

TEACHING THE
GENOME
GENERATION

*THE CURIOUS CASE OF
DR. JAMES LUPSKI*

Case Study: Seeking Answers Through Genomics

In this exercise, you will use gene databases and genome browsers to follow the path to discovery of one man's debilitating disease. You will investigate gene function and its potential relationship to disease, assess genetic homology between species, and debate the best course of action for studying this disease.

This is a similar process that scientists and doctors must undergo when trying to develop models for the study of disease.



Dr. James Lupski, Professor at Baylor College of Medicine.



Dr. Lupski's foot.

Imagine you are a family doctor...

Today you have an appointment with Professor James Lupski, a geneticist at Baylor College of Medicine in Texas. He has been living with a rather troublesome disease since childhood. He has symptoms such as foot deformities (pictured above), muscle weakness and scoliosis that has slowly gotten worse over the years. Three of his seven siblings have also displayed similar symptoms.

Using Wikipedia www.wikipedia.com and/or OMIM www.omim.org, can you make a diagnosis based on Professor Lupski's symptoms?

What is the cause of this disease? Can you provide an explanation why only three of his seven siblings have this disease?

Can you offer a cure for Professor Lupski?

Finding the genetic cause

Professor Lupski thanks you for the diagnosis of Charcot-Marie-Tooth Disease (CMT, named for the doctors who first described it), but because he is a scientist, he wants to know more.

Professor Lupski, after genetic counseling, decides to sequence his own genome and publishes his results in the *New England Journal of Medicine*. At the next appointment, he shares the results with you.

The sequencing yielded over 3.4 million single nucleotide polymorphisms (SNPs) that were unique to Professor Lupski as compared to the published human genome. By focusing on genes known to be involved in CMT, Professor Lupski and his colleagues identified two recessive mutations (one missense, one nonsense) in the SH3TC2 gene.

Lupski et al. (2010) Whole-Genome Sequencing in a Patient with Charcot-Marie-Tooth Neuropathy. *New England J. of Medicine* 362, 13.

You've never heard of this gene before, so you consult a gene database.

You navigate to NCBI Gene database, www.ncbi.nlm.nih.gov/gene, and search for SH3TC2. You click on the human reference.

Does the Summary indicate what type of CMT Professor Lupski has?

Of course, your goal as a doctor is to alleviate Professor Lupski's symptoms. Since there is no readily available cure or even FDA-approved treatment, you want to give Professor Lupski peace of mind that researchers are currently looking for one.

Back at the OMIM CMT Type 4C page, you look for an **Animal Model** of the disease in the left navigation panel.

What type of animal is used as a model for this human disease?

What type of mutation in Sh3tc2 does this model have?

What do researchers think is the normal function of this gene?

Making connections across species

You question how good a *mouse* model of CMT is. Will researchers really be able to find a cure for your *human* patient by using a rodent?

Model organisms, much like model airplanes, are a representation/imitation/example of another (often larger or more complex) thing. In experimental biology, organisms like bacteria, flies and even mice are used as simplified representations of human biology and disease. These organisms can be more easily housed and fed, controlled for genetics and manipulated in experimental situations than humans. While technology is rapidly advancing scientists ability to understand human disease in the human, model organisms are still the preferred vehicle for rapid results. However, some model organisms are better representations of specific human systems or conditions than others. Scientists must choose which organism will be the best model for their research.

You navigate to the Ensembl genome browser, www.ensembl.org, to investigate gene conservation.

1 Click **Human** under the **Favourite Genomes** heading.

2 In the search bar, search for SH3TC2 and click on the first hit.

3 On the left navigation, click **Orthologues** under the **Comparatives Genomics** heading.

4 Check the box next to **Rodents** to display more details about this order of the animal kingdom.

5 Scroll down to find the mouse (*Mus musculus*) entry.



The Jackson Laboratory has thousands of different mouse models available to the research community to advance the understanding of human health and disease.

6 Click **View Sequence Alignments** and then **View cDNA Alignment**.

Each row has the human DNA sequence piled on top of the mouse DNA sequence for 50 bases per row (there are more than 3,800 bases in SH3TC2 cDNA, so keep scrolling down!). When the bases match, there is a * underneath that location.

Record %identity and %coverage.

7 Navigate back to the mouse orthologue entry. Click **View Sequence Alignments** and then **View protein Alignment**.

Each row has the human amino acid sequence piled on top of the mouse amino acid sequence for 50 amino acids per row (there are more than 1,200 amino acids in SH3TC2 protein, so keep scrolling down!). When the amino acids match, there is a * underneath that location. If they are similar in charge or polarity they either have a (.) or (:).

Record %identity and %coverage.

How would you determine if this a reasonable amount of genetic conservation for DNA and protein?

What is the value of an animal model if it doesn't have perfect genetic conservation?

8 Navigate back to the mouse orthologue entry. Click **View Gene Tree**. Gene Tree is located in its own section on the left side, under Comparative Genomics.

The gene tree not only shows the phylogenetic relationships of species (as determined by Sh3tc2 sequence only) but also shows a map of conservation across the gene.

Based on the Gene Tree, name a better animal model for studying Sh3tc2 than the mouse. Explain your reasoning.

Name an animal model for studying Sh3tc2 that is worse than the mouse. Explain your reasoning.

For what reasons do you think researchers chose to create a mouse animal model for CMT?

Now that you are confident that the mouse is a reasonable model for human CMT, you want to know if there is active research on this disease.

You navigate back to the OMIM CMT Type 4C Animal Model Entry where the original article about the mouse model is linked.

1 Click on the link to the paper, **Arnaud et al. (2009)**.

2 Click on the link to the PubMed ID number, **19805030**.

3 In the right hand column, click the **See all...** link under the **Cited by** heading.

All of these articles have cited Arnaud et al. (2009) in the paper and are likely using the mouse model they created.

Can you confidently tell Professor Lupski that scientists are actively researching his disease?

Hint: Look for the date of publication on the third line of the citation.