Sequential genome-wide association studies for pharmacovigilance

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Outline

1. Pharmacovigilance and genetics
2. Fixed sample size test
3. Sequential testing
4. An example
5. Summary & issues

Pharmacovigilance & genetics

Adverse events (AEs) may prevent regulatory approval

If AEs are limited to some subgroup

drug can be targeted

adverse event rate reduced

drug may be safely used

Pharmacovigilance & genetics

Can we identify whether patients with AEs differ from those that do not have AEs?

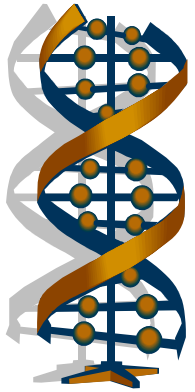
Present

Patient medical history

Future

Large scale genotyping becoming available

e.g. > 500,000 SNP markers across genome



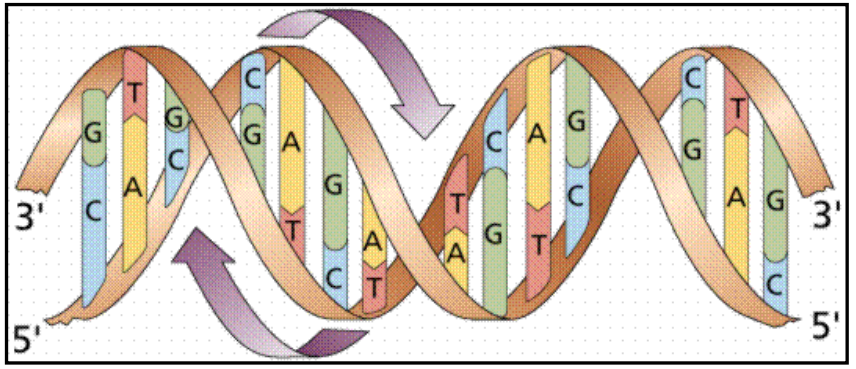
Pharmacovigilance & genetics

SNP (single nucleotide polymorphism)

A single base in the DNA sequence that can be observed to be different between individuals in the population

e.g. **AACGTATGGACCGA**

AACGTATCGACCGA



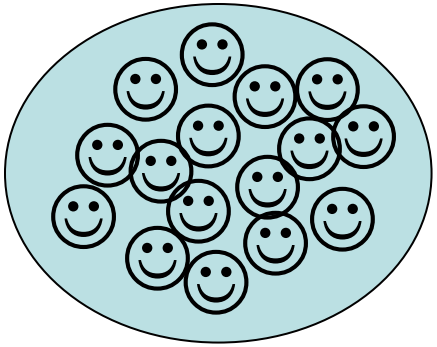
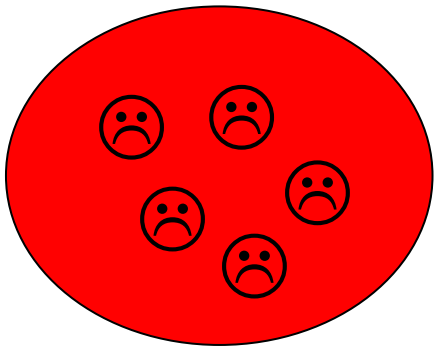
Since chromosomes occur in pairs we have three genotypes

Pharmacovigilance & genetics

Case = patient with AE ☹

Control = patient without AE ☺

Are cases genetically different from controls?

Conduct a test  versus 

Pharmacovigilance & genetics

Cases ☹

Rare
Conduct fixed sample size test ✗
Drug withdrawn due to safety concerns

Aim

Conduct a test as each new case occurs
i.e. a sequential approach

Controls ☺

Patients in same trial may become cases ✗
Want a large number
⇒ Select in advance, i.e. fixed in number

Fixed sample test - one SNP

3 genotypes – AA, AG, GG

$k = 0, 1, 2$

Are the genotype probabilities for cases the same as the controls?

$$H_0: p_{☹0} = p_{☺0},\ p_{☹1} = p_{☺1},\ p_{☹2} = p_{☺2}$$

$p_{☹0}, p_{☹1}, p_{☹2}$ genotype probabilities for controls

$p_{☺0}, p_{☺1}, p_{☺2}$ genotype probabilities for cases

Fixed sample test - one SNP

Can test H_0 using a likelihood ratio test statistic, Λ

$$\Lambda = \frac{\prod_{k=0}^{2} \binom{n_{\text{☺}k} + n_{\text{☹}k}}{n_{\text{☺}k} + n_{\text{☹}k}}}{\prod_{k=0}^{2} \binom{n_{\text{☺}k}}{n_{\text{☺}}}^{n_{\text{☺}}} \prod_{k=0}^{2} \binom{n_{\text{☹}k}}{n_{\text{☹}}}^{n_{\text{☹}}}}$$

Controls $n_{\text{☺}0}$, $n_{\text{☺}1}$, $n_{\text{☺}2}$ $\quad n_{\text{☺}} = n_{\text{☺}0} + n_{\text{☺}1} + n_{\text{☺}2}$

Cases $n_{\text{☹}0}$, $n_{\text{☹}1}$, $n_{\text{☹}2}$ $\quad n_{\text{☹}} = n_{\text{☹}0} + n_{\text{☹}1} + n_{\text{☹}2}$

Under H_0 , $-2 \log \Lambda \sim \chi^2_2$

Fixed sample test – many SNPs

Suppose there are L SNPs

Are the genotype probabilities for cases the same as the controls for **all L SNPs**?

H_0: $p_{☹01} = p_{☺01}, p_{☹11} = p_{☺11}, p_{☹21} = p_{☺21}$; (SNP 1)

$p_{☹02} = p_{☺02}, p_{☹12} = p_{☺12}, p_{☹22} = p_{☺22}$; (SNP 2)

...

$p_{☹0L} = p_{☺0L}, p_{☹1L} = p_{☺1L}, p_{☹2L} = p_{☺2L}$ (SNP L)

Fixed sample test – many SNPs

Likelihood ratio test statistic, Λ, becomes

$$\Lambda = \prod_{j=1}^{L} \left[\frac{\prod_{k=0}^{2} \binom{n_{\text{☺}kj} + n_{\text{☹}kj}}{n_{\text{☺}kj}}^{n_{\text{☺}kj} + n_{\text{☹}kj}}}{\prod_{k=0}^{2} \binom{n_{\text{☺}kj}}{n_{\text{☺}}}^{n_{\text{☺}}} \prod_{k=0}^{2} \binom{n_{\text{☹}kj}}{n_{\text{☹}}}^{n_{\text{☹}kj}}} \right]$$

$n_{\text{☺}0j}$, $n_{\text{☺}1j}$, $n_{\text{☺}2j}$ for controls at SNP j

$n_{\text{☹}0j}$, $n_{\text{☹}1j}$, $n_{\text{☹}2j}$ for cases at SNP j

Fixed sample test – many SNPs

If asymptotics hold and SNPs are independent then

under H_0, $-2 \log \Lambda \sim \chi^2_{2L}$

However!

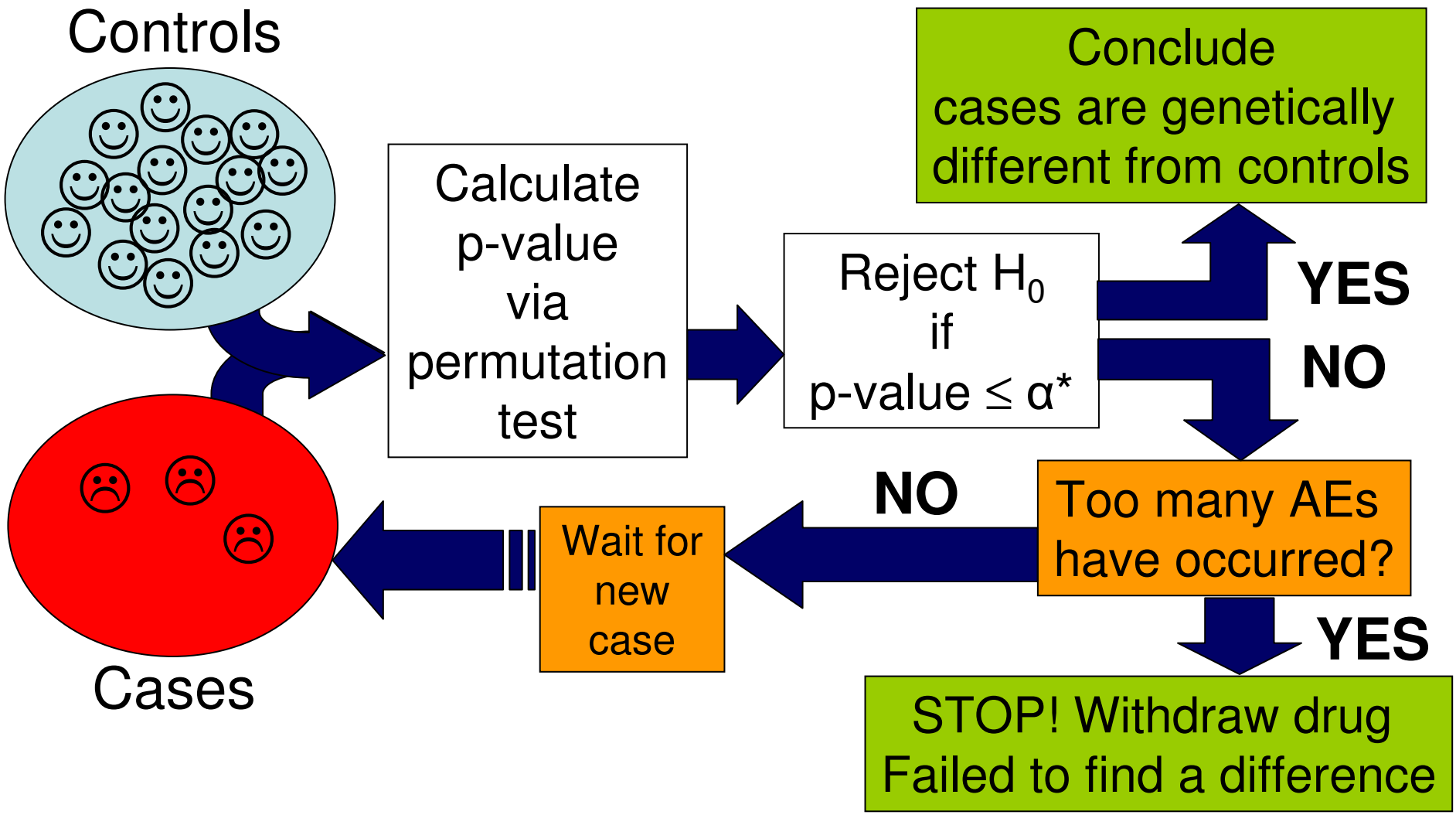
Some genotypes are rare $\Rightarrow$ asymptotics poor

SNPs are not independent (linkage disequilibrium)

Overcome problem by using a **permutation test** to obtain p-value

Correlation structure of genome is preserved

Sequential testing



Sequential testing

We plan up to M tests

Need to account for the multiple testing

Otherwise type I error rate, α, will be inflated

How can we control the type I error rate?

- Adjust the nominal significance level α* accordingly
- Can't use standard sequential methods

Sequential testing

Standard multiple testing methods

Sidak $\alpha^* = 1 - (1 - \alpha)^{1/M}$

e.g. $M = 20$, $\alpha = 0.05 \Rightarrow \alpha^* \approx 0.0026$

Assumes tests are independent

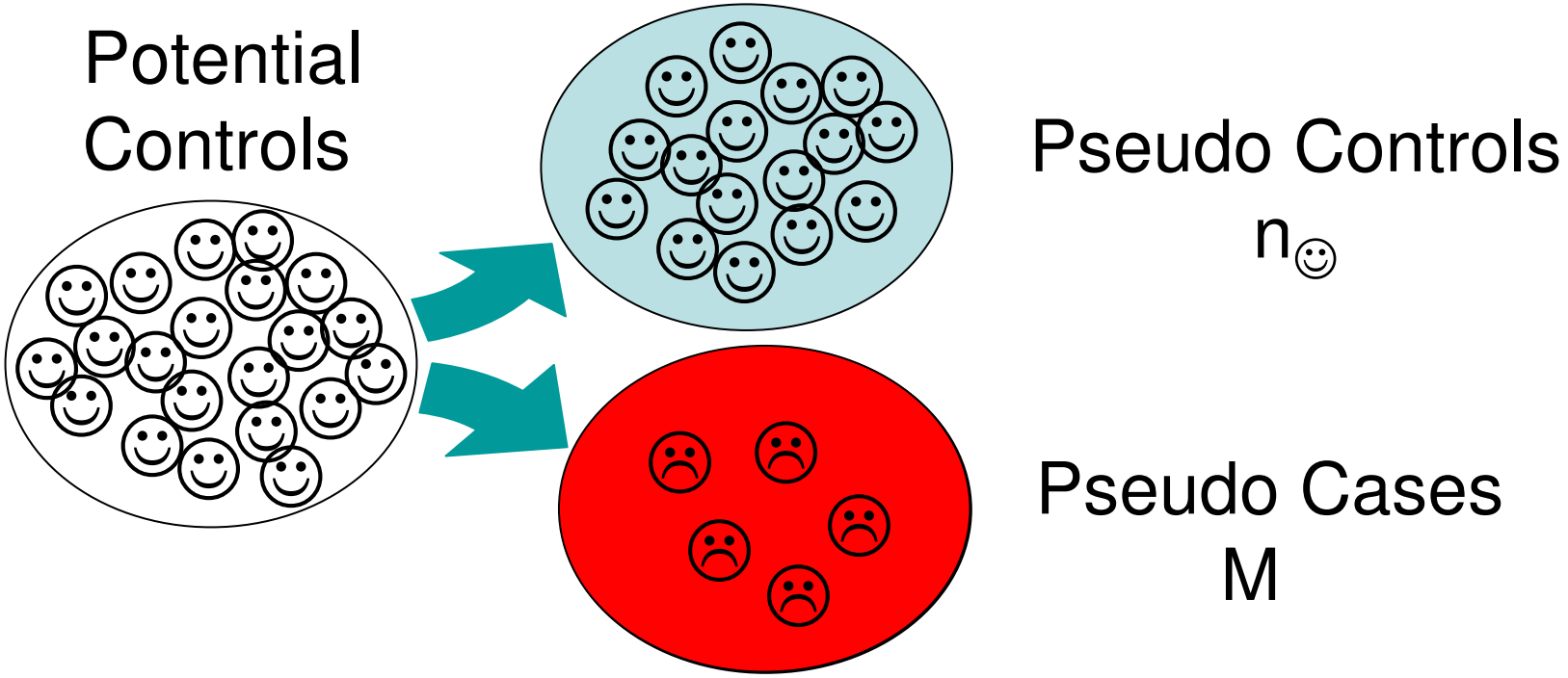
But tests are correlated!

Analysis will be conservative

Sequential testing

Sampling-based approach

Randomly select



Sequential testing

Sampling-based approach

With pseudo data set

conduct sequential procedure

using significance level α^*

Reject H_0?

Repeat many times (e.g 10,000) to estimate α

Find α^* which gives required α

Example

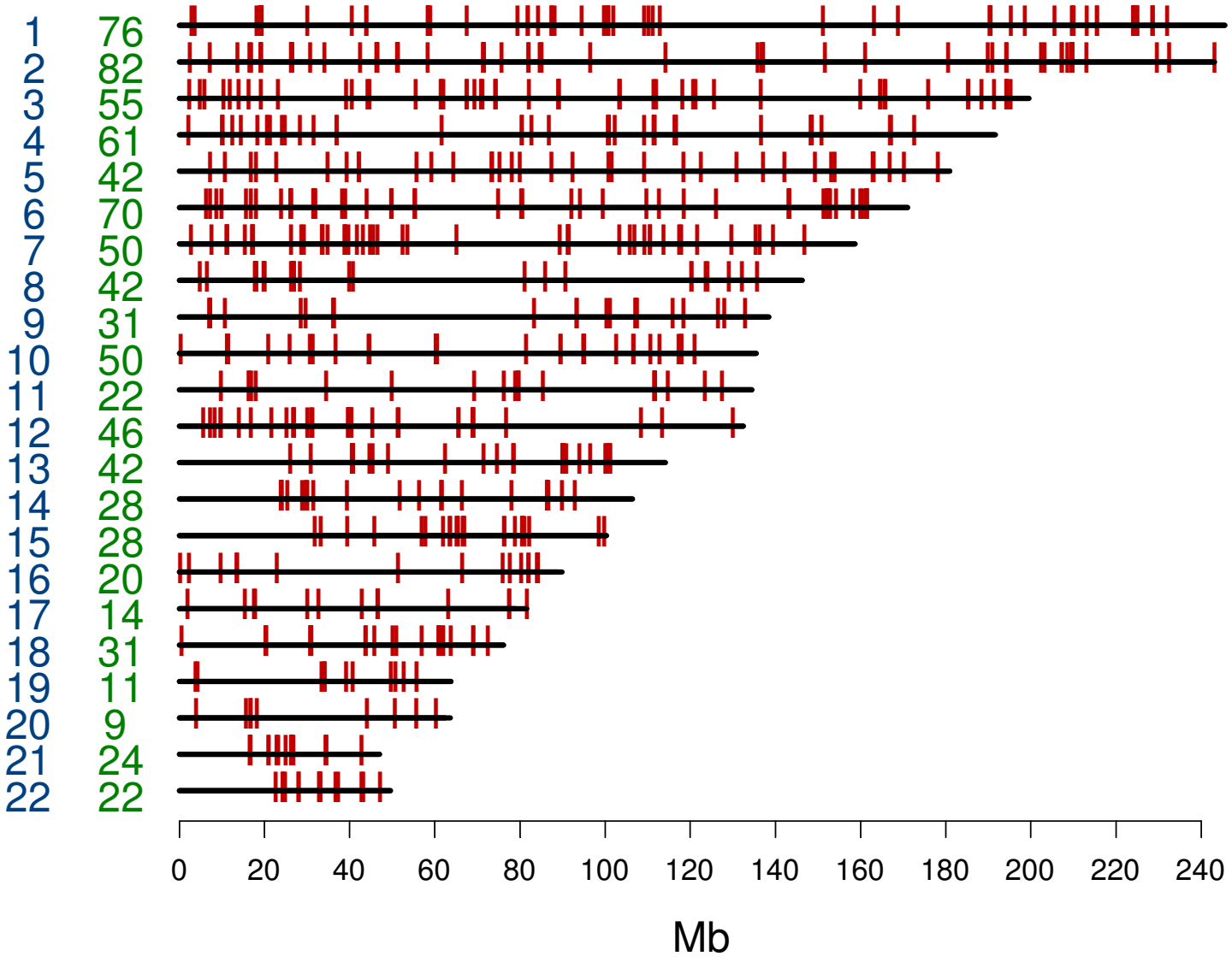
Abacavir : anti-viral treatment for HIV

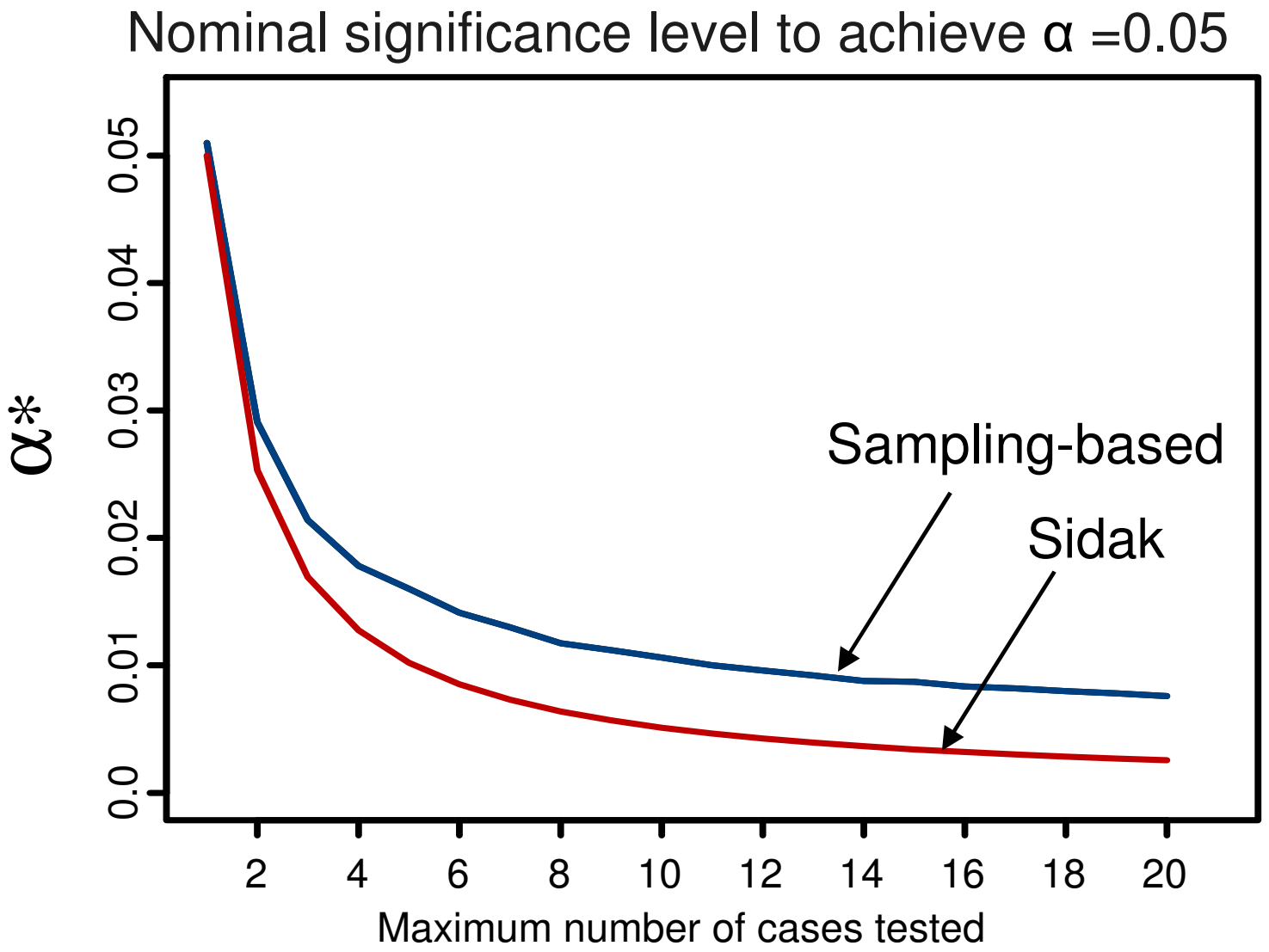
AE: hypersensitivity (5-8% of patients)

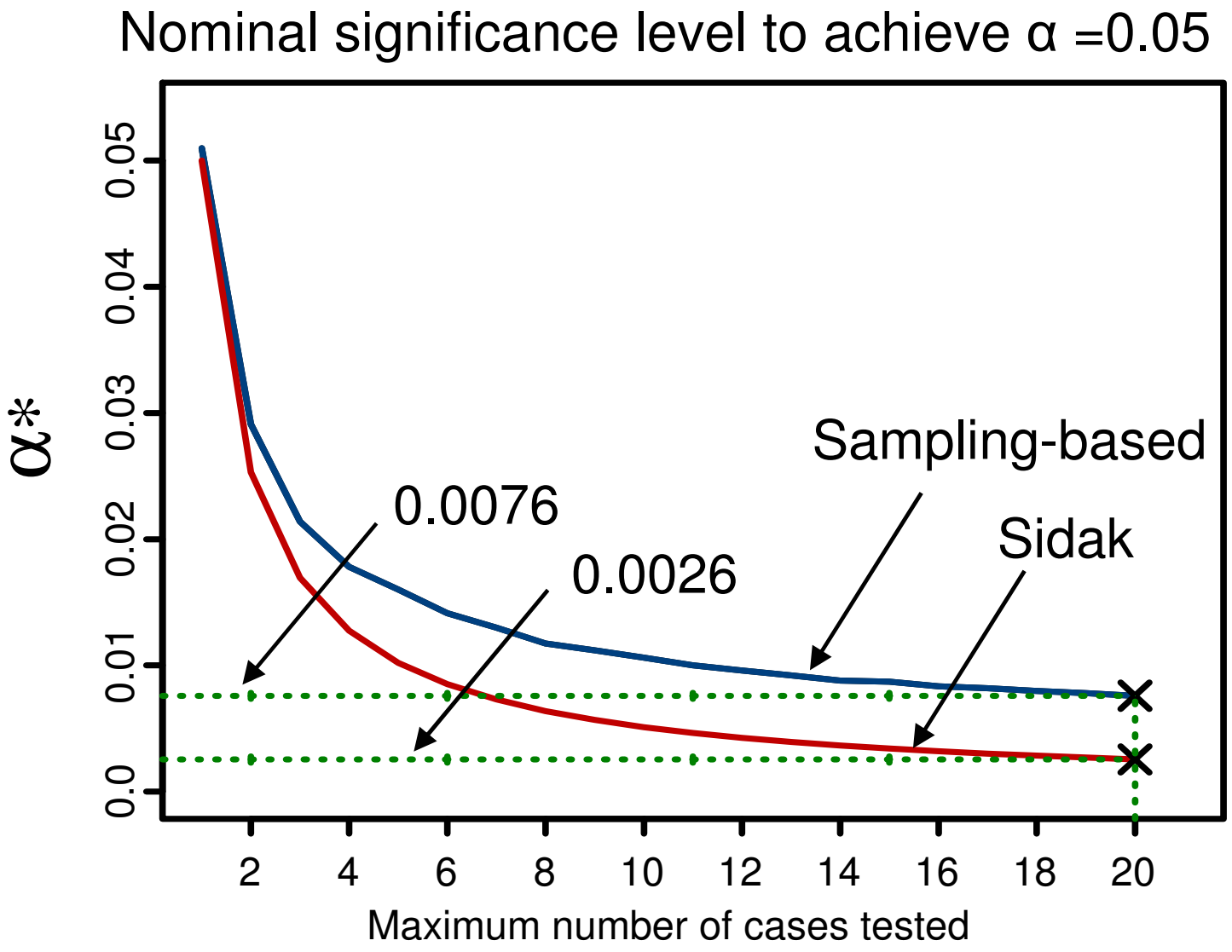
523 patients with AE (pool of cases)

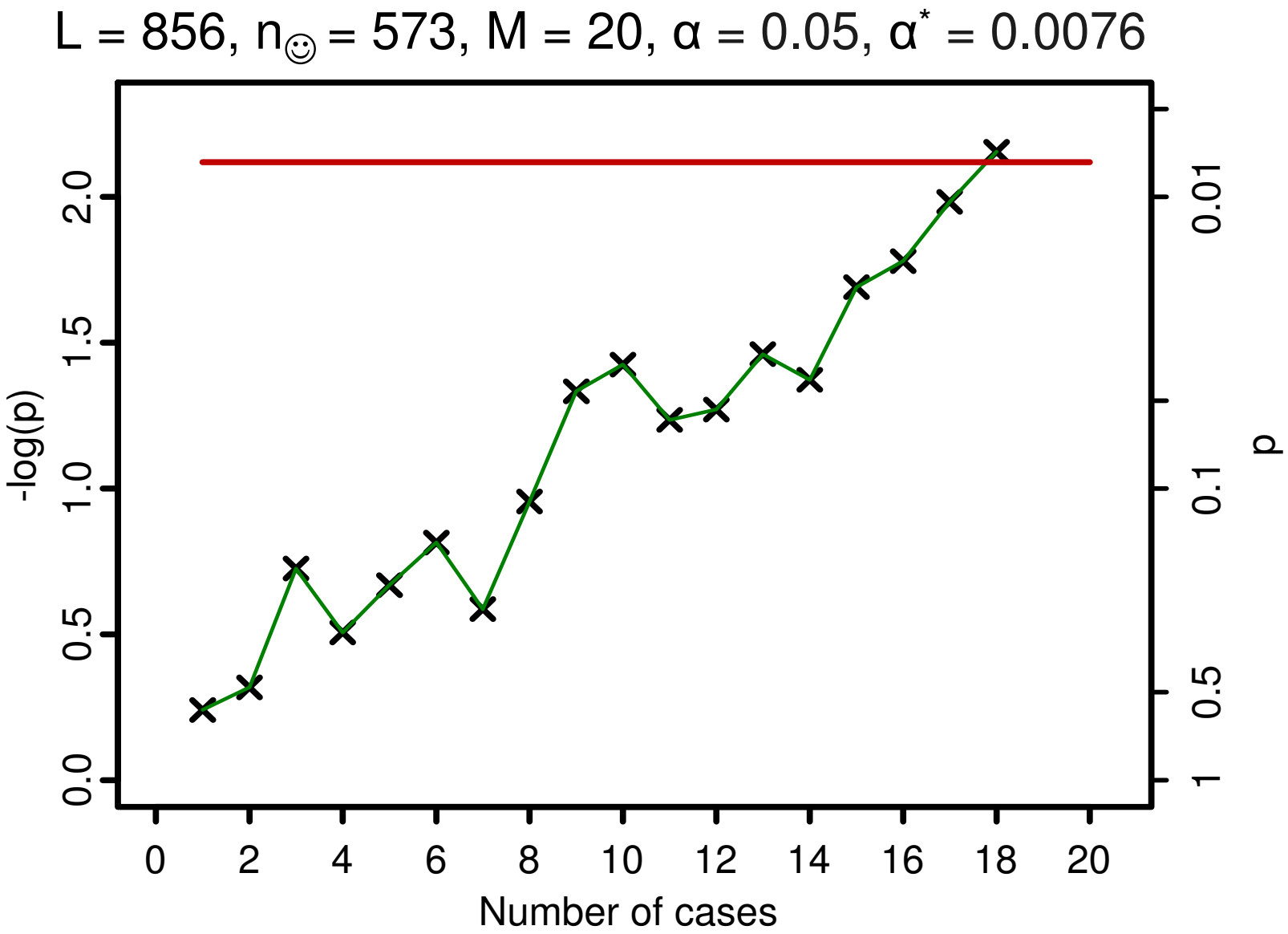
593 patients without AE (pool of controls)

Retrospective application


L = 856 SNP markers
1 76
2 82
3 55
4 61
5 42
6 70
7 50
8 42
9 31
10 50
11 22
12 46
13 42
14 28
15 28
16 20
17 14
18 31
19 11
20 9
21 24
22 22
0 20 40 60 80 100 120 140 160 180 200 220 240
Mb


Nominal significance level to achieve α =0.05
α*
0.0
0.01
0.02
0.03
0.04
0.05
2
4
6
8
10
12
14
16
18
20
Maximum number of cases tested
Sampling-based
Sidak


Nominal significance level to achieve α =0.05
α*
0.0
0.01
0.02
0.03
0.04
0.05
2
4
6
8
10
12
14
16
18
20
Maximum number of cases tested
Sampling-based
Sidak
0.0076
0.0026


L = 856, n☺ = 573, M = 20, α = 0.05, α* = 0.0076
-log(p)
0.0
0.5
1.0
1.5
2.0
p
1
0.5
0.1
0.01
0
2
4
6
8
10
12
14
16
18
20
Number of cases

Summary

Permutations for fixed sample test

- allows for correlation between SNP markers
- obtain a valid global p-value for genome

Sampling-based sequential testing

- adjust nominal significance level to account for repeated testing
- allows for correlation between successive tests
- simple and easy

Summary

Requirements

- must specify the maximum number of tests planned
- must have group of controls in advance
- must have sufficient computing facilities
  - very computer intensive!

Issues

How do you select the controls?

Can we develop a less computer intensive method?

If we reject H_0, how do we identify those patients who should be excluded from receiving the drug?

References

Kelly PJ, Stallard N, Zhou Y, Whitehead J, Bowman C.

Sequential genome-wide association studies for monitoring adverse events in the clinical evaluation of new drugs. *Statistics in Medicine* 2006; 25: 3081-3092

Kelly PJ, Stallard N, Whittaker JC.

Statistical design and analysis of pharmacogenetics trials. *Statistics in Medicine*, 2005; 24: 1495-1508