Assessing Radiation Exposure Claims Using Next-Generation Genomics

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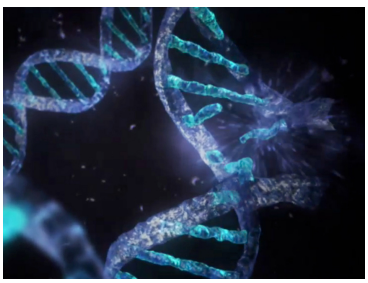
How Can Exposure to Ionizing Radiation Occur?

Ionizing radiation (IR) is all around us: in the air we breathe, the water we drink, the food we eat, and the ground on which we stand. Radiation is emitted from numerous natural and man-made sources including the sun, industrial & scientific equipment, and particulates from the earth. Radioactive particles decay creating daughter particles and emit radiation in a process that, in some cases, can last for tens of thousands of years. Radiation is considered "ionizing" if it has enough energy to "knock" an electron off of an atom or molecule and becomes extremely significant when it involves a living tissue, like blood and skin, where it can lead to mutations in DNA.



NASA illustration of cosmic radiation damaging DNA within a cell.

Since radiation is ubiquitous and occurs naturally, we routinely encounter extremely small, harmless amounts every day. Naturally occurring radioactive materials (NORM) are one potential source of IR exposure. There are natural and intentional processes that bring these materials to the surface in large quantities. The term technologically enhanced naturally occurring radioactive materials (TENORM) is used when human activities concentrate or expose radioactive materials, incidentally or intentionally, during the handling and treatment of ores, soils, water, or other natural products. In addition to the production of TENORM, occupational and incidental exposures can also take place when attempting to dispose of or reuse TENORM. Issues of occupational exposure arise when workers have the potential to be exposed to radioactive material on the job. Occupational ionizing radiation exposure does not solely come from the ground, it can also be produced by X-ray equipment and atomic particle accelerators used in research, medical, and industrial settings. When employees have worked at locations where they believe radiation exposure was/is a possibility, either intentionally or unintentionally, employers can be the target of blame for those exposures.

How Does Exposure to Ionizing Radiation Impact Genes?

Avoiding all exposure to ionizing radiation is impossible, but unnecessary exposure should be avoided since it can have detrimental health effects, such as causing cancer, typically after a period of latency. DNA is the material in a cell that encodes genes and is made of a series of building blocks named nucleotides and commonly represented as A, C, T, G. IR exposure causes DNA damage and cells possess mechanisms to repair damaged DNA. However if the damage goes unrepaired, various alterations to nucleotide composition occur. If these alterations, also known as mutations, occur in a vital part of the gene its function can be modified or turned off completely. Regardless of the source of the IR, the potential for damage to DNA is the same. Depending on the specific gene, type of mutation, and the tissue in which the damage occurs the potential for the development of disease increases. The type and location of the cancer, however, can be influenced by the radionuclide to which a person was exposed. For instance, iodine, vital to thyroid function, localizes to the thyroid when ingested and radioiodine (^{131}I) exposure, typically from nuclear fallout, will specifically increase the risk of thyroid cancer over other types of cancer. Similarly, strontium (^{90}Sr), accumulates in skeletal tissues, areas that are otherwise high in calcium, and increase the risk for developing bone cancer, cancer in surrounding soft tissues, and leukemia. In addition to cancer, radiation exposure may also cause birth defects such as mental retardation and heart disease in adults.

Implications for Disease Etiology

After diagnosis of a major illness, such as cancer, doctors and patients want to understand the etiology of the disease as it can often help with the treatment. Diseases can naturally occur through genetic disorders, such as von Hippel-Lindau syndrome or due to exposure to a toxicant such as IR. It can often be hard to distinguish whether a disease was engendered by natural causes or by exposure to a toxicant. In an attempt to address the etiology, epidemiological studies are performed to investigate the patterns, causes and effects of diseases in defined populations. The objective is to determine why and how often diseases affect different groups of people and by observing trends in the population. This type of study is very helpful in public health when trying to improve health conditions and implement safety guidelines and procedures. Although it can reveal risk factors associated with the disease, it cannot truly distinguish an individual that was exposed to a toxicant from one whose illness arose for reasons unrelated to exposure. This has presented an opportunity for significant vagary in the prosecution and defense of toxic tort claims. Fortunately, for both the individuals impacted by a disease and the corporations deluged with claims, genomic science is now being used to bring clarity and understanding to elucidate the sources of diseases. For the affected individual, it provides better treatment decisions and for the toxic-tort litigator, a better assignment of responsibility.

Applying Next Generation Genomics

Technology advancements in the field of Genomics have led to major scientific and medical breakthroughs. Next Generation Sequencing (NGS) is a powerful tool to study a person's genes and how the genes are turned on and off in response to cues from the environment in a process called gene expression. IR exposure leaves an identifiable, quantifiable mark on gene expression and can be used to detect if radiation exposure took place. This measureable change can be used to determine if an individual's gene expression profile follows that of an IR-exposed gene expression profile and whether it is statistically different from a normal non-exposed gene expression profile. This allows for confirmation or denial of exposure.

In addition, NGS and other methods can be applied to look at the sequence of DNA to identify mutations that can address the question of predisposition and exposure. Mutations in certain genes are associated with an increased risk of developing diseases or may be associated with exposure. Some mutations can be inherited from parents while others are acquired during an individual's lifetime. Predisposition is an inherited mutation that, in previous studies, has been associated with an increased risk of developing a given disease. If a person was born with a malfunctioning gene, the likelihood that IR was the sole causative factor in disease development is greatly diminished. If an acquired mutation is identified and found to be associated with disease development, the potential cause of that mutation must be deduced. Some acquired mutations are nown to be associated with lifestyle choices, such as smoking or obesity. others, however, may only have been present in radiation exposed populations.

Some researchers develop simple individual tests built around low cost techniques in order to give a quick answer to questions of disease source or type. These types of tests, like NGS, have their place in the toolkit used by doctors in the treatment of patients. However, unlike other technologies, Next Generation Genomics can provide the necessary data to better assign responsibility and therefore definitive verdicts. For toxic tort cases, a careful study of the scientific peer reviewed literature is required to find applicable and pertinent research. In the case of radiation exposure, a number of studies have reported predictive gene signatures capable of distinguishing not only if radiation exposure occurred, but also the radiation dose to which a person was exposed. With advanced genomics techniques, these studies can be applied to relevant IR-related toxic tort litigation.

Admissibility

One area of concern for all new technology is the application of the Frye and Daubert standards for the admissibility of new science. Genetic and Genomic testing are no longer new science. In the United States, 100% of the Top 100 Cancer Hospitals currently utilize Genetic or Genomic testing to classify the source of tumors and determine the appropriate treatment protocol. Most insurance companies, often the last to accept new technology

until significant efficacy and clinical utility has been demonstrated, now offer coverage for many types of Genomic and Genetic testing. ArrayXpress has been the provider of genomics analyses in legal cases where genetic evidence was admitted and the jury considered the evidence in their decision. There are a number of other cases in progress where judges, at both the State and the Federal level, have ordered the tissues be provided and the Genomic and Genetic testing be performed.

With Next Generation Genomics technologies the etiology of many previously enigmatic diseases has been made clear. Additionally, gene expression signatures have been developed to determine whether exposure to ionizing radiation has taken place. These two developments grant the court the evidence needed to distinguish those individuals exposed from those who were not exposed and can potentially put an end to the long, drawn-out cases with a definitive answer concerning exposure.

The Company

AX provides an end-to-end service. We work with the client and their medical and toxicology experts to review the pathology reports and the claims and then design the most appropriate and scientifically valid approach to determine exposure or causation. We then use our internally developed data sets or integrate new data sets from peer-reviewed published literature, to address the disease and the mode of action. We actively collaborate with the legal team in the development of affidavits to secure the necessary tissue(s), discriminated by an external pathologist, for genomic testing. We conduct the laboratory work, sequencing, analyze the data using state-of-the-art bioinformatics tools, and provide written reports to aid in the confirmation or rejection of the scientific hypothesis. These data are then submitted to the medical and toxicological experts for their subsequent evaluation and conclusions. Upon the client's request we can also provide expert or fact witness testimony, attorney assistance, and supporting research during the conduct of a case.

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Your Contract Research Partner for Next Generation Genomics

ArrayXpress is a Next Generation Genomics and Bioinformatics services company specializing in Toxic Tort litigation, Bioprocess Optimization, and Functional Genomics studies. AX designs and conducts investigational studies to examine the validity of toxic tort claims. AX is able to apply extremely powerful and unparalleled analytical, bioinformatics, and statistical, capabilities to such scientific ventures. We can be reached at toxictort@arrayxpress.com or via our website at www.arrayxpress.com.