# CANCER GENOME LANDSCAPES

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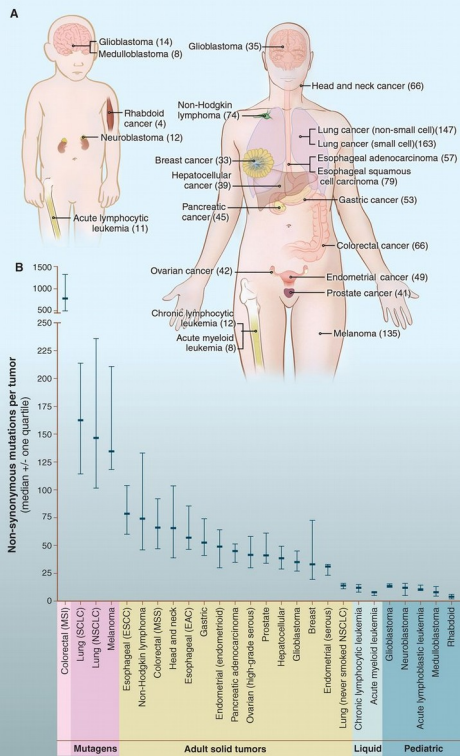



# How Many Genes Are Subtly Mutated in a Typical Human Cancer?

Common Solid Tumors: 33 to 66 genes

- single base(95% ){missense :90.7%, nonsense: 7.6%, 1.7 % splice site variations,UTR}
- indels

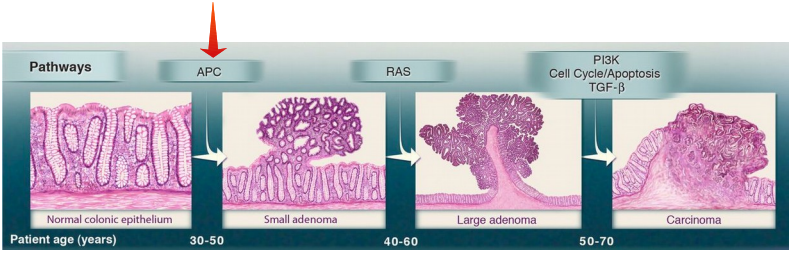
Outliers

- Melanomas and lung tumors: (200 nonnsynonymous) (potent mutagens)
- Defect in DNA repair (>1000)
- Mutations in POLD

# Benign to Malignant

- Outgrows the surrounding cells
- Microscopic clone
- Grows slowly

Gatekeeping mutation




**Genetic alteration and progression of colorectal cancer**

Driver Mutations: The mutations that confer a selective growth advantage to the tumor cell are called “driver” mutations

Passenger mutations: mutations that have no effect on the neoplastic process.

Driver Mutations:

- Mut-driver genes
- Epi-driver genes

# 20/20 rule

- Oncogene: >20% mutations at recurrent positions and are missense
- Suppressor >20% mutations inactivating

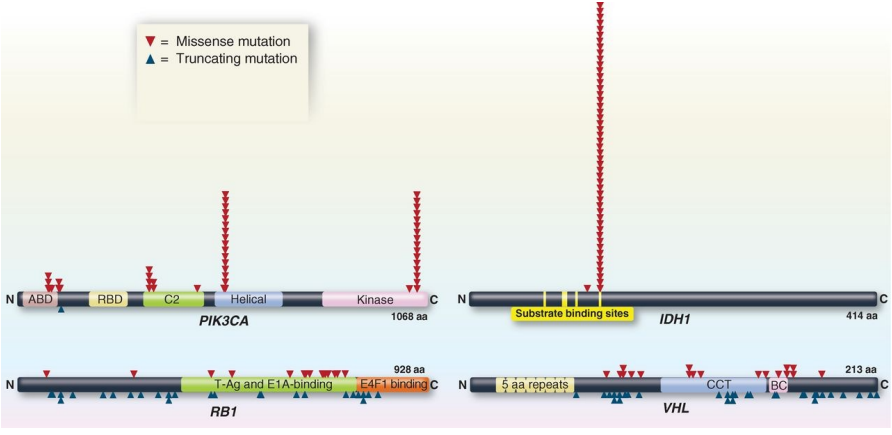
  (from COSMIC database( Catalogue of Somatic Mutations in Cancer )

- IDH1 (brain tumor) and
- NOTCH1 :

  liquid tumors (recurrent and non truncating)

  squamous cell carcinomas( not recurrent and were usually inactivating)
- the same gene can function in completely opposite ways in different cell type

# Distribution of mutations in two oncogenes (PIK3CA and IDH1) and two tumor suppressor genes (RB1 and VHL)



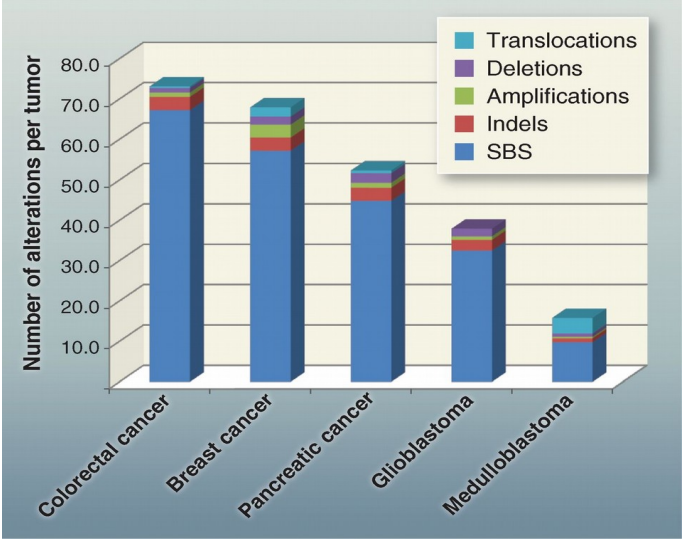
# Number of mut genes

- 20,000 protein coding genes,
- 3284 tumors
- 294881 mutations reported
- 125 mut genes(71 supp, 54 oncogenes)
- Plateau reached?
- These genes are involved in chromatin regulation
- MRNA splicing factors
- All these genes have a telomere elongation process “ALT”
- Translocations, amplifications and deletions
- Plus 13 Mut-driver genes( not point mut, but recurrent amplifications nd homozygous deletion ) : takes the count to 138.

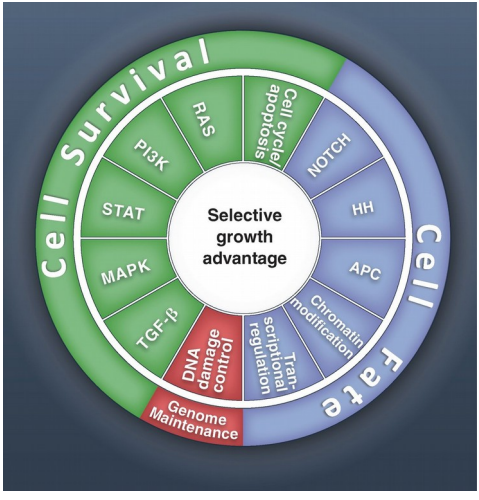
# Other Types of Genetic Alterations in Tumors

- Rate of point mutations (cancer~normal)
- Chromosomal changes in cancer is elevated (aneuploidy, inversions, deletions,  translocations)
- In duplications or deletions,It becomes difficult to pinpoint the gene that gave the cell its growth advantage.

# Total alterations affecting protein-coding genes in selected tumors.



# Signaling Pathways in Tumors



# Conclusion

- Most human cancers are caused by two to eight sequential alterations that develop over the course of 20 to 30 years.
- Each of these alterations directly or indirectly increases the ratio of cell birth to cell death; that is, each alteration causes a selective growth advantage to the cell in which it resides.
- The evidence to date suggests that there are ~140 genes whose intragenic mutations contribute to cancer (so-called Mut-driver genes). There are probably other genes (Epi-driver genes) that are altered by epigenetic mechanisms and cause a selective growth advantage, but the definitive identification of these genes has been challenging.
- The known driver genes function through a dozen signaling pathways that regulate three core cellular processes: cell fate determination, cell survival, and genome maintenance.
- Every individual tumor, even of the same histopathologic subtype as another tumor, is distinct with respect to its genetic alterations, but the pathways affected in different tumors are similar.
- Genetic heterogeneity among the cells of an individual tumor always exists and can impact the response to therapeutics.
- In the future, the most appropriate management plan for a patient with cancer will be informed by an assessment of the components of the patient's germline genome and the genome of his or her tumor.
- The information from cancer genome studies can also be exploited to improve methods for prevention and early detection of cancer, which will be essential to reduce cancer morbidity and mortality.

THANK YOU!