

The Face of a Rare Genetic Disease

by

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Part I – I Am Chromosome 16

I am chromosome 16. I began my existence inside the dank darkness of a human cell. Inside the nucleus of that cell I was surrounded by my brothers and sisters, all 46 of us carrying within us the mysterious code of life. This ancient cipher of life, otherwise called the genetic code, has been handed down through our ancestral line going back a hundred and fifty thousand years, ever since modern human beings first walked this earth. I am one of the keepers of that great legacy created for the sole purpose of faithfully carrying part of that ancient code and handing it down through the generations.

Happily, I along with my brothers and sisters went about our business and duplicated faithfully time and time again creating instructions for the cells to follow as a little human baby boy slowly grew inside his mother's womb. It was a time of great joy for his mother, who looked forward in great anticipation to the birth of her first child, but little did she know that she carried within her genetic code a tiny little alteration that would bring her happy little family much anguish and pain.

Questions

1. Where are human chromosomes located in the cell?
2. How many chromosomes does a normal human being have in one somatic cell?
Refer to the following resource for more information:
 - Khan Academy. *n.d.* Chromosomes [webpage]. <<https://www.khanacademy.org/science/high-school-biology/hs-reproduction-and-cell-division/hs-chromosome-structure-and-numbers/a/dna-and-chromosomes-article>>
3. Why are the chromosomes replicating? Why is this necessary for the embryo? (*Hint*: think about mitosis.)
4. What could happen if the chromosomes stopped replicating?
5. What is the relationship between cells, the nucleus, chromosomes, genes and DNA? Explain and draw a figure to illustrate the concept.
Explore the following resources for more information:
 - MedlinePlus. 2021. What is a chromosome [webpage]? <<https://ghr.nlm.nih.gov/primer/basics/chromosome>>
 - MedlinePlus. 2021. What is a cell [webpage]? <<https://ghr.nlm.nih.gov/primer/basics/cell>>
6. What is the term given to a small alteration in the DNA?

Part II – The Story of Chromosomes and Genes

As you may have realized, I am not a normal chromosome 16 of the young mother-to-be, Iris, because I carry within me a genetic mutation preserved through generations of Iris’s ancestors, and I am to be handed down to her child. Like most of my brothers and sisters I have two arms: a *p* arm and a *q* arm. My *p* arm is smaller than my *q* arm (in fact, *p* stands for “petite”), and my arms are held together by a centromere. If you look at the karyotype (a karyotype is a photograph of the arrangement of chromosomes from larger to smaller in one somatic cell) in Figure 1 you will see me with all my brothers and sisters in the baby’s genome. We are numbered from one to twenty-two. The remaining two chromosomes are the sex chromosomes; XX in females, XY in males.

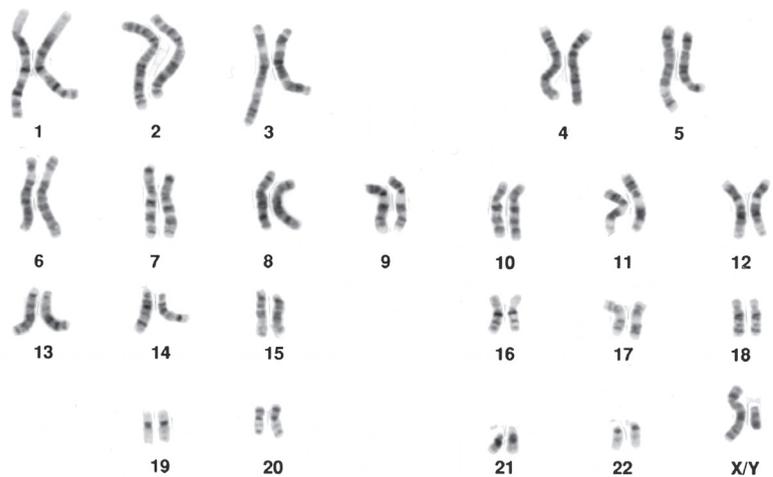


Figure 1. Normal karyotype.

Coming back to me, see how my mutated gene is located in my *p*-arm (Figure 2, purple arrow)? It’s designated as 16p13.11. That sounds like some sort of secret code, but it’s really simple to decipher, just like a puzzle: 16 is me, chromosome 16; *p* designates my small arm; 13.11 means band 1, sub band 3, sub-sub band 1, etc., and this is the position where my mutated gene lies. Using this system you can locate any gene in the human genome.

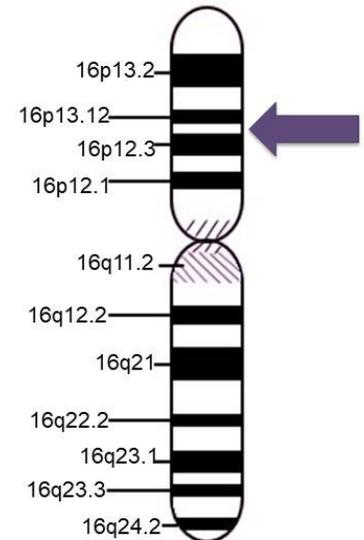


Figure 2. Chromosome 16.

Questions

1. Which of the chromosome arms is shorter, *p* or *q*?
2. What is meant by the term *karyotype*?
3. How is a karyotype prepared? What is the practical application of a karyotype?

Refer to the following:

- O’Connor, C. 2008. Karyotyping for chromosomal abnormalities. *Nature Education* 1(1): 27. <<https://www.nature.com/scitable/topicpage/karyotyping-for-chromosomal-abnormalities-298>>

4. Decipher what 16q21 means.
5. Most human genes have both *exons* and *introns*; what do these terms mean?

Refer to the following:

- Loewe, L. 2008. Genetic mutation. *Nature Education* 1(1): 113. <<https://www.nature.com/scitable/topicpage/genetic-mutation-1127>>

Part III – Baby Scott Is Born

As baby Scott's birth grew near, Iris could hardly contain her joy. Finally, one chilly September morning as the leaves started to turn a golden yellow, baby Scott came into this world, seemingly a perfectly healthy little baby boy. As the years went by, baby Scott grew into a boisterous seven-year-old who was always getting into trouble and kept Iris on her toes. One day as she was helping Scott with his bath she noticed some bumpy rash-like spots on his neck. At the time she didn't think much of it, and after tucking Scott into bed and reading him his goodnight story she went about her usual evening routine. But later that night she couldn't sleep and her mind kept going back to Scott's mysterious rash.

Questions

Use the following resources to help you answer the questions below.

- Moitra, K., S. Garcia, M. Jaldin, C. Etoundi, D. Cooper, A. Roland, ... and M. Dean. 2017. *ABCC6* and pseudoxanthoma elasticum: the face of a rare disease from genetics to advocacy. *International Journal of Molecular Sciences* 18(7): 1488. <<https://doi.org/10.3390/ijms18071488>>
 - PXE International [website]. <<https://www.pxe.org/>>
1. Do some research on the *ABCC6* gene at 16p13.11 and see if mutations on this gene may be responsible for a genetic disease. Name this disease and the gene that is responsible for the disease.
 2. From your research what is the clinical term for the rash on Scott's neck?
 3. Is this disease a common or rare genetic disorder? What percentage of people in the world are affected by this disease?
 4. Which protein does this gene code for?
 5. Describe the main symptoms of this genetic disease and how it is diagnosed in patients.
 6. What kind of therapeutic intervention exists for the disease? Describe briefly these interventions/treatments.
 7. The R1141X mutation accounts for around 30% of Caucasian mutations in this disease. Explain why this is called a *R1141X* mutation. What does *R* stand for? What does *1141* mean? What does *X* mean?

The following resources will help you to answer this question:

- MedlinePlus. 2021. What kinds of gene mutations are possible [webpage]? <<https://ghr.nlm.nih.gov/primer/mutationsanddisorders/possiblemutations>>
- Scitable by Nature Education. *n.d.* Nonsense mutation [webpage]. <<https://www.nature.com/scitable/definition/nonsense-mutation-228>>
- Andersen, P. 2012. Mutations [video]. *Bozeman Science*. Running time: 7:02 min. <<https://youtu.be/eDbK0cxKKsk>>

Part IV – A Visit to Dr. Garcia

Iris took Scott to the pediatrician the next day to get his rash checked out, just to be safe.

Dr. Garcia referred Scott to a dermatologist for testing. The sad news came back just before spring break; Scott had a rare genetic disorder. Iris was devastated and wanted to learn more about this rare disease that her son had inherited and about some of the possible outcomes. Dr. Garcia advised Iris to get in touch with patient advocacy groups like PXE International (<https://www.pxe.org/>) and Genetic Alliance (<http://www.geneticalliance.org/>) to learn more about the genetic disorder and get support from other families who were raising children with this disease. With their help and support Iris has learned about pseudoxanthoma elasticum and is raising her son in a happy and supportive environment.

Questions and Tasks for Small Groups

1. What is meant by a patient-advocacy group? What do these groups do? Discuss the different aspects of patient advocacy in small groups and prepare and present a figure outlining the ways in which patient advocacy groups help families with their struggle.

Revisit the following resources for help:

- Moitra, K., S. Garcia, M. Jaldin, C. Etoundi, D. Cooper, A. Roland, ... and M. Dean. 2017. *ABCC6* and pseudoxanthoma elasticum: the face of a rare disease from genetics to advocacy. *International Journal of Molecular Sciences* 18(7): 1488. <<https://doi.org/10.3390/ijms18071488>>
- PXE International [website]. <<https://www.pxe.org/>>

2. Watch the following TED talk:

- Terry, Sharon. 2016. Science didn't understand my kids' rare disease until I decided to study it [video]. *TEDMED*. Running time: 14:54 min. <https://www.ted.com/talks/sharon_terry_science_didn_t_understand_my_kids_rare_disease_until_i_decided_to_study_it>

Sharon Terry is the real-life character on which this case study is based. Read the inspiring story about Sharon and her family here:

- McClurg, L. 2017. When scientists failed them, parents unlocked genetics of kids' disease. *KQED*. <<https://www.kqed.org/futureofyou/300937/when-scientists-failed-them-parents-unlocked-genetics-of-kids-disease>>

In small groups, discuss what inspired you the most about Sharon's story. Did putting a real "human face" to the disease help you connect with the scientific material? Why (or why not)?

3. Brainstorm and write down several ideas about how you can raise awareness about rare genetic diseases. (Feel free to contact patient advocacy groups in your area and offer to volunteer.)