LIFECODES ACADEMY

TP53 Mutations

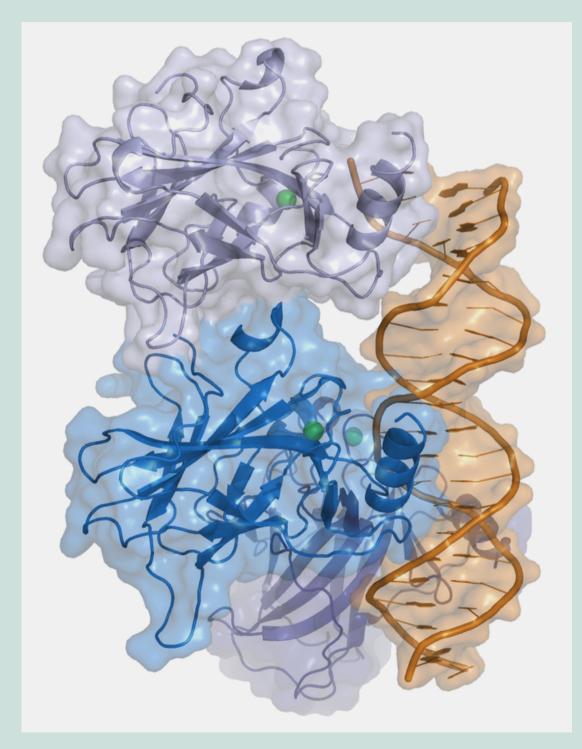Demi Zheng

"

Cancer is still a word that strikes fear into people's hearts, producing a deep sense of powerlessness.

"

Angelina Jolie

Image from: https://en.wikipedia.org/wiki/P53

Purpose

Awareness & Education

Background

TP53 Gene

Sequencing

11/23/23

"Guardian of the Genome"

The **TP53** gene, located on chromosome 17, contains instructions for the production of a protein called tumor protein **p53**.

- **tumor suppressor**
- **cell repair or self-destruction (apoptosis)?**
- **12 different isoforms**
- **most frequently mutated**

Mutations & Cancer

- Lung Cancer
- Li-Fraumeni Syndrome
  - Breast Cancer
- etc.

History

1st Decade: Oncogene -> Tumor Supressor

2nd Decade: function of p53

3rd Decade: regulation of metabolic pathways and cytokines required for embryo implantation

Current: new p53-based drugs to treat cancer

Ongoing TP53-related Cancer Therapy Research:
1. Reactivator drug **APR-246**
2. degradation/depletion drugs **HSP90 inhibitors or statins**
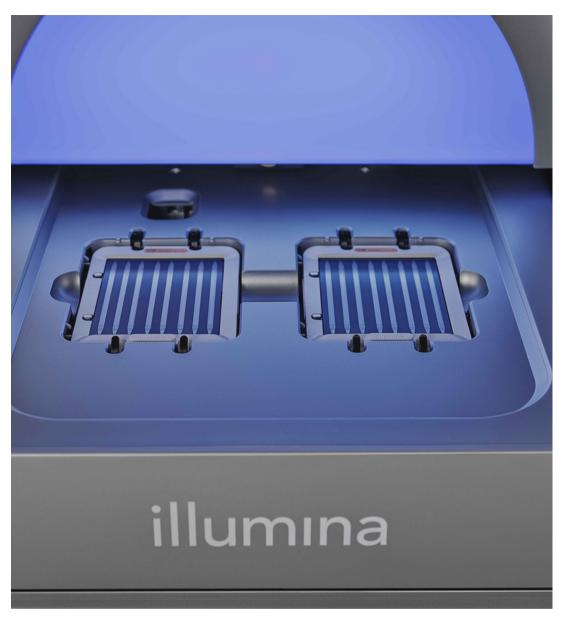3. cell death drugs **Wee1 inhibitors**

History of the TP53 Gene: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2966958/*

Drugs Targeting p53 Mutations: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9856662/*

First Generation Sequencing

- can only sequence one at a time
- accurate but costly and slow

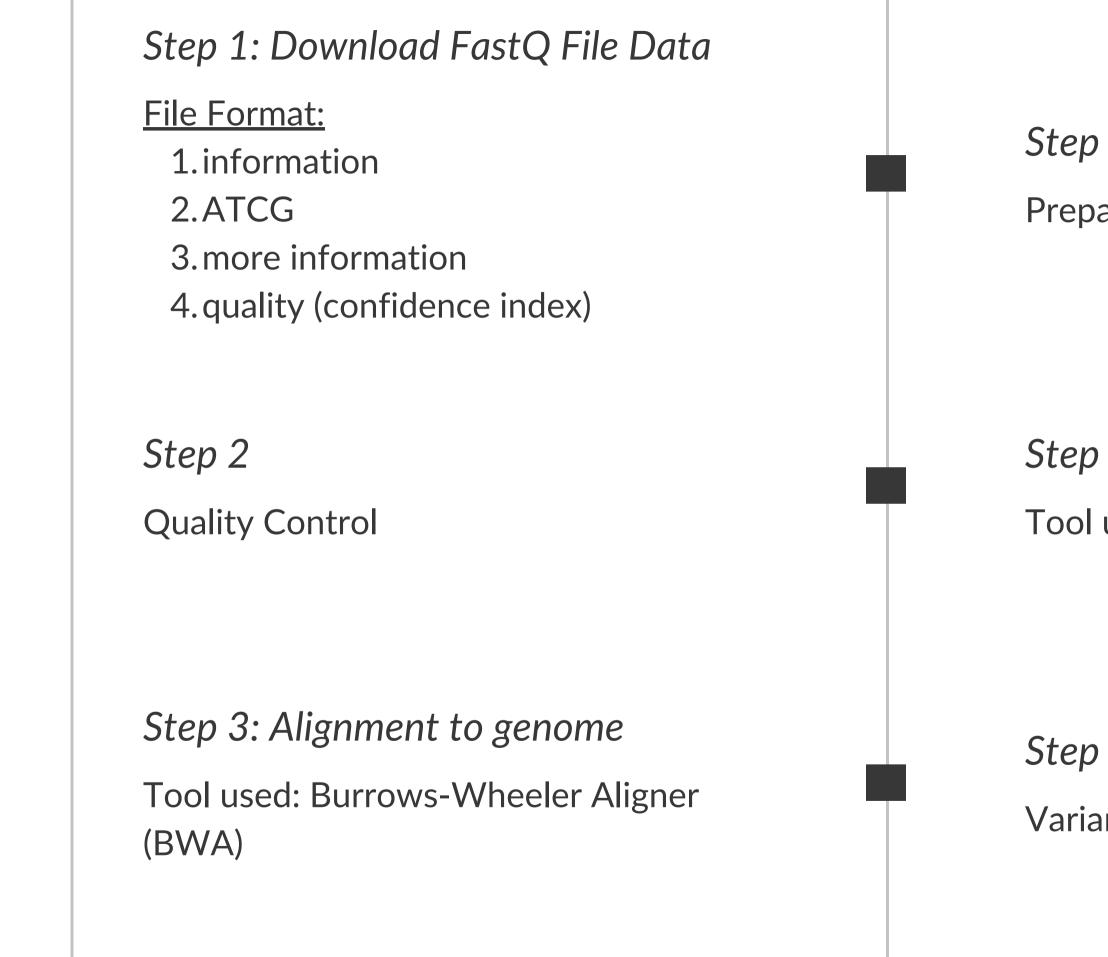## Next Generation Sequencing (NGS)

evolved based on need to sequence large quantities and reduce cost

- massive parallel sequencing
- much faster and less costly

Method

Data Analysis

Step 1: Download FastQ File Data

File Format:
1. information
2. ATCG
3. more information
4. quality (confidence index)

Step 2

Quality Control

Step 3: Alignment to genome

Tool used: Burrows-Wheeler Aligner (BWA)

Step 4: Alignment Cleanup

Prepares BAM file for variant calling

Step 5: Variant Calling

Tool used - FreeBayes

Step 6: Annotating

Variant Effect Predictor

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Results & Conclusion

Samples 1-3 & 5-8 & 10

8/10 have the same exact variants for the TP53 gene -- suggesting germline mutation

Many missense mutations
- labeled "benign/pathogenic"
- very likely cancerous -- Li Fraumeni Syndrome
- 3 have SIFT scores of "deleterious"

Uploaded variant	Location	Allele	Consequence	Symbol	Gene	Feature type	Feature
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	upstream_gene_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	upstream_gene_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	non_coding_transcript_exon_variant	TP53	ENSG00000141510	Transcript	ENST0000
.	17:7676154-7676154	C	missense_variant	TP53	ENSG00000141510	Transcript	ENST0000

Sample 4

Includes all the variants as on the right side, with additional variants such as: intron variant, synonymous variant, upstream gene variant etc.

same conclusion as previous samples

17:7676261-7676261	T	synonymous_variant	TP53
17:7676261-7676261	T	synonymous_variant	TP53
17:7676261-7676261	T	synonymous_variant	TP53
17:7676261-7676261	T	synonymous_variant	TP53
17:7676261-7676261	T	synonymous_variant	TP53
17:7676261-7676261	T	synonymous_variant	TP53
17:7676261-7676261	T	upstream_gene_variant	TP53

Sample 9

No TP53 Mutations

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More Research

understand p35 pathway & molecular mechanism

Database Expansion

- aids scientists and doctors by expediting variant effect predictor process
- makes the predictions as well as diagnoses more accurate

TP53 Gene Therapy

link p53 mutation status to cancer treatment and clinical outcome

Future Advancements

TP53

Further Reading & Resources

The TP53 Database

https://tp53.isb-cgc.org/

p53: The Gene that Cracked the Cancer Code

https://www.amazon.com/p53-Gene-that-Cracked-Cancer/dp/1472910524#:~:text=p53%3A%20The%20Gene%20that%20Cracked%20the%20Cancer%20Code%20tells%20the,cells%20when%20they%20turn%20cancerous.

Recent Advances in p53

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7913554/

Citations

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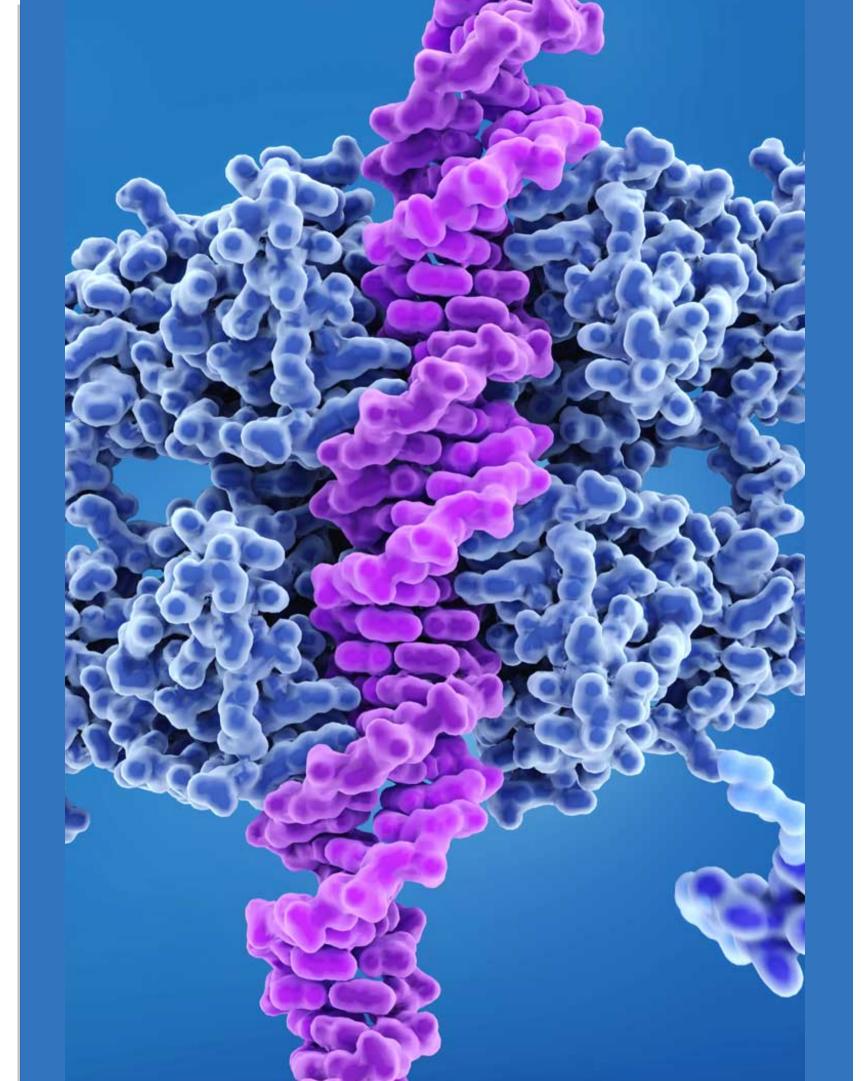
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LifeCodes Academy

Thank You!

Any Questions?