GENOMICS

We are individuals

Improved sequencing technology has provided researchers with the tools to assess the genomic and transcriptomic landscape of tumour specimens at high resolution. The information gained from these mapping exercises could provide important insights into tumour-initiating events and how a tumour might evolve. Therefore, Marco Marra, Samuel Aparicio and colleagues sequenced the genome and transcriptome from a primary and a metastatic oestrogen receptor-α-positive lobular breast tumour from the same patient.

Shah, Morin and colleagues used paired-end sequencing to find, and Sanger re-sequencing or fluorescence *in situ* hybridization to validate, single nucleotide variations (SNVs), insertions and deletions, gene fusions, translocations, inversions and copy number variations in DNA from the tumour samples. In the metastatic tumour, they found a low-level amplification of the insulin receptor (*INSR*), which had not previously been described. They also found 405 new coding non-synonymous SNVs that were not found in the normal tissue of the patient, 32 of which were found to be new non-synonymous coding somatic point mutations. Moreover, of 9 of these somatic point mutations, none were found in 112 lobular and 90 ductal breast tumour samples, although some similarities were observed. For example, in the metastatic tumour, and lobular and ductal breast tumours they observed variants and deletions affecting the coding region of the *ERBB2* kinase domain, as well as truncations of *HAUS3*, which encodes a subunit of the augmin complex that regulates kinetochore attachment and centrosome morphogenesis.

The primary tumour arose 9 years earlier, and the authors sequenced the loci that contained 30 of the 32 somatic point mutations identified in the recurrent tumour. Although there was some degree of overlap, they observed varying levels of abundance of some mutations between the 2 tumours, and 19 of the recurrent tumour mutations were not detected in the primary tumour, indicating that substantial heterogeneity of somatic mutations exists in tumours. However, it was not determined whether this variation reflected the evolution of the disease and so a requirement for additional oncogenic mutation for tumour progression, or occurred as a result of treatment with radiotherapy.

Next, the authors assessed the transcriptome of the recurrent tumour using deep high-throughput sequencing for evidence of alternative splicing, biased allelic expression and RNA editing, which could further change the proteome. They found that *ADAR*, which encodes a major RNA-editing enzyme, was one of the top 5% of genes expressed, and they identified 3,122 candidate RNA-editing events, 536 of which were predicted to result in non-synonymous substitutions. This highlights an additional mechanism that could become deregulated in tumours to induce variation that might confer growth or survival advantages. Furthermore, the heterogeneity and variation that can be created at both the genomic and the transcriptomic level highlights the importance of integrating genomic, transcriptomic and proteomic analyses of tumours.

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ORIGINAL RESEARCH PAPER Shah, S. P. *et al.* Mutational evolution in a lobular breast tumour profiled at single nucleotide resolution. *Nature* **461**, 809–813 (2009)