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Identification of SNPs associated with susceptibility for development of adverse reactions to radiotherapy

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Abstract

Although cancer treatment with radiation can produce high cure rates, adverse effects often result from radiotherapy. These toxicities are manifested as damage to normal tissues and organs in the radiation field. In recognition of the substantial variation in the intrinsic response of individuals to radiation, an effort began approximately 10 years ago to discover the genetic markers, primarily SNPs, which are associated with susceptibility for the development of these adverse responses to radiation therapy. The goal of this research is to identify the SNPs that could serve as the basis of an assay to predict which cancer patients are most likely to develop complications resulting from radiotherapy. This would permit personalization and optimization of the treatment plan for each cancer patient.

Keywords

genome-wide association studies; personalized medicine; radiogenomics; radiotherapy

As with all forms of cancer treatment, the goal of radiotherapy is to provide cancer patients with a sustainable cure for their tumor, or at least prevent disease progression, without causing substantial damage to normal tissues and organ function. Clearly, there have been great advances to conform the radiation dose to the cancer. However, even with these dosimetric improvements, some volume of normal tissue still receives a substantial radiation dose during the course of radiotherapy [1]. This radiation exposure often results in toxicity that compromises organ function and affects the quality of life for the cancer survivor. In rare instances, such radiation injuries can be fatal. Thus, a fundamental goal of radiotherapy is to minimize toxicity without a loss of treatment efficacy.

It has long been recognized that cancer patients exhibit a heterogeneous response to radiotherapy manifested as normal tissue toxicity, despite uniform treatments. This could represent a random variation. However, evidence in support of genetic factors being responsible for variation in radiosensitivity was obtained from an examination of radiation-

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induced adverse effects in radiotherapy patients. It was observed in this study that individual variation in the progression rate to the development of normal tissue toxicities was relatively large for the same radiation treatment, with an estimated 80–90% of the variation being due to deterministic effects that were possibly related to the existence of genetic differences between individuals. By contrast, only 10–20% of the difference could be explained through stochastic events arising from the random nature of radiation-induced cell killing and random variations in dosimetry and dose delivery [2].

Efforts to develop predictive assays for intrinsic radiosensitivity

These findings stimulated many researchers to hunt for the basis of intrinsic radiosensitivity with a goal of creating an assay that could predict which patients were most likely to develop radiation-induced complications. The initial research focused upon measurement of the radiation sensitivity of skin fibroblasts derived from radiotherapy patients. Several initial studies reported an association between dermal fibroblasts and radiation toxicity. However, replication studies were not able to validate these initial findings [3]. Additional work has been performed using lymphocyte radiosensitivity as the basis for an assay and an inverse correlation has been reported between radiation-induced T-lymphocyte apoptosis with the development of late radiation effects [4]. Another approach is the use of gene-expression arrays. Through this work, genes have been identified whose expression correlated with the risk for development of fibrotic responses [5]. Although lymphocyte apoptosis and expression arrays appear promising, the results are preliminary and require validation before they can serve as the basis of a useful predictive assay.

Radiogenomics

The main approach taken by most investigators in this field has been an effort to identify genetic markers, primarily SNPs, that are associated with the development of adverse effects resulting from radiotherapy. It should be noted that SNPs represent relatively common genetic alterations, typically characterized by a low level of penetrance. This is in contrast to mutations, which are usually rare, but are associated with high penetrance. Thus, investigators embarked upon a series of case–control studies in which SNPs in candidate gene studies were genotyped in patients who either developed a particular complication resulting from radiotherapy or similarly treated individuals who did not exhibit such a response in an effort to identify the genetic markers that are associated with radiation injury. This field of research has been termed ‘radiogenomics’.

Similar to pharmacogenomics, radiogenomics is the branch of radiation oncology that examines the influence of genetic variation on the response of cancer patients to radiation and attempts to correlate SNPs or other genetic alterations, such as copy number variants, with responses to radiotherapy. The goal of this field is to identify the genetic markers that can serve as the basis for personalized radiotherapy in which cancer management is formulated so that it optimizes the treatment plan for each patient based on their genetic background.

The aspect of radiogenomics that has received the largest focus has been the identification of SNPs associated with the development of complications resulting from cancer radiotherapy. It is anticipated that through the use of such information, recommendations for strictly surgical or chemotherapeutic treatment could be made if they posed a reasonable alternative. Another approach may be that patients possessing SNP alleles associated with radiation injury would most benefit from the use of more sophisticated forms of radiotherapy such as intensity modulated radiation therapy or the use of protons. These approaches result in more conformal treatments in which the radiation dose is focused primarily on the tumor and normal tissues receive lower and less damaging amounts of radiation. However, these forms

of radiotherapy are generally more expensive than a standard protocol. Thus, a predictive assay could serve to more specifically identify the patients who would most benefit from a more costly form of treatment, thereby providing savings to the healthcare system. In this context, it has also been recognized that the importance of adjusting for radiation dose distribution in normal tissue biomarker studies is essential [6].

Alternatively, a patient possessing SNPs associated with normal tissue toxicities may in fact be an ideal candidate for radiotherapy since these same genetic variants may render this person's cancer radiosensitive. For such a patient, the use of a standard radiation dose may be unnecessarily high and it is possible that such an individual could be cured using a lower dose that is less likely to cause injury. It should also be noted that an added benefit resulting from identification of genetic factors associated with radiation sensitivity is that it may then be possible to treat the vast majority of cancer patients, who do not possess these genetic alterations, with higher radiation doses and improve their chances for cure.

Candidate gene SNP studies

An updated summary of the published candidate gene SNP studies that have been previously reviewed [7–10] is provided below and organized in the context of cancers for which the subjects in the study were treated.

Prostate cancer

An association between the possession of significant mutations in *ATM* with proctitis and cystitis in prostate cancer patients treated with radiotherapy was first reported by Hall *et al.* [11]. This publication was followed by two reports [12–13] that demonstrated an association between missense SNPs in *ATM* and rectal bleeding and erectile dysfunction. Here, the impact of the SNPs upon proctitis was radiation dose dependent. In contrast to these positive findings, no association between the codon 1054 SNP in *ATM* with either urinary morbidity or erectile dysfunction was detected [14]. Studies were also performed in which SNPs in multiple genes were genotyped and an association between SNPs in *LIG4*, *ERCC2*, *CP2D6**4 and *MDC1* with bladder and rectal toxicity was identified [15–16]. A correlation between SNPs in *TGFB1* with both erectile dysfunction and rectal bleeding was also detected [17]. In addition, it was reported that patients with a particular SNP in *XRCC1* were more likely to develop erectile dysfunction and that men who possessed either a specific SNP in *SOD2* or a combination of SNPs in *SOD2* and *XRCC3* displayed an increased incidence of rectal bleeding [18]. Patients who had undergone carbon ion radiotherapy were screened for 450 SNPs in 118 genes and an association was found between SNPs in *SART1*, *ID3*, *EPDR1*, *PAH* and *XRCC6* with urinary morbidity [19].

Breast cancer

A correlation between SNPs in *ATM* with subcutaneous fibrosis and telangiectasias was reported [20–21]. However, further study did not confirm an association between SNPs in *ATM* with radiation effects [22]. Interestingly, a protective effect against the development of telangiectasia with a SNP in *ATM* has also been reported [23]. Andreassen *et al.* reported an association between SNPs in *TGFB1*, *SOD2*, *XRCC3*, *XRCC1* and *ATM* with subcutaneous fibrosis [24–26]. However, a validation study in which a separate replication set of subjects was screened was unable to confirm their initial findings [27]. Separate studies also failed to validate associations between SNPs in either *TGFB1* or *XRCC3* with toxicity resulting from radiotherapy [28,29]. Additional studies [23,30–38] found associations between adverse radiation responses with SNPs in either *APE1*, *ATM*, *eNOS*, *MSH2*, *MSH3*, *MPO*, *TP53*, *XRCC1*, *TGFB1*, *XRCC1* and *GSTP1*. In order to expand the number of SNPs being screened, 999 SNPs in a total of 137 candidate genes have been screened [39]. It was

discovered in this study that haplotypes in six loci were associated with the development of early skin reactions. In addition, 3144 SNPs covering 494 genes were genotyped in breast cancer patients and SNPs in *ABCA1* and *IL12RB2* were found to be associated with the development of severe radiation dermatitis [40].

Head & neck cancer

An association was observed for SNPs in *TGFB1* and *XRCC1* with a lower grade of fibrosis [41]. Although the presence of SNPs in *TGFB1* was associated with overall survival following radiotherapy, no correlation was detected with severe mucosal reactions to irradiation [42]. SNPs in *MDM2* and *TP53* were reported not to be associated with submucosal fibrosis [43].

Lung cancer

SNPs in *TGFB1* and *NOS3* were associated with a lower risk for radiation pneumonitis [44,45] whereas SNPs in *ATM*, *IL1A*, *IL8*, *TNF*, *TNFRSF1B* and *MIF* correlated with an increased risk of radiation pneumonitis [45,46]. In addition, SNPs in *COX-2*, *GSS*, *ABCC2* and *XRCC1* were associated with survival [47,48].

Other sites

A correlation between SNPs in *XRCC3* and *TGFB1* with an increased risk of late radiation effects following treatment for either cervical or endometrial cancers was reported [49,50], whereas a SNP in *XRCC1* was associated with a reduced incidence of late effects. In addition, an association between a SNP in *RAD21* with radiation effects following treatment at any one of multiple sites has been published [51]. In a study of patients who underwent allogeneic hematopoietic cell transplant, SNPs in *OGG1*, *LIG3* and *MUTYH* were associated with an increased incidence of transplant related mortality whereas SNPs in *TDG* correlated with a decreased risk of death at 1 year following transplant [52]. SNPs in *MC1R* have correlated with severe acute reactions in radiotherapy patients [53]. SNPs in *ATM*, *SOD2*, *XRCC1*, *XRCC3*, *TGFB1* and *RAD21* were associated with radiation toxicity in patients treated with radiotherapy for several forms of cancer [54].

In order to provide a summary of the studies for the genes that have been focused upon in candidate gene studies, Table 1 lists all of the studies for genes that have been screened in a minimum of five studies. As can be observed from the information provided in the table, contradictory results have been obtained for all the genes and SNPs examined.

In summing up the candidate gene studies that have been performed, many positive initial reports of statistically significant associations have been published between SNPs in a variety of genes with adverse radiotherapy effects, which lends support to the hypothesis that genetic variants play an important role conferring susceptibility to the development of radiation toxicity. However, none of the positive associations reported have been consistently validated in subsequent studies with other patient cohorts. Thus, at this time, no single gene or SNP has been identified that can serve as the basis for a predictive assay.

Genome-wide SNP association studies

In response to the lack of success in candidate gene studies and the subsequent recognition that this approach is too limited in scope, radiogenomics investigators have now begun a much broader search to identify genes and SNPs associated with radiation response. Several large-scale genome wide association (GWA) studies have been initiated in which radiotherapy patients are being genotyped for large numbers of common SNPs. One of the main reasons for GWA studies is owing to the recognition that only a very rudimentary

knowledge of the molecular pathways and proteins involved in the development of most normal tissue responses to radiation exists. Thus, it is anticipated that through the use of a GWA approach, not only will SNPs be identified that can serve as the basis of a predictive assay, but this will also lead to the discovery of genes whose products play an important role in the response to radiation. It is expected that this information will help to elucidate the pathways involved in the development of radiation effects that could lead to the development of drugs capable of either preventing or mitigating radiation toxicity.

Although the GWA approach has proved somewhat limited in its ability to explain the genetic basis for most disease susceptibilities, it is anticipated that greater success will be achieved in the identification of genetic markers associated with radiation response. One reason is that the 'environmental agent', responsible for causing the effect, radiation, is clearly known and typically the doses to which the various tissues and organs are irradiated are accurately determined for radiotherapy patients. This is in contrast to most disease-association studies in which the agent(s) causing the effect is either not known or there may be a range of factors that influence the disease development. Another important reason to expect that GWA studies will yield useful results in radiotherapy is that it is unlikely that the SNPs associated with radiosensitivity would have been selected against in evolution since it is only in recent decades that individuals, most of whom are beyond their procreative years, are being exposed to the high radiation doses associated with radiotherapy. Thus, selective pressures against radiosensitivity SNPs would not be expected as may be the case for SNPs associated with disease susceptibility.

Recently, the first GWA study in radiogenomics that was designed to identify SNPs associated with adverse effects in patients treated with radiotherapy, was published [55]. The goal of this study was to discover SNPs associated with erectile dysfunction among African-American prostate cancer patients treated with radiotherapy. The SNP found to be most significantly associated (unadjusted p-value = 5.46×10^{-8} ; Bonferroni p-value = 0.028) with erectile dysfunction, rs2268363, was located in the *FSHR* gene, whose encoded product plays a role in male gonad development and function. It is notable that this SNP is located in a gene associated with normal erectile function rather than one more specifically linked to radiation response, which represents the class of genes screened in most of the candidate SNP studies performed to date. It is therefore very unlikely that this SNP would have been identified using a candidate gene approach. Another key finding of this project is that the four SNPs most strongly associated with erectile dysfunction were specific to people of African ancestry, and would therefore, not have been identified had a cohort of strictly European ancestry been screened. The results of a GWA study screening lymphoblastoid cell lines have published reporting that SNPs in *C13orf34*, *MAD2L1*, *PLK4*, *TPD52* and *DEPDC1B* are associated with radiation cytotoxicity [56].

Another advantage of the GWA approach in radiogenomics is that the genotyping of enormous numbers of subjects is not essential. This is owing to the fact that it would be of little clinical use to identify genetic markers that only slightly increase the risk for adverse effects as there are many other factors involved in treatment that impact radiotherapy response. However, even though a more modest sample size for GWA studies in radiogenomics is necessary compared with disease association studies, it is critical that this work is performed on a collaborative basis since cohorts involving thousands of radiotherapy patients must be available to obtain sufficient numbers of patients for genotyping who develop radiation injuries. To achieve such a joint effort, an international Radiogenomics Consortium has been established [57,58]. The goal of this consortium is to provide a structure in which tissue samples and data can be pooled from investigators performing work in radiogenomics on a global scale to create a large biorepository and databank. This will substantially strengthen the statistical power of these studies. Once

initial GWA studies have been performed and evidence for the involvement of specific genes has emerged from this work, the Radiogenomics Consortium will also play an important role in the critical validation studies in which additional radiotherapy cohorts will be genotyped. It is only through the replication of initial associations that the goal of identifying SNPs that can serve as the basis of a useful assay to predict which cancer patients are most likely to develop adverse effects resulting from radiotherapy will be achieved.

Future perspective

It is anticipated that over the next few years, SNPs correlated with susceptibility for the development of adverse effects resulting from radiotherapy will be identified from GWA studies. Some, but not all of these SNPs will be validated in additional radiotherapy patient cohorts that could then serve as the basis of an assay to predict which cancer patients are most likely to develop radiation-induced injuries. It is expected that this genetic information will be used in prospective clinical trials performed by cooperative groups in which patients will be genotyped and randomized to treatment arms in which they either receive a standard radiation protocol, a reduced radiation dose, a more conformal form of radiotherapy or a nonradiation treatment. The results from these trials will provide the basis for the development of a predictive assay that will serve to personalize and optimize cancer treatment.

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Executive summary

Efforts to develop predictive assays for intrinsic radiosensitivity

- Evidence has long existed which suggests that individuals treated with radiotherapy exhibit a range of responses with underlying genetic bases for this heterogeneity.

Radiogenomics

- The main approach for identifying the genetic basis for the variation in radiation response has been the identification of SNPs that correlate with the development of radiation-induced toxicities in cancer patients treated with radiotherapy.
- The goal of this area of research, termed 'radiogenomics', is to identify the genetic markers, primarily SNPs, which can serve as the basis of an assay to predict which cancer patients are most likely to develop adverse effects from radiotherapy.
- An additional goal of radiogenomics is to identify the genes and elucidate the molecular pathways through which radiation damage to normal tissues and organs arise.

Candidate gene SNP studies

- A series of candidate gene studies has been performed over the past 10 years.
- Although positive associations have been reported between certain SNPs and several normal tissue toxicities, no specific SNP has been definitively linked with radiation sensitivity.

Genome-wide SNP association studies

- In recognition of the fact that the initial candidate gene studies were too narrowly focused, genome-wide association studies have been initiated and represent the focus of most research currently underway in radiogenomics.
- In order to facilitate the performance of large genome-wide association studies and the validation of SNPs identified through initial studies, a Radiogenomics Consortium has been established.

Future perspective

- It is expected that a set of clinically validated assays, based on the possession of specific SNPs, will be developed in the next 5–10 years. These assays will accurately predict which patients are most likely to suffer normal tissue and organ damage resulting from cancer treatment with radiation.
- The development of predictive assays will offer a powerful tool to individually tailor and optimize treatment protocols for cancer patients and will help to further the implementation of personalized medicine in radiotherapy.

Table 1Summary of candidate gene SNP studies[†].

Study	Irradiated site	Subjects (n)	Result	Ref.
ATM				
Hall <i>et al.</i>	Prostate	17	Association between 'significant mutations' with proctitis and cystitis	[11]
Iannuzzi <i>et al.</i>	Breast	46	Association between 'significant' SNPs with subcutaneous fibrosis and telangiectasia	[20]
Angele <i>et al.</i>	Breast	566	Association between SNPs rs1801516 and at nucleotides IVS22-77 and IVS48 + 238 with adverse radiation responses	[30]
Bremer <i>et al.</i>	Breast	1100	No association between protein truncation mutations with either acute or late radiation effects	[22]
Andreassen <i>et al.</i>	Breast	52	No association between any of the screened SNPs with altered breast appearance	[25]
Andreassen <i>et al.</i>	Breast	120	No association with risk of subcutaneous fibrosis for any of the screened SNPs	[27]
Cesaretti <i>et al.</i>	Prostate	37	Association between missense SNPs (cause substitution of the encoded amino acid) with rectal bleeding and erectile dysfunction	[13]
Andreassen <i>et al.</i>	Breast	41	Association between SNP rs1801516 with subcutaneous fibrosis	[26]
Damaraju <i>et al.</i>	Prostate	124	No association between genotyped SNPs with bladder and rectal toxicity	[15]
Cesaretti <i>et al.</i>	Prostate	108	Association between multiple SNPs with proctitis when the radiation dose to rectal tissue was quantified	[12]
Edvardsen <i>et al.</i>	Breast	462	Association between the rs1801516 SNP with telangiectasia and the rs1800058 SNP with pleural thickening and lung fibrosis	[23]
Ho <i>et al.</i>	Breast	131	Association between the codon 1853 SNP with fibrosis and telangiectasia	[59]
Meyer <i>et al.</i>	Prostate	721	No association between the codon 1054 SNP with either urinary morbidity or erectile dysfunction	[14]
Pugh <i>et al.</i>	Prostate	41	No association between screened SNPs with 'high toxicity'	[16]
TGFBI				
Andreassen <i>et al.</i>	Breast	41	Association between SNPs rs1800470 and rs1800469 with subcutaneous fibrosis	[24]
Quarmby <i>et al.</i>	Breast	103	Association between SNPs rs1800469 and rs1800470 with subcutaneous fibrosis	[60]
Andreassen <i>et al.</i>	Breast	52	Association between SNPs rs1800470 and rs1800469 with altered breast appearance	[25]
Andreassen <i>et al.</i>	Breast	120	No association for any of the screened SNPs with risk for subcutaneous fibrosis	[27]
Damaraju <i>et al.</i>	Prostate	124	No association between genotyped SNPs with bladder and rectal toxicity	[15]
Barnett <i>et al.</i>	Breast	778	No association between SNPs rs1800469 and rs1800470 with late radiation toxicity	[28]
De Ruyck <i>et al.</i>	Cervix/endometrium	218	Association between the SNPs at nucleotides -1.552delAGG, -509 and in codon 10 with development of late radiotherapy effects	[50]
Giotopoulos <i>et al.</i>	Breast	167	Association between SNP rs1800469 with fibrosis	[31]
Peters <i>et al.</i>	Prostate	141	Association between SNPs rs1800469, rs1800471 and rs1982073 with erectile function Association between SNP rs1800469 with late rectal bleeding	[17]

Study	Irradiated site	Subjects (n)	Result	Ref.
Yuan <i>et al.</i>	Non-small-cell lung cancer	164	Association between SNP rs1982073 with radiation pneumonitis	[44]
<i>SOD2</i>				
Andreassen <i>et al.</i>	Breast	41	Association between a SNP in codon 16 with subcutaneous fibrosis	[24]
Andreassen <i>et al.</i>	Breast	52	No association between genotyped SNPs with altered breast appearance	[25]
Andreassen <i>et al.</i>	Breast	120	No association for any of the screened SNPs with risk for subcutaneous fibrosis	[27]
Ahn <i>et al.</i>	Breast	446	No association between genotyped SNPs with acute skin toxicities	[33]
Kuptsova <i>et al.</i>	Breast	390	No association between genotyped SNPs with telangiectasia	[36]
<i>XRCC1</i>				
Andreassen <i>et al.</i>	Breast	41	Association between a SNP in codon 399 with subcutaneous fibrosis	[24]
Moullan <i>et al.</i>	Breast	566	Association between codons 194 and 399 SNPs with adverse radiation effects	[61]
Andreassen <i>et al.</i>	Breast	52	No association between genotyped SNPs with altered breast appearance	[25]
Chang-Claude <i>et al.</i>	Breast	446	Association between codon 399 SNP with acute skin toxicities in patients with BMI >25	[32]
De Ruyck <i>et al.</i>	Cervix/endometrium	62	Association between a SNP in codon 194 with late effects	[49]
Andreassen <i>et al.</i>	Breast	120	No association for any of the screened SNPs with risk for subcutaneous fibrosis	[27]
Damaraju <i>et al.</i>	Prostate		No association between genotyped SNPs with bladder and rectal toxicity	[15]
Giotopoulos <i>et al.</i>	Breast	167	Association between a codon 399 SNP with telangiectasia	[31]
Chang-Claude <i>et al.</i>	Breast	409	No association between screened SNPs with telangiectasia	[37]
Mangoni <i>et al.</i>	Breast	87	Association between SNPs in codons 194 and 399 with increased acute skin reactions	[38]
Sun <i>et al.</i>	Lung	248	Association between SNPs rs2854510 and rs1001581 with survival	[48]
<i>XRCC3</i>				
Andreassen <i>et al.</i>	Breast	41	Association between a SNP in codon 241 with subcutaneous fibrosis	[24]
Andreassen <i>et al.</i>	Breast	52	No association between genotyped SNPs with altered breast appearance	[25]
De Ruyck <i>et al.</i>	Cervix/endometrium	62	Association between a SNP at nucleotide IVS5-14 with late effects	[49]
Andreassen <i>et al.</i>	Breast	120	No association for any of the screened SNPs with risk for subcutaneous fibrosis	[27]
Damaraju <i>et al.</i>	Prostate		No association between genotyped SNPs with bladder and rectal toxicity	[15]
Popanda <i>et al.</i>	Breast	446	No association between SNP rs861539 in <i>XRCC3</i> with acute skin toxicity	[29]
Chang-Claude <i>et al.</i>	Breast	409	No association between screened SNPs with telangiectasia	[37]
Werbrouck <i>et al.</i>	Head and neck	88	Association between SNP rs861539 with severe dysphasia	[62]
Mangoni <i>et al.</i>	Breast	87	Association between a SNP in codon 241 with increased acute skin reactions	[38]

[†] Compilation of data for candidate genes in which SNPs were genotyped in a minimum of five studies.