Module 4.1: Learn - Biology

4.1 Biology

Chromosome Y

The Y chromosome is most famous for being the main sex determination chromosome in mammals (and other species with an XY sex determination system), as the presence of a Y chromosome leads to the development of male reproductive organs and lack of it leads to female reproductive organs. Specifically, it is the SRY gene on the Y chromosome that triggers male development. There are many other cool and important things that the Y chromosome is responsible for.

Fun facts about the Y chromosome

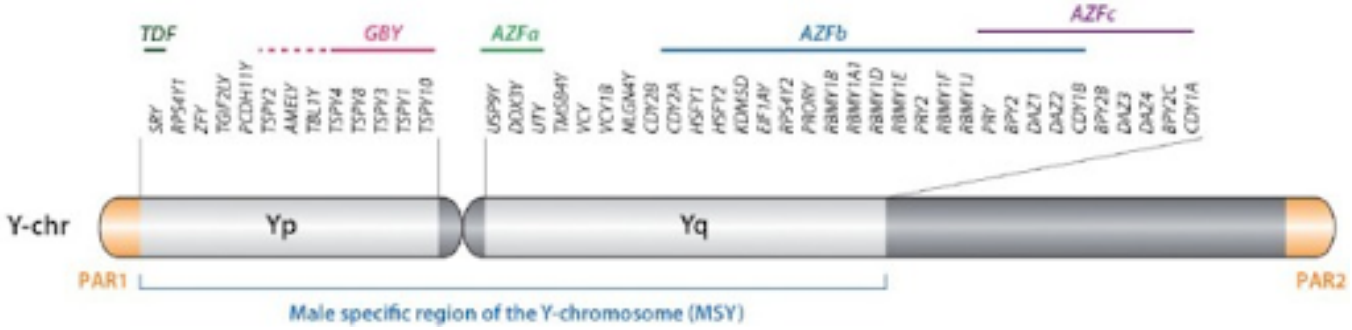
- In addition to SRY, the human Y chromosome contains many other genes
  - 107 are protein-coding, though some of these genes are repeated making the number of unique protein-coding genes only about 42 (according to the latest release of the human reference genome)
    - Y chromosome carries many testis-expressed genes that are often found in palindromes (inverted repeats)
      - These genes are thought to affect fertility and possibly compete with genes in similar ampliconic regions on the X chromosome for transmission to sperm cells during male spermatogenesis
      - Palindromes allow for exchange of genetic material between the two arms of the Y chromosome by non-allelic homologous recombination thereby reducing the divergence between the two arms, offers a way to repair deleterious mutations, and lead to large structural and copy number variants
- The human Y chromosome can be classified structurally into three regions:
  - male-specific region of the Y chromosome (MSY) which contains 23 protein-coding genes
  - pseudoautosomal regions (PAR1 and PAR2) which are identical to regions on the X chromosome which contain 20 protein coding genes

    - heterochromatin (transcriptionally inactive) region on Yq (see figure below)
- While genes in PARs are present in both X and Y chromosomes and undergo meiotic recombination just like genes in the male-specific region (MSY) are excluded from meiotic recombination with a homologous chromo
    - MSY is inherited from father to son without recombination and its evolution therefore reflects mutation, drif males and follows a single evolutionary history
- The Y chromosome is generally highly repetitive, which made it difficult to get the true full sequence (highly re up short sequencing reads to get a full sequence)

A huge effort to understand the Y chromosome in more detail has been underway lately and has resulted in two b out in August 2023. Dr.Wilson is on one! See the additional resources for this section for more information.

Chromosome Y genes

The male-specific region of the Y chromosome (MSY) genes can be classified into two groups according to their Group-I genes are expressed almost ubiquitously, and Group-II genes are expressed specifically/predominantly i postulated that Group-I MSY genes, including DDX3Y, EIF1AY, KDM5D, RPS4Y, TBL1Y, USP9Y, UTY, and ZFY, expressed regulators for gene expression and protein stability as maintaining dosage of homologous gametologs On the other hand, Group-II genes, including HSFY, SRY, RNA-binding motif protein, Y-linked (RBMY), and testis encoded (TSPY), may play diverse functions from their X homologs.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430935/figure/F1/ (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430935/figure/F1/)

Schematic diagram of human Y chromosome indicating the protein-coding genes within the male-specific region

Since we are looking across cell lines from cancer in many tissue types, we would do better to assess the expres chromosome Y genes that are ubiquitously expressed should be a better choice as evidence for presence of a Y be assigned a specific gene to analyze this week (more on this in the Coding section).

Chromosome Y genes in human cancer

As the Y chromosome is specific to genetic males, it is thought that cancers in which incidence (rate of developin (how much the cancer is hurting the tissue) has a male bias might have to do with specific interactions with chron dysregulated. For example, the TSPY gene was initially identified as a testis-specific chromosome Y gene, but it expressed in several cancer tissues. TSPY and the protein complexes it forms have roles in cell cycle and chron healthy tissues and expression of TSPY in cell line models accelerates cell proliferation as is expected for genes tumor progression. Chromosome Y genes are involved in many cellular processes and are likely to play a role in tumor cells.

In addition to incorrect expression of chromosome Y genes in cancer tissue, loss of chromosome Y has been obs illnesses including multiple cancer types. We will be reading the paper that reported these findings from bladder data in Module 5, but the conclusion was that patients with low chromosome Y gene expression had significantly compared to those with high chromosome Y gene expression. 4 genes– KDM5D, UTY (aka KDM6C), TBL1Y, an associated with poor prognosis. The proposed mechanism for this is through the immune system (more on this i These genes are definitely among the genes we will be looking at in the CCLE as a group.

Sex chromosome gene expression in healthy tissues

Activity: Lookup what is known about your assigned gene

There are many ways to learn about genes, but an easy and effective place to start is the GeneCards website (**https://www.genecards.org/** **(https://www.genecards.org/)**). Open this website in a browser and type the na gene in the search bar at the top. Usually the first result is an exact match; click on the search result to learn abo including known structure and function, diseases it has been linked to, and where it is expressed in humans and you click on a result, the first thing you usually learn is any other names this gene has been called ("Aliases"). G different names as they are being studied in the years following the gene's discovery. When reading about genes can find different names and different spellings for the same gene. This is why in addition to gene names, other

specific gene information databases are given to help reduce confusion when sharing results. As you browse thr
entry for your gene, you will see references to many different databases of information.

Activity: Lookup your assigned sex chromosome gene in GTEx

Using the instructions in Module 3.1, look up your assigned sex chromosome gene on GTEx and report your find
progress report the same way we did for XIST.

Sex differences in cancer

A simple measure of sex differences in cancer can be determined by looking up yearly statistics collected by orga
American Cancer Society. These statistics reports are broken down by sex of the patient, regions of the tissues v
developed, and other aspects that might be specific to a cancer type such as infections that might have helped to
formation. If you see that the type of cancer you are studying (or subtype of cancer) is reported much more in on
that might be a good first clue that there are sex differences that you can investigate at the gene expression level

There are many ways in which sex differences can happen in tumors. To get a sense of what is currently known
think the best way is to read a review article. A review article summarizes findings from many recent, published s
reader get an idea on what is currently known in a broader sense about a specific topic. This review article talks
cancer and how they are affected by sex differences.

Journal Club: Sex differences in cancer mechanisms

**https://bsd.biomedcentral.com/articles/10.1186/s13293-020-00291-x (https://bsd.biomedcentral.com/article
00291-x)**

To help make sure you don't get too lost in the details, as you go through the article ask yourself the following stu

1. Which cancers that show a sex difference in incidence and survival, which sex tends to get cancer more o
2. What hormones are likely to have an effect on tumor tissues when sex differences are observed?
3. What is epigenetics? Studies on sex differences in epigenetics have been mostly performed in what organ
4. How can XX females be protected against the negative effects of cancer-causing mutations compared to X
5. What is metabolic reprogramming? Which metabolic processes are upregulated in males versus females?

6. What is the most frequently mutated gene in cancer? How does this gene affect chromosome X gene exp genes modulate the function of this gene differently in females versus males?

Please go to the Journal Club assignment for this module to participate in the discussion. Here are those Perusa if you need them:

- **Accessing Perusall through Canvas (https://www.youtube.com/watch?v=bs_Z_3wqib4)** (**Accessing Peru Canvas Video Transcript (https://docs.google.com/document/d/1ql6li6Au6ccO-xoTpQRM_iIF5Z6FMeGtbRG usp=sharing)**)
- **Intro to Perusall (https://www.youtube.com/watch?v=M8bOP7yF_6I)** (**Perusall Introduction Video Transc (https://docs.google.com/document/d/1OPT_i7YrembK3518QiKaYcgClgsM-BRbuCCc7Y-BQXU/edit?usp=sharing)**

Additional Resources

- Chromosome Y
  - **https://en.wikipedia.org/wiki/Y_chromosome (https://en.wikipedia.org/wiki/Y_chromosome)**
- The complete sequence of a human Y chromosome (with Dr. Wilson as an author!)
  - **https://www.nature.com/articles/s41586-023-06457-y (https://www.nature.com/articles/s41586-023-06**
- Assembly of 43 human Y chromosomes reveals extensive complexity and variation
  - **https://www.nature.com/articles/s41586-023-06425-6 (https://www.nature.com/articles/s41586-023-06**
- Analysis of 62 hybrid assembled human Y chromosomes exposes rapid structural changes and high rates of
  - **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5591018/ (https://www.ncbi.nlm.nih.gov/pmc/articles/**
- Roles of Y chromosome genes in cancer
  - **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430935/ (https://www.ncbi.nlm.nih.gov/pmc/articles/**
- Y chromosome loss in cancer drives growth by evasion of adaptive immunity
  - **https://www.nature.com/articles/s41586-023-06234-x (https://www.nature.com/articles/s41586-023-06**
- Example of a mechanism by which you can see sex differences in tumor biology
  - Sexually dimorphic RB inactivation underlies mesenchymal glioblastoma prevalence in males
    - **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151215/ (https://www.ncbi.nlm.nih.gov/pmc/artic**