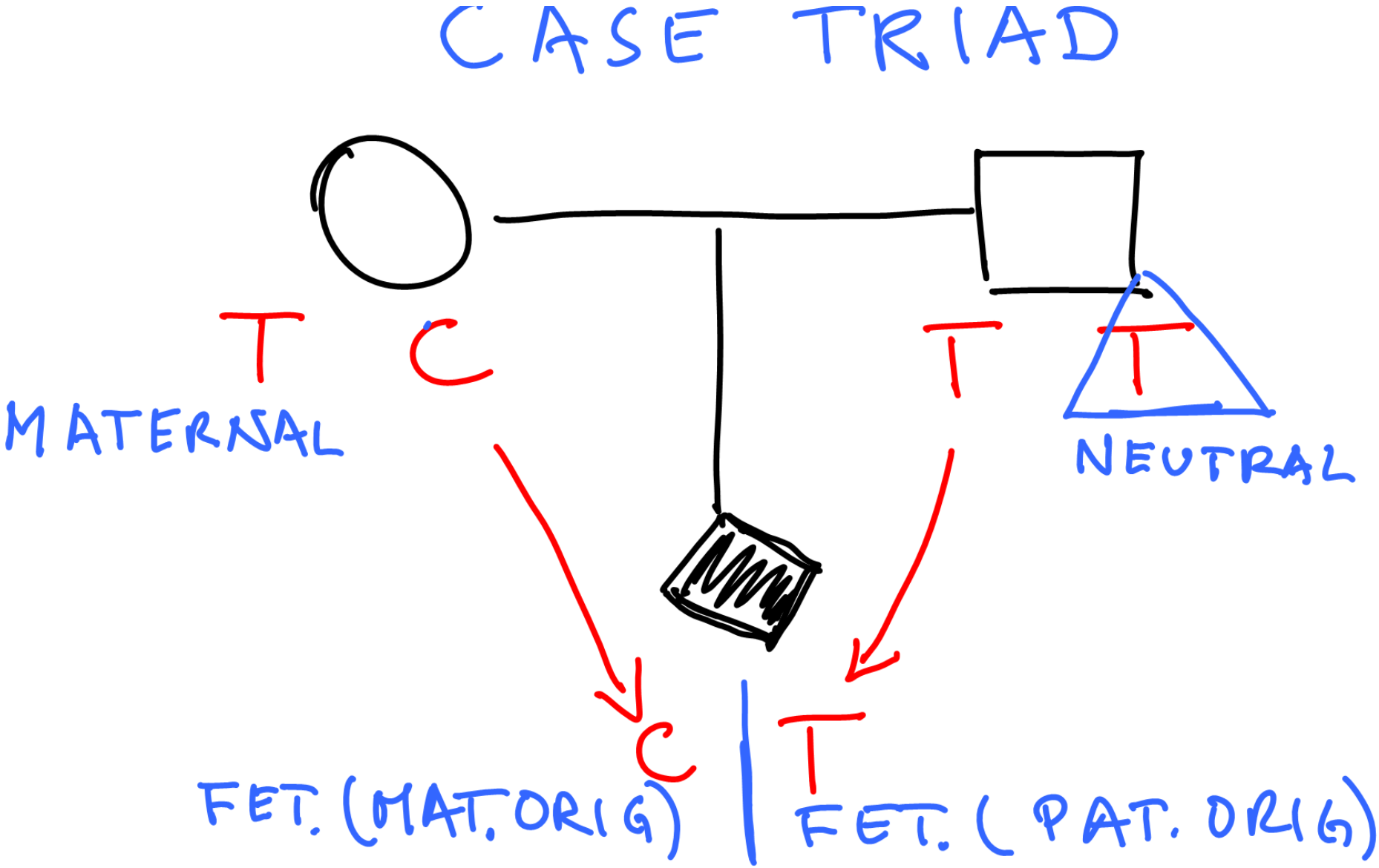
“Special effects”

and

X-models

WHICH ALLELE ESTIMATES WHICH EFFECT?



EFFECT OF MATERNAL HAPLOTYPES

- Haplotypes of three first SNPs
- Impute missing
- `maternal = T` includes effect of maternal haplotypes

```
haplin(data = pres.data, markers = 1:3, use.missing = T,
  reference = "ref.cat", maternal = T)
```

Effect of maternal haplotypes

Maternal haplotypes:

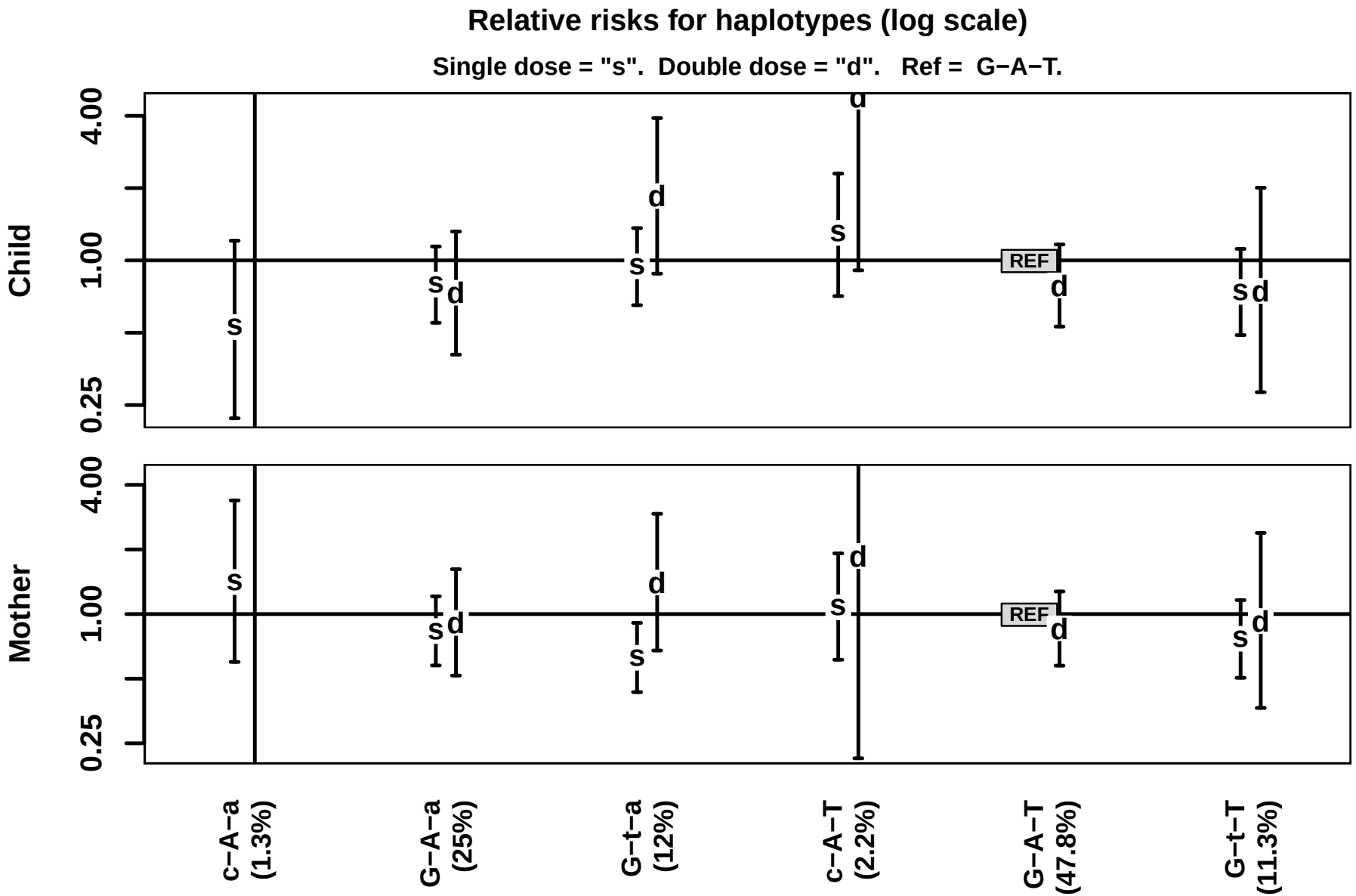
- The effect of the mother's own haplotypes
- The haplotypes of the mother influence the fetus during pregnancy through the mother
- Often studied by comparing case mothers with control mothers
- **But this is flawed:** The haplotype is also often passed on to the child
- So the haplotype can have an effect either in the mother or in the child
- The models must thus distinguish between maternal haplotypes and child haplotypes

HAPLIN OUTPUT: EFFECT ESTIMATES, MATERNAL HAPLOTYPES

```
----Child haplotypes----
 Haplotype Dose     Relative Risk Lower CI   Upper CI   P-value
 c-A-a     Single   0.528         0.22       1.21       0.132
 c-A-a     Double   4.5e+15       0          Inf        0.986

... etc.

----Maternal haplotypes----
 Haplotype Dose     Relative Risk Lower CI   Upper CI   P-value
 c-A-a     Single   1.41          0.598      3.38       0.44
 c-A-a     Double   0.000631      0          Inf        0.995

 G-A-a     Single   0.833         0.576      1.21       0.329
 G-A-a     Double   0.909         0.517      1.62       0.742

 G-t-a     Single   0.626         0.433      0.91       0.0138
 G-t-a     Double   1.4           0.676      2.93       0.364

 c-A-T     Single   1.08          0.613      1.92       0.805
 c-A-T     Double   1.86          0.213      15.6       0.572

 G-A-T     Single   REF
 G-A-T     Double   0.858         0.575      1.27       0.46

 G-t-T     Single   0.767         0.505      1.16       0.208
 G-t-T     Double   0.928         0.365      2.39       0.877
```

Suggests a protective effect of haplotype `G-t-a`.
But unlikely to survive multiple testing corrections.

HAPLIN OUTPUT: EFFECT ESTIMATES



HAPLIN OUTPUT: LIKELIHOOD RATIO TEST

```
LIKELIHOOD RATIO TEST:
 Loglike null model:          -2825.41339
 Loglike full model:          -2808.32255
 df:                             22.00000
 Likelihood ratio p-value:        0.04707
```

The likelihood test suggests something borderline.

Important:

- the Likelihood Ratio Test here applies to *the combination* of fetal and maternal genes

PARENT-OF-ORIGIN EFFECTS

- Haplotypes of three first SNPs
- Impute missing
- `poo = T` splits the fetal effects into maternal and paternal

```
haplin(data = pres.data, markers = 1:3,
 use.missing = T, reference = "ref.cat", poo = T)
```

PARENT-OF-ORIGIN EFFECTS

Parent-of-origin effects:

- The effect of the fetal haplotype may depend on parent of origin
- Parental imprinting may silence (partially or totally) the haplotype deriving from either the mother or the father
- Compares the effects of the two alleles *in the child*
- Must distinguish between maternal haplotypes and child haplotype inherited from the mother

EFFECT ESTIMATES, PARENT-OF-ORIGIN

Haplin estimates:

- RRcm, the relative risk associated with an allele transmitted from the mother (Single-mat)
- RRcf, the relative risk associated with an allele transmitted from the father (Single-pat)
- The double dose effect of inheriting it from both (Double)
- The ratio $\mathrm{RRR} = \mathrm{RRcm}/\mathrm{RRCF}$ (Ratio m/p)

Interpretation:

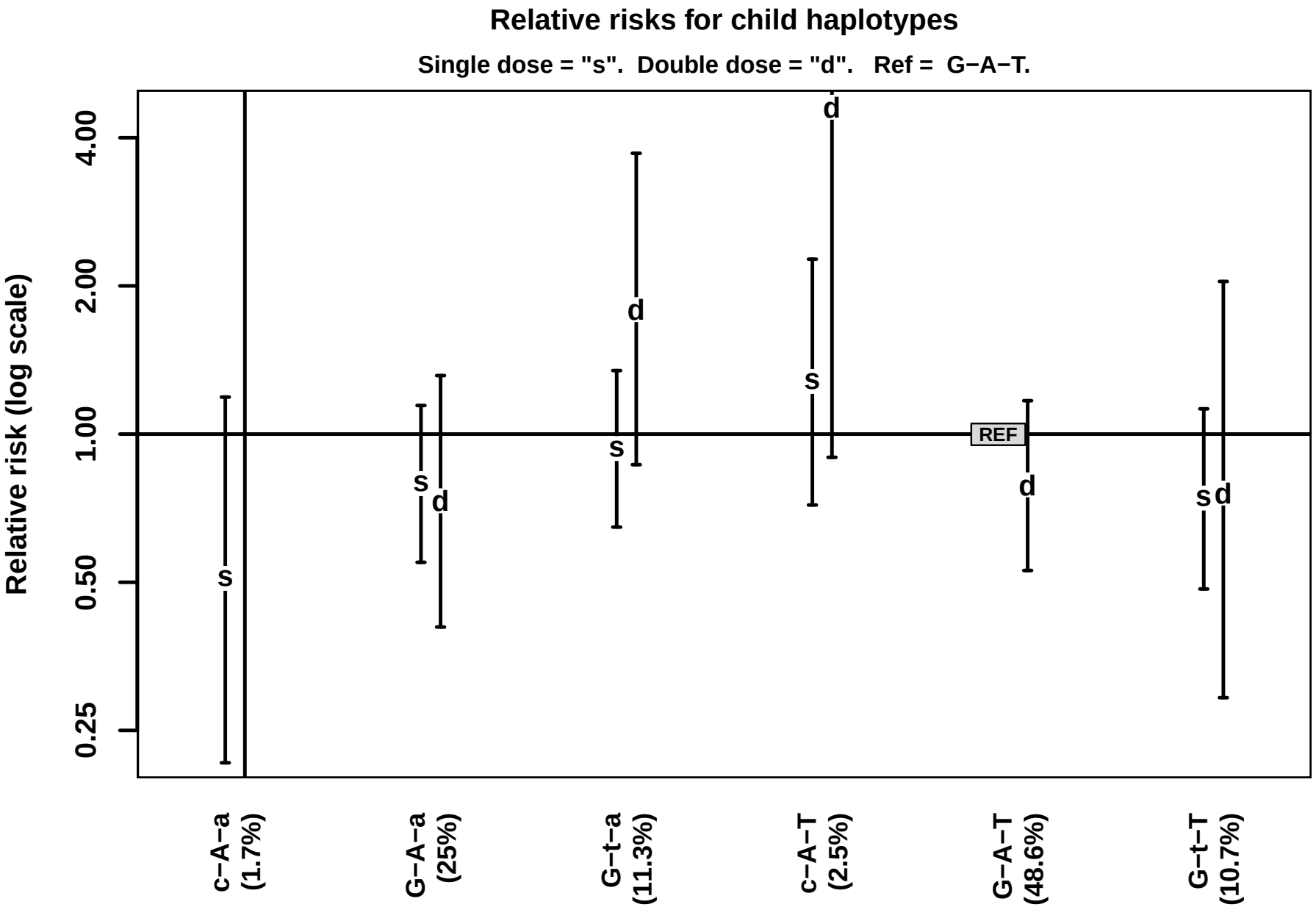
- If $\mathrm{RRcm} = \mathrm{RRcf}$ then
  $\mathrm{RRR} = \mathrm{RRcm}/\mathrm{RRcf} = 1$
- This means no parent-of-origin effect
- If $\mathrm{RRcm} = 2\mathrm{RRcf}$ then
  $\mathrm{RRR} = \mathrm{RRcm}/\mathrm{RRcf} = 2$
- This means there IS a parent-of-origin effect;
  the risk is double when inherited from the mother (compared to from the father)

EFFECT ESTIMATES, PARENT-OF-ORIGIN

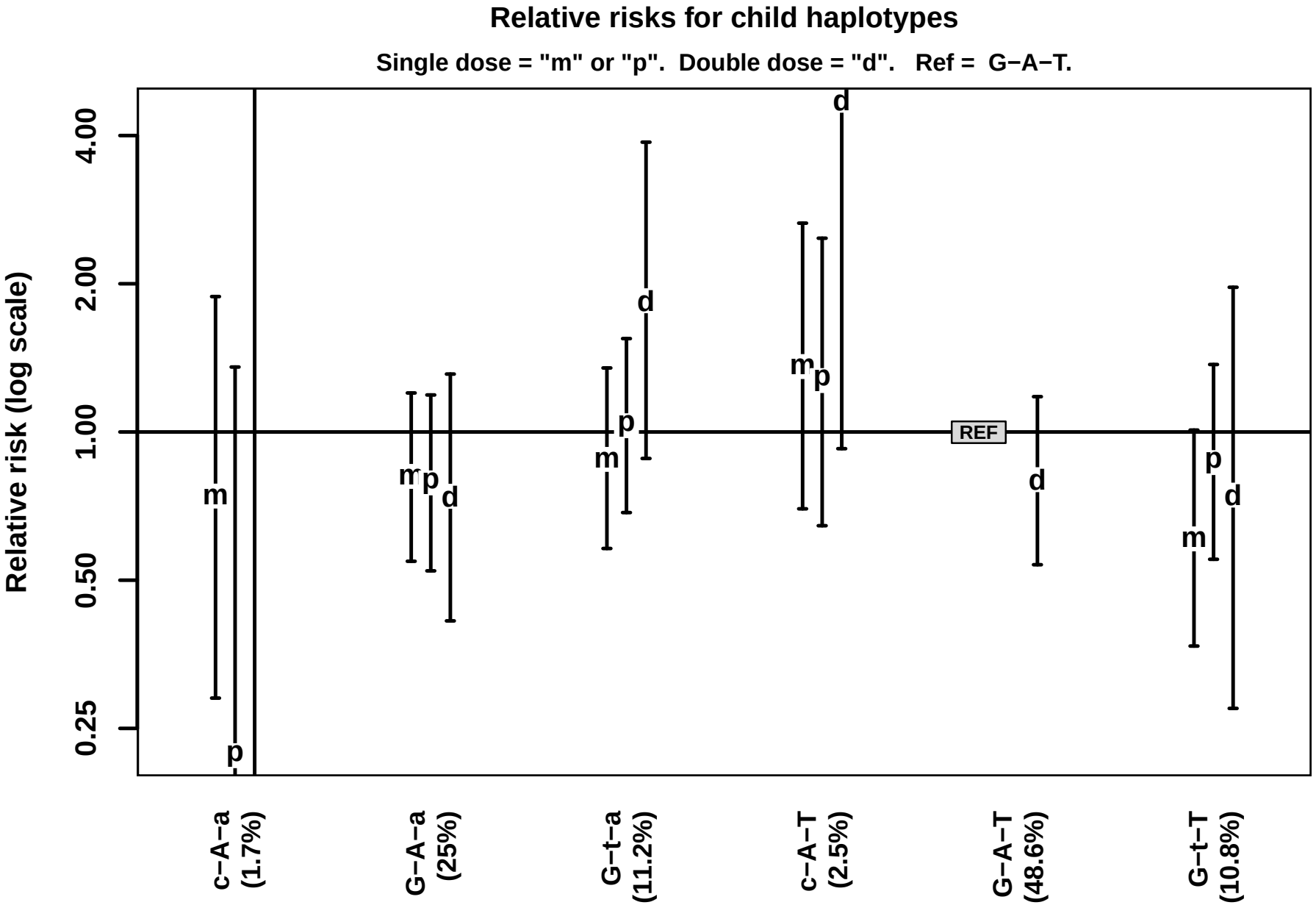
```
----Child haplotypes----
 Haplotype Dose       Relative Risk Lower CI   Upper CI   P-value
 c-A-a     Single-mat 0.741         0.288      1.88       0.528
 c-A-a     Single-pat 0.22          0.0373     1.35       0.0978
 c-A-a     Double     3.38e-07      0          Inf        0.988
 c-A-a     Ratio m/p  3.33          0.512      21.3       0.208

 G-A-a     Single-mat 0.812         0.546      1.2        0.302
 G-A-a     Single-pat 0.788         0.522      1.19       0.253
 G-A-a     Double     0.74          0.413      1.31       0.308
 G-A-a     Ratio m/p  1.03          0.736      1.45       0.871

 G-t-a     Single-mat 0.88          0.58       1.35       0.544
 G-t-a     Single-pat 1.03          0.686      1.55       0.893
 G-t-a     Double     1.85          0.883      3.88       0.109
 G-t-a     Ratio m/p  0.853         0.562      1.29       0.466

 c-A-T     Single-mat 1.36          0.698      2.66       0.372
 c-A-T     Single-pat 1.27          0.645      2.47       0.493
 c-A-T     Double     4.72          0.925      24.4       0.0634
 c-A-T     Ratio m/p  1.07          0.556      2.07       0.835

 G-A-T     Single-mat REF
 G-A-T     Single-pat REF
 G-A-T     Double     0.8           0.538      1.18       0.259
 G-A-T     Ratio m/p  REF
... etc.
```

Perhaps a harmful effect of `G-t-a` in double dose. No signs of POO effects.

EFFECT ESTIMATES, *without* PARENT-OF-ORIGIN



EFFECT ESTIMATES, PARENT-OF-ORIGIN



HAPLIN OUTPUT: LIKELIHOOD RATIO TEST

```
LIKELIHOOD RATIO TEST:
 Loglike null model:          -2825.4134
 Loglike full model:          -2815.3111
 df:                             16.0000
 Likelihood ratio p-value:        0.2111
```

The likelihood test shows no significance overall.

Note:

- the Likelihood Ratio Test here is a test for overall fetal effects, *not* a parent-of-origin effect

HAPLIN RUN, X-CHROMOSOME

Load:

```
pres.data <- genDataLoad(filename = "data_preprocessed",
 dir.in = "data")
```

For the time being, there is no dedicated way to select the X-chromosome.

Use the map file!

```
map <- read.table("data/pres.map", header = T)
X.chrom <- which(map$chr == 23)
head(X.chrom)
```

```
[1] 305 306 307 308 309 310
```

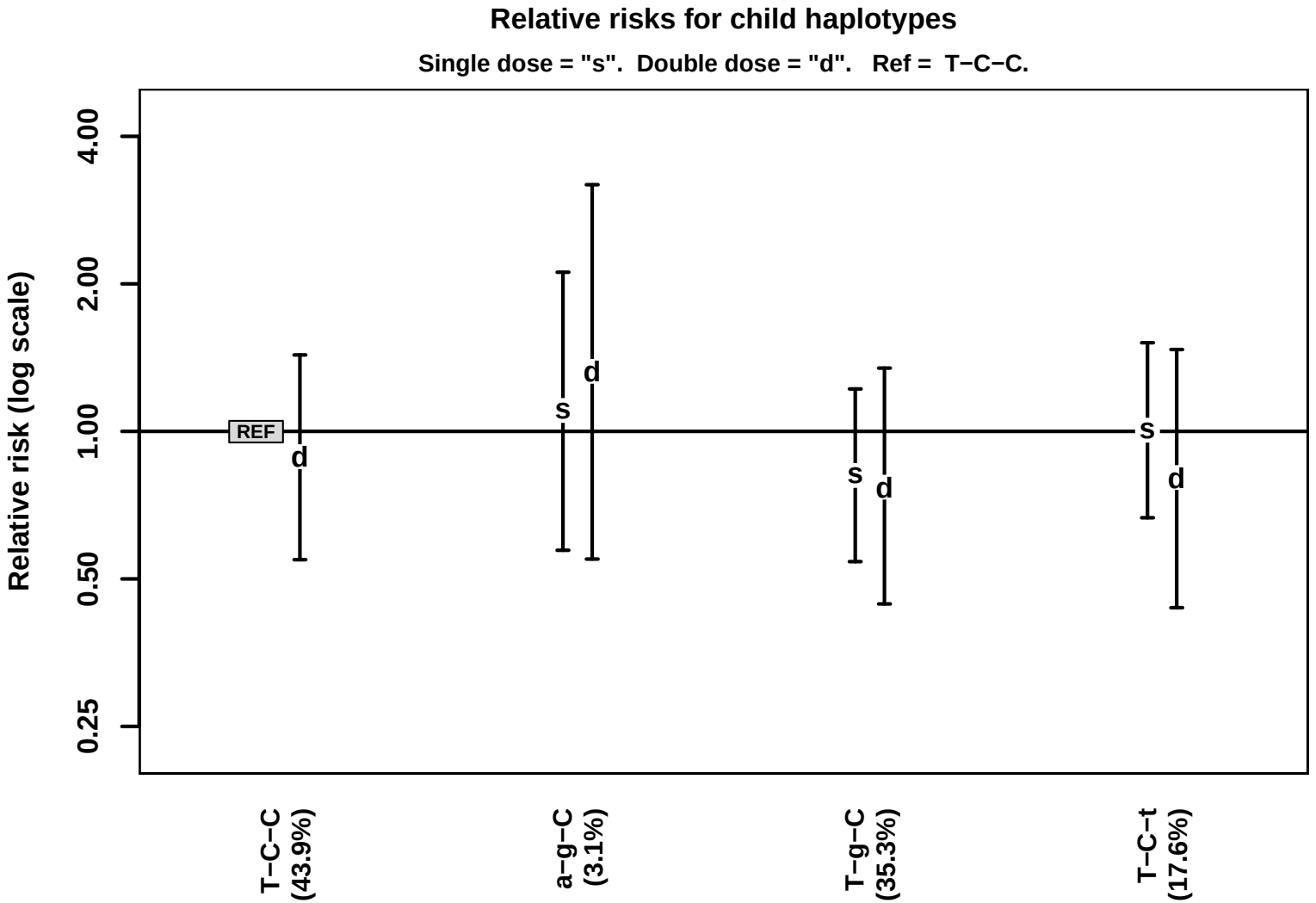
HAPLIN RUN, X-CHROMOSOME

X-chromosome run:

- Haplotypes of SNPs 2, 3, 4 *on the X-chromosome*
- Impute missing
- **Important:** Use `xchrom = T` to let `haplin` know!

```
haplin(data = pres.data, markers = 306:308, use.missing = T,
 xchrom = T, reference = "ref.cat")
```

HAPLIN OUTPUT: EFFECT ESTIMATES, X-CHROMOSOME



Drew a blank...

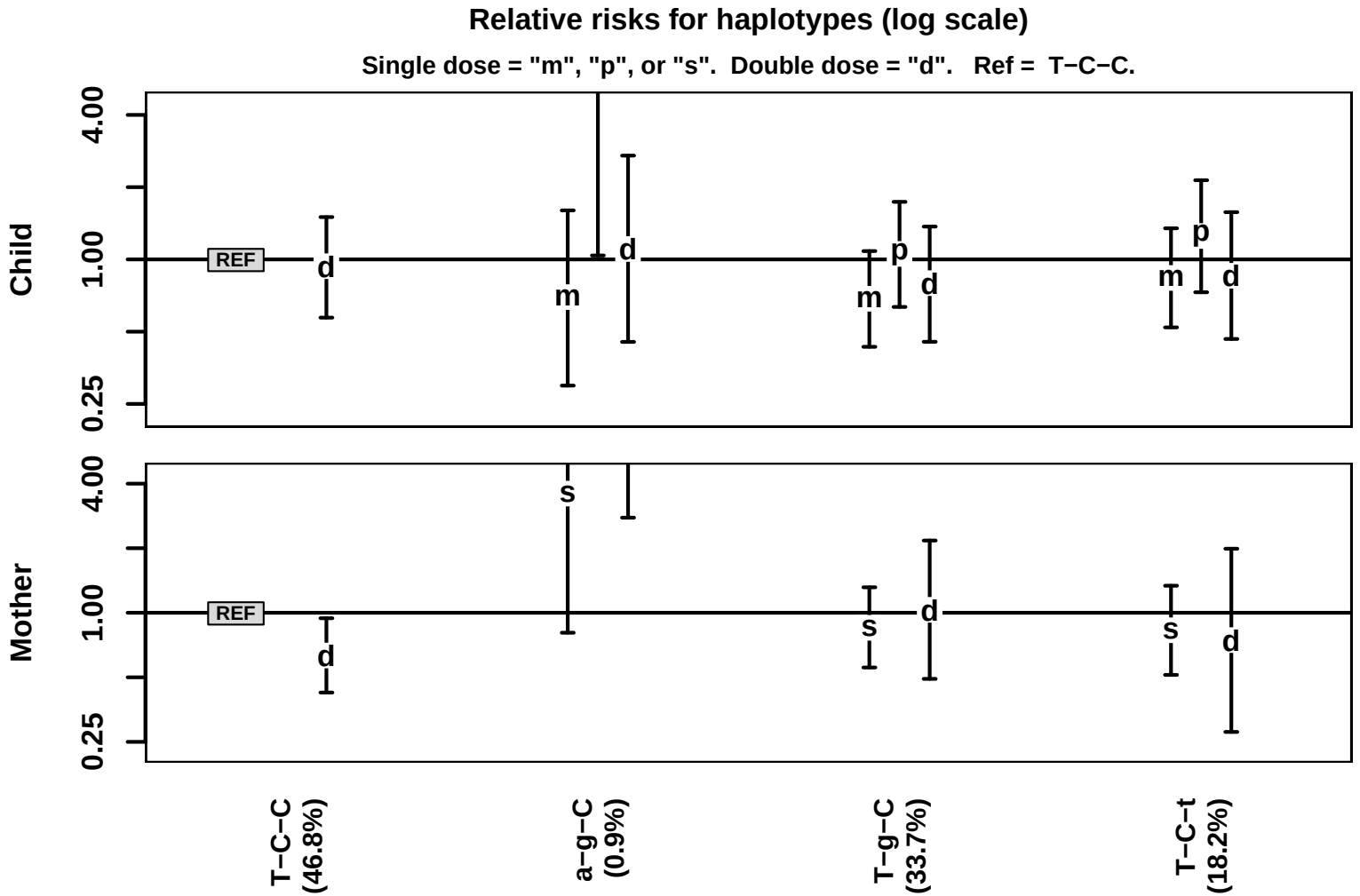
HAPLIN RUN, X-CHROMOSOME WITH MATERNAL AND POO

```
haplin(data = pres.data, markers = 306:308, use.missing = T,
 xchrom = T, maternal = T, poo = T)
```

Note:

- Maternal effects are measured as before
- Parent-of-origin effects are measured only in girls

HAPLIN OUTPUT: EFFECT ESTIMATES, X-CHROMSOME



Perhaps?

HAPLIN OUTPUT: EFFECT ESTIMATES, X-CHROMSOME

----Child haplotypes----

Haplotype	Dose	Relative Risk	Lower CI	Upper CI	P-value
T-C-C	Single-mat	REF			
T-C-C	Single-pat	REF			
T-C-C	Double	0.937	0.572	1.5	0.791
T-C-C	Ratio m/p	REF			
a-g-C	Single-mat	0.696	0.298	1.6	0.396
a-g-C	Single-pat	5.05	1.04	23.3	0.0444
a-g-C	Double	1.1	0.453	2.71	0.833
a-g-C	Ratio m/p	0.137	0.0248	0.795	0.0262
T-g-C	Single-mat	0.685	0.432	1.08	0.11
T-g-C	Single-pat	1.05	0.634	1.74	0.84
T-g-C	Double	0.796	0.454	1.37	0.411
T-g-C	Ratio m/p	0.649	0.396	1.07	0.0928
T-C-t	Single-mat	0.837	0.521	1.35	0.471
T-C-t	Single-pat	1.25	0.73	2.14	0.411
T-C-t	Double	0.855	0.466	1.57	0.607
T-C-t	Ratio m/p	0.665	0.372	1.22	0.19

Again, not very convincing considering the number of effects tested.

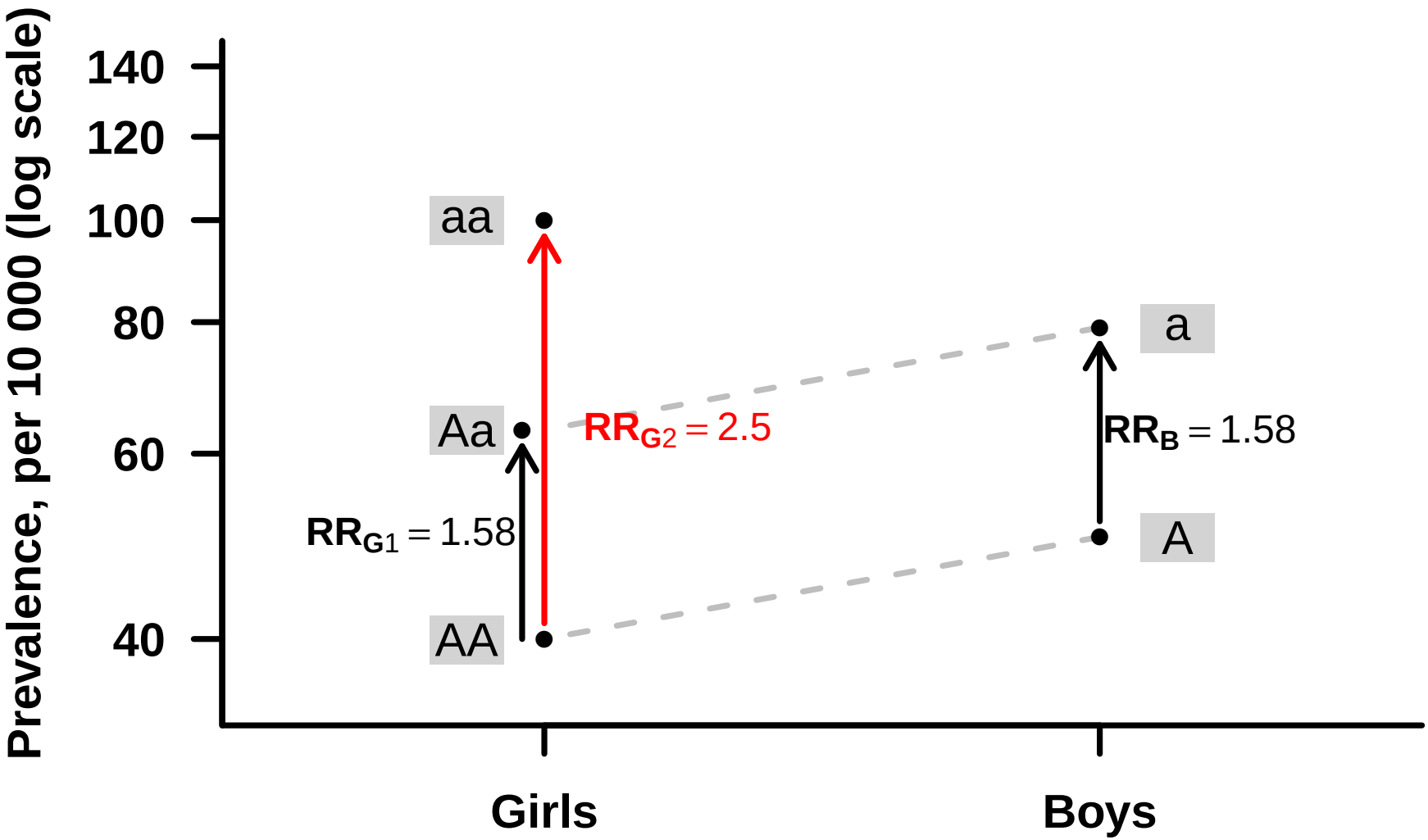
HAPLIN OUTPUT: EFFECT ESTIMATES, X-CHROMSOME

```
LIKELIHOOD RATIO TEST:
 Loglike null model:          -2225.37019
 Loglike full model:          -2212.94983
 df:                             17.00000
 Likelihood ratio p-value:        0.09833
```

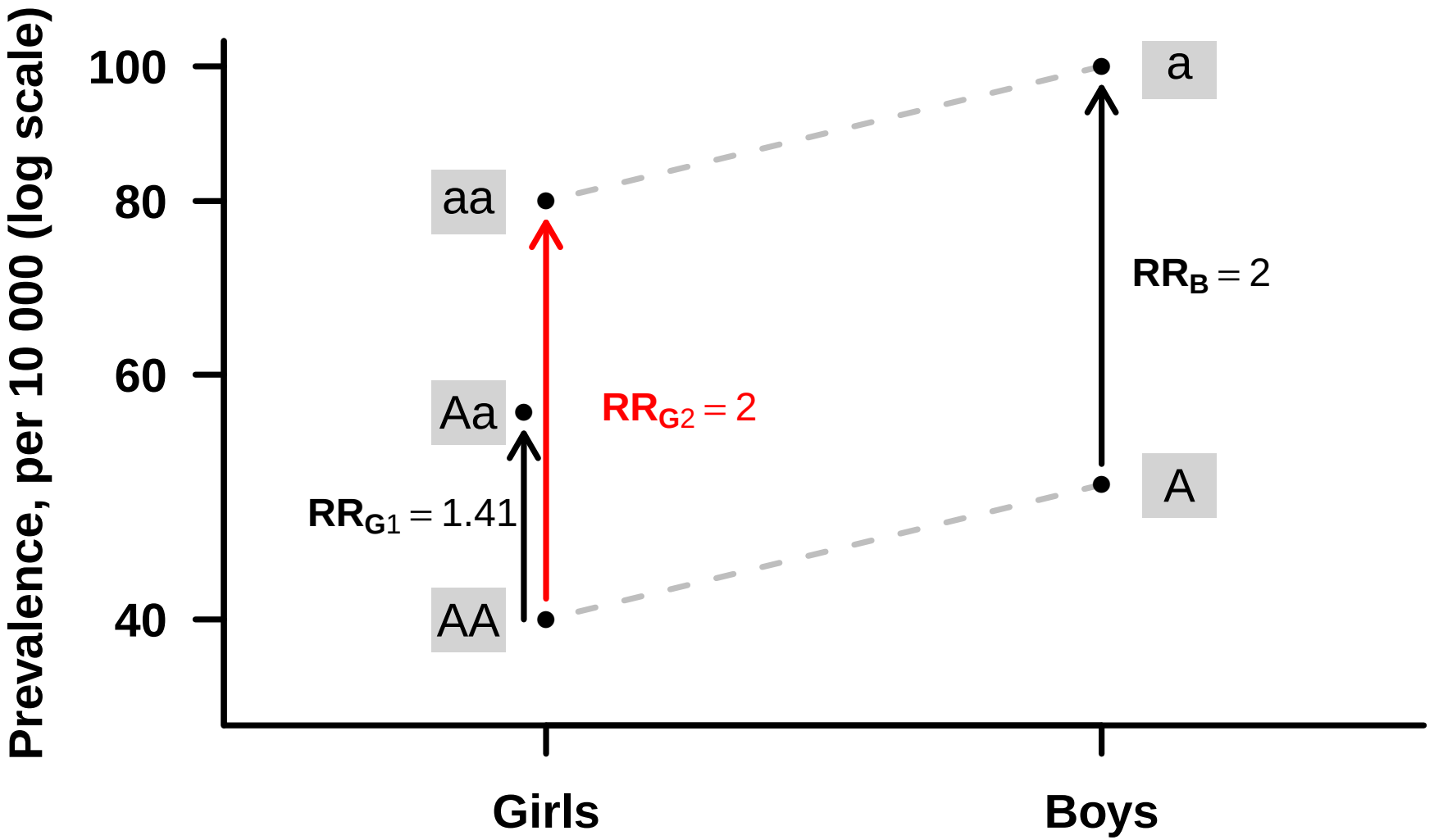
Again:

- The LRT is an overall test of *all* effects included in the model

No X-inactivation. Multiplicative dose-response.



X-INACTIVATION. MULTIPLICATIVE DOSE-RESPONSE.

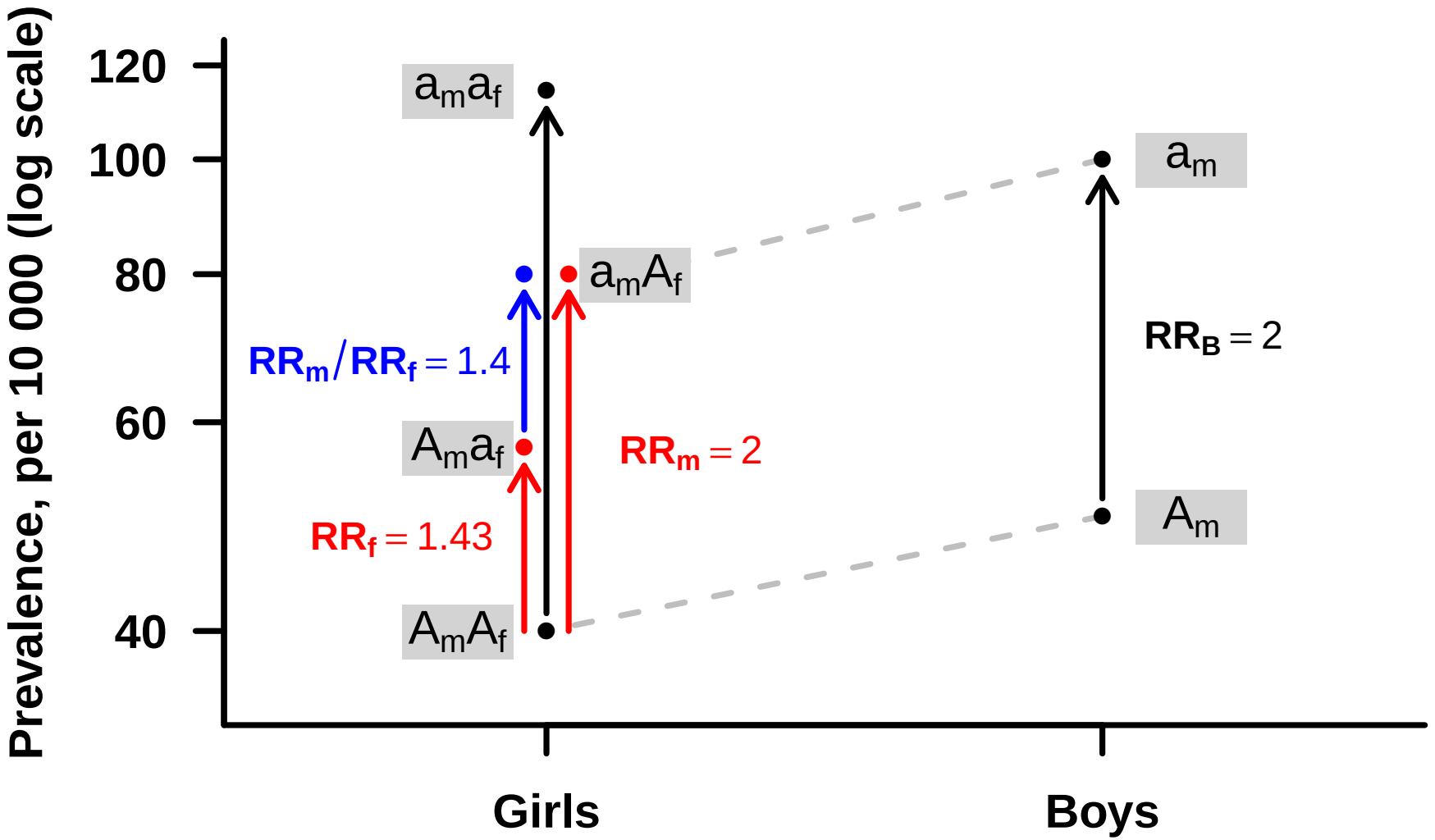


HAPLIN: A NOTE ON X-CHROMOSOME RESPONSE MODELS

- Default: `comb.sex = "double"`
  - Single dose in males equals double in females
  - I.e. corresponds to X-inactivation
- Alternative: `comb.sex = "single"`
  - Single dose in males equals single in females
- Alternative: `comb.sex = "females"`
  - Analysis performed only on females
- Alternative: `comb.sex = "males"`
  - Analysis performed only on males
  - `response` - argument no effect

NOTE: All models assume different *baseline* risks for females and males

No X-inactivation, and parent-of-origin effects. Multiplicative dose-response.



X-INACTIVATION, AND PARENT-OF-ORIGIN EFFECTS. MULTIPLICATIVE DOSE-RESPONSE.