

Scientists find genetic link to mesothelioma

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Scientists have found that individuals who carry a mutation in a gene called *BAP1* are susceptible to developing two forms of cancer – mesothelioma, and melanoma of the eye. Additionally, when these individuals are exposed to asbestos or similar mineral fibers, their risk of developing mesothelioma, an aggressive cancer of the lining of the chest and abdomen, may be markedly increased.

The study, published online Aug. 28, 2011, in *Nature Genetics*, describes two U.S. families with a high incidence of [mesothelioma](#), as well as other cancers, associated with mutations of the *BAP1* gene. The research was funded by the National Cancer Institute (NCI), part of the National Institutes of Health, and led by scientists at the University of Hawaii Cancer Center, Honolulu, and Fox Chase Cancer Center, Philadelphia.

Mesothelioma tumors are typically associated with asbestos and erionite exposure. Erionite, a naturally occurring mineral fiber similar to asbestos, is found in rock formations and volcanic ash. Deposits have been located in at least 12 states.

Only a small fraction of individuals exposed to erionite or asbestos actually develop mesothelioma, one of the deadliest forms of cancer that kills about 3,000 people each year in the United States, with half of those diagnosed dying within one year. Additionally, rates of new cases of mesothelioma in parts of the world, including Europe and China, have risen steadily over the past decade.

"This discovery is a first step in understanding the role of the *BAP1* gene

and its potential utility when screening for mutations in those at high risk," said Michele Carbone, M.D., Ph.D., study co-leader and director of the University of Hawaii Cancer Center. "Identifying people at greatest risk for developing mesothelioma, especially those exposed to dangerous levels of asbestos and erionite worldwide, is a task made easier by virtue of this discovery."

Joseph R. Testa, Ph.D., study co-leader and Carol and Kenneth E. Weg chair in Human Genetics at Fox Chase Cancer Center, added, "This is the first study to demonstrate that individual genetic makeup can greatly influence susceptibility to mesothelioma. People exposed to dangerous levels of asbestos or erionite, those with a strong family history of mesothelioma, or those who have been previously diagnosed with a rare tumor of the eye known as uveal melanoma, may benefit from this new discovery."

The study found evidence that some people with *BAP1* gene mutations also developed breast, ovarian, pancreatic or renal cancers, suggesting the gene mutation may be involved in multiple cancer types. Only about 10 percent of women with an inherited risk of breast or ovarian cancer carry mutations in the genes *BRCA1* or *BRCA2*, which are known to be associated with those diseases. Consequently, some inherited risk of breast and ovarian cancer may stem from mutations in *BAP1* genes. "Also, it appears likely that other genes, in addition to *BAP1*, will be found to be associated with elevated risk of mesothelioma," said Testa.

The researchers first suspected that mutations in the *BAP1* gene might underlie mesothelioma in people with a strong family history of the disease after noticing genetic changes in or near other stretches of DNA where the *BAP1* gene is located. Looking more closely at two families with unusually high rates of mesothelioma, they saw that every person who had provided a sample and had developed mesothelioma or melanoma of the eye also carried mutations in the *BAP1* gene. Further

investigation led to sequencing the gene in 26 individuals who had developed mesothelioma but did not have a family history of the disease. Tumors from about 25 percent of this group carried mutations in the *BAP1* gene, and in two cases the mutations were inherited. Both of the individuals with inherited [mutations](#) had previously developed melanoma of the eye.

"The discovery that the *BAP1* gene is involved in a new [cancer](#) syndrome characterized especially by uveal [melanoma](#) and mesothelioma provides yet another example of the critical importance of the detailed genetic analysis of human tumors," said Donald Blair, Ph.D., NCI. "Such analysis can lead to the discovery of genes involved in the same tumors that arise spontaneously. This is an important advance in developing our understanding of the biological mechanisms underlying these tumors."

Another component of NIH, the National Institute of Environmental Health Sciences, is continuing to work on this public health problem in a number of critical research areas, including understanding how people, especially children, are exposed to asbestos. Efforts are also under way to improve knowledge of what makes fibers hazardous in terms of their physical characteristics and an individual's susceptibility.

More information: Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, Cox NJ, Dogan AU, Pass H, Trusa S, Hesdorffer M, Nasu M, Powers A, Rivera Z, Comertpay S, Tanji M, Gaudino G, Yang, H and Carbone M. Germline BAP1 mutations predispose to malignant Mesothelioma. Nature Genetics. Online August 28, 2011. [DOI: 10.1038/ng.912](#)

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