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Common Genetic Variants in Sudden Cardiac Death

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A complex mixture of environmental, metabolic and genetic factors contributes to the risk of premature death in the setting of heart disease. The term sudden cardiac death (SCD) refers to the abrupt cessation of heart function most commonly caused by ventricular arrhythmia. The incidence of SCD in the United States has been estimated to be as high as 450,000 per year¹ and accounts for a large fraction of total mortality due to heart disease clearly representing a substantial public health burden.

There are many established risk factors for SCD ascertained from epidemiological studies and include the major categories of cardiovascular disease such as myocardial ischemia and infarction, left ventricular dysfunction and heart failure, hypertension, and primary electrical disturbances. The contribution of genetic factors has been inferred by the importance of a positive family history for SCD risk and by advances in delineating the inherited basis of rare familial arrhythmia susceptibility disorders (e.g. long-QT syndrome, Brugada syndrome) and the familial cardiomyopathies. Although the paradigm of increased arrhythmia susceptibility in rare familial disorders is compelling, the majority of cases of SCD occur in persons that are not affected with these conditions. Other genetic factors including common variants have been postulated to contribute to SCD risk in general populations.

This review will highlight basic concepts and recent evidence defining the contribution of common genetic variants to the risk of SCD in general populations.

Genetic concepts relevant to common diseases

There are two broad categories of genetic diseases: Mendelian or monogenic disorders that arise from mutations in single genes, and complex traits or polygenic disorders that arise from multiple genetic variants in two or more genes coupled with environmental exposures (Fig. 1). Strategies for identifying genetic determinants of disease risk have evolved considerably since the early days of pedigree-based linkage analysis and positional cloning of genes responsible for Mendelian disorders. In the new era, genome-wide association studies map genomic regions conferring risk for more common, genetically complex diseases.

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In Mendelian disorders, rare genetic variants, usually referred to as mutations (see Box 1), confer a major portion of disease risk making it feasible to construct a genotype-phenotype relationship, enable use of genetic testing and genetic counseling to assess disease risk in individuals. However, mutations causing Mendelian disorders have limited value in predicting disease risk in general populations because the alleles are rare. For complex traits, genome-wide association studies address the “common disease-common variant” hypothesis that posits a major portion of risk for a common disease in populations is conferred by a limited number of common genetic variants.² A competing theory, the common disease-rare variant hypothesis, which posits that multiple rare variants confer risk for common diseases, is expected to gain traction as newer DNA sequencing technologies mature.

Allele Frequency vs Effect Size

Determinants of the genetic contribution to disease risk include differences in the population frequency of susceptibility alleles (allele frequency) and the corresponding impact that a given allele has on health (effect size; Fig. 2). Although mutations associated with inherited arrhythmia susceptibility are rare in the population, individual alleles exert potent effects and are highly penetrant. Penetrance is an expression of the degree to which the presence of a mutation predicts the occurrence of the disease. High penetrance implies that carrying the mutation is associated with a high probability of symptomatic disease. By contrast, common genetic variants occur frequently in the population but exert small effect size and exhibit low penetrance. Between these two extremes are less common variants that have moderate effect size.

Genes vs Environment

All diseases with genetic risk have varying levels of environmental contribution. In Mendelian disorders such as congenital long-QT syndrome (LQTS), risk for ventricular arrhythmia and sudden death is conferred predominantly by mutation in a single gene. However some variability in expression of the mutation effect may be attributable to environmental or acquired factors. For example in type 2 LQTS, mutations in *KCNH2* confer increased arrhythmia risk that may be triggered by audiogenic stimuli such as sudden loud noises. By contrast, drug-induced LQTS is triggered by an environmental exposure (i.e., drug), but even in this pharmacological syndrome there may be some contribution of genetic factors to increasing the risk associated with drug exposure.^{3, 4} Most disease afflicting adults arises because of mixed genetic and environmental influences. Susceptibility to SCD in the general population likely stems from a complex interplay of various genetic susceptibilities with environmental factors.

Genetic Risk of Sudden Cardiac Death

Several epidemiological studies have reported that family history of SCD is an independent risk factor for sudden death. In the King County, Washington survey of out-of-hospital primary cardiac arrest, Friedlander and colleagues reported that the rate of myocardial infarction and primary cardiac arrest among first-degree relatives of cardiac arrest subjects was 57% greater than that of first degree relatives of control subjects even after adjustment for other common risk factors.⁵ These observations were even more significant when considering a family history of early onset SCD in parents. A parental history of early (age < 65 years) SCD was associated with ~2.7-fold greater risk than among similarly aged subjects.⁶ These associations were independent of other traditional risk factors as well as parental history of myocardial infarction. These findings suggested that the genetic risk for myocardial infarction and sudden cardiac death may be somewhat independent.

Similar observations were made in the Paris Prospective Study that tracked the health status of 7079 men aged 42 – 52 years for an average follow-up of 23 years.⁷ There were 118 sudden

deaths among a total of 603 cardiovascular deaths. Parental history of sudden death was a significant risk factor for the occurrence of SCD in this study. The risk ratio conferred by parental history of sudden death was 1.89 in the case of a single affected parent. In the case of both parents suffering sudden death, the risk to the subject was 9.4-fold greater as compared to subjects without any family history.

Family history of SCD is also a significant risk factor among individuals suffering acute myocardial infarction. In the Finnish Genetic Study of Arrhythmic Events, a case-control study compared the incidence of family history of SCD in consecutive victims of sudden death associated with acute coronary events confirmed by autopsy.⁸ A family history of SCD in two or more first-degree relatives was significantly more common among victims of sudden cardiac than among a cohort of acute myocardial infarction survivors (odds ratio = 3.3) or population controls (odds ratio = 11.3). A similar conclusion was drawn by investigators in The Netherlands who reported that familial SCD occurred significantly more frequently among subjects suffering primary ventricular fibrillation in the setting of ST-elevation myocardial infarction than in controls (odds ratio = 2.72).⁹

Candidate Gene Studies

Two general approaches have been used to identify genetic risk factors in SCD: candidate gene studies and genome-wide association. In both cases, genetic associations were sought between genetic markers and either sudden death as the clinical end point or the QT interval as a heritable quantitative trait and intermediate phenotype predictive of SCD risk. Investigations of genetic determinants of the QT interval were based upon the hypothesis that genetic factors that impair cardiac repolarization and lengthen the QT interval would increase risk for SCD.

Three broad categories of genetic candidates that have been evaluated include genes involved in atherosclerosis and thrombosis, determinants of myocardial excitability and repolarization, and genes involved in autonomic control of cardiac function. In this brief review, studies addressing SCD risk based on the genetics of atherosclerosis and thrombosis will not be discussed.

Association of LQTS Genetic Variants with QT Interval

Earlier studies testing candidate gene hypotheses related to the QT interval examined genes responsible for the congenital LQTS in different populations. A study of 166 healthy German twins (100 monozygotic, 66 dizygotic) demonstrated a high heritability of the QT interval, and linkage of QT variation to genetic markers at two of the five LQTS loci known at that time (*LQT1*, *LQT4*).¹⁰ These findings suggested that certain genes causing inherited LQTS may be determinants of QT variation in healthy persons.

In one of the first population-based studies to define genetic determinants of myocardial repolarization, common variants in *KCNQ1*, *KCNH2*, and *KCNE1* were found associated with QT interval variation.¹¹ This study examined 174 common variants in 3,966 individuals ascertained from Augsburg Germany as part of a large epidemiological study (Cooperative Health Research in the Region Augsburg, KORA study). The QT interval was adjusted for heart rate, age and sex using a correction formula derived from Framingham Heart Study data (QTc_RAS). Genetic association was performed using a two-step procedure in which a screening sample of 689 subjects was tested initially for all variants then a second confirmation sample of 3,277 different subjects was used to validate significant results for 13 SNPs identified in the first step. Three variants demonstrated to have significant association with QTc_RAS in both groups of subjects included a SNP in *KCNQ1* intron 1, a common non-synonymous *KCNH2* variant (K897T), and a SNP located 5' to the first exon of *KCNE1*. The *KCNQ1* and *KCNE1* variants were associated with longer (1.2 - 1.7 ms per copy of the minor allele)

QTc_RAS whereas *KCNH2*-K897T was associated with shorter (-1.9 ms per minor allele copy) QTc_RAS. Individual common variants explained less than 1% of QTc_RAS variance in this population, however an analysis of the combined effect of multiple SNPs demonstrated a 10.5 ms difference in average QTc_RAS for the group of subjects carrying the greatest number of variant alleles as compared to those without any variants.

Investigators in France tested DNA from participants of the D.E.S.I.R. study population to examine LQTS genes for association with QT interval.¹² In this non-replicated study, two subgroups of 200 subjects representing 10% of the total study population having either the longest or shortest QTc intervals (heart rate correction using Fridericia formula) were screened for *KCNQ1* sequence variation and genotyped for known common variants in *SCN5A*, *KCNH2* and *KCNE1*. No *KCNQ1* variants were associated with QTc, but the minor allele frequencies of specific SNPs in *SCN5A*, *KCNH2* and *KCNE1* were associated with either the longest (*SCN5A*-H558R, *KCNE1*-D85N) or shortest (*SCN5A*-D1818D, *KCNH2*-K897T) QTc values.

The association of *KCNH2*-K897T with shorter QT intervals in both the KORA and D.E.S.I.R. studies has not been observed in other studies. Four other studies have examined the association of *KCNH2*-K897T with the QT interval.¹³⁻¹⁶ Three of these studies found that the variant was associated with longer QTc intervals rather than shorter. Two studies from Finland demonstrated that *KCNH2*-K897T was associated with longer QTc only in females in a general population,¹³ and was associated with longer QTc during maximum exercise in carriers of a *KCNQ1* founder mutation associated with LQTS in Finland.¹⁴ Similarly, *KCNH2*-K897T was associated with longer QT intervals in participants of the Framingham Heart Study.¹⁶ A longer QTc correlates more logically with data from functional characterizations of this variant in heterologous cells demonstrating partial loss-of-function for the rapid delayed rectifier (I_{Kr}), a major repolarizing current. We previously demonstrated that this common variant can also accentuate the risk of ventricular arrhythmia in a family segregating a rare *KCNH2* mutation suggesting that K897T is a genetic modifier of latent congenital LQTS.¹⁷

Common Variant *SCN5A*-S1103Y and SCD Risk

A non-synonymous variant (S1103Y)^a in the cardiac sodium channel gene *SCN5A* has been associated with increased SCD risk in adults and infants. This variant is common in African-Americans (13% carrier frequency) but is rare or absent in other ethnic groups. In a study by Splawski, et al., S1103Y was associated with cardiac arrhythmia in a small cohort of African-American arrhythmia cases.¹⁸ Arrhythmia risk in this cohort was elevated more than 8-fold in carriers of the variant allele. Functional studies of the variant allele demonstrated increased persistent current indicating impaired sodium channel inactivation. Further, computational modeling of action potentials that incorporated the functional characteristics of the variant sodium channel demonstrated an increased propensity for early afterdepolarizations when combined with simulated partial block of I_{Kr} and hypokalemia.

In a subsequent study of the prevalence of S1103Y in African-American SCD cases ascertained by the Maryland Medical Examiner, the minor allele frequency was observed to be significantly greater among sudden-death cases associated with either mild cardiac abnormalities or no cardiac disease determined by autopsy as compared with the general population.¹⁹ These studies suggest that *SCN5A*-S1103Y is associated with an increased risk of sudden death and ventricular arrhythmia in African-American adults. These findings also suggest that *SCN5A*-

^aThe *SCN5A*-S1103Y variant has also been designated as S1102Y based on the amino acid sequence of an alternatively spliced transcript. To be consistent with the numbering scheme used widely for *SCN5A* mutations, we prefer to use S1103Y based upon the canonical transcript.

S1103Y may explain part of the increased risk for sudden death among African-Americans in general.¹⁹

Infant carriers of *SCN5A*-S1103Y may also be at greater risk of SCD. Plant and colleagues demonstrated that S1103Y carriers were more common among African-American SIDS victims than non-SIDS controls.²⁰ Although the minor allele frequency was similar between SIDS cases (0.07, n=133) and non-SIDS controls (0.06, n=1056) as was the proportion of subjects carrying at least one variant allele copy (13.6% vs 12.9%), there was a 4-fold excess of homozygous carriers of the variant allele among the SIDS cases and correspondingly a 24-fold greater risk of sudden death. Functional studies demonstrated increased persistent current but only upon exposure to acidosis suggesting that a metabolic abnormality may be required to unmask a latent functional defect associated with this common variant. Confirmation of this observation was provided by Van Nordstrom, et al., by demonstrating a significantly increased prevalence of S1103Y heterozygous carriers among SIDS cases (22.5%) as compared with African-American controls (11.6%).²¹ This study did not observe homozygous subjects. Several other *SCN5A* variants have been detected in SIDS cases but most are considered rare variants or mutations.²²⁻²⁵ One common allele (V1951L) that is common in Hispanic populations but rare in other ethnic groups was found in Caucasian SIDS cases.²⁴ Functional studies demonstrated that this variant predisposed to increased persistent current when exposed to acidosis in the context of a common splice variant that excludes glutamine 1077.²⁵

Rare *SCN5A* variants have also been identified in women with SCD followed by two large prospective cohorts, the Nurses' Health Study and the Health Professional Follow-Up Study.²⁶ The investigation involved the screening of five major LQTS genes in 113 SCD cases (60 women, 53 men). Five rare *SCN5A* variants were discovered in 6 women but none of the men. A similar screen for LQTS gene variants performed in 67 SCD cases ascertained by the Oregon Sudden Unexplained Death Study (Ore-SUDS) identified a single novel non-synonymous rare *SCN5A* variant in a male.²⁷ *SCN5A*-S1103Y was not reported by either of these two studies but African-Americans were underrepresented among SCD cases.

Common Variants Influencing Autonomic Function

The sympathetic and parasympathetic nervous systems exert important influences on heart rate, cardiac contractility and vascular tone. Activation of the sympathetic nervous system can promote ventricular arrhythmias particularly in the setting of acute myocardial infarction. Two studies have examined candidate genes vital to the function of the autonomic nervous system to test genetic associations with SCD. Snapir et al., utilized participants in the Helsinki Sudden-Death Study including 700 out-of-hospital sudden deaths evaluated by autopsy.²⁸ Two hundred eighty-eight subjects were classified as SCD that occurred in combination with a variety of co-morbidities including acute myocardial infarction (28%), prior infarction with scar (42%), diabetes, hypertension and smoking. The primary hypothesis was that an insertion/deletion polymorphism in the α_{2B} -adrenergic receptor gene (*ADRA2B*) may predispose to SCD. The variant allele encodes a receptor with three missing glutamate residues that exhibits impaired agonist-induced desensitization.²⁹ In the study, there was a greater proportion of subjects homozygous for the deletion allele (DD genotype) among SCD cases as compared with non-SCD cases.²⁸ This finding indicated a 2-fold increase in SCD risk for DD carriers as compared with individuals who carried only one or no copies of the deletion allele. The association was stronger in men less than 55 years of age where a 4.5-fold increase in SCD risk was observed among DD carriers. The DD genotype was also associated with an increased risk for pre-hospital fatal acute myocardial infarction. Although the study provided compelling results, there was no replication in an independent population. However, carriers of the *ADRA2B* deletion allele among members of an Afrikaner LQTS founder population (mutation KCNQ1-

A341V) exhibited significantly greater baroreflex sensitivity than non-carriers and were predisposed to a higher risk of symptomatic disease.³⁰

A separate investigation assessed genetic association between common variants in the β_2 -adrenergic receptor gene (*ADRB2*) and SCD in subjects ascertained by the Cardiovascular Health Study.³¹ Two non-synonymous SNPs (G16R, Q27E) that were known to alter receptor function in heterologous cell systems were studied. The two variants are in strong linkage disequilibrium creating a limited number of common haplotypes in general populations. The study found that homozygosity for the common allele (glutamine) at Q27E was associated with increased SCD risk (hazard ratio = 1.56). This was evident in white subjects but was not statistically significant in African-Americans. The finding was replicated in the King County, Washington Cardiac Arrest Blood Study with similar findings of increased SCD risk in participants homozygous for the common allele. Prior characterization of the variant receptor proteins demonstrated variable agonist-induced desensitization with the E27 variant exhibiting complete resistance to desensitization.³² No mechanistic studies have been performed to elucidate the connection between SCD and homozygosity for Q27. Logically, the variant allele (E27) associated with resistance to agonist-induced desensitization should predispose myocytes to unrelenting activation of β -adrenergic signal transduction in the presence of circulating catecholamines. However, increased SCD risk was associated with the common allele rather than the functionally altered minor allele. These two studies provide evidence suggesting that genetic variation in autonomic nervous system molecules may influence SCD risk but the precise mechanisms underlying these associations have not been fully investigated.

Genome-Association Studies of QT Duration and SCD

Candidate gene association studies are limited by current knowledge of the pathophysiology underlying risks for SCD. By contrast, genome-wide association studies are unbiased by present day knowledge and therefore provide opportunities for discovery of new genetic determinants of SCD risk. However, this approach also has limitations related to the assumption that common variants explain risk for common disease. The genotyping platforms used for genome-wide association studies typically interrogate genetic variants that are quite common in the population (minor allele frequency $\geq 5\%$) and merely provide signposts along the genomic highway rather than represent causative alleles. This strategy is designed to identify genomic loci conferring susceptibility to the trait being investigated rather than pinpoint the direct cause of genetic risk. Replication of association in independent populations is a critical step for validating results from genome-wide association studies. A frequent observation from more than 100 such studies in a variety of common medical conditions³³ is that common variants account for only a small proportion of population attributable risk (i.e., the reduction in disease incidence that would occur in the absence of the variant) implying that no single common risk genotype or haplotype has much predictive power by itself.³⁴ In other words, statistical significance in these studies does not easily translate into results that are clinically meaningful.³⁵ This observation is crucial to understanding the limitations in using results from any single genomic studies for predicting individual disease susceptibility.³⁶ Nonetheless, genome-wide association studies have provided new discoveries that may translate into greater insight into the biology of disease risk for some conditions.³³

Associations of *NOS1AP* with QT Interval and SCD

Recent evidence from genome-wide association studies have indicated that common variants in *NOS1AP* are associated with QT interval duration and SCD risk in general populations. *NOS1AP* encodes a nitric oxide synthase adaptor protein (designated CAPON) that is expressed widely in human tissues including brain and heart but was not previously known to influence cardiac function generally or myocardial repolarization specifically. Arking et al., performed

a genome-wide association study of QT_RAS in healthy Germans participating in the KORA study.³⁷ The strategy used a three tiered design starting first with a genome-wide analysis using 115,000 SNPs in 100 women in both the top and bottom 7.5th percentile of QT_RAS. The top 10 SNPs rank ordered by p-value were subjected to a second stage analysis with 300 females from each QT_RAS extreme followed by a final stage where both males and females from the entire 3,366 study population were tested for association. Common variants in *NOS1AP* were significantly associated with QTc_RAS with the minor allele conferring risk for a longer QTc_RAS. This association was validated in two independent populations from either Germany or the Framingham Heart Study. Although the association of *NOS1AP* with QTc_RAS was statistically robust and validated, the presence of the minor allele explains only 1.5% of the QT interval variation in these populations. This finding has now been replicated in several distinct populations.³⁸⁻⁴⁶

One of the replication studies also investigated the association between *NOS1AP* variants and SCD in two large adult populations ascertained by either the Atherosclerosis Risk in Community (ARIC) Study or the Cardiovascular Health Study.⁴⁷ This investigation demonstrated association of common *NOS1AP* variants with the QT interval and SCD in white participants with approximately 30% increased SCD risk per minor allele copy of the most informative SNP. By contrast, there was no significant association between *NOS1AP* and either the QT interval or SCD risk in African-American subjects.

The discovery of genetic association between *NOS1AP* and QT interval as well as SCD does not provide direct information about the physiological mechanism responsible for these traits although involvement of this gene in myocardial repolarization was implied. To further investigate the specific biological role of *NOS1AP* in repolarization, Chang and colleagues used an adenoviral strategy to over-express the protein product of *NOS1AP* (CAPON) in cultured guinea pig ventricular myocytes coupled with electrophysiological studies to assess the impact on myocyte excitability and repolarization.⁴⁸ Over-expression of CAPON in ventricular myocytes caused shortening of action potentials that could be explained largely by a significant reduction in peak L-type calcium current density. Further, myocytes over expressing CAPON exhibited greater stability in protein levels of nitric oxide synthase 1 (NOS1) and inhibition of this enzyme reversed the effects on action potential duration and calcium current density. This work implicates mediators of nitric oxide (NO) signaling in cardiac myocyte repolarization and suggests that further investigations into these mechanisms may provide more direct explanations for the genetic association of *NOS1AP* with a the QT interval and SCD.

Other Genomic Loci Associated with QT Duration

Additional large-scale genome-wide association studies that compiled data from multiple population-based cohorts identified additional genomic loci associated with QT interval duration. In the QTGEN study, genotyping data from 13,685 individuals of European ancestry compiled from the Framingham Heart Study, the Rotterdam Study and the Cardiovascular Health Study were used to identify 10 loci significantly associated with QT interval duration.⁴⁵ Four of these loci are within or near genes associated with congenital LQTS (*KCNQ1*, *KCNE1*, *KCNH2*, *SCN5A*) and a fifth locus was *NOS1AP*. In addition to these loci that had known associations with myocardial repolarization, there were five newly identified loci on chromosomes 1p36, 6q22, 16p13, 16q21 and 17q12. Some of these novel loci are located near genes with tantalizing associations with cardiac physiology. For example, markers on chromosome 6q22 fall within an intron of a predicted gene (*c6orf204*) with no known function but are also located 122,000 nucleotides from *PLN* encoding phospholamban, a known inhibitor of the cardiac sarcoplasmic reticulum Ca^{2+} -ATPase. Also of interest is the 16q21 locus located near a cluster of genes including *GINS3* that encodes a protein involved with

initiation of DNA replication. Interestingly, an insertional mutant in the zebrafish homolog of *GINS3* confers resistance to the QT prolonging effects of dofetilide.⁴⁹ The other three novel loci identified in this investigation fall within or near genes that have unknown relevance to myocardial repolarization.

In an accompanying paper, investigators in the QTSCD study analyzed genome-wide data from five other population-based cohorts including 15,842 subjects of European ancestry to identify genomic loci associated with QT interval duration.⁴⁶ Eight of the 10 loci identified by the QTGEN study were also observed by QTSCD investigators. Four of the loci identified by QTSCD were genes responsible for inherited arrhythmias syndromes (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNJ2*), in addition to *NOS1AP* and *PLN*. Only two novel loci near genes encoding *KCNJ2* and *ATP1B1* encoding a β -subunit of sodium-potassium ATPase were uniquely identified by QTSCD, but this study did not identify common variants within *KCNE1* or the 17q12 locus that were significantly associated in QTGEN. A smaller scale meta-analysis of three genome-wide association studies involving 3,558 subjects from population-based cohorts in the United Kingdom confirmed the significant association of *NOS1AP* and *PLN* with variation in QT interval duration.⁵⁰

In an attempt to provide a more clinically meaningful interpretation of these data, the QTSCD investigators derived a simple additive scoring system based on the number of QT prolonging alleles. On average, there was a 1.5 ms increase in mean QT interval for each additional QT prolonging allele, and individuals with a greater number of alleles had increased risk of having an overtly prolonged QT interval defined as ≥ 440 ms for males and ≥ 450 ms for females. Subjects with ≥ 11 QT prolonging alleles had a 49% increased risk of having an overtly prolonged QT interval, and subjects with carrying ≥ 14 alleles had an odds ratio of 2.52 for an overtly prolonged QT interval compared to those with ≤ 8 alleles.

Summary

Susceptibility to SCD is a heritable trait in general populations. Recent progress in dissecting genetic components of SCD risk have succeeded in identifying more than 10 genes contributing to QT interval duration, an intermediate phenotype providing a surrogate risk marker. Further progress is needed to explain a larger proportion of the genetic variance in QT duration, understanding the molecular and cellular mechanisms underlying genetic influences on myocardial repolarization, and validating clinical strategies for using genomic testing for formulating SCD risk in individuals. While progress in these important areas may take several years, physicians are encouraged to collect detailed and accurate family history data to enable an assessment of SCD risk.

Box 1

Definitions of genetic terms

Polymorphism or variant

any heritable DNA sequence variation

Single nucleotide polymorphism (SNP)

the simplest type of DNA variant

Non-synonymous SNP

a SNP that changes the coding region of a gene resulting in an amino acid substitution

Synonymous SNP

a SNP within a protein-coding region that does not result in an amino acid substitution

Mutation

any heritable DNA sequence variation that causes disease or disease susceptibility

Benign variant

a DNA sequence variation that does not

cause disease or disease susceptibility
Common variant
 a polymorphism found in > 1% of a population
Alleles
 alternative forms of a DNA sequence
Penetrance
 the proportion of individuals carrying a genetic variation
 who exhibit an associated trait or disease

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Fig. 1.
Illustration of relative contributions of genetic and environmental factors in susceptibility to different diseases.

Fig. 2.
Illustration of the relationship between allele frequency and effect size with possible cardiac disease examples.