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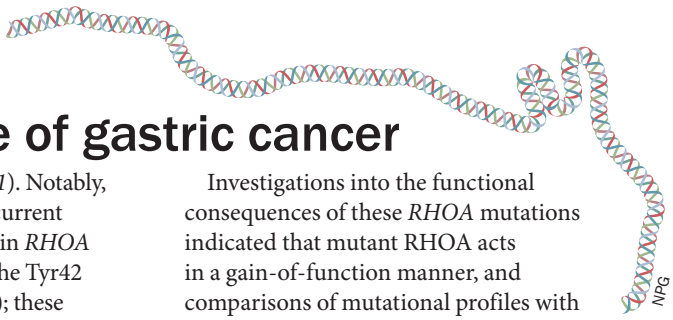
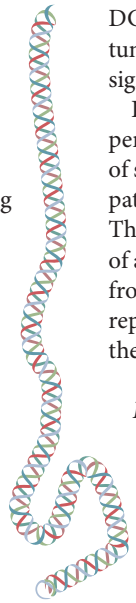


GENETICS

Revealing the genomic landscape of gastric cancer

New insights into the genetics of gastric cancer have been revealed by two studies published in *Nature Genetics*, identifying important new driver mutations and striking diversity in tumour types. Crucially, both studies identify mutations in *RHOA* (encoding a protein involved in actin reorganization and cell-cycle maintenance) as recurrent in gastric cancer, particularly in diffuse-type gastric cancer (DGC).



In the first study, the researchers performed whole-genome sequencing in 100 pairs of gastric cancer samples and non-neoplastic gastric samples. They also conducted integrative genomic analysis, including profiling of DNA copy number, gene expression and methylation patterns.

Subtype-specific epigenetic and genetic alterations in gastric cancer were identified. The researchers reported new driver genes with mutations in gastric cancer (including *MUC6* and *RNF43*) and confirmed previously identified driver genes (*TP53* and *CDH1*). Notably, the investigators observed recurrent 'hotspot' mutations clustered in *RHOA* (the most frequent affecting the Tyr42 residue in the RHOA protein); these mutations were found in 14.3% of 98 DGC tumours, but not in intestinal-type tumours, and caused defective RHOA signalling and evasion of anoikis.

In the second study, Kakiuchi *et al.* performed whole-exome sequencing of surgical resection samples from 30 patients with DGC (the discovery set). They also performed targeted sequencing of a validation set, consisting of samples from a further 57 patients with DGC, and repeated sequencing of 30 samples from the discovery set.

Recurrent somatic mutations in *RHOA* were observed in 23% of the discovery set samples. Sequencing of the validation set identified *RHOA* mutations in 25.3% of samples, with mutational 'hotspots' affecting the Tyr42, Arg5 and Gly17 residues in the RHOA protein.

Investigations into the functional consequences of these *RHOA* mutations indicated that mutant RHOA acts in a gain-of-function manner, and comparisons of mutational profiles with the other major gastric cancer subtypes implied that *RHOA* mutations occur specifically in DGC.

"We can now really begin to appreciate the molecular complexity of gastric cancer ... and also evaluate the mutational landscape and unique mutational signatures in relation to patient and molecular parameters," says Suet-Yi Leung, author of the first study. Comprehensive genomic analyses of gastric cancer such as these could, hopefully, lead to much-needed new targets for drug development.

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Original articles Wang, K. *et al.* Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat. Genet.* doi:10.1038/ng.2983 | Kakiuchi, M. *et al.* Recurrent gain-of-function mutations in *RHOA* in diffuse-type gastric carcinoma. *Nat. Genet.* doi:10.1038/ng.2984