FREQUENCY OF INVERSIONS IN THE T-LYMPHOCYTE CHROMOSOMES OF EXPOSED RESIDENTS OF THE SOUTHERN URALS

Krivoshchapova YaV ✉, Vozilova AV

Urals Research Center for Radiation Medicine of the Federal Medical Biological Agency, Chelyabinsk, Russia

It is well-known that ionizing radiation is among factors increasing the rate of chromosomal rearrangements. The inversion rate was poorly understood due to difficulty of inversion identification by the conventional differential staining method. A comprehensive study of chromatin and its complex rearrangements has become possible with the use of the high-tech molecular genetic method, fluorescence *in situ* hybridization (FISH). The study was aimed to assess frequency of inversions involving the chromosome telomeric regions in 36 residents of the South Urals, almost all of them were affected by combined chronic exposure. The calculated individualized cumulative external and internal doses were 0.0001–4.7 Gy. Inversions were identified by fluorescence staining of the chromosome telomeric region. It was found that chromatid inversions were more abundant than chromosomal variants (9 : 0.3 per 100 cells ($p < 0.001$). No relationship between the studied parameters and the absorbed dose, sex and age at the time of the examination was revealed.

Keywords: chromosomal aberrations, inversions, telomeric regions of chromosomes, ionizing radiation, FISH, Techa River

Funding: the study was supported in part by the Russian Foundation for Basic Research (RFBR) grant together with the Government of the Chelyabinsk Region (Contract № 20-44-740007\20 of 28.01.2021), as well as by the Federal Target Program of FMBA of Russia "Modernization of Hightech Methods Aimed at Identifying Medical Consequences of Radiation Exposure in Personnel of the Mayak PA and the Population of the Ural Region" (code "Medical Consequences-21").

Acknowledgments: the authors would like to express their gratitude to Savkova N.F., senior laboratory assistant, for technical and laboratory support.

Author contribution: Vozilova AV — study concept, research priority setting, literature review, manuscript writing; Krivoshchapova YaV — developing criteria for analysis, staining and slide assessment, statistics, manuscript writing.

Compliance with the ethical standards: the study was approved by the Ethics Committee of the Urals Research Center for Radiation Medicine (protocol № 7 dated 20 October 2023); individuals, who were through cytogenetic testing, submitted the informed consent to blood sampling and further assessment.

✉ **Correspondence should be addressed:** Yana V. Krivoshchapova
Vorovsky, 68A, Chelyabinsk, 454141, Russia; yana_ho@mail.ru

Received: 08.08.2023 **Accepted:** 15.10.2023 **Published online:** 21.11.2023

DOI: 10.47183/mes.2023.047

ЧАСТОТА ИНВЕРСИЙ В ХРОМОСОМАХ Т-ЛИМФОЦИТОВ У ОБЛУЧЕННЫХ ЖИТЕЛЕЙ ЮЖНОГО УРАЛА

Я. В. Кривощапова ✉, А. В. Возилова

Уральский научно-практический центр радиационной медицины Федерального медико-биологического агентства, Челябинск, Россия

Известно, что ионизирующее излучение — это один из факторов, повышающих частоту хромосомных перестроек. Распространенность инверсий была мало изучена из-за сложности их выявления общепринятым методом дифференциальной окраски. Комплексное изучение хроматина, его сложных перестроек стало возможно с применением высокотехнологичного молекулярно-генетического метода — флуоресцентной *in situ* гибридизации (FISH). Целью исследования было изучить частоту инверсий с вовлечением теломерных участков хромосом у 36 жителей Южного Урала, почти все из которых подверглись сочетанному хроническому облучению. Рассчитанные индивидуализированные суммарные дозы от внешнего и внутреннего облучения — от 0,0001 до 4,7 Гр. Инверсии выявляли методом флуоресцентной окраски теломерного участка хромосом. В результате обнаружили, что распространены преимущественно хроматидные инверсии по сравнению с хромосомными вариантами (9 : 0,3 на 100 клеток ($p < 0,001$). Не выявлено зависимости исследованных показателей от дозы облучения, пола и возраста на момент обследования.

Ключевые слова: хромосомные аберрации, инверсии, теломерные районы хромосом, ионизирующее излучение, FISH, река Теча

Финансирование: работа была частично поддержана грантом Российского Фонда Фундаментальных исследований (РФФИ) совместно с Правительством Челябинской области, договор № 20-44-740007\20 от 28.01.2021, а также ФМБА РФ ФЦП «Модернизация высокотехнологичных методов, направленных на выявление медицинских последствий радиационных воздействий на персонал ПО "Маяк" и население Уральского региона» (шифр «Медицинские последствия-21»).

Благодарности: авторы выражают благодарность старшему лаборанту Н. Ф. Савковой за техническую и лабораторную поддержку.

Вклад авторов: А. В. Возилова — идея исследования, постановка научных задач, анализ литературы, написание статьи; Я. В. Кривощапова — разработка критериев анализа, покраска и анализ стекол, статистика, анализ литературы, написание статьи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом УНПЦ РМ (протокол № 7 от 20 октября 2023 г.), у лиц, участвующих в цитогенетических исследованиях, было получено информированное согласие на забор образцов крови и дальнейшие исследования.

✉ **Для корреспонденции:** Яна Владимировна Кривощапова
ул. Воровского, д. 68А, г. Челябинск, 454141, Россия; yana_ho@mail.ru

Статья получена: 08.08.2023 **Статья принята к печати:** 15.10.2023 **Опубликована онлайн:** 21.11.2023

DOI: 10.47183/mes.2023.047

For more than 60 years individuals, chronically exposed due to the Mayak PA liquid radioactive waste releases into the Techa River (Southern Urals), have been undergoing medical examinations in the Urals Research Center for Radiation Medicine of the Federal Medical Biological Agency of Russia (URCRM). The long-term follow-up of the cohorts of exposed people leads the researchers to the understanding of the complex interaction of radiation and non-radiation factors and its further effects on human health. Studying the chronic exposure effects on the body remains an essential task for researchers and medical professionals, since it helps to reveal the mechanisms underlying the

effects of radiation and prevent adverse impact of radiation exposure [1].

Great amount of research is focused on exploring the mechanisms underlying the emergence of chromosomal mutations and identifying their role in evolution of species, implementation of the ontogenesis, effects on the organs and tissues of a human body [2, 3]. The exposure to ionizing radiation can trigger development of various biological effects, also including chromosomal aberrations [4, 5], translocations (stable aberrations), as well as ring and dicentric chromosomes (unstable aberrations) being the most thoroughly studied ones. Follow-up of the cohort of individuals affected by combined chronic exposure (hereinafter referred to as exposure) in the Southern Urals demonstrates high frequency of translocations and unstable chromosomal aberrations relative to background indicators even 70 years after the beginning of exposure [6]. Today, there are sporadic reports showing the direct correlation between the increased frequency of chromosomal rearrangements and diseases in humans. Some investigations consider cancer as an effect. The studies have shown that up to 70% tumor cells contain chromosomal rearrangements of various types [7].

In recent years, the researchers' attention was focused on exploring the chromatin packaging and behavior in the nucleus, since the range of methods suitable for such studies expanded. The scientists construct models and predict the effects of various factors and genetic mutations on the chromatin architecture based on the data on the frequencies of various types of chromosomal rearrangements and differentiated chromatin arrangement in the cell nucleus in the 3D format [8].

Chromatin, consisting of heterochromatin and euchromatin regions, has a complex structure and compaction. It is well-known that chromosomal rearrangements result in redistribution of these structures across the chromosome arms or different chromosomes in the nucleus or in elimination of certain regions, which inevitably affects expression of oncogenes, suppressor genes, etc., as well as cell functioning.

Among stable chromosomal aberrations, inversions are the most poorly understood, because these are difficult to identify. Inversions are chromosomal rearrangements in which the chromosome structure alteration is caused by the 180-degree turn of one of its regions. Inversions are divided into two classes: pericentric and paracentric. Pericentric inversion includes the centromere and changes the chromosome structure, which makes it easy to verify during karyotyping. Paracentric inversion is less easy to detect, since it does not change the ratio of the chromosome arms. The DNA breakage/fusion mechanism underlies the emergence of inversion [9].

Inversion plays an important biological role. According to the published data, inversions in chromosomes are most often found in the cells that are undergoing malignant transformation, in individuals with congenital syndromes associated with developmental delay, autism and epilepsy [10, 11]. It is well-known that inversion affects the occurrence of crossing over between sister chromatids and segregation of chromosomes into daughter cells, which can result in aneuploidy or cell death [12].

There are various methods to detect chromosomal inversion. Among cytogenetic approaches, G-banding (GTG-banding) is the most widely used and affordable one. However, the complex and time-consuming nature of the analysis made it impossible to widely use the approach to assess the abundance of various types of inversions in human cells. Fluorescence in situ hybridization, to be more specific high-resolution multicolour banding FISH (mBAND), is a modern high-tech method to determine chromosomal inversion [13–15]. This method is reliable, but rather expensive to study the population frequencies of inversions in human cells. We have tried to use FISH with locus-specific telomeric probes for this purpose [16]. When assessing the length of the metaphase chromosome telomeric regions, we sometimes detected fluorescence signals of telomeres within chromosome arms, which was indicative of the chromatin inversion involving the chromosome terminal regions. The pilot-stage findings of the study of the frequency of inversions involving telomeric regions were presented in our previous paper [16], however, to be confident in the obtained results it was necessary to expand the sample and then assess the relationship between the indicators and the radiation and non-radiation factors.

The objective of the study was to assess the frequency of inversions involving the metaphase chromosome telomeric regions in T-lymphocytes of individuals affected by combined chronic exposure on the Techa River. To accomplish this objective a task was set to assess the relationship between the frequency of inversions and the cumulative external and internal dose, as well as the age at the time of examination and sex.

METHODS

Characteristics of examined individuals

The study involved residents of the Southern Urals born before 1960, the majority of them had cumulative absorbed doses to RBM (red bone marrow) of 0.0001–4.7 Gy (calculated according to the TRDS-2016). These individuals were either members of the Techa River Cohort (TRC) or Techa River In Utero Exposed Cohort (TRCIU). Information about the studied sample and health status of exposed individuals was provided by the "Database "Man" Department. Individualized cumulative external and internal doses (hereinafter referred to as doses) to RBM were calculated using the TRDS-2016 in the Biophysics laboratory, the data on the history of cancer in the examined individuals were provided by the Epidemiology Laboratory of the Urals Research Center for Radiation Medicine (URCRM) [1].

The fact of combined exposure (internal β- and external γ-exposure in a wide dose range) was the specific feature of chronic exposure of the residents of the Techa Riverside villages. A total of 29 females and 7 males were examined during the study. Inclusion criteria: age 61–81 years. Ten donors had high absorbed doses to RBM (1–4.7 Gy), 12 individuals had the absorbed doses to RBM within the range of 0.3–0.9 Gy. The comparison group included two non-exposed individuals and 12 exposed individuals with the absorbed doses to RBM of 0.0001–0.01 Gy.

Exclusion criteria: individuals born in 1961 and later; history of autoimmune diseases, cancer, exacerbation of chronic inflammatory diseases. People taking cytostatics, antibiotics were not included. The characteristics of studied groups are provided in Table 1.

Obtaining the peripheral blood T-lymphocyte metaphase chromosome preparations

The cytogenetic study involved metaphases of the peripheral blood T-lymphocytes stimulated with phytohemagglutinin (PHA). The chromosome preparations were obtained in accordance with the protocol including four consecutive stages: cell culturing to the metaphase stage, hypotonic treatment of cells, metaphase plate fixation and making

Table 1. Characteristics of studied groups

Dose group, Gy	Number of donors (total) Age, years		Females		Males	
	Number, *n*	Age, years	Number, *n*	Age, years	Number, *n*	Age, years
0–0.01	14	62–72	10	62–72	4	62–70
0.3–0.9	12	69–81	11	69–81	1	72
1–4.7	10	70–76	8	70–76	2	71–72
Total	36	62–81	29	62–81	7	62–72

the chromosome preparations [17]. When drops of the cell suspension were pipetted onto the slides, slides were dried at 42 °C on the slide dryer, then stored in the freezer at –20 °C prior to fluorescent staining.

Telomeric region staining by fluorescence in situ hybridization (FISH) with locus-specific probes

Chromosomal inversions involving telomeric regions were assessed using the Telomere FISH Kit/Cy3 telomeric probes (Dako; Denmark). The Cy3-conjugated peptide nucleic acid used to produce the probe is synthetic DNA analog capable of binding to DNA of chromosomes in accordance with the base pairing rules. In peptide nucleic acid, the sugar-phosphate backbone is replaced with the neutral peptide-polyamide backbone, however, the distance between base pairs remains the same as in DNA. It is important to note that the probe from this set does not recognize subtelomeric chromatin sequences and therefore enables staining of the chromosome telomeric regions only [18]. Chromosomes were stained in accordance with the protocol of the probe manufacturer. The fluorescence-stained preparations were analyzed using the Axio Imager Z2 microscope (Zeiss; Germany) with the DAPI and SpO (Spectrum Orange) filter and the Isis software package. Metaphases containing 46 chromosomes without overlapping or artifacts were included in the analysis. All the chromosomes were analyzed in each cell to find inversions. A total of 100 cells per donor were counted, a total of 3,600 cells were analyzed during the study. We estimated total number of inversions by types and the sum of all inversions per 100 cells, as well as the group-average values. Since the criteria of dividing inversions into chromatid and chromosomal were discussed in detail in previous report [16], here we provide a brief reminder of the mechanisms underlying the emergence of inversions and various inversion types (Fig. 1, 2).

Statistical analysis

The results were analyzed using the STATISTICA 10 software package (StatSoft; USA). Statistical processing of the results was performed using the nonparametric Mann–Whitney U test.

RESULTS

Frequency of chromosomal inversions in the range of 0–2 was reported in 9 individuals, while chromatid inversions in the range of 3–26 were reported in all examined individuals. In non-exposed individuals (2 people), the chromatid inversion frequency was 6 and 19% and the chromosomal inversion frequency was 0 and 1%, respectively. The ratio of average frequencies of chromatid and chromosomal inversions was 9 : 0.3 per 100 cells ($p < 0.001$) (Table 2).

As it is shown in Table 2, frequency of inversions in the studied groups with increasing absorbed dose to RBM demonstrates no significant differences. Low values were observed in individuals with the highest doses of 1–4.7 Gy. Maximum values were typical of chromatid inversions (frequency was 9.2, 9.5 and 8.7, respectively). The chromosomal inversion frequency was between 0.4 in the first two dose subgroups and 0.2 in the subgroup of individuals exposed at high doses.

The dependence of the inversion frequency on the age at the time of examination is provided in Fig. 3.

Therefore, no age-dependence of the inversion frequency was found in the studied age range (60–80 years).

No dependence of the inversion frequency on the absorbed dose to RBM was revealed either.

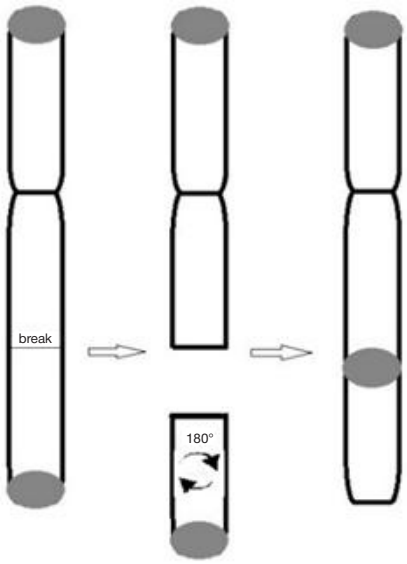

Fig. 1. Potential mechanism underlying the emergence of inversion involving the chromosome telomeric region

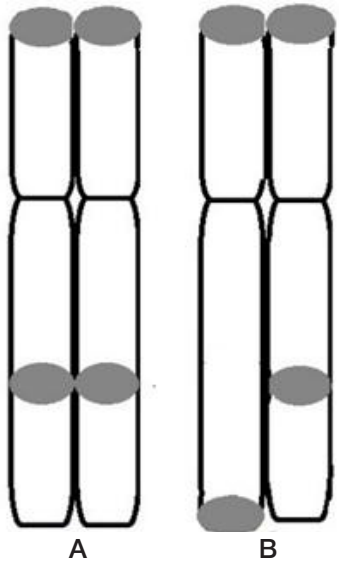

Fig. 2. Inversion types: chromosomal (**A**) and chromatid (**B**) (telomeric region is highlighted in *gray*)

Table 2. Frequency of inversions (M ± SD) (median, 25 and 75%) involving telomeric regions in T cells of exposed residents of the Southern Urals (per 100 cells)

Dose groups, Gy (*n*)	Chromatid inversions M ± SD, Median, (25–75%)	Chromosomal inversions M ± SD, Median, (25–75%)	Total inversions M ± SD, Median, (25–75%)
Comparison group (13)	9.2 ± 4.7 9 (6–11)	0.4 ± 0.7 0 (0–1)	9.6 ± 5.1 9.5 (6–12.5)
0.3–0.9 (11)	9.5 ± 6.0 8 (6.5–9)	0.4 ± 0.2 0 (0–0)	9.6 ± 6.0 8 (7.5–9)
1.00–4.7 (11)	8.7 ± 3.7 7 (6–10.5)	0.2 ± 0.4 0 (0–0)	8.3 ± 4.8 7 (6–10.5)
Entire group (36)	9.1 ± 4.8 8.5 (6–11)	0.3 ± 0.5 0 (0–0.25)	9.4 ± 5.0 8.5 (6–11)

There were few men in the studied sample. That is why, to assess the sex effect on the studied parameter a group of women was formed. Women were selected in accordance with the case-control principle for each examined man taking into account the absorbed dose to RBM and age (Table 3).

Thus, no dependence of the inversion frequency on the sex of the examined individuals was revealed.

DISCUSSION

The study reported in the paper is a continuation of a pilot project started more than two years ago in the Laboratory of Radiation Genetics, Urals Research Center for Radiation Medicine as part of the Russian Foundation for Basic Research grant. During this project we assessed the metaphase chromosome inversion frequency in the cultured peripheral blood T cells of exposed residents of the Southern Urals [16]. For this purpose a method of fluorescent staining of the chromosome telomeric regions was proposed and tested. In the given paper the size of the examined individuals sample was increased and the impact of radiation and non-radiation factors on chromosomal rearrangements (inversions involving telomeric regions of chromosomes) was analyzed. It has been found that thanks to the increase in the sample size the earlier reported frequencies of inversions have been confirmed: chromatid inversions were the most abundant and their ratio to chromosomal inversions was 9 : 0.3.

It is obvious that chromatid inversion is formed in one of the sister chromatids after the cell is through the synthesis phase of cell division, while chromosomal inversion results from the inversion emerged before the synthesis phase, which eventually causes duplication of the inverted chromatid during this phase. In this case the ends of the sister chromatid arms are left without telomeric regions, which is a marker of the cell death. This thesis is proven by lower frequencies of chromosomal inversions. If cells could survive such rearrangements, we would see high frequencies of chromosomal inversions or other chromosome rearrangements (for example, translocations or di- or multiple-centric chromosomes, ring chromosomes). However, this was not observed when assessing preparations.

The analysis of the published papers gives reasons to believe that there are some mechanisms that eliminate damaged chromosomes or cells, which makes it possible to preserve integrity of chromosomes in the cell and the genome in all cells of the body.

Our findings show that a large number of inversions contain telomeric repeats. The analysis of the published papers has allowed us to find reports noting that telomeric sequences are found in the chromosomal chromatin of many organisms, including human beings, and are referred to as interstitial telomeric sequences (ITSs) [19, 20]. Such regions are considered to result from genomic rearrangements during the course of karyotype evolution, which emphasizes the importance of studying these regions. There are assumptions explaining the mechanisms underlying the telomeric region insertion during repair. It is believed that short telomeric repeats can be inserted by the double-strand break repair systems involving telomerase [21] or result from replication induced by the double-strand

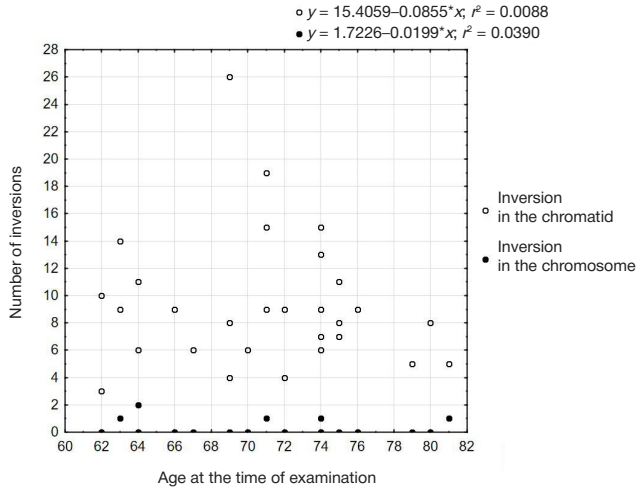

Fig. 3. Graph of inversion frequency versus age

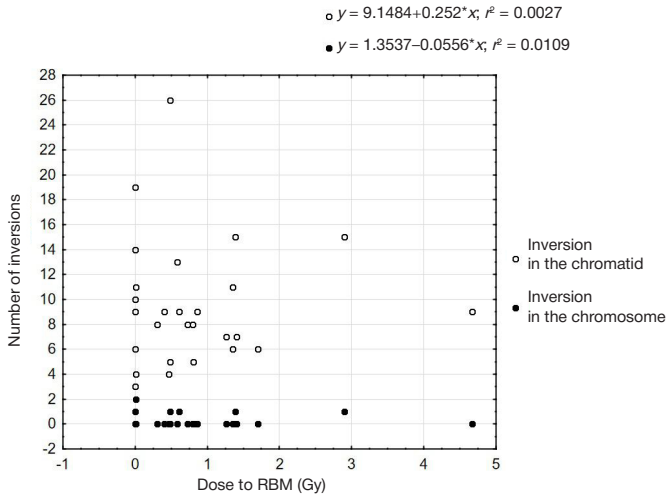

Fig. 4. Inversion frequency versus absorbed doses in the examined individuals

Table 3. Inversion frequency versus sex (M ± SD) per 100 cells

Sex (*n*)	Age, years	Dose, Gy	Chromatid inversions	Chromosomal inversions	Total inversions
M (7)	61–72	0.003–1.35	8.3 ± 4.3	0.1 ± 0.4	8.4 ± 4.6
F (7)	62–75	0.0001–1.35	7.7 ± 3.4	0.3 ± 0.5	8 ± 3.8

breaks or targeted insertion of telomeric sequences [22] based on the mechanism of alternative lenghthening of telomeres involving some homologous recombination components [23]. The loops formed by telomeric sequences are an important component of three-dimensional chromatin organization in the nucleus, which, in turn, is an important aspect of functional regulation of all processes in the genome [24]. Thus, ITSs can mediate telomeric regulation of the genome regions located far from the telomeres.

Considering the fact that the mechanism underlying inversion is the same as that underlying translocation (DNA breakage/fusion), it can be assumed that deletion of genes encoding proteins ensuring the chromosome end stabilization (such as TRF2) occurs due to the effects of regulatory mechanisms, which results in the chromosomal rearrangement. Consequently, the chromosome can either be eliminated, form a ring or "escape" via inversion. The single-stranded telomeric sequence, once inside the chromosome, is probably completed by telomerase, which is triggered by the interaction between the RNA matrix and the single-stranded primer. Telomerase adds nucleotides to the primer following the order dictated by the matrix structure [25].

Previously, we have reported the frequencies of chromosomal aberrations obtained for the group of individuals exposed to high-dose radiation in the Southern Urals [16]. Thus, during the analysis of chromosome preparations, chromatid inversions were the most abundant (9%), simple translocations accounted for 5%, complex translocations for 0.6%, and chromosomal inversions were the least abundant (0.3%). Given that each chromosome occupies a strictly defined space in the nucleus and normally does not overlap with chromatin of other chromosomes, the fact that the most frequent alterations are found within a single chromatid (chromosome) becomes quite explicable [8]. Thus, it is well-known that up to 55,000 single-stranded DNA breaks, which are mostly repaired, occur in the human cell. However, we have confirmed that when there are some chromatin loop structural disruptions, a chromatid inversion occurs during repair. It is clear that when it comes to exchange of regions between different chromosomes, simple translocations are more probable than complex rearrangements involving simultaneous breaks in different chromosomes and their close proximity to the repair systems. Our findings show that such rearrangements are 10 times less abundant than simple translocations. Rare findings of chromosomal inversions indirectly confirm our assumption that such aberrations are lethal to the cell or such chromosomes are eliminated during cell division. This thesis requires further confirmation.

Thus, we believe that further investigation of the cell nucleus chromatin structure, specifically chromosomal inversions, is important for understanding how genes interact with one another and what biological mechanisms underly such interaction at the chromosome level.

CONCLUSIONS

The frequency of inversions involving the T-lymphocyte chromosome telomeric regions in the sample of residents of the Southern Urals affected by combined chronic exposure with the absorbed doses to RBM between 0.0001 and 4.7 Gy was 1–26 per 100 cells.The ratio of chromatid inversion frequency to chromosomal inversion frequency is 9 : 0.3 per 100 cells. No relationship between the chromatid and chromosomal inversion frequency and the cumulative absorbed dose to RBM has been revealed.No relationship between the chromatid and chromosomal inversion frequency and age within the range of 60–80 years and sex has been revealed.

References

1. Akleev AV, editor. Consequences of radioactive contamination of the river Techa. Chelyabinsk: The Book, 2016; p. 400. Russian.
2. Venkatesan S, Natarajan AT, Hande MP. Chromosomal instability-mechanisms and consequences Mutat. Res Gen Toxicol Environ Mutagen. 2015; 793: 176–84.
3. Bailey SM, Bedford JS. Studies on chromosome aberration induction: What can they tell us about DNA repair? DNA repair. 2006; 5: 1171– 81.
4. Cytogenetic analysis for radiation dose assessment: a manual. International Atomic Energy Agency Technical Reports Series. 2001; 405: 30–45.
5. Vozilova AV. Assessment of the effect of chronic exposure on premature aging of human T-lymphocytes based on unstable chromosome aberrations. Extreme medicine. 2023; 2 (25): 50–5. Russian.
6. Vozilova AV, Shagina NB, Degteva MO, Akleyev AV. Chronic radioisotope effects on residents of the Techa river (Russia) region: cytogenetic analysis more than 50 years after onset of exposure Mutation Research. 2013; 756 (1–2); 115–8.
7. Bonassi S, Norppa H, Ceppi M, Strömberg U, Vermeulen R, Znaor A, et al. Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22 358 subjects in 11 countries. Carcinogenesis. 2008; 29 (6): 1178–83.
8. Eidelman YA, Salnikov IV, Slanina SV, Andreev SG. Chromosome folding promotes intrachromosomal aberrations under radiation- and nuclease-induced DNA breakage. Int J Mol Sci. 2021; 22 (22): 12186. DOI: 10.3390/ijms222212186.
9. Bunting SF, Nussenzweig A. End-joining, translocations and cancer. Nat Rev Cancer. 2013; 13 (7): 443–54.
10. Iourov IY, Vorsanova SG, et al. The Cytogenomic "Theory of Evrything" chromohelikosis may underlie chromosomal instability and mosaicism in disease and aging. Int. J. Sci. 2020; 21: 8328.
11. Puig M, Casillas S, Villatoro S, et al. Human inversions and their functional consequences. Briefings in Functional Genomics. 2015; 14 (5): 369–79.
12. Hoffmann AA, Rieseberg LH. Revisiting the impact of inversions in evolution: from population genetic markers to drivers of adaptive shifts and speciation. Annu Rev Ecol Evol Syst. 2008; 39: 21–42.
13. Ray FA, Zimmerman E, et al. Directional genomic hybridization for chromosomal inversion discovery and detection. Chromosome

Res. 2013; 21: 165–74.
14. Livingston GK, Ryan T, Smith TL, et al. Detection of simple, complex, and clonal chromosome translocations induced by internal radioiodine exposure: a cytogenetic follow-up case study after 25 years. Cytogen Genome Res. 2019; 159: 169–81.
15. Luxton J, McKenna M, Lewis A, et al. Telomere length dynamics and DNA damage responses associated with long-duration spaceflight. Cell Rep. 2020; 33 (10): 108457. DOI: 10.1016/j.celrep.2020.108457.
16. Vozilova AV, Krivoshchapova YaV. Investigation of the frequency of inversions and complex translocations in T-lymphocytes in irradiated residents of the Southern Urals. Radiation Biology. Radioecology. 2022; 62 (4): 408–15. Russian.
17. Vozilova AV, Shagina NB, Degteva MO, et al. Chronic radioisotope effects on residents of the Techa river (Russia) region: cytogenetic analysis more than 50 years after onset of exposure Mutation Research. 2013; 756 (1–2): 115–8.
18. Nielsen PE, Egholm M, Berg RH, Buchardt O. Sequence-selective recognition of DNA by strand displacement with a thymine-substituted polyamide. Sci. 1991; 254 (5037): 1497–500.
19. Ruiz-Herrera A, Nergadze SG, Santagostino M, Giulotto E. Telomeric repeats far from the ends: Mechanisms of origin and role in evolution. Cytogenetic and Genome Research. 2009; 122 (3–4): 219–28.
20. Bolzán AD. Interstitial telomeric sequences in vertebrate chromosomes: Origin, function, instability and evolution. Mutation Research. 2017; 773: 51–65.
21. Nergadze SG, Santagostino MA, Salzano A, Mondello C, Giulotto E. Contribution of telomerase RNA retrotranscription to DNA double-strand break repair during mammalian genome evolution. Genome Biology. 2007; 8 (12): R260.
22. Marzec P, Armenise C, Pérot G, Roumelioti FM, Basyuk E, Gagos S, et al. Nuclear-receptor-mediated telomere insertion leads to genome instability in ALT cancers. Cell. 2015; 160 (5): 913–27.
23. Muntoni A, Reddel RR. The first molecular details of ALT in human tumor cells. Human Molecular Genetics. 2005; 14 (2): 191–6.
24. Gonzalez-Suarez I, Gonzalo S, Crosstalk between chromatin structure, nuclear compartmentalization, and telomere biology. Cytogenetic and Genome Research. 2009; 122 (3–4): 202–10.
25. Lewin B. Genes. M.: BINOM. Laboratoriya znaniy, 2011; 896 c. Russian.

Литература

1. Аклеев А. В., редактор. Последствия радиоактивного загрязнения реки Теча. Челябинск: Книга, 2016; 400 с.
2. Venkatesan S, Natarajan AT, Hande MP. Chromosomal instability-mechanisms and consequences. Mutat Res Gen Toxicol Environ Mutagen. 2015; 793: 176–84.
3. Bailey SM, Bedford JS. Studies on chromosome aberration induction: What can they tell us about DNA repair? DNA repair. 2006; 5: 1171– 81.
4. Cytogenetic analysis for radiation dose assessment: a manual. International Atomic Energy Agency Technical Reports Series. 2001; 405: 30–45.
5. Возилова А. В. Оценка влияния хронического облучения на преждевременное старение Т-лимфоцитов человека на основе нестабильных хромосомных аберраций. Медицина экстремальных ситуаций. 2023; 2 (25): 50–5.
6. Vozilova AV, Shagina NB, Degteva MO, Akleyev AV. Chronic radioisotope effects on residents of the Techa river (Russia) region: cytogenetic analysis more than 50 years after onset of exposure Mutation Research. 2013; 756 (1–2); 115–8.
7. Bonassi S, Norppa H, Ceppi M, Strömberg U, Vermeulen R, Znaor A, et al. Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22 358 subjects in 11 countries. Carcinogenesis. 2008; 29 (6): 1178–83.
8. Eidelman YA, Salnikov IV, Slanina SV, Andreev SG. Chromosome folding promotes intrachromosomal aberrations under radiation- and nuclease-induced DNA breakage. Int J Mol Sci. 2021; 22 (22): 12186. DOI: 10.3390/ijms222212186.
9. Bunting SF, Nussenzweig A. End-joining, translocations and cancer. Nat Rev Cancer. 2013; 13 (7): 443–54.
10. Iourov IY, Vorsanova SG, et al. The Cytogenomic “Theory of Evrything” chromohelikosis may underlie chromosomal instability and mosaicism in disease and aging. Int. J. Sci. 2020; 21: 8328.
11. Puig M, Casillas S, Villatoro S, et al. Human inversions and their functional consequences. Briefings in Functional Genomics. 2015; 14 (5): 369–79.
12. Hoffmann AA, Rieseberg LH. Revisiting the impact of inversions in evolution: from population genetic markers to drivers of adaptive shifts and speciation. Annu Rev Ecol Evol Syst. 2008; 39: 21–42.
13. Ray FA, Zimmerman E, et al. Directional genomic hybridization for chromosomal inversion discovery and detection. Chromosome Res. 2013; 21: 165–74.
14. Livingston GK, Ryan T, Smith TL, et al. Detection of simple, complex, and clonal chromosome translocations induced by internal radioiodine exposure: a cytogenetic follow-up case study after 25 years. Cytogen Genome Res. 2019; 159: 169–81.
15. Luxton J, McKenna M, Lewis A, et al. Telomere length dynamics and DNA damage responses associated with long-duration spaceflight. Cell Rep. 2020; 33 (10): 108457. DOI: 10.1016/j.celrep.2020.108457.
16. Возилова А. В., Кривощапова Я. В. Исследование частоты инверсий и комплексных транслокаций в Т-лимфоцитах у облученных жителей Южного Урала. Радиационная биология. Радиоэкология. 2022; 62 (4): 408–15.
17. Vozilova AV, Shagina NB, Degteva MO, et al. Chronic radioisotope effects on residents of the Techa river (Russia) region: cytogenetic analysis more than 50 years after onset of exposure Mutation Research. 2013; 756 (1–2): 115–8.
18. Nielsen PE, Egholm M, Berg RH, Buchardt O. Sequence-selective recognition of DNA by strand displacement with a thymine-substituted polyamide. Sci. 1991; 254 (5037): 1497–500.
19. Ruiz-Herrera A, Nergadze SG, Santagostino M, Giulotto E. Telomeric repeats far from the ends: Mechanisms of origin and role in evolution. Cytogenetic and Genome Research. 2009; 122 (3–4): 219–28.
20. Bolzán AD. Interstitial telomeric sequences in vertebrate chromosomes: Origin, function, instability and evolution. Mutation Research. 2017; 773: 51–65.
21. Nergadze SG, Santagostino MA, Salzano A, Mondello C, Giulotto E. Contribution of telomerase RNA retrotranscription to DNA double-strand break repair during mammalian genome evolution. Genome Biology. 2007; 8 (12): R260.
22. Marzec P, Armenise C, Pérot G, Roumelioti FM, Basyuk E, Gagos S, et al. Nuclear-receptor-mediated telomere insertion leads to genome instability in ALT cancers. Cell. 2015; 160 (5): 913–27.
23. Muntoni A, Reddel RR. The first molecular details of ALT in human tumor cells. Human Molecular Genetics. 2005; 14 (2): 191–6.
24. Gonzalez-Suarez I, Gonzalo S, Crosstalk between chromatin structure, nuclear compartmentalization, and telomere biology. Cytogenetic and Genome Research. 2009; 122 (3–4): 202–10.
25. Льюин Б. Гены. М.: БИНОМ. Лаборатория знаний, 2011; 896 с.