University of Jordan
Faculty of Medicine

GENETICS & Molecular Biology

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This lecture was more of a discussion. Most of the information mentioned in this lecture is a revision for all of the material. The whole idea of this lecture is to make you understand how to tackle clinical cases, so just enjoy it.

Introduction to Clinical Genetics

- What does it mean to be a clinical geneticist?

  There's a whole subspecialty in medicine called clinical genetics. There's also a subspecialty that is based on lab work. Health care providers in this field are generally referred to as **genetic counsellors**. A genetic counsellor can see patients independently, or work alongside a physician to advise the physician regarding the lab tests that should be done for each patient. Look it up if you're interested. Medicine is not just about surgery, sub surgery, paediatrics, etc.

- What do you think a geneticist does in medicine? What do they do in a clinic? How do they come up in those genetic associations? *(Hint: Think of cases).*

  They draw pedigree charts and look through patients' files and interview patients.

- What information should do you look for when interviewing patients?

  This is something that you don't necessarily learn from a book, it is something that you learn from experience and interaction with a team.

  Let's take some scenarios where a geneticist may be involved. It's not all about memorizing sign and symptoms and looking for them.

The aim of this lecture is to make you think clinically.

Clinical Cases

Case 1 – Liver Diseases

A patient presents to your clinic. Let's say your patient is a young female. You should be thinking of names now because your patients are not just patient A or patient B, they should have names. The young girl is accompanied by her mother.

Why did this mother show up with her adorable young child to the clinic today? Let's say she has abdominal pain (non specific symptom). What could the differential diagnosis be? What is in the abdomen? Appendix, pancreas, ovaries, liver and all other referred pains.

Where in the abdomen is this pain? Abdominal pain is a very common presentation, how could it be potentially a presentation for a genetic disease? What directed questions are you going to ask the mother if you are thinking of lactose intolerance? Does she feel abdominal pain after drinking milk? Is there diarrhea with the abdominal pain?

The mother answers, "No, she drinks milk, she eats normally, so there is no problem with her diet." You examine the patient, there's no real bloating. Then you start thinking it may not be lactose intolerance.

Suppose the pain is in the right upper quadrant, now we are thinking of the gallbladder and liver. What genetic disorder affects the liver? It can't be Reye's syndrome. If it was Reye's syndrome, then instead of presenting as a happy little girl to your clinic, she would present to the ER, and the first thing you would have noticed is jaundice! Therefore, the girl's genetic disorder is not damaging the liver, but still it is in the area of the liver. After you palpate the right upper quadrant, you find out that the liver is enlarged.

Which of the diseases we previously talked about are associated with hepatomegaly? Glycogen storage diseases, Niemann-Pick, some lysosomal storage diseases, etc.

The next thing that you are going to ask about is family history. Are we looking for autosomal dominant, autosomal recessive, or X-linked recessive? As a result, you are narrowing it down as you are drawing a pedigree. That is how you should think as a geneticist.

Case 2 – Breast Cancer

You are an oncologist and an adult female presents to you with a lump in her breast. A typical workup after you take history and do a physical examination (most physicians would not take a proper history) is to take a biopsy of that lump.

Unfortunately, it turns out to be malignant. What are the genetic mutations that you should be thinking about? BRCA1, BRCA2, HER2. If the first health care provider who saw the patient did not take a thorough history and physical examination, you should ask about family history: how many of your siblings have had any type of cancer? How many of them had cancer in a considerably young age? Did any of your siblings have a particularly unusual cancer type?

It turns out that siblings 3, 4 and 6, for example, had different types of cancers and a couple of them had 2 separate cancers in two different locations. Therefore, this is a heterogeneous family. What should you be thinking about? P53 mutation and Li-Fraumeni syndrome.

This is how you come up with clinical case scenario; you think of a person and possible signs and symptoms. This is how you should be thinking all the time. As soon as someone gives you a dry piece of information that relates to a disease, you should start synthesizing the clinical case scenario in your head.

Case 3 – Inborn Errors of Metabolism

A mother presents to your clinic with her 6 month-old infant. At 6 months of age, babies start eating a variety of foods, so they would show up with some of the metabolic diseases we talked about. Other metabolic diseases like galactosemia might show up earlier.

Case 4 – Sickle Cell Anemia

A patients presents to you with sickle cell anemia. As a scientist you would think that there is a single point mutation in the beta-haemoglobin gene. As a clinician, you should know that your patient may be anaemic. Furthermore, the sickle shape would cause blockage, causing mini-strokes and ischemias all over the body. Therefore, the patient might present with pain, spleen problems (left upper quadrant pain), bone pains because the small capillaries that go through the bones could get blocked especially if the patient has been hypoxic. Patient can also present with breathing problems. When did the pain start? The patient will say, “I got up a hill”, so that is an exertion and the patient got less oxygen (due to lower partial pressure of oxygen at high altitudes). On the other hand, the patient could have something that would result in

reduced oxygen transport. Thus, pneumonia for a patient who has sickle cell anemia (which is not quite symptomatic) can result in a sickle cell crisis.

Why don't they present at birth? A newborn mostly has fetal haemoglobin, so it takes time for sickle cell anemia to show up. Symptoms start showing up as the fetal haemoglobin levels decline. The life span of an RBC is 120 days (3 to 4 months). Presentation depends on severity (whether they are homozygous or not). Children are not hypoxic unless they are diseased because they do not become hypoxic by exerting a lot of effort.

Heterozygous sickle cell trait patients present with some symptoms but not with severe crisis or that kind of pain. They may present with some mild anemia.

If being heterozygous caused a full-blown disease, it wouldn't have been naturally selected in the African continent as the more dominant genotype. Sickle cell trait people have resistance to malaria. If that trait causes severe disease, it wouldn't have been naturally selected to protect people from malaria.

Case 5 – Cystic Fibrosis

A patient presents with difficulty breathing more than a usual lung infection. You start thinking of cystic fibrosis. You might assume that this patient also has steatorrhea because of pancreatic insufficiency. However, you are still thinking like a scientist when you assumed that the patient has steatorrhea. Think about it like a patient. Not all patients check their feces after they finish when they go to the bathroom. Therefore, a patient would not really present to the clinic because of steatorrhea.

If a person who was diagnosed as diabetic suddenly show up with multiple lung infections, then you should start thinking of cystic fibrosis.

Suppose it is an infant, what would the mother tell you? Mothers like to kiss their babies. They might present to your clinic complaining that their child tastes salty. Thus, take that molecular knowledge that you have and think of the signs and symptoms it would produce.

Case 6 - Neurofibromatosis

Patients with neurofibromatosis have cafe-au-lait spots on their skin. As a physician, you should look for cafe-au-lait spots. If a patient presents with something else and you notice cafe-au-lait spots then you should think that this might be a case of neurofibromatosis.

Start thinking in more common things; things that would make you go to the doctor. Then, try to link those to the diseases you already know about. That's the whole point of being a medical doctor.

NF1 vs. NF2
Type one has the various malignant types of cancers while type two has benign acoustic neuroma and schwannomas. Hearing loss is associated with NF2.
However, because these tumors are inside the patient's head, it doesn't matter whether they're benign or malignant. A tumor takes space and eventually causes problems in other areas. The first problem it is going to cause is compression of auditory nerve but eventually it is going to damage other structures too.

Case 7 - Mucopolysaccharidosis

A mother presents to you with a child that is about a year old complaining that the boy did not stand up and didn't say a word. This is kind of a developmental delay so you should start thinking of something neurological. After examining the boy, you've noticed that his front teeth are particularly apart. Your first thought would be mucopolysaccharidosis type 2 (Hunter syndrome) because it is milder than type 1. Type 1 has very characteristic facial features. Patients who have type 2 mucopolysaccharidosis don't have distinct facial features, but they still have these gapped teeth and they present with developmental delay.

Case 8 – Wilson's Disease

A patient presents to you with edematous legs and forgetfulness. You suspect that this is a case of Wilson's disease. Copper level increases and it's deposited everywhere. It accumulates in the liver and causes liver failure drastically increasing AST/ALT levels. However, you shouldn't jump to lab results. You should talk to the patient first. Liver failure would cause hyperammonemia, affecting the brain, so the patient would become increasingly forgetful and he'll notice that his legs are edematous. If you are thinking of Wilson disease, the next place you look at before asking for copper levels and doing liver biopsy is the

patient's cornea. You should see Kayser-Fleischer rings (green to brown deposits of copper in the Descemet membrane in the limbus of the cornea).

Case 9 – Turner Syndrome

A young lady presents to your clinic saying that she hasn't had her first period and all of her friends in class got theirs. All of her friends' breasts are developing except hers. You are her paediatrician. What are you going to look for in this patient? A webbed neck might not be entirely obvious. When she walked in, did you notice how tall or short she was? Girls with turner syndrome are of short stature.

Unfortunately, in our society, girls tend to be shorter than average, so having a short girl coming into your clinic might not raise an alarm. A patient with Turner syndrome has a broad chest so your next question should be, "Do you find it difficult to buy clothes that fit you?" The answer is yes! You didn't ask the patient to undress yet and you already have an idea what her chest looks like. During physical examination, if you notice widely spaced nipples rather than nipples in front and centered, then this could be another indication of Turner syndrome.

Revision

- Autosomal recessive means that both alleles should be lost to have the disease. Typically autosomal recessives diseases are enzymatic diseases, because if someone has 50% of an enzyme, unless they have haploinsufficiency, he/she will be phenotypically normal.
- Dominant negative: one protein disables an entire multiprotein complex. For example, in APC/WNT/ β-catenin pathway there is a receptor on the cell surface and a ligand called WNT. WNT attaches to its receptor, the receptor signals and causes the β-catenin destruction complex which is made of APC, β-catenin, GSK3-β and few other proteins, to stop destroying β-catenin. However, should you have a mutation in APC, you will have FAP (familial adenomatous polyposis syndrome). Patients who have FAP have lots of polyps because they have a mutation in APC which it is part of the destruction complex and this mutation makes a truncated APC or a dysfunctional APC.
  Is this destruction complex still going to destroy β-catenin? No.
  Haemoglobin is another example where one abnormal subunit would affect the blood's ability to transport oxygen.
  Regardless of whether there are multiple copies of the same protein in a complex or multiple proteins in a complex, if one copy

disrupts the whole complex, this is called a dominant negative effect*. It has nothing to do with the mode of inheritance, it is a molecular effect*.

- X-chromosome inactivation: 15% of the X-chromosome escapes inactivation (pseudoautosomal regions of the X and Y chromosomes; they are the same on the Y chromosome). You need two alleles of the genes at the area that escapes inactivation to be phenotypically normal. And if any gene at this region was mutated, its mode of inheritance would be just like any other gene on an autosomal chromosome, and that is why they were called pseudoautosomal regions.
  The only difference between the pseudoautosomal region and the autosomes is that it depends on which of the X or Y chromosome the mutation occurred and therefore would affect males versus females depending on which parent have the mutation on which chromosome. Suppose that the Y chromosome has the mutation (the father is carrying the mutation). In that case, only the males could be affected. If it is on the X chromosome of the mother, it could affect both males and females. If the X chromosome of the father is carrying the mutation, only the daughters would be affected. Therefore, it is kind of a mix between autosomal and sex-linked.
- Thalassemia: There are 6 genes for thalassemia; 4 alphas and 2 betas, the betas are on the X-chromosome but the alphas are not. The inheritance pattern depends on whether you are alpha thalassemic or beta thalassemic. Thalassemia is divided into approximately 8 or 12 different subgroups depending on whether you have mutations in alpha 1, 2, 3, or 4 (mutation in 4 is generally lethal). The betas can be compensated for by the fetal beta-globin.

Good Luck!

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