GENETIC SUSCEPTIBILITY

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In the routine application of radiation protection, the implicit assumption is made that the human population is homogeneous in its response to radiation, except for a small number of individuals, such as ATM homozygotes, who are easily identified by their clinical symptoms. Recent evidence challenges the validity of this assumption and points to the existence of a radiosensitive sub-population.

In the long run it may prove possible to use global gene expression arrays to identify genes, or families of genes, which control radiosensitivity, but this approach has not, to date, proved to be productive. The alternative strategy is to investigate low frequency, high penetrance genes such as ATM, BRCA1 and RAD9, that are already known, or suspected, of influencing radiosensitivity, and to test their effect on both deterministic and stochastic endpoints using knock-out mice.

Ocular cataracts. Mice heterozygous for ATM, BRCA1 or RAD9 form cataracts earlier than wild type animals when exposed to x-rays. Double heterozygotes (ATM/RAD9) are even more radiosensitive.

Oncogenic transformation in mouse embryo fibroblasts. In comparison with wild type animals, mice heterozygous for the Atm, BRCA1, or Mrad9 gene showed a doubling of transformation induced by γ-rays, while the double hets showed a trebling of the incidence of oncogenic transformation.

Apoptosis in mouse thymocytes. The data for the incidence of apoptosis by γ-rays in mouse thymocytes are a mirror image of the transformation data. Haploinsufficiency for Atm, BRCA1 or mRad9, reduces the incidence of cells undergoing apoptosis, while haplo-insufficiency for both genes reduces apoptosis further.

Conclusion. There is mounting evidence from animal studies that heterozygosity for several genes, leads to radiosensitivity. It is already known that several percent of the human population are heterozygous for the comparable genes and thus may constitute a radiosensitive sub-population.