On the impact of relatedness on SNP association analysis

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Background

When testing for SNP (single nucleotide polymorphism) associations in related individuals, observations are not independent and simple linear regression analysis results in an increased type I error and the power of the test is also affected in a more complicate manner. We investigate how heritability and strength of relatedness contribute to variance inflation of the effect estimate and study the consequences of variance inflation on hypothesis testing.

Modelling a SNP-Phenotype association

True model

Phenotypes follow the mixed model

$$\mathbf{y} = b_1 + b_2\mathbf{s} + \mathbf{g} + \mathbf{e}$$

with

- phenotypes $\mathbf{y}$ for n samples
- intercept b_1, genetic effect b_2
- SNP genotypes $\mathbf{s}$, $s_i \in \{0, 1, 2\}$
- polygenic random effects $\mathbf{g} \sim \mathrm{N}_n(0, \sigma^2_\mathrm{g}\mathbf{G})$, variance σ^2_g, relatedness matrix $\mathbf{G}$
- uncorrelated residuals $\mathbf{e} \sim \mathrm{N}_n(0, \sigma^2_\mathrm{e}\mathbf{I})$, variance σ^2_e, identity matrix $\mathbf{I}$.

Simplified model

Phenotypes are analysed with the model

$$\mathbf{y} = \beta_1 + \beta_2\mathbf{s} + \boldsymbol{\epsilon}$$

assuming uncorrelated residuals $\boldsymbol{\epsilon}$ only. It can be shown that $\mathrm{E}(\hat{\beta}_2) = b_2$ and

$$\mathrm{V}(\hat{\beta}_2) = \frac{\lambda}{1 - R^2_\mathrm{h}} V_\beta$$

with

- inflation factor λ
- heritability R^2_h
- variance V_β of $\hat{\beta}_2$ without heritability.

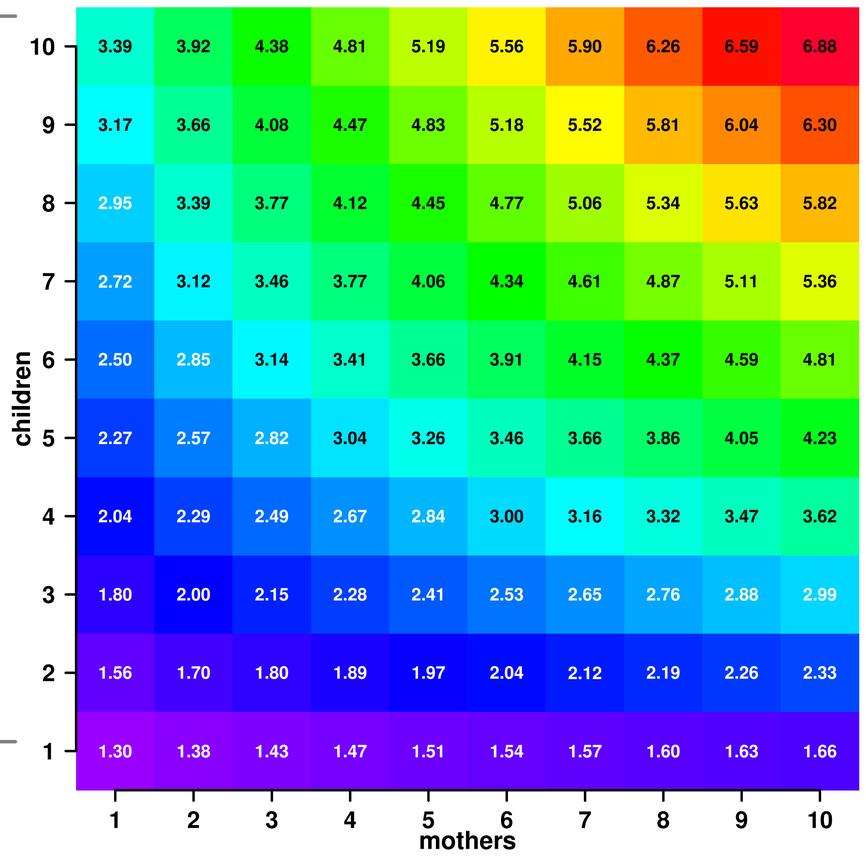
Inflation factor

Expected variance inflation is

$$\lambda = 1 + R^2_\mathrm{h} \frac{\sum_i \sum_{j \neq i} G^2_{ij} - \frac{2}{n} \sum_i \left(\sum_{j \neq i} G_{ij} \right)^2}{n - 1}$$

Properties are

- stronger relatedness increases inflation
- higher heritability increases inflation
- inflation is independent from allele frequency.



The figure presents the expected variance inflation for 90% heritability and family studies with varying numbers of children per mother and mothers per family/father. The number of families is constrained by *n*=1000 individuals.

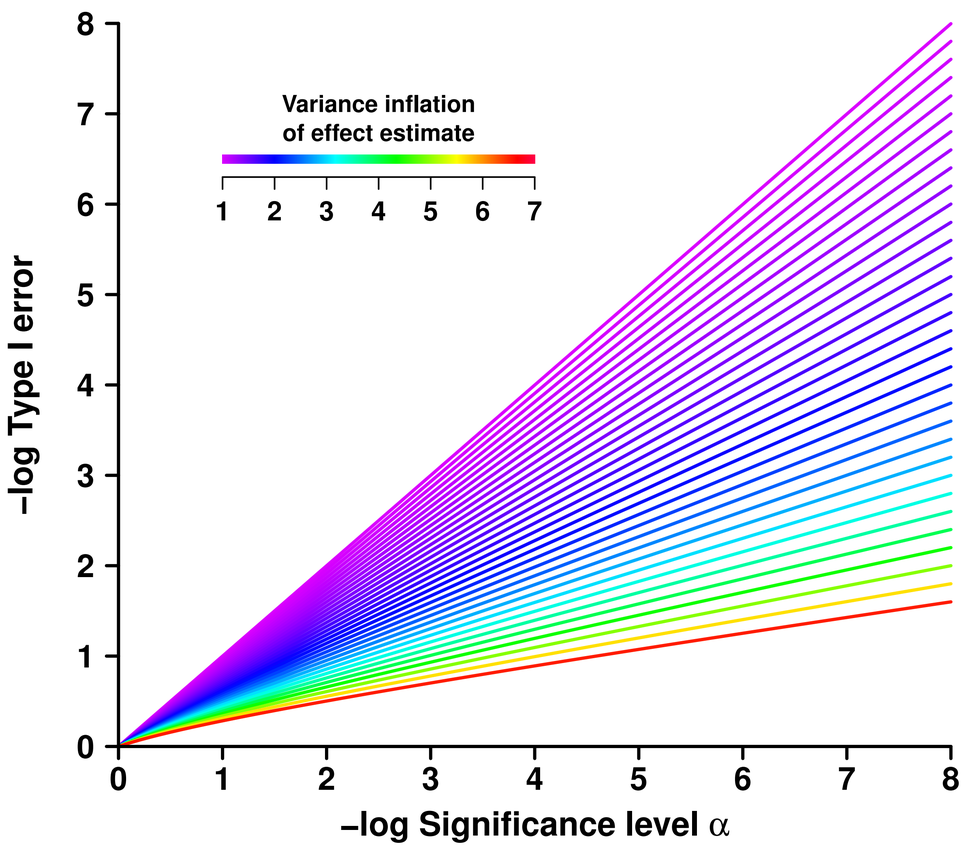
Hypothesis testing

Type I error

Under the null hypothesis $b_2 = 0$, it approximately holds that

$$T \sim \mathrm{N}(0, \lambda)$$

for test statistic $T = \hat{\beta}_2 / S_\beta$ with empirical variance S^2_β of $\hat{\beta}_2$.



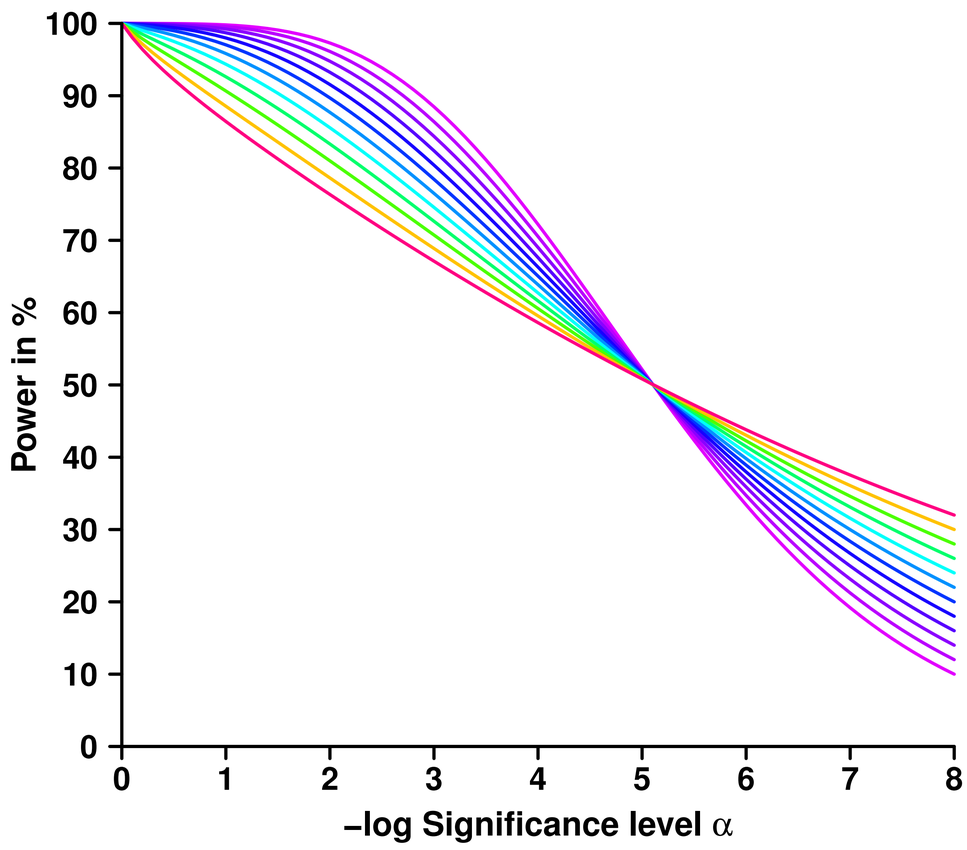
Comparison of type I errors with respect to different degrees of variance inflation. The negative common logarithm is presented for significance level α as well as the type I error.

Power of test

Under the alternative hypothesis $b_2 \neq 0$, it approximately holds that

$$T \sim \mathrm{N}(\sqrt{(n-1)R^2_\mathrm{s}}, \lambda)$$

with sample size n and explained variance by the SNP R^2_s.



Comparison of power with respect to different degrees of variance inflation assuming *n*=1000 and 2% explained variance by the SNP. The negative common logarithm is presented for significance level α.

Conclusions

We provide a simple formula for estimating variance inflation given the relatedness structure and the heritability of a phenotype. Stronger relatedness as well as higher heritability result in increased variance of the effect estimate of simple linear regression. While type I error rates are generally inflated, the behaviour of power is more complex since power can be increased or reduced in dependence on the significance level. For additional information, have a look at https://bmcgenet.biomedcentral.com/articles/10.1186/s12863-017-0571-x or use the QR Code: