Nature Reviews Genetics | AOP, published online 14 February 2012; doi:10.1038/nrg3181

CANCER GENOMICS

Histone modification at the gene level

High-throughput sequencing studies are being used to characterize the genomic architectures of increasing numbers of cancer subtypes. Various cancers are known to have alterations of the chromatin modification and remodelling machineries; now, two sequencing studies have identified cancer-associated mutations in histones themselves.

Both investigations involved the genome-scale sequencing of paediatric gliomas followed by the targeted resequencing of candidate mutant genes in additional samples. Schwartzentruber *et al.* sequenced the exomes of 48 paediatric glioblastomas and went on to analyse 784 samples of diverse gliomas. In a separate study, Wu *et al.* achieved whole-genome sequencing of seven samples of diffuse intrinsic pontine glioma (DIPG) followed by analysis of 43 DIPGs and 36 non-brainstem glioblastomas.

The two studies identified recurrent mutations in *H3F3A*, particularly in high-grade paediatric gliomas, such as in 30% of paediatric glioblastomas and in 60% of DIPGs. Consistent with this specificity, Wu *et al.* found no evidence of *H3F3A* mutations in >200 paediatric tumours of other tissue types and from other organs. *H3F3A* encodes the histone variant H3.3, and the mutations were focused on two amino acids, K27 and G34. These sites are on the post-translationally modified histone tail region, suggesting that the mutations might alter the methylation or acetylation of K27 or the nearby K36. Although this hypothesis is difficult to test in clinical samples, Schwartzentruber *et al.* found increased levels of H3K36 trimethylation in a G34V-mutant tumour.

Do these histone mutations alter transcription? Interestingly, despite K27- and G34-mutant tumours being histologically indistinguishable, gene expression microarray analyses revealed distinct transcriptional programmes between these two mutant types. This result also indicates that these mutations have pleiotropic effects on gene expression, as might be expected from disruptions to chromatin. However, whether any tumour-promoting effects of these mutations involve the dysregulated expression of a few or many cancer genes is currently unknown.

Indicating that chromatin might be disrupted at multiple levels, Schwartzentruber *et al.* also identified mutations in *ATRX* and *DAXX* in paediatric glioblastomas. These genes encode members of a chromatin-remodelling complex that deposits H3.3 onto chromatin, and mutations in these genes have previously been identified in other cancer types. Additionally, Wu *et al.* found mutations in *HIST1H3B* — which encodes histone H3.1 — in 18% of DIPGs.

It remains to be deciphered why *H3F3A* mutations have such propensity for high-grade paediatric gliomas, and functional studies will be required to establish whether mutant *H3F3A* is an oncogenic driver.

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ORIGINAL RESEARCH PAPERS
Schwartzentruber, J. *et al.* Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* 29 Jan 2012 (doi:10.1038/nature10833) | Wu, G. *et al.* Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nature Genet.* 29 Jan 2012 (doi:10.1038/ng.1102)