Cancer Genetics

A BiographI module by

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Information for instructors

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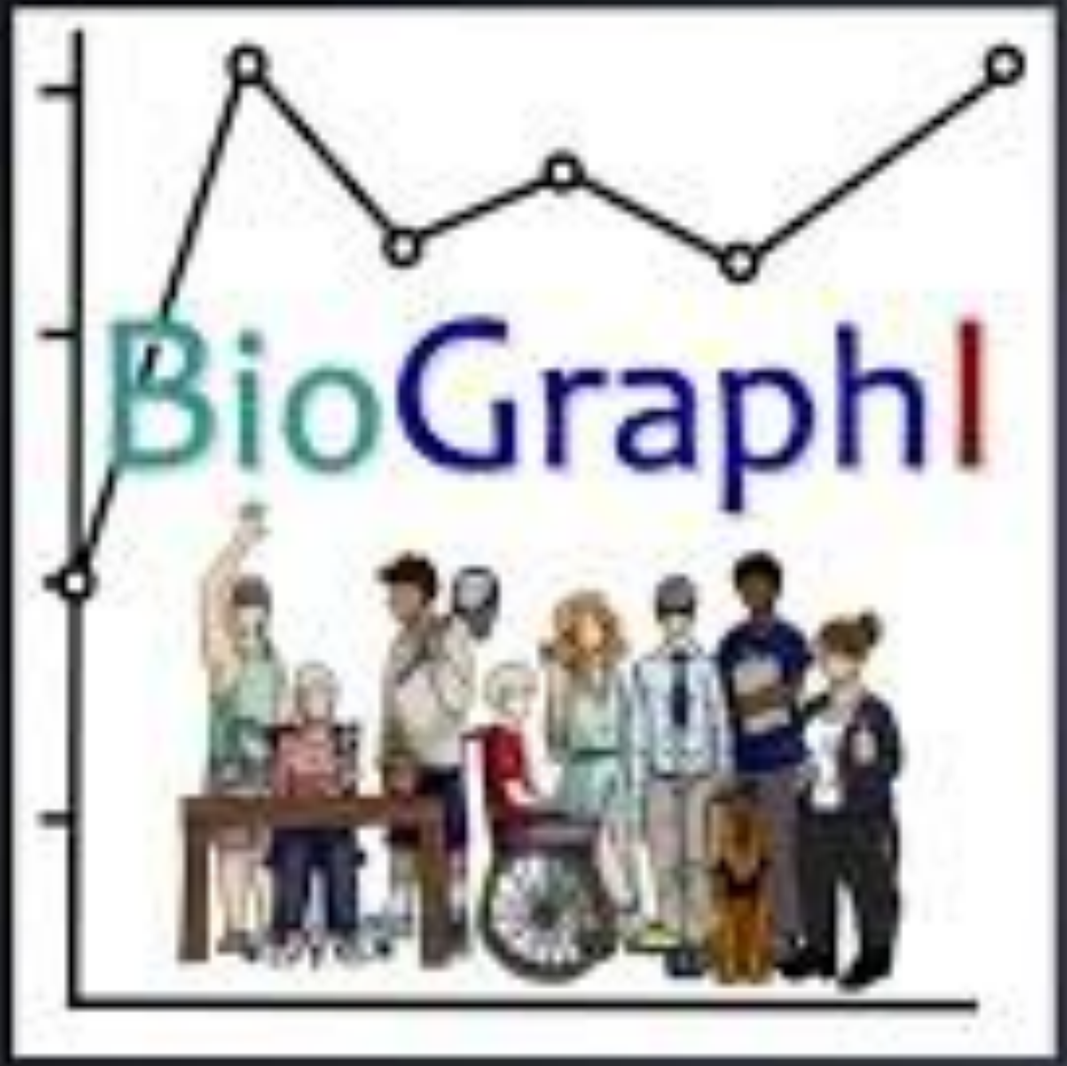
Department/Program: Biology
Level: Major-level
Course type: Lecture
Delivery mode: In-person
Students: Majors
Number of students: Any
Estimated duration of activity: one class period; two assignments

Interview with Megan Majocha



Healthy cells live together in relative harmony, because

Contact inhibition

Cells in many tissues stop dividing if they sense there are cells around them

Intact DNA repair systems

Slow the rate of accumulation of mutations

Intact cell cycle checkpoints

Prevents cells with DNA damage from dividing

Intact apoptosis systems

Abnormal cells can be tagged by immune cells and triggered to undergo immediate apoptosis

Cancer cells have mutations in oncogenes and tumor suppressors

Oncogenes

genes that help cells grow
over-expression of these genes can lead to uncontrolled cell growth
often referred to as proto-oncogenes before mutation

Tumor suppressors

genes that prevent uncontrolled cell growth and tumor development
mutations in these genes diminishes the cell's ability to regulate cell growth
also known as anti-oncogenes

Mutations in oncogenes and tumor suppressors set cells on the path to becoming increasingly cancerous

Mutations

all mutations accumulate naturally with age

mutations are also caused by mutagenic agents such as environmental exposure to radiation, chemicals, and certain viruses

cells become increasingly cancerous as they accumulate specific mutations

Genetic susceptibility to cancer is because of an inherited mutation in an oncogene or tumor suppressor

p53 mutations

In some families one copy of *p53* is mutated

BRCA mutations

Defect in DNA mismatch repair

Increases risk of breast, ovarian, and other cancers

Lynch syndrome (*MLH1*, *MSH2*, *MSH6,* and other mutations)

Defect in DNA mismatch repair

Increases risk of early colorectal cancer

Only 5-10% of cancer cases arise from inherited mutations!

The remaining 90-95% of cases are from age, environment and lifestyle

Cancer terminology

tumor

benign

malignant

cancer

carcinogenesis

metastasis

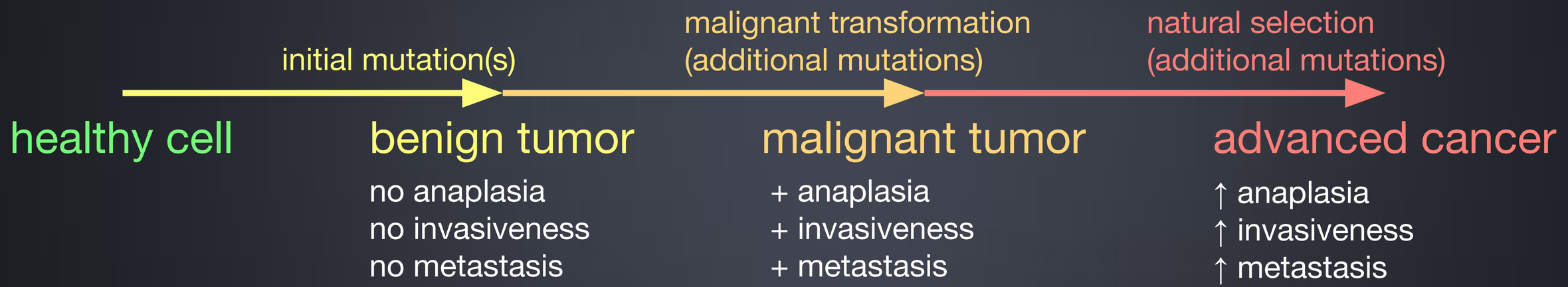
anaplasia

tumor load

tumor latency

genomics

Cancers increase in their malignancy over time as they accumulate further mutations



We can use biotechnology to identify genes that are driving cancerous cells

Genome Wide Association Studies (GWAS)

allows us to map regions of the genome that are statistically associated with a characteristic
generally limited to discrete traits
expensive

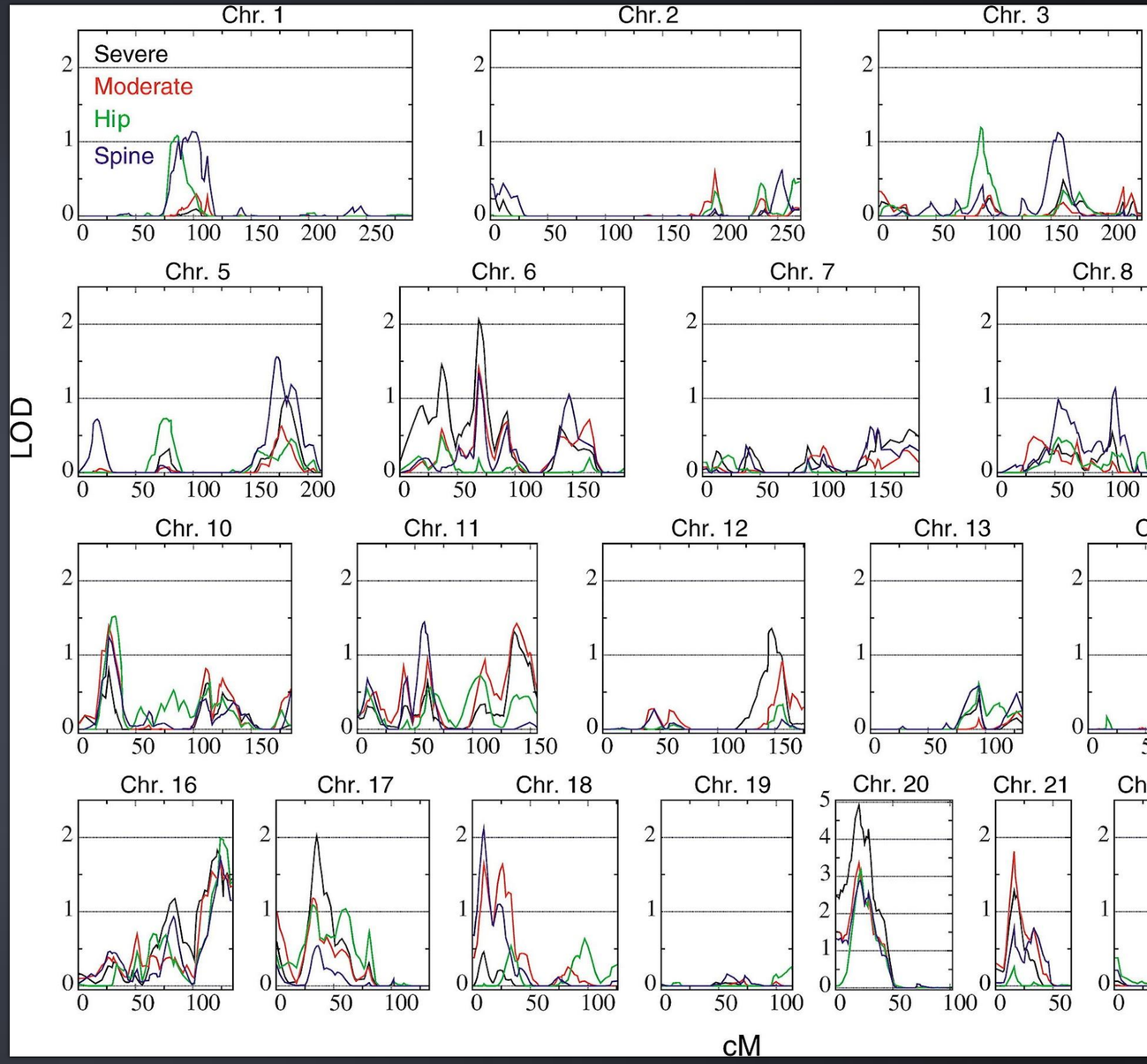
Quantitative Trait Locus (QTL) Mapping

like GWAS, but often targeted to certain chromosomes or certain regions
better suited for polygenic analysis
better suited for continuous trait analysis
less expensive and better throughput

Example of QTL Mapping for osteoporosis

LOD (log of odds) scores
tell us the log of the probability ratio that the locus is correlated with the characteristic we're measuring

In practice, we look for LOD scores >3 (1:1000 probability ratio)



Ha N-H, Long J, Cai Q, Shu XO, Hunter KW. The Circadian Rhythm Gene Arntl2 Is a Metastasis Susceptibility Gene for Estrogen Receptor-Negative Breast Cancer. PLOS Genet. 2016 Sep 22. doi: 10.1371/journal.pgen.1006267

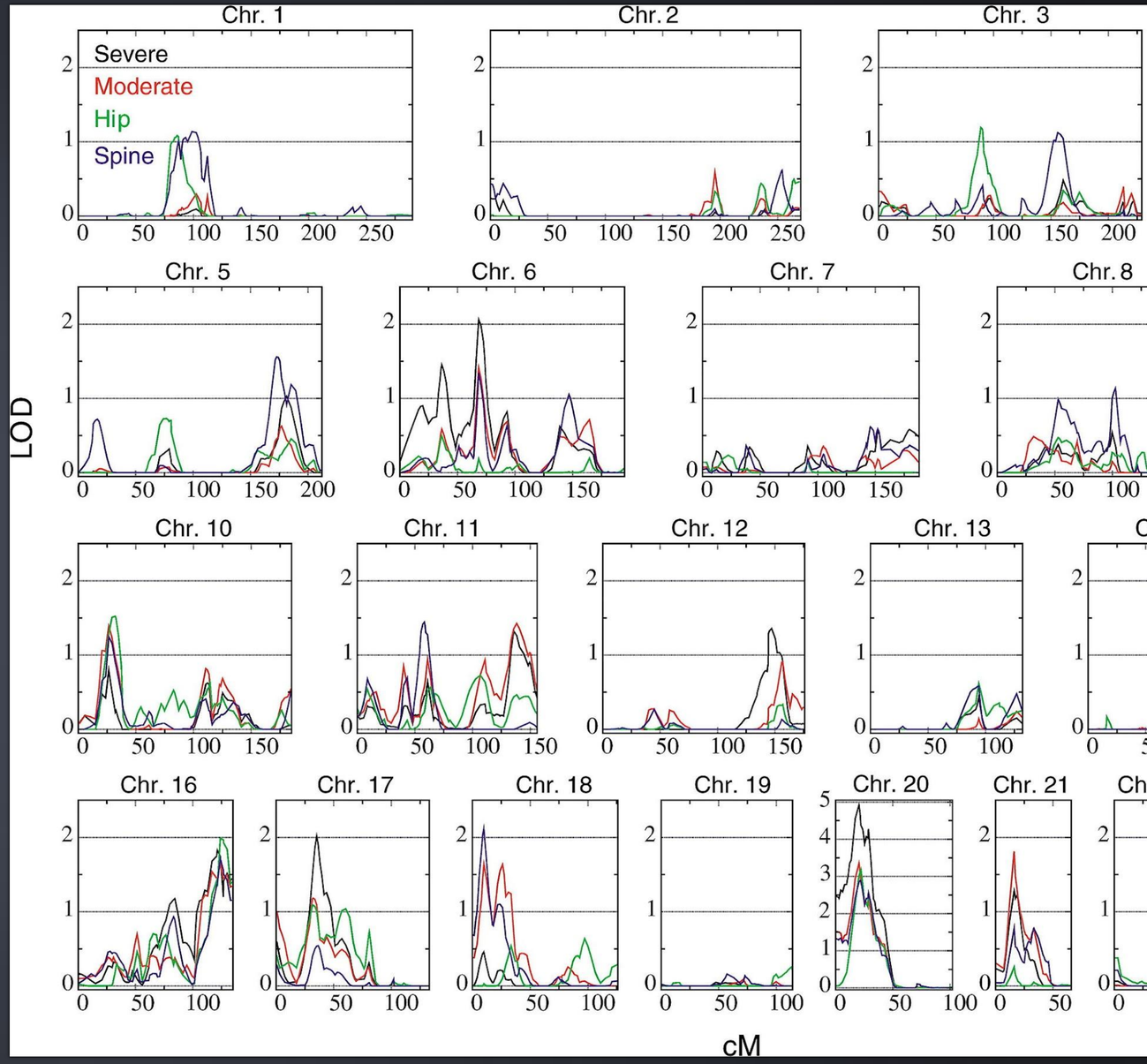
Which region is most associated with osteoporosis?

Look at the QTL map

Where are the peaks?

Do any of these peaks have high LOD scores?

Typically we want LOD >3



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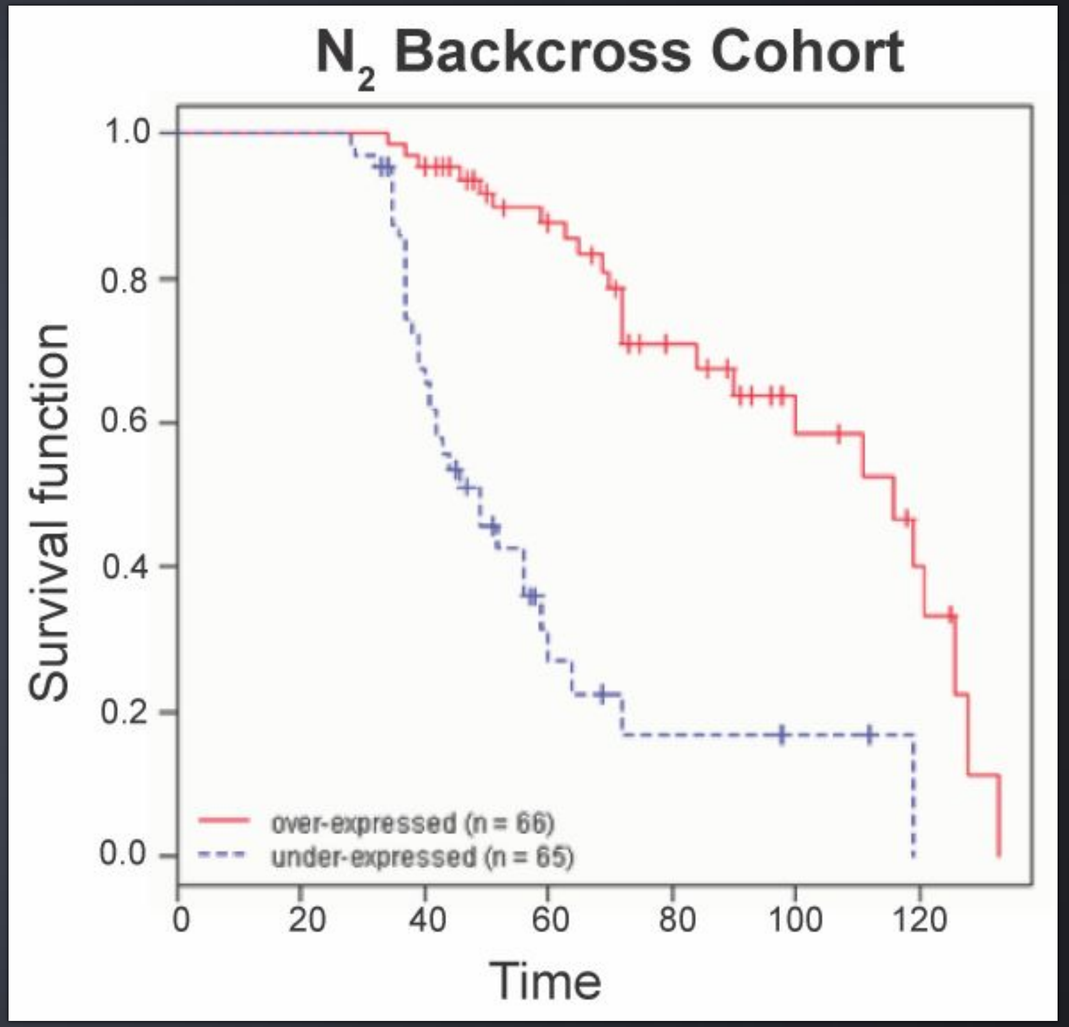
Example of survival curve for a tumor suppressor gene

Survival Curve Basics

the line almost always starts at 100%, and shows the percentage of the group that is still alive over time

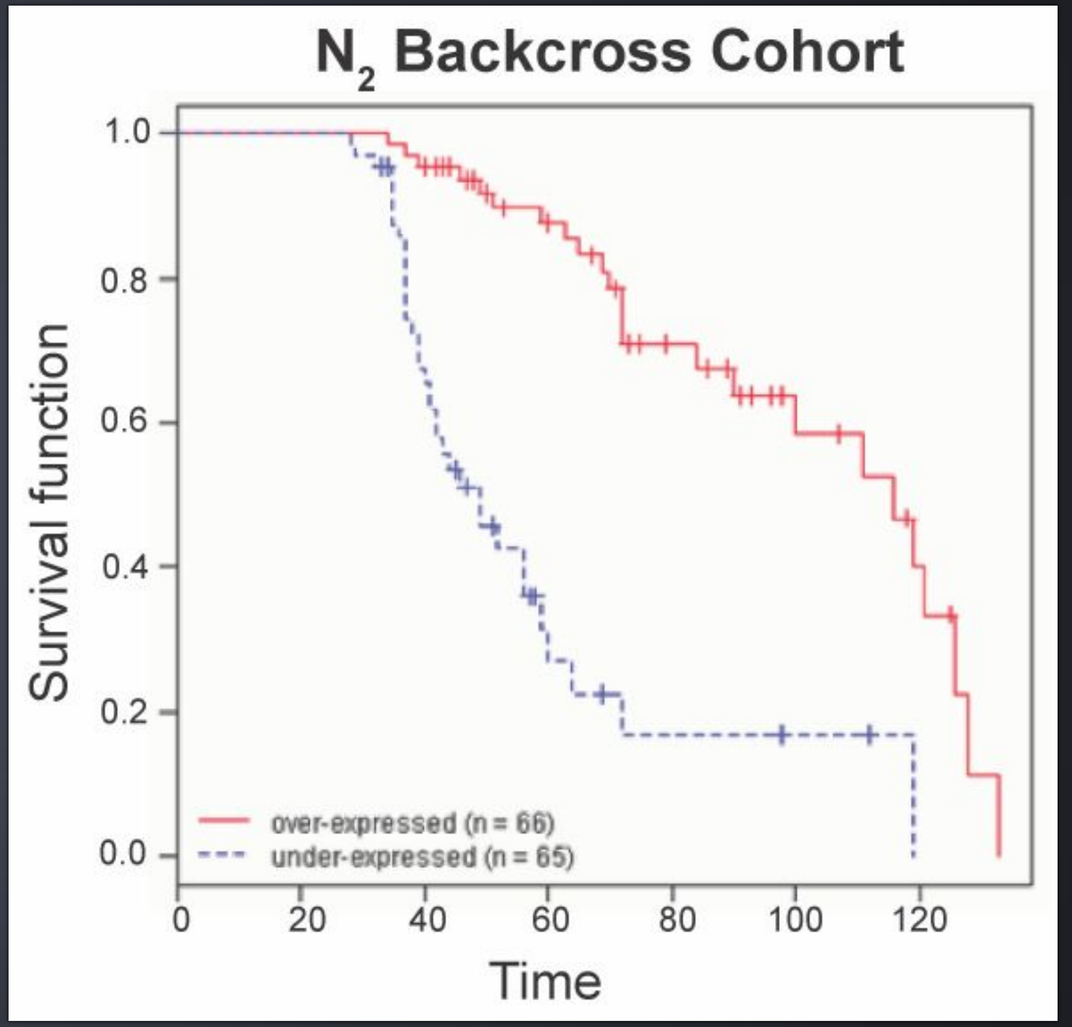


Majocha MR, Jackson DE *et al*. Resf1 is a compound G4 quadruplex-associated tumor suppressor for triple negative breast cancerPLOS Genet. 2024 May 9. doi: 10.1371/journal.pgen.1011236

Which level of expression of the gene is associated with better survival?

Look at the y- and x-axis on the graph

Which curve has higher survival function and time?



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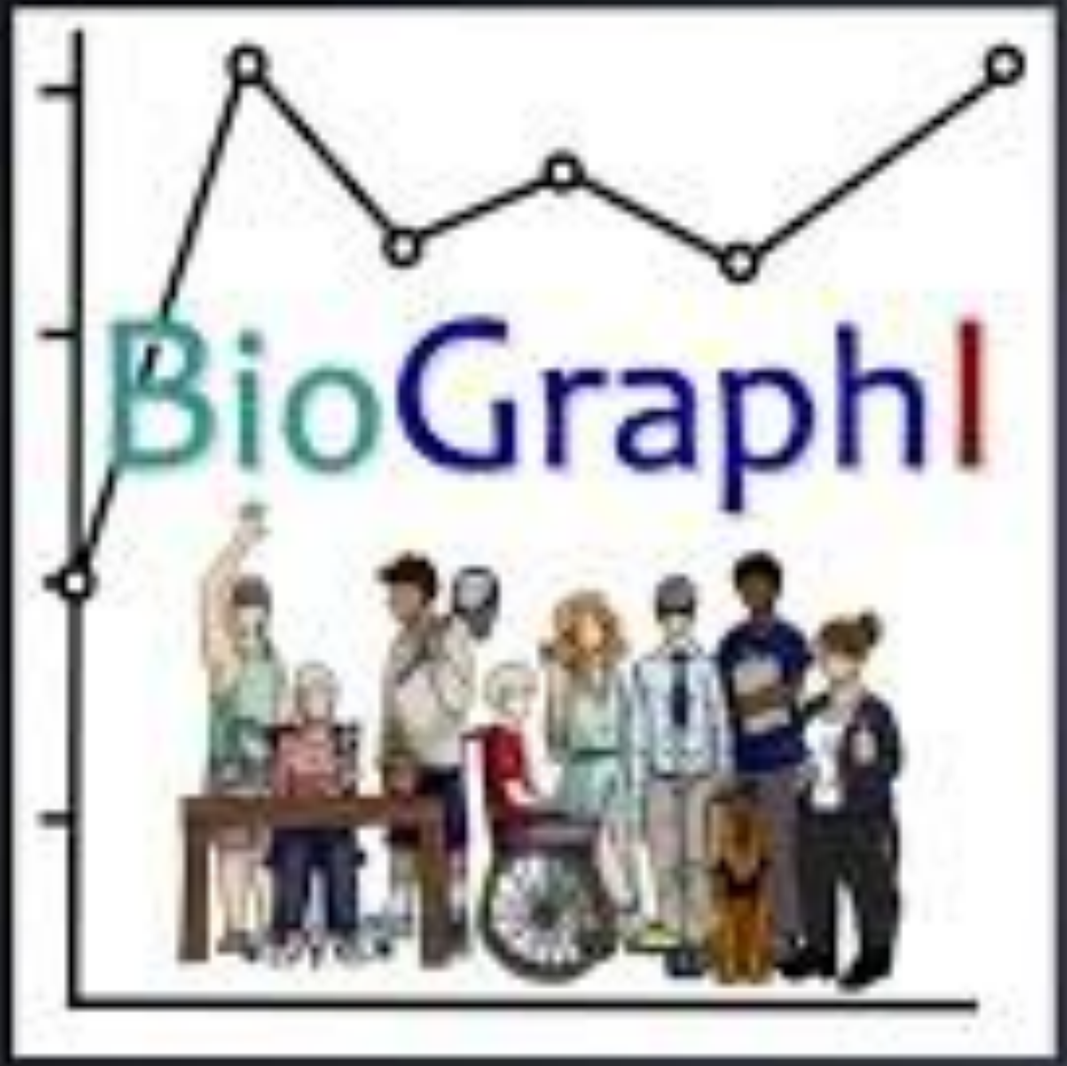
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