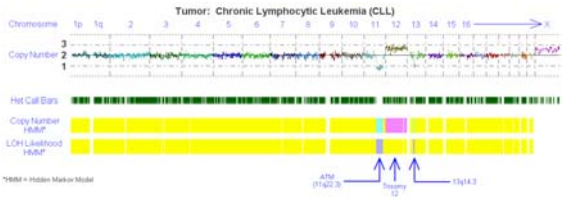
Variation

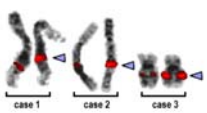
- CNVs
- Mutations in Cancer

Virtual karyotype - SNP arrays



CNV Methods

- Sequencing



- FISH - Fluorescence *in situ* hybridization
- Comparative genomic hybridization
- Array comparative genomic hybridization
- SNP arrays

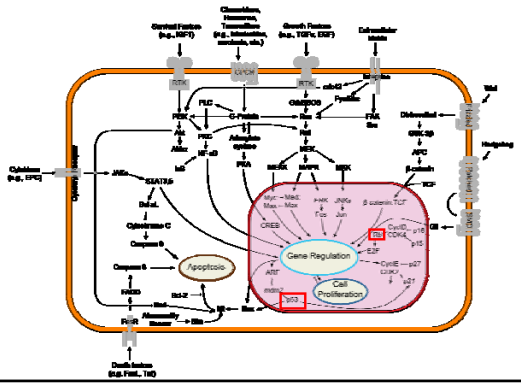
CNV – Copy number variation

- Developmental disorders – e.g. Smith-Magenis syndrome, Williams-Beuren syndrome, Prader-Willi syndrome
- Disease due to variation of expression of genes effected (SMS) or distant genes (PWS)

Mutations in cancer

- Somatic vs germline
- Cancer-related genes (oncogenes/anti-oncogenes)
  - Related to cell proliferation
  - Related to cell death e.g. p53
  - DNA repair e.g. BRCA, p53

Apoptosis/Cell proliferation signal pathway

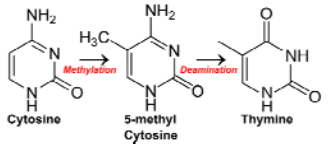


Cause of mutation > Type of mutation

- SNPs
  - C>A, C>G, C>T, T>A, T>C, T>G
  - C>T most common
  - Spontaneous mutations due to age?
- Indels
  - Small, 1bp, “microsatellite instability”
  - Defective DNA mismatch repair

CpG Islands

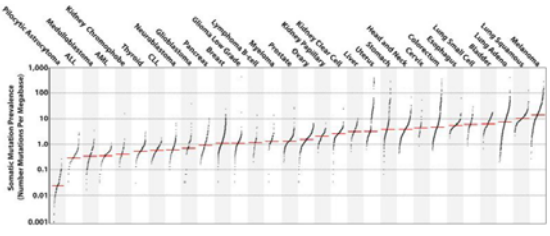
- C modified by methylation to methyl-C
- Methyl-C frequently mutates to T



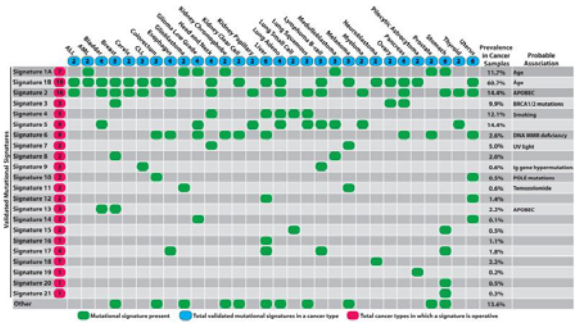
- CpG is normally ~5 fold under-represented from genomic GC% (in intergenic regions)
- CpG more frequent where methylation is suppressed (e.g. gene promoter regions)

Cancer signatures – number of mutations

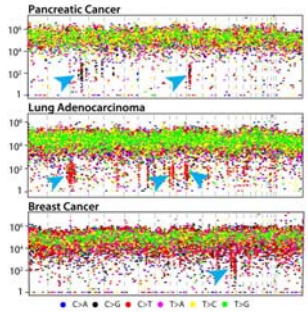
- Childhood cancers fewest mutations
- Cancers related to chronic mutagenic exposures e.g. lung (tobacco), malignant melanoma (UV) most mutations



Cancer signatures – type of mutations



Localized hypermutation - *kataegis*



- 1 to 1000s of mutations
- often in the vicinity of genomic rearrangements
- caused by APOBEC – RNA editing enzymes

Cancer CNVs - germline

- Some common CNVs involved in cancer
- 40% of cancer-related genes have CNV
- Minor increase in disease risk

Cancer CNVs - somatic

- CNVs common in cancer cells
- Accumulated with time
- Both at existing loci (oncogenes) and new loci

Databases

- The Cancer Genome Atlas (TCGA)
  - http://cancergenome.nih.gov/
  - https://tcga-data.nci.nih.gov/tcga/
- The International Cancer Genome Consortium (ICGC)
  - https://icgc.org/
  - https://dcc.icgc.org/

References

- Alexandrov *et al.* - Signatures of mutational processes in human cancer – Nature 2013
- Shlien *et al.* - Copy number variations and cancer - Genome Med. 2009

Next week

- Lecture times changed
- A2 Presentations will happen in the Tuesday Lecture/Practical Spot – BUT IN DIFFERENT ROOM – MR2
- Need D-sub connector to your laptop