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Programme Book

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The development of cancer is a continuous process of mutation and clonal evolution. Whole genome sequencing presents the endpoint of a cell's journey to cancer, but the data can contain information that permits the reconstruction of events during a tumour's evolutionary past.

Here, we apply such life history analyses on an unprecedented scale, to a set of 2,778 tumours spanning 39 cancer types. Pan-cancer, these analyses show that mutations in canonical driver genes, distinctive chromosomal gains and losses, and mutational processes associated with exposure to carcinogens, are amongst the earliest events in tumour evolution. Later stages of clonal evolution, however, are characterised by an increase in genome instability, and the acceleration of mutational processes derived from defective DNA repair mechanisms. Furthermore, we extract tissue-specific patterns of somatic evolution, which include both well-established and potentially novel pathways of tumour development. For example, by making use of sports statistics models to obtain a relative ordering of mutational events in colorectal adenocarcinoma, we are able to recapitulate the typical progression of *APC-KRAS-TP53* proposed by Vogelstein and Fearon. Alternatively, in glioblastoma, a quantitative approach to timing copy number gains demonstrates a novel pattern of early tumour evolution characterised by distinctive chromosomal gains of 7, 19 and 20. Using clock-like mutational signatures, we provide real time estimates for major events during tumour evolution, such as whole genome duplication and the emergence of the most recent common ancestor, and find that these events may precede diagnosis by many years.

Taken together, these data indicate that most cancers commonly have several predefined and ordered event trajectories, which might be crucial in understanding specific tumour biology, and in providing new opportunities for early detection and cancer prevention.

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Detection of microsatellite instability and loss of heterozygosity of *DVL1*, *DVL2* and *DVL3* gene in astrocytic brain tumors

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Astrocytomas are the most common and deadliest form of primary brain tumours. According to the WHO classification, there are four grades of astrocytoma, considering their histology, molecular characteristics and prognosis. Despite recent advances in understanding the molecular basis of development and progression of astrocytomas, additional research is required to develop more effective therapies. Although aberrant functioning of Wnt signalling pathway has been detected in variety of human cancers, little is known about its role in astrocytoma. We aim to investigate the incompletely understood role of Dishevelled (DVL) gene family, which is considered to be the central hub of Wnt signalling. In the present study, DNA isolated from 80 human astrocytoma with different clinical grades and their matched blood samples were analysed for PCR/loss of heterozygosity (LOH)/microsatellite instability (MSI), by using polymorphic microsatellite markers D1S468 and D1S243 for *DVL1*, D1S17960 for *DVL2* and D3S1262 for *DVL3* gene. Constant presence of microsatellite instability was observed in all loci investigated and in each astrocytoma grade, while allelic loss of polymorphic repeats was present mainly in high grade astrocytoma. The highest frequency of MSI was identified at locus D1S468 (27%), while D1S243, D17S960 and D3S1262 markers showed 14,3%, 18% and 18% of MSI of all informative cases, respectively. Marker D1S468 showed statistically significant difference of MSI between grades ($p=0.016$). LOH was found in 4,5%, 8,6%, 20% and 18% of analysed heterozygous samples for markers D1S468, D1S243, D17S960 and D3S1262, respectively. These data show that astrocytoma harbor defective cellular DNA MMR mechanisms and suggest that MSI is an early event in brain tumorigenesis while LOH may occur at a later stage.