Questions paper 1_week8

**In this study, 2658 genomes from different cancer types were analyzed. To identify cancer mutations, how many samples do they need to examine?**

Ideally, double the number because they need the normal tissue/blood to identify germline variation and the tumor tissue to identify cancer-specific mutations

**What type of event can lead to hotspot noncoding mutations? Which mechanisms are altered? (fig. 1a)**

Age **(why?)- accumulation of mutations with time/**
APOBEC alterations affect cytidine deaminase (error in DNA repair)
UV – thymidine dimers
AID (similar to APOBEC, although more active in hematological malignancies)

**Why are they defined as candidate drivers? (fig. 1b)**
Because they are not experimentally validated

**Why did they observe great variability across cancer types? (fig. 1b)**

Inter-tumor heterogeneity, each tumor is driven by a specific alteration that is tissue-specific

**To call non-coding elements drivers, what type of evidence do they include in their analyses? (fig. 2a)**

Mutation call
Chromosomal breakpoints
Copy number status
Expression data

**Why consider expression data? (fig.2a)**

Because mutations in the promoter, 5'UTRcan affect gene expression,
The 3'UTR can affect gene stability because it changes the ability of microRNA to bind 3'UTR. and microRNA regulates mRNA degradation.

**What type of alterations affect the non-coding regions of p53?**
**Would the 10 out of 11 patients considered heterozygotes or homozygotes altered for p53? (fig.2b)**

They have two distinct events, a mutation and a loss of heterozygosity (LOH) i.e., heterozygous deletions, but both copies of p53 are altered, thus the patient can be described as a homozygous loss of p53.

**Do all mutations in 3'UTR have the same effect on gene expression? (Fig. 2c-d)**

No, some of the mutations can be passengers

**What is a structural variant? (We will discuss this in more detail in week 9 and week 10)**
Change is the organization of the chromosomes that can lead to gene fusion, i.e. generating new oncogenic protein.

**Which parameter/feature is associated with an increase in mutation burden, and what type of structural variation? (Fig 3b)**

Replication time (late replication) induces an accumulation of mutations and it increases of the acquisition of structural variations at fragile sites.

**Why microdeletion in 5'UTR of Brd4 reduce the expression of this gene not of NOTCH3? (Fig. 3c-d)**

Because the deletion might disrupt a specific regulatory element in the genome that controls BRD4 but not NOTCH3

**Are oncogenic fusions common to many tumor types? (Figure 4f)**

Yes, they can be found in several tumor types, but they are tissue-specific

**What is the most frequent effect of SRJ?**

Generate truncated or chimeric proteins; most of the time, these are not functional proteins

**If we increase the number of WGS in cancer, will we find more driver mutations in noncoding regions?**

Probably not, because the power analyses considered that the cohort analyzed in this study is not underpowered

**Why is there variability in the ability to detect mutations in the TERT promoter across tumor types?**

The lack of coverage in promoter regions, but this variability can also be attributed to intra-tumor heterogeneity.

*Presentation of the figures*

Group 1 Figure 1

Group 3 Figure 2

Group 4  Figure 3

Group 2  Figure 4