BUILDING THE FOUNDATIONS FOR PRECISION ONCOLOGY IN SOUTHEAST ASIA

Genomic data from CANCER PATIENTS IN THAILAND is a step towards more accurate diagnostic tests and treatments tailored more precisely to individuals in the region.

Genetic and environmental factors both influence differences in cancer population characteristics. For example, in the north-eastern region of Thailand, very high rates of the bile duct cancer, cholangiocarcinoma, has long been attributed to an infestation by liver flukes, a type of parasitic flatworm. But according to Manop Pithukpakorn from the Siriraj Center of Research Excellence in Precision Medicine at Mahidol University in Bangkok, in the last five to 10 years it has been observed that liver fluke doesn't seem to be a factor in populations in other parts of Thailand, and so genetics might also be at play.

Differences between global cancer populations are equally complex. For example, head and neck cancers are more prevalent in southeast Asia and east Asia than in Western populations. Meanwhile, human papilloma virus infection is a major risk factor for cancers in Western populations, but appears less significant in Thai populations.

Genetic factors are thought to be associated with 8–12% of cancers. To unravel the environmental and genetic contributions, Thai researchers must better understand the country's cancer genes.

Non-European populations are also under-represented in human genetic datasets, which is another reason, in 2019, the Thai government established the Genomics Thailand Initiative, one arm of which is collecting germline variant (heritable mutation) data on Thai cancer patients. Eligible Thai patents are invited to participate, with eligibility defined according to personal and family history.

Project researchers particularly want to examine three cancer types: rare cancers, childhood cancers, and cancers in which there is a high frequency of known pathogenic variants, which are genetic alterations that cause a higher predisposition to a cancer. Cancers with high frequencies of pathogenic variants include breast, ovarian and colorectal cancer.

"We aim to create a panel of known cancer-associated genes to test eligible patients," says Pithukpakorn.

Not only will germline variant testing look for cancer risk, but also at genes that might affect how a patient responds to treatment, such as those involved in producing drug-metabolizing enzymes.

If a heritable mutation is identified in a cancer patient, family members are invited for testing; if they are found to carry the mutation they are monitored and preventive measures implemented where possible.

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Genetic breast cancer risks

Global differences in cancer incidence and germline variant frequency are strikingly illustrated by breast cancer in Thailand. Thai people have more triple-negative breast cancer, a type in which cancer cells lack the three most commonly found receptors in breast cancer cells. Patients also tend to be younger than in Western populations and carry more genetic markers indicating a genetic predisposition to the disease.

"In a study of 400 breast cancer patients eligible for germline testing, we found that 23–24% carry pathogenic or likely pathogenic mutations," says Pithukpakorn. In contrast, the rate of pathogenic mutations in Western populations is only about 10%. Of these mutations, 80% are in the *BRCA1* or *BRCA2* genes, which normally play an important role in preventing cancer. In Western populations *BRCA1* has a higher frequency than *BRCA2*, with frequency ratios in European populations between 2:1 and 4:1. In Thailand the approximate ratio is 1:1.

Tumour testing

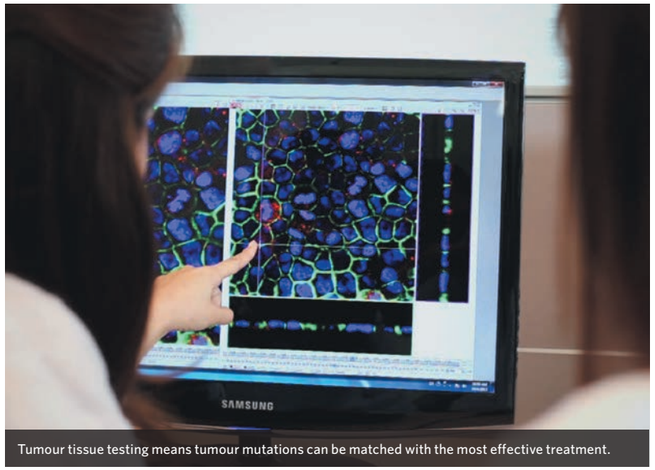
Another part of the Genomics Thailand Initiative focuses on testing the tumour tissues of a subset of the cancer cohort. Dramatic clinical responses have been seen in patients in which tumour mutations can be matched with an appropriate treatment.

For cancers such as breast, lung, and colorectal cancer, where several pathogenic mutations are known, identifying the particular mutation can point to a specific treatment or can indicate whether a treatment will be effective. This can have huge financial implications as many newer cancer treatments are very expensive.

Up to 50% of colorectal cancers, for example, are associated with a mutation in the *KRAS* gene. The mutation means that treatment with epidermal growth factor receptor blockers will not be useful. Particular mutations in the *KRAS* and *FBXW7* genes have been shown to occur at a slightly higher frequency in the Thai population. Currently, identification of a *KRAS* mutation has clinical value, whereas identification of *FBXW7* mutations only has diagnostic or prognostic value. But with more research, this could change.

However, only about 10% of tumour testing will reveal actionable targets, in contrast to germline testing, which has been shown to be cost-effective for patients. "We have to convince policy-makers that tumour testing is worthwhile to bolster research," says Pithukpakorn.

Despite tumour testing providing less immediate benefit, more and more patients are willing to have their tumours tested to benefit other people in the future, he says. "Gathering more data on tumour mutations will provide valuable information, which will prompt scientists to research the pathways involved in those genes and find treatments for currently non-actionable mutations." ■



Tumour tissue testing means tumour mutations can be matched with the most effective treatment.


PCR thermal cyclers prepping samples for genome sequencing.


A scientist at Mahidol University loads DNA on to a gel for separation via electrophoresis.

GENOMICS THAILAND

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