TEACHING THE GENOME GENERATION

Exploring Hereditary Cancer on the cBioPortal

The Jackson Laboratory

Leading the search for tomorrow's cures

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Introduction

Dr. Myra Ortiz sat down at her office desk early one morning. Her computer screen automatically brought up today's schedule and her virtual assistant prompted her, "Do you want to review the files and histories for the patients you will see today?" The doctor agreed and her assistant brought up the first patient, Monica age 25.

"Another young one," Dr. Ortiz thought to herself. As a doctor who treats cancer patients, also called an oncologist, she specializes in melanoma, a type of skin cancer. Dr. Ortiz typically saw middle-aged patients, but every so often came across younger patients in their second or third decade of life. Cases presenting at this age can, but not always, have an inherited gene variant increasing risk for cancer. The doctor asked her virtual assistant to find Monica's Newborn Genomic Report (NGR). The assistant successfully located the NGR and Dr. Ortiz searched the report for cancer risk. Sure enough, Monica has a variant in the *CDKN2A* gene, which increases her risk for hereditary melanoma. "Ah yes, *CDKN2A*," Dr. Ortiz thought about the function of this gene. *CDKN2A* codes for a protein that acts as a guardian for the cell and prevents cells from growing out of control when something goes wrong. However, when one copy of this protein is not functioning properly, the risk for cancer increases.

After reviewing the rest of the day's patients and histories, Dr. Ortiz stood up, took a deep breath, and walked into the clinic.

Quick Knowledge Check:

a. How old is Monica and what type of cancer does she have?

b. What is an oncologist?

c. Which gene appeared on Monica's newborn genomic report as a variant increasing her risk for cancer?

d. What does this gene normally do in the cell?

Activity 1: Exploring Hereditary Cancer on the cBioPortal

Is Dr. Ortiz's patient Monica an outlier? Cancer is typically a disease of the aged. As people grow, they accumulate variants (mutations) in their DNA and therefore, advanced age is considered one of the most significant risk factors for cancer diagnosis.

1. Have a look at this graph from the National Cancer Institute's SEER database[1] (see **Figure 1**).

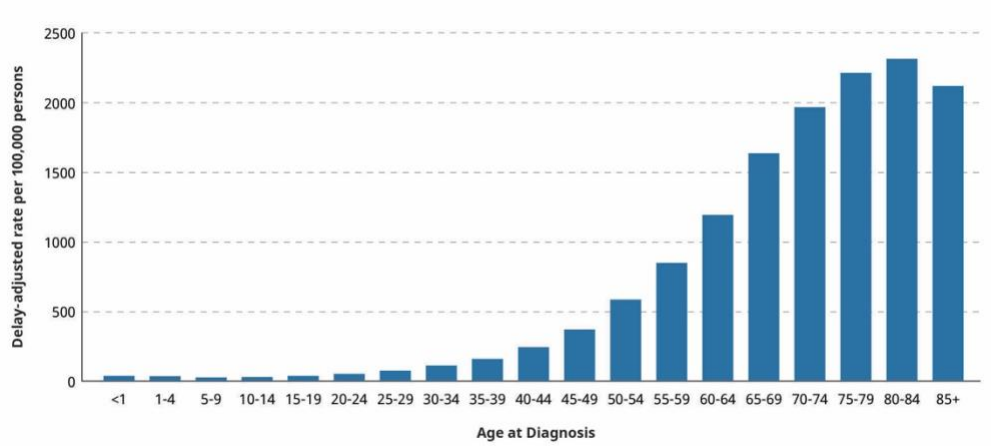

Figure 1. Cancer diagnosis increases as a function of age. New diagnoses of all types of cancer broken down into age groups. The data was collected by National Cancer Institute from 2013-17 for all races and both assigned sexes.

a) What do you notice about the shape of the graph?

b) At what age do you notice a steep increase in cancer diagnoses?

c) Use this graph to estimate the median age of cancer diagnosis.

Now let's explore the average age of diagnosis for patients with melanoma, which is the type of cancer Monica has.

2. Navigate to the cBioPortal and find the Metastatic Melanoma (DFCI, Science 2015) study. First, find the "Age of Diagnosis" histogram.

> *See cBioPortal Tutorial Series: Introduction & homepage navigation; Navigating a single study; Locating demographic data; Calculating age of diagnosis range; Calculating median age of diagnosis*

a) *Use the median feature to calculate the range and median age of diagnosis for patients in this metastatic melanoma study.*
   i. *What are the ages of the oldest and youngest patient in this study?*
   ii. *What is diagnosis age range?*
   iii. *What is the median age of diagnosis?*

b) *Is this median higher or lower than the one for the overall median age of diagnosis for all cancers that you estimated in question 1c?*

c) *What factors do you think contribute to the age of diagnosis for melanoma, a type of skin cancer?*

Monica has a *CDKN2A* gene variant. While *CDKN2A* variants are rare in the overall population, 20-40% of individuals with hereditary melanoma have an inherited *CDKN2A* gene variant. As Dr. Ortiz described, *CDKN2A* codes for factors that act as guardians in the cell, which are also called tumor suppressors. Tumor suppressors prevent cells from growing out of control. Let's investigate *CDKN2A* within this melanoma study.

See cBioPortal Tutorial Series: Locating gene variants within a single study; Sorting a study by gene name

3. Locate the list of "Mutated Genes" on the study main page. Use the search bar at the bottom of the list to find mutations in the gene *CDKN2A*.

   a. *How many mutations were identified in* CDKN2A *in this study?*

   b. *How many patients in this study have mutations in* CDKN2A*?*

   c. *How do you account for this discrepancy?*

4. Sort the study data to display only the patients who have mutations in *CDKN2A*, which has variants that can be inherited. Find the "Mutated Genes" table and scroll or search to find the *CDKN2A* gene. Check the box under "#" and click "Select samples" to display the data for only the patients with this mutation.

5. Once the data is sorted, locate the "Age of Diagnosis" histogram.

a. *What do you notice about the shape of the histogram?*

b. *What is the range of age of diagnosis for this group of patients?*

c. *What is the median age of diagnosis for patients with* CDKN2A *mutations?*

d. *Is the median age of diagnosis for patients with* CDKN2A *mutations different than the median age for the entire study (see Question 2)?*

e. *Is the median age for people with* CDKN2A *variants surprising to you? Why or why not?*

6. Still focusing on the *CDKN2A* sorted data, click the "Clinical Data" tab at the top of the study page. Then find the patients Pat 110 and Pat127. Without clicking on the patient ID numbers, find the "Age at Diagnosis" listed for each patient.

See cBioPortal Tutorial Series: Locating individual patient data

a. *How old were each of these patients when they received their melanoma diagnoses?*

b. *What factors do you think contribute to someone getting melanoma earlier in life versus later in life?*

c. *If both individuals have melanoma resulting from inherited mutations in* CDKN2A*, how can you explain this age difference?*

d. *Challenge: Reflect on your answer to question 6c in connection with the shape of the histogram you observed in question 5a. Formulate a hypothesis that could be tested to explain the observed distribution of the age of diagnosis histogram.*

Resources

1. cBioPortal Written Tutorials
2. cBioPortal Video Tutorial YouTube Playlist

Reference

National Cancer Institute. Age and Cancer Risk. March 5, 2021. https://www.cancer.gov/about-cancer/causes-prevention/risk/age