

Transgenerational Effects in Mice Exposed to Continuous Low-Dose-Rate Gamma-Rays
– Analysis of Germ Cell Mutation –

Keiji OGURA, Katuyoshi FUJIKAWA, Satoshi TANAKA, Ignacia TANAKA,
Kazuaki ICHINOHE, Yoichi OGISO, Kimio TANAKA
Department of Radiobiology

Abstract

Transgenerational effects of continuous low-dose-rate (LDR) gamma-ray irradiation of male mice have not been well studied. To clarify incidence of copy number aberrations (CNAs) on the progeny of mice exposed to radiation, progeny of male C57BL/6J mice continuously exposed to LDR (20 mGy/22 h/day) gamma-rays for 400 days (total dose: 8000 mGy) was analyzed. Using oligo-microarray CGH (Agilent Technologies), we have, so far, analyzed a total of 229 genomes (66 progenies from 12 pairs of parents in LDR-irradiated group and 103 progenies from 18 pairs of parents in non-irradiated group). The results indicate that progeny from LDR-irradiated mice had significantly higher frequencies of genomic aberrations than progeny from non-irradiated mice (1.06 loci/genome vs. 0.19 loci/genome). The nucleotide sequences were determined at three loci (1.4 kb, 1.5 kb and 135kb deletion) from the LDR-irradiated mice group. The nucleotide sequences suggest that the 1.4 kb and 1.5 kb deletions were formed by single strand annealing (SSA) repair, and the 135 kb deletion was formed by non-homologous end-joining (NHEJ) repair.

Table 1 Results of the genomic aberrations analysis using the oligo-microarray CGH

| | No. of analyzed F1 mice | No. of mice with aberrations | No. of loci aberrating | No. of mice with multiple aberrations |
|---------------------------------|-------------------------|------------------------------|--------------------------------|---------------------------------------|
| 20 mGy/22h/day irradiated group | 66 | 21 (32%) | 85 (Ave. 1.29 loci/generation) | 4 (6%) |
| Non irradiated group | 103 | 15 (15%) | 19 (Ave. 0.18 loci/generation) | 0 (0%) |
| | | P =0.03 | P <0.001 | |



1. Mutation frequency in the 20 mGy/22h/day irradiated group is significantly higher than the non-irradiated group.
2. Multiple aberrations were found only in the 20 mGy/22h/day irradiated group.
3. Increase in copy number aberrations (CNAs) were less frequent than decreases.

Table 2 *De novo* genomic aberrations found in F1 mice

| 20 mGy/22h/day irradiated group | | | | | | | Non-irradiated group | | | | | | |
|---------------------------------|----|------|----------------|-----|-----------|---------|--------------------------|----|------|----------------|-----|-----------|--------|
| P | F1 | Copy | Probe ID | Chr | Start | size | P | F1 | Copy | Probe ID | Chr | Start | size |
| Large aberrations | | | | | | | Large aberrations | | | | | | |
| A | 1 | d | A_67_P06933980 | 9 | 113994878 | 133572 | G | 2 | d | A_67_P04226288 | 1 | 114741818 | 72062 |
| E | 1 | d | A_67_P01942010 | 9 | 57473630 | 234921 | H | 5 | d | A_67_P00568664 | 2 | 177113983 | 688713 |
| E | 5 | i | A_67_P05889421 | 6 | 48005970 | 305969 | H | 5 | d | A_67_P07597258 | 12 | 41196414 | 146136 |
| G | 2 | d | A_67_P08093213 | 14 | 41807207 | 3286 | K | 4 | d | A_67_P04816742 | 3 | 5533449 | 34160 |
| I | 5 | d | A_67_P02200316 | 10 | 98677432 | 744874 | K | 5 | d | A_67_P07881467 | 13 | 55020816 | 25412 |
| L | 2 | d | A_67_P08087383 | 14 | 38727785 | 23540 | Small aberrations | | | | | | |
| L | 4 | d | A_67_P01456795 | 6 | 138658494 | 32881 | E | 4 | i | A_53_P142487 | 8 | 125951601 | 1535 |
| L | 5 | d | A_67_P07898663 | 13 | 63501120 | 1908639 | F | 5 | i | A_67_P06477612 | 8 | 37019826 | 68 |
| L | 8 | d | A_67_P05018303 | 3 | 105191509 | 132898 | G | 2 | d | A_67_P04434755 | 2 | 13957250 | 346 |
| Small aberrations | | | | | | | G | 5 | i | A_67_P06783170 | 9 | 49529393 | 412 |
| B | 3 | d | A_67_P05197589 | 4 | 33730804 | 94 | H | 1 | d | A_67_P06382618 | 7 | 142916412 | 98 |
| B | 5 | d | A_67_P02151317 | 10 | 68882829 | 1040 | H | 1 | d | A_67_P06671121 | 8 | 125525315 | 594 |
| B | 5 | d | A_67_P07398579 | 11 | 74609783 | 175 | I | 3 | d | A_67_P02693109 | 13 | 53303865 | 89 |
| E | 3 | d | A_67_P00341736 | 2 | 34273487 | 100 | L | 6 | d | A_67_P07000727 | 10 | 22555501 | 86 |
| G | 5 | d | A_67_P04083311 | 1 | 44861301 | 948 | N | 5 | i | A_67_P04221500 | 1 | 111527682 | 66 |
| G | 7 | d | A_67_P05313129 | 4 | 89899132 | 1878 | O | 7 | i | A_67_P04007022 | 1 | 7313469 | 153 |
| G | 7 | d | A_67_P04259545 | 1 | 131185842 | 617 | P | 3 | d | A_67_P00830676 | 4 | 22048320 | 230 |
| I | 4 | d | A_67_P02060678 | 10 | 8393959 | 460 | P | 3 | d | A_67_P06620732 | 8 | 105555233 | 93 |
| J | 4 | d | A_67_P06860168 | 9 | 81442835 | 327 | P | 7 | i | A_67_P03082883 | 15 | 81575653 | 71 |
| J | 4 | d | A_67_P00912069 | 4 | 81088876 | 122 | Q | 2 | d | A_67_P08008520 | 13 | 117033940 | 66 |
| L | 4 | d | A_67_P05080618 | 3 | 133586473 | 428 | | | | | | | |
| Multiple aberrations | | | | | | | | | | | | | |
| A | 2 | d | 35 loci | | <1.5 kb | | | | | | | | |
| F | 5 | d | 15 loci | | <1.6 kb | | | | | | | | |
| H | 6 | d | 10 loci | | <0.6 kb | | | | | | | | |
| L | 1 | d | 5 loci | | <0.5 kb | | | | | | | | |

Mice with two *de novo* genomic aberrations are marked in red. Type of aberrations is indicated as d (deletion) or i (increase). Multiple aberrations (more than five aberrations in one mouse) are shown in the lower left side.