Received: 07 January 2025 / Accepted: 14 April 2025 / Published online: 30 April 2025

DOI 10.34689/SH.2025.27.2.017

UDC 616.-006.782-071-053.2(574)

GENETIC SUSCEPTIBILITY TO RADIATION-RELATED DISEASES: A REVIEW OF CURRENT LITERATURE

Altay A. Dyussupov[1], Gulshara Zh. Abildinova[2], Dariya M. Shabdarbayeva[1], Meruert R. Massabayeva[1]*, Lyudmila M. Pivina[1], Andrey Yu. Orekhov[1], Alexandra V. Lipikhina, Zhanargyl K. Smailova[1], Rauana M. Kisina[1], Galiya A. Alibayeva[3], Ainash S. Orazalina[1], Ayaulym M. Yesentayeva[1], Vladlena R. Sabitova[1], Assel Zh. Baibussinova[1], Askar B. Qasymov[4], Aleksei Klivenko[4], Madina B. Abenova[1], Diana G. Ygyyeva[1], Saulesh A. Apbassova[1], Murat N. Lepesbayev, Nailya Zh. Chaizhunusova[1]

[1] NJSC "Semey Medical University", Semey, Republic of Kazakhstan;
[2] Hospital of the Medical Center of the Administrative Department of the President of the Republic of Kazakhstan, Astana, Republic of Kazakhstan;
[3] Emergency Medical Hospital of Semey, Semey, Republic of Kazakhstan;
[4] NJSC "Shakarim University of Semey", Semey, Republic of Kazakhstan;
[5] NJSC "Astana Medical University", Astana, Republic of Kazakhstan.

Abstract

This review aims to synthesize current knowledge on genetic determinants of radiosensitivity, emphasizing findings from candidate gene studies and genome-wide association studies (GWAS), and discuss their clinical implications.

Methods: We conducted a literature-based analysis of genetic polymorphisms associated with radiation-related outcomes, focusing on genes involved in DNA repair, cell cycle regulation, oxidative stress response, and tissue remodeling.

Results: Variants in genes such as *XRCC1, XRCC3, TP53, TGFβ1*, and *SOD2* have been linked to increased radiosensitivity and risk of adverse outcomes following radiation exposure. GWAS have identified novel loci (*TANC1, RAD51L1, KIF26B*) associated with normal tissue toxicity and secondary malignancies. While promising, most findings require further validation in diverse populations and clinical settings.

Conclusion: Understanding genetic susceptibility to radiation is essential for advancing personalized radiotherapy and improving public health strategies. Future research should prioritize multi-locus models, functional validation, and the ethical integration of genetic data into clinical and occupational contexts.

Keywords: *genetic susceptibility, radiosensitivity, ionizing radiation, GWAS.*

For citation:

Dyussupov A.A., Abildinova G.Zh., Shabdarbayeva D.M., Massabayeva M.R., Pivina L.M., Orekhov A.Yu., Lipikhina A.V., Smailova Zh.K., Kisina R., Alibayeva G.A., Orazalina A.S., Yesentayeva A.M., Sabitova V.R., Baibussinova A.Zh., Qasymov A.B., Klivenko A., Abenova M.B., Ygyyeva D.G, Apbasova S.A., Lepesbayev M.N., Shaizhunussova N.Zh. Genetic susceptibility to radiation-related diseases: a review of current literature // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (2), pp. 145-153. *doi 10.34689/SH.2025.27.2.017*

Аннотация

ГЕНЕТИЧЕСКАЯ ПРЕДРАСПОЛОЖЕННОСТЬ К ЗАБОЛЕВАНИЯМ, СВЯЗАННЫМ С РАДИАЦИОННЫМ ВОЗДЕЙСТВИЕМ: ОБЗОР СОВРЕМЕННОЙ ЛИТЕРАТУРЫ

Алтай А. Дюсупов[1], Гульшара Ж. Абильдинова[2], Дария М. Шабдарбаева[1], Меруерт Р. Масабаева[1]*, Людмила М. Пивина[1], Андрей Ю. Орехов[1], Александра В. Липихина, Жанаргуль К. Смаилова[1], Рауана М. Кисина[1], Галия А. Алибаева[3], Айнаш С. Оразалина[1], Аяулым М. Есентаева [1], Владлена Р. Сабитова[1], Асель Ж. Байбусинова[1], Аскар Б. Касымов[4], Алексей Кливенко[4], Мадина Б. Абенова[1], Диана Г. Ыгыева[1], Саулеш А. Апбасова[1], Мурат Н. Лепесбаев, Найля Ж. Чайжунусова[1]

[1] НАО «Медицинский университет Семей», г. Семей, Республика Казхстан;
[2] Больница Медицинского центра Управления делами Президента Республики Казахстан, г. Астана, Республика Казахстан;

[3] Больница скорой медицинской помощи города Семей, г. Семей, Республика Казхстан;
[4] НАО «Университет имени Шакарима города Семей», г. Семей, Республика Казхстан;
[5] НАО Медицинский университет «Астана», г. Астана, Республика Казахстан.

Цель данного обзора — обобщить современные данные о генетических детерминантах радиочувствительности, с акцентом на исследования генов-кандидатов и геномные ассоциативные исследования (GWAS), а также рассмотреть их клиническое значение.

Методы: Проведен анализ литературных источников, описывающих генетические полиморфизмы, ассоциированные с последствиями воздействия радиации. Основное внимание уделено генам, участвующим в репарации ДНК, регуляции клеточного цикла, ответе на окислительный стресс и ремоделировании тканей.

Результаты: Полиморфизмы в таких генах, как *XRCC1, XRCC3, TP53, TGFβ1* и *SOD2*, связаны с повышенной радиочувствительностью и риском неблагоприятных эффектов после облучения. GWAS-исследования выявили новые локусы (*TANC1, RAD51L1, KIF26B*), ассоциированные с токсичностью нормальных тканей и вторичными опухолями. Несмотря на перспективность, большинство находок требуют дальнейшей валидации в различных популяциях и клинических условиях.

Заключение: Понимание генетической предрасположенности к радиации имеет ключевое значение для развития персонализированной радиотерапии и улучшения стратегий общественного здравоохранения. Будущие исследования должны быть сосредоточены на мультигенных моделях, функциональной валидации и этичной интеграции генетических данных в клиническую и профессиональную практику.

Ключевые слова: *генетическая предрасположенность; радиочувствительность; ионизирующее излучение; геномные ассоциативные исследования (GWAS).*

Для цитирования:

Дюсупов А.А., Абильдинова Г.Ж., Шабдарбаева Д.М., Масабаева М.Р., Пивина Л.М., Орехов А.Ю., Липихина А.В., Смаилова Ж.К., Кисина Р., Алибаева Г.А., Оразалина А.С., Есентаева А.М., Сабитова В.Р., Байбусинова А.Ж., Касымов А., Кливенко А., Абенова М.Б., Ыгыева Д., Апбасова С.А., Лепесбаев М., Чайжунусова Н.Ж. Генетическая предрасположенность к заболеваниям, связанным с радиационным воздействием: обзор современной литературы // Наука и Здравоохранение. 2025. Т.27 (2), С. 145–153. doi: 10.34689/SH.2025.27.2.017

Түйіндеме

РАДИАЦИЯЛЫҚ ӘСЕРГЕ БАЙЛАНЫСТЫ АУРУЛАРҒА ГЕНЕТИКАЛЫҚ БЕЙІМДІЛІК: ҚАЗІРГІ ӘДЕБИЕТТЕРГЕ ШОЛУ

Алтай А. Дюсупов[1], Гульшара Ж. Абильдинова[2], Дария М. Шабдарбаева[1], Меруерт Р. Масабаева[1*], Людмила М. Пивина[1], Андрей Ю. Орехов[1], Александра В. Липихина, Жанаргуль К. Смаилова[1], Рауана М. Кисина[1], Галия А. Алибаева[3], Айнаш С. Оразалина[1], Аяулым М. Есентаева[1], Владлена Р. Сабитова[1], Асель Ж. Байбусинова[1], Аскар Б. Касымов[4], Алексей Кливенко[4], Мадина Б. Абенова[1], Диана Г. Ыгыева[1], Саулеш А. Апбасова[1], Мурат Н. Лепесбаев, Найля Ж. Чайжунусова[1]

[1] «Семей медицина университеті» КеАҚ, Семей қ., Қазақстан Республикасы;
[2] Қазақстан Республикасы Президентінің Іс Басқармасы Медициналық орталығының ауруханасы, Астана қ, Қазақстан Республикасы;
[3] «Жедел медициналық жәрдем ауруханасы» ШЖҚ КМК, Семей қ., Қазақстан Республикасы;
[4] «Семей қаласының Шәкәрім атындағы университеті» КеАҚ, Семей қ., Қазақстан Республикасы;
[5] «Астана медицина университеті» КеАҚ, Астан қ.а, Қазақстан Республикасы.

Бұл шолудың **мақсаты** — радиосезімталдықтың генетикалық детерминанттары туралы қазіргі білімді жинақтау, кандидат гендерге және геном бойынша ассоциациялық зерттеулерге (GWAS) негізделген нәтижелерге назар аудару, сондай-ақ олардың клиникалық маңызын талқылау.

Әдістер: Сәулеленудің әсерінен туындайтын салдарлармен байланысы бар генетикалық полиморфизмдерді сипаттайтын әдебиеттерге талдау жүргізілді. Негізгі назар ДНҚ қалпына келтіру, жасушалық циклді реттеу, тотығу стрессіне жауап және тіндердің қайта құрылуы процестеріне қатысатын гендерге аударылды.

Нәтижелер: *XRCC1, XRCC3, TP53, TGFβ1* және *SOD2* сияқты гендердегі полиморфизмдер сәулеге жоғары сезімталдықпен және жағымсыз әсерлердің жоғары қаупімен байланысты. GWAS зерттеулері *TANC1, RAD51L1, KIF26B* сияқты жаңа локустарды анықтады, олар қалыпты тіндердің уыттылығымен және екінші реттік қатерлі ісіктермен байланысты. Дегенмен, бұл нәтижелердің көпшілігін әртүрлі популяциялар мен клиникалық жағдайларда қосымша растау қажет.

Қорытынды: Сәулеге генетикалық бейімділікті түсіну — жекелендірілген радиотерапияны дамыту және қоғамдық денсаулықты қорғау стратегияларын жетілдіру үшін өте маңызды. Алдағы зерттеулер көпгендік модельдерге, функционалдық растауға және генетикалық ақпаратты клиникалық және кәсіптік практикаға этикалық енгізуге басымдық беруі тиіс.

Түйінді сөздер: *генетикалық бейімділік; радиосезімталдық; иондаушы сәулелену; геном бойынша ассоциациялық зерттеулер (GWAS).*

Дәйексөз үшін:

Дюсупов А.А., Абильдинова Г.Ж., Шабдарбаева Д.М., Масабаева М.Р., Пивина Л.М., Орехов А.Ю., Липихина А.В., Смаилова Ж.К., Кисина Р., Алибаева Г.А., Оразалина А.С., Есентаева А.М., Сабитова В.Р., Байбусинова А.Ж., Касымов А., Кливенко А., Абенова М.Б., Ыгыева Д., Апбасова С.А., Лепесбаев М., Чайжунусова Н.Ж. Радиациялық әсерге байланысты ауруларға генетикалық бейімділік: қазіргі әдебиеттерге шолу // Ғылым және Денсаулық. 2025. Т.27 (2), Б.145–153. doi: 10.34689/SH.2025.27.2.017

Introduction

Ionizing radiation (IR) is a well-established environmental carcinogen, with its detrimental effects on human health extensively documented through studies of atomic bomb survivors, nuclear industry workers, and patients undergoing radiotherapy. While IR remains indispensable in medical diagnostics and cancer treatment, its potential to induce secondary malignancies and other long-term complications necessitates a deeper understanding of individual susceptibility factors.

Recent advancements in genomics have shed light on the role of genetic predisposition in modulating individual responses to radiation exposure. Genome-wide association studies (GWAS) have identified specific genetic variants associated with an increased risk of radiation-induced side effects, suggesting that genetic factors contribute significantly to the variability observed in clinical and epidemiological outcomes. For instance, polymorphisms in genes involved in DNA repair, oxidative stress response, and cell cycle regulation have been linked to enhanced radiosensitivity, underscoring the pivotal role of genetic makeup in determining the radiation response.

Despite these findings, the integration of genetic susceptibility data into routine radiation risk assessment remains limited. The complexity of gene–environment interactions, population heterogeneity, and the multifactorial nature of radiation-induced diseases pose significant challenges to clinical translation. Nevertheless, understanding the genetic underpinnings of radiation response holds considerable promise for precision medicine. By identifying individuals at higher risk, it may be possible to tailor radiation therapies that minimize adverse effects while maximizing therapeutic efficacy.

This review synthesizes current evidence on genetic susceptibility to radiation-induced diseases, emphasizing key genetic determinants, biological mechanisms, clinical relevance, and implications for personalized treatment strategies.

Materials and Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A systematic literature search was performed in three electronic databases: PubMed, Scopus, and Web of Science, covering the period from January 2010 to December 2024.

Search strategy

Search terms included combinations of the following keywords: "*genetic susceptibility*", "*ionizing radiation*", "*radiosensitivity*", "*radiotherapy toxicity*", "*DNA repair genes*", "*GWAS*", "*single nucleotide polymorphisms*", "*radiogenomics*". Boolean operators (AND/OR) were applied to maximize search sensitivity.

*Inclusion criteria: p*eer-reviewed studies in English; human subjects only; original research or meta-analyses; studies assessing genetic variants (SNPs or CNVs) associated with radiation response, toxicity, or carcinogenesis; both candidate gene studies and genome-wide association studies (GWAS).

Exclusion criteria: animal or in vitro studies; case reports or narrative reviews; non-genetic studies of radiation effects; articles without extractable genetic or clinical data.

Two independent reviewers conducted title and abstract screening, followed by full-text assessment. Disagreements were resolved through discussion and consensus. Data were extracted on study design, population characteristics, radiation exposure parameters, genotyping methods, and reported associations between genetic variants and radiosensitivity or radiation-induced effects.

A schematic overview of the article selection process is presented in Figure 1.

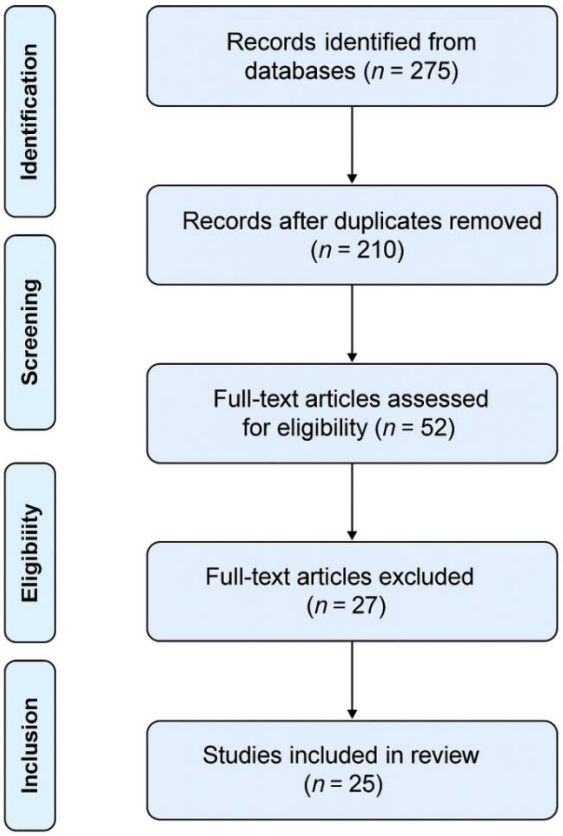

Figure 1. PRISMA Flow Diagram Showing the Selection Process for Studies Included in the Review.

Results.

1. Mechanisms of Radiation-Induced Biological Damage.

Ionizing radiation exerts its harmful effects primarily through the generation of DNA damage, either directly by ionizing atoms within the DNA molecule or indirectly through the production of reactive oxygen species (ROS) that damage cellular components. Among the various forms of DNA damage, double-strand breaks (DSBs) are particularly lethal, as their misrepair can lead to chromosomal aberrations, genomic instability, and malignant transformation.

Cells possess sophisticated DNA damage response (DDR) mechanisms to detect, signal, and repair radiation-induced damage. These include the activation of sensor proteins such as ATM (ataxia-telangiectasia mutated) and ATR (ATM and Rad3-related), which initiate signaling cascades that coordinate cell cycle checkpoints, DNA repair, apoptosis, or senescence. Key DNA repair pathways include non-homologous end joining (NHEJ) and homologous recombination (HR), both of which are critical for the repair of DSBs.

2. Genetic Determinants of Radiosensitivity

Interindividual variability in response to ionizing radiation is influenced by environmental and physiological factors and genetic differences that affect key cellular processes such as DNA repair, oxidative stress response, cell cycle control, and apoptosis. Individuals harboring certain genetic variants may exhibit increased radiosensitivity, predisposing them to greater risks of radiation-induced damage and related pathologies [13,21].

Genes involved in detecting and repairing DNA double-strand breaks (DSBs) are among the most studied in the context of radiation response. For example, mutations in ATM result in heightened radiosensitivity and predisposition to cancer, as seen in patients with ataxia-telangiectasia [1,21]. Variants in TP53 have been associated with differential radiation responses and cancer risk [1,5]. This tumor suppressor gene regulates cell cycle arrest and apoptosis in response to DNA damage. BRCA1/2 is involved in homologous recombination, mutations in these genes impair DSB repair and are linked to increased sensitivity to radiation and certain chemotherapeutics [1].

Genes regulating the cell cycle and programmed cell death also modulate radiation responses. For example, CDKN1A (p21): A downstream target of TP53, p21 mediates cell cycle arrest. Polymorphisms in this gene can alter cellular radiosensitivity [1]. BAX and BCL2 genes regulate mitochondrial-mediated apoptosis, and their expression balance influences whether a cell survives or dies following radiation exposure [6].

Ionizing radiation generates reactive oxygen species (ROS), which damage lipids, proteins, and DNA. Genes such as SOD2 (superoxide dismutase 2) encodes a mitochondrial enzyme that detoxifies superoxide radicals. Polymorphisms in SOD2 may affect the cell's capacity to mitigate radiation-induced oxidative stress. GPX1 and CAT genes encode glutathione peroxidase and catalase, respectively-key enzymes in ROS detoxification. Variants may influence long-term radiation outcomes [1].

Certain hereditary syndromes are characterized by mutations in genes involved in genome stability and confer marked radiosensitivity. These include: the ATM gene (Ataxia-telangiectasia); the NBN gene (Nijmegen breakage syndrome); and multiple FANC genes (Fanconi anemia).

These syndromes provide crucial insights into mechanisms of radiosensitivity and help identify candidate genes for further investigation in the general population [1,5].

3. Epidemiological and Clinical Evidence of Genetic Susceptibility to Radiation.

Large-scale epidemiological studies have provided compelling evidence that individual genetic variation contributes to the risk of developing radiation-related diseases. Populations with documented radiation exposure, such as atomic bomb survivors, Chernobyl cleanup workers, and patients undergoing radiotherapy, have served as critical sources of data in identifying genetic risk modifiers.

The Life Span Study of Hiroshima and Nagasaki survivors remains the cornerstone of radiation epidemiology. Long-term follow-up of this cohort has revealed significant interindividual variability in cancer incidence that cannot be explained by radiation dose alone [13]. Genetic studies nested within LSS have suggested that inherited variation in genes involved in DNA repair, inflammation, and immune regulation may influence cancer susceptibility [21].

The Chernobyl accident in 1986 exposed a large number of workers and civilians to varying levels of radiation. Studies have identified increased incidence of thyroid cancer, leukemia, and other malignancies among exposed individuals [17]. Emerging genetic analyses have implicated variants in DNA repair genes such as XRCC1, XRCC3, and APEX1 as possible modifiers of cancer risk in these populations [3,20].

In the clinical setting, patients undergoing radiotherapy often show varied tolerance to treatment. Some develop severe normal tissue toxicity or secondary malignancies despite receiving comparable doses. Polymorphisms in genes such as ATM, TP53, and TGFβ1 have been associated with radiation-induced side effects, including fibrosis, mucositis, and cardiovascular complications [1,5].

A genome-wide association study (GWAS) in breast cancer patients treated with radiotherapy identified SNPs in the region of TANC1 as predictors of pelvic radiation toxicity [9]. Similarly, GWAS efforts in prostate cancer patients have found variants associated with late-onset urinary and gastrointestinal complications [15].

Children are generally more radiosensitive than adults due to higher rates of cell division and longer post-exposure life expectancy. Studies have found that pediatric cancer survivors treated with radiation are at increased risk of second malignancies, particularly when carrying high-risk genetic variants in pathways such as NER (nucleotide excision repair) and HR [18].

4. Candidate Gene Studies and GWAS Findings

Genetic studies investigating individual radiosensitivity have traditionally followed two main approaches: candidate gene studies and genome-wide association studies (GWAS). While candidate gene studies focus on known genes with plausible biological roles, GWAS offer an unbiased method to uncover novel loci associated with radiation responses (table 1).

Table 1.

Key Genetic Variants Associated with Radiosensitivity.

Gene	SNP / Polymorphism	Reported Effect	Biological Mechanism	References
XRCC1	rs25487 (Arg399Gln)	Increased chromosomal instability, risk of fibrosis	Base excision repair dysfunction	[1.12]
XRCC3	rs861539 (Thr241Met)	Elevated DNA damage, risk of secondary tumors	Homologous recombination repair	[12]
TP53	rs1042522 (Arg72Pro)	Altered apoptotic sensitivity	Cell cycle and apoptosis regulation	[1,14]
TGFβ1	rs1800469	Increased risk of radiation-induced fibrosis	Fibroblast activation and chronic inflammation	[5,19]
SOD2	rs4880 (Val16Ala)	Reduced antioxidant defense	Elevated oxidative stress	[23]
TANC1	rs10484561	Associated with pelvic late toxicity in prostate cancer patients	Tissue remodeling and stress response	[9]
RAD51L1	GWAS-identified	Linked to secondary malignancies after breast irradiation	DNA double-strand break repair	[15]
DNAJC18	GWAS-identified	Associated with gastrointestinal toxicity	Protein folding and stress response	[15]
KIF26B	GWAS-identified	Linked to bladder damage following pelvic radiation	Cell migration and tissue regeneration	[15]

Candidate gene studies have identified numerous single nucleotide polymorphisms (SNPs) associated with radiation-induced toxicity or cancer risk. These studies often target genes involved in DNA damage repair, oxidative stress, and inflammation. XRCC1 (X-ray repair cross-complementing 1): The Arg399Gln polymorphism (rs25487) has been associated with increased chromosomal aberrations and late tissue toxicity following radiotherapy, particularly in breast and head and neck cancer patients [1,12]. XRCC3: The Thr241Met polymorphism (rs861539) has been implicated in heightened radiation-induced DNA damage and risk of secondary cancers [12]. TP53: Polymorphism Arg72Pro (rs1042522) influences apoptosis and has been linked to variable sensitivity to radiation, especially in lung and colorectal cancers [1]. TGFβ1 (transforming growth factor beta 1): The SNP rs1800469 has been correlated with increased risk of radiation-induced fibrosis and adverse late effects [5].

Despite promising findings from GWAS, several limitations persist. These include modest effect sizes of individual SNPs, population-specific associations limiting generalizability, and the 'missing heritability' problem - wherein identified loci account for only a fraction of phenotypic variance. Functional validation is hindered by the prevalence of non-coding variants, necessitating integration with transcriptomic and epigenomic data. Additionally, replication in diverse cohorts and harmonization of toxicity phenotypes remain significant challenges.

A GWAS conducted among prostate cancer patients identified SNPs near TANC1 as predictive of pelvic radiation toxicity (rs10484561), suggesting a novel role for this gene in tissue remodeling and repair [9].

In breast cancer cohorts, SNPs in loci near RAD51L1 and PRDM1 have been associated with normal tissue toxicity and second primary malignancies after radiation [15].

Recent meta-analyses incorporating thousands of patients have highlighted variants in DNAJC18, SLC14A2, and KIF26B in relation to rectal bleeding and urinary toxicity following radiotherapy [9,15].

These findings are beginning to inform polygenic risk models, which may eventually be used to personalize radiation treatment strategies.

Although GWAS have yielded promising candidates, functional validation of identified variants remains a major challenge. Many SNPs lie in non-coding regions, suggesting regulatory functions that require integration with expression data, eQTL mapping, and epigenomic profiling. Moreover, GWAS findings are often population-specific, necessitating replication in diverse cohorts to ensure generalizability.

5. Mechanistic Pathways Linking Genetic Variants and Radiation Effects

Understanding how genetic variants influence biological responses to IR is critical for identifying individuals at increased risk for adverse effects and radiation-induced diseases. The primary mechanistic pathways through which genetic factors modulate radiosensitivity include DNA damage recognition and repair, oxidative stress response, cell cycle control, inflammatory signaling, and fibrosis development.

Ionizing radiation primarily induces DNA double-strand breaks (DSBs), which are lethal if unrepaired or misrepaired. Genetic variants in key repair genes, such as ATM, BRCA1/2, XRCC1, and XRCC3, alter the efficiency and fidelity of DSB repair through non-homologous end joining (NHEJ) and homologous recombination (HR) [1,23]. For example, the XRCC1 Arg399Gln variant has been associated with impaired base excision repair capacity, leading to accumulation of DNA lesions and increased chromosomal instability [1,12].

Similarly, mutations in BRCA1/2 compromise HR-mediated repair, rendering cells vulnerable to radiation-induced apoptosis or carcinogenic transformation [1,23].

IR generates reactive oxygen species (ROS), which induce oxidative damage to DNA, proteins, and lipids. Genetic variants in antioxidant defense genes such as SOD2, GPX1, and CAT modulate cellular ability to detoxify ROS [1,14]. For instance, the SOD2 Val16Ala polymorphism (rs4880) alters mitochondrial targeting of the enzyme, influencing mitochondrial oxidative stress burden

after irradiation. Individuals carrying the Ala allele may exhibit reduced ROS clearance and increased tissue damage [14].

Variants in genes controlling cell cycle checkpoints and programmed cell death influence whether cells repair damage or undergo apoptosis. The TP53 Arg72Pro polymorphism affects apoptotic potential, while CDKN1A (p21) variants modulate radiation-induced cell cycle arrest [1,19].

Impaired regulation in these pathways can lead to genomic instability or resistance to cell death, contributing to carcinogenesis or abnormal tissue remodeling post-radiotherapy.

Radiation exposure activates pro-inflammatory and pro-fibrotic cytokine networks, which contribute to late normal tissue toxicity. Polymorphisms in TGFβ1 (e.g., rs1800469) are linked to radiation-induced fibrosis in lung, breast, and pelvic tissues [2,5].

TGFβ1 plays a central role in fibroblast activation and extracellular matrix deposition. Enhanced cytokine signaling in carriers of risk alleles may exacerbate chronic inflammation and fibrotic remodeling [2].

Recent GWAS have uncovered variants near genes with previously unrecognized roles in radiation response: TANC1 is involved in cytoskeletal remodeling and may influence tissue repair capacity [10]; DNAJC18 is implicated in protein folding and stress responses, potentially affecting radiation-induced proteotoxicity [15]; KIF26B, a kinesin family member, may regulate cell motility and survival signaling during tissue regeneration [15].

These findings highlight the complexity of radiosensitivity and the importance of integrating genomic, transcriptomic, and epigenomic data to elucidate mechanisms.

Discussion

The expanding body of evidence linking genetic variants to individual radiosensitivity has significant implications for both radiation oncology and public health. Incorporating genomic information into clinical decision-making could enhance treatment safety and efficacy, particularly through the development of personalized radiotherapy protocols and improved radiation risk assessment.

The current one-size-fits-all approach to radiotherapy does not adequately account for inter-individual differences in normal tissue response. Genetic markers such as XRCC1 rs25487 (Arg399Gln) and TGFβ1 rs1800469 may enable the stratification of patients into high- and low-risk groups for radiation-induced toxicity [2,5,12]. Such stratification could support dose modification strategies or the use of radioprotective agents for genetically susceptible individuals.

These insights have practical applications across various clinical and public health contexts. Table 2 summarizes potential scenarios in which genetic markers may improve radiation response prediction and patient management.

Table 2.

Potential Clinical Scenarios for the Use of Genetic Markers in Radiation Response.

Clinical Context	Genetic Marker(s)	Application	Potential Benefit
Radiotherapy in breast cancer	XRCC1 rs25487, TGFβ1 rs1800469	Predict late fibrosis risk	Dose adaptation, risk mitigation
Pediatric cancer survivors	BRCA1/2, NER SNPs	Assess second malignancy risk	Individualized follow-up protocols, lifestyle interventions
Occupational radiation exposure	ATM, SOD2, XRCC3	Identify radiosensitive individuals	Enhanced monitoring, job reassignment
Post-nuclear accident public health	APEX1, NBN, TP53	Risk stratification of exposed groups	Focused medical response, early diagnostics
Prostate cancer radiotherapy	TANC1, DNAJC18	Predict GI/GU toxicity	Treatment technique adjustment, e.g., IMRT guidance
Personalized risk models	Polygenic SNP panels	Integrated risk in treatment planning	Improved outcome prediction

Genome-wide association studies (GWAS) have identified novel loci such as TANC1 and KIF26B, which show promise for predicting late tissue toxicity and guiding post-treatment surveillance [9,15]. However, translating these findings into clinical practice remains challenging due to the lack of prospective validation and standardized genotyping platforms.

Genetic susceptibility information is also valuable for individuals exposed to low-dose radiation, such as nuclear workers or residents of contaminated areas. Risk-based surveillance and informed public health strategies can be developed by identifying radiosensitive genotypes [1,17].

Recent advancements in radiogenomics include the integration of polygenic risk scores (PRS) into radiotherapy planning to improve personalized care [6,8]. Simultaneously, accumulating data suggest that epigenetic modifications (e.g., DNA methylation, histone acetylation) and long noncoding RNAs may significantly influence radiation response, offering new targets for diagnostics and therapy [4,24].

Nevertheless, several limitations hinder widespread clinical application. The modest effect size of individual SNPs often precludes their use as standalone predictive tools. Additionally, population stratification, ethnic differences in allele frequencies, and unmeasured confounders (e.g., smoking, comorbidities) complicate interpretation. Heterogeneity in phenotype definitions—such as variation in toxicity scoring—further reduces reproducibility.

While many associations have been reported, replication remains inconsistent. For example, XRCC1 rs25487 has shown variable predictive performance across cohorts, likely due to differences in protocols, genotyping platforms, and endpoint definitions.

Moreover, many non-coding GWAS hits, including SNPs near TANC1 and KIF26B, lack functional validation, leaving mechanistic roles uncertain. Addressing these knowledge gaps will require CRISPR-based functional genomics and systems biology approaches.

Ethical considerations are also critical. The implementation of genetic screening for radiosensitivity raises concerns about data privacy, informed consent, and potential discrimination. Equitable access and robust policy frameworks must be established before routine use in clinical or public health settings.

To address the current limitations and accelerate clinical translation, future efforts should focus on several key areas. First, replication and validation of existing genetic associations in large-scale, multiethnic, prospective studies are essential. These studies must employ harmonized phenotyping protocols to ensure comparability and reproducibility of findings.

Second, the development of polygenic risk models and the use of machine learning algorithms that integrate genomic, clinical, and dosimetric data hold promise for enhancing predictive accuracy and clinical decision-making [3]. Understanding gene–environment interactions, including lifestyle factors and comorbidities, will also be critical in refining individual risk estimates.

Encouragingly, several prospective clinical trials have already started incorporating genetic markers such as XRCC1 and TGFβ1 into treatment planning frameworks, marking a shift toward genomically informed radiotherapy [16,25]. In parallel, machine learning tools are being increasingly used to predict radiation toxicity, showing improved model performance and translational potential in clinical settings [7,22].

Ultimately, the integration of genetic information into radiation medicine aligns with the broader objectives of precision oncology, offering the potential for safer, more effective, and personalized treatments for cancer patients and radiation-exposed populations [11,10].

Conclusion

Genetic susceptibility plays a pivotal role in shaping individual responses to ionizing radiation, influencing both therapeutic efficacy and long-term risk. Discoveries from candidate gene studies and GWAS have revealed multiple polymorphisms—particularly in pathways related to DNA repair, oxidative stress, and cell cycle regulation—that contribute to inter-individual variability in radiosensitivity.

However, clinical implementation remains limited due to small SNP effect sizes, population heterogeneity, and complex gene–environment interactions. Overcoming these barriers will require large-scale, harmonized studies, cutting-edge functional genomics, and integrated analytical frameworks.

Embedding genetic data into radiotherapy planning, population-level risk assessment, and radiation protection policy holds the potential to significantly reduce radiation-induced morbidity and facilitate the transition to truly personalized medicine.

Achieving this vision will depend on close collaboration among geneticists, radiation oncologists, epidemiologists, data scientists, and bioethicists. As our understanding of the genetic architecture of radiosensitivity deepens, we will be better equipped to improve patient outcomes and mount informed responses to medical, occupational, and environmental radiation exposure scenarios.

Funding

This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. BR28512329).

Author Contributions

Conceptualization: *A.A.D., M.R.M., G.Zh.A.*

Methodology*: M.R.M., A.Yu.O., L.M.P., V.R.S.*

Investigation: *Zh.K.S., R.K., G.A.A., A.S.O., D.Y.*

Formal analysis and data curation: *A.V.L., M.B.A., M.L., S.A.A., A.Zh.B.*

Writing – original draft: *M.R.M., D.M.Sh., A.M.Y., N.Zh.Sh.*

Writing – review & editing*: A.A.D., A.Q., A.K., A.Yu.O.*

Visualization: *A.V.L., A.Q., A.K.*

Supervision: *A.A.D., L.M.P., G.Zh.A.*

Project administration: *M.R.M., A.S.O., G.A.A.*

Resources and funding acquisition: *A.A.D., D.M.Sh., N.Zh.Sh.*

Conflicts of Interest

The authors declare no conflict of interest.

References:

1.*Andreassen C.N., Alsner J.* Genetic variants and normal tissue toxicity after radiotherapy: A systematic review. Radiother. Oncol. 2009. Vol. 92, № 3. P. 299–309. https://doi.org//10.1016/j.radonc.2009.06.015

2.*Anscher M.S., Kong F.M., Andrews K., et al.* Plasma transforming growth factor beta1 as a predictor of radiation pneumonitis. Int. J. Radiat. Oncol. Biol. Phys. 1998. Vol. 41, № 5. P. 1029–1035. https://doi.org//10.1016/s0360-3016(98)00154-0

3.*Barnett G.C., West C.M., Dunning A.M., et al.* Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat. Rev. Cancer. 2009. Vol. 9, № 2. P. 134–142. https://doi.org//10.1038/nrc2587

4.*Belli M., Tabocchini M.A.* Ionizing radiation-induced epigenetic modifications and their relevance to radiation protection. Int. J. Mol. Sci. 2020. Vol. 21, № 17. P. 5993. https://doi.org//10.3390/ijms21175993

5.*Bentzen S.M.* Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat. Rev. Cancer. 2006. Vol. 6, № 9. P. 702–713. https://doi.org//10.1038/nrc1950

6.*Cargnin S., Barizzone N., Basagni C., et al.* Targeted next-generation sequencing for the identification of genetic predictors of radiation-induced late skin toxicity in breast cancer patients: a preliminary study. J. Pers. Med. 2021. Vol. 11, № 10. P. 967. https://doi.org//10.3390/jpm11100967

7.*Field M., Hardcastle N., Jameson M., et al.* Machine learning applications in radiation oncology. Phys. Imaging Radiat. Oncol. 2021. Vol. 19. P. 13–24. https://doi.org//10.1016/j.phro.2021.05.007

8.*Chen H., Huang L., Wan X., et al.* Polygenic risk score for prediction of radiotherapy efficacy and radiosensitivity in patients with non-metastatic breast cancer. Radiat. Med. Prot. 2023. Vol. 4, № 1. P. 33–42. https://doi.org//10.1016/j.radmp.2023.01.001

9.*Kerns S.L., Chuang K.H., Hall W., et al.* Radiation biology and oncology in the genomic era. Br. J. Radiol. 2018. Vol. 91, № 1091. P. 20170949. https://doi.org//10.1259/bjr.20170949

10. *Kerns S.L., Dorling L., Fachal L., et al.* Meta-analysis of genome-wide association studies identifies genetic markers of late toxicity after radiotherapy for prostate cancer. Nat. Commun. 2020. Vol. 11, № 1. P. 4159. https://doi.org//10.1016/j.ijrobp.2018.01.054

11. *Chen M., Lu H., Copley S.J., et al.* A novel radiogenomics biomarker for predicting treatment response and pneumotoxicity from programmed cell death protein or ligand-1 inhibition immunotherapy in NSCLC. J. Thorac. Oncol. 2023. Vol. 18, № 6. P. 718–730. https://doi.org//10.1016/j.jtho.2023.01.089

12. *Morton L.M., Karyadi D.M., Stewart C., et al.* Radiation-related genomic profile of papillary thyroid carcinoma after the Chernobyl accident // Science. – 2021. – Vol. 372, № 6543. – P. eabg2538. https://doi.org//10.1126/science.abg2538

13. *Preston D.L., Ron E., Tokuoka S., et al.* Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat. Res. 2007. Vol. 168, № 1. P. 1–64. https://doi.org//10.1667/RR0763.1

14. *Rübe C.E., Grudzenski S., Kühne M., et al.* DNA double-strand break repair of blood lymphocytes and normal tissue toxicity after radiotherapy. Nat. Med. 2008. Vol. 14, № 7. P. 735–741. https://doi.org//10.1158/1078-0432.CCR-07-5147

15. *Kerns S.L., Fachal L., Dorling L., et al.* Radiogenomics Consortium genome-wide association study meta-analysis of late toxicity after prostate cancer radiotherapy. JNCI J. Natl. Cancer Inst. 2020. Vol. 112, № 2. P. 179–190. https://doi.org//10.1093/jnci/djz075

16. *Thenault R., Gasmi A., Khene Z.E., et al.* Radiogenomics in prostate cancer evaluation. Curr. Opin. Urol. 2021. Vol. 31, № 4. P. 424–429. https://doi.org//10.1097/MOU.0000000000000902

17. *Tronko M.D., Howe G.R., Bogdanova T.I., et al.* A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: thyroid cancer in Ukraine detected during first screening. J. Natl. Cancer Inst. 2006. – Vol. 98, № 13. P. 897–903. https://doi.org//10.1093/jnci/djj244

18. *Turcotte L.M., Whitton J.A., Friedman D.L., et al.* Risk of subsequent neoplasms during the fifth and sixth decades of life in the childhood cancer survivor study cohort. J. Clin. Oncol. 2015. Vol. 33, № 31. P. 3568–3575. https://doi.org//10.1200/JCO.2015.60.9487

19. *Vousden K.H., Lane D.P.* p53 in health and disease. Nat. Rev. Mol. Cell Biol. 2007. Vol. 8, № 4. P. 275–283. https://doi.org//10.1038/nrm2147

20. *Shakhtarin V.V., Tsyb A.F., Stepanenko V.F., et al.* Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident. Int. J. Epidemiol. 2003. Vol. 32, № 4. P. 584–591. https://doi.org//10.1093/ije/dyg205

21. *Rühm W., Laurier D., Wakeford R.* Cancer risk following low doses of ionising radiation – current epidemiological evidence and implications for radiological protection. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 2022. Vol. 873. P. 503436. https://doi.org//10.1016/j.mrgentox.2021.503436

22. *Hall W.A., Bergom C., Thompson R.F., et al.* Precision oncology and genomically guided radiation therapy: a report from the American Society for Radiation Oncology/American Association of Physicists in Medicine/National Cancer Institute Precision Medicine Conference. Int. J. Radiat. Oncol. Biol. Phys. 2018. Vol. 101, № 2. P. 274–284. https://doi.org//10.1016/j.ijrobp.2017.05.044

23. *Wood R.D., Mitchell M., Sgouros J., Lindahl T.* Human DNA repair genes. Science. 2001. Vol. 291, № 5507. P. 1284–1289. https://doi.org//10.1126/science.1056154

24. *Zhang X., Yang J.* Role of non-coding RNAs on the radiotherapy sensitivity and resistance of head and neck cancer: from basic research to clinical application. Front. Cell Dev. Biol. 2020. Vol. 8. P. 637435. https://doi.org//10.3389/fcell.2020.637435

25. *Xu L., Osei B., Osei E.* A review of radiation genomics: integrating patient radiation response with genomics for personalised and targeted radiation therapy. J. Radiother. Pract. 2019. Vol. 18, № 2. P. 198–209. https://doi.org//10.1017/S1460396918000547

Author Information:

Altay A. Dyussupov – Doctor of Medical Sciences, Professor, Chairman of the Board – Rector NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0003-0875-1020;

Gulshara Zh. Abildinova – Doctor of Medical Sciences, Head of the Laboratory of Personalized Genomic Diagnostics, Hospital of the Medical Center of the Administration of the President of the Republic of Kazakhstan, Astana, Republic of Kazakhstan. https://orcid.org/0000-0003-0543-9568;

Dariya M. Shabdarbayeva – Doctor of Medical Sciences, Professor, Vice-Rector for Science and Strategic Development, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0001-9463-1935;

Meruyert R. Massabayeva – PhD, Associate Professor, Chief Researcher, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0001-8240-361X;

Lyudmila M. Pivina – MD, Professor, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-8035-4866;

Andrey Yu. Orekhov – PhD, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0001-7201-1399;

Alexandra V. Lipikhina – PhD, Deputy Director for Research, Research Institute of Radiation Medicine and Ecology, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0001-6980-999X;

Zhanargul K. Smailova – Candidate of Medical Sciences, Associate Professor, Vice-Rector for Academic and Educational Work, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-4513-4614;

Rauana M. Kisina – PhD student, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-1503-4663;

Galiya A. Alibayeva – Deputy Director for Medical Affairs and Strategic Development, Emergency Medical Hospital of Semey, Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-1503-4663;
Orazalina Ainash Saparovna – Candidate of Biological Sciences, Associate Professor, Head of the Department of Molecular Biology and Medical Genetics named after Academician of the National Academy of Sciences of the Republic of Kazakhstan T.K. Raisov, NJSC «Semey Medical University», phone; +7-777-235-47-72; e-mail: ainash.orazalina@smu.edu.kz; https://orcid.org/0000- 0003-4594-0138; Semey, Kazakhstan;
Ayaulym M. Yesentayeva – NJSC "Semey Medical University", Semey, Republic of Kazakhstan ORCID: –;
Vladlena R. Sabitova – NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-5893-3618;
Assel Zh. Baibussinova – PhD, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0003-3447-6245;
Askar B. Qasymov – Vice-Rector for Strategy and Social Development, NJSC "Shakarim University of Semey", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-1983-6508;
Aleksei Klivenko – Head of the Scientific Center for Radioecological Research, NJSC "Shakarim University of Semey", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-8971-686X;
Madina B. Abenova – PhD, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-4219-5737;
Diana Ygyyeva – NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0001-8391-8842;
Saulesh A. Apbasova – NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0001-6981-5441;
Murat N. Lepesbayev – Resident, Department of Forensic Medicine, JSC "Astana Medical University", Astana, Republic of Kazakhstan. https://orcid.org/0009-0006-9810-9232;
Nailya Zh. Shaizhunussova – Doctor of Medical Sciences, Professor, NJSC "Semey Medical University", Semey, Republic of Kazakhstan. https://orcid.org/0000-0002-6660-7118.

***Corresponding Author:**
Meruyert R. Massabayeva – PhD, Associate Professor, Chief Researcher, NJSC "Semey Medical University", Semey, Republic of Kazakhstan; **ORCID:** 0000-0001-8240-361X
Postal address: 103 Abai Avenue, Semey, 071400, Republic of Kazakhstan
Email: meruyert.massabayeva@smu.edu.kz
Mobile phone number: +7 700 777 02 30