

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

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## Part I—Pedigree Construction

Greg and Olga were both a little worried. Starting a family presented choices and responsibilities far longer 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, Greg 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

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 50 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.

"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

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.

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**

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

## **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 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
2. Greg's cousin has inherited the md gene?
5. What is the possibility that Greg and Olga's children could inherit the md gene?

## **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 ..." 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?

## 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?

## Part V—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?