APPENDIX 5

Genetic testing and epilepsy

Genetic testing may be recommended for individuals with epilepsy. Having an overview of DNA, genes, and chromosomes, and their relationship to one another is helpful to understanding the process of genetic testing.

This relationship is depicted in Figure A5.1 and terms are described below:[1]

- **DNA:** The building block of genes.
- **Gene:** A segment of DNA.
- **Chromosomes:** Units of packaged genetic materials made up of DNA and proteins. Chromosomes exist in pairs,* with both males and females† having 23 pairs of chromosomes (46 total, in each cell‡); one pair in the set are sex chromosomes, differing males from females. Males have both an X and a Y sex chromosome while females have two X sex chromosomes. A child will inherit one copy of each chromosome from the female parent and one copy of each chromosome from the male parent, thereby inheriting 50 percent of the genetic material from the female parent and 50 percent from the male parent. Since females do not have a Y chromosome, males always inherit the Y chromosome from the male parent.
- **Nucleus:** Found in the center of the cell and contains most of the genetic material; responsible for controlling and regulating the activities of the cell.

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* In this description, the sex chromosomes are considered a pair; although the male has two different chromosomes (X and Y), which are not an exact pair. Another way to describe the number of chromosomes is to state that humans have 22 sets of autosomes (nonsex chromosomes) and one set of sex chromosomes.

† "Male" and "female" refer to biologic sex, not gender.

‡ Sperm cells and egg cells contain only half the genetic material (just one copy of each chromosome) as other cells in the human body.[2]

- **Mitochondria:** The structure that surrounds the nucleus of the cell and contains some genetic material; responsible for supplying the cell with energy. Genetic material from the mitochondria is primarily inherited by a child from the female parent.[3]
- **Nucleotides:** The building blocks of DNA. The order of nucleotides in DNA is examined (called sequencing) in genetic testing.[4] Multiple nucleotides are found in DNA (listed in the figure).

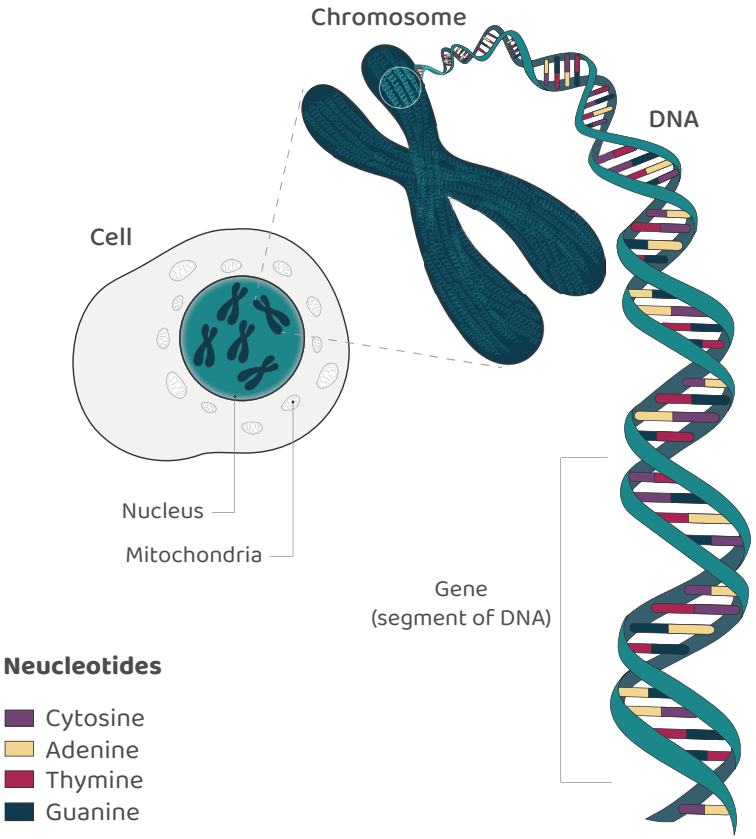

Figure A5.1 DNA, genes, and chromosomes.

Genetic tests used in individuals with epilepsy include:

- **Karyotype:** Produces a picture of the pairs of chromosomes in an individual. Karyotypes are useful in identifying missing, extra, or large structural changes in chromosomes.[5]
- **Chromosomal microarray analysis** (CMA, also known as comparative genomic hybridization): Produces a high resolution molecular karyotype and helps detect atypical, small changes related to the number of chromosomes, the shape of the chromosomes, or extra or missing segments of chromosomes.[6] CMA detects changes known as copy number variants on stretches of DNA. CMA has replaced karyotype as a first-line genetic test in most genetic settings.
- **Gene panel:** A test that targets and investigates specific genes known to be involved in specific conditions:[7] for example, epilepsy. An epilepsy gene panel is used when a specific type of epilepsy known to be associated with a particular gene is suspected.

- **Whole exome sequencing:** A test sequencing all the protein-coding regions of genes in the genome, known as the exome. The exome makes up only about 1.5 percent of the entire genome, but is associated with 85 percent of all variants.[8,9,10]
- **Mitochondrial DNA sequencing:** A genomic technique for sequencing the genes located on the mitochondrial DNA.
- **Whole genome sequencing:** A technique involving sequencing of all the protein-coding regions and nonprotein-coding regions of genes in a genome.[5]

Genetic testing typically produces one of the following results:

- **No abnormalities detected:** This result is also known as normal, negative, or benign (not harmful). In an individual with epilepsy, this means a genetic cause of epilepsy was not identified using the genetic test performed. It does not completely rule out the possibility of genetic cause, however, and more testing may be recommended.[11]
- **Pathogenic variants detected:** This result is also known as abnormal, positive, or as disease-causative. In an individual with epilepsy, this means the genetic change is identified as the cause of epilepsy.[11]
- **Variant of uncertain significance detected:** This result is also known as genetic variant of uncertain significance (VUS) and means a genetic change was detected, but the meaning of the finding is not fully understood. In this situation, it may be recommended that other family members be tested, other in-depth testing be done, and/or the results be reevaluated later (in one to two years). With ongoing research, genetic causes may be identified in the future. A VUS today might later be reclassified as normal, as a genetic epilepsy, or another condition.[11]

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