

# NEW PERSPECTIVES FOR DETECTING ENVIRONMENTALLY INDUCED GENETIC CHANGES IN THE GERM-LINE

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Before the discovery of the role of mutation in cancer, heritable mutations and genetic risk assessment were the main focus of environmental mutagenesis. However, despite years of intensive search and strong evidence for the existence of germ cell mutagens in rodents, conclusive evidence for human germ cell mutagens could not be obtained, ostensibly because of technical limitations and the intrinsic complexity of the epidemiological approach.

Recently, new knowledge on the organization of the human genome and technical developments for DNA sequencing have opened new perspectives for investigating de novo heritable changes and the possible impact of environmental mutagens on the germline genome (Singer and Yauk, *Environ Mol Mutagen* 51, 919-928, 2010). Among the about 40 agents shown to induce mutations in rodent germ cells, a few have been identified that would be amenable to an epidemiological investigation in highly exposed human cohorts such as cigarette smoke, chemotherapeutic drugs and ionizing radiation (DeMarini, *Environ Mol Mutagen*, 53, 166-172, 2012). A tiered approach has been recommended by an ad-hoc working group on environmentally induced germline mutation analysis (ENIGMA), established by the American Environmental Mutagenesis and Genomics Society (Yauk et al., *Mutation Research* 752, 6-9, 2013). This approach comprises foundational studies to establish background genomic variability, studies with animals under genetically and environmentally controlled conditions, and accurate exposure assessment. Definitive studies should also aim to include epigenomics, creating an integrated understanding of the epigenetic, genetic, and environmental factors explaining heritable human disease.

It has been proposed that, when genomic data became available, a IARC-type panel could be established, to assess the data and proceed to a classification of exposures for their likelihood of being human germ cell mutagens, by an approach similar to that in place for carcinogens (DeMarini et al., 2012).

Finally, this revived interest on germ-line mutations has also met the attention of the Organization for Economic Cooperation and Development in the frame of its initiative to produce an inventory of documents for the so-called Adverse Outcome Pathways (AOP). This initiative aims at integrating knowledge of the relevant chemicals' interactions with biological systems (i.e. the molecular initiating events) with knowledge of the relevant biological responses or perturbations leading to the apical outcome of interest, to make the best possible use of mechanistic information for risk assessment. In this frame, projects are underway to prepare AOPs for well-characterized mutational pathways in the germ-line, such as the induction of aneuploidy in mammalian oocytes by tubulin binding chemicals, or the induction of gene mutations in spermatogonia by alkylating agents.

The presentation will shortly discuss this novel scenario of opportunities for germ cell mutagenicity studies.