Genetic Basis of Ventricular Arrhythmias

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KEYWORDS

• Ventricular arrhythmia • Genetics • Channelopathy
• Brugada syndrome • Arrhythmogenic cardiomyopathy

Sudden cardiac death caused by malignant ventricular arrhythmias is the most important cause of death in the industrialized world. Most of these lethal arrhythmias occur in the setting of ischemic heart disease. A significant number of sudden deaths, especially in young individuals, are caused by inherited ventricular arrhythmic disorders, however. Genetically induced ventricular arrhythmias can be divided in two subgroups: the primary electrical disorders or channelopathies, in which no apparent structural heart disease can be identified, and the secondary arrhythmogenic cardiomyopathies. In these "single gene disorders," mutations are restricted to one gene, rendering a predictable mendelian fashion of transmission. The highly variable phenotypic expression of these monogenic mutations (even within the same family) makes risk assessment of a single individual difficult, if not impossible. This article focuses on the genetic background of these electrical disorders and the current knowledge of genotype-phenotype interactions.

MONOGENIC MODES OF TRANSMISSION

Protein-coding sequences comprise less than 1.5% of the human genome.[1] The rest contain RNA genes, regulatory sequences, introns, and so-called "junk DNA." Each individual has two copies of each gene (called alleles), which are localized along 23 chromosome pairs (22 pairs of autosomes, 1 pair of sex chromosomes). Each parent contributes one member of each chromosome pair, thus providing one copy of each gene. An individual is considered "homozygous" for a specific gene locus when both gene loci are occupied by two identical alleles or "heterozygous" when both alleles differ. According to Mendel's first law, each of the two alleles separates independently and is passed on to the next generation. Most of the single gene disorders are caused by point mutations (alteration of a single nucleotide), in which a nucleotide is substituted, resulting in formation of a different amino acid (missense mutation), a truncated protein (caused by mutation to a stop codon), or an elongated protein (caused by elimination of a stop codon). If the phenotype is expressed in the presence of only one mutated allele, the inheritance is called dominant. When phenotype expression requires both alleles to be mutant, the pattern of inheritance is called recessive (**Fig. 1**).

AUTOSOMAL DOMINANT INHERITANCE

The phenotype can be expressed in a heterozygous setting, in which only one of the two alleles

This article originally appeared in *Cardiology Clinics of North America*, Volume 26, Issue 3.
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Heart Failure Clin 6 (2010) 249–266
doi:10.1016/j.hfc.2009.12.005

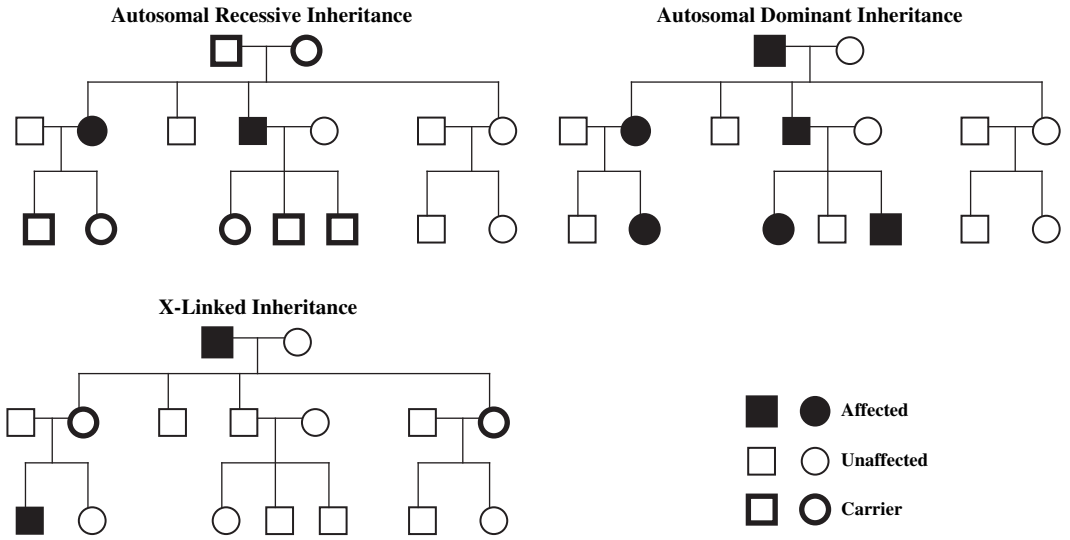

Fig. 1. Monogenic patterns of inheritance.

is affected. In the presence of identical mutations, different individuals may express different clinical features because of a different degree of expressivity, which is amenable to environmental and genetic factors. In an autosomal dominant trait, men and women are equally prone to inherit the mutation, and each child has a 50% chance of being affected by receiving the mutant allele. Each affected person has an affected parent. Normal children of an affected parent are noncarriers and cannot pass on the disease. In most autosomal dominant inherited diseases, the onset of the first phenotypic expression is delayed.

AUTOSOMAL RECESSIVE INHERITANCE

In autosomal recessive disorders, the phenotype can only manifest when both alleles are mutated at the locus responsible for the disease. Because 1 of the 22 autosomes is involved, there is an equal distribution between male and female subjects. Because of the early onset of expression, recessive disorders are mainly diagnosed during childhood. Each child has a 25% chance of being affected, and heterozygote parents are clinically normal.

X-LINKED INHERITANCE

Disorders caused by genes located on the sex chromosomes (X-linked) demonstrate a significantly different pattern of transmission with a different clinical outcome between both sexes. In women, one or both X chromosomes can be affected, with dominant or recessive properties. Because men only carry one X chromosome, the probability that the disease will manifest in the presence of a mutant gene is much higher. Mutant X genes can be received from the affected father or the homozygote (affected) or heterozygote mother. No male-to-male transmission is possible (genetic material from father to son is located on the Y chromosome), and all daughters of affected men are carriers.

CHANNELOPATHIES

The genetic background and detailed pathogenic mechanisms of these primary electrical disorders have been studied extensively in the last two decades.[2] At first, because of a lack of systematic investigation and low patient numbers, information was obtained from animal models, which were extrapolated to humans. Later, genetic linkage techniques and long-term information of multigenerational families increased our understanding of these relatively new diseases. Currently, several genes have been identified coding for the expression of ion channel proteins, located in the membrane of the cardiomyocyte. The principal function of these cardiac channels is the formation of an electrical potential. Ion currents are regulated by synchronized opening and closing of these channels. Gene mutations alter their pore-forming capacities and gate function, which results in an impaired depolarization or repolarization. This results in an increased vulnerability of the cardiomyocyte for dangerous arrhythmias. The channelopathies show a pronounced genetic