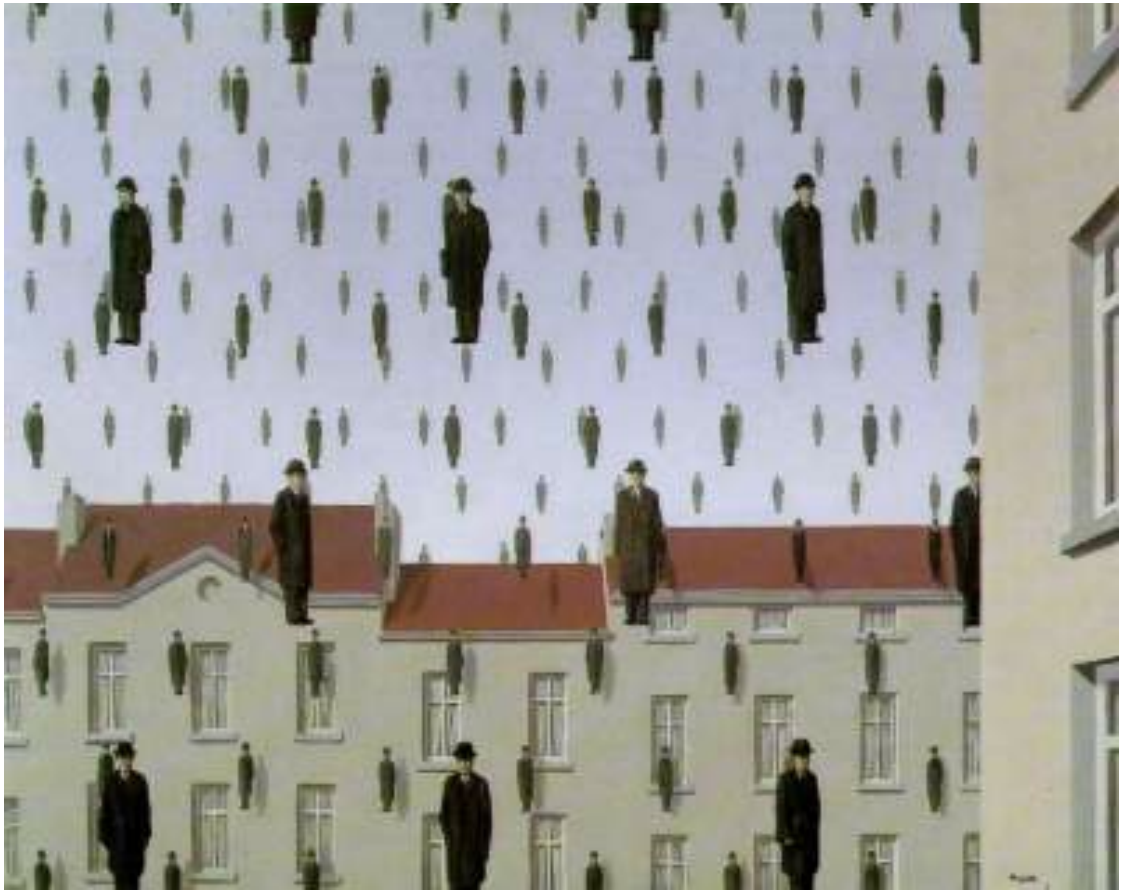
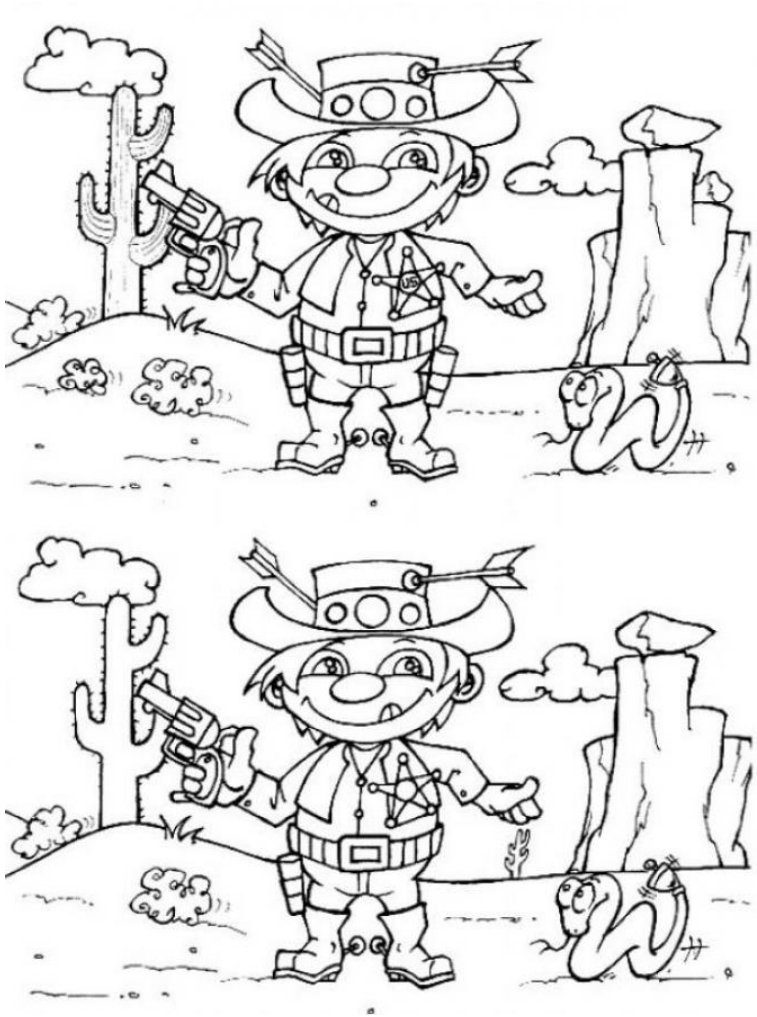
Polimorfismi a singolo nucleotide e tossicità tardiva radioindotta

Monica Mangoni
Università di Firenze

Not all the patients react the same way to radiotherapy



Find the differences



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Radiotherapy and Oncology 64 (2002) 131–140

RADIOTHERAPY & ONCOLOGY

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Does variability in normal tissue reactions after radiotherapy have a genetic basis – where and how to look for it?

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hyper-responsive clinical phenotype

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Radiotherapy and Oncology 69 (2003) 127–135

RADIOTHERAPY & ONCOLOGY

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Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes

Christian Nicolaj Andreassen[a,*], Jan Alsner[a], Marie Overgaard[b], Jens Overgaard[a]

Single Nucleotide Polymorphisms

Radiotherapy and Oncology 99 (2011) 356–361

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journal homepage: www.thegreenjournal.com

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Clinical radiobiology

Association between single nucleotide polymorphisms in the XRCC1 and RAD51 genes and clinical radiosensitivity in head and neck cancer

Nicola Pratesi [a], Monica Mangoni [b,*], Irene Mancini [a], Fabiola Paiar [b], Lisa Simi [a], Lorenzo Livi [b], Sara Cassani [b], Michela Buglione [c], Salvatore Grisanti [d], Camillo Almici [e], Caterina Polli [f], Calogero Saieva [g], Stefano Maria Magrini [c], Giampaolo Biti [b], Mario Pazzagli [a], Claudio Orlando [a]

ELSEVIER CME ASTRO

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 52–58, 2011

0360-3016/$–see front matter

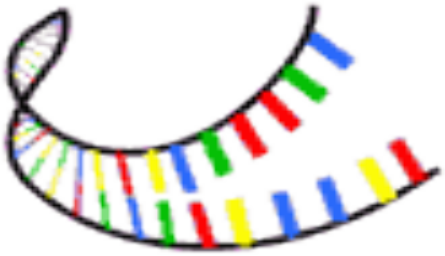
doi:10.1016/j.ijrobp.2010.04.023

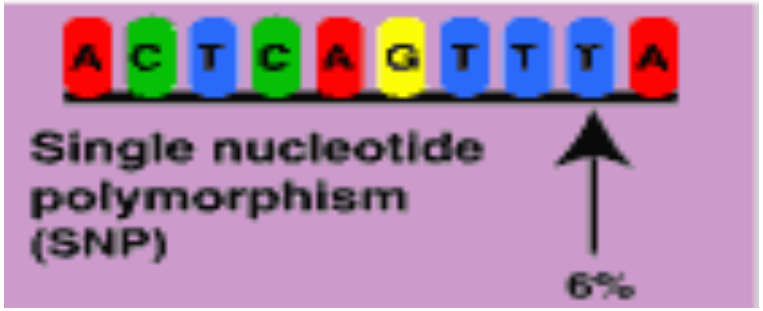
CLINICAL INVESTIGATION **Breast**

ASSOCIATION BETWEEN GENETIC POLYMORPHISMS IN THE XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2, MLH1, MSH3, AND MGMT GENES AND RADIOSENSITIVITY IN BREAST CANCER PATIENTS

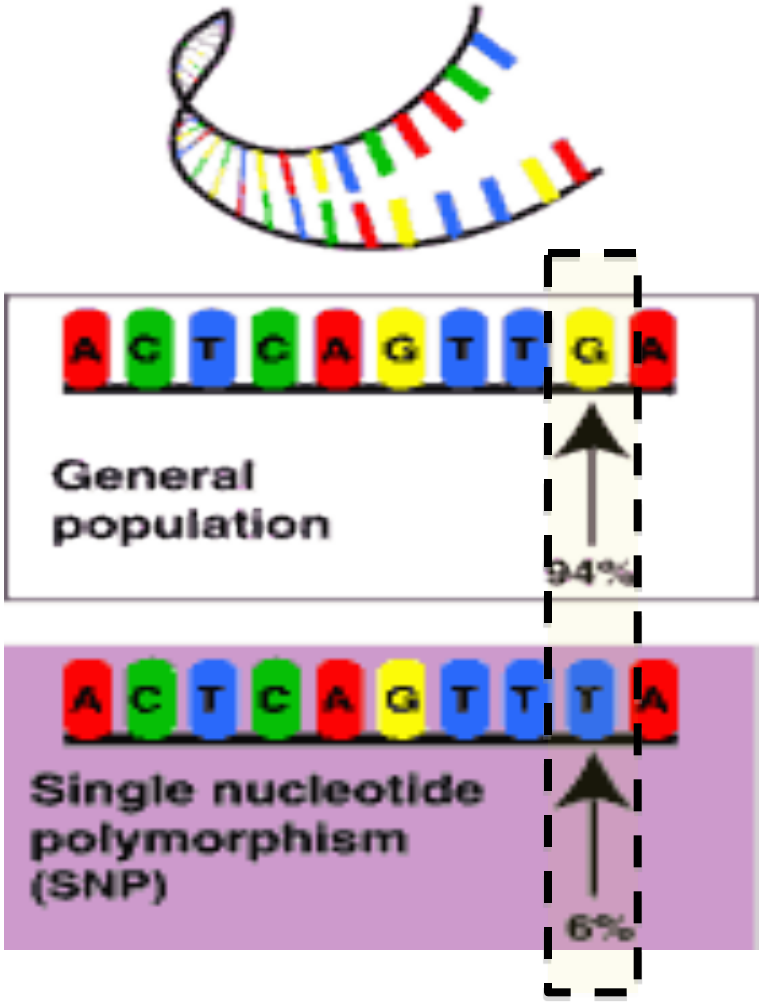
MONICA MANGONI, M.D., PH.D.,* SIMONETTA BISANZI, M.SC.,† FRANCESCA CAROZZI, PH.D.,† CRISTINA SANI, M.SC.,† GIAMPAOLO BITI, M.D.,* LORENZO LIVI, M.D.,* EMANUELA BARLETTA, M.D., PH.D.,‡ ADELE SENIORI COSTANTINI, M.D.,§ AND GIUSEPPE GORINI, M.D.§

Single Nucleotide Polymorphisms (SNPs)



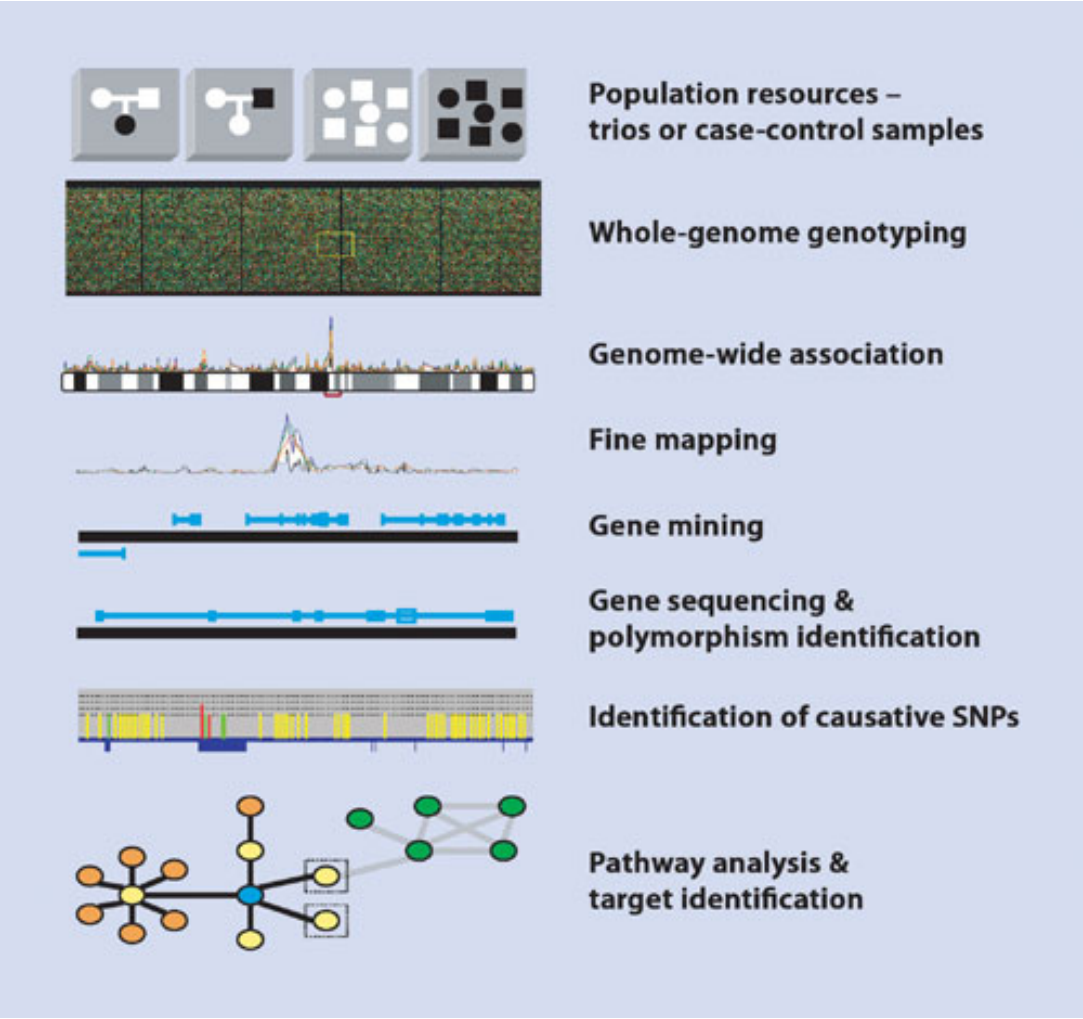


Single Nucleotide Polymorphisms (SNPs)



Genetic variants in which an alternate base pair is present at a particular nucleotide location

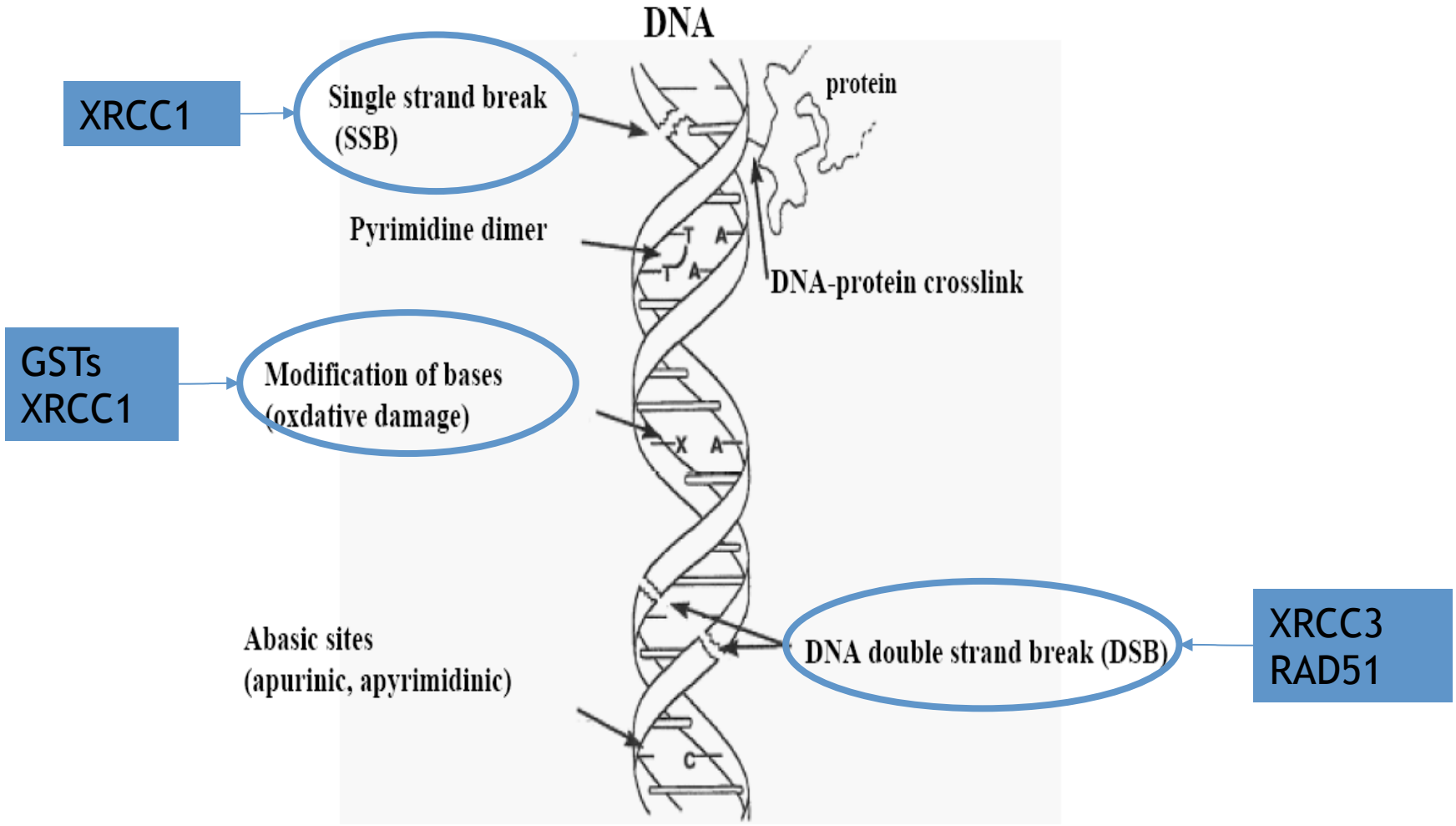
Human Genome-Wide Association Studies



GWAS permit a comprehensive scan of the genome in an unbiased fashion and thus have the potential to identify totally novel susceptibility factors.

where to look for it?

candidate gene approach



Genes related to the endogenous oxidative stress defense

- GSTM1, GSTT1, GSTA1, GSTP1
- SOD2, MPO, eNOS

- ***SOD2* (Val16Ala)** (rs4880 T/C): severe **skin fibrosis** in breast cancer

  (Andreassen CN, Radiother Oncol 2003; 69:127-135)

but other studies haven't confirmed this observation

(Green H, Radiother Oncol 2002; 63: 213-216)

(Andreassen CN, Radiother Oncol 2005; 75: 18-21)

- ***GSTP1* Ile105Val** (rs1695) (variant with low activity): **pleural thickening**

  (Edvardsen H, IJROBP 2007; 67: 1163-71)

- **variant form of the *GSTA1*: increased teleangectasia**
- ***eNOS* T allele** (lower activity): **lower risk of teleangectasia**

  (Kuptsova N, Int J cancer 2008; 122: 1333-1339)

Genes involved in the inflammatory response and in cytokine activity related to fibrosis

➢ TGFβ

- **TGFß1 509 C>T** in the promoter region: **elevated TGF ß1 serum levels**
- **TGFß1 869 T>C** and **TGFß1 915 G>C** (amino acid changes): **fibrosis** in breast cancer

(Andreassen CN, Radiother Oncol 2003; 69: 127-35)

(Andreassen CN, Radiother Oncol 2005; 75: 18-21)

but data haven't been confirmed in another study

(Andreassen CN, Int J Radiat Biol 2006; 82: 577-86)

nor for other types of tumors (cervical, endometrial, prostate tumour)

(De Ruyck k, IJROBP 2006, 65: 1240-8)

(Damaraju D, Clin Canc Res 2006; 12: 2545-54)

- **TGFß1 509 C>T: decline in erectile function** and **rectal bleeding** in prostate cancer

(Peters CA, IJROBP 2008; 70: 752-9)

Genes contributing to DNA damage signalling and cell cycle control

➢ ATM

- ***ATM* 5557G>A**: **fibrosis** and **telangiectasia** in breast cancer
  (Andreassen CN, Radiother Oncol 2005; 75: 18-21)

however results were not confirmed in other cohorts

(Andreassen CN, Int J Radiat Biol 2006; 82: 577-586)

(Ho AY, IJROBP 2007; 69: 677-84)

- ***ATM* 4258C>T (rs1800058): pleural thickening** and **lung fibrosis**
  (Edvardsen H, Radiat Oncol 2007: 2:25)

- ***ATM* sequence alterations**: **proctitis** and **decline of erectile function** with125I brachytherapy
  (Cesaretti JA, IJROBP 2005; 61: 196-202)

DNA repair genes

- **BER**: XRCC1, APEX1, OGG1, LIG3
- **NER**: ERCC2/XPD, ERCC4/XPF, RAD9A
- **HR and NHEJ**: RAD51, RAD52, XRCC3, XRCC2,NBN, LIG4, BRCA1, BRCA2

- ***XRCC3* 18067 C > T**: severe **fibrosis**

  (Andreassen CN, Radiother Oncol 2003; 69: 127-135)

but other findings could not be confirmed in the other studies

- ***XRCC3* 17893 A>G**: **late** adverse effects in cervical and endometrial carcinoma

  (De Ruyck K, IJROBP 2006; 65: 1240-8)

- ***LIG4* Asp568Asp**: late **bladder or rectal toxicity** in prostate cancer

  (Damaraju D, Clin Cancer Res 2006; 12: 2545-54)

DNA repair genes

- **BER**: XRCC1, APEX1, OGG1, LIG3
- **NER**: ERCC2/XPD, ERCC4/XPF, RAD9A
- **HR and NHEJ**: RAD51, RAD52, XRCC3, XRCC2,NBN, LIG4, BRCA1, BRCA2

- ***XRCC1* 28152G**: severe **fibrosis** and **telangiectasia** in breast cancer

  (Andreassen CN, Radiother Oncol 2003; 69: 127-35)

  (Gitopoulos G, Br J Cancer 2007; 96: 1001-7)
- ***XRCC1* 26304T**: **late** adverse effects in breast cancer
- ***XRCC1* 28152G in combination with *XRCC1* 26304T**: side effects

  (Moullan N, Cancer Epidemiol Biomarkers Prev 2003; 12: 1168-74)

In one study with only a small number of patients: no effects of *XRCC1* SNPs

(Andreassen CN, Radiother Oncol 2005; 75: 18-21)

- ***XRCC1* polymorphisms**: no significant effect in gynecological and in prostate cancer

  (De Ruyck K, IJROBP 2006; 651240-8)

  (Damaraju D, Clin Cancer Res 2006; 12: 2545-54)

Single Nucleotide Polymorphisms and radiation-induced late toxicity in prostate cancer

Cipressi et al, AIRO 2011

Case-control study on 46 patients affected by prostate cancer

GSTP1 A313G

XRCC3 c.722C>T
RAD51 c.3429G>C
RAD51 c.3392G>T

- **GSTP1c313A>G**: late rectal and bladder toxicities
- **XRCC1 c.1196A>G**: late rectal and bladder toxicities

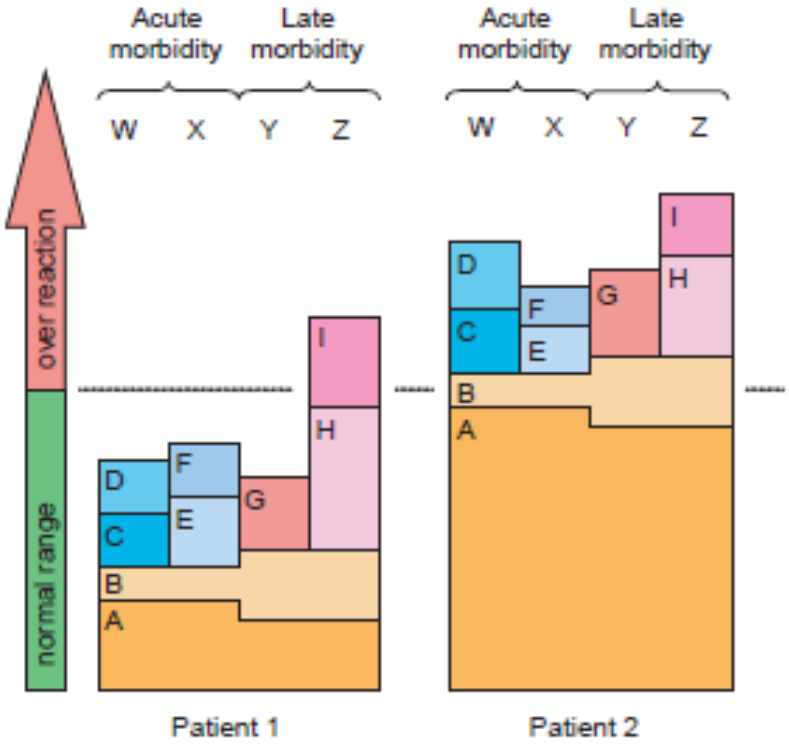
≠ *XRCC1* polymorphisms: no significant effect in prostate cancer

(De Ruyck K, IJROBP 2006; 651240-8)
(Damaraju D, Clin Cancer Res 2006; 12: 2545-54)

Bias of the available studies

- ✓ candidate gene approach is insufficient: the physiology underlying a given phenotype is very complex or poorly understood
- ✓ investigate haplotypes rather than individual SNPs (tag SNPs)
- ✓ different normal tissue damage endpoints used to evaluate radiosensitivity (basic vs complex endpoints, acute vs late vs effects considered together)
- ✓ numerous confounding factors
  - ✓ commorbidities
  - ✓ different treatments: External beam vs brachiterapy vs fractionation (BED) vs carbon ions (EBR)

Clinical normal tissue radiosensitivity: complex trait



Andreassen CN, Acta Oncologica, 2005; 44: 801-15

Conclusions

- ✓ We are still far from having a comprehensive understanding of the sequence alterations that may underlie variability in clinical normal tissue radiosensitivity.

- ✓ On the other hand, the available data seem to provide a reasonable proof of principle that the risk of radiation induced normal tissue complications among unselected cancer patients is influenced by genetic factors

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S145–S150, 2010

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doi:10.1016/j.ijrobp.2009.08.076

QUANTEC

QUANTEC: VISION PAPER

BIOMARKERS AND SURROGATE ENDPOINTS FOR NORMAL-TISSUE EFFECTS OF RADIATION THERAPY: THE IMPORTANCE OF DOSE–VOLUME EFFECTS

Søren M. Bentzen, Ph.D., D.Sc.,*† Matthew Parliament, M.D.,‡ Josepi Adam Dicker, M.D., Ph.D.,†¶ Walter J. Curran, M.D.,¶‖ Jacqueline P. and Barry S. Rosenstein, Ph.D.††

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Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1295–1296, 2010

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doi:10.1016/j.ijrobp.2009.12.017

GENEPI
Europe

REPORT

ESTABLISHMENT OF A RADIOGENOMICS CONSORTIUM

Catharine West* and Barry S. Rosenstein† On behalf of: Jan Alsner, David Azria, Gillian Barnett, Adrian Begg, Søren Bentzen, Neil Burnet, Jenny Chang-Claude, Eric Chuang, Charlotte Coles, Kim De Ruyck, Dirk De Ruysscher, Alison Dunning, Rebecca Elliott, Laura Fachal, Janet Hall, Karin Haustermans, Carsten Herskind, Tobias Hoelscher, Takashi Imai, Mayumi Iwakawa, Don Jones, Cecilia Kulich on behalf of EQUAL-ESTRO, Jan-Hans Langendijk, Peter O'Neill, Mahmut Ozsahin, Matthew Parliament, Andrzej Polanski, Barry Rosenstein, ds, Chris Talbot, Hubert Thierens, Ana Vega, Catharine West, & John Yarnold.

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0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.03.006

REPORT

*GENE*TIC *P*REDICTORS OF *A*DVERSE *R*ADIOTHERAPY *E*FFECTS: THE GENE-PARE PROJECT

Alice Y. Ho, M.D.,* David P. Atencio, Ph.D.,* Sheila Peters, B.A.,* Richard G. Stock, M.D.,* Silvia C. Formenti, M.D.,§ Jamie A. Cesaretti, M.D.,* Sheryl Green, M.D.,* Bruce Haffty, M.D.,¶ Karen Drumea, M.D.,‖ Larisa Leitzin, M.D.,‖ Abraham Kuten, M.D.,‖ David Azria, M.D., Ph.D.,# Mahmut Ozsahin, M.D., Ph.D.,** Jens Overgaard, M.D., D.M.Sc., F.A.C.R., F.R.C.R.,†† Christian N. Andreassen, M.D.,†† Cynthia S. Trop, M.D.,‡‡ Janelle Park, M.D.,§§ and Barry S. Rosenstein, Ph.D.*†‡§

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