Case Workbook in Human Genetics

Third Edition

Ricki Lewis

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in

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The University at Albany



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Case Workbook in HUMAN GENETICS, THIRD EDITION RICKI LEWIS

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PREFACE

The study of human genetics is the study of inherited variations among people. Often these variations cause diseases. The goal of this Case Workbook is to place the information in *Human Genetics: Concepts and Applications* into a real context. Most of the cases come from the medical or scientific literature, with an emphasis on the unusual. Many introduce information and details that are not found in textbooks. Each case includes information, the source in either Online Mendelian Inheritance in Man and/or journals, and questions. The cases are organized to follow the chapter outline of the textbook, with a final part devoted to "Connections and Synthesis." These final cases depart from the rather artificial division of topics in a textbook. They are an excellent means to study for a final exam.

Most of the questions require thinking and problem-solving, rather than straight recall of facts or terminology. This approach reflects the skills required of a genetic counselor – powerful observation, data interpretation, thinking and communicating. For years, the primary tools of the genetic counselor and medical geneticist were the pedigree and karyotype. Today, analysis of an inherited condition often embraces molecular information too. Applying Mendel's laws to predict recurrence risks and to identify carriers, as well as interpreting DNA microarray tests, requires applying the rules of probability, as well as logic. Would a person with a particular condition live long enough or feel well enough to have children? Under what conditions would an extremely rare disorder be unusually prevalent? Where in the body must a gene therapy be targeted to alleviate symptoms? More generally, which facts in a case are relevant to answering particular questions? Solving genetic problems may help you to get the most out of other types of information too. Have fun!

Thanks to Daniel Plyler of the University of North Carolina at Wilmington and Ruth Sporer of the University of Pennsylvania for their comments during the development of this edition of the Case Workbook.

Ricki Lewis

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PART ONE

INTRODUCTION

CHAPTER 1 OVERVIEW OF GENETICS

Genetics in the news

CHAPTER 2 CELLS

Carnitine-acylcarnitine translocase deficiency Combined factors V and VIII deficiency

DEVELOPMENT CHAPTER 3

Embryos and fetuses in research

Chapter 1 is an overview of many of the topics in the textbook. Consult recent newspapers, magazines, or online sources and describe examples of the following phenomena:

A DNA chip

A prenatal test

A cancer diagnosis or treatment based on genetics

A medical condition for which a person has an increased risk because of inheriting a particular gene variant

A genetically modified plant or animal

A drug made possible using biotechnology

DNA fingerprinting in a forensics application

Genetic determinism

Controversy over the use of stem cells or cloning a human

Gene therapy

CARNITINE-ACYLCARNITINE TRANSLOCASE DEFICIENCY

Jim D. died at 4 days of age, 2 days after suffering cardiac arrest. The pregnancy had been uneventful, and he had seemed normal at birth. His older sister was healthy. Two years after Jim's death, his parents had another son.

Like Jim, Kerry seemed healthy at birth. But at 36 hours, his heart rate fell, he had a seizure, and he stopped breathing. Doctors were able to resuscitate him. Knowing Jim's history, the doctor ordered several tests and discovered excess long-chain fatty acids in Kerry's blood. These are components of triglyceride fats that are broken down by mitochondria in the liver, to provide glucose for energy during starvation. Nurses had noted that Kerry had not eaten since birth.

Kerry was fed a special infant formula low in fatty acids, and his parents were instructed to feed him often. Despite this treatment, the child was frequently hospitalized for vomiting, lethargy, an enlarged liver, and poor muscle control. Once he went into a coma after a feeding was delayed. Each time he became ill, it would take two to three weeks for the boy to recover. His weakness and fatigue worsened, and triglycerides began to accumulate in his muscles. His liver enlarged. Finally, just before his third birthday, Kerry died in the hospital of respiratory failure.

The brothers had a rare inborn error of metabolism called carnitineacylcarnitine translocase deficiency. Their cells lack an enzyme produced in mitochondria.

SOURCE: OMIM 212138

WORKSHEET:

1. Why is this disorder considered to be lethal in an evolutionary sense, even though it is not fatal for a few years to the individual?

2. A s	symptom	that is	consistent	with the	site o	of abno	ormality	in the	cell is	,

CHAPTER 2

I he special foo fatty acids that bu underlying bioche	ilt up in his bl	ood. Anothe	•	
		-		
		·		

4. The children's mother is taking a course in biology, and she learns that mitochondria are passed from the mother only. When the doctor explained that her sons had abnormal mitochondria, she began to feel guilty for having transmitted the disorder to them. What is the evidence that she is incorrect in thinking that her mitochondrial gene made the boys ill?

Blood clotting requires 11 enzyme-catalyzed chemical reactions. Several dozen families have poor clotting because of inherited deficiencies of two clotting factors, V and VIII. Deficiency of factor V causes an autosomal recessive condition called parahemophilia, and factor VIII deficiency causes the more familiar X-linked hemophilia A. However, the combined deficiency is inherited as a distinct autosomal recessive condition. That is, it affects both sexes and is inherited from two carrier parents.

Researchers expected to find an inborn error of metabolism that affects an enzyme that functions in the clotting pathway before factors V and VIII act. Instead, they discovered a gene that encodes a carrier protein that shuttles certain glycoproteins between the ER and the Golgi apparatus for secretion. The protein normally transports factors V and VIII, which are similar glycoproteins.

SOURCES: OMIM 227310

Nichols, William C. and David Ginsburg. June 1999. From the ER to the Golgi: insights from the study of combined factors V and VIII deficiency. *The American Journal of Human Genetics* 64:1493.

WORKSHEET:

1. Clotting factors, enzymes, and carrier proteins have very different functions. How can they all be products of gene activity?

2. How would the original hypothesis of an earlier defect in a shared biochemical pathway explain the double clotting factor deficiency?

3. Describe what happens to the product of the gene that causes the double clotting factor disorder in the ER and the Golgi apparatus.	
4. What is the evidence that a mutation in a single gene causes this double deficiency? That is, how does the inheritance pattern differ from what it would f families inherited each condition independently?	be

A human organism cannot survive outside the uterus, using current technology, prior to 24 weeks of gestation. The period of the embryo lasts until the end of the eighth week, by which time the rudiments of all organs have appeared, and the period of the fetus then extends until the time of birth. The status of the prenatal human is the topic of diverse arguments and unending debate, with opinions differing even within groups who are united in other matters.

Until the late 1990s, concern about using embryos in research centered around the problem of what to do with frozen "extras" from in vitro fertilization (see Chapter 21). Then in 1998, when two groups of researchers succeeded in culturing human embryonic stem (ES) cells, the possibility of using these cells in regenerative medicine and other applications created excitement in the scientific and medical communities, at the same time that it alarmed many in the general population. Vigorous debate ensued, continues, and likely will not cease, no matter what type of legislation passes. Below are some varied viewpoints on the status of embryos, which has bearings on the ethics of experimentation with embryos. Of course, not all people who follow a particular religion agree with the majority viewpoint on this highly controversial matter.

- Fifteenth century Islamic scholar Hajar al-Asqalani stated that the human fetus is "like a plant" and that for the first 40 days of prenatal development, the embryo is "as a drop of matter." The soul enters after 120 days.
- According to Jewish law, the embryo before 40 days has no moral status, and is "as if they were simply water."
- Buddhists and Hindus maintain that because a "transmigration of consciousness" occurs at conception, the embryo is a being.
- In the United Kingdom, Canada, Sweden and Finland, research can be conducted on embryos before 14 days of gestation. This is the time when the primitive streak establishes the body axis.
- In 1994, an advisory panel to the National Institutes of Health concluded that day 22, when the heart begins to beat, is "... the first time the embryo can be perceived (through ultrasound) by the outside world. ... despite experience with brain death, it is the beating heart that is most strongly perceived to be the difference between life and death."
- Biology textbooks avoid certain terms, such as referring to a pregnant woman as a mother, a fetus as an unborn child, or prenatal life. On the other hand, although an embryo could not survive outside of a uterus, it does carry out processes that are part of life, such as DNA replication and metabolism.

SOURCE: *The New York Times*, Science Times, December 18, 2001, has several articles from which this case was developed.

WORKSHEET:

1. Compare the structures that are present i	n the human embryo at the inner cell
mass stage, day 14, and day 22.	

2. Which characteristics or qualities do you think are important to consider in deciding whether or not an embryo or fetus should be afforded the same rights and considerations as a person?

3. Therapeutic cloning is a theoretical and therefore experimental procedure that uses cells from the inner cell mass to generate human embryonic stem cells. The ES cells are then used to culture tissues that can be used as grafts to help a person with a disorder such as Parkinson disease or a spinal cord injury. The rest of the embryo is then discarded. Do you think that this type of work should be legal? Cite a reason for your answer.

4. Do you think that early human embryos should be used in research to learn more about development? Cite an alternative to this approach, and its advantages and disadvantages compared to using human cells.

PART TWO

TRANSMISSION GENETICS

CHAPTER 4 MENDELIAN INHERITANCE

Acrocephalosyndactyly
Carnosinemia
Huntington-like disorder
Restless leg syndrome
Schneckenbecken dysplasia

CHAPTER 5 EXTENSIONS AND EXCEPTIONS TO MENDEL'S LAWS

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CHAPTER 7 MULTIFACTORIAL TRAITS

Cleft lip with or without cleft palate Complex traits among the Hutterites

CHAPTER 8 THE GENETICS OF BEHAVIOR

Alcoholism

ACROCEPHALOSYNDACTYLY

Wayne and Marge had always thought that their identical twin sons Wally and Todd had unusually large toes. This was cute when they were infants, but as they began to walk, their feet did not fit easily into shoes. The problem worsened as they grew older, but then they discovered a certain brand of running shoe that fit well. Wayne's mother Cecile recalled that she had similar problems fitting Wayne and his sister Colleen with shoes when they were children. Cecile's deceased husband George had very bizarre feet. Colleen and her husband Jack have a 4-year-old daughter, Leah, who has the family's large toes too.

Colleen is a geneticist. She suspected that Willy, George, Todd, Wayne, Leah, and herself have a form of acrocephalosyndactyly, an inherited disorder. She suggested that the affected relatives have their toes x-rayed and, as she suspected, they all had the unusual sign of this condition – double bones in each toe.

SOURCE: OMIM 105200

WORKSHEET:

1. This disorder is very rare. Of known affected families, there are no instances of consanguinity. Does this support a mode of inheritance of autosomal recessive or autosomal dominant inheritance? Why?

2. If the trait is inherited as an autosomal dominant, and Leah marries John, a	a
ballet dancer with exquisite, slim toes, the probability that a child of theirs wo	uld
inherit normal toes is	