Text S2: Additive Model

I will first calculate the expected contribution under an additive model to the prevalence $E(K_L)$ and the recurrence risk $E(KK_L)$. Then I will show the individual terms for calculating $Pr(AA_R|H,S)$ that are used in equation (8).

The contribution to prevalence can be calculated by integrating over all possible effect sizes

$$E(K_L) = \int [p^2(\omega_1 + \omega_2) + 2p(1-p)\omega_1]\, f(\omega_1)f(\omega_2)d\omega_1 d\omega_2 = 2p\int \omega f(\omega)d\omega = 2p\mu$$

Conditioning on $S = 0$:

$E(K_L K_{LR}|S = 0) = E(K_L)^2 = 4p^2\mu^2$.

When considering relative pairs with shared carrier chromosomes, some risk haplotypes may occur in multiple individuals IBD. The contribution of these chromosomes to the overall penetrance includes the term $\int \omega_S^2 f(\omega)d\omega = \mu^2 + \sigma^2$. When conditioning on $S = 1$, define the penetrance ω_S of shared chromosome and the penetrances $\omega_1, \omega_2$of the 2 non-shared chromosomes.

$$E(K_L K_{LR}|S = 1) = p(1-p)^2\int \omega_S{}^2 f(\omega_S)d\omega_S + p^2(1-p)\int (\omega_1 + \omega_S)\omega_S f(\omega_1)f(\omega_S)d\omega_1 d\omega_S$$

$$+p^2\,(1-p)\int (\omega_2 + \omega_S)\omega_S\, f(\omega_2)f(\omega_S)d\omega_1\, d\omega_S + p^2\,(1-p)\int \omega_1\,\omega_2\, f(\omega_1)f(\omega_2)d\omega_1\, d\omega_2$$

$$+p^3\int (\omega_1 + \omega_S)(\omega_2 + \omega_S)f(\omega_1)f(\omega_2)f(\omega_S)d\omega_1\, d\omega_2\, d\omega_S = 3p^2\,\mu^2 + p(\mu^2 + \sigma^2)$$

When conditioning on two shared chromosomes, integrate over the penetrances ω_{S1}, ω_{S2}:

$$E(K_L K_{LR}|S = 2) = \; 2p(1-p)\int \omega_{S1}^2 f(\omega_{S1})d\,\omega_{S1} + \; p^2\int (\omega_{S1} + \omega_{S2})^2\, f(\omega_{S1})f(\omega_{S2})d\omega_{S1}\, d\omega_{S2}$$

$$= \; 2p^2\,\mu^2 + 2p(\mu^2 + \sigma^2\;)$$

Hence the expectation of $K_L K_{LR}$ is then: $E(K_L K_{LR}) = Pr(S = 0)\cdot 4p^2\mu^2 + Pr(S = 1)\cdot(3p^2\mu^2 + p(\mu^2 + \sigma^2) + Pr(S = 2)\cdot(2p^2\mu^2 + 2p(\mu^2 + \sigma^2)$.

The individual terms $Pr(AA_R|H,S)$ can be calculated by integrating over the genotype in the affected relative H_R: Conditional on $S = 0$, the additive effect of all risk haplotypes is independent. Hence:

$$Pr(AA_R|H = h_1, H_R = h_2, S = 0) = h_1h_2\mu^2 + (h_1 + h_2)\mu K_G + K_G K_{GR}.$$

To account for such shared risk chromosomes for $S > 0$, define H_S for the number of shared risk haplotypes ($H_S \leq S$). Then

$$Pr(AA_R|H = h_1, H_R = h_2, H_S = h_s) = h_1 h_2 \mu^2 + h_S \sigma^2 + (h_1 + h_2)\mu K_G + K_G K_{GR}.$$

From this, $\Pr(AA_R)$ can then be calculated by integrating over H_R.

$Pr(AA_R|H = 0, S = 0) = (2p\mu)K_G + K_G K_{GR}$

$Pr(AA_R|H = 1, S = 0) = 2p\mu^2 + (\mu + 2p\mu)K_G + K_G K_{GR}$

$Pr(AA_R|H = 2, S = 0) = 4p\mu^2 + (2\mu + 2p\mu)K_G + K_G K_{GR}$

$Pr(AA_R|H = 0, S = 1) = (p\mu)K_G + K_G K_{GR}$

$Pr(AA_R|H = 1, S = 1) = \frac{1}{2}(p\mu^2 + (\mu + p\mu)K_G) + \frac{1}{2}(p\mu^2 + \mu^2 + \sigma^2 + (2\mu + p\mu)K_G) + K_G K_{GR} =$

$p\mu^2 + \frac{1}{2}(\mu^2 + \sigma^2) + \left(\frac{3}{2}\mu + p\mu\right)K_G + K_G K_{GR}$

$Pr(AA_R|H = 2, S = 1) = 2\mu^2 + 2p\mu^2 + \sigma^2 + (3 + p)\mu K_G + K_G K_{GR}$

$Pr(AA_R|H = 0, S = 2) = K_G K_{GR}$

$Pr(AA_R|H = 1, S = 2) = (\mu^2 + \sigma^2) + 2\mu K_G + K_G K_{GR}$

$Pr(AA_R|H = 2, S = 2) = 2(\mu^2 + \sigma^2) + 2\mu^2 + 4\mu K_G + K_G K_{GR}$