Nature Reviews Cancer | Published online 24 May 2017

IN BRIEF

GENETICS

Gender-specific factors in cancer susceptibility

Two studies published in *Nature Genetics* have delved into the complex genetics of cancer susceptibility and have shown links of both timing of puberty onset and mosaic loss of chromosome Y (mLOY) to cancer risk.

Previous genomic analyses have indicated various genetic factors associated with the puberty milestones age at menarche (AAM) in females and age at voice breaking in males. These analyses were relatively small, and Day ***et al.*** now report a much larger analysis using the 1000 Genomes Project in ~330,000 women, with independent replication in data from ~40,000 women in the deCODE Icelandic study. Their data implicate ~250 genes in the regulation of AAM. Body mass index-independent analyses indicated that increasing AAM was associated with lower risk of oestrogen receptor (ER)-positive breast cancer, serous ovarian cancer and endometrial cancer in women. AAM variants also affect age at voice breaking in males, and their analyses also indicated a protective effect of later puberty onset on prostate cancer risk in men.

mLOY, a form of aneuploidy, is the most common somatic alteration in men, but its clinical relevance is not clear. Using genomic data from ~85,000 men, Wright ***et al.*** identified 19 genomic regions and 36 differentially methylated sites associated with mLOY; many of these are involved in cell cycle regulation, DNA synthesis, DNA damage responses and apoptosis. In addition, mLOY was associated with increased cancer susceptibility, and the authors observed substantial overlap in the genetic architecture of cancer and mLOY. Interestingly, the types of genes identified in this analysis, together with the authors' finding that mLOY variants also affect X chormosome loss in women, suggest that these genetic variations might be involved in other forms of aneuploidy.

ORIGINAL ARTICLES Day, F. R. *et al.* Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3841 (2017) | Wright, D. J. *et al.* Genetic variants associated with mosaic Y chromosome loss highlight cell cycle genes and overlap with cancer susceptibility. *Nat. Genet.* **49**, 674–679 (2017)

IMMUNOTHERAPY

Programming T cells *in situ*

Adoptive T cell therapy with patient-derived cells engineered *ex vivo* to express chimeric antigen receptors (CARs) is a promising therapeutic strategy in cancer, but producing these cells for a large number of patients is both technically challenging and cost prohibitive. Smith ***et al.*** describe a method of programming T cells *in situ* using DNA-carrying nanoparticles. Nanoparticles were targeted to T cells and loaded with DNA encoding the leukaemia-specific CD19–4-1BB–CD3ζ (194-1BBz) CAR; this DNA sequence was flanked by piggyBac transposons, and DNA encoding the piggyBac transposase was also included, to allow chromosomal integration and persistent CAR expression. These nanoparticles induced CAR expression in T cells *in vitro* and in immunocompetent mice. Furthermore, the nanoparticles induced tumour regression and increased survival of mice bearing B cell acute lymphoblastic leukaemias, with a therapeutic efficacy similar to that of *ex vivo* engineered T cells expressing the 194-1BBz CAR. As the manufacture and storage of these nanoparticles is fairly easy, this strategy could provide a viable alternative to *ex vivo* T cell engineering approaches.

ORIGINAL ARTICLE Smith, T. T. *et al. In situ* programming of leukaemia-specific T cells using synthetic DNA nanocarriers. *Nat. Nanotechnol.* http://dx.doi.org/10.1038/nnano.2017.57 (2017)