

***Variance components on the risk scale using the unconstrained risk model.***

Following our previous derivations [10], the total genetic variance on the risk scale can be expressed as  $V_{G_{01}} = \text{var}(f_n \tau^x) = E[(f_n \tau^x)^2] - (E[f_n \tau^x])^2 = f_n^2 [(1 + p(\tau^2 - 1))^{2n} - (1 + p(\tau - 1))^{4n}]$ . Using  $f_n = K/(1 + p(\tau - 1))^{2n}$

$$V_{G_{01}} = K^2 [(1 + v)^{2n} - 1],$$

where  $v = p(1-p)(\tau - 1)^2 / [1 + p(\tau - 1)]^2$  and parameterises the contribution to the genetic variance of each risk allele. Additive ( $V_{A_{01}}$ ) and dominance ( $V_{D_{01}}$ ) variance are obtained by summing the single locus variances (which are given in [3,10,11]).

Hence,  $V_{A_{01}} = 2nvK^2$  and  $V_{D_{01}} = nv^2K^2$ . By definition, the total amount of epistatic variance is  $V_{G_{01}} - V_{A_{01}} - V_{D_{01}}$ . The total genetic variance can also be written as  $V_{G_{01}} = K^2 [(1 + 2v + v^2)^n - 1]$ . A binomial expansion of the term  $(1 + 2v + v^2)^n - 1$  gives terms which correspond to all additive and non-additive variance components:

$$K^2 [(1 + 2v + v^2)^n - 1] = K^2 [2nv + nv^2 + 0.5n(n-1)(4v^2 + 4v^3 + v^4) + \dots]$$

$$V_{A_{01}} \quad V_{D_{01}} \quad V_{AA_{01}} \quad V_{AD_{01}} \quad V_{DD_{01}} + \text{etc.}$$

Single locus terms      Two locus terms      > 2 locus terms

With many loci,  $(\lambda - 1)$  is small, so  $v$  is small ( $< 1$ ) and  $v^2$  is even smaller.

Consequently, the dominance components become negligible. The epistatic AA, AAA, etc. components do not become negligible, however, because they are multiplied by higher powers of  $n$  than the dominance components. For large  $n$ ,  $V_{G_{01}} \approx K^2 (e^{2nv} - 1)$ .

Therefore, the proportion of genetic variance that is non-additive depends on the size of  $2nv$  which is the scaled additive variance on the risk scale. The ratio of the additive to total genetic variance on the risk scale is  $V_{A_{01}} / V_{G_{01}} \approx 2nv / (e^{2nv} - 1)$ . Hence, paradoxically, if  $2nv$  and therefore the additive variance is large, then epistatic variance is even larger and most of the genetic variance on the risk scale is non-additive.