When Genes Speak: The Narratives of Genetic Mutation
By Mali Axinn

Introduction

Bridging the Gap between Biomedical and Personal Narratives of Genetic Disease and Disability

First year biology at Haverford, and most colleges, is a survey course. We are taught how cells function and about the cellular processes that occur inside our bodies. Sometimes we discuss what happens when an essential process isn't functioning "properly". In this context, we are introduced to the idea of disease and disability.

The cellular processes leading to disease are discussed in biology class in purely scientific form. We discuss abnormalities in DNA sequencing that jumpstart a cascade of biological dysfunction. For homework, we research biological processes and write reports on the specific diseases that result when "something goes wrong" in a DNA sequence. From protein misfolding, to red blood cell deficit, to the accumulation of cellular material, we learn about the diseases and disabilities which change people's lives.

This anthology brings together the narratives of two genetic conditions, pyruvate kinase deficiency and cystic fibrosis, in order to explore how the narratives of these diseases change depending on who is telling the story. It is often difficult to find a common thread when comparing the narratives told by the first year biology student, the genetic researcher and individuals who carry genes with genetic mutations. This anthology attempts to bring these narratives in conversation with each other, hoping to bridge the gap between the biomedical understanding of genetic disease and the personal stories of those affected. While understanding the biological mechanisms of genetic disease is essential, the discourse of disabilities studies helps tell the personal stories by privileging the human narrative.

This anthology provides three distinct narratives of disease. The first narratives are my biology class reports on pyruvate kinase and cystic fibrosis told with the help of my biology textbook and scholarly reports. These narratives explain the basic chromosomal mutations which cause pyruvate kinase and cystic fibrosis without reference to the life experiences beyond the DNA. The diseases are characterized by their symptoms and labelled "genetic dysfunctions", reflecting the pragmatic, impersonal, and technical tone of a scholarly abstract. In this biological framework, disease and disability are presented as mutations in DNA and cellular dysfunction is a topic to be studied, and perhaps in time, corrected with gene editing and emerging technologies.

The second narratives tell the story of genetic disease through the clinical studies of doctors seeking to understand and treat abnormalities. In these narratives, the doctors describe their patient's diagnosis in clinical language that is often inaccessible to a lay reader. Their symptoms and treatments are essentially laundry lists of measurements and procedures. In these studies, the patients are medical subjects only, and their stories are documentation of disease and treatment.

The final narratives in the anthology are patient testimonials. These personal narratives help explore the meaning, nature, and consequences of disability by giving voice to people with pyruvate kinase and cystic fibrosis. Each patient testimonial is presented in both written and spoken form. Written narratives and spoken words are two different paths to engaging with these stories. As a learner, I have always been more engaged by spoken words and hope that by giving voice to the stories the personal narratives will be meaningful conveyed.

This anthology brings these three different narrative perspectives into conversation with each other, hoping to expand our understanding of genetic disease and encourage the discourse to extend beyond the current medical construct of "genetic mutation" as an error that should be edited or fixed. I believe that reading this collection of stories together challenges a common assumption within scientific writing that the medical symptoms of a disease can stand alone. I hope that by reading and hearing the patient testimonials it becomes clear that the individual life stories behind the genes are essential to understanding the disease. The disabled community is loud, proud, and active, and their life experiences show how "genetic dysfunction" gives rise to a range of stories that need to be heard. Afterall, how can a student truly learn about health and disease without hearing the human stories behind the DNA?

Collection 1: Narratives of Pyruvate Kinase Deficiency (PKD)

Collection 1 presents biological, medical, visual, and personal narratives of pyruvate kinase deficiency, a genetic condition that affects red blood cells. While engaging with the collection, please consider the unique perspective of each narrative.

Use the following questions to guide your reading/listening: How is pyruvate kinase described/defined? Who is the intended audience of the narrative? How accessible is the information? What has this narrative taught you about pyruvate kinase deficiency? What aspects of the disease are not addressed by the narrative? How has the narrative expanded your understanding of living with pyruvate kinase deficiency?

Biological Report on Pyruvate Kinase Deficiency for Biology 202, Haverford College (Axinn, 2019)

Pyruvate kinase deficiency (PKD) is the most frequent enzyme abnormality of glycolysis with more than 180 associated mutations in the *PKLR* gene.[1] In the last step of glycolysis, pyruvate

kinase catalyzes the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding one molecule of pyruvate and one molecule of ATP. Without the proper function of pyruvate kinase, the release of ATP and pyruvate is blocked causing insufficient amounts of ATP in red blood cells which can result in hemolytic anemia.[2] Individuals with hemolytic anemia have a reduced flow of oxygen to the body's organs, causing fatigue, dizziness, and paleness.[3] Severe cases of hemolytic anemia can be fatal during the neonatal period and early childhood.[2] A 2016 study explored gene therapy approaches to treat PKD in mice. The research team used lentiviral vectors, a therapeutic method by which genes are modified using a family of viruses, to transduce mouse PKD hematopoietic stem cells. After genetic modification, the cells were transplanted into myeloablative PKD mice.[2] The findings of the study demonstrated the functional correction of the glycolytic pathway in the mouse PKD cells, suggesting the potential of using gene therapy to cure PKD and other metabolic genetic disorders.

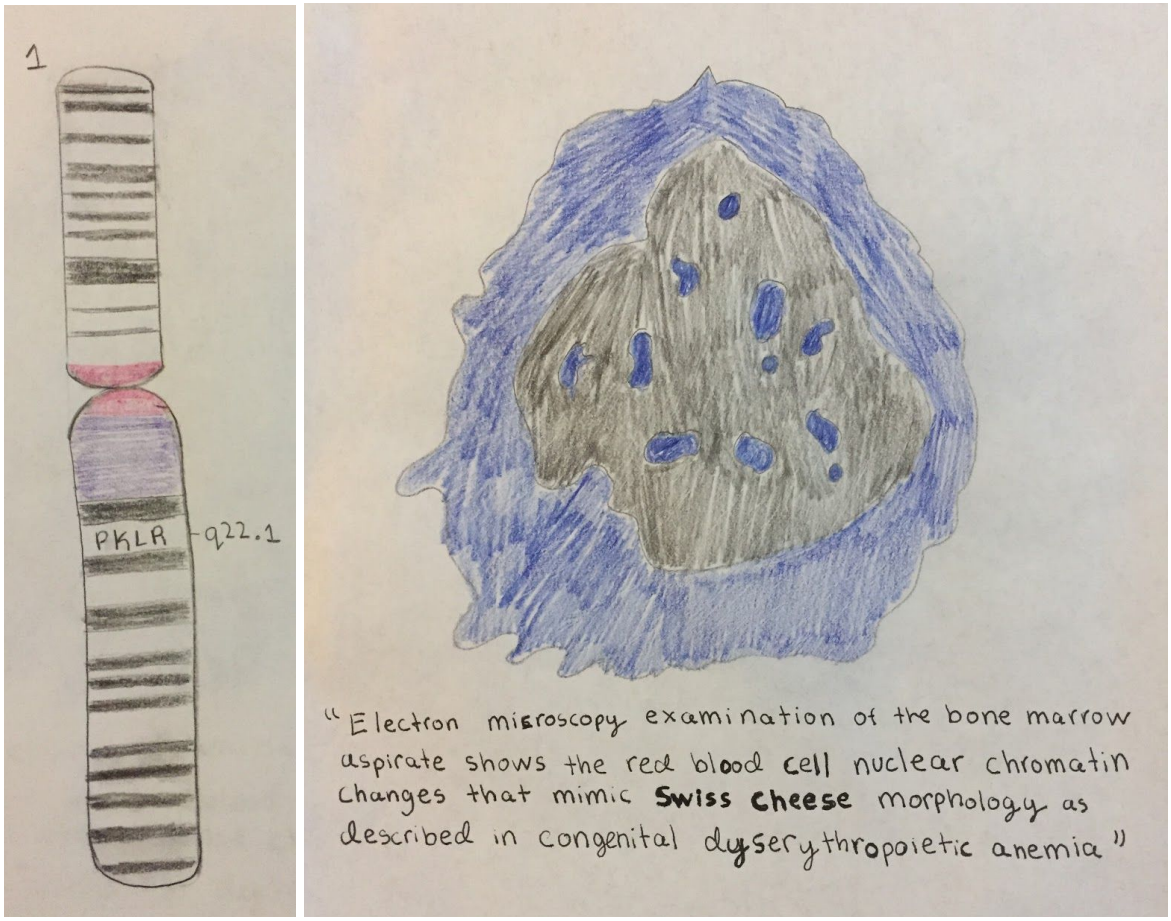
Excerpted Medical Case Report, *Dyserythropoiesis in a child with pyruvate kinase deficiency and coexistent unilateral multicystic dysplastic kidney* (Haija et al. 2014)

The patient was born full term, child of an 18-year-old mother mixed Hispanic and European. At birth, pale. Resuscitation and oxygen requirement. Tests reveal a low erythrocyte PK enzyme, his peripheral smear shows spiculated red cells. Bone marrow aspiration at 3 months.

By electron microscopy, nucleated red cells in bone marrow mimic swiss cheese.

PKLR gene testing was positive with two heterozygous mutations c.1378G>A p.Val460- Met, and c.341T>C p.Ile114Thr. The patient received a total of three pRBC transfusions for low hemoglobin every 3–4 weeks in the first few months of life. At 1 year of age, patient is clinically doing well with normal growth and development.Continues to receive pRBC transfusions.

Biomedical Visual Representations (Axinn, 2019)



Patient Testimonials of Life with Pyruvate Kinase

Woman, 20 years old, USA[10]
Read by Isabel Clements

I was born in 1994. My mother's pregnancy went fine. When I was born, someone realized something was wrong. I was born with no color. My dad says I was grey. Doctors say I had barely any blood running through my body, so the moment I was pushed out I was rushed out to get a transfusion. I got 1 blood transfusion. I was in the hospital for about 2 weeks and then I was able to go home. No one had any idea what was wrong with me so I just went on being a kid.

When I turned 10, I started to notice my eyes turning yellow. I was told it was just jaundice and I found out I was anemic. I expected to be tired and weak. Still, I went on with life as a normal teenager. One night, I was sleeping and I felt a horrible pain in my side. I was 15 at this time and

figured it was cramps. But the pain got worse. My mom rushed me to the hospital and turned out to be an ovarian cyst. But, the doctor who was working with me wasn't too worried about my cyst but the coloring of my eyes. He said it's more than just me being anemic. He ran some test and my Hb was extremely low. If I´m not mistaken it was a 6 g/dl. He did some research and that's how I found out I had Pyruvate Kinase Deficiency. I met up with a blood specialist and went over everything that I was going to go through. I got 2 blood transfusions and it made me feel better. I felt normal, well, normal from feeling tired my whole life.

About a year later I was looking into joining the military. When I was told I couldn't because I have a blood disorder and I don't have a spleen, my dreams felt like they were just stolen from me. I was angry, I blamed my parents for giving me this. I hated it. I was extremely depressed for the longest time because it stopped me from doing what I wanted to do.

By 18, I noticed I was starting to feel how I did before I found out I had Pyruvate Kinase Deficiency. The doctors were confused because they said I shouldn't feel like this. I should feel better. They decided to see if my spleen had grown back. 3 years laters and my spleen had grown back. So I got ready for yet another surgery. March 2013, I went in yet another time to have my spleen removed. As I lay in the bed, I just thought about my life. How much stuff I've been through and as I looked around I saw that it could be worse.

That's when I realized what I wanted to do. My goal now is to be a nurse. I see what these wonderful people do for me, and for me to say 'Thank you' isn't enough. I want to do what they do. It's been an year since my last surgery and I feel amazing. I'm about to graduate high school and go to college. I dance a lot and walk to maintain my exercise. I am just happy to be alive. I'm still going to go to school to be a nurse. I'm still on antibiotics and I still have to watch out for any flus or colds. Getting sick comes a normal thing. I'm not letting it stop me though. I'm now at peace with having PKD. My doctor has been a Dr. for 20 years and I'm the 2nd person he's met with Pyruvate Kinase Deficiency. Overall, I'm just happy to be living this life.

Female, 28 years old, Belgium[10]
Read by Carley Pazzi

My 3 years older sister has Pyruvate Kinase Deficiency. When she was born in 1984 having severe jaundice and a low hemoglobin, the doctors had to run a lot of tests to make a diagnose. My mother read the medical file afterwards and was shocked by all the terrible diseases they were investigating. After some months, the diagnosis of PKD was made. My sister has a quite mild type of PKD and she didn't need to be transfused often.

When my sister was 2 years old, my parents wanted to have another child. They went to a genetic counselor, who told them they had 50% chance a second child would also be affected, but the disease could be 10 times more severe. He was quite pessimistic, but luckily my parents didn't listen to him and conceived a second child. When I was born, in 1986, I was as yellow as a banana. My parents immediately knew I had PKD. I had an exchange transfusion and was put under the UV-lamp.

Until the age of 6, I had a blood transfusion every 6 weeks. My parents learned to read the signs of low hemoglobin. Sometimes my Hb dropped to 3 g/dl and I happily ran around without noticing I was running in a zigzag line. My parents would then rush me to the hospital for a transfusion. When I entered the pediatric service, the nurses called me "snow white", and when I left the service after the transfusion, they called me "little red riding hood". As a kid, I really liked the transfusions, because in the hospital room I could watch Disney movies on the tv.

When I was 6, my spleen and gallbladder were removed. I don't remember much from the surgery, except for the annoying tube in my nose. I had a lot of visits in the hospital from my friends and family and got a lot of attention (and presents), which was nice at that age. My sister had her spleen, gallbladder and appendix removed a year earlier. After the spleen removal, my hemoglobin went from an average of 5 g/dl to 8 g/dl. Both my sister and I didn't need transfusions anymore. We took antibiotics for about a year and from that moment, we only went to the hospital once a year for a checkup with our hematologist.

I lived a very active life: our parents wanted us to do a lot of activities, so our weeks were filled with music classes, singing in the opera choir, horse riding, theater, ballet, jazz dance, … Every day after school, I had another activity to attend. Even though I'm not the most sportive girl, I was perfectly able to live a normal life. Having Pyruvate Kinase Deficiency was something I could easily forget, if it wasn't for the yellow skin and eyes. Being a teenager, it sometimes was annoying having to answer the same question over and over again: "why are your eyes so yellow?". But luckily, I wasn't bullied for it at school nor anywhere else.

After high school, I went to university to become a pharmacist. I had a lot fun, partied a lot and had no difficulties with studying. I graduated with great distinction and started to work as a pharmacist. I am now 29 years old, and with my partner we enjoy travelling, camping, hiking and backpacking. We did some serious treks in the mountains and I did even climb Half Dome (!). My hematologist always warned me for high altitude, so I try to avoid heavy exercise above 3500m (11.500 feet), but I like pushing my limits.

Collection 2: Narratives of Cystic Fibrosis

Collection 2 presents biological, medical, visual, and personal narratives of cystic fibrosis, a genetic condition that affects the lungs and digestive system. Each narrative takes on its own form, offering a distinct perspective on cystic fibrosis. When approaching this second collection consider the distinct language and tone of each of the narratives. Also note what is included and what is left out of the narratives depending on who is telling the story.

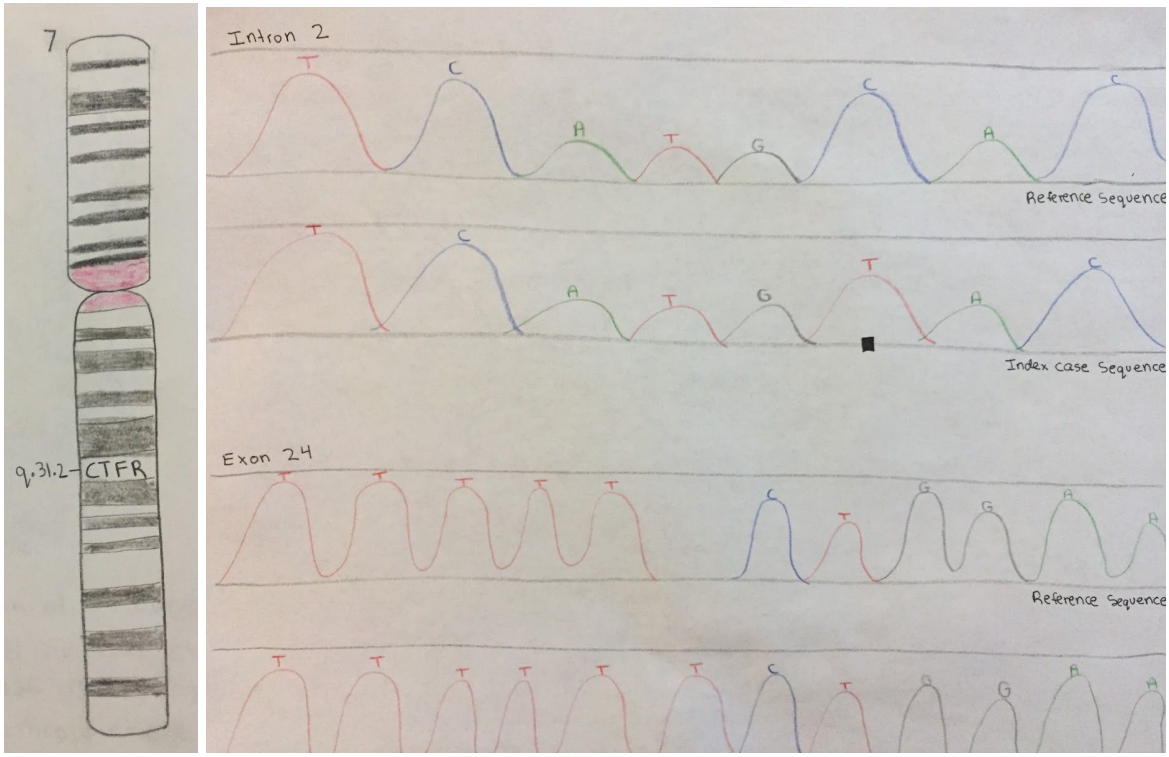
Consider the following guiding question for your reading/listening: How does the inclusion of the personal narrative help to expand your understanding of the genetic condition?

Biological Report on Cystic Fibrosis for Biology 102, Haverford College (Axinn, 2019)
Researchers have discovered nearly 1,900 mutations in the CFTR gene associated with cystic fibrosis, a genetic disease that damages the lungs and digestive system.[4] In the population affected by cystic fibrosis, chloride ions become trapped inside their cells resulting in increased sodium and water absorption and liquid depletion on the surface of the airway. As a result, thick secretions of mucus collect, depressing breathing and increasing susceptibility to infection and inflammation.[5] Delta F508 is the most common cystic fibrosis mutation, present in nearly 90% of cystic fibrosis patients. In this mutation, a three base pair deletion results in the loss of phenylalanine residue at position 508 in the CFTR protein.[6] A study using molecular dynamic simulations found F508 causes a disruption of a hydrophobic cluster located at the interface between a nucleotide binding domain and intracellular loop.[7] The study also found the F508 deletion to impair the dimerization of the subunits of the protein. Both of these findings identify possible origins for the functional defects of the F508 mutation, providing insights for drugs designed to treat cystic fibrosis.

Excerpted Medical Case Report. ***The first case report of double homozygous of 2 different mutations in the CFTR gene in Saudi Arabia*** (Banjar et al. 2017)
A 6-year-old female patient of Saudi descent and the product of a full-term pregnancy. Birth weight of 2.2 kg and presented at 2 months of age with a history of vomiting, poor feeding, multiple episodes of diarrhea since birth, recurrent chest infections, failure to thrive, increased sweating, persistent runny nose and the subsequent development of generalized edema. The patient was given NG tube feeding with a high-calorie diet and pancreatic enzymes, MCT oil and multivitamins. On physical examination, she was pale and malnourished, with both weight (5.2 Kg) and height (45 cm) below the 5th percentile for age, a low body mass index (BMI) of 13.5, a Z score for weight of (−2.5), and a Z score for height of (−2.3) At 5 years of age, the patient

presented with recurrent attacks of partial complex seizure in the form of deviation of the mouth which lasted from half a minute to 2 min, 4 times a day sequence analysis identified variant of a consensus splice donor-site mutation, c.164+12T>C (IVS2+12T>C) in intron 2, and a second reported homozygous disease-causing single nucleotide insertion, c.3889_3890insT (p.S1297FfsX5), in exon 24 of the CFTR gene. The patient was started on ventolin, fluticasone inhalation, amoxicillin/clavolinic acid for 2 weeks, hypertonic saline 7% on nebulization, ADEK vitamins, and Creon pancreatic enzyme replacement. Her growth parameters gradually improved with treatment with normal growth and development and minimal chest x-ray changes.

Biomedical Visual Representations (Axinn, 2019)



Patient Testimonials of Cystic Fibrosis

Taylor Jarvis, 24 years old, USA[12]
Read by Izzy Axinn

I am currently 24. I was diagnosed with CF right before my 16th birthday in 2010. I was tested because for my entire life I had what they thought were terrible allergies and “faked” stomach pains — every doctor I had seen was adamant that I was faking to skip school.

My dad, who is in the U.S. Army, got stationed in Hawaii, and the military hospital just so happened to be a CF center. After a few visits for the same [stomach] issues with my new doctor

there, he believed my symptoms and was determined to help me. He put together all the pieces, met with the CF team and decided to sweat test me. The first [test] was borderline, as was the second. So, we did genetic testing and it came back to show I carried the deltaF508 genes — two of them. Once I was diagnosed, they tested my entire family and my mom was diagnosed in her mid-30s. We were all really shocked; we had never even heard of CF before!

Sabrina Walker, 29 years old, USA[9]
Read by Mali Axinn

My life journey with cystic fibrosis (CF) began over 25 years ago, when I was diagnosed with the double F508del mutation at the age of four years. I am one-quarter Tlingit(KLIN-KIT) Indian (Alaska Native) and live in Anchorage, Alaska. Because CF is not usually found among Native American/Alaska Native people, it took a lot of time before a sweat test was suggested.

My running journey started when I was 12 years old. My mother wisely believed that running could be used as a form of airway clearance. She would take me to a local track in Anchorage and set a goal for me to run 10 minutes straight. She always ran with me. We learned that running helped me to loosen the thick mucus from my lungs and cough it out.

When I was 18 years old, doctors found a cancerous tumor on my spine, and I was diagnosed with non-Hodgkin's lymphoma. This was a brutal time. The chemotherapy and radiation treatments made it difficult to continue my running routine and I eventually had to stop altogether.

My running revival came in 2010 after being in remission for five years. I wanted to become more proactive in regards to my cystic fibrosis and my overall health. Once I started running again, I realized how much mucus I was bringing up and how clear my lungs were feeling after each run. I started out by setting goals like running a 5k race. After I accomplished that, my new goal was a 10k, then a half marathon, then a 16-mile mountain run, then a full marathon!

My lung function will sometimes drop and indicate that I need antibiotics or hospitalizations, but that always reminds me how important running is in my life and to my health.

My main motivation for running has been to outrun cystic fibrosis and to prevent further lung deterioration. I am determined to run and exercise for my health. I now have a wonderful son, Leo, and It's not just about me anymore. I have a child who needs me; I want Leo to grow up with his mom.

Discussion

The goal of this anthology is to apply a disability perspective to biomedical narratives of pyruvate kinase deficiency and cystic fibrosis. My hope is to construct a more humanistic narrative of disease and disability that can complement and expand the genetic models. While there is a premium on time and space in biology class and medical papers, I believe that including these patient testimonials furthers the understanding and treatment of disease.

The stories of individuals with genetic conditions don't fall under one category because each individual experience is distinct, however the themes of coping with illness, physical and emotional discomfort, and overcoming adversity touch many of these stories. Perhaps the most essential takeaway from these narratives is how can you live with disease and not let it define life. Ultimately, these stories are testimonials that symptoms alone cannot define life.

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