ARTICLE

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Signatures of mutational processes in human cancer

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All cancers are caused by somatic mutations; however, understanding of the biological processes generating these mutations is limited. The catalogue of somatic mutations from a cancer genome bears the signatures of the mutational processes that have been operative. Here we analysed 4,938,362 mutations from 7,042 cancers and extracted more than 20 distinct mutational signatures. Some are present in many cancer types, notably a signature attributed to the APOBEC family of cytidine deaminases, whereas others are confined to a single cancer class. Certain signatures are associated with age of the patient at cancer diagnosis, known mutagenic exposures or defects in DNA maintenance, but many are of cryptic origin. In addition to these genome–wide mutational signatures, hypermutation localized to small genomic regions, 'kataegis', is found in many cancer types. The results reveal the diversity of mutational processes underlying the development of cancer, with potential implications for understanding of cancer aetiology, prevention and therapy.

Somatic mutations found in cancer genomes[1] may be the consequence of the intrinsic slight infidelity of the DNA replication machinery, exogenous or endogenous mutagen exposures, enzymatic modification of DNA, or defective DNA repair. In some cancer types, a substantial proportion of somatic mutations are known to be generated by exposures, for example, tobacco smoking in lung cancers and ultraviolet light in skin cancers[2], or by abnormalities of DNA maintenance, for example, defective DNA mismatch repair in some colorectal cancers[3]. However, our understanding of the mutational processes that cause somatic mutations in most cancer classes is remarkably limited.

Different mutational processes often generate different combinations of mutation types, termed 'signatures'. Until recently, mutational signatures in human cancer have been explored through a small number of frequently mutated cancer genes, notably *TP53* (ref. 4). Although informative, these studies have limitations. To generate a mutational signature, a single mutation from each cancer sample is entered into a mutation set aggregated from several cases of a particular cancer type. A signature that contributes the large majority of somatic mutations in the tumour class is accurately reported. However, if multiple mutational processes are operative, a jumbled composite signature is generated. Furthermore, because such studies are based on 'driver' mutations[1], signatures of selection are superimposed on the signatures of mutational processes.

Recent advances in sequencing technology have overcome past limitations of scale[1]. Thousands of somatic mutations can now be identified in a single cancer sample, offering the possibility of deciphering mutational signatures even when several mutational processes are

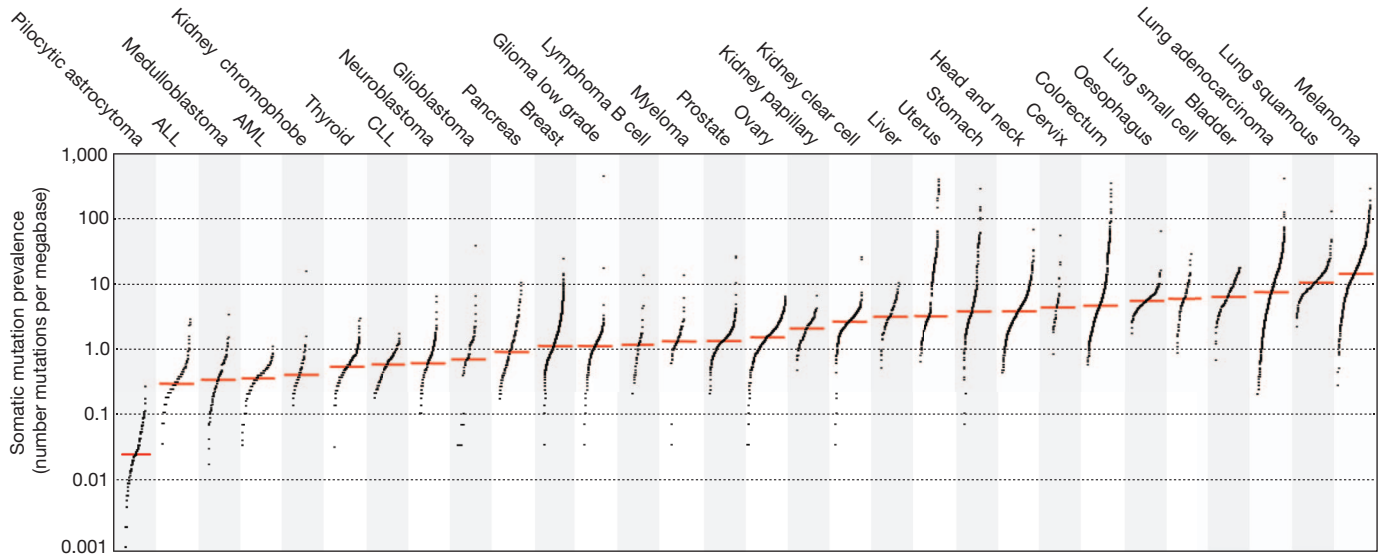

Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.