CANCER

Next-generation sequencing for detecting thyroid cancer

Targeted next-generation sequencing enables simultaneous testing for multiple mutations in thyroid cancer, new data reveal.

Unnecessary diagnostic surgery for patients with thyroid nodules that are cytologically indeterminate after fine-needle aspiration (FNA) biopsy but found to be benign remains a substantial health-care problem. Molecular tests for common mutations of thyroid cancer are one approach to improve the sensitivity of cancer detection in individuals with cytologically indeterminate thyroid nodules, although only a minority of the known mutational markers for thyroid cancer are currently tested. Nikiforova *et al.* designed and tested a custom panel (ThyroSeq) for next-generation sequencing that enables simultaneous detection of mutations in 284 hotspots of 12 genes with mutations that are found in thyroid cancer.

The accuracy of ThyroSeq was first successfully validated using DNA samples with known or no thyroid cancer mutations. DNA from 228 thyroid specimens, including neoplastic and non-neoplastic specimens, was then tested. Of note, very small DNA samples (5–10 ng) obtained by FNA from thyroid nodules was sufficient for analysis. Molecular profiles were generated of different types of thyroid cancer and point mutations were

identified in 30–83% of specific cancer types. Interestingly, mutations in *TP53*, which were thought to occur predominantly in dedifferentiated thyroid tumours, occurred fairly frequently in well differentiated oncolytic follicular carcinomas.

The analysis revealed several insights, including the finding that whereas most tumours had a single mutation, several had multiple mutations, suggestive of aggressive tumour behaviour. “The ability to detect multiple mutations suggests that in the near future we might be able to predict tumour aggressiveness preoperatively, which should individualize surgical approaches for these patients,” comments senior author Yuri Nikiforov of the University of Pittsburgh, USA. In addition, the researchers used quantitative assessment of mutant alleles to confirm that *BRAF* and other key mutations are present in the majority of tumour cells in thyroid cancer nodules.

“The use of next-generation sequencing by Nikiforova *et al.* enabled a considerable improvement in the rate of detection of specific mutations and, most of all, the possibility to explore many more mutations,” comments Furio Pacini of the University of Siena, Italy, who was not involved in the study. “In this manner, it seems that the problems we faced with time-consuming PCR-based techniques, are solved.”

The team now plan to validate ThyroSeq for clinical use and then apply it to routine cancer diagnosis in thyroid nodules. “We will also continue our research to apply the same next-generation sequencing methodology to create a panel to detect a large variety of gene fusions known to occur in thyroid cancer,” explains Nikiforov. “Ultimately, we hope to create a perfect molecular test for thyroid nodules with indeterminate cytology, which will eliminate entirely the uncertainty of indeterminate thyroid cytology.”

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