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Estimation of transgenerational effects of radiation in male germ cells of mice using high-density microarray CGH platform

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We used two methods to estimate genetic effects of radiation. The first method was the comparative genomic hybridization (CGH) with high-density microarray containing 2.1 million probes (HD-2 microarray), which permits high-resolution examination of copy number changes (CNV: deletions and amplifications) throughout the whole genomes between two DNA samples. Refinement of the experimental and analytical protocols allowed accurate detection of small (2-3 kb, harboring only two adjacent probes) to large deletions which were previously characterized. The HD-2 microarray CGH approach was used for detection of deletion/amplification mutations among the genomes of 80 F1 mice derived from 4-Gy gamma irradiated spermatogonia and 80 control mice. A total of 22 mutations, 10 in the exposed group (6 deletions in 6 mice, 4 amplifications in 4 mice) and 12 mutations in the control (7 deletions in 7 mice, 5 amplifications in 3 mice, i.e., 1 mouse had 3 amplifications) were detected. The second was Restriction Landmark Genome Scanning (RLGS), a method which visualizes several thousand DNA fragments as spots and permits the detection of an autosomal deletion as a half-normal intensity spot. We applied the RLGS method for a genome-wide assessment of the induction rate of deletion mutations. Examinations were made on 1,007 progeny (502 control and 505 derived from spermatogonia exposed to 4 Gy of X rays). The results showed 1 deletion mutation in the un-irradiated paternal genomes of 502 offspring (0.2%) and 5 deletions in the irradiated paternal genomes of 505 offspring (1%). The deletion sizes ranged from 2 to 13 Mb. If the frequencies are taken at face values, the net increase was 4 deletions after an exposure of 4 Gy, or 1 deletion per Gy per individual if a linear dose response is assumed. Since the present RLGS screened about 0.2% of the total genome, the probability of any deletion mutation induced in the whole genome is estimated as 500 times (i.e. 1/0.002) of 0.2%, or about 1 per Gy. On the other hand, the CGH method using HD-2 microarray, containing 2.1 million probes distributed at approximately 1-kb intervals, searched deletion mutations at about 70% of the whole genome. The number of deletion mutation in the 80 exposed offspring is much smaller than that expected from the RLGS results (about 220; 80 × 1 deletion/Gy × 4 Gy × 70%). The results imply that the number of large deletions induced by radiation exposure maybe considerably smaller than currently estimated.

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