GENETICS

GENETICS OF BILIARY TRACT CANCER

Two new studies have used next-generation whole-exome sequencing to reveal a potential key role for chromatin remodelling in the development of cholangiocarcinoma. The findings, reported in *Nature Genetics*, provide new clues to the underlying biology of biliary tract cancers and highlight new therapeutic targets, a crucial step forward given that no effective therapies other than surgery are currently available.

In the first study, Laura Wood and colleagues performed whole-exome sequencing on 32 intrahepatic cholangiocarcinomas and nine gallbladder carcinomas in a bid to identify alterations that drive tumour formation. The researchers identified nearly 2,000 somatic mutations, and found that three chromatin-remodelling genes in particular—*BAP1*, *ARID1A* and *PBRM1*—potentially had a role in the development of intrahepatic cholangiocarcinoma. “Together, these genes were mutated in almost half of the cancers sequenced, and their mutations were strongly enriched for inactivating mutations, pointing to their role as tumour suppressors,” notes Wood.

Using a similar strategy in a separate study, Bin Tean Teh and co-workers profiled 209 cholangiocarcinoma samples from patients in Asia and Europe, including 108 cases caused by liver fluke infection. The investigators also identified somatic mutations in *BAP1* and *ARID1A* in cholangiocarcinoma; functional studies revealed tumour suppressive activity of both these genes. Moreover, Teh *et al.* observed notable differences in the mutation frequencies of key genes identified: “For example, in the Thai sample, *TP53* mutation was very high (40%), but relatively low in other samples (<10%), whereas *IDH1–IDH2* were low in the Thai samples (2–3%) but high (~20%) in the Singapore samples”. “All these findings suggest that a drug developed to treat cancer in the West might not be as effective for the same cancer type in the East and vice versa,” Teh explains.

Clearly, more research is needed to determine the mechanisms by which chromatin remodelling is involved in tumorigenesis. Moreover, whether these mutations affect sensitivity to certain drugs remains to be determined.

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Original articles Jiao, W. *et al.* Exome sequencing identifies frequent inactivating mutations in *BAP1*, *ARID1A* and *PBRM1* in intrahepatic cholangiocarcinomas. *Nat. Genet.* doi:10.1038/ng.2813 | Chan-on, W. *et al.* Exome sequencing identifies distinct mutational patterns in liver fluke-related and non-infection-related bile duct cancers. *Nat. Genet.* doi:10.1038/ng.2806