This note explains the calculation of the probability information inside the original TADA method for the alternative model (Model 1 or M_1).

Let X, μ and γ be the gene-level count, the mutation rate and the relative risk of one variant category at the tested gene, and let N be the number of trios.

- Gene-level de novo count (X) for model 1 (a risk gene)

  $X \sim Poisson(2N\mu\gamma)$

  $P(X|\gamma) = \frac{e^{-2N\mu\gamma}(2N\mu\gamma)^x}{x!}$ **(1)**

- Prior information for γ:

  $\gamma \sim Gamma(\bar{\gamma}\beta, \beta)$

  Let $\alpha = \bar{\gamma}\beta$, then $P(\gamma) = \frac{\beta^\alpha}{\Gamma(\alpha)}\gamma^{\alpha-1}e^{-\beta\gamma}$ **(2)**

- We have $P(X|M_1) = \int P(X,\gamma)d\gamma = \int P(X|\gamma)P(\gamma)d\gamma$

  Use **(1)** and **(2)**

  $P(X|M_1)$ = $\int \frac{e^{-2N\mu\gamma}(2N\mu\gamma)^x}{x!} \frac{\beta^\alpha}{\Gamma(\alpha)} \gamma^{\alpha-1}e^{-\beta\gamma}d\gamma$

  $P(X|M_1) = \frac{\beta^\alpha(2N\mu)^x}{\Gamma(\alpha)x!} \int \gamma^{x+\alpha-1}e^{-\gamma(2N\mu+\beta)}d\gamma$

  We add some parts to create a density function for a Gamma distribution inside the integral.

  $P(X|M_1) = \frac{\beta^\alpha(2N\mu)^x}{\Gamma(\alpha)x!} \frac{\Gamma(x+\alpha)}{(\beta+2N\mu)^{x+\alpha}} \left(\int \frac{(\beta+2N\mu)^{x+\alpha}}{\Gamma(x+\alpha)}\gamma^{x+\alpha-1}e^{-\gamma(\beta+2N\mu)}d\gamma\right)$

  The expression in side the bracket is equal to 1 (the integral of a probability density function); therefore, we have:

  $P(X|M_1) = \frac{\beta^\alpha(2N\mu)^x}{\Gamma(\alpha)x!} \frac{\Gamma(x+\alpha)}{(\beta+2N\mu)^{x+\alpha}}$ = $\left(\frac{\beta}{\beta+2N\mu}\right)^\alpha \left(\frac{2N\mu}{\beta+2N\mu}\right)^x \frac{\Gamma(x+\alpha)}{\Gamma(\alpha)x!}$

- In the R language (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/NegBinomial.html), the negative binomial distribution with size = n and prob = p has density $p^n(1-p)^x \frac{\Gamma(x+n)}{\Gamma(n)x!}$

and **the R function** is $dnbinom(x, size, prob, mu, log = FALSE)$

We can use the $dnbinom$ function for X in which $\frac{\beta}{\beta+2N\mu}$ is a main parameter:
$dnbinom(x, size = \alpha, prob = \frac{\beta}{\beta+2N\mu}$) OR $dnbinom(x, size = \bar{\gamma}\beta, prob = \frac{\beta}{\beta+2N\mu})$.