Genomics

Global sites for mutations of unknown origins

Irene Franco & Fran Supek

Genetic sequencing of human kidney cancers worldwide has revealed associations between geographical locations and specific mutation patterns, indicating exposure to known and unknown mutation-promoting agents. **See p.910**

Daily exposure to chemical agents can cause cells in the body to accumulate genetic changes called somatic mutations. Most of these changes do not appreciably affect cellular function, but a small fraction can corrupt genetic instructions and turn a normal cell into a cancer cell. On page 910, Senkin *et al.*[1] report their study of more than 900 samples of a type of kidney tumour, called clear cell renal cell carcinoma, from different parts of the world.

This research provides insight into the environmental exposures and lifestyle factors that favour the accumulation of various types of somatic mutation in the kidney. The authors also found associations between geographical locations and specific mutation patterns. These associations can map the global distribution of known and as-yet-unknown mutation-promoting agents, termed mutagens, that change the genome sequence. Many mutagens can drive cancer and these are called carcinogens (not all carcinogens are mutagens).

The advent of next-generation sequencing has greatly facilitated genomic analyses and their applications in the clinic. Among these, the sequencing of genomic DNA from cancer cells can detect genetic changes that are found in the tumour and not in the individual's other cells, and statistical analyses can help to identify those few genetic variants that are drivers of tumour formation. Knowledge about these drivers can have implications for clinical decisions, and cancer genomics therefore provides an example of personalized medicine. Motivated by the promise of clinical benefit, sequencing of cancer genomes is becoming widespread. For example, the 100,000 Genomes Project in the United Kingdom is processing thousands of genomes from various types of cancer[2].

The massive influx of data has also invigorated another field of study — analyses of mutational patterns to understand mechanisms of DNA damage and repair. Exposure to mutagens and other physiological or disease-associated events (such as defects in DNA repair) modifies the genome sequence of cells during a person's lifetime and leaves permanent 'tracks' or 'scars' in the genome. To decode these traces of exposure to mutagens, scientists have developed increasingly sophisticated statistical methods. The main approach is based on the analysis of changes, termed single-base substitutions (SBSs), of a single nucleotide in the DNA sequence[3].

Depending on the type of mutagen exposure, some classes of SBS become more frequent than others. For example, the chemical benzo[a]pyrene from tobacco smoke, also found in polluted air, interacts with a specific base (guanine) in a nucleotide, resulting in the base ultimately being substituted with another base — thymine. Consequently, cells exposed to this chemical, such as those in the lungs or throat, will have many guanines replaced by thymines, whereas cells less exposed to this chemical, such as those in the brain or colon, will rarely acquire this type of nucleotide substitution.

However, patterns observed are usually highly complicated because the mutational signature induced by a mutagen often contains many types of SBS, with different mutation risk for different trinucleotide sequences of DNA. Moreover, cells are simultaneously exposed to a variety of mutational processes, each one impressing its own signature on the genome[3].

Methods for isolating specific mutational signatures from the mixture of other signatures in tumour genome data have currently catalogued around 100 SBS signatures, but only about half of these are associated with a known mutagen[4]. In an attempt to match signatures to their causes, scientists have monitored mutations accumulating after *in vitro* exposure to DNA-damaging agents or to known or suspected carcinogens. Many, but not all, of these agents induced a characteristic spectrum of mutations[5,6].

These findings underscore the utility of mutational signatures as an information-rich genomic readout that can classify mutagenic agents. Worryingly, some compounds whose mutagenic activity was either not suspected or underestimated produced a mutational signature after exposure[7,8], highlighting the need for more vigilance and more assessment of mutagenic activity concerning commonplace exposure to environmental chemicals and drugs.

Exposure to mutagens in the environment might explain the differential incidence of specific cancer types around the globe. One striking example of this is kidney cancer, given that some regions of Europe have an incidence of this type of cancer that is several times higher than in other parts of the world. Although greater vigilance in the use of diagnostics might account for some differences in prevalence, other explanations are also possible, such as a contribution from environmental mutagens or genetic ancestry. Senkin and colleagues' analyses reveal extensive geographical patterning of mutational signatures in kidney cancers across the globe, and point to opportunities for public-health interventions in affected regions, such as measures to minimize mutagen exposures or improve

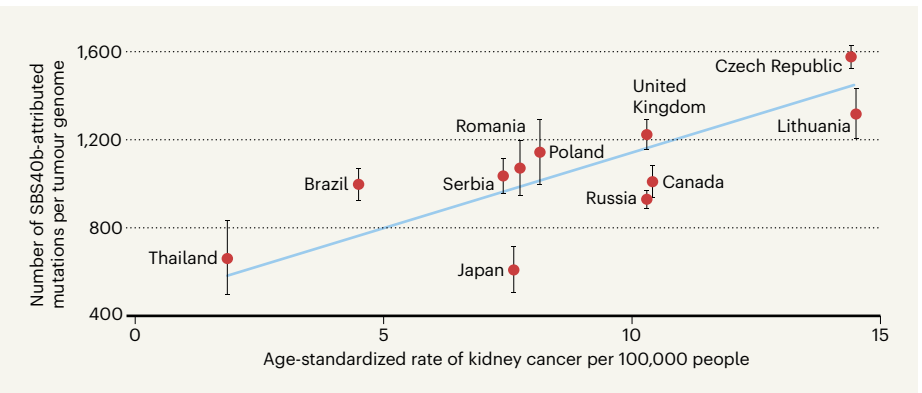

Figure 1 | A mutational signature associated with kidney cancer. Senkin *et al.*[1] examined mutation patterns in samples of kidney tumours from people around the globe. The signature termed SBS40b is more common in locations associated with a higher risk of kidney cancer than in those with a lower risk, and this might indicate that these higher-risk locations are associated with a higher level of exposure to an as-yet unknown mutation-promoting agent (mutagen). (Adapted from Fig. 4 of ref. 1.)

testing for people at risk.

The authors reported a mutational signature uniquely linked to exposure to the carcinogen aristolochic acid. Although the exposure and the signature were known[9], the study defined an affected area in the Balkans region of southeastern Europe that is wider than expected. Another region-specific exposure was found in Japan, where a high fraction of kidney cancers showed a signature (named SBS12) that was previously thought to be mainly specific to liver cancer and whose cause remains unknown[4].

A ubiquitous signature of unknown origin contributed a high number of mutations. This signature, named SBS40, is found in many other types of cancer and also in normal kidney cells[4,10]. However, thanks to their large and kidney-focused data set, Senkin and colleagues could further split this pattern into three distinct signatures, one of which, termed SBS40b, is specific to kidney cancer and whose signal intensity is associated with geographical areas where there is an elevated kidney cancer risk (Fig. 1).

The cause of the signature is suggested to be an unknown process that occurs normally in kidney cells, because it affects most kidney tumours. The authors report that high levels of the SBS40b signature also correlate with the presence of biochemical markers of impaired kidney function detected in blood samples of people with tumours. This result supports epidemiological and functional studies that point to kidney damage (both acute and chronic) as being a factor that can contribute to the risk of developing kidney cancer[11].

At this point, it cannot be ruled out that the differential geographical localization of the mutational signatures results from heritable genetic factors, instead of (or in addition to) environmental mutagen exposures. Future studies focusing on groups of individuals with diverse genetic ancestries at each location will shed light on this.

Although the methods for analysing mutation patterns and the reference catalogues of mutational signatures are still evolving, the study of somatic mutations is shaping up to be a robust tool to clarify causes of mutations linked with cancer risk. Moreover, mutational signatures could guide cancer therapies by revealing tumour characteristics such as deficiencies in DNA repair, which might be exploited as tumour vulnerabilities[12,13]. Extensive studies such as this research by Senkin and colleagues generate precious resources for future human genomics studies, and provide insights into mutagenic mechanisms as well as guidance for policymakers on how to better identify and manage cancer risks.

Irene Franco is in the Division of Genetics and Cell Biology, San Raffaele University, 20132 Milan, Italy and at IRCCS San Raffaele Scientific Institute, Milan. **Fran Supek** is at the Biotech Research and Innovation Centre, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark, and at the Institute for Research in Biomedicine, the Barcelona Institute of Science and Technology, Barcelona, Spain.
e-mails: franco.irene@hsr.it; fran.supek@bric.ku.dk

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