

HOSPITAL PHYSICIAN®

NEUROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Neurology Board Review Manual* is a study guide for residents and practicing physicians preparing for board examinations in neurology. Each quarterly manual reviews a topic essential to the current practice of neurology.

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Neurogenetics Review

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Neurogenetics Review

Catherine L. Gallagher, MD

INTRODUCTION

In the past half century, an explosion of knowledge in the field of molecular genetics has revolutionized our understanding of human diseases. One third of known single gene defects cause diseases that affect the nervous system, so knowledge of the clinical approach to genetic disorders is essential for the practicing neurologist. This manual provides a survey of single gene defects that affect the nervous system, based on the most prominently affected neuroanatomic region.

BASIC CONCEPTS

Genetic Basis of Inheritance

Humans have 22 pairs of autosomes and 1 pair of sex chromosomes. Each chromosome is made up of 2 complementary strands of DNA consisting of a double helical structure surrounding matched nucleotide base pairs (guanine with cytosine, adenine with thymine). Each set of 3 DNA base pairs, or *codon*, codes for 1 amino acid. DNA is *transcribed* into messenger RNA (mRNA) by RNA polymerase and then *translated* into protein. *Introns* and *untranslated regions* are portions of the DNA sequence that are transcribed but not translated.

A *gene* is a portion of the DNA sequence that is the basic unit of inheritance. *Genotype* is an individual's genetic makeup; *phenotype* is an individual's physical traits or morphology. *Expressivity* of a gene is the degree to which a trait attributable to the gene is evident in the phenotype. *Gene expression* is more frequently used to describe the quantity and location of mRNA and protein transcribed and translated from the gene. *Transcription factors* are proteins that bind to DNA to regulate gene expression.

Alleles are variations in the sequence of nucleotides that make up a gene. An individual inherits 2 alleles of each gene, 1 from each parent. If the alleles are identical, the genotype is *homozygous*; if they are different, the genotype is *heterozygous*. The *penetrance* of an allele is the proportion of individuals that express its phenotypic manifestations (ie, disease). Penetrance is frequently variable, particularly in autosomal dominant disorders. A *proband* is the first person within a family or kinship to

be identified with a genetic disorder. *Founder effect* is when a particular (especially recessive) mutation is overrepresented in a population due to a small genetic pool. An example would be the propagation of X-linked hemophilia in European royalty in the nineteenth and twentieth centuries. A *polymorphism* is an allele (DNA sequence variation) that occurs in at least 1% of the normal population.

Genomic *imprinting* is the preferential inactivation (by methylation) of some regions of a chromosome based on its parental origin. The most striking examples of imprinting are **Prader-Willi syndrome** and **Angelman's syndrome**, both caused by deletion of genes on the proximal long arm of chromosome 15. Prader-Willi syndrome (obesity, hypotonia, mild mental retardation, small hands and feet) is caused by a deficiency of paternal gene expression within this region, whereas Angelman's syndrome (severe mental retardation, epilepsy, facial abnormalities, jerky movements, hypopigmentation, frequent laughter) is caused by a deficiency of maternal gene expression.¹

Patterns of Inheritance

Single gene disorders are traits produced by the effects of a single gene or gene pair. Such traits are inherited in patterns originally described by Mendel as either *dominant* (transmitted virtually unchanged by hybridization) or *recessive* (masked in the process). Four inheritance patterns are seen in genetic disorders of the nervous system: *autosomal dominant*, *autosomal recessive*, *X-linked*, and *mitochondrial*. A patient presenting with a genetic disease without a family history is said to be a *sporadic* or *isolated* case; explanations that should be considered in such cases include new mutations (common in certain conditions), false paternity, variable penetrance, and recessive inheritance.

Autosomal dominant. A dominant trait will manifest in both the heterozygote and homozygote, meaning that a single copy of the mutant allele is sufficient to produce the trait. Characteristics of an autosomal dominant disorder include: multiple successive generations are affected, males and females are affected in similar proportions, both males and females transmit disease, and at least 1 instance of male-to-male transmission is seen.