

In Sickness and in Health: A Trip to the Genetic Counselor

by

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Part I—Pedigree Construction

Greg and Olga were both a little worried. Starting a family presented choices and responsibilities far more long-reaching and complex than anything either of them had encountered before, and sitting here in the reception area of the genetic counselor's office they were beginning to feel the pressure. They had met four years earlier in the hemophilia clinic where Greg was waiting for his brother Jeff to get an injection of factor VIII, a protein that helps the blood to clot. When a person's factor VIII level is very low (less than 1% of normal), even the smallest cuts can be troublesome and uncontrolled internal bleeding is common. Complications include swelling, joint damage, and an increased likelihood of neurological complications due to intracerebral bleeding. Even simple surgical procedures such as tooth extractions become far more risky. Jeff's condition was noted by his pediatrician shortly after birth when his circumcision bled profusely. Since then, Jeff has received monthly injections of factor VIII, either at home or (twice a year) at a clinic where his physical condition is reviewed by a physician's assistant. At first these injections contained clotting factor isolated from the blood of human donors but, for the last 10 years or so, he has received recombinant clotting factor, which is genetically engineered.

It was in that clinic waiting room that Greg struck up a conversation with Olga, who was waiting for her uncle to finish his exam and receive an injection of clotting factor. Like Jeff, Olga's uncle also suffered from hemophilia A due to factor VIII deficiency. Beginning with this common experience, Jeff and Olga quickly fell in love and were married the following year.

They are now thinking about starting a family of their own, but are concerned about the risks of passing on genetic diseases to their children. They know for example that hemophilia A is an inherited disease, and several of Greg's relatives suffer from myotonic dystrophy, a muscle weakening disease that also runs in families.

As a first step, the genetic counselor has asked them to fill out a narrative history listing their relatives, relationships, and if they were affected by any genetic diseases that they know of. The forms are seen below.

NAME: Greg [REDACTED]

I have one brother and one sister, neither of whom are married. My brother suffers from factor VIII deficiency, but no one else in my family does. My mother has two brothers and one sister. One of my uncles and one of my aunts are affected by myotonic dystrophy. My affected aunt married an unaffected man and they have a young, seemingly unaffected daughter. My other uncle is unaffected, as is my mother. Our primary care doctor has said that because both my mother and uncle are over fifty years old and show no symptoms, they do not have the disease. My father is completely normal. He was adopted from an orphanage and nothing is known about his family. My maternal grandmother was an only child who also suffered from myotonic dystrophy. Her husband (my grandfather) was one of seven children (four boys and three girls). No one in the family seems to know much about the health status of my grandfather or his brothers. Both of my parents are alive but all of my grandparents are deceased.

NAME: Olga

I have two brothers, one of whom has factor VIII deficiency. The brother with the disease is married to a woman who does not have the disease. They have two young boys, both normal. My father is an only child who does not suffer from anything and his parents also are only children who do not suffer from any diseases. They are all still living. My maternal grandmother is healthy and had a sister who died just after birth. She married my grandfather who was one of four children, all boys, none of whom were affected by any disease that anyone is aware of. My grandparents had two children, my mother and my uncle. My uncle has hemophilia but my mom doesn't. My uncle married my aunt (who is unaffected) and they had two children, neither of whom showed any sign of any disease. Their boy is still single but their girl got married, to a normal man, and had a son, who has hemophilia A.

“Good afternoon” said the woman rising to greet them, “I’m Dr. Ciletti. It’s good to finally meet you in person.”

“Nice to finally put a face to the voice. I’m Greg and this is my wife Olga.”

“Nice to meet you,” Olga said, taking a seat across the desk from Dr. Ciletti. “This whole having-kids thing is more nerve-wracking when you really start to think about it.”

“You’re doing exactly the right thing. There is no sense in worrying about things unless you have to. Maybe I can set your mind at ease a little bit. To begin with, I know that you’re both concerned about factor VIII deficiency and myotonic dystrophy because of the family history. Is there anything else that you’d like to know?”

“Well,” began Olga, “the fact that we both have these diseases in our family and there is a chance that we could pass them on to our children has opened our eyes a little bit, but we’d also like to know if you can predict other diseases that don’t run in our family. Like my best friend in high school had cystic fibrosis and she died when she was only twenty four, and was sick almost all the time.”

“Okay, well, cystic fibrosis doesn’t look like it is in either of your family histories so it’s probably not worth worrying about. But, we can spend a little time going over the chance that you both carry a gene that has never before shown its face. The first step is we have to convert the family information you two have provided into a graphical representation called a pedigree. From there we can begin to correlate family relationships with the appearance of specific diseases.”

Question

- I. What would a pedigree of Greg and Olga’s families look like? Concentrate simply on family relationships and affected persons.

Reference

Human Genetics for First Year Students: Pedigree Construction
<http://www.uic.edu/classes/bms/bms655/lesson3.html>



Part II—Autosomal Dominant Traits

“Great, so this looks like an accurate representation of your family, right?” Dr. Ciletti asked.

“Looks good to me,” replied Greg.

“My family is so small, there’s not much to miss until you get to my grandparents,” said Olga.

“Well, factor VIII deficiency and myotonic dystrophy are inherited in completely different ways. Come to think of it, you asked about CF as well and ...”

“CF?” asked Greg.

“Cystic fibrosis,” Dr. Ciletti continued. “I was about to say that cystic fibrosis is inherited in a manner different than both of the other diseases you are concerned about, but let’s tackle them one at a time.”

“Myotonic dystrophy is an autosomal dominant disease and it is the easiest to pick out of a pedigree. Now Greg, even though you have an uncle and aunt as well as a grandmother who all have the disease, you don’t and there is no way that you will pass this disease on to your children. So that is the first piece of good news.”

“But don’t a lot of genetic diseases skip a generation?” Greg asked. “And even if it doesn’t, my mom has two siblings with the disease. Could she be a carrier and just pass the disease on to me? For that matter, could I be a carrier?”

“Yes, could he be a carrier?” Olga added.

“Absolutely not,” Dr. Ciletti said. “Let me show you why.”

Questions

1. Do autosomal dominant disorders skip generations?
2. Could Greg or his mother be carriers of the gene that causes myotonic dystrophy?
3. Is there a possibility that Greg’s aunt or uncle is homozygous for the myotonic dystrophy (MD) gene?
4. Symptoms of myotonic dystrophy sometimes don’t show up until after age fifty. What is the possibility that Greg’s cousin has inherited the MD gene?
5. What is the possibility that Greg and Olga’s children could inherit the MD gene?

References

Myotonic Dystrophy Fact Sheet

<http://www.mda.org.au/specific/mdamyt.html>

Human Genetics for First Year Students: Pedigree Construction

<http://www.uic.edu/classes/bms/bms655/lesson3.html>



Part III—Autosomal Recessive Traits

“Well, I certainly feel better about that,” said Greg. “I guess there is no reason to worry about passing on MD to our children. They’ll just have to worry about inheriting their father’s incredible good looks, fabulous sense of humor, creativity ...”

“And modesty ... Hold on a second, God’s gift to the world,” Olga chimed in. “We still haven’t talked about factor VIII deficiency, which is why we came here in the first place.”

“Well,” Dr. Ciletti began, “factor VIII deficiency is what’s known as a sex-linked disease. Before we get to that, let’s take a look at a disease with a slightly simpler mode of inheritance. Many traits, whether or not they are considered to be diseases, are described as autosomal recessive traits. These are the ones you alluded to earlier when you talked about diseases that skip generations and about people being carriers. Some common recessive traits include albinism, sickle cell disease, and cystic fibrosis, which I promise we will get to, Olga. Now, let’s look at some of the rules governing these types of traits.”

Questions

1. What are the hallmarks of an autosomal recessive trait?
2. What does consanguineous mean? Why is this concept especially important when discussing recessive genetic disorders?
3. What is it about the inheritance pattern of factor VIII deficiency seen in Greg and Olga’s pedigree that point toward it not being an autosomal recessive trait?

References

Autosomal Recessive Inheritance

<http://www.uic.edu/classes/bms/bms655/lesson5.html>

What is Albinism?

http://www.albinism.org/publications/what_is_albinism.html

Genetic Disease Profile: Sickle Cell Anemia

http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/sca.shtml

Genetics Home Reference: Cystic fibrosis

<http://ghr.nlm.nih.gov/condition=cysticfibrosis>



Part IV—Sex-Linked Inheritance

“Alright,” Olga began, “so factor VIII deficiency is sex-linked because it only affects men. Does it require the presence of testosterone or something like that?”

“No, but there are many traits that do depend on the presence or absence of sex hormones. We call them sex-influenced traits. Sex-linked traits get their name from the fact that the genes that cause them are carried on the X chromosome, which is one of the chromosomes responsible for determining what sex a person will become. Let’s take a look at how factor VIII deficiency runs in both your families.”

Questions

1. What are the characteristics of X-linked recessive inheritance?
2. Why does a son never inherit his father’s defective X chromosome?
3. What is required for a woman to display a sex-linked recessive trait?
4. Return to the pedigree drawn earlier for Greg and Olga; mark those persons who are carriers of the factor VIII deficiency gene.
5. What is the chance that Olga carries the gene for factor VIII deficiency? Calculate the probability that she will pass it to her offspring. Will male children be affected in a different way than female children?
6. What is the chance that Greg carries the factor VIII gene? Can he pass the gene on to his sons? His daughters? How will each be affected?

References

Human Genetics for First Year Students: X-linked Recessive Inheritance
<http://www.uic.edu/classes/bms/bms655/lesson7.html>

X-linked Inheritance: Red-Green Color Blindness, Hemophilia A
http://www.musckids.com/health_library/genetics/xlink.htm



Part V—Population Genetics

“Finally,” Dr. Ciletti began, “let’s talk about cystic fibrosis. Now I mentioned that it is probably not something to worry about since neither of you has it in your family history, but there is a way to figure out the odds of being a carrier even without a past family history. Remember that in the case of a recessive autosomal disease like CF, for the disease to show up unexpectedly in your offspring both you and Greg would have to be carriers. We can estimate the probability of each of you being carriers by looking at the population as a whole.”

“You mean all the people on earth?” Olga asked.

“No. For purposes of genetics you each belong to different populations,” Dr. Ciletti began. “Now Olga, you’re of European descent, correct?”

“Yes, Swedish and German.”

“And obviously Caucasian. Now I can look up the carrier frequency, that is, the fraction of people in your population group that carry the most common cystic fibrosis allele. As it happens, one of every twenty-three Caucasians of European descent carries a recessive allele for CF.”

“That doesn’t sound very encouraging,” Olga interjected. “I have a 1 in 23 chance of having a child with cystic fibrosis.”

“Not at all. You just have a 1 in 23 chance of carrying the CF gene.” Dr. Ciletti replied. “Now Greg is Asian American and within his population group the carrier frequency is 1 out of 180. Making the odds even longer is the fact that if you are a carrier you have only a 50-50 chance of passing on your disease causing allele. So the chance of you two producing a baby with CF is actually $1/23 \times 1/180 \times 1/2 \times 1/2$ or 1 out of 16560. So, just how big a family were you planning to have?”

“But wait,” said Greg. “If a carrier is someone who doesn’t display any of the features of a disease, how can you know how many carriers are in a population?”

“Good question, Greg. As an old professor of mine once said, ‘It all comes down to minding your P’s and Q’s.’ In a large population, the carrier frequency can be estimated by looking at the number of persons with the disease and then doing a little algebra. There are two equations we need to remember. The first describes all the alleles in the population and it just says that $p + q = 1$. In other words, of all the alleles in the population, a percentage of them are the healthy version, which we can call p. So if 65% of the alleles in a population are healthy, then p must be .65. The rest of the alleles must be the disease causing form, or q. If p is .65, then q must be .35, so that $p + q = 1$.

“But how do you know the percentage of q alleles in a population?” asked Olga. “The only people you can really identify are the people with the disease.”

“Exactly, and that brings us to the second equation we need to look at.”

Questions

1. What is the second equation?
2. The incidence of cystic fibrosis in Hispanic Americans is 1/4500 while in African Americans cystic fibrosis is seen in 1 of every 15,000 births. What is the carrier frequency for each of these populations?
3. What is the probability of two Hispanic Americans having a child with cystic fibrosis, given that there is no history of the disease in either’s family?
4. Carol is an African American woman who does not suffer from CF. Both of her parents are healthy but her brother has cystic fibrosis. Carol is planning a family with her husband Marcus, who is also African American but who has no history of CF in his family. What is the probability of their having a child with CF?

References

Hardy-Weinberg Equilibrium: Demo problem 1
<http://science.nhmccd.edu/biol/hwe/q1d.html>

Mayo Foundation: Cystic Fibrosis
<http://www.mayoclinic.com/health/systic-fibrosis/DS00287>



Part VI—Unsettled Issues

“So, is it possible to test for each of these diseases?” asked Greg.

“Yes, but for the sake of practicality, or expense, as some would say, we only test for those diseases that are reasonably likely based on a patient’s history. We wouldn’t for example test either of you for the presence of the CF allele.”

“Wait a minute,” Olga began, “what about a disease that doesn’t show up until later in life. Greg’s uncle didn’t show any symptoms of myotonic dystrophy until he was something like forty ...”

“Forty three,” Greg corrected.

“Yeah, anyway, if a genetic test shows that you are going to get a genetic disease and it becomes part of your medical history, could an insurance company exclude it as a pre-existing condition, even though you don’t have it yet?”

“Well, the law is actually quite unsettled about the issue. Genetic testing has the power to predict the occurrence, or at least the likelihood of occurrence, of many diseases—cancer, Alzheimer’s disease, and diabetes just to name a few. Many people are not comfortable with that information being part of their medical records because they are afraid it could lead to a loss of insurance, losing out on a job, or some other form of discrimination. But,” Dr. Ciletti said with finality, “that is a subject to take up with lawmakers. It is entirely possible that after the conversation we’ve just had that you two know far more about the subject of genetic testing than your congressman or senators. If you’re concerned about the legal ramifications of genetic testing, you should let them know. It was a pleasure meeting both of you.”

“Likewise, Doctor. You really helped to put my mind at ease,” Olga said.

“Yeah, I think we both feel a lot better, thanks,” said Greg.

Questions

1. What are some of the risks and benefits of genetic testing as it relates to legal (not medical) issues?
2. Do you think an unintended consequence of genetic testing could be that people would be less liable to seek medical care out of fear that they could later be denied life or health insurance? What laws should be used to govern the use of genetic data of this type?

References

Mayo Foundation: Genetic Testing

<http://www.mayoclinic.com/health/genetic-testing/FL00076>

Private Medical Information Isn’t So Private

<http://www.bankrate.com/brm/news/pf/20050830a1.asp>

National Society of Genetic Counselors

http://www.nsgc.org/newsroom/NSGC_SACGHS_October_2004.pdf



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