Genetics of radiation-related non-cancer diseases

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DCEG Radiation Epidemiology and Dosimetry Course 2019

Learning outcomes (1)

- Studies in patients receiving therapeutic radiation can increase understanding of the genetics of radiation-related non-cancer diseases
- Genetic studies of radiation toxicity must allow for potential confounders and modifiers
- The genetic determinants of non-cancer effects will involve rare variants with large effects, low frequency variants with moderate effects and common variants with small effects

Learning outcomes (2)

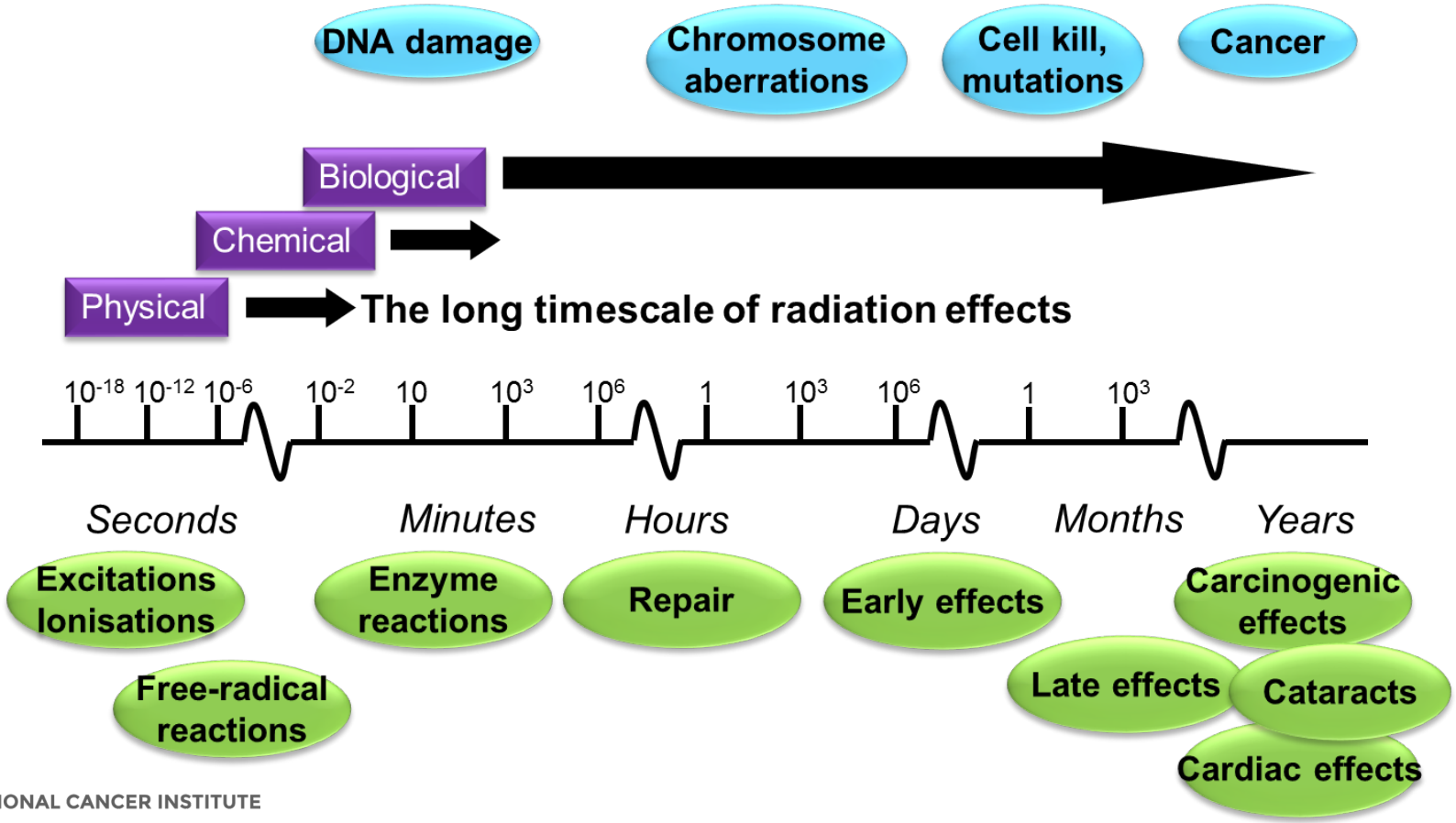
- Building cohorts with good quality data and sample collections is key and a consortium approach is required
- Study design considerations include: retrospective/prospective, case-control/cohort, time-point for assessing toxicity, allowing for baseline toxicity, harmonizing data collected using different scoring systems, variables to include in multivariable analyses, statistical power
- Studies should follow STROGAR reporting guidelines
- Fine-mapping identifies the probable genetic variant (or variants) and provides mechanistic understanding

Non-cancer effects of radiation

- Cataracts
- Circulatory disease – vascular damage
- Non-malignant respiratory and digestive diseases
- Cognitive impairment
- Little MP *Radiat Environ Biophys* 2013; 52:435-49
- **Radiotherapy toxicity**

Studies in patients receiving therapeutic radiation can increase understanding of the genetics of radiation-related non-cancer diseases

Effects of radiation on normal tissues are tissue and time dependent

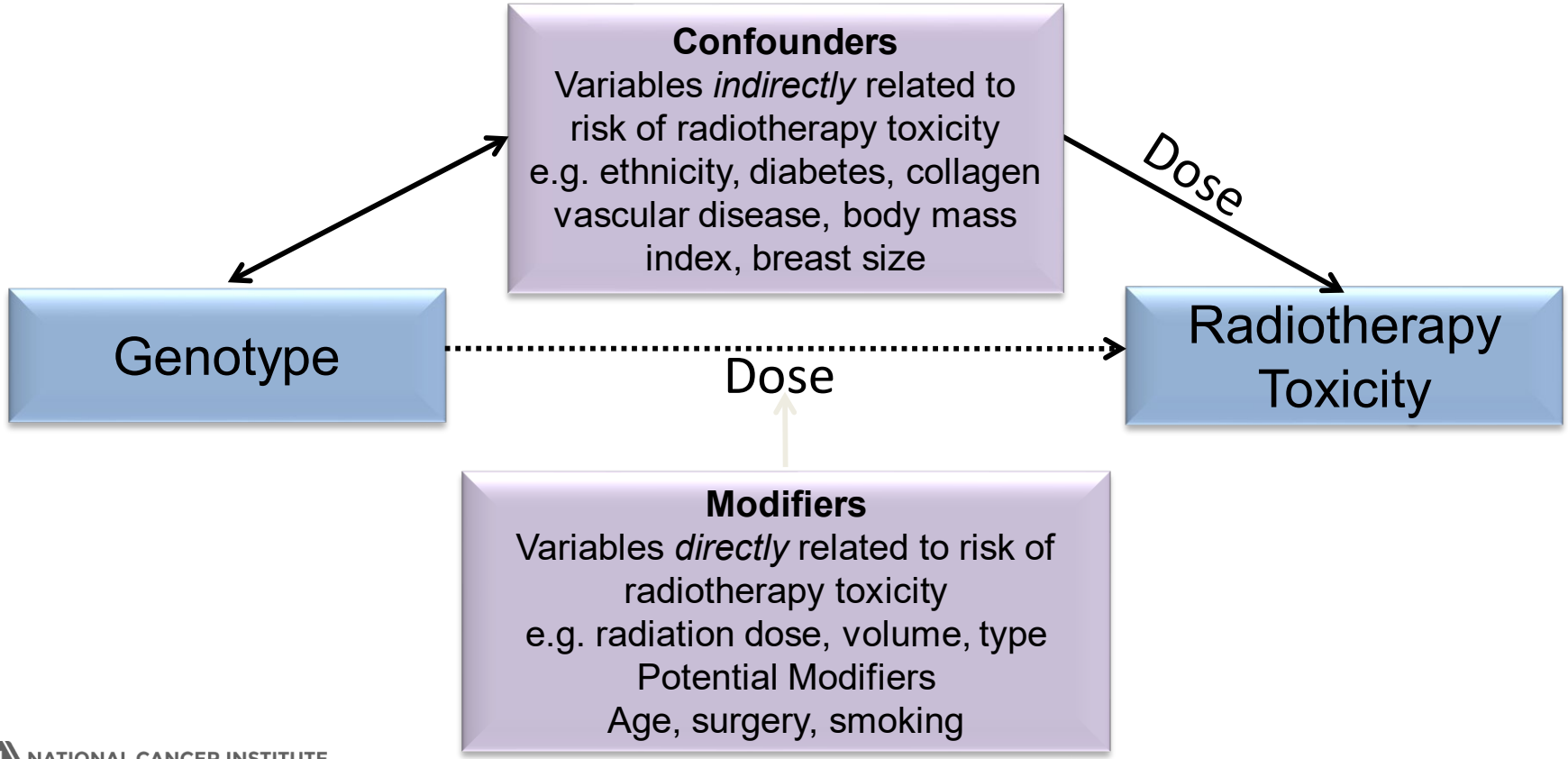


Many factors affect risk of radiotherapy toxicity

- Physical factors: radiation dose, volume and type
- Treatment factors: prior surgery, use of chemotherapy or other treatments
- Patient factors: age, smoking, co-morbidities
- **Genetics**

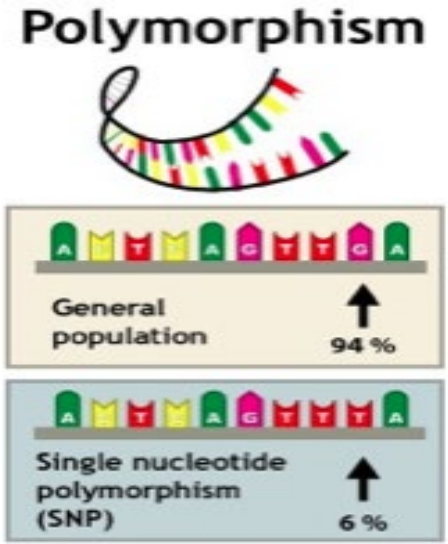
Genetic studies of radiation toxicity must allow for potential confounders & modifiers

The relationship between genotype and radiation effects is affected by modifiers and confounders



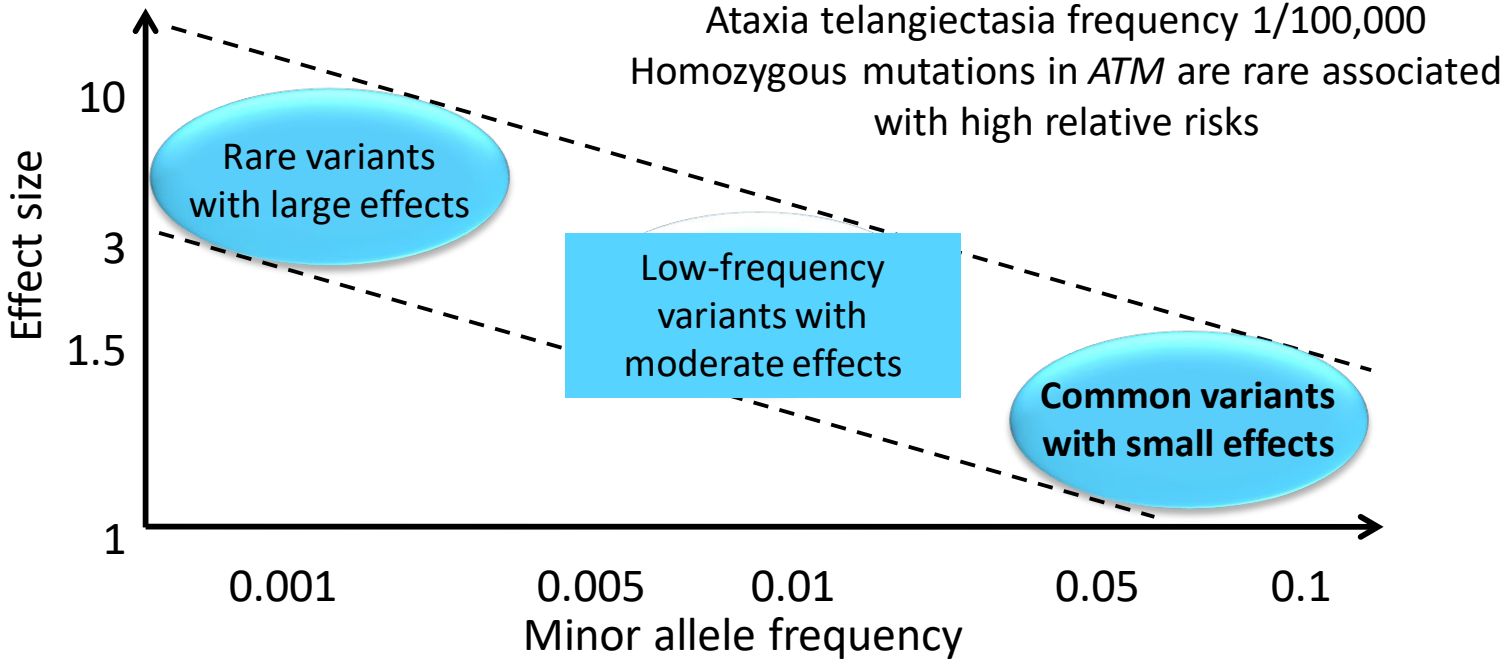
Radiogenomics aims to identify the genetic determinants of radiotherapy toxicity

- Single nucleotide variants (SNVs): mutations, **common** single nucleotide polymorphisms (SNPs)
- Copy number variation (insertions/deletions - indels)
- Epigenetics is also likely to be involved - methylation



Identifying patients with an increased risk of toxicity to personalise treatments

The genetic determinants of non-cancer effects will involve rare variants with large effects, low frequency variants with moderate effects and common variants with small effects



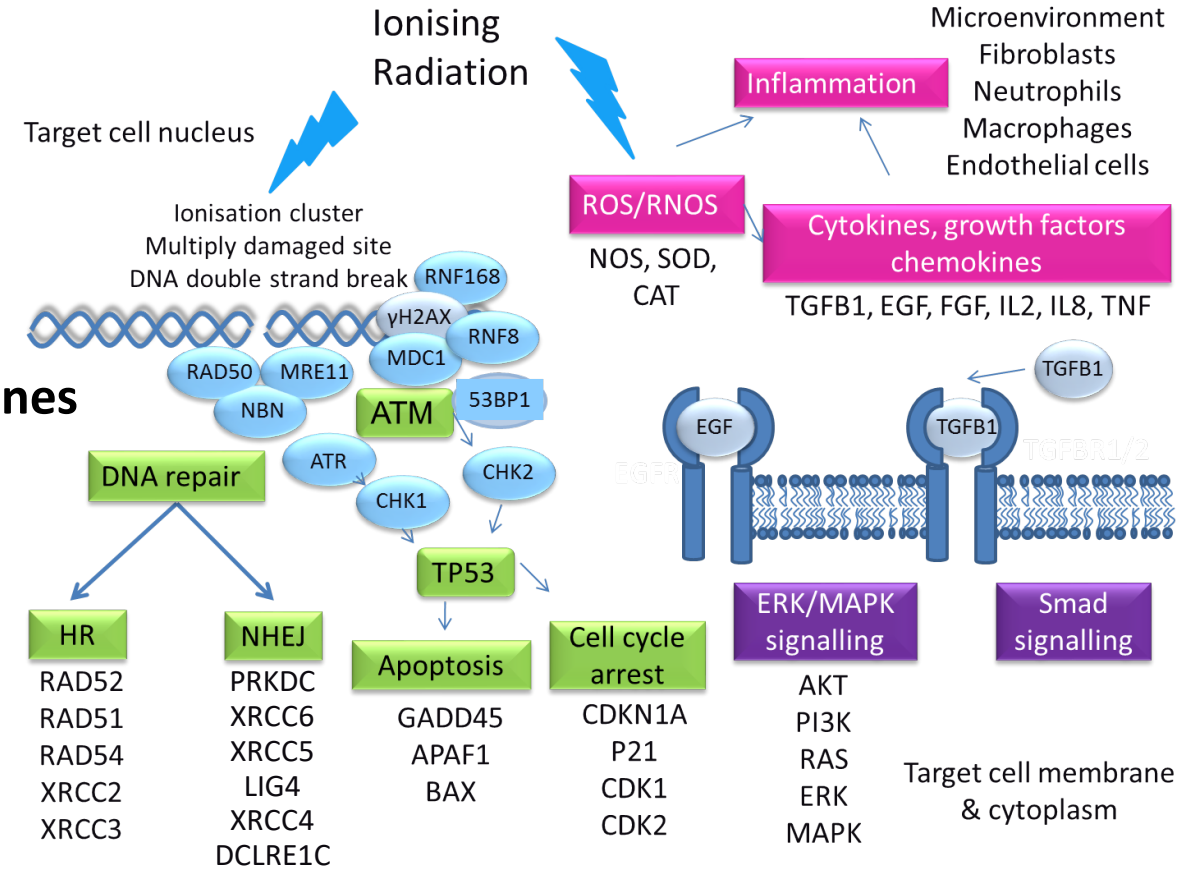
Allelic architecture: number, type, effect size and frequency of susceptibility variants of a trait

Rare homozygote variants with large effects

Syndrome	Mutated Gene(s)	Associated with
Ataxia telangiectasia (AT)	***ATM***	Radiotherapy side effects
AT-like disorder-1	***MRE11***	Cellular radiosensitivity
Cornelia de Lange syndrome	***SMCL1A***	Variable radiosensitivity
Cowden syndrome	***PTEN***	Radiotherapy side effects
Fanconi anemia	**Numerous**	Radiotherapy side effects in some
Gorlin syndrome	***PTCH1***	Cellular radiosensitivity, risk of second cancer
Li-Fraumeni syndrome	***TP53***	Risk of second malignancy
Ligase IV syndrome	***LIG4***	Radiotherapy toxicity
Neurofibromatosis type 1	***NF1***	Risk of second malignancy
Nijmegen breakage syndrome (NBS)	***NBN***	Radiotherapy toxicity
NBS-like syndrome	***RAD50***	Cellular radiosensitivity
Radiosensitive SCID	***DCLRE1C, PRKDC***	Cellular radiosensitivity
Retinoblastoma	***RB1***	Moderate radiosensitivity, risk of second cancer
RIDDLE syndrome	***RNF168***	Cellular radiosensitivity

Mechanism of action of radiation involves multiple genes/pathways

Candidate genes



Common variants have small effects

Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study

Gillian C Barnett, Charlotte E Coles, Rebecca M Elliott, Caroline Baynes, Craig Luccarini, Don Conroy, Jennifer S Wilkinson, Jonathan Tyrer, Vivek Misra, Radka Platte, Sarah L Gulliford, Matthew R Sydes, Emma Hall, Søren M Bentzen, David P Dearnaley, Neil G Burnet, Paul D P Pharoah, Alison M Dunning, Catharine M L West

Summary

Background Several studies have reported associations between radiation toxicity and single nucleotide polymorphisms (SNPs) in candidate genes. Few associations have been tested in independent validation studies. This prospective study aimed to validate reported associations between genotype and radiation toxicity in a large independent dataset.

Lancet Oncol 2012; 13: 65-77
Published Online
December 13, 2011
DOI:10.1016/S1470-

- Strongest association for *ATM* rs4988023 OR 1.53; 95% CI 1.08-2.18
- Previously reported late toxicity associations were not replicated
- Individual effect sizes are small and not clinically relevant
- Large studies needed

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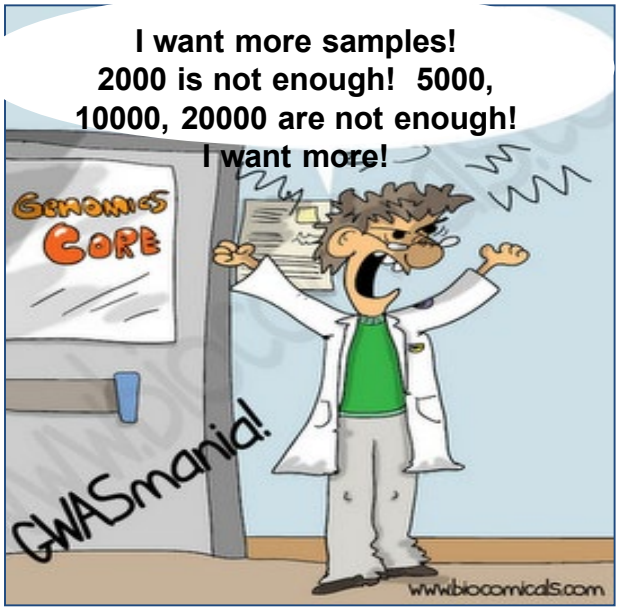
CANCER RESEARCH UK

RAPPER

Finding the unknown unknowns requires GWAS



Radiogenomics Consortium

REQUITE

Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality-of-Life in Cancer Survivors

RAPPER

Building cohorts with good quality data and sample collections is key and a consortium approach is required

Identifying genetic variants requires careful consideration of study design

- Prospective or retrospective?
- Which toxicity data scoring system or how can data collected using different scoring systems be harmonized?
- If baseline toxicity data are available, should it be used to correct for?
- What is the best time point for assessing toxicity?
- Case-control or cohort (all patients at a particular time-point) study?

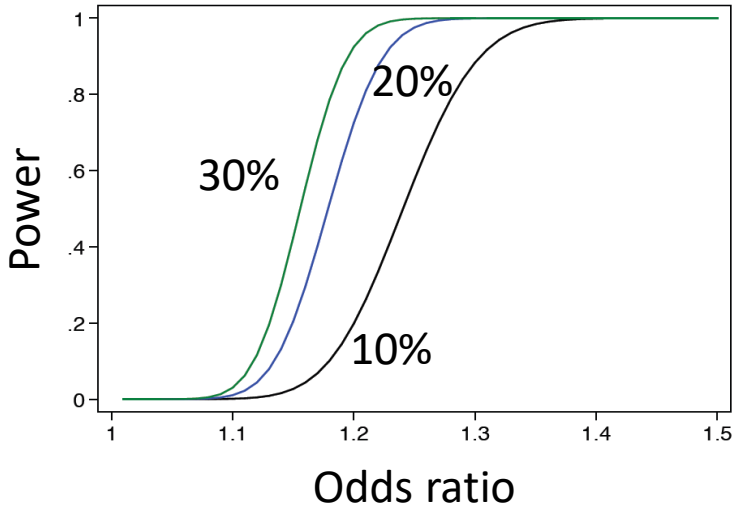
Identifying genetic variants requires careful consideration of study design

- Fixed time point or time-to-event?
- What data should be included in multivariable analyses?
- Is it possible to deal with missing data?
- Candidate gene or genome wide association study (GWAS)?
- What is the level of statistical power?

Study design considerations include: retrospective/prospective, case-control/cohort, time-point for assessing toxicity, allowing for baseline toxicity, harmonizing data collected using different scoring systems, variables to include in multivariable analyses, statistical power

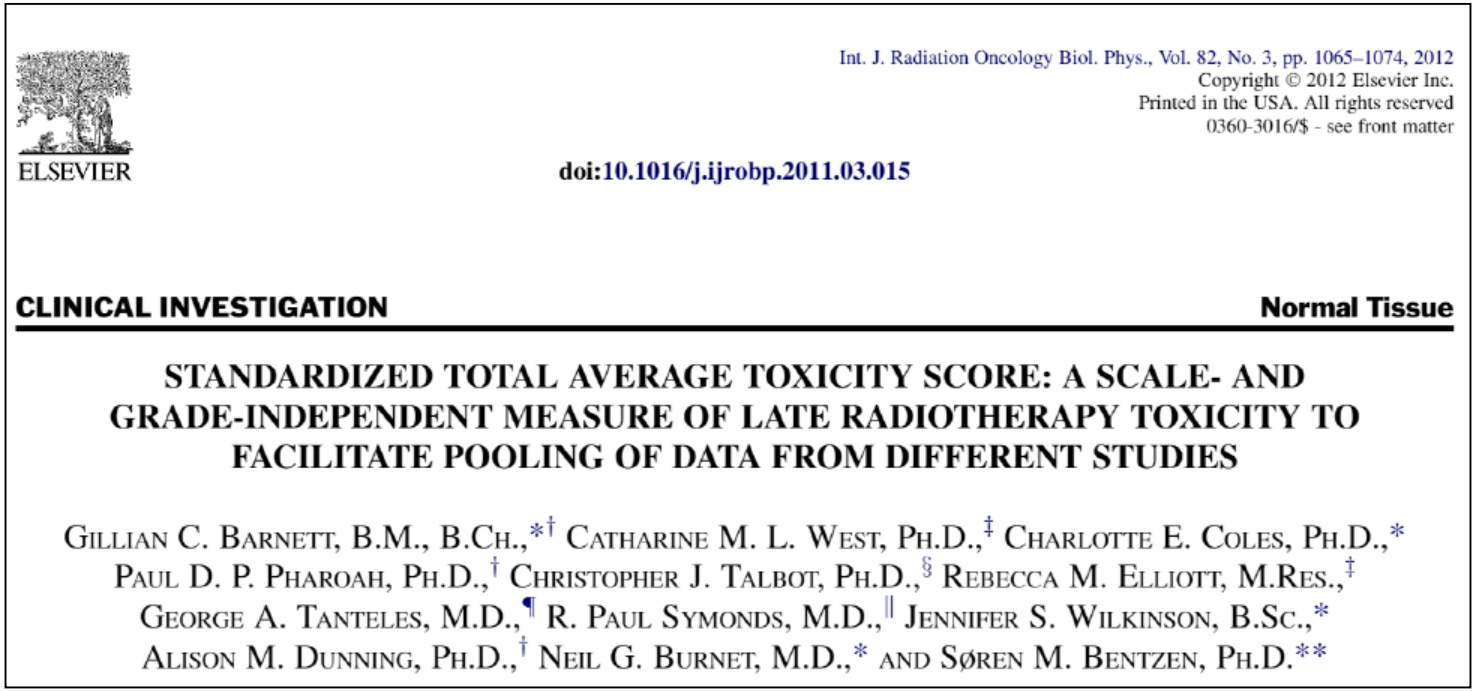
Statistical power

- The power to detect a genetic variant depends on allelic effect size, marker allele frequency and toxicity endpoint prevalence
- Common risk alleles for most complex traits confer relative risks of 1.05 - 1.2
- Power to detect most alleles is limited



Power of 10,000 cases GWAS to detect risk alleles of frequency 0.2 for toxicities of prevalences of 10, 20 and 30%

A standardized total average toxicity (STAT) score to pool data from different studies



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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 3, pp. 1065–1074, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.03.015

CLINICAL INVESTIGATION **Normal Tissue**

STANDARDIZED TOTAL AVERAGE TOXICITY SCORE: A SCALE- AND GRADE-INDEPENDENT MEASURE OF LATE RADIOTHERAPY TOXICITY TO FACILITATE POOLING OF DATA FROM DIFFERENT STUDIES

GILLIAN C. BARNETT, B.M., B.CH.,*† CATHARINE M. L. WEST, PH.D.,‡ CHARLOTTE E. COLES, PH.D.,* PAUL D. P. PHAROAH, PH.D.,† CHRISTOPHER J. TALBOT, PH.D.,§ REBECCA M. ELLIOTT, M.RES.,‡ GEORGE A. TANTELES, M.D.,¶ R. PAUL SYMONDS, M.D.,‖ JENNIFER S. WILKINSON, B.SC.,* ALISON M. DUNNING, PH.D.,† NEIL G. BURNET, M.D.,* AND SØREN M. BENTZEN, PH.D.**

Reporting guidelines should be followed

Radiotherapy and Oncology 110 (2014) 182–188

Contents lists available at ScienceDirect

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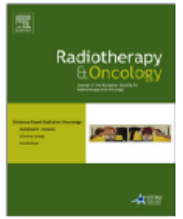


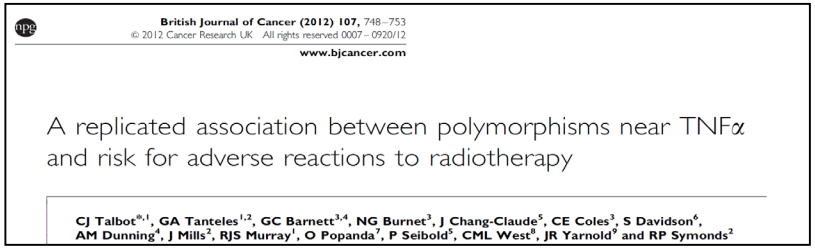
Guidelines

STROGAR – STrengthening the Reporting Of Genetic Association studies in Radiogenomics

Sarah L. Kerns [a,b,c], Dirk de Ruysscher [d], Christian N. Andreassen [e], David Azria [f], Gillian C. Barnett [g], Jenny Chang-Claude [h], Susan Davidson [i], Joseph O. Deasy [j], Alison M. Dunning [k], Harry Ostrer [b,c], Barry S. Rosenstein [a], Catharine M.L. West [l], Søren M. Bentzen [m,*]

Studies should follow STROGAR reporting guidelines

Recent *large* candidate gene studies identified risk variants



British Journal of Cancer (2012) 107, 748–753
© 2012 Cancer Research UK All rights reserved 0007 – 0920/12
www.bjcancer.com

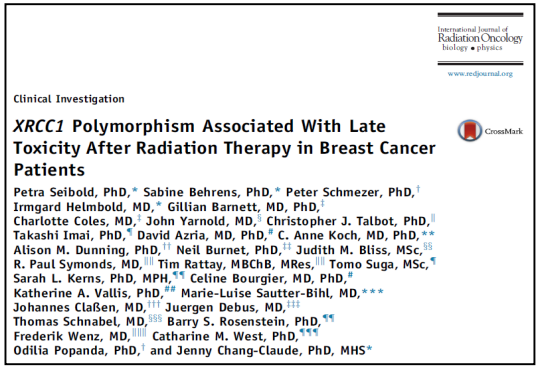
A replicated association between polymorphisms near TNFα and risk for adverse reactions to radiotherapy

CJ Talbot[6,1], GA Tanteles[1,2], GC Barnett[3,4], NG Burnet[3], J Chang-Claude[5], CE Coles[3], S Davidson[6], AM Dunning[4], J Mills[2], RJS Murray[1], O Popanda[7], P Seibold[5], CML West[8], JR Yarnold[9] and RP Symonds[2]

***TNF* rs1800629**

2,036 breast cancer patients

OR=2.4 for late effects



International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

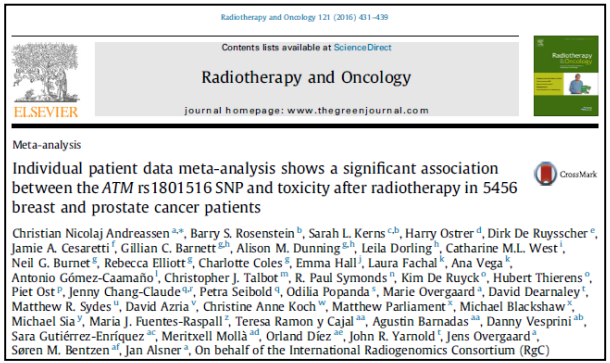
***XRCC1* Polymorphism Associated With Late Toxicity After Radiation Therapy in Breast Cancer Patients**

Petra Seibold, PhD,* Sabine Behrens, PhD,* Peter Schmezer, PhD,† Irmgard Helmbold, MD,* Gillian Barnett, MD, PhD,† Charlotte Coles, MD,† John Yarnold, MD,‡ Christopher J. Talbot, PhD,‖ Takashi Imai, PhD,¶ David Azria, MD, PhD,# C. Anne Koch, MD, PhD,** Alison M. Dunning, PhD,†† Neil Burnet, PhD,‡‡ Judith M. Bliss, MSc,§§ R. Paul Symonds, MD,‖‖ Tim Rattay, MBChB, MRes,‖‖ Tomo Suga, MSc,¶ Sarah L. Kerns, PhD, MPH,¶¶ Celine Bourgier, MD, PhD,# Katherine A. Vallis, PhD,## Marie-Luise Sautter-Bihl, MD,*** Johannes Claßen, MD,††† Juergen Debus, MD,‡‡‡ Thomas Schnabel, MD,§§§ Barry S. Rosenstein, PhD,¶¶ Frederik Wenz, MD,‖‖‖ Catharine M. West, PhD,¶¶¶ Odilia Popanda, PhD,† and Jenny Chang-Claude, PhD, MHS*

***XRCC1* rs2682585**

2,636 breast cancer patients

OR=0.77 for late effects



Radiotherapy and Oncology 121 (2016) 431–439

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Meta-analysis

Individual patient data meta-analysis shows a significant association between the *ATM* rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients

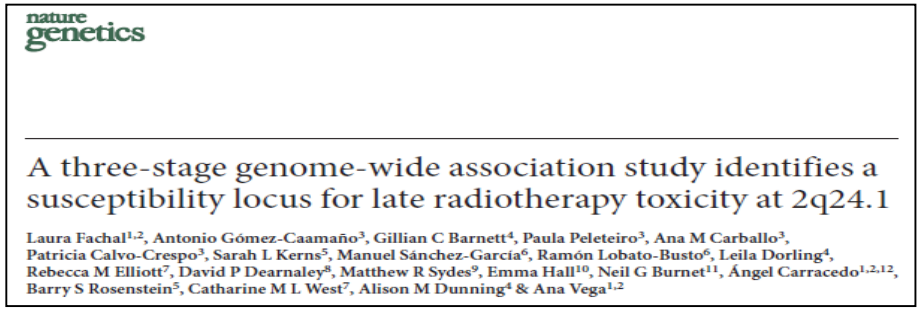
Christian Nicolaj Andreassen[a,*], Barry S. Rosenstein[b], Sarah L. Kerns[c,b], Harry Ostrer[d], Dirk De Ruysscher[e], Jamie A. Cesaretti[f], Gillian C. Barnett[g,h], Alison M. Dunning[g,h], Leila Dorling[h], Catharine M.L. West[i], Neil G. Burnet[g], Rebecca Elliott[g], Charlotte Coles[g], Emma Hall[j], Laura Fachal[k], Ana Vega[k], Antonio Gómez-Caamaño[l], Christopher J. Talbot[m], R. Paul Symonds[n], Kim De Ruyck[o], Hubert Thierens[o], Piet Ost[p], Jenny Chang-Claude[q,r], Petra Seibold[q], Odilia Popanda[s], Marie Overgaard[a], David Dearnaley[t], Matthew R. Sydes[u], David Azria[v], Christine Anne Koch[w], Matthew Parliament[x], Michael Blackshaw[x], Michael Sia[y], Maria J. Fuentes-Raspall[z], Teresa Ramon y Cajal[aa], Agustin Barnadas[ab], Danny Vesprini[ab], Sara Gutiérrez-Enríquez[ac], Meritxell Mollà[ad], Orland Díez[ae], John R. Yarnold[f], Jens Overgaard[a], Søren M. Bentzen[af], Jan Alsner[a], On behalf of the International Radiogenomics Consortium (RgC)

***ATM* rs1801516**

5,458 breast & prostate cancer patients

OR~1.5 for early effects and 1.2 for late effects

GWAS identified novel genes

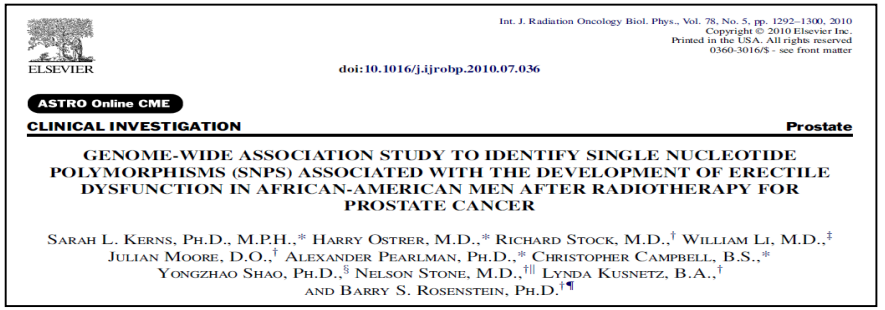


nature genetics

A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1

Laura Fachal[1,2], Antonio Gómez-Caamaño[3], Gillian C Barnett[4], Paula Peleteiro[3], Ana M Carballo[3], Patricia Calvo-Crespo[3], Sarah L Kerns[5], Manuel Sánchez-García[6], Ramón Lobato-Busto[6], Leila Dorling[4], Rebecca M Elliott[7], David P Dearnaley[8], Matthew R Sydes[9], Emma Hall[10], Neil G Burnet[11], Ángel Carracedo[1,2,12], Barry S Rosenstein[5], Catharine M L West[7], Alison M Dunning[4] & Ana Vega[1,2]

Gene involved in muscle cell regeneration with overall toxicity



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0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.07.036

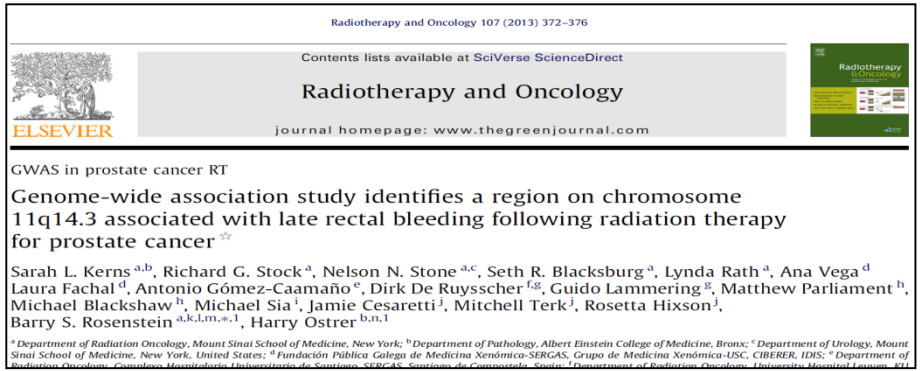
ASTRO Online CME

CLINICAL INVESTIGATION Prostate

GENOME-WIDE ASSOCIATION STUDY TO IDENTIFY SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) ASSOCIATED WITH THE DEVELOPMENT OF ERECTILE DYSFUNCTION IN AFRICAN-AMERICAN MEN AFTER RADIOTHERAPY FOR PROSTATE CANCER

Sarah L. Kerns, Ph.D., M.P.H.,* Harry Ostrer, M.D.,* Richard Stock, M.D.,† William Li, M.D.,‡ Julian Moore, D.O.,† Alexander Pearlman, Ph.D.,* Christopher Campbell, B.S.,* Yongzhao Shao, Ph.D.,§ Nelson Stone, M.D.,†‖ Lynda Kusnetz, B.A.,† and Barry S. Rosenstein, Ph.D.†¶

Gene involved in erectile function with erectile dysfunction



Radiotherapy and Oncology 107 (2013) 372–376

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journal homepage: www.thegreenjournal.com

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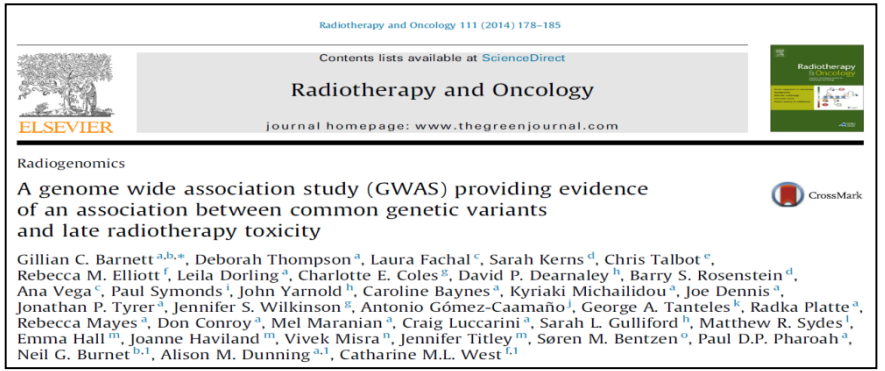
GWAS in prostate cancer RT

Genome-wide association study identifies a region on chromosome 11q14.3 associated with late rectal bleeding following radiation therapy for prostate cancer ☆

Sarah L. Kerns[a,b], Richard G. Stock[a], Nelson N. Stone[a,c], Seth R. Blacksburg[a], Lynda Rath[a], Ana Vega[d] Laura Fachal[d], Antonio Gómez-Caamaño[e], Dirk De Ruysscher[f,g], Guido Lammering[g], Matthew Parliament[h], Michael Blackshaw[h], Michael Sia[i], Jamie Cesaretti[j], Mitchell Terk[j], Rosetta Hixson[j], Barry S. Rosenstein[a,k,l,m,*,1], Harry Ostrer[b,n,1]

[a] Department of Radiation Oncology, Mount Sinai School of Medicine, New York; [b] Department of Pathology, Albert Einstein College of Medicine, Bronx; [c] Department of Urology, Mount Sinai School of Medicine, New York, United States; [d] Fundación Pública Galega de Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica-USC, CIBERER, IDIS; [e] Department of Radiation Oncology, Complexo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain; [f] Department of Radiation Oncology, University Hospital Leuven, KU

Gene involved in regulation of angiogenesis and rectal bleeding



Radiotherapy and Oncology 111 (2014) 178–185

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journal homepage: www.thegreenjournal.com

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Radiogenomics

A genome wide association study (GWAS) providing evidence of an association between common genetic variants and late radiotherapy toxicity

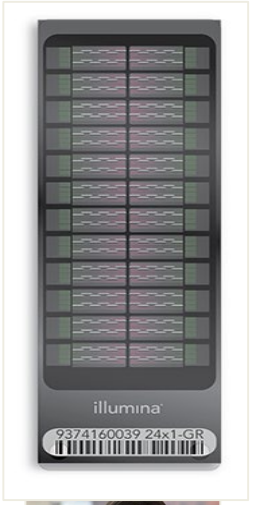
CrossMark

Gillian C. Barnett[a,b,*], Deborah Thompson[a], Laura Fachal[c], Sarah Kerns[d], Chris Talbot[e], Rebecca M. Elliott[f], Leila Dorling[a], Charlotte E. Coles[g], David P. Dearnaley[h], Barry S. Rosenstein[d], Ana Vega[c], Paul Symonds[i], John Yarnold[h], Caroline Baynes[a], Kyriaki Michailidou[a], Joe Dennis[a], Jonathan P. Tyrer[a], Jennifer S. Wilkinson[g], Antonio Gómez-Caamaño[j], George A. Tanteles[k], Radka Platte[a], Rebecca Mayes[a], Don Conroy[a], Mel Maranian[a], Craig Luccarini[a], Sarah L. Gulliford[h], Matthew R. Sydes[l], Emma Hall[m], Joanne Haviland[m], Vivek Misra[n], Jennifer Titley[m], Søren M. Bentzen[o], Paul D.P. Pharoah[a], Neil G. Burnet[b,1], Alison M. Dunning[a,1], Catharine M.L. West[f,1]

Gene involved in smooth muscle contraction and rectal incontinence

Most recent Radiogenomics Consortium meta-analysis

Kerns SL, Fachal L, Dorling L, Barnett GC, Baran A, Peterson DR, Hollenberg M, Hao K, Narzo AD, Ahsen ME, Pandey G, Bentzen SM, Janelsins M, Elliott RM, Pharoah PDP, Burnet NG, Dearnaley DP, Gulliford SL, Hall E, Sydes MR, Aguado-Barrera ME, Gómez-Caamaño A, Carballo AM, Peleteiro P, Lobato-Busto R, Stock R, Stone NN, Ostrer H, Usmani N, Singhal S, Tsuji H, Imai T, Saito S, Eeles R, DeRuyck K, Parliament M, Dunning AM, Vega A, Rosenstein BS, West CML. **Radiogenomics Consortium Genome-Wide Association Study Meta-analysis of Late Toxicity after Prostate Cancer Radiotherapy.** *J Natl Cancer Inst.* 2019 May 16.



- 5,705 prostate cancer patients, 3,874 analyzed
- ↑ urinary frequency, ↓ urinary stream, hematuria, rectal bleeding
- Baselines corrected late toxicity: time to first ≥grade 2 toxicity event
- Multivariable analysis: androgen deprivation therapy, prior prostatectomy, age at treatment, and total BED

Radiogenomics Consortium Meta-analysis

OncoArray-500K, ~7 million SNPs
Time to grade 2/3 toxicity, n=3,874

	RAPPER n=2,010	RADIOGEN n=658	GenePARE n=495	UGhent n=311	CCI-BT n=252	CCI-EBRT n=148
Median age (yr)	68	72	65	65	65	68
Intermed/high risk	60%	81%	53%	74%	38%	92%
Prior surgery	0%	20%	0%	31%	0%	0%
Hormones	100%	70%	51%	64%	22%	49%
Median BED (Gy)	120	123	204	136	158	153

CCI=Cross Cancer Institute; BED=biological effective dose

Sarah Kerns et al 2019, *JNCI* May 16

Three new SNPs identified

p-values must be $<5 \times 10^{-8}$

SNP	MAF	Toxicity	HR (95% CI)	P	BFDP
rs17055178	0.09	Rectal bleeding	1.95 (1.58, 2.43)	6.2×10^{-10}	0.09%
rs10969913	0.05	Decreased stream	3.92 (2.50, 5.83)	2.9×10^{-10}	1.07%
rs11122573	0.06	Hematuria	1.92 (1.53, 2.42)	1.8×10^{-8}	1.96%

MAF = minor allele frequency; BFDP = Bayesian false discovery probability

Kerns et al 2019 *JNCI* May 16

Radiogenomics Consortium

Previously identified variants validated

SNP	MAF	Toxicity	HR (95% CI)	P
rs17599026 *KDM3B*	0.07	Urinary frequency	1.55 (1.23, 1.95)	1.8×10^{-4}
rs7720298 *DNAH5*	0.30	Decreased stream	1.43 (1.14, 1.78)	1.6×10^{-3}
rs1801516 *ATM*	0.22	Overall toxicity	1.29 (1.07, 1.55)	6.3×10^{-3}
rs7582141 *TANC1*	0.05	Overall toxicity	1.99 (1.33, 2.98)	8.3×10^{-4}

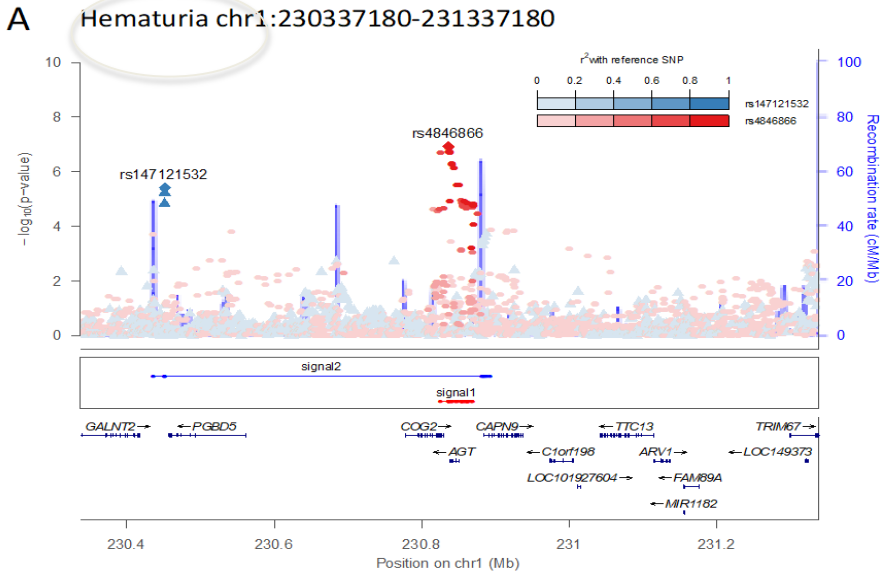
MAF=minor allele frequency

Kerns et al 2019 *JNCI*

Radiogenomics Consortium

Fine scale mapping

- GWAS find associations between a genomic region and a trait
- It is assumed at least one causal variant exists
- Fine-mapping identifies the probable genetic variant (or variants)
- Less common variants with larger effects can be found



- Second independent signal
- rs147121532 with hematuria
- MAF 0.01%
- HR 4.43, 95% CI 2.35 - 8.33
- P = 4.7×10^{-6}

Radiogenomics Consortium

Radiogenomics can increase mechanistic understanding

- Credible causal variants (CCVs) associated with differential expression of local protein coding gene (*AGT*)
- *AGT* encoding angiotensinogen is converted to the active enzyme angiotensin II by angiotensin converting enzyme
- Prior studies suggest angiotensin signaling may influence radiation-induced blood vessel wall injury and interstitial fibrosis
- Pathway analysis identified ‘platelet adhesion to exposed collagen’

‘platelet adhesion to exposed collagen’

- Platelet adhesion is the first step in the formation of a platelet plug, formed in response to blood vessel injury
- Collagens are involved in the process and are abundant in vascular epithelia
- Several collagen binding proteins are expressed on platelets e.g. integrins
- The integrin pathway was also associated with rectal bleeding

Fine-mapping identifies the probable genetic variant (or variants) and provides mechanistic understanding

Radiogenomics for particle beam therapy

Rs17599026 in *KDMB3* associated with decreased urinary stream

Cohort	MAF	n	Radiation	HR (95% CI)
RGC	0.07	3,874	Photons	1.55 (1.23, 1.95)
PRRG	0.11	170	Photons	1.51 (0.56, 4.05)
NTMC	0.11	254	Protons	1.13 (0.49, 2.64)
PRRG	0.11	538	Carbon ions	0.63 (0.27, 1.49)

Kerns S, Rosenstein B, Tsuji H, Imai T, Saito S

Learning outcomes

- Studies in patients receiving therapeutic radiation can increase understanding of the genetics of radiation-related non-cancer diseases
- Genetic studies of radiation toxicity must allow for potential confounders and modifiers
- The genetic determinants of non-cancer effects will involve rare variants with large effects, low frequency variants with moderate effects and common variants with small effects

Learning outcomes

- Building cohorts with good quality data and sample collections is key and a consortium approach is required
- Study design considerations include: retrospective/prospective, case-control/cohort, time-point for assessing toxicity, allowing for baseline toxicity, harmonizing data collected using different scoring systems, variables to include in multivariable analyses, statistical power
- Studies should follow STROGAR reporting guidelines
- Fine-mapping identifies the probable genetic variant (or variants) and provides mechanistic understanding

Summary

- Radiogenomic studies of radiotherapy toxicity can increase understanding of the genetics of non-cancer diseases
- Collaborative work within the Radiogenomics Consortium has (and is) developing the methodology and best study designs by working with experts within and outside the radiation community
- The approaches can be applied to study the genetics of other non-cancer diseases of interest to the radiation epidemiology community

Further reading

- Bergom C, West CM, Higginson DS, et al. The implications of genetic testing on radiotherapy decisions: a guide for radiation oncologists. *Int J Radiat Oncol Biol Phys* 2019 Aug 2.
- Kerns SL, Fachal L, Dorling L, et al. Radiogenomics Consortium Genome-Wide Association Study Meta-analysis of Late Toxicity after Prostate Cancer Radiotherapy. *J Natl Cancer Inst* 2019 May 16.
- West CM, Barnett GC. Genetics and genomics of radiotherapy toxicity: towards prediction. *Genome Med* 2011 Aug 23;3(8):52.
- Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, Burnet NG. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nat Rev Cancer* 2009 Feb;9(2):134-42

The genetic determinants of radiotherapy toxicity involve:

A. Rare mutations with small effects
B. Common single nucleotide polymorphisms (SNPs) with large effects
C. Low frequency variants with moderate effects
D. Only mutations and SNPs

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A. Are retrospective
B. Are case control
C. Use univariate analyses
D. Follow STROGAR guidelines

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