Nature Reviews Clinical Oncology | Published online 19 Aug 2016; doi:10.1038/nrclinonc.2016.131

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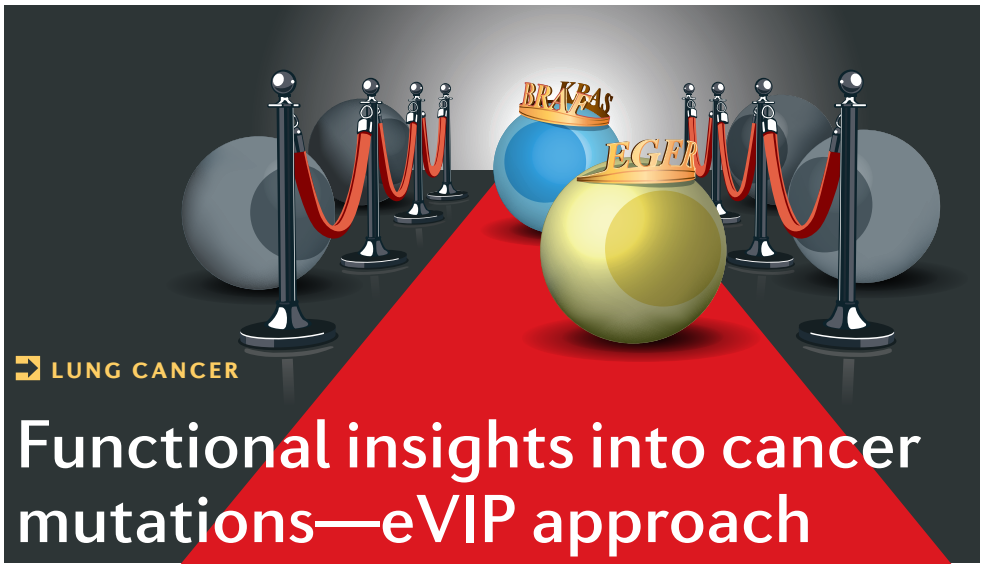

LUNG CANCER

Functional insights into cancer mutations—eVIP approach

Genome sequencing efforts have identified millions of somatic mutations in patients with cancer. The traditional approach of elucidating disease allele function involves detailed investigation. Although these functional characterization efforts have been incredibly powerful, unfortunately, they do not match the pace of genetic discovery, and the functional effects of most variants are unclear. In a study now published in *Cancer Cell,* Jesse Boehm, Matthew Meyerson and co-authors hypothesized that "it might be possible to create a generalizable framework to systematically map the molecular and phenotypic consequences of cancer variants". The researchers decided to test this hypothesis in lung adenocarcinoma because this tumour type is characterized by a high mutation rate and, as a consequence, such cancers are associated with large numbers of uncharacterized mutations.

Previous work had indicated that gene-expression profiling to assign gene function, tumorigenesis assays, and lung cancer sequencing were each sufficiently mature to test whether integrating these powerful components could accelerate the functional characterization of target alleles in lung cancer. In the past, the precision genetics community exclusively used computational prediction methods and prior clinical experience to determine which cancer variants were functional. As a consequence, this approach identified specific patients with lung cancer that should be enrolled in clinical trials of targeted treatments. Boehm's group found that such prediction methods don't always agree and that functional laboratory data can be helpful as a complementary assessment of allele activity. The researchers demonstrated the functional importance of rare genetic variations in tumours, including the well-studied cancer genes *BRAF*, *KRAS* and *EGFR* that are the subject of intense drug development efforts.

Boehm and Meyerson's team characterized 194 somatic mutations identified in primary lung adenocarcinomas. The researchers developed an expression-based variant-impact phenotyping (eVIP) method that uses gene-expression changes to distinguish 'impactful' from neutral somatic mutations. As Boehm explains: "our work demonstrates that a high-throughput eVIP approach is possible. We deployed a suite of molecular and phenotypic assays, largely agnostic to gene function, to characterize nearly 200 variants across 53 distinct genes in a high-throughput fashion." The researchers showed that this approach can accurately segregate rare gain-of-function and loss-of-function genes from functionally neutral variations in known and novel lung cancer driver genes. They discovered gain-of-function activity of over a dozen rare variants encoded by the *ARAF*, *BRAF*, *EGFR*, *ERBB2*, *KRAS*, and *RIT1* oncogenes. Crucially, the researchers found that modest missense changes in tumour suppressor genes, which are typically overlooked as likely causes of gene inactivation, actually do inactivate the gene. In other words, they present functional evidence to support inclusion of these rare noncanonical variants as driver oncogenes. Finally, the researchers showed "that mapping the activity of alleles provides a hypothesis on how to optimally use combination drug therapies, for instance combining agents that inhibit EGFR and MEK, to suppress this activity."

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In terms of the future implications of this work, Boehm posits: "the success of precision medicine in lung cancer hinges on our ability to correctly infer both common as well as rare allele function. This work demonstrates that an iterative genome interpretation engine that includes not only statistical genomics, but also 'precision functional genomics' will gradually improve the assignment of mutation function." It is hoped that the application of these latest approaches for the classification of mutations will begin to match the pace of genomic discovery and will accelerate the translation of genomic knowledge to the clinical care of patients with lung cancer and other tumour types.

Lisa Hutchinson

ORIGINAL ARTICLE Berger, A. H. *et al.* High-throughput phenotyping of lung cancer somatic mutations. *Cancer Cell* **30**, 1–15 (2016)
FURTHER READING Kim, E. *et al.* Systematic functional interrogaton of rare cancer variants identifies oncogene alleles. *Cancer Discov.* **6**, 714–726 (2016)