EDITORIAL

Germline minisatellite mutations in the offspring of irradiated parents

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Epidemiological studies to date have not provided clear evidence of heritable effects of radiation exposure in humans. Consequently, current genetic risk estimates for radiation are derived from measured germline mutation frequencies in male mice for a small number of marker genes, which have very low spontaneous and induced mutation frequencies (typically induced by radiation at about 1 in 100,000 per gene per Gy of x-rays) (International Commission on Radiological Protection 2007, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2010).

An investigation of the raised incidence of leukaemia and non-Hodgkin lymphoma among children living in Seascale near the Sellafield nuclear complex in North-west England showed a statistically significant association with paternal employment at Sellafield and the recorded external radiation dose prior to conception (Gardner et al 1990) and triggered a large volume of work on the possible health consequences in the offspring of fathers who had been exposed to radiation (paternal preconceptional irradiation, PPI). A review of many subsequent studies in various other radiation-exposed groups (Kinlen et al 1993, McLaughlin et al 1993, Little et al 1994a, 1994b, Draper et al 1997, Maconochie et al 1999) led the Committee on Medical Aspects of Radiation in the Environment (COMARE) to conclude in its 7th Report (Committee on Medical Aspects of Radiation in the Environment (COMARE) 2002) that there was no convincing evidence to suggest that ionising radiation alone at the doses to which male nuclear industry radiation workers have been exposed results in an increased incidence of childhood cancer, a conclusion reached also by others (Little et al 1995, Dickinson and Parker 2002, Wakeford 2003). In its 8th report COMARE also found ‘little epidemiological evidence that pregnancy outcomes in general are related to parental exposure to radiation. If there is an association, it is most likely a link between paternal (not maternal) radiation exposure and incidence of stillbirths and neural tube defects (spina bifida and anencephaly)’ (Committee on Medical Aspects of Radiation in the Environment (COMARE) 2004).

A number of reports suggested an elevation in mutation frequencies in offspring of radiation-exposed groups. In particular, analysis of a Belarusian population exposed as a result of the Chernobyl nuclear accident suggested excess minisatellite mutations (Dubrova et al 1996, 1997). A similar magnitude of excess risk was suggested in a population exposed as a result of nuclear weapons tests in Kazakhstan (Dubrova et al 2002), and in a study of persons living along the Techa river and exposed to discharges from the Mayak nuclear plant in Russia (Dubrova et al 2006), the parental gonadal doses in which are likely to be considerably higher than in the Belarus studies. These results are in striking contrast to the negative findings in relation to elevation of minisatellite frequencies in offspring of Sellafield workers implied by the study of (Tawn et al 2014) published in this issue of the Journal, in offspring of the Japanese atomic bomb survivors (Kodaira et al 1995, Satoh et al 1996, Kodaira et al 2004), and in offspring of various other exposed groups (Livshits et al 2001, Kiuru et al 2003, Slebos et al 2004, Tawn et al 2011); negative evidence also comes from the absence of excess minisatellite mutations in sperm DNA from seminoma patients after radiotherapy (May et al 2000). Shorter microsatellite aberrations have not been associated with pre-conceptional radiation

There is a large body of animal data in relation to a similar class of aberrations, so called expanded simple tandem repeat (ESTR) loci, reviewed elsewhere (Little et al 2013). ESTRs are structurally similar to microsatellites, simply being longer (Bouffler et al 2006); however as noted by Little et al (2013) ESTRs are very different in their mutational characteristics from minisatellites, and so the relevance of findings for this endpoint to the present study (Tawn et al 2014) is questionable. Expansions of specific microsatellite sequences are known to be associated with several human genetic disorders (Mirkin 2007, Batra et al 2010) although no specific roles for ESTR expansions in human disease are known.

Possible reasons for the discrepancy between the positive findings of the University of Leicester environmental exposure studies and those of the present study (Tawn et al 2014) and others should be considered. The study of Dubrova et al (1996) is very difficult to interpret because of use of non-comparable UK controls; the results should therefore be largely discounted. Gonadal doses were only estimated in the second of the two Belarus studies, and are likely to be particularly uncertain, being calculated via group-averaged estimates of exposure from various sources by district (Dubrova et al 1997); however the errors are likely to be Berksonian in form, and so would not be expected to bias the dose response (Carroll et al 2006). The gonadal doses in some groups (Kodaira et al 2004, Tawn et al 2011), are considerably higher, and given at much higher dose rates, than those in the environmental exposure studies of Dubrova et al (1996, 1997, 2002, 2006), in the present study (Tawn et al 2014) and in the three Chernobyl liquidator studies (Livshits et al 2001, Kiuru et al 2003, Slebos et al 2004). The timing of exposure in relation to the time of sampling is variable, but in the Chernobyl studies of Dubrova et al children were born about 8 years after parental exposure from the accident, a little bit later than the corresponding interval (which was generally less than 6 years) in the Chernobyl liquidator studies (Livshits et al 2001, Kiuru et al 2003, Slebos et al 2004). The period of exposure, and in particular high dose exposure, in relation to the period of birth of the index children in the present study (Tawn et al 2014) is likely to be comparable with that of the Techa river study (Dubrova et al 2006). The minisatellite probes used in the various studies differ, but it is notable that those in the present study (Tawn et al 2014) and in one of the atomic bomb survivor studies (Kodaira et al 2004) are identical with those used by Dubrova et al.

Where does this leave the issue of radiation-induced minisatellites? On the face of it the discrepancy between the positive findings in the four environmental exposure studies from the University of Leicester (Dubrova et al 1996, 1997, 2002, 2006) and the entirely negative ones in the present study (Tawn et al 2014), and in the other datasets discussed above (Kodaira et al 1995, Satoh et al 1996, May et al 2000, Livshits et al 2001, Kiuru et al 2003, Kodaira et al 2004, Slebos et al 2004, Tawn et al 2011) are troubling, and somewhat difficult to reconcile. One would generally expect that exposures at lower dose rate, a characteristic of all the environmental exposure studies of Dubrova et al, would have reduced effect; however, even if that was not the case, the present study (Tawn et al 2014) is also characterized by low dose-rate exposure, and is negative. In some of the radiotherapy studies there was concomitant chemotherapy (Tawn et al 2011); however this had no effect on minisatellite mutation rate. In any event, even if credence were to be attached to the positive findings in the four environmental exposure studies of the University of Leicester (and as noted above, the first of these (Dubrova et al 1996) is effectively uninterpretable), and if the negative findings of other studies are set aside, it remains unclear what relevance such genomic aberrations may have for chronic disease in humans (Bouffler et al 2006, Little et al 2013).
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