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Statistical analysis of low dose-rate mouse experiments with WGS technology and quantitative reproduction of mutation frequency using Whack-a-Mole model

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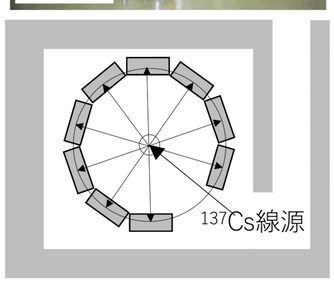
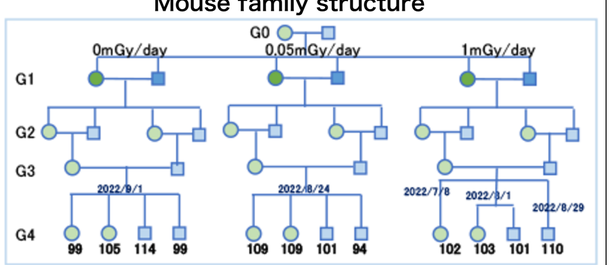


Institute for Environmental Sciences

Y. Gondo: Oral presentation in this conference
Whole Genome Sequencing (WGS)

Mouse family structure



de novo mutations

Ultra law dose rate for four generations
in about 400 days

Experiments were performed at low dose rates.
Four generations for 400day duration.

WGS technology (A. Uchimura: Oral presentation in this conference)

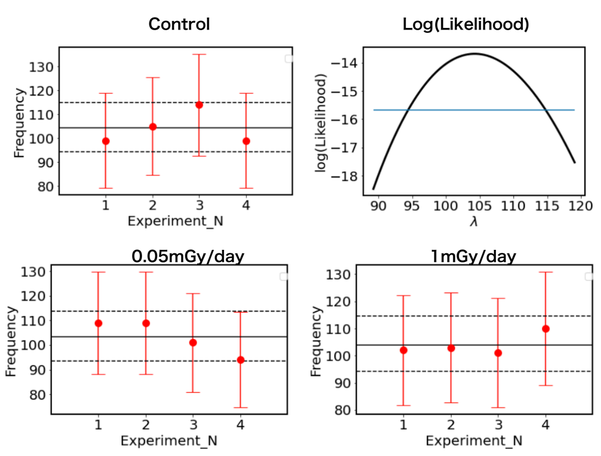
Single Nucleotide Variation (SNV)	
Control	99 105 114 99
0.05mGy/day	109 109 101 94
1mGy/day	102 103 101 110

Statistical Analysis
(Our contribution)

Most Likelihood method

$$L(\lambda) = \Pi_k \frac{\lambda^k}{k!} e^{-\lambda}$$

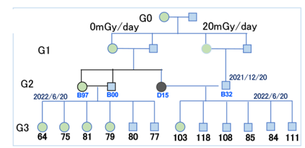
	λ 95%CL
Control	104.3 [94.5, 114.9]
0.05mGy/day	103.3 [93.5, 113.9]
1mGy/day	104.0 [94.2, 114.6]



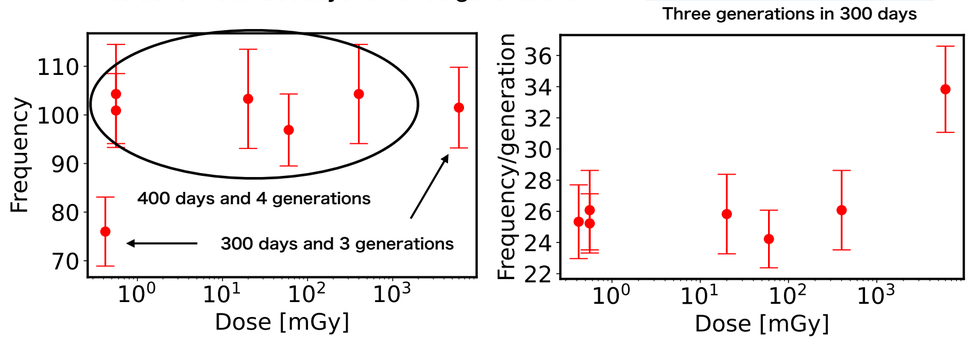
Statistical analysis was made.
Average with 95% confidence level.

Further experiments at 0.15mGy/day and 20mGy/day
by Gondo et al (This conference)

The experiment with 20mGy/day radiation
was done within 300days for three generations.



Three generations in 300 days



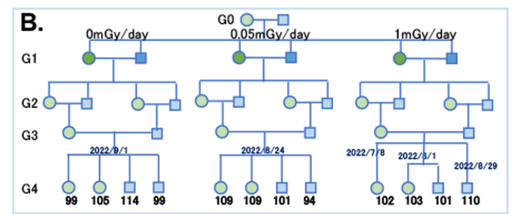
We better plot the numbers of SNVs per generation instead of total numbers.

SNVs per generation have better behavior.

We have to extract the number of mutations for each generation.
We calculate mutations in the fertilized eggs in each generation.
We then sum up the mutations using the sum rule of the Poisson distribution.

Number of mutations x — Mendel's law — Number of mutations in exposure y

$x/8 + 6x/8 = 7x/8$ — $x/8 + 6x//8 = 7x/8$
$x/2 + x/2$ — $y/2 + y/2$
$x/2 + x/2$ — $y/2 + y/2$
x — y
$(3 + 7/8)x = 3.875x$ — $3y + 0.875x$
$3.875x = \lambda$ — $3y + 0.875x = \lambda$



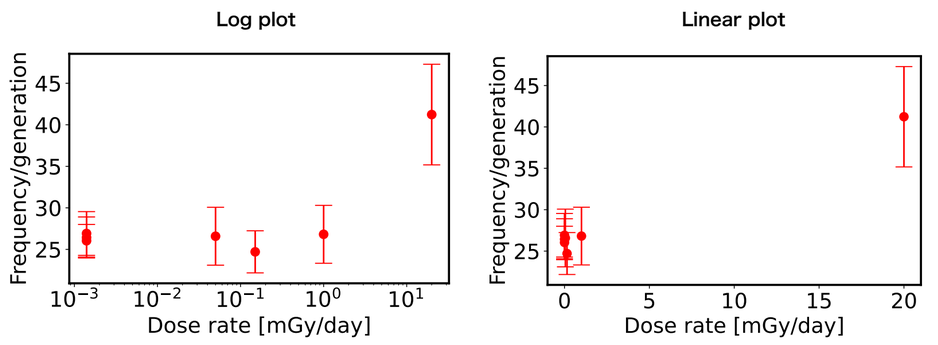
Sum rule of Poisson distribution

$$P(i,a) = \frac{a^i}{i!} e^{-a}$$

$$\sum_i P(i,a)P(k-i,b) = P(k,a+b)$$

The statistical analysis of the SNVs in this work.

Number of SNVs per generation as a function of dose rate



The numbers of SNVs per generation are unchanged
until d=1mGy/day within the 95% confidence level.

The sum rule of poisson distribution exists.
Sum of average values provide the net distribution.

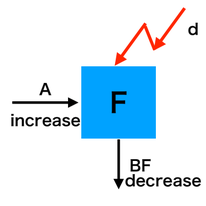
SNVs per generation vs. dose rate.
Mutation frequencies are unchanged until 1mGy/day within 95% confidence level.

Wack-a-Mole Model (Presented by M. Bando in poster session)
WAM can handle dynamical steady state

$$\frac{dF}{dt} = A - BF \qquad F : \text{mutation frequency}$$

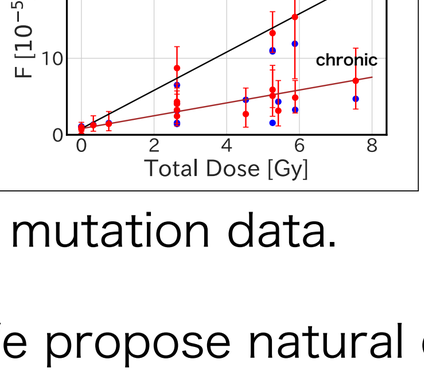
$$A = a_0 + a_1 d \qquad B = b_0 + b_1 d$$

$$\frac{dF}{dt} = 0 \quad \text{Steady state} \quad \rightarrow \quad F = \frac{A}{B} = \frac{a_0 + a_1 d}{b_0 + b_1 d}$$



$a_0 = 3.24 \times 10^{-8}$
$a_1 = 2.94 \times 10^{-5}$
$b_0 = 3.00 \times 10^{-3}$
$b_1 = 1.36 \times 10^{-1}$

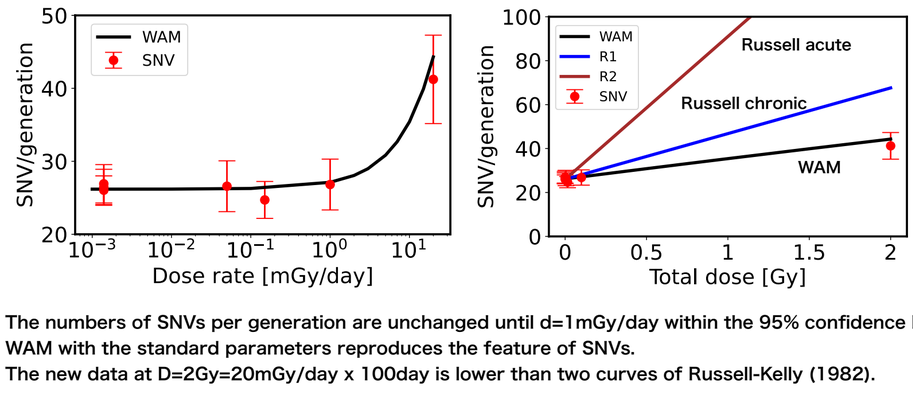
Russell-Kelly (1982) vs WAM



1. WAM can provide the mutation frequency of endogenous mutations (d=0 case).
2. WAM can provide good account of mutation rates of mega mouse experiments [Russell-Kelly (1982)].
3. WAM can provide dose-rate dependence.

$N = 1.08 \times 10^{-5}/1650 \times 2 \times 2 \times 10^9 = 26$
1 locus=1650 bp WGS

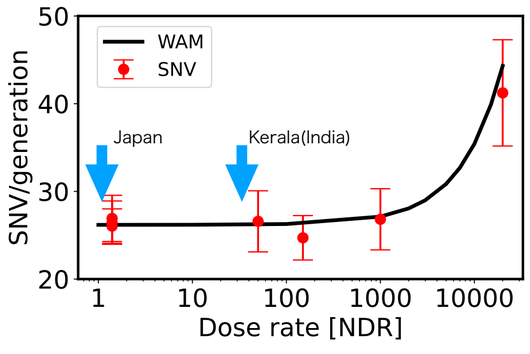
$D = d \times 100$
1 generation=100days



The numbers of SNVs per generation are unchanged until d=1mGy/day within the 95% confidence level.
WAM with the standard parameters reproduces the feature of SNVs.
The new data at D=2Gy=20mGy/day x 100day is lower than two curves of Russell-Kelly (1982).

WAM provides Russell mutation data.

WAM reproduces the SNV data



We propose natural dose rate unit (NDR).
1NDR=0.001mGy/day=1μGy/day