Academic Pathology: Volume 7
DOI: 10.1177/2374289520935588
journals.sagepub.com/home/apc

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Educational Case: Cytogenetics

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, diagnostic medicine, genomics, cytogenetics, genetic mechanisms, chromosomal abnormalities, testing for genetic disorders, chromosomal disorders

Received May 31, 2019. Received revised February 12, 2020. Accepted for publication May 9, 2020.

Primary Objective

Objective GE1.9: Cytogenetics. Define the following cytogenetic terms and nomenclature: karyotype, euploidy, aneuploidy, monosomy, trisomy, deletion, ring chromosome, inversion, isochromosome, translocation, balanced reciprocal translocation, Robertsonian translocation.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic GE—Genomics; Learning Goal 1: Genes.

Secondary Objectives

Objective GM1.4: Chromosomal Abnormalities. Discuss mechanisms that result in developmental abnormalities involving abnormal chromosomal number and provide examples of diseases associated with trisomies or chromosomal deletions.

Competency 1: Disease Mechanisms and Processes; Topic GM—Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Objective GE2.1: Testing for Genetic Disorders. Describe the genetic and epigenetic causes, pathophysiology and clinical manifestations, and optimal laboratory tests used to diagnose the following specific genetic disorders: Mendelian, autosomal disorders (dominant and recessive), X-linked disorders, chromosomal disorders, and disorders of nonclassic inheritance.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic GE—Genomics; Learning Goal 2: Chromosomal Disorders.

Patient Presentation

A term newborn female is referred to pediatrics for dysmorphic features noted on physical examination. The pregnancy was uncomplicated, but the parents had declined prenatal testing.

Diagnostic Findings, Part 1

A complete physical examination revealed flattened facial profile with abundant neck skin, upslanted palpebral fissures,

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single prominent palmar crease, low-set ears, and macroglossia (large tongue).

Questions/Discussion Points, Part 1

What Syndrome Should Be Suspected in a Patient With the Above Clinical Findings?

This clinical picture is suspicious for Down syndrome, which is the most common chromosomal abnormality and occurs in 1 in 691 live births annually in the United States.[2] Newborns with Down syndrome may show a spectrum of phenotypic abnormalities, including flattened facial features, microcephaly, macroglossia, upslanted palpebral fissures, arched palate, Brushfield spots (hypopigmentation of the iris), low-set and folded ears, epicanthal folds, broad hands with shortened fingers, a single palmar crease, and hypotonia. While each morphologic feature may be seen in other entities, the constellation of findings seen here is specific for Down syndrome.

What Additional Internal Abnormalities May Be Present in Neonates With Down Syndrome?

Patients with Down syndrome may have a variety of medical disorders. Congenital heart disease is common and abnormalities include endocardial cushion defects, ventricular septal defects, atrial septal defects, and patent ductus arteriosus.[3] Gastrointestinal manifestations include duodenal atresia, tracheoesophageal fistula, omphalocele, pyloric stenosis, and Hirschsprung disease.[3] Congenital thyroid disease, cataracts, hearing loss, leukemia, neonatal thrombocytopenia, and developmental delays are also more frequent than the general population. Thus, care of these patients requires multidisciplinary collaboration.

In a Child With Multiple Congenital Anomalies, What Underlying Disease Process Should Be Suspected and How Would You Confirm?

Children with multiple congenital anomalies often have an underlying genetic abnormality. A karyotype is often one of the first tests ordered in this scenario and is performed in the cytogenetics laboratory. Cytogenetics is the study of chromosome structure, morphology, function, and behavior. A karyotype is an organized profile of an individual's chromosomes typically obtained from a dividing cell in metaphase and can give quick information about the number and structure of a patient's chromosomes. Chromosomes in their native state are colorless and can only be observed under a phase-contrast microscope. Over time, many different staining methods have been introduced to help visualize chromosomes; the most common is "G-banding," which produces the classic light and dark bands associated with chromosomes. G-banded chromosomes produce distinct patterns for each chromosome which enables us to easily karyotype (organize) a cell's chromosomes. Other diagnostic tests, such as fluorescent in situ hybridization (FISH) or chromosomal microarray (CMA), may also be ordered in the workup of children with congenital anomalies. In FISH, fluorescent probes that bind to known genetic sequences are added to patient DNA, allowing visualization of specific gene locations. In CMA, differences between patient DNA and reference DNA are identified via high-volume analysis.

Diagnostic Findings, Part 2

The karyotype in this patient is shown in Figure 1.

Questions/Discussion Points, Part 2

What Is Your Interpretation of This Karyotype?

The first thing to notice is that the total number of chromosomes is abnormal: there are 47 instead of 46. This is due to an extra copy of chromosome 21, or trisomy 21. The second thing to notice is that there are 2 copies of the X chromosome, so the patient is female.

How Would You Write the Nomenclature of This Karyotype?

An international nomenclature for describing human chromosomes is widely accepted and is referred to as the ISCN (International System for Human Cytogenetic Nomenclature).[4] According to the ISCN, chromosome nomenclature begins with the total number of chromosomes, followed by the sex chromosomes, followed by any structural or numeric abnormalities. In this case, it would look like: (47,XX,+21). This means that there are 47 total chromosomes, the patient is a female (XX), and there is an extra chromosome 21 (+21) which accounts for the extra chromosome. Trisomy 21 is diagnostic for Down syndrome.

How Do We Characterize Abnormalities Related to Chromosome Number?

Once a karyotype is organized, it is evaluated for ploidy, or the total number of chromosomes within the cell. Human somatic cells are diploid, meaning there are 2 sets of 23 chromosomes (written 46,XX for female, and 46,XY for male). A haploid cell contains one single set of unpaired chromosomes, which for humans means 23 chromosomes, and is the typical chromosome complement of gametes. Euploidy is the term used to refer to the loss or gain of one or more entire haploid sets of chromosomes. For example, a normal human diploid cell has 46 chromosomes, a triploid cell has 69 chromosomes (3 haploid sets), and a tetraploid cell has 96 chromosomes (4 haploid sets). Aneuploidy is the term used to describe a loss or gain of less than an entire haploid set of 23 chromosomes. Examples of aneuploidy include Turner syndrome where there is loss of 1 X chromosome (45,X) and Klinefelter syndrome where there is gain of one X chromosome (47,XXY). Loss of 1 chromosome is known as monosomy, while gain of 1 chromosome is a

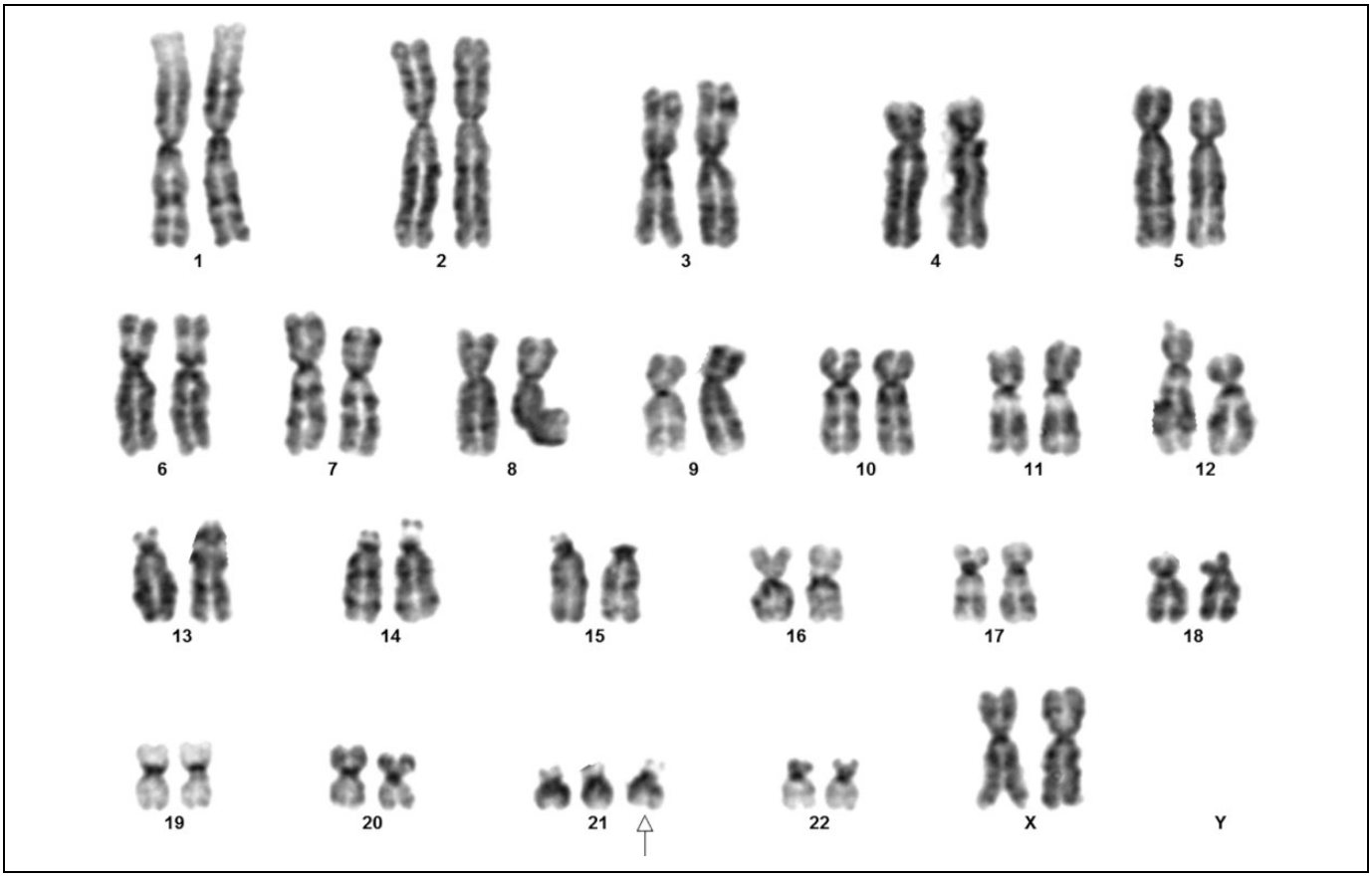

Figure 1. G-banded conventional karyotype showing 3 copies of chromosome 21 resulting in 47 total chromosomes. White arrow denotes extra chromosome. See text for nomenclature.

trisomy. Trisomy 13, 18, and 21 are some of the more common aneuploidies that can be present in term infants.

What Structural Abnormalities May Also Result in Trisomy 21?

Beyond numerical abnormalities, the karyotype can also identify large structural chromosome abnormalities. A translocation occurs when parts of chromosomes are exchanged. A balanced reciprocal translocation is when 2 or more different chromosomes exchange material and there is no loss or gain of chromosomal material. A Robertsonian translocation is a special type of translocation involving 2 acrocentric chromosomes. An acrocentric chromosome is a chromosome where the centromere is located very close to the end of the chromosome which makes it appear as though it does not have a short arm (p-arm). The acrocentric chromosomes are chromosomes 13, 14, 15, 21, and 22. A Robertsonian translocation occurs when the long arms of 2 acrocentric chromosomes fuse at the centromere. This type of translocation involving a chromosome 21 may result in 3 copies of chromosome 21 (trisomy 21) if the patient also has 2 normal copies of chromosome 21. An isochromosome is a type of structural abnormality in which the arms of the chromosome are mirror images of each other, formed from the duplication of one arm of a chromosome and the deletion of the other arm. An isochromosome 21 and a normal chromosome 21 will also result in 3 copies of genetic material from chromosome 21 (Figure 2).

In Addition to Unbalanced Translocations, What Other Structural Chromosome Abnormalities May Be Detected by Karyotype Analysis?

Other large structural chromosome abnormalities include deletions, ring chromosomes, and inversions. A deletion is a partial loss of a chromosome. A ring chromosome is a fascinating type of structural abnormality where the ends of a chromosome break and rejoin with each other to form a structure that looks like a ring! An inversion occurs when a chromosome undergoes breakage and reunion within itself; a segment of chromosome is essentially clipped out, turned upside down, and then reinserted back into the same chromosome. The end result is a segment of the chromosome is reversed end to end. Inversions can be pericentric, which means they include the centromere and involve both the p and q arms of a chromosome, or paracentric, which means they do not include the centromere and only involve 1 arm of the chromosome (Figure 3).

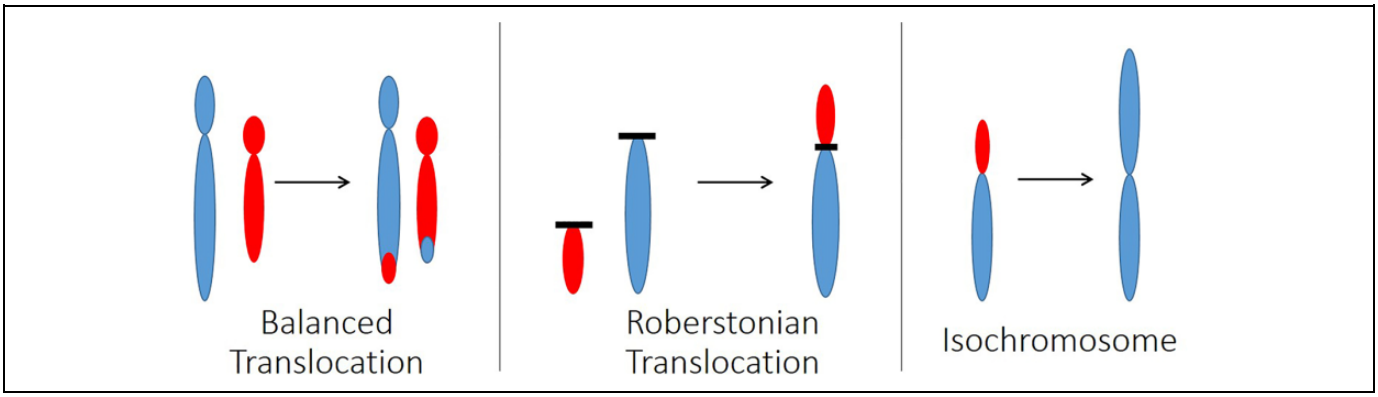

Figure 2. Common structural chromosomal abnormalities.

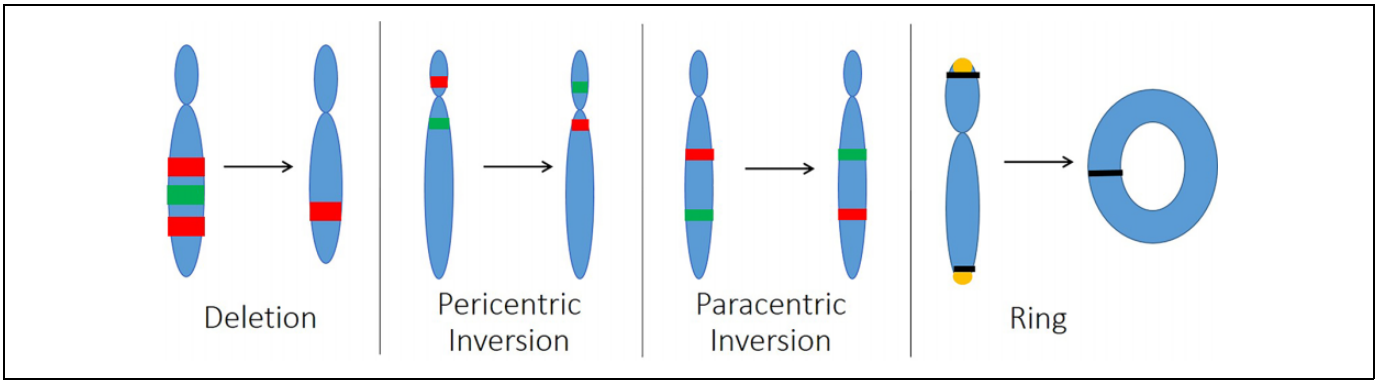

Figure 3. Additional common structural chromosomal abnormalities.

Can a Genetic Defect Be Ruled Out on the Basis of a Normal Karyotype?

No. The sensitivity of karyotype is in the range of 5 to 10 Mb. This means that defects of less than 5 to 10 million base pairs may not be detected with karyotype. For perspective, the human genome contains 3 billion base pairs! There are other tests that can detect smaller abnormalities, such as microarray, FISH, and polymerase chain reaction (PCR).[5]

Teaching Points

- In a child with congenital anomalies, the spectrum of phenotypic features can provide clues and may point to a specific syndrome.
- Characteristics of Down syndrome include flattened facial features, microcephaly, macroglossia, upslanted palpebral fissures, arched palate, Brushfield spots (hypopigmentation of the iris), low-set and folded ears, epicanthal folds, broad hands with shortened fingers, a single palmar crease, hypotonia, cardiac defects, hematologic abnormalities, feeding difficulties, and hearing and thyroid dysfunction.
- Cytogenetic analysis with karyotype is helpful in identifying abnormalities in chromosome number and structure.
- Numeric chromosome abnormalities include euploidy, aneuploidy, monosomy, and trisomy.
- Structural chromosome abnormalities include deletion, inversion, isochromosomes, rings, and translocations.
- Other tests, such as microarray, FISH, and PCR, can detect smaller chromosomal abnormalities than conventional karyotype.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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