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ASHG 2008: In-Common Loss of Heterozygosity in 3 Carcinomas May Guide Treatment

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November 20, 2008 (Philadelphia, Pennsylvania) — Cleveland Clinic researchers have identified common genomic changes in the epithelium, the stroma, or both regions in 3 types of carcinoma. Among the 15 in-common genetic markers found, 11 were specific to the stromal compartment. The presence of common markers in multiple cancer types holds promise for future therapeutic options.

The group also identified 1 marker associated with tumor grade in breast cancer and prostate cancer. Another marker was linked to nodal metastases in breast cancer and head and neck squamous cell carcinomas (HNSCC).

The study was presented here at the American Society of Human Genetics 58th Annual Meeting, the day after a press briefing with senior author Charis Eng, MD, PhD, director and chair of the Cleveland Clinic Genomic Medicine Institute, and professor and vice chair of the Department of Genetics, Case Western Reserve University School of Medicine, in Ohio.

"We focused on 'in-common' because that...probably represents the most important genes, possibly posing a new target for treatment," Dr. Eng told *Medscape Pathology & Lab Medicine*. "They must be very important genes if they are truly in-common in all the 3 solid tumors.... Squamous cells have different histology than the other 2 carcinomas, so it's something that's important in carcinoma in general," Dr. Eng explained.

Many studies focus on cells of the tumor epithelium, but the tumor stroma — consisting largely of fibroblasts and structural elements — also contains genetic alterations important in tumor growth and development. "The whole compartment, the whole stroma, is now a new target," said Dr. Eng, "because [up to now], we were targeting the epithelium, and we should be thinking about the environment and the microenvironment."

This investigation focused on genomic changes in tumor epithelium and/or tumor stroma in at least 2 of the 3 types of carcinoma studied: breast cancer (n = 175), prostate cancer (n = 116), and HNSCC (n = 122) tumors. Tumor epithelium and stroma were separated by microdissection, and each sample was genotyped and subjected to genomewide analysis for loss of heterozygosity (LOH). LOH is frequent in tumor cells and has been reported in the literature to be the most frequent mutation in breast tumor DNA. LOH may entail loss of tumor suppression or unmask harmful mutations in the affected genomic region.

Medscape Pathology & Lab Medicine spoke with presenter Mohammed S. Orloff, PhD, from the Genomic Medicine Institute at the Cleveland Clinic, in Ohio. "The hypothesis was that we have common genetic variation throughout the LOHs...in multiple cancer types. These are 3 cancer types that we study in the lab," said Dr. Orloff. "The 15 LOHs were in-common for the cancer types, but there's the other issue that we're also looking at: the compartments — that it's epithelium or the stroma. So some [LOHs] were in the epithelium, some were in the stroma, and some we find in both the epithelium and the stroma."

Of the 15 LOHs in-common for the 3 cancers, 11 LOHs were present only in stromal cells, 2 were specific to epithelial cells, and 2 were found in both epithelium and stroma. The study also identified genes within 100 kilobases of each LOH and took note of several signaling pathways associated with genes in the LOH regions: the Wnt receptor signaling pathway, a steroid hormone-receptor signaling pathway, a Ras protein signal transduction pathway, and a pathway that regulates programmed

cell death.

The study also identified a genetic marker near the *TMPRSS6* gene that was associated with tumor grade specifically in prostate cancer and breast cancer epithelium. Another genetic marker, near the *DEGS2* gene, was associated with regional nodal metastases in the stroma of HNSCC and in breast cancer. These LOHs appear to be associated with clinicophysiological features of the tumors.

As the authors summarized in the abstract, "our observations help to limit the number of molecular targets for treatment or prevention across several common carcinomas, hence facilitating more precise and compartment-specific therapeutic options."

Comoderator Cynthia C. Morton, PhD, professor of Obstetrics, Gynecology and Reproductive Biology and professor of Pathology, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, also discussed the study with *Medscape Pathology & Lab Medicine*.

"I think one thing...people are looking for these days are previously unsuspected overlaps that lead to the applications of drugs that are already in practice, and approved, and efficacious. The drug pipeline is so long nowadays," said Dr. Morton.

"You can find a drug that maybe — when you look at 2 diseases and you do gene-expression analyses and you find that they're related in some way that you didn't suspect — you can try that drug in a different disease, and perhaps really speed up the time for some treatment," Dr. Morton suggested. "So this [study] could be something that would lead to that."

Dr. Eng, Dr. Orloff, and Dr. Morton have disclosed no relevant financial relationships.

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