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GENETICS

HOTNET2—SEE THE WOOD FOR THE TREES

Numerous mutations in diverse genes occur at low frequencies in cancer, but might nevertheless have important influences on tumour biology and therapy. Identifying these rarely mutated genes in necessarily large genomic studies has proved difficult; existing data analysis algorithms, such as HotNet, can reveal significantly mutated genes, but have limited capacity to decipher which rare alterations are relevant driver, rather than passenger, mutations. "The difference in mutation frequency/significance between rarely mutated genes and commonly mutated genes—such as *TP53*—is so great that the latter would dominate the signal," explains Benjamin Raphael, who led a study to create a modified algorithm, HotNet2, that addresses this issue.

The HotNet2 algorithm builds significantly mutated gene 'subnetworks' based on mutational frequencies and known interaction networks. HotNet2 was applied to The Cancer Genome Atlas Pan-Cancer data from 3,281 samples—harbouring >11,500 mutated genes—across 12 cancer types. The analysis identified 16 subnetworks comprising 147 genes, including 13 genes encoding linker proteins involved in >1 of the subnetworks. "Within these subnetworks we found new genes that were rarely mutated, or rare mutations in genes commonly mutated in other cancer types," states Raphael. "We also found a few novel subnetworks; for example, we identified the condensin complex as rarely mutated across tumour types." Indeed, 92 of the mutated genes are not known drivers of cancer (although some are implicated in tumorigenesis) and warrant investigation.

Raphael *et al*. are pursuing multiple avenues of investigation with HotNet2. "One is to extend the analysis to non-coding variants," he says. "A second direction is to examine relationships between genetic changes and phenotypes; ideally, we would like to examine clinical phenotypes as well, such as drug response." Importantly, many therapies are available for patients with particular genetic aberrations; however, patients with rare mutations within distinct genes in the same pathways might also respond to these drugs. "Our Pan-Cancer analysis with HotNet2 helps organize aberrations in networks across tumour types, and thus might be an effective way to identify such cases," Raphael concludes.

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Original article Leiserson, M. D. *et al*. Pan-cancer network analysis identifies combinations of rare somatic mutations across pathways and protein complexes. *Nat. Genet*. doi:10.1038/ng.3168