International Conference on Modern Radiotherapy

# The range of radiosensitivity in the human population: hyper- and hypo-sensitivity

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# Indicators of radiosenitivity

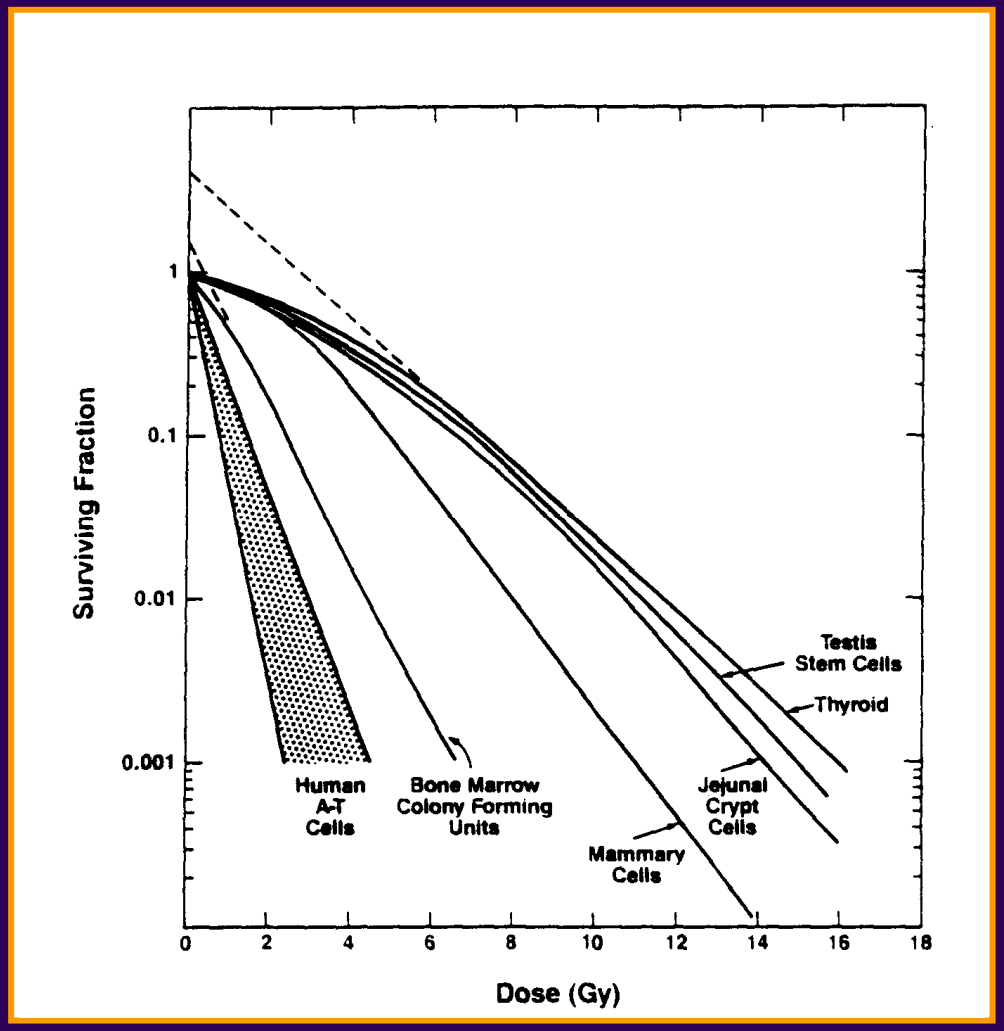
*In Patients*

- Acute reactions – eg burns
- Late reactions – eg fibrosis
- Second cancers

*In experimental systems*

- Disease indicators – eg experimental animal cancers
- Tissue indicators – normal tissue damage
- Cellular indicators – eg killing, chromosome damage etc.
- Molecular indicators – eg gene expression
- Genomic indicators – gene variants/SNPs

# Tissue radiosensitivity




*From Hall, 1994 Radiobiololgy for the Radiologist*

# Extreme radiosensitivity

*Ataxia telangiectasia*

- cellular radiosensitivity
- chromosomal radiosensitivity
- *ATM* link to DNA damage response

*Other syndromes*

- Nijmegen Breakage Syndrome (DSB repair)
- Cornelia de Lange Syndrome (sister chromatid cohesion)
- dyskeratosis congenita (telomere complex)

# Sensitivity to radiation carcinogenesis

- Gorlin syndrome
  - *multiple basal cell skin cancers in radiation fields*
- Retinoblastoma (Rb)
  - *soft tissue sarcomas in radiation fields*
- Neurofibromatosis type 1 (NF1)
  - *second cancers associated with radiotherapy of gliomas*
- Li Fraumeni syndrome (LFS)
  - *high RR of 2nd cancers related to RT*

*See Kleinerman (2009) Paediatr. Radiol. 39: 527-531*

# What about AT carriers etc?

- AT carriers show modest radiosensitivity
  - G2 assay *(Scott et al 1994 IJRB 66: S157-S163)*
  - cell cycle response *(Lavin et al 1992 Cancer Genet. Cytogenet. 60: 183-187)*
- AT carriers show ~2.4 fold elevated breast cancer risk *(Renwick et al, 2006 Nat. Genet. 38: 873-875)*

# AT carrier radiosensitivity

| | Mean | | Range | |
|---|---|---|---|---|
| Parameter | Normal | AT carrier | Normal | AT Carrier |
| G2/G1 ratio | 0.43 | 0.57 | 0.2 - 0.83 | 0.29 - 0.97 |
| G2 delay index | 72.2 | 78.6 | 58.2 - 87.1 | 55.7 - 109.1 |
| Apoptosis score | 15.8 | 21.9 | 8.3 - 23.2 | 10.8 - 32.8 |

*Finnon et al. 2008 Hum. Genet. 123: 485-493*

# Endpoints associating with cancer risk

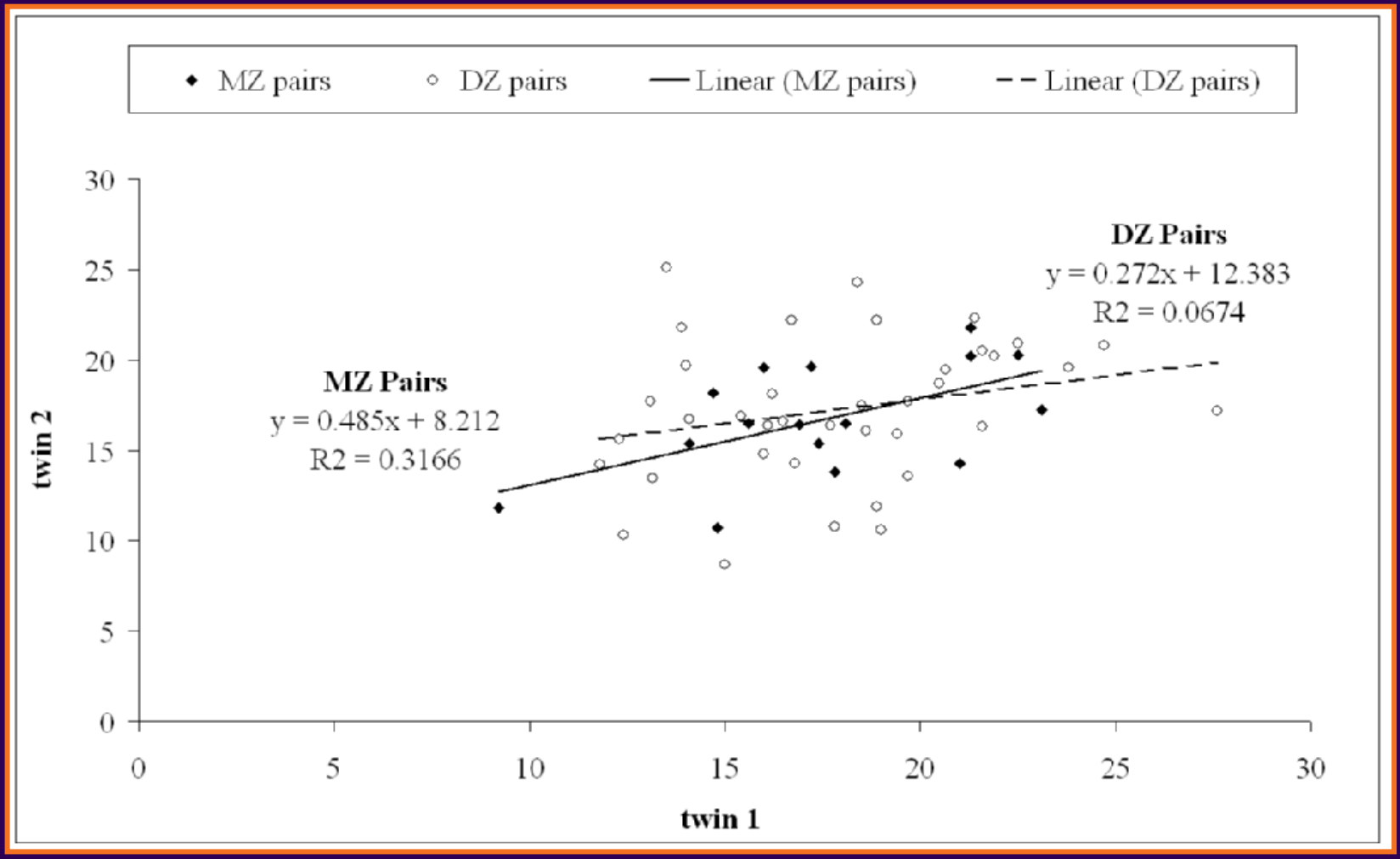
- G2 chromosomal radiosensitivity
  *(Scott 2004 Cytogenet. Genome Res. 104: 365-370)*
- Radiation-induced apoptosis
  *(Camplejohn et al 2003 Br. J. Cancer 88: 487-490)*
- Radiation-induced cell cycle delay
  *(Hu et al 2002 Environ. Mol. Mutagen. 39: 208-215)*

# Twin study of radiosensitivity

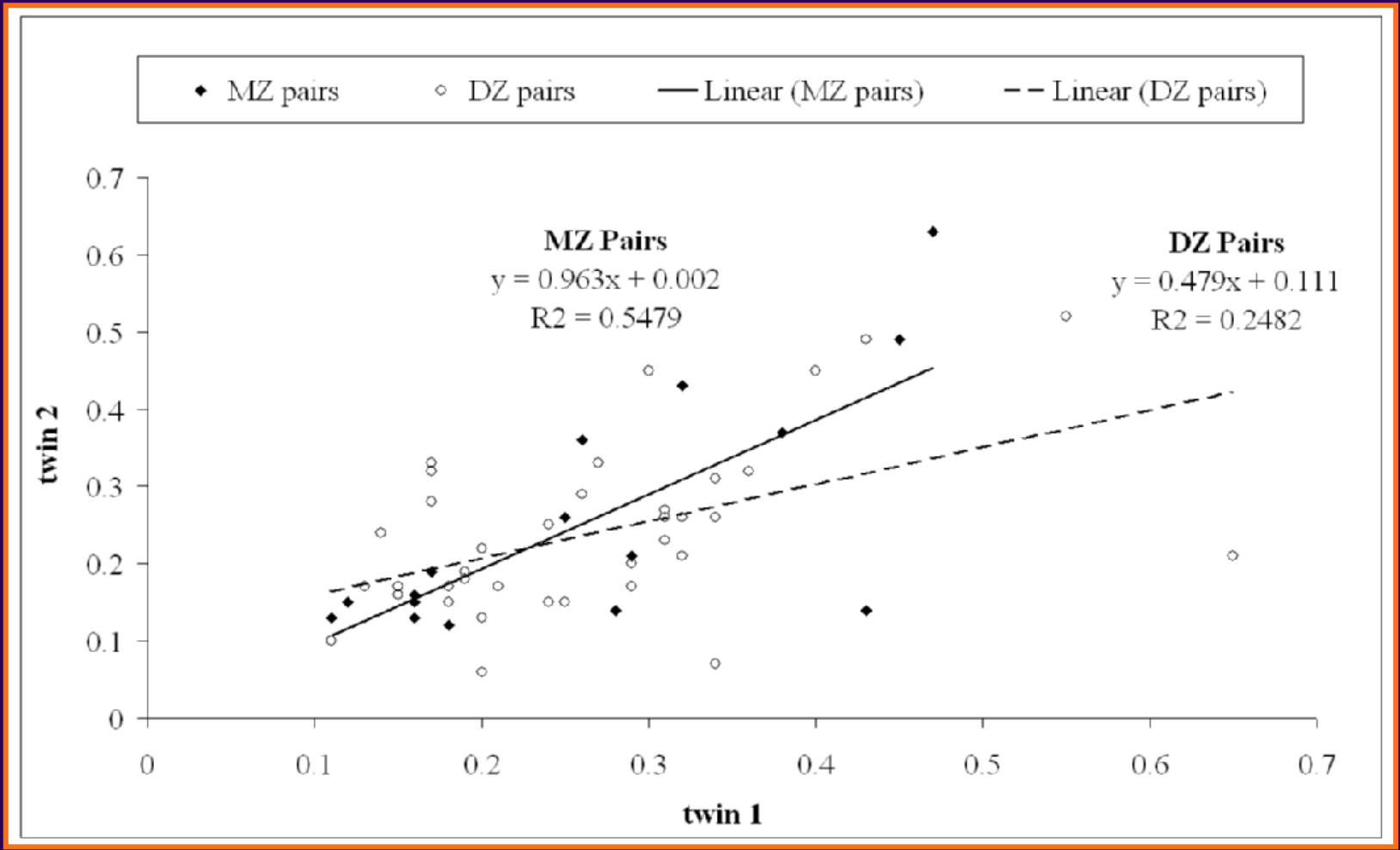
## Mean and ranges of radiosensitivity in 54 twin pair samples

| Parameter | x-ray dose (Gy) | mean ± SD | Range |
|---|---|---|---|
| G2/G1 ratio | 3 | 0.25 ± 0.01 | 0.06 - 0.65 |
| Apoptosis score | 5 | 17.4 ± 0.5 | 8.7 - 27.6 |

# Intra pair correlations cell cycle



# Intra pair correlations apoptosis



# Heritability estimates

Based on AE model -

Cell cycle:

68% (95% CI 44-82%)

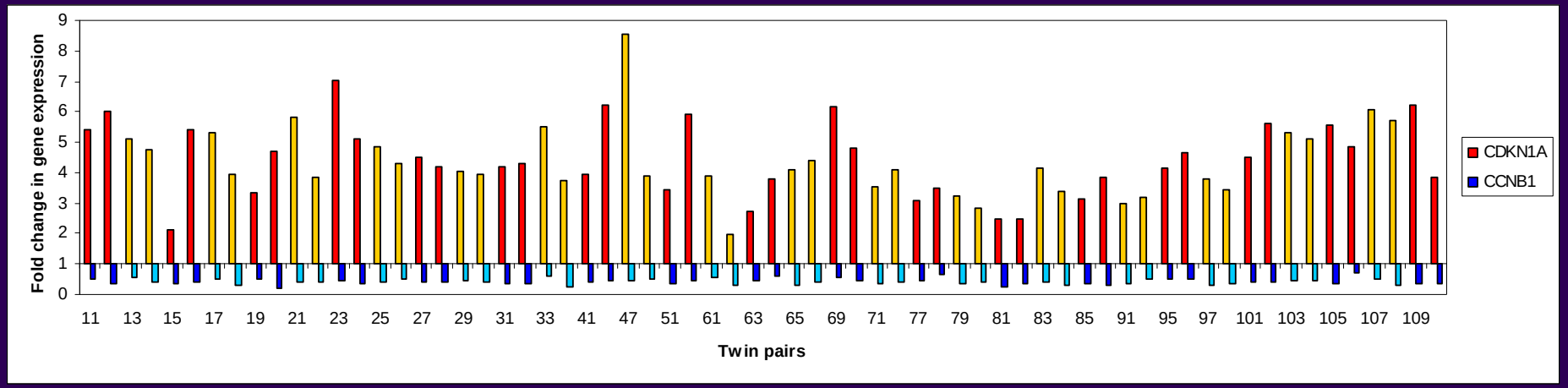
Apoptosis:

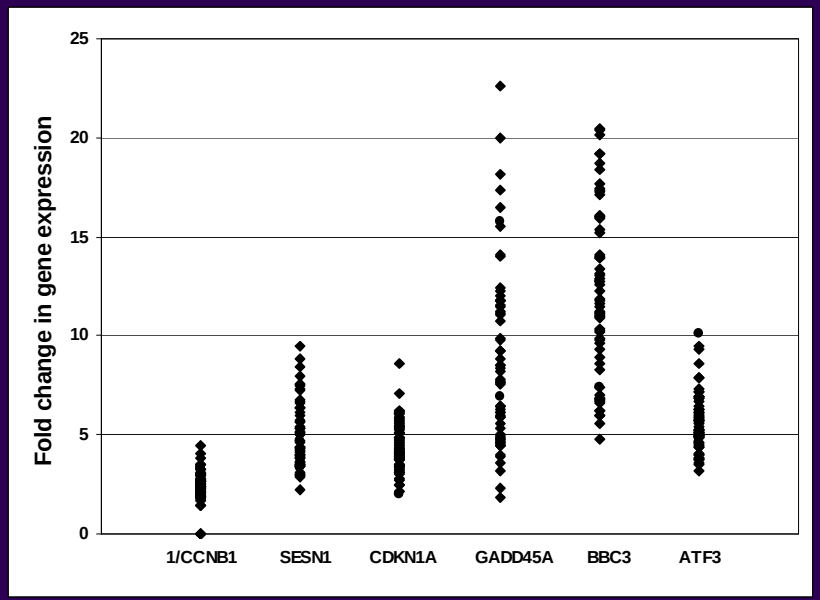
59% (95% CI 22-79%)

# Twin radiosensitivity

- Wu et al (2006) Cancer Res. 66: 5993-5996 (G2 assay)
- Camplejohn et al (2006) Br. J. Cancer 95: 520-524 (apoptosis)
- Finnon et al (2008) Hum. Genet. 123: 485-493 (cell cycle apoptosis)

# Gene expression variation in twins






*Badie et al, unpublished*

# Gene expression and RT reactions

- Late tissue reaction classifiers

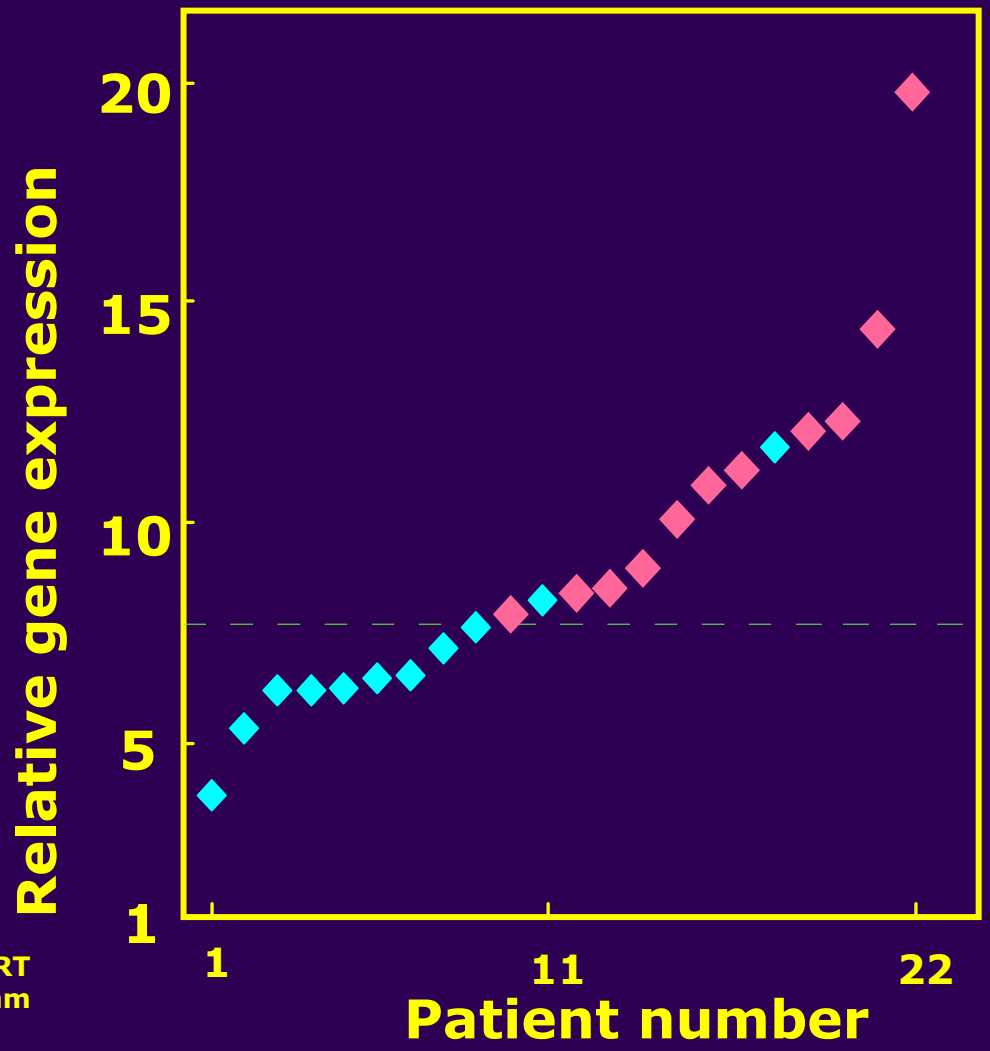
  *(eg Svensson et al 2006 PLOS Med 3: e422)*

- Acute tissue reaction classifiers

  *(eg Reiger et al 2004 PNAS 101: 6635-6640)*

*Consensus on genes sets with predictive power not yet achieved*

# CDKN1A as a marker of severe early radiation toxicity




◆ severe reactor
◆ normal reactor

Prediction of reaction sensitivity>90%



*Badie et al 2008 Br. J. Cancer 98: 1843-1851*

# Modification of risk is complex - *Xrcc2* hemizygosity in mice

*Apc*$^{min/+}$*Xrcc2*$^{+/-}$ compared to *Apc*$^{min/+}$*Xrcc2*$^{+/+}$ :

- have reduced spontaneous intestinal and mammary tumour yields
- have elevated mammary cancer yields following 2 Gy x-ray
- show no increase in intestinal tumour yields following 2 Gy x-ray

*Gillan, Thacker et al, in preparation*

# Summary

- Extreme radiosensitivity exists in the human population
- A wide range of radiosensitivity exists in the clinically normal human population
- Genetic factors contribute significantly to this variation

# Challenges

- Knowledge of genes, proteins, pathways affecting radiosensitivity is incomplete
- Relationship between clinical indicators (eg early burns, late fibrosis, second cancers etc) is essentially unknown
- Causes of radiosensitivity likely to have some tissue specificity
- Relationship between intrinsic radiosensitivity and tumour radiosensitivity is unclear but might be clinically important