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Children with Disabilities

8th EDITION

Paul H. Brookes Publishing Co.
Post Office Box 10624
Baltimore, Maryland 21285-0624
USA
www.brookespublishing.com

Typeset by Progressive Publishing Solutions, York, Pennsylvania.
Manufactured in the United States of America by
Sheridan Books, Inc., Chelsea, Michigan.

Appendix C, Commonly Used Medications, which appears in the back matter and in the book's online materials, provides information about numerous drugs frequently used to treat children with disabilities. This appendix is in no way meant to substitute for a physician's advice or expert opinion; readers should consult a medical practitioner if they are interested in more information.

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The vignettes presented in this book are composite accounts that do not represent the lives or experiences of specific individuals, and no implications should be inferred. In all instances, names and identifying details have been changed to protect confidentiality.

Library of Congress Cataloging-in-Publication Data

Names: Batshaw, Mark L., 1945- editor. | Roizen, Nancy J., editor. | Pellegrino, Louis, editor.
Title: Children with disabilities / edited by Mark L. Batshaw, M.D., Nancy J. Roizen, M.D., and Louis Pellegrino, M.D.
Description: Eighth edition. | Baltimore : Paul H. Brookes Publishing Co., [2019] | Includes bibliographical references and index.
Identifiers: LCCN 2018048552 (print) | LCCN 2018059190 (ebook) | ISBN 9781681253213 (epub) | ISBN 9781681253220 (pdf) | ISBN 9781681253206 (hardcover)
Subjects: LCSH: Developmental disabilities. | Developmentally disabled children—Care. | Children with disabilities—Care.
Classification: LCC RJ135 (ebook) | LCC RJ135 .B38 2019 (print) | DDC 618.92/8588—dc23
LC record available at https://lccn.loc.gov/2018048552

British Library Cataloguing in Publication data are available from the British Library.

2023 2022 2021 2020 2019
10 9 8 7 6 5 4 3 2 1

Contents

Preface

One of the first questions asked about a subsequent edition of a textbook is, "What's new?" The challenge of determining what to revise, what to add, and, in some cases, what to delete is always significant in preparing a new edition in a field that is changing as rapidly as developmental disabilities. Since the publication of the seventh edition in 2013, advances in the fields of neuroscience and genetics have greatly enhanced our understanding of the brain and inheritance. This creates opportunities for treatments previously not thought possible for some children with developmental disabilities. Genomic sequencing is now used routinely (and sometimes recreationally), gene therapy is being used to correct birth defects, and the brain can be probed noninvasively by functional imaging techniques.

The need to examine and explain this advanced knowledge and its significance for children with disabilities has necessitated an increase in the depth and breadth of the subjects covered in the book. Yet, although the book is now more expansive and has several new chapters, we have worked hard to ensure that it retains its clarity and cohesion. Its mission continues to be to provide the individual working with and caring for children with disabilities the necessary background to understand different disabilities and their treatments, thereby enabling affected children to reach their full potential.

THE AUDIENCE

Since it was originally published, *Children with Disabilities* has been used by students in a wide range of disciplines as a medical textbook addressing the impact of disabilities on child development and function. It has also served as a professional reference for special educators, general educators, physical therapists, occupational therapists, speech-language pathologists, psychologists, child-life specialists, social workers, pediatric residents and medical students, psychiatrists, neurologists, pediatric nurses and nurse practitioners, advocates, and other practitioners who provide care for children with disabilities. Finally, as a family resource, parents, grandparents, siblings, and other family members and friends have used the book. They have found useful information on the medical and rehabilitative aspects of care for the child with developmental disabilities.

FEATURES FOR THE READER

We have been told that the strengths of previous editions of this book have been the accessible writing style, the clear illustrations, and the up-to-date information and references. We have dedicated our efforts to retaining these strengths and building on them with the addition of new features to highlight the application of content to evidence-based practice. Some of the features you will find in the eighth edition include the following.

- *Learning goals:* Each chapter begins with learning outcomes to orient you to the key content of that particular chapter.
- *Thought questions:* Questions have been crafted to "prime" the reader for what he or she should be thinking about while reading the chapter.
- *Case studies:* Most chapters include one or more situational examples to help bring alive the conditions and issues discussed in the chapter.
- *Key terms:* As key medical terms pertaining to a specific chapter are introduced in the text, they appear in boldface type at their first use; definitions for these terms appear in the Glossary (Appendix A).
- *Illustrations and tables:* More than 200 drawings, photographs, radiographs, imaging scans, and tables reinforce important concepts and provide ways for you to more easily understand and remember the material you are reading.
- *Summary:* Each chapter closes with a final section that in a bulleted list summarizes its key elements and provides you with an abstract of the covered material.
- *References:* The reference list accompanying each chapter can be considered more than just a list of the literature cited in the chapter. These citations

include review articles, reports of study findings, research discoveries, and other key references that can help you find additional information. We have tried to keep the majority of the references within 5 years of the book's publication so they are recent and relevant, although classic research is often still relevant and included.

- *Interdisciplinary boxes:* New to this edition, chapters include special boxes that summarize the role of specific disciplines relevant to the chapter's content. This feature emphasizes the interprofessional nature of caring for children with developmental disabilities.
- *Evidence-based practice boxes:* This new feature acknowledges the importance of evidence-based practice by summarizing the results of current research relevant to the topic and providing a "take-away message" so readers can apply the information to practice.
- *Appendices:* In addition to the Glossary, there are two other helpful appendices: 1) Syndromes and Inborn Errors of Metabolism, a mini-reference of pertinent information on inherited disorders causing developmental disabilities, and 2) Commonly Used Medications, to describe indications and side effects of medications often prescribed for children with disabilities.
- *Web site:* We have created a web site specific for *Children with Disabilities* that has additional content, including the following: 1) a resource directory of a wide range of national organizations, federal agencies, information sources, self-advocacy and accessibility programs, and support groups that can provide assistance to families and professionals; 2) a bank of 250 test questions for instructors; and 3) study questions and extension activities for every chapter. This content will be continuously updated.

CONTENT

In developing this eighth edition, we have aimed for a balance between consistency with the text that many of you have come to know so well and appreciate in its previous editions and innovation in exploring the new topics that demand our attention. All chapters have been substantially revised, and many have been rewritten to include an expanded focus on the psychosocial, rehabilitative, and educational interventions, as well as to provide information discovered through educational, medical, and scientific advances since 2013.

Seven new chapters have been added, including the following.

- Chapter 7: The Senses: The World We See, Hear, and Feel
- Chapter 11: Child Development
- Chapter 28: Sleep Disorders
- Chapter 30: Interdisciplinary Education and Practice
- Chapter 38: Pharmacological Therapy
- Chapter 42: Racial and Ethnic Disparities

The new chapters focus on recently gained knowledge that is transforming our understanding of the causes and treatment of developmental disabilities.

The chapters are grouped into seven parts and organized to help guide readers through the breadth of content. Each part is detailed next.

Part I: The book starts with a section titled As Life Begins, which addresses what happens before, during, and/or shortly after birth to cause a child to be at increased risk for a developmental disability. The concepts and consequences of genetics, environmental influences, prenatal diagnosis, newborn screening, neonatal complication, and prematurity are explained.

Part II: The next section of the book, The Child's Body: Physiology, covers embryonic and fetal development, the sensory systems, the brain and central nervous system, muscles, bones and nerves, and the gastrointestinal tract—how they develop and work, and what can go wrong.

Part III : The third section covers Developmental Assessment. It includes chapters on typical and atypical development, diagnosing developmental disabilities, assessing physical disabilities, and neurocognitive and behavioral assessment.

Part IV: As its title implies, the fourth section, Developmental Disabilities, provides comprehensive descriptions of the major developmental disabilities and genetic syndromes that cause disabilities. This section includes chapters on intellectual disability, Down syndrome and fragile x syndrome, inborn errors of metabolism, speech and language disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder, specific learning disabilities, cerebral palsy, epilepsy, acquired brain injury, and chronic diseases with related developmental disabilities.

Part V: The fifth section addresses Associated Disabilities, those disorders that occur more commonly in individuals with developmental disabilities. Chapters

include discussions on visual deficits, hearing impairment, behavioral/mental health issues, sleep disorders and feeding disorders.

Part VI: The sixth section focuses on Interventions. It contains chapters on interdisciplinary care, early intervention and special education services, (re)habilitative services, oral health care, behavioral therapy, assistive technology, family assistance, medication, and complementary health approaches.

Part VII: The final section is directed at Outcomes. This section concentrates on transition to adulthood, the effect of health care systems on outcomes, and health care disparities and their effect on outcomes in children with developmental disabilities.

THE CONTRIBUTORS AND REVIEW PROCESS

For contributors to this edition, we chose educators, physicians, dentists, psychologists, social workers, genetic counselors, occupational and physical therapists, speech-language pathologists, and other health care professionals who are experts in the areas they write about. Many are colleagues from Children's National Medical Center in Washington, D.C. Each chapter in the book has undergone editing at Paul H. Brookes Publishing Co. to ensure consistency in style and accessibility of content. Once the initial drafts were completed, each chapter was sent for peer review by major clinical and academic leaders in the field and was revised according to their input.

A FEW NOTES ABOUT TERMINOLOGY AND STYLE

As is the case with any book of this scope, the editors and contributors make decisions about the use of particular words and the presentation style of information. We would like to share with you some of the decisions we have made for this book.

- *Categories of intellectual disability:* This book uses the American Psychiatric Association's categories according to the term *intellectual disability* (i.e., mild, moderate, severe, profound) when discussing medical diagnosis and treatment, and uses the categories that the American Association on Intellectual and Developmental Disabilities (formerly the American Association on Mental Retardation) established in 1992 (i.e., requiring limited, intermittent, extensive, or pervasive support) when discussing educational and other interventions, thus emphasizing the capabilities rather than the impairments of individuals with intellectual disability.
- *"Typical" versus "normal":* Recognizing diversity and the fact that no one type of person or lifestyle is inherently "normal," we have chosen to refer to the general population of children as "typical" or "typically developing," meaning that they follow the natural continuum of development.
- *Person-first language:* We have tried to preserve the dignity and personhood of all individuals with disabilities by consistently using person-first language, speaking, for example, of "a child with cerebral palsy," instead of "a cerebral palsied child." In this way, we are able to emphasize the person, not define him or her by the condition.

As you read this eighth edition of *Children with Disabilities*, we hope you will find that the text continues to address the frequently asked question, "Why this child?" and to provide the medical background you need to care for children with developmental disabilities.

CHAPTER 1

The Genetics Underlying Developmental Disabilities

Mark L. Batshaw, Eyby Leon, and Monisha S. Kisling

Upon completion of this chapter, the reader will

- Know about the human genome and its implication for the origins of developmental disabilities
- Be able to explain how errors in cell division can cause genetic syndromes
- Know about Mendelian inheritance
- Recognize the importance of mutations and genetic variation
- Understand the ways that genes can be affected by the environment in which they reside, i.e., epigenetics
- Know about genetic testing for the origins of developmental disability
- Be aware of novel genetic treatment approaches

Whether we have brown or blue eyes is determined by genes passed on to us from our parents. Other traits, such as height and weight, are affected by genes and by our environment both before and after birth. In a similar manner, genes alone or in combination with environmental factors can place children at increased risk for many developmental disorders, including birth defects such as meningomyelocoele (spina bifida). In the case of meningomyelocoele, a maternal nutritional deficiency of folic acid can markedly increase the risk of the genetic disorder. Disorders associated with developmental disabilities have a spectrum of genetic and environmental origins. Some disorders are purely genetic, such as Tay-Sachs disease (a progressive neurologic disorder) and result from a defect in a **single gene,** while others like Down syndrome (see Chapter 15), result from a chromosomal error, in which an extra chromosome containing hundreds of genes exists. Other developmental disorders result from purely environmental exposures, including prenatal viral infections such as cytomegalovirus and teratogenic agents like alcohol and thalidomide (see Chapter 2). There are also conditions in which genes are affected by their environment, leading to epigenetic disorders such as fragile X syndrome and Angelman syndrome.

As an introduction to the topics discussed in the other chapters of this volume, this chapter describes the human cell and explains chromosomes and genes. It also reviews and provides illustrations and examples of the errors that can occur in the processes of **meiosis** (reductive cell division) and **mitosis** (cell replication), summarizes inheritance patterns of single-gene disorders, and presents the concept of epigenetics. Furthermore, this chapter discusses innovative treatments

that manipulate or use an understanding of the child's genome to improve an outcome. It is important to understand that while these disorders are individually rare, genetic alterations underlie almost half of developmental disabilities. Medical treatment is increasingly available for a number of these disorders, though often at great cost.

CASE STUDY

Katy developed typically until she was 2 years old, when she started to have episodes of vomiting and lethargy after high-protein meals. Her parents became very concerned because their older son, Andrew, had died in infancy after an episode of lethargy and seizures was followed by coma, although no specific diagnosis had been made. After extensive testing by a genetic specialist, Katy was discovered to have a specific mutation or error in the gene that codes for ornithine transcarbamylase (OTC), an enzyme that prevents the accumulation of toxic ammonia in the body and brain. The OTC gene is located on the X chromosome; since girls have two X chromosomes, when one X has the mutation, there is a second normal copy to mitigate the defect. As a result, girls are less likely to be affected by X-linked disorders than boys, and, when affected, they generally have less severe symptoms. After Katy was diagnosed with OTC deficiency, her specialist tested DNA that was extracted before Andrew's death and found that he too carried this mutation. Katy was placed on a low-protein diet and given a medicine to provide an alternate pathway to rid the body of ammonia, and she has done well. Now age 7, she appears to have a mild nonverbal learning disability resulting from her prior metabolic crises; if Katy had been left untreated, she would probably not be alive.

Thought Questions:

How often do we miss a genetic diagnosis as a cause of developmental disabilities? Could earlier diagnosis and treatment improve outcomes in many of these cases?

GENETIC DISORDERS

The human body is composed of approximately 100 trillion cells. There are many cell types: nerve cells, muscle cells, white blood cells, liver cells and skin cells, to name a few. All cells, with the exception of the red blood cell, are divided into two compartments: a central, enclosed core—the **nucleus**—and an outer area—the **cytoplasm** (Figure 1.1). The red blood cell differs insofar as it does not have a nucleus. The nucleus houses **chromosomes,** structures that contain the genetic code—DNA (**deoxyribonucleic acid**), which is organized into hundreds of

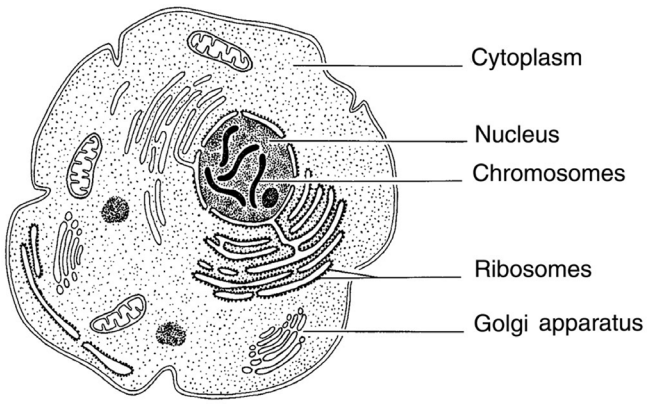

Figure 1.1. An idealized cell. The genes within chromosomes direct the creation of a product on the ribosomes. The product is then packaged in the Golgi apparatus and released from the cell.

genes (units of heredity) in each chromosome. There are 23 pairs of chromosomes and about 20,000 protein-coding genes that collectively make up the human **genome.** These genes are responsible for our physical attributes and for the biological functioning of our bodies. Under the direction of the genes, the products that are needed for the organism's development and functions, such as waste disposal and the release of energy, are made in the cytoplasm. The nucleus contains the blueprint for the organism's growth and development, and the cytoplasm manufactures the products needed to complete the task.

When there is a defect within this system, the result may be a genetic disorder, often causing developmental disabilities. These disorders take many forms. They include the addition of an entire chromosome in each cell (e.g., Down syndrome), the loss of an entire chromosome in each cell (e.g., Turner syndrome), and the loss or deletion of a significant portion of a chromosome (e.g., Cri-du-chat syndrome). There can also be a **microdeletion** of a number of closely spaced or contiguous genes within a chromosome (e.g., chromosome 22q11.2 deletion syndrome, also called velocardiofacial syndrome [VCFS]). Microdeletions may have varied expression depending on stochastic (randomly determined) and environmental processes, as well as on genetic effects, with these factors potentially acting alone or in combination (Bertini et al., 2017). Finally, there can be a defect within a single gene (e.g., phenylketonuria) or altered expression of the gene (e.g., Rett syndrome). This chapter discusses each of these types of genetic defects.

CHROMOSOMES

Each organism has a fixed number of chromosomes that directs the cell's activities. In each human cell,

there are normally 46 chromosomes. Each chromosome contains many genes, but some chromosomes have more (e.g., 500–800 gene loci in chromosomes 1, 19, and X) and others have fewer (50–120 in chromosomes 13, 18, 21, and Y). The 46 chromosomes are organized into 23 pairs. Typically, one chromosome in each pair comes from the mother and the other from the father. Egg and sperm cells, unlike all other human cells, each contains only 23 chromosomes. During conception, these **germ cells** (i.e., sperm and eggs) fuse to produce a fertilized egg with the full complement of 46 chromosomes.

Among the 23 pairs of chromosomes, 22 are termed **autosomes.** The 23rd pair consists of the X and Y chromosomes and are called the **sex chromosomes.** The Y chromosome, which is involved in male sex determination and development, is one-third to one-half the size of the X chromosome, has a different shape, and has far fewer genes. Two X chromosomes determine the child to be female; an X and a Y chromosome determine the child to be male.

CELL DIVISION AND ITS DISORDERS

Cells have the ability to divide into daughter cells that contain genetic information that is identical to the information from the parent cell. The prenatal development of a human being is accomplished through cell division, differentiation into different cell types, and movement of cells to different locations in the body. There are two kinds of cell division: **mitosis** and **meiosis.** In mitosis, or nonreductive division, 2 daughter cells, each containing 46 chromosomes, are formed from 1 parent cell. In meiosis, or reductive division, 4 daughter cells, each containing only 23 chromosomes, are formed from 1 parent cell. Although mitosis occurs in all cells, meiosis takes place only in the germ cells.

The ability of cells to continue to undergo mitosis throughout the life span is essential for proper bodily functioning. Cells divide at different rates, however, ranging from once every 10 hours for skin cells to once a year for liver cells. This is why a skin abrasion heals in a few days but the liver may take a year to recover from hepatitis. By adulthood, some cells, including neurons and muscle cells, appear to have a significantly decreased ability to divide. This limits the body's capacity to recover after medical events, such as strokes, or from traumatic injuries.

One of the primary differences between mitosis and meiosis can be seen during the first of the two meiotic divisions. During this cell division, the corresponding chromosomes line up beside each other in pairs (e.g., both copies of chromosome 1 line up together). Unlike in mitosis, however, they intertwine and may "cross over," exchanging genetic material. This adds variability. Although this crossing over (or recombination) of the chromosomes may result in disorders (e.g., deletions), it also allows for the mutual transfer of genetic information, reducing the chance that siblings end up as exact copies (clones) of each other. Some of the variability among siblings can also be attributed to the random assortment of maternal and paternal chromosomes during the first of the two meiotic divisions.

Throughout the life span of the male, meiosis of the immature sperm produces **spermatocytes** with 23 chromosomes each. These cells will lose most of their cytoplasm, sprout tails, and become mature sperm. This process is termed spermatogenesis. In the female, meiosis forms oocytes that will ultimately become mature eggs in a process called oogenesis. By the time a girl is born, her body has produced all of the approximately 2 million eggs she will ever have.

A number of events that adversely affect a child's development can occur during meiosis. When chromosomes divide unequally, a process known as **nondisjunction** occurs; as a result, 1 daughter egg or sperm contains 24 chromosomes and the other 22 chromosomes. Meiotic nondisjunction, particularly in oogenesis, is the most common mutational mechanism in humans responsible for chromosomally atypical fetuses. Usually, these cells do not survive, but occasionally they do and can lead to the child being born with too many chromosomes (e.g., Down syndrome) or too few (e.g., Turner syndrome). Notably, the most commonly found **trisomy** in miscarriages is trisomy 16, and embryos with trisomy 16 are never carried to term (Nussbaum, McInnes, & Willard, 2016). The chromosome 16 contains so many genes important for normal development that its disruption is incompatible with life. Conversely, trisomies 13, 18, and 21 are the most commonly observed full trisomies at birth (Mai et al., 2013). However, even in these conditions, the vast majority of embryos with the defect do not survive.

The majority of fetuses carrying chromosomal abnormalities are spontaneously aborted. Among those children who survive these genetic missteps, **intellectual disability,** unusual (dysmorphic) facial appearances, and various congenital organ malformations are common. In the general population, chromosomal errors causing disorders occur in 6–9 per 1,000 of all live births. In children who have intellectual disability, however, the prevalence of chromosomal abnormality increases, being responsible for 20% of the cases (Martin & Ledbetter, 2017). It is also clear that as the woman ages, the risk of errors in meiosis increases, as is typified by Down syndrome.

Chromosomal Gain: Down Syndrome

The most frequent chromosomal abnormality is unequal division of non-sex chromosomes, and the most common clinical consequence is trisomy 21, or Down syndrome (Nussbaum, McInnes, & Willard, 2016; also see Chapter 15). Nondisjunction can occur during either mitosis or meiosis but is more common in meiosis (Figure 1.2). When nondisjunction occurs during the first meiotic division, both copies of chromosome 21 end up in one cell. Instead of an equal distribution of chromosomes among cells (23 each), 1 daughter cell receives 24 chromosomes and the other receives only 22. The cell containing 22 chromosomes is unable to survive. However, the egg (or sperm) with 24 chromosomes occasionally can survive. After fertilization with a sperm (or egg) containing 23 chromosomes, the resulting embryo contains 3 copies of chromosome 21, or trisomy 21. The child will be born with 47 rather than 46 chromosomes in each cell and will thus have Down syndrome (Figure 1.3).

The majority of individuals with Down syndrome (approximately 95%) have trisomy 21. This trisomy results from nondisjunction during meiosis in oogenesis in 90% of the cases and from nondisjunction during spermatogenesis in 10% (Nussbaum, McInnes, & Willard, 2016). This disparity is partially due to the increased rate of autosomal nondisjunction in egg production, but also to the lack of viability of sperm with an extra chromosome 21. Another 3%–4% of individuals

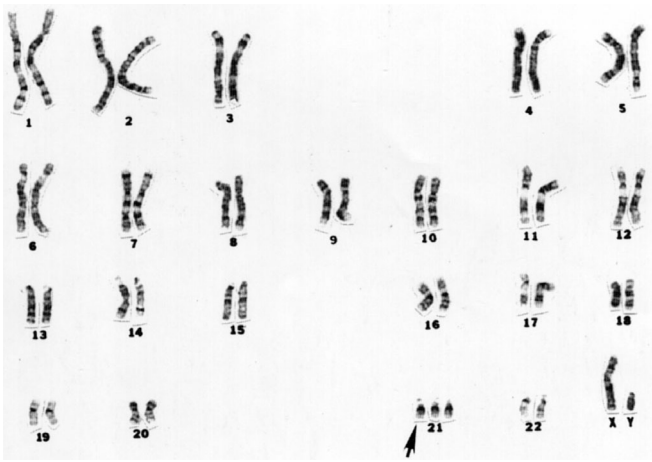

Figure 1.3. Karyotype of a boy with Down syndrome (47, XY). Note that the child has 47 chromosomes; the extra one is a chromosome 21.

acquire Down syndrome as a result of **translocation** (discussed later) and 1%–2% acquire it from **mosaicism** (some cells being affected and others not; this is also discussed later).

Chromosomal Loss: Turner Syndrome

Turner syndrome is the only disorder in which a fetus can survive despite the loss of an entire chromosome. Even so, more than 99% of the 45,X conceptions appear

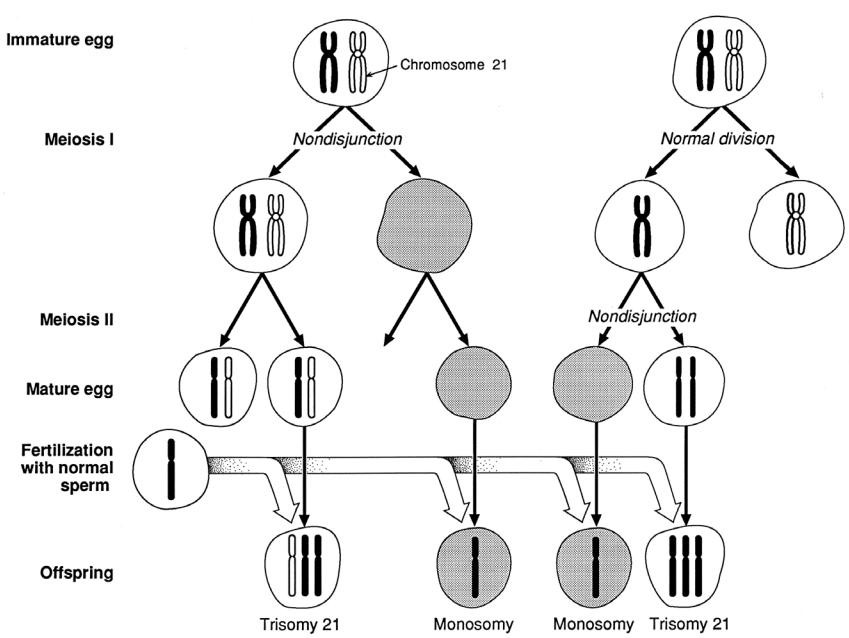

Figure 1.2. Nondisjunction of chromosome 21 in meiosis. Unequal division during meiosis I or meiosis II can result in trisomy or monosomy.

to be miscarried (Hook & Warburton, 2014). Females with Turner syndrome (1 in every 5,000 live births) have a single X chromosome and no second X or Y chromosome, for a total of 45, rather than 46, chromosomes. In contrast to Down syndrome, 80% of individuals with **monosomy** X conditions are affected by meiotic errors in sperm production; these children usually receive an X chromosome from their mothers but no sex chromosome from their fathers.

Girls with Turner syndrome typically have short stature, a webbed neck, a broad "shield-like" chest with widely spaced nipples, and nonfunctional ovaries. Twenty percent have obstruction of the left side of the heart, most commonly caused by a **coarctation** of the **aorta.** Unlike children with Down syndrome, most girls with Turner syndrome develop typically. They do, however, have visual–perceptual impairments that predispose them to develop nonverbal learning disabilities (Table 1.1; Hong & Reiss, 2014). Human growth hormone injections have been effective in increasing height in girls with Turner syndrome, and **estrogen** supplementation can lead to the emergence of secondary sexual characteristics; however, these girls remain infertile.

Mosaicism

In mosaicism, cells in the same individual have different genetic makeups (Nussbaum, McInnes, & Willard, 2016). For example, a child with the mosaic form of Down syndrome may have trisomy 21 in skin cells but not in blood cells. or the individual may have trisomy 21 in some, but not all, brain cells. Children with mosaicism often appear as though they have a particular condition (in this example, Down syndrome); however, the physical/organ and cognitive impairments may be less severe. Usually mosaicism occurs when some cells in a trisomy conception lose the extra chromosome via nondisjunction during mitosis. Mosaicism also can occur if some cells lose a chromosome after a normal conception (e.g., some cells lose an X chromosome in mosaic Turner syndrome). Mosaicism is present in only 5%–10% of all children with chromosomal abnormalities.

Translocations

A relatively common dysfunction in cell division, translocation can occur during mitosis and meiosis when the chromosomes break and then exchange parts with other chromosomes. Translocation involves the transfer of a portion of one chromosome to a completely different chromosome. For example, a portion of chromosome 21 might attach itself to chromosome 14 (Figure 1.4). If this occurs during meiosis, 1 daughter cell will then have 23 chromosomes but will have both a chromosome 21 and a chromosome 14/21 translocation. Fertilization of this egg, by a sperm with a cell containing the normal complement of 23 chromosomes, will result in a child with 46 chromosomes. This includes two copies of chromosome 21, one chromosome 14/21, and one chromosome 14. This child will have Down syndrome because of the functional trisomy 21 caused by the translocation.

Deletions

Another somewhat common dysfunction in cell division is deletion. Here, part, but not all, of a chromosome is lost. Chromosomal deletions occur in two forms: visible deletions and microdeletions. Those that are large enough to be seen through the microscope are called visible deletions. Those that are so small that they can only be detected at the molecular level are called microdeletions and can be identified by a test called chromosomal microarray.

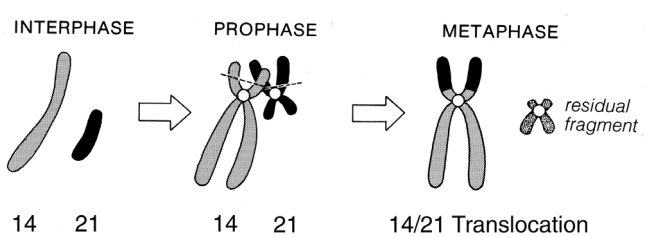

Figure 1.4. Translocation. During **prophase** of meiosis in a parent, there may be a transfer of a portion of one chromosome to another. In this figure, the long arm of chromosome 21 is translocated to chromosome 14, and the residual fragments are lost.

Table 1.1. Neurocognitive deficits in Turner syndrome

Intellectual function	Typical but 5–10 points below siblings; verbal IQ > performance IQ
Visual spatial	Deficits in spatial orientation
Math	Difficulties with calculation
Executive function	Impairment in attention, processing speed, working memory, cognitive flexibility, and planning
Social	Impairments in face recognition and social reciprocity
Behavior	Overall risk of attention-deficit/hyperactivity disorder and dyscalculia; equivocal evidence for autism

Source: Hong and Reiss (2014).

Cri-du-chat ("cat cry") syndrome is an example of a visible chromosomal deletion in which a portion of the short arm of chromosome 5 is lost. Cri-du-chat syndrome affects approximately 1 in 50,000 children, causing microcephaly and an unusual facial appearance with a round face, widely spaced eyes, **epicanthal folds,** and low-set ears. Children with the syndrome have a high-pitched cry and intellectual disability (Cerruti Mainardi, 2006).

Examples of **microdeletion syndromes** (also called **contiguous gene syndromes** because they involve the deletion of a number of adjacent genes) include Smith-Magenis syndrome, Williams syndrome, and VCFS (Weischenfeldt, Symmons, Spitz, & Korbel, 2013). Smith-Magenis is caused by a microdeletion in the short arm of chromosome 17, Williams syndrome by a deletion in the long arm of chromosome 7, and VCFS by a deletion in the long arm of chromosome 22. Children with Smith-Magenis syndrome have feeding difficulties, hypotonia, distinctive facial features, self-injurious behavior, and intellectual disability. Children with Williams syndrome likewise have intellectual disability with a distinctive facial appearance, but they also have cardiac defects and a unique cognitive profile with apparent expressive language skills beyond what would be expected based on their cognitive abilities. Children with VCFS syndrome may have a cleft palate, a congenital heart defect, a characteristic facial appearance, and/or a nonverbal learning disability. Cognitive problems are often present, and many affected children satisfy the criteria for a diagnosis of autism.

Frequency of Chromosomal Abnormalities

In total, approximately 25% of eggs and 3%–4% of sperm have an extra or missing chromosome, and an additional 1% and 5%, respectively, have a structural chromosomal abnormality (Hassold, Hall, & Hunt, 2007). As a result, 10%–15% of all conceptions have a chromosomal abnormality. Somewhat more than 50% of these abnormalities are trisomies, 20% are monosomies, and 15% are **triploidies** (69 chromosomes). The remaining chromosomal abnormalities are composed of structural abnormalities and **tetraploidies** (92 chromosomes). It may therefore seem surprising that more children are not born with chromosomal abnormalities. The explanation is that more than 95% of fetuses with chromosomal abnormalities do not survive to term. In fact, many are lost very early in gestation, even before a pregnancy may be recognized.

GENES AND THEIR DISORDERS

The underlying problem with the previously mentioned chromosomal disorders is the presence of too many or too few genes resulting from extra or missing chromosomal material. Genetic disorders can also result from an abnormality in a single gene. As noted above, there are about 20,000 genes in the human genome. This is quite remarkable given that the fruit fly has approximately 13,000 genes, the round worm 19,000 genes, and a simple plant 26,000 genes. It was previously thought that each gene regulated the production of a single protein. Now it is known that the situation is much more complex; single genes in humans code for multiple proteins, giving humans the combinational diversity that lower organisms lack. Humans can produce approximately 100,000 proteins from less than one-quarter of that many genes. However, it must be acknowledged that the chimp shares 99% of the human genome. Having now examined the genome of innumerable organisms, the minimum number of genes necessary for life appears to be approximately 300; all living organisms share these same 300 genes.

The mechanism by which genes act as blueprints for producing specific proteins needed for body functions is as follows. Genes are composed of various lengths of DNA that, together with intervening DNA sequences, form chromosomes. DNA is formed as a **double helix,** a structure that resembles a twisted ladder (Figure 1.5). The sides of the ladder are composed of sugar and phosphate molecules, whereas the "rungs" are made up of four chemicals called **nucleotide bases: cytosine** (C), **guanine** (G), **adenine** (A), and **thymine** (T). Pairs of nucleotide bases interlock to form each rung: cytosine bonds with guanine, and adenine bonds with thymine. The sequence of nucleotide bases on a segment of DNA (spelled out by the four-letter alphabet C, G, A, T) make up an individual's genetic code. Individual genes range in size, containing from 1,500 to more than 2 million nucleotide–base pairs. Overall, there are approximately 3.3 billion base pairs in the human genome, but only about 1% encode genes that serve as a blueprint for protein production. It should also be noted that all genes are not "turned on" or expressed at all times. Some are only active during fetal

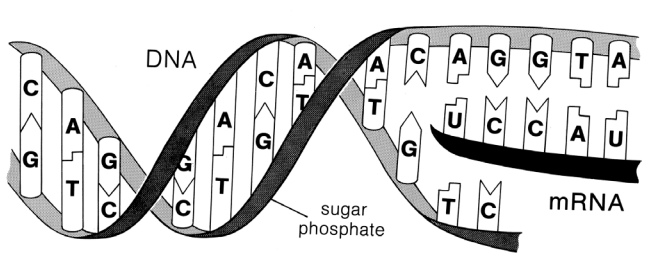

Figure 1.5. Deoxyribonucleic acid (DNA). Four nucleotides (C, cytosine; G, guanine; A, adenosine; T, thymine) form the genetic code. On the mRNA molecule, uracil (U) substitutes for thymine. The DNA unzips to transcribe its message as mRNA.

life (e.g., the fetal hemoglobin gene), and it is hoped that some are never expressed (e.g., oncogenes, which have the potential to cause cancer). The turning on and off of genes usually follows a carefully developmentally regulated process, but it can also be influenced by the environment. Regulation of gene expression plays a particularly important role during fetal development; as a result, problems involving gene expression during fetal development can be particularly devastating. The way gene expression is regulated involves a number of structural changes to the DNA and its architecture without altering the actual nucleotide sequence of the DNA. This process is termed *epigenetics* and is a cause of a number of genetic syndromes that are associated with developmental disabilities.

Transcription

The production of a specific protein begins when the DNA comprising that gene unwinds and the two strands (the sides of the ladder) unzip to expose the genetic code (Jorde, Carey, & Bamshad, 2015). The exposed DNA sequence then serves as a template for the formation, or **transcription** (the writing out), of a similar nucleotide sequence called **messenger ribonucleic acid** (mRNA; Figure 1.6). In all RNA, the nucleotides are the same as in DNA except that uracil (U) substitutes for thymine (T). In most genes, coding regions (**exons**) are interrupted by noncoding regions (**introns**). During transcription, the entire gene is copied into a pre-mRNA, which includes exons and introns. During the process of RNA splicing, introns are removed and exons are joined to form a contiguous coding sequence. In its entirety, the part of the human genome formed by exons is called the **exome.** As might be expected, errors or mutations may occur during transcription; however, a proofreading enzyme generally catches and repairs these errors. If not corrected, however, transcription errors can lead to the production of a disordered protein and a disease state.

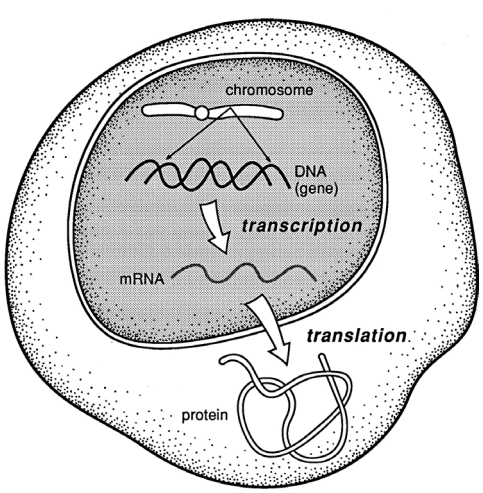

Figure 1.6. A summary of the steps leading from gene to protein formation. Transcription of the DNA (gene) onto mRNA occurs in the cell nucleus. The mRNA is then transported to the cytoplasm, where translation into protein occurs.

Translation

Once transcribed, the single-stranded mRNA detaches and the double-stranded DNA zips back together. The mRNA then moves out of the nucleus into the cytoplasm, where it provides instructions for the production of a protein, a process termed **translation** (Figure 1.7). The mRNA attaches itself to a **ribosome.** The ribosome moves along the mRNA strand, reading the message in three-letter "words," or **codons,** such as GCU, CUA, and UAG. Most of these triplets code for specific **amino acids,** the building blocks of proteins. As these triplets are read, another type of RNA, transfer RNA (tRNA), carries the requisite amino acids to the ribosome, where they are linked to form a protein.

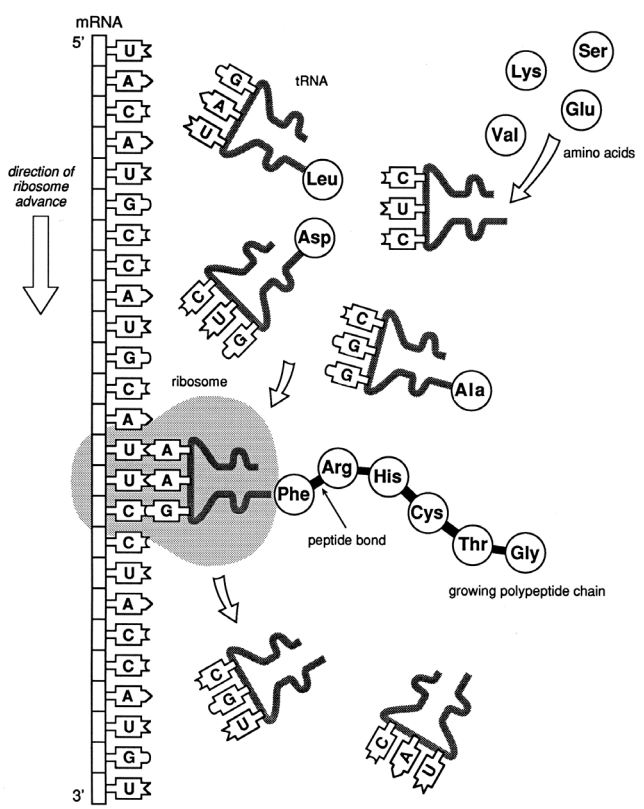

Figure 1.7. Translation of mRNA into protein. The ribosome moves along the mRNA strand assembling a growing polypeptide chain using tRNA–amino acid complexes. In this example, it has already assembled six amino acids (phenylalanine [Phe], arginine [Arg], histidine [His], cystine [Cys], threonine [Thr], and glycine [Gly]) into a polypeptide chain that will become a protein.

Certain triplets, termed *stop codons*, instruct the ribosome to terminate the sequence by indicating that all of the correct amino acids are in place to form the complete protein, for example, thyroid hormone.

Once the protein is complete, the mRNA, ribosome, and protein separate. The protein is released into the cytoplasm and is either used by the cytoplasm or prepared for secretion into the bloodstream. If the protein is to be secreted, it is transferred to the **Golgi apparatus** (Figure 1.1), which packages it in a form that can be released through the cell membrane and carried throughout the body.

Mutations

An abnormality at any step in the transcription or translation process can cause the body to produce a structurally abnormal protein, reduced amounts of a protein, or no protein at all. When the error occurs in the gene itself, thus disrupting the subsequent steps, that mistake is termed a *mutation*. The likelihood of mutations occurring increases with the size of the gene. In sperm cells, the point mutation rate also increases with paternal age. Although most mutations occur spontaneously, they can be induced by radiation, toxins, and viruses. Once they occur, mutations become part of a person's genetic code. If they are present in the germline, they can be passed on from one generation to the next.

Point Mutations The most common type of mutation is a single base pair substitution (Jorde et al., 2015), also called a **point mutation.** Because there is redundancy in human DNA, many point mutations have no adverse consequences. Depending on where in the gene they occur, however, point mutations are capable of causing a **missense mutation** or a **nonsense mutation** (Figure 1.8). A missense mutation results in a change in the triplet code that substitutes a different amino acid in the protein chain. For example, in most cases of the inborn error of metabolism, **phenylketonuria** (PKU), a single base substitution causes an error in the production of phenylalanine hydroxylase, the enzyme necessary to metabolize the amino acid **phenylalanine.** The result is an accumulation of phenylalanine that can cause brain damage (see Chapter 16). In a nonsense mutation, the single base pair substitution produces a stop codon that prematurely terminates the protein formation. In this case, no useful protein is formed. **Neurofibromatosis-1** (NF1) is an example of a disorder commonly caused by a nonsense mutation. In NF1 a tumor suppressor, neurofibromin, is not formed. As a result, multiple benign neurofibroma tumors form on the body and in the brain. Children with NF1 also have a high incidence of attention-deficit/hyperactivity disorder (Friedman, 2014).

Insertions and Deletions Mutations can also involve the insertion or deletion of one or more nucleotide bases. As one example, insertion of nucleotides in the fukutin gene (expressed in muscle, brain, and eyes) can affect its function when associated with other mutations and cause Fukuyama congenital muscular dystrophy (Saito, 2012). In contrast, a common mutation in another inherited muscle disease, Duchenne muscular dystrophy, usually involves a deletion in the dystrophin gene (see Chapter 9).

Base additions or subtractions may also lead to a **frame shift** in which the three-base-pair reading frame is shifted. All subsequent triplets are misread, often leading to the production of a stop codon and a nonfunctional protein. Certain children with Tay-Sachs disease have this type of mutation. Other mutations

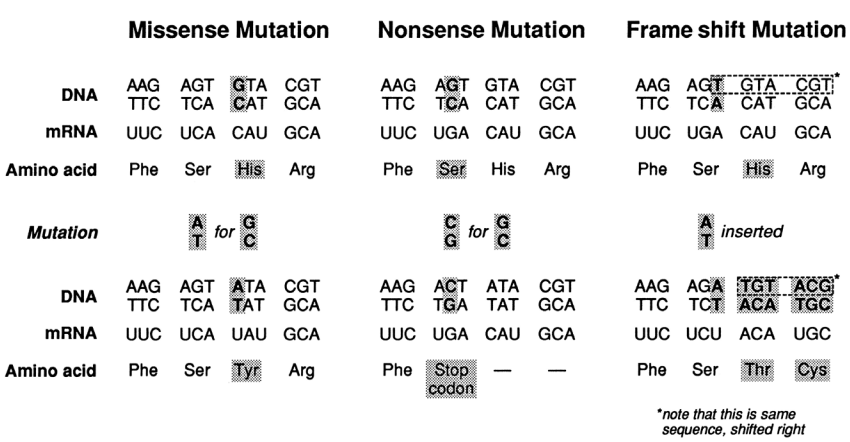

Figure 1.8. Examples of point mutations: Missense mutation, nonsense mutation, and frame shift mutation. The shaded areas mark the point of mutation.

can affect regions of the gene that regulate transcription but that do not actually code for an amino acid. These areas are called promoter and enhancer areas. They help turn other genes on and off and are very important in the normal development of the fetus. A mutation in a transcription gene leads to **Rubinstein-Taybi syndrome,** which is associated with multiple congenital malformations and severe intellectual disability (Spena, Gervasini, & Milani, 2015). Mutations in a transcription gene also may result in a normal protein being formed but at a much slower rate than usual, leading to an enzyme or other protein deficiency. An example is **Cornelia de Lange syndrome,** in which patients have a mutation in the NIPBL gene that codes for the developmentally important cohesin-loading protein, delangin. Affected children manifest growth delay, a dysmorphic appearance including confluent eyebrows, limb impairments, and intellectual disability.

Selective Advantage

The **incidence** of a genetic disease in a population depends on the difference between the rate of mutation production and that of mutation removal. Typically, genetic diseases enter populations through mutation errors. Natural selection, the process by which individuals with a selective advantage survive and pass on their genes, works to remove these errors. For instance, because individuals with sickle cell disease (an **autosomal recessive** inherited blood disorder) historically have had a decreased life span, the gene that causes this disorder would have been expected to be removed from the gene pool over time. Sometimes natural selection, however, favors the individual who is a carrier of one copy of a mutated recessive gene. In the case of sickle cell disease, unaffected carriers (called heterozygotes) who appear clinically healthy actually have minor differences in their hemoglobin structure that make it more resistant to a malarial parasite (López, Saravia, Gomez, Hoebeke, & Patarroyo, 2010). In Africa, where malaria is endemic, carriers of this disorder have a selective advantage. This selective advantage has maintained the sickle cell trait among Africans. Northern Europeans, for whom malaria is not an issue, rarely carry the sickle cell gene at all; this mutation has presumably died out via natural selection in this population (Jorde et al., 2015).

Single Nucleotide Polymorphisms

Despite the more than 3 billion base pairs in the genetic code, people of all races and geography share a 99.9% genetic identity (Ridley, 2006). Although this is quite remarkable, that 0.1% difference means there are about 3 million DNA sequence variations, also called **single nucleotide polymorphisms** (SNPs). This genetic variation is the basis of evolution, but it can also contribute to health, unique traits, or disease. One SNP involved in muscle formation, if present, makes individuals much more likely to become "buff" if they weight lift; another SNP is associated with perfect musical pitch. There is an SNP that makes individuals more susceptible to adverse effects from certain medications because it leads to slower metabolism of drugs by the liver. There also are SNPs that place people at greater risk for developing Alzheimer's disease and an inflammatory bowel disease called Crohn's disease (Uniken Venema, Voskuil, Dijkstra, Weersma, & Festen, 2016). Knowledge of these SNPs, as well as candidate disease genes, allows a better understanding of certain genetic conditions, which can lead to the development of novel treatments.

Single-Gene (Mendelian) Disorders

Gregor Mendel (1822–1884), an Austrian monk, pioneered our understanding of single-gene defects. While cultivating pea plants, he noted that when he bred two differently colored plants—yellow and green—the **hybrid** offspring all were green rather than mixed in color. Mendel concluded that the green trait was **dominant,** whereas the yellow trait was **recessive** (from the Latin word for "hidden"). However, the yellow trait sometimes appeared in subsequent generations. Later, scientists determined that many human traits, including some birth defects, are also inherited in this fashion. They are referred to as **Mendelian traits.**

Table 1.2 indicates the prevalence of some common single-gene disorders associated with developmental disabilities. Approximately 1% of the population has a known single-gene disorder. These disorders can be transmitted to offspring on the autosomes or on the X chromosome. Mendelian traits may be either dominant or recessive. Thus, Mendelian disorders are characterized as being **autosomal recessive, autosomal dominant,** or **X-linked**.

Autosomal Recessive Disorders Among the currently recognized Mendelian disorders, over 1,000 are inherited as autosomal recessive traits (McKusick-Nathans Institute of Genetic Medicine & The National Center for Biotechnology Information, 2017). For a child to have a disorder that is autosomal recessive, he or she must carry an abnormal gene on both copies of the relevant chromosome. In the vast majority of cases, this means that the child receives an abnormal copy from both parents. The one exception is uniparental disomy, which is discussed in the next section.

Table 1.2. Prevalence of genetic disorders

Disease	Appropriate prevalence
Chromosomal disorders	
Down syndrome (trisomy 21)	1/850
Klinefelter syndrome (47, XXY)	1/600
Trisomy 13	1/12,000–1/20,000
Trisomy 18	1/6,000–8,000
Turner syndrome (45, X)	1/2,500–1/4,000 females
Single-gene disorders	
Duchenne muscular dystrophy	1/3,300 males
Fragile X syndrome	1/3,000–1/4,000 males; 1/8,000 females
Neurofibromatosis type I	1/3,000
Phenylketonuria	1/5,000 to 1/10,000
Tay-Sachs disease	1/3,600 Ashkenazi Jews
Mitochondrial inheritance	
Leber hereditary optic neuropathy	Rare 1/30,000–1/50,000
MERRF	Rare (< 1/100,000)
MELAS	Rare, unknown

Sources: Nussbaum, McInnes, and Willard (2016) and Adam, Ardinger, Pagon, Wallace, Bean, Stephens, and Amemiya (1993–2018).

Key: MELAS, mitochondrial encephalomyelopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy and ragged red fibers.

Tay-Sachs disease is an example of an autosomal recessive condition. It is caused by the absence of an enzyme, hexosaminidase A, which normally metabolizes a potentially toxic product of nerve cells (Kaback & Desnick, 2011). In affected children, this product cannot be broken down and is stored in the brain, leading to progressive brain damage and early death.

Alternate forms of the gene for hexosaminidase A are known to exist. The different forms of a gene, called **alleles,** include the normal gene, which can be symbolized by a capital "A" because it is dominant, and the mutated allele (in this example, carrying Tay-Sachs disease), which can be symbolized by the lowercase "a" because it is recessive (Figure 1.9). Upon fertilization, the embryo receives two genes for hexosaminidase A, one from the father and one from the mother. The following combinations of alleles are possible: **homozygous** (carrying the same allele) combinations, AA or aa, and **heterozygous** (carrying alternate alleles) combinations, aA or Aa. Because Tay-Sachs disease is a recessive disorder, two abnormal recessive genes (aa) are needed to produce a child who has the disease. Therefore, a child with aa would be homozygous for the Tay-Sachs mutation (i.e., have two copies of the mutated gene and manifest the disease), a child with aA or Aa would be heterozygous and a healthy carrier of the Tay-Sachs mutation, and a child with AA would be a healthy noncarrier.

If two heterozygotes (carrying alternate alleles) were to have children (aA × Aa or Aa × aA), the following combinations could occur: AA, aA or Aa, or aa (Figure 1.9). According to the law of probability, each pregnancy would carry a one in four chance of the child

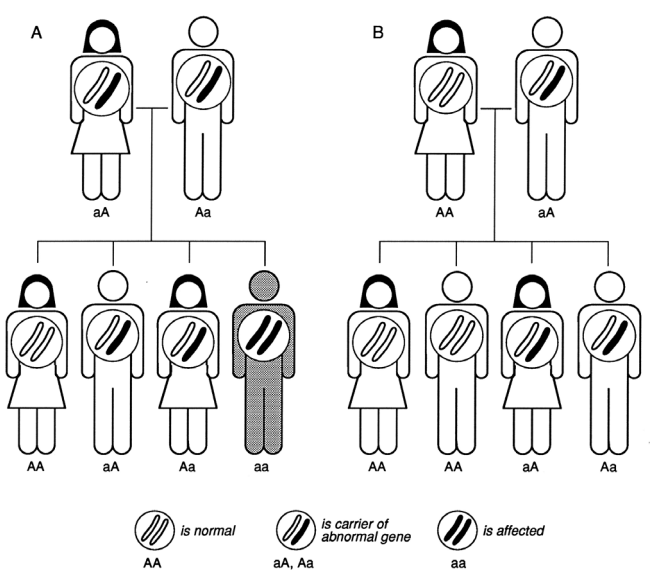

Figure 1.9. Inheritance of autosomal recessive disorders. Two copies of the abnormal gene (aa) must be present to produce the disease state: A) Two carriers mating will result, on average, in 25% of the children being affected, 50% being carriers, and 25% noncarriers; B) A carrier and a noncarrier mating will result in 50% noncarriers and 50% carriers and no children will be affected.

being a noncarrier (AA), a one in two chance of the child being a carrier (aA or Aa), and a one in four risk of the child having Tay-Sachs disease (aa). If a carrier has children with a noncarrier (aA × AA), each pregnancy carries a one in two chance of the child being a carrier (aA, Aa), a one in two chance of the child being a noncarrier (AA), and virtually no chance of the child having the disease (Figure 1.9). Siblings of affected children, even if they are carriers, are unlikely to produce children with the disease because this can only occur if they have children with another carrier, which is an unlikely occurrence in these rare diseases except in cases of intermarriage.

The one in four risk when two carriers have children is a probability risk. This does not mean that if a family has one affected child the next three will be unaffected. Each new pregnancy carries the same one in four risk; the parents could, by chance, have three affected children in a row or five unaffected children. In the case of Tay-Sachs disease, carrier screening is used to identify at-risk couples and prenatal diagnosis to provide information about whether the fetus is affected (see Chapter 3).

Because it is unlikely for a carrier of a rare condition to have children with another carrier of the same disease, autosomal recessive disorders are quite rare in the general population, ranging from 1 in 2,000 to 1 in 200,000 or fewer births (McKusick-Nathans Institute of Genetic Medicine & The National Center for Biotechnology Information, 2017). When a union occurs within an extended family, also called consanguinity (e.g., cousin marriage; Figure 1.10) or when unions among ethnically, religiously, or geographically isolated populations occur, the incidence of these disorders increases markedly. Some ethnic populations have higher carrier frequency than others; for example, carrier frequency for cystic fibrosis in people of Northern European background is 1 in 28, but for Asians, the carrier frequency is 1 in 118 (Ong et al., 2017).

Like Tay-Sachs disease, certain other autosomal recessive disorders are caused by mutations that lead to an enzyme deficiency of some kind. In most cases, there are a number of different mutations within the gene that can produce the same disease. Because these enzyme deficiencies generally lead to biochemical abnormalities involving either the insufficient production of a needed product or the buildup of toxic materials, **developmental disabilities** or early death may result (see Chapter 16). Autosomal recessive disorders affect males and females equally, and there tends to be clustering in families (i.e., more than one affected child per family). However, a history of the disease in past generations rarely exists unless there has been intermarriage.

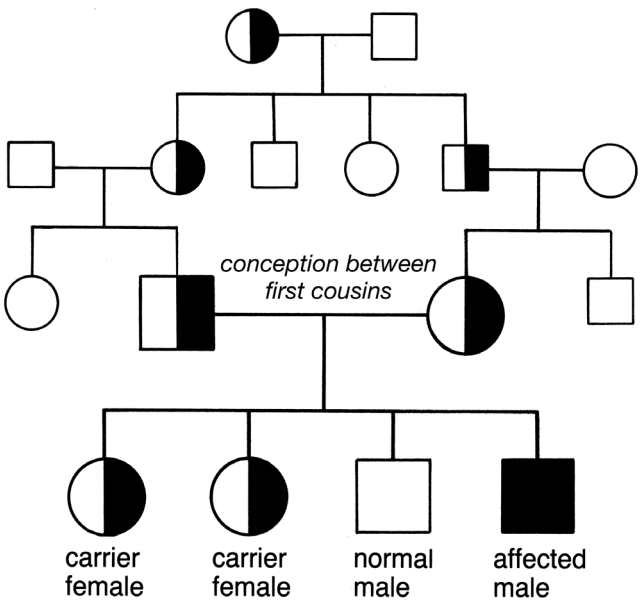

Figure 1.10. A family tree illustrating the effect of consanguinity (in this case, a marriage between first cousins) on the risk of inheriting an autosomal recessive disorder. The chance of both parents being carriers is usually less than 1 in 300. When first cousins conceive a child, however, the chance of both parents being carriers rises to 1 in 8. The risk, then, of having an affected child increases almost 40-fold.

Autosomal Dominant Disorders Over 1,000 autosomal dominant disorders have been identified, the most common ones having a frequency of 1 in 200 births (Youngblom et al., 2016). Autosomal dominant disorders are quite different from autosomal recessive disorders in mechanism, incidence, and clinical characteristics (Table 1.3). Because autosomal dominant

Table 1.3. Comparison of autosomal recessive, autosomal dominant, and X-linked inheritance patterns

	Autosomal recessive	Autosomal dominant	X-linked
Type of disorder	Enzyme deficiency	Structural abnormalities	Mixed
Examples of disorder	Tay-Sachs disease	Achondroplasia	Fragile X syndrome
	Phenylketonuria (PKU)	Neurofibromatosis	Muscular dystrophy
Carrier expresses disorder	No	Yes	Sometimes
Increased risk in other family members from intermarriage/consanguinity	Yes	No	No

disorders are caused by a single abnormal allele, individuals with the **genotypes** Aa or aA are both affected to some degree.

To better understand this, consider NF1, the neurological disorder discussed previously. Suppose *a* represents the normal recessive gene and *A* indicates the mutated dominant gene for NF1. If a person with NF1 (aA or Aa) has a child with an unaffected individual (aa), there is a one in two risk, statistically speaking, that the child will have the disorder (aA or Aa) and a one in two chance he or she will be unaffected (aa; Figure 1.11). An unaffected child will not carry the abnormal allele and therefore cannot pass it on to his or her children.

Autosomal dominant disorders affect men and women with equal frequency. They tend to involve physical impairments (tumors in the case of NF1) rather than enzymatic defects. In affected individuals, there is often a family history of the disease; however, approximately half of affected individuals represent a new mutation. Although individuals with a new mutation will risk passing the mutated gene to their offspring, their parents are unaffected and at no greater risk than the general population of having a second affected child. In some cases, a mutation occurs early in the development of eggs and sperm. This is called germline, or gonadal, mosaicism and is estimated to occur approximately 1.3% of the time. If gonadal mosaicism is present in a parent, theoretically two siblings can be affected with the same condition and neither parent appears to be affected (Rahbari et al., 2015). There can also be partial penetrance of the gene, which produces a less severe disorder (e.g., in NF1 or tuberous sclerosis), or a delayed onset form of the disease (e.g., in Huntington disease).

X-Linked Disorders Unlike autosomal recessive and autosomal dominant disorders, which involve genes located on the 22 non-sex chromosomes (autosomes), X-linked (previously called sex-linked) disorders involve mutant genes located on the X chromosome. X-linked disorders primarily affect males (Genetics Home Reference, 2017a). The reason for this is that males have only one X chromosome; therefore, a single dose of the abnormal gene causes disease. Because females have two X chromosomes, a single recessive allele usually does not cause disease provided there is a normal allele on the second X chromosome (Figure 1.12). Approximately 1,000 X-linked disorders have been described, including Duchenne muscular dystrophy and hemophilia (McKusick-Nathans Institute of Genetic Medicine & The National Center for Biotechnology Information, 2017). Carrier mothers in two-thirds of the cases pass on these disorders from one generation to the next; one-third of these cases represent new mutations.

As an example of an X-linked disorder, children with Duchenne muscular dystrophy develop a

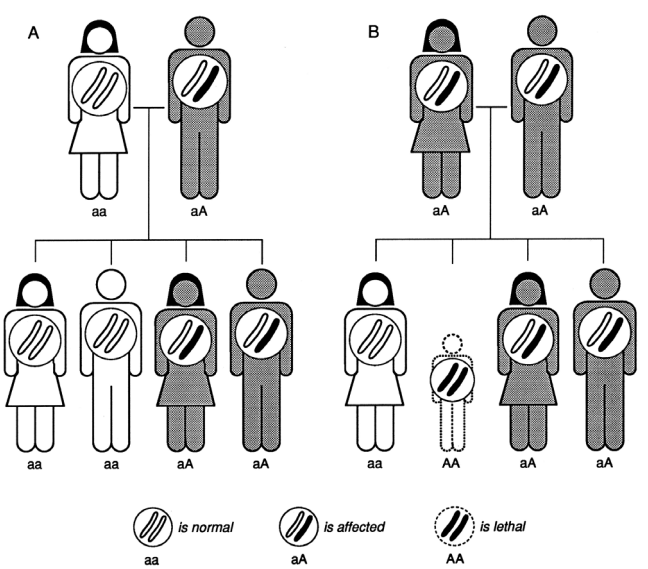

Figure 1.11. Inheritance of autosomal dominant disorders. Only one copy of the abnormal gene (A) must be present to produce the disease state: A) If an affected person conceives a child with an unaffected person, statistically speaking, 50% of the children will be affected and 50% will be unaffected; B) If two affected people have children, 25% of the children will be unaffected, 50% will have the disorder, and 25% will have a severe (often fatal) form of the disorder as a result of a double dose of the abnormal gene.

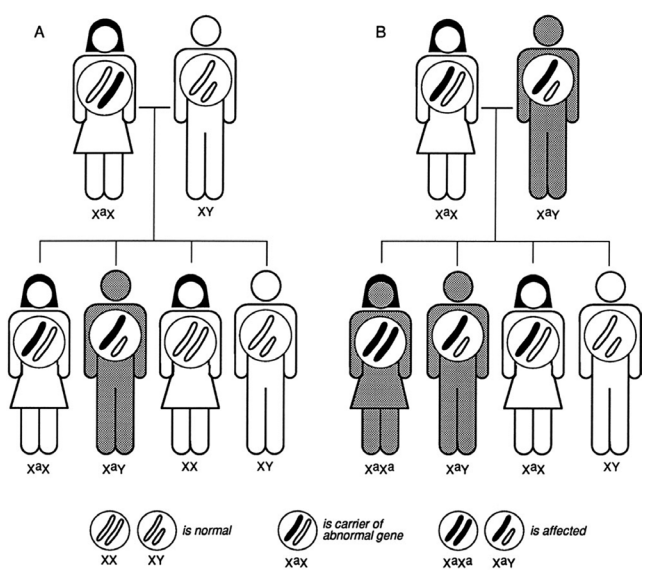

Figure 1.12. Inheritance of X-linked disorders: A) A carrier woman has a child with an unaffected man. Among the female children, statistically speaking, 50% will be carriers and 50% will be unaffected. Among the male children, 50% will be affected and 50% will be unaffected; B) A carrier woman has a child with an affected man. Of the female children, 50% will be carriers and 50% will be affected. Of the male children, statistically speaking, 50% will be unaffected and 50% will be affected.

progressive muscle weakness (Bushby et al., 2010a, 2010b; Suthar & Sankhyan, 2017). The disease results from a mutation in the dystrophin gene (located on the X chromosome), the function of which is to ensure stability of the muscle cell membrane. Because the disease affects all muscles, eventually the heart muscle and the diaphragmatic muscles needed for circulation and breathing respectively are impaired. Dystrophin is also required for typical brain development and function, so affected boys may have cognitive impairments.

In fact, approximately 10% of males with intellectual disability and l0% of females with learning disabilities are affected by X-linked conditions (Inlow & Restifo, 2004). Males are more than twice as likely to have intellectual disability than females. This finding is attributable to a combination of factors: first, X-linked disorders affect males disproportionately more than females, and second, there is an unusually large number of genes residing on the X chromosome that are critical for normal brain development, nerve cell function, learning, and memory. Up to 10% of all known genetic errors causing intellectual disability are on the X chromosome despite the X chromosome containing only 4% of the human genome.

The mechanism for passing an X-linked recessive trait to the next generation is as follows: Women who have a recessive mutation (Xa) on one of their X chromosomes and a normal allele on the other (X) are carriers of the gene (XaX). Although these women are usually clinically unaffected, they can pass on the abnormal gene to their children. Assuming the father is unaffected, each female child born to a carrier mother has a one in two chance of being a carrier (i.e., inheriting the mutant Xa allele from her mother and the normal X allele from her father; Figure 1.12). A male child (who has only one X chromosome), however, has a one in two risk of having the disorder. This occurs if he inherits the X chromosome containing the mutated gene (XaY) instead of the normal one (XY). A family tree frequently reveals that some maternal uncles and male siblings have the disease. X-linked disorders are never passed from father to son because boys inherit their Y chromosome from their father and their X chromosome from their mother.

Occasionally, females are affected by X-linked diseases. This can occur if the woman has adverse **lyonization** (inactivation of one of the X chromosomes) or if the disorder is X-linked "dominant." Regarding the former mechanism, the geneticist Mary Lyon questioned why women have the same amount of X chromosome–directed gene product as men instead of twice as much, as would be predicted from their genetic makeup. Dr. Lyon postulated that early in embryogenesis, one of the two X chromosomes in each cell is inactivated, making every female fetus a mosaic. This implied that some cells would contain an active X chromosome derived from the father, whereas others would contain an active X chromosome derived from the mother. This "lyonization" hypothesis was later proven to be correct. In most instances, the cells in a woman's body have a fairly equal division between maternally and paternally derived active X chromosomes. In a small fraction of women, however, the distribution is very unequal. If the normal X chromosome is inactivated preferentially in cells of a carrier of an X-linked disorder, the woman will manifest the disease, although usually in a less severe form than the male. An example is OTC deficiency, the disorder Katy had in this chapter's opening case study (see also Chapter 16).

The second mechanism for a female to manifest an X-linked disorder is if the disorder is transmitted as X-linked dominant. Although most X-linked disorders are recessive, a few appear to be dominant. One example is Rett syndrome (Chahrour & Zoghbi, 2007; Liyanage & Rastegar, 2014; Matijevic, Knezevic, Slavica, & Pavelic, 2009; Percy, 2008). It appears that in this disorder, the presence of the mutated transcription gene *MECP2* on the X chromosome of a male embryo nearly always leads to lethality. When it occurs in one of the X chromosomes of the female, however, it is compatible with survival but results in a syndrome marked by microcephaly, developmental regression, intellectual disability, and autism-like behaviors. That is why virtually all children with Rett syndrome are girls.

Mitochondrial Inheritance

Each cell contains several hundred mitochondria in its cytoplasm (Figure 1.1). Mitochondria produce the energy needed for cellular function through a complex process termed **oxidative phosphorylation.** It has been proposed that mitochondria were originally independent microorganisms that invaded our bodies during the process of human evolution and then developed a symbiotic relationship with the cells in the human body. They are unique among cellular **organelles** (the specialized parts of a cell) in that they possess their own DNA, which is in a double-stranded circular pattern rather than the double-helical pattern of nuclear DNA and contains genes that are different from those contained in nuclear DNA (Figure 1.13). Most of the proteins necessary for mitochondrial function are coded by nuclear genes, and disorders caused by abnormalities in these genes are most often inherited in an autosomal recessive manner. Certain mitochondrial functions, however, are dependent on genes encoded on the mitochondrial DNA. A mutation in

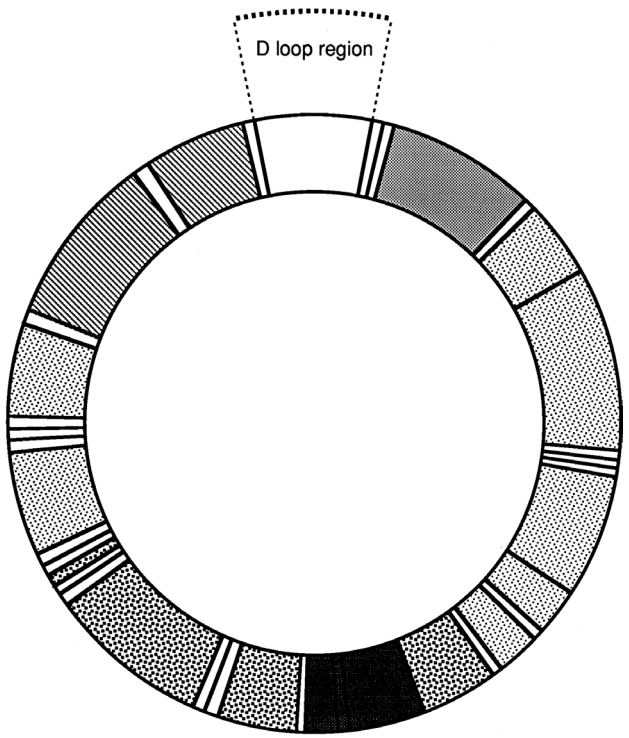

Figure 1.13. Mitochondrial DNA genome. The genes code for various enzyme complexes involved in energy production in the cell. The displacement loop (D loop) is not involved in energy production. (This figure was published in *Medical genetics*, revised 2nd edition, by Jorde, L.B., Carey, J.C., & Bamshad, M.J., et al., p. 105, Copyright C.V. Mosby [2001]; adapted by permission.) (*Key:* ▨ Complex I genes [NADH dehydrogenase], ▩ Complex III genes [ubiquinol: cytochrome c oxidoreductase], □ tRNA genes, ▩ Complex IV genes [cytochrome *c* oxidase], ■ Complex V genes [ATP synthase], ▧ ribosomal RNA genes.)

a mitochondrial gene can result in defective energy production and a disease state, particularly affecting organs with high energy demands, such as the heart, skeletal muscle, and brain (Gorman, 2016). An example of a disorder with mitochondrial inheritance is mitochondrial encephalomyelopathy, lactic acidosis, and stroke-like episodes (MELAS), a progressive neurological disorder marked by episodes of stroke and dementia. Other disorders with mitochondrial inheritance can lead to blindness, deafness, or muscle weakness. There are hundreds of mitochondrial diseases, some of which have clear genetic causes, while others do not. Every cell contains many mitochondria, but not every mitochondrion may carry a given mutation. In many disorders that are inherited through the mitochondrial genome, there is great clinical variability based on the **heteroplasmy** or the mix of different mitochondrial genomes within a single individual. There may be significant variability among specific tissues in an individual; some organs or tissues may be affected by the mitochondrial disorder and others may not.

Because eggs, but not sperm, contain cytoplasm, mitochondria are inherited from one's mother. As a result, mitochondrial DNA disorders are passed on from generally unaffected mothers to their children, both male and female (Figure 1.14). Men affected by a mitochondrial disorder cannot pass the trait to their children. In some cases, a mother with significant heteroplasmy may have only mild effects of a disease but may pass on only mutated mitochondrial genomes to a child. In that case, a child would have a homoplasmic mitochondrial mutation and would have a much more severe clinical course.

Trinucleotide Repeat Expansion Disorders

There has been an increased recognition that **copy number variability** accounts for several developmental disabilities (Sansović, Ivankov, Bobinec, Kero, & Barišić, 2017). One particular type of copy number variation is the trinucleotide repeat expansion (triplet repeat disorder), which has been linked to a number of disorders that do not follow typical Mendelian inheritance. Trinucleotide repeat disorders result from problems in recombination and replication during meiosis. Certain genes have highly repetitive sequences of trinucleotides. These repetitive sequences may expand (or contract) in size during meiosis. Once the repetitive sequence reaches a certain size threshold, it may interfere with the function of the gene and lead to a clinically apparent disorder. The expansion length is linked to the phenotype, with the longer expansions often presenting with earlier and more severe clinical signs and symptoms.

The first triplet repeat disorder discovered was fragile X syndrome, the most common inherited cause of intellectual disability. Boys and girls with fragile X syndrome have a phenotype that includes

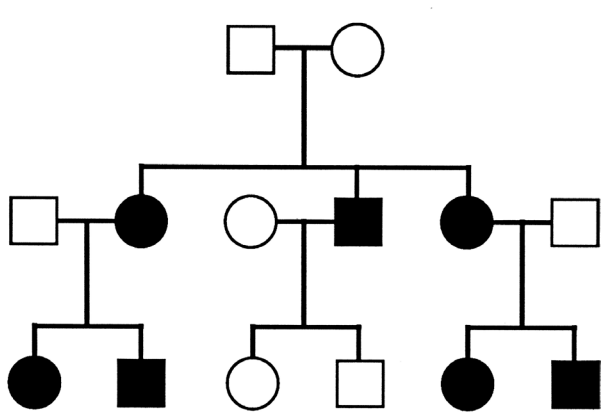

Figure 1.14. Mitochondrial inheritance. Because mitochondria are inherited exclusively from the mother, defects in mitochondrial disease will be passed on from the mother to her children, as illustrated in this pedigree.

a characteristic physical appearance, cognitive skills impairments, and impaired adaptive behaviors (Chonchaiya, Schneider, & Hagerman, 2009; Schneider, Hagerman, & Hessl, 2009; also see Chapter 15). Many affected children satisfy the criteria for the diagnosis of autism. The prevalence of fragile X syndrome (the full mutation) for males is about 1 in 3,600. The prevalence of the full mutation in females is estimated to be at least 1 in 4,000 to 1 in 6,000. Fragile X syndrome arises from an expansion of the number of cytosine-guanine-guanine (CGG) trinucleotide repeats occurring within the fragile X mental retardation protein (*FMR1*) gene. Inheritance of the instability in CGG regions leads to expansion from the normal number of repeats (6–40) to a premutation state (50–200 repeats) or from a premutation state to full mutation (>200 repeats). The stability of the CGG repeat depends upon the length of the repeat, as well as the sex of the individual passing on the mutation. The increased risk of CGG expansion from one generation to another is a phenomenon termed **anticipation.** Anticipation leads to an increasingly severe clinical phenotype in successive generations. When a child is suspected of having fragile X syndrome, the diagnosis can be confirmed by detecting the number of trinucleotide repeats in FMR1 using a clinically available molecular genetic blood test (Collins et al., 2010). There is a correlation between the number of trinucleotide repeats and the severity of disease. Other trinucleotide repeat disorders include myotonic dystrophy and Huntington's disease.

EPIGENETICS

The diagnostic evaluation of children with intellectual disability and other developmental disabilities has become increasingly complex in recent years due to a number of newly recognized genetic mechanisms and the availability of sophisticated methods to diagnose them. It has been appreciated that changes in gene expression can occur by mechanisms that do not permanently alter the DNA sequence (Urdinguio, Sanchez-Mut, & Esteller, 2009), a phenomenon termed **epigenetics.** Epigenetic mechanisms are important regulators of biological processes because they include genome reprogramming during embryogenesis (Kumar, 2008). Epigenetic modification, which is important in developmental processes, may have long-term effects on learning and memory formation. Epigenetic impairments may result from dysfunction of certain enzymes, genomic imprinting, and triplet repeat copy number variation. A number of conditions causing developmental disabilities, including fragile X syndrome, Rett syndrome, Rubinstein-Taybi syndrome, Prader-Willi syndrome, and VCFS, can be attributed to disruptions in epigenetic function. It is interesting to note that virtually all epigenetic disorders have been found to have a high incidence of symptoms consistent with autism spectrum disorder or other neurodevelopmental disorders (Moss & Howlin, 2009). In addition, the risk of epigenetic disorders has been found to be increased in pregnancies assisted by *in vitro* fertilization (Lazaraviciute, Kauser, Bhattacharya, Haggarty, & Bhattacharya, 2014).

According to Mendelian genetics, the **phenotype,** or appearance of an individual should be the same whether the given gene is inherited from the mother or the father. This is not always the case, however, because of **genomic imprinting.** This is an epigenetic phenomenon in which the activity of the gene is modified depending upon the sex of the transmitting parent (Genetics Home Reference, 2017b). Most autosomal genes are expressed in both maternal and paternal alleles. However, imprinted genes show expression from only one allele (the other is silenced or used differently), and this is determined during production of the egg or sperm. Imprinting implies that the gene carries a "tag" placed on it during spermatogenesis or oogenesis. This is most often accomplished by adding methyl groups to the DNA, affecting the expression of the methylated genes. Imprinted genes are important in development and differentiation, and if expression from both alleles is not maintained, disturbances in development can result (Soellner et al., 2017).

The first human imprinting disorder discovered was Prader-Willi syndrome. It is caused by a paternal deletion in chromosome 15 or by maternal uniparental disomy in which both chromosome 15s come from the mother. It can also result if both copies of chromosome 15 are imprinted as if they came from the mother regardless of the actual parent of origin (Conlin et al., 2010; Driscoll, Miller, Schwartz, & Cassidy, 2017). Prader-Willi syndrome is characterized by severe hypotonia and feeding difficulties in early childhood, followed by an insatiable appetite and obesity by school age. It features significant motor and language delays in the first 2 years of life; borderline to moderate intellectual disability; and severe behavioral problems, including compulsive and hording behaviors. Many affected children satisfy the criteria for the diagnosis of autism (Driscoll et al., 2017; Goldstone, Holland, Hauffa, Hokken-Koelega, & Tauber, 2008). Other examples of imprinted neurogenetic disorders include Angelman syndrome and Beckwith-Wiedemann syndrome (Dan, 2009; Gurrieri & Accadia, 2009; Soellner et al., 2017).

GENETIC TESTING

Genetic tests have been developed for many of the roughly 7,000 rare diseases identified, including all

those described in this chapter. Most tests look at single genes and are used to diagnose rare genetic disorders, such as fragile X syndrome and Duchenne muscular dystrophy. In addition, some genetic tests look at rare inherited mutations of otherwise protective genes that are responsible for some hereditary breast and ovarian cancers. An increasing number of tests are being developed to look at multiple genes that may increase or decrease a person's risk for developing common diseases, such as cancer or diabetes. In addition, pharmacogenetic tests may be used to help identify genetic variations that influence a person's response to medicines. Here, we will focus on genetic testing used in diagnosing causes of developmental disabilities.

There are three types of genetic testing currently being used to detect genomic-based causes of developmental disabilities: **chromosomal microarray analysis, next-generation sequencing,** and **whole-exome/genome sequencing.** Chromosomal microarrays use probes to test for known DNA sequences and can identify disorders where the specific genetic abnormality is caused by a microdeletion or microduplication, as seen in Williams syndrome or chromosome 15q duplication syndrome. Microarrays cannot be used to identify mutations (alterations of a single nucleotide, such as a point mutation) in a gene. In general, a chromosomal microarray is the first-line test recommended for a child presenting with developmental delays or autism (see Box 1.1). The second type of genetic testing, next-generation sequencing, allows detection of mutations in single genes, such as *NF1* associated with neurofibromatosis type 1, or *CFTR*, in which two mutations are needed to cause cystic fibrosis. The final approach is whole-exome/genome sequencing and may be used in a case where no genetic cause has been identified for the child's phenotype. Whole-exome sequencing is typically utilized when a child's clinical history is suspicious for a genetic condition based on the presence of multiple congenital anomalies, developmental delays, or other undiagnosed issues. Here, exome sequencing (sequencing the entire exome) can help identify alterations in genes all at once rather than looking at

BOX 1.1 EVIDENCE-BASED PRACTICE

Autism and Genetic Testing

Autism spectrum disorder (ASD) is a highly variable group of neurodevelopmental conditions. There is evidence that children with ASD more commonly have medical issues and/or physical differences and dysmorphic features. Because of this high level of variability, the genetic workup may differ depending on the child's clinical issues. Stratification of children with ASD can help to determine what type of genetic testing might be most appropriate for a patient. The general recommendation is that chromosomal microarray (CMA) is the first-line test for a child with ASD.

Tammimies et al. (2015) reported molecular diagnostic yields for CMA and whole-exome sequencing (WES) in a population of 258 children with ASD stratified by clinical features, including number and type of physical anomalies. Each child was classified as having essential, equivocal, or complex ASD based on their morphology score. The main outcomes measured were the clinical differences, the yield of molecular diagnosis from CMA and WES, and the differences in the diagnostic yields between the three categories

Most of the patients had essential autism (approximately 70%), while approximately 20% had equivocal autism and approximately 10% were classified as complex. Of the 258 subjects, the WES diagnostic yield was 8.4% and the CMA yield was 9.3%. In children who received both tests, the diagnostic yield was 15.8%. In children with complex ASD, the molecular diagnostic yield was near 35% when both CMA and WES were performed. Age at diagnosis with ASD was also significantly older for this complex group. In the children with essential autism, the diagnostic yield was much lower when using both CMA and WES.

Points to Remember

- CMA should still be considered the first-line test for children with autism. A medical genetics evaluation should be completed **prior** to ordering any genetic testing.
- Medical genetics evaluation might help identify patients more likely to achieve a molecular diagnosis with genetic testing; complex patients might benefit from WES if properly counseled by a medical geneticist and genetic counselor.
- Patients with complex medical issues receive later diagnoses of autism; it is important to be aware of these symptoms and provide an autism evaluation when features are first noted.

each gene individually. It does this by selecting the approximately 180,000 exons that constitute about 1% of the human genome (or approximately 30 million base pairs) and then sequencing the DNA using a high-throughput DNA sequencing technology. This technique has been used to identify genetic variants seen in autism. Exome sequencing, however, is only able to identify those variants found in the coding region of genes that affect protein function. It is not able to identify structural and non-coding variants associated with disease; this can be found using whole-genome sequencing. Presently, whole-genome sequencing is typically not utilized in the clinical setting due to the high costs and time associated with sequencing full genomes. In addition to these challenges, our understanding of much of our genome is still in its infancy. As our knowledge continues to grow, clinicians will be able to more accurately interpret results and provide appropriate genetic counseling for families.

There are many other types of genetic tests available for specific disorders. For example, some inborn errors of metabolism can be identified by detecting the accumulation of specific compounds in blood, urine, or other tissue samples. Testing for methylation patterns on DNA samples detects certain epigenetic disorders. Other genetic disorders may be detected radiologically. The decision about which tests are most appropriate for a specific patient is complex, and physicians with expertise in medical genetics can help guide testing and interpret results. While some tests, such as karyotype analysis to detect large chromosome abnormalities or rearrangements (like those seen in Down syndrome and Klinefelter syndrome), are no longer commonly used during evaluation of a child with developmental delay, they may be appropriate depending on a child's clinical presentation. For example, a girl referred for mild developmental delays, short stature, webbed neck, and a heart defect should first undergo a karyotype to evaluate for Turner syndrome; microarray and next-generation sequencing would not be the most appropriate initial tests for this patient. Medical geneticists and genetic counselors can help determine the correct test for a patient based on utility and cost effectiveness. They can also ensure that the patient is properly consented and understands the implications of these complex analyses (see Box 1.2).

ENVIRONMENTAL INFLUENCES ON HEREDITY

The particular genes that a person possesses determine his or her genotype, and the expression of the genes results in the physical appearance of traits—that is, the phenotype of the individual. For some traits and clinical disorders, however, the same genotype can produce quite different phenotypes depending on environmental influences. In terms of traits, bright parents tend to have bright children and tall parents tend to have tall children; however, the interaction of genetics with the prenatal and postnatal environments allows for many possible outcomes. For example, it has been found that, as a result of an increased protein intake during childhood, Asians who grow up in the United States are significantly taller than their parents who grew up in Asia. Disorders that have both genetic and environmental influences include diabetes, meningomyelocele, cleft palate, and pyloric stenosis (Au, Ashley-Koch, & Northrup, 2010). Considering the example of PKU, an affected child will develop intellectual disability if the PKU is not treated early but will have typical development if it is treated with a diet low in phenylalanine from infancy (Feillet et al., 2010; also see Chapter 16).

BOX 1.2 INTERDISCIPLINARY CARE

What Is a Genetic Counselor?

Genetic counselors are health care professionals with specialized, master's-level training in human genetics. They are an excellent resource for both patients and providers of children with rare diseases and developmental disabilities, as they are able to explain complex genetic ideas while also providing psychosocial support. Genetic counselors can guide patients on how inherited diseases might affect them or their families, analyze family histories, and help determine what kind of genetic testing might be most appropriate for a patient. In a pediatric setting, genetic counselors work alongside medical geneticists and are often the patient's point of contact within their team of genetic care providers. Genetic counselors also work with pregnant women, cancer patients, and people with more common conditions such as heart disease, diabetes, and Alzheimer's disease. Genetic counselors also meet with couples planning a pregnancy to help determine risks for future children. For more information or to find a genetic counselor, please visit www.nsgc.org.

GENETIC THERAPIES

A range of approaches is being used to treat genetic disorders. In the case of inborn errors of metabolism, treatment has focused on either replacing the deficient product of the defective enzyme (e.g., in thyroid hormone deficiency) preventing the accumulation of toxic material because the enzyme does not break it down or replacing the defective enzyme (see Chapter 16). Preventing accumulation of toxic metabolites often relies on dietary manipulation (e.g., PKU) or stimulation of an alternate pathway around the enzyme block (urea cycle disorders). In a few cases, enzyme replacement therapy is available (e.g., in Gaucher disease). Here the missing or defective enzyme is given intravenously at intervals to correct the metabolic defect. Bone marrow transplantation (e.g., in sickle cell disease) or liver transplantation (e.g., in OTC deficiency) has been used to correct other genetic disorders by replacing the organ that is producing the defective product with an organ that can produce a normal one. While these approaches to genetic disorders have improved outcomes in a number of disorders, they represent only a fraction of all the genetic causes of developmental disabilities and their cost can be up to $500,000 per year.

More recently, the concepts of exon skipping, gene therapy, and gene editing have been advanced and are in clinical trials. In **exon skipping,** a form of RNA splicing is used to cause cells to "skip" over faulty sections of the genetic code, leading to a truncated but still functional protein despite the genetic mutation (Kole & Krieg, 2015). The first exon skipping drug was approved in 2016 for use in a subgroup of individuals with Duchenne muscular dystrophy who have a specific mutation. In **gene therapy,** copies of the normal gene are infused most commonly using a virus transporter in order to "replace" the defective gene. At the writing of this edition, the only approved gene therapy drugs are for cancer and HIV, although gene therapy clinical trials for several single gene defects causing developmental disabilities are currently in process. **Gene editing** is a form of gene therapy in which a technology called CRISPR/Cas9 is used to cut the gene at the point of the mutation and to replace it with a corrected gene sequence. The first successful case of gene editing in an embryo in the United States was reported in 2017 (Ma et al., 2017). Researchers targeted and edited a gene associated with cardiac disease at the level of the embryo. Although gene editing technology is available, many ethical considerations exist around this type of practice. Some argue that gene editing of an embryo allows prevention of serious genetic diseases, while others express concerns around creating "designer babies" or selecting traits such as desirable physical characteristics or gender.

SUMMARY

- Each human cell contains a full complement of genetic information encoded in genes contained in 46 chromosomes.
- The unequal division of the reproductive cells, the deletion of a part of a chromosome, the mutation in a single gene, or the modification of gene expression can each lead to developmental disabilities.
- There are numerous genetic tests available to diagnose many of these genetic disorders.
- Early identification may lead to improved outcome as a result of therapies that are now available for certain rare genetic disorders associated with developmental disabilities.

ADDITIONAL RESOURCES

National Library of Medicine (NLM): http://www.nlm.nih.gov

Genetic Alliance: http://www.geneticalliance.org

Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/omim

Additional resources can be found online in Appendix D: Childhood Disabilities Resources, Services, and Organizations (see About the Online Companion Materials).

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