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NCI Team Reports on NCI-60 Cancer Cell Panel Exome Sequence Resource

By a GenomeWeb staff reporter
NEW YORK (GenomeWeb News) – Researchers from the National Cancer Institute have sequenced the protein-coding portions of the NCI-60 human cancer cell line genomes, using the data to look for genetic contributors to drug response in the well-characterized cell line panel.

As they reported online today in *Cancer Research*, the researchers initially used whole-exome sequence data for the 60 cancer cell lines to put together a list of mutations suspected of being cancer-specific.

By folding in drug response data for hundreds of approved or proposed anti-cancer agents, meanwhile, the group was also able to start looking for coding variants within the NCI-60 lines that corresponded to enhanced or subdued responses to those compounds — a search that uncovered apparent pharmacogenetic roles for several genes that are frequently mutated in cancer.

"[W]e identify pharmacogenomics correlations between specific variants in genes such as TP53, BRAF, ERBBs, and ATAB5 and anti-cancer agents such as nutlin, vemurafenib, erlotinib, and bleomycin," co-corresponding authors Paul Meltzer, a genetics researcher at NCI, and Yves Pommier with NCI's Laboratory of Molecular Pharmacology, and their colleagues wrote, "showing one of many ways that the data could be used to validate and generate novel hypotheses for further investigation."

Already more than two decades old, the NCI-60 panel has been tapped for a variety of past studies — from targeted mutation testing and protein phosphorylation profiling to studies of cancer metabolism or of expression signatures associated with treatment resistance.

For the current study, researchers captured protein-coding sequences from each of the NCI-60 cancer cell lines using Agilent's SureSelect All Exon kit it before sequencing the exomes with Illumina's GAIIx.

By comparing exome sequences from the NCI-60 lines to one another and to sequence databases such as the Catalogue of Somatic Mutations in Cancer, the study's authors identified more than one million relatively common variants in the cancer cell lines, many of which are suspected germline variants. Another 60,000

or so variants had properties that led researchers to classify them as being potentially cancer-specific mutations.

A more extensive analysis of variant profiles in relation to the type of cancer considered gave the investigators a sense of the mutations that tend to occur within specific cancer types, both in terms of the genes affected, mutation frequency, and the nature of the mutations themselves.

Not surprisingly, for instance, the lung cancer lines tended to show the sorts of mutation events that have been linked to tobacco exposure, while melanomas were more apt to carry mutation profiles pointing to past UV-light exposure.

Many of the apparent somatic mutations clustered in cancer cell lines known to have microsatellite instability, the team found. Even so, the most mutation-rich cell line — a colon cancer line called HCC2998 — contained a slew of single nucleotide changes but no signs of microsatellite instability.

To highlight potential applications of the new data set, the team also decided to take a crack at using the NCI-60 exome sequences as part of a pharmocogenomic analysis, searching for mutations that corresponded with the cell lines' documented responses to 103 US Food and Drug Administration approved anti-cancer drugs and 207 investigational compounds.

For that analysis, the researchers were able to track down several apparent drug response interactions by focusing on genes that harbored cancer-associated mutations in five or more of the NCI-60 cell lines.

For example, cell lines harboring TP53 gene mutations tended to show a diminished response to so-called MDM2 inhibitor drugs, while the effects of several kinase inhibiting compounds seemed to vary with the presence or absence of mutations in half a dozen different genes, including BRAF, PIK3CA, and ERRB2.

In addition to providing clues about responses to treatments that have already been proposed for cancer, the study's authors noted that the NCI-60 sequence data may ultimately serve as a useful resource for finding and testing new treatment targets as well.

"The [whole-exome sequence] data that we are providing for the NCI-60 … enables the vast compound activity database to be used as a resource for drug development to complement genomic studies conducted using larger cell line panels," they wrote. "That is, when one discovers a genomic variant as a molecular target using other cell line resources, using the [whole-exome sequence] data for the NCI-60 one can potentially identify screened compounds with selective activity for that target."

Data generated for the study is available online through the CellMiner database, NCI's Developmental Therapeutics Program, and the Qiagen Ingenuity Systems

database.