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Commentary

In this issue of the *JCI*, Bowers et al. show that the common polymorphism of the cardiac voltage-gated sodium channel, type Vα (SCN5A), designated S1103Y, found in African Americans is associated with an increased risk of sudden infant death syndrome (SIDS). Wild-type and mutant SCN5A channels both functioned typically under normal conditions in vitro, but exposure to acidic intracellular pH levels such as those found in respiratory acidosis — a known risk factor for SIDS — produced abnormal gain-of-function late reopenings of S1103Y channels, behavior that is often associated with cardiac arrhythmias. These pathologic late reopenings were suppressed by low levels of the channel-blocking drug mexiletine. These findings provide an excellent illustration of a causal relationship between the interaction of the environment and genetic background in SIDS and also raise interesting questions about the linkage of a genetic abnormality with a clinical phenotype.

SIDS: genetic and environmental influences may cause arrhythmia in this silent killer

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In this issue of the *JCI*, Bowers et al. show that the common polymorphism of the cardiac voltage-gated sodium channel, type Vα (SCN5A), designated S1103Y, found in African Americans is associated with an increased risk of sudden infant death syndrome (SIDS) (see the related article beginning on page 430). Wild-type and mutant SCN5A channels both functioned typically under normal conditions in vitro, but exposure to acidic intracellular pH levels such as those found in respiratory acidosis — a known risk factor for SIDS — produced abnormal gain-of-function late reopenings of S1103Y channels, behavior that is often associated with cardiac arrhythmias. These pathologic late reopenings were suppressed by low levels of the channel-blocking drug mexiletine. These findings provide an excellent illustration of a causal relationship between the interaction of the environment and genetic background in SIDS and also raise interesting questions about the linkage of a genetic abnormality with a clinical phenotype.

The search for an etiology for sudden infant death syndrome (SIDS) and any associated risk factors has involved multiple potential neurological, endocrine, pulmonary, and cardiac causes. In 1976, Schwartz suggested a pathogenic link between cardiac sympathetic innervation, the hereditary disorder of the heart's electrical rhythm known as long QT syndrome (LQTS), and SIDS (1), and Maron et al. provided evidence for a role of LQTS in SIDS (2). In the 1990s, mutations in cardiac ion channel genes were found to underlie many cases of inherited arrhythmia syndromes, including LQTS (3). A mutation in the cardiac voltage-gated sodium channel, type Vα (SCN5A), was reported in a "near miss" SIDS case in 2000 (4), and in 2001 a population-based study of 93 SIDS cases revealed 2 mutations in *SCN5A* that resulted in phenotypic changes in this sodium channel at the molecular level that were similar to those observed in LQTS type 3 (LQT3) (5), which is characterized by the molecular phenotype of increased late Na^+ current (6, 7).

Nonstandard abbreviations used: LQTS, long QT syndrome; LQT3, LQTS type 3; SCN5A, voltage-gated sodium channel, type Vα; SIDS, sudden infant death syndrome.

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Linking genotypes with phenotypes

How is a genetic abnormality ascribed a causal role in a clinical phenotype such as SIDS? In a sufficiently large family, classic linkage analysis can establish an association between the genotype and clinical phenotype. Population studies can also allow an association to be drawn. In the population-based study reported in this issue of the *JCI* by Bowers et al. (8), the authors found an increased frequency of the *SCN5A* polymorphism S1103Y in 224 autopsy-confirmed unrelated cases of SIDS. Homozygosity for the S1103Y mutation in African American SIDS cases was found to be associated with a 24-fold increase in risk compared with controls, revealing a novel and significant basis for the existence of a genetic predisposition to SIDS. This mutation has an allelic frequency of approximately 10% in the African American population (9) and had previously been associated with an increased risk of ventricular arrhythmia (6). This study, however, goes beyond an association analysis and provides evidence for a pathogenetic mechanism or etiology underlying SIDS. The authors used recombinant DNA techniques to introduce the S1103Y mutation into *SCN5A*. The constructs were expressed in HEK-293 cells, an immortalized non–muscle cell culture system, where they could be studied by voltage clamp. Sodium current is typically activated rapidly over hundreds of microseconds, then decays completely over several milliseconds, leaving only about 0.5% of the total current as late Na^+ current. In channels with typical mutations associated with LQT3, late reopenings of these channels, which substantially increase late Na^+ current, are observed. This late current prolongs the action potential at the cellular level, causing prolongation of repolarization, prolongation of the QT interval at the surface, and torsade de pointes arrhythmia (Figure 1). Expression of the S1103Y channel in heterologous cell culture, however, did not result in the typical LQT3 "molecular phenotype" of increased late Na^+ current. Not until the mutant channels were exposed to acidosis in the heterologous system was the increase in late Na^+ current apparent. This molecular phenotype can be plausibly linked to sudden cardiac death through the clinical phenotype of LQT3 (Figure 1).

The importance of the experimental model

The proper environmental conditions, genetic background, and experimental model may be crucial to identifying the molecular phenotype that links the genetic abnormality underlying SIDS to the clinical phenotype. In the present study (8), the environmental influence was acidosis, but in other cases it may be adrenergic stimulation or other conditions such as hyperkalemia (elevated serum K^+ levels), which can result in cardiac arrhythmias. The genetic background of the individual may also be important. For SCN5A, the dysfunction caused by mutations depends upon the splice variant background in which it is expressed (7, 10) and also upon the presence or absence of common polymorphisms (11). The expression of human channels in non–muscle cell cultures such as HEK-293 cells is a standard technique for assessing channel function, but could we be missing aspects of the molecular phenotype by using this system?

It is increasingly apparent that SCN5A (like other ion channels) is a macromolecular complex (12, 13), and HEK and other non–muscle cells do not necessarily express the necessary subunits and associated pro-

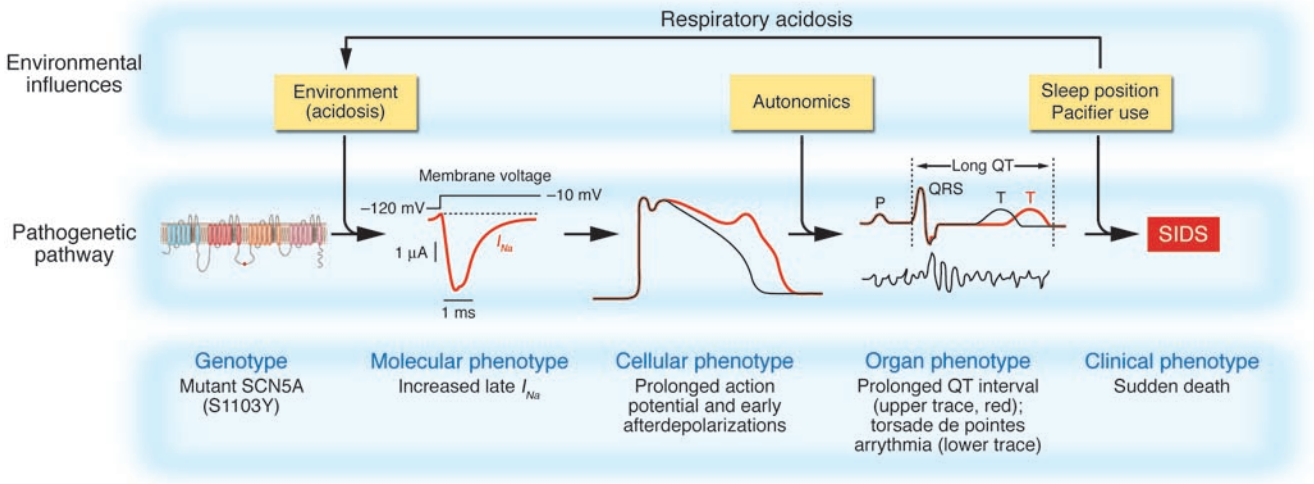

Figure 1
An arrhythmogenic pathogenetic pathway for SIDS from patient genotype to clinical phenotype. The figure denotes the pathogenic pathway from genotype to clinical phenotype, with environmental influences noted. The genetic abnormality, in this instance a polymorphism in the cardiac Na^+ channel SCN5A, causes a molecular phenotype of increased late Na^+ current (I_{Na}) under the influence of environmental factors such as acidosis. Interacting with other ion currents that may themselves be altered by genetic and environmental factors, the late Na^+ current causes a cellular phenotype of prolonged action potential duration as well as early afterdepolarizations. Prolonged action potential in the cells of the ventricular myocardium and further interaction with environmental factors such as autonomic innervation, which in turn may be affected by genetic factors, produce a tissue/organ phenotype of a prolonged QT interval on the ECG and torsade de pointes arrhythmia in the whole heart. If this is sustained or degenerates to ventricular fibrillation, the clinical phenotype of SIDS results. Environmental and multiple genetic factors may interact at many different levels to produce the characteristic phenotypes at the molecular, cellular, tissue, organ, and clinical levels. The study by Bowers et al. in this issue of the *JCI* (8) demonstrates the importance of environmental influences, in this case acidosis, in the pathogenetic pathway of SIDS.

teins required for full channel function. Moreover, these cell culture systems do not have the full panoply of cardiac ion channels needed to produce a cardiac action potential, and thus the "cellular phenotype" of the mutation cannot be determined. Resorting to in silico simulations of what the effect on the action potential might be (6) has predictive and heuristic value, but should not be regarded in the same light as actual experimental data in the native cellular environment. Transgenic mouse models of arrhythmia of genetic origin (14) may provide a more complete environment, but mouse and human molecular makeup and electrophysiology differ. Perhaps human cardiac myocytes differentiated from stem cells may one day provide a human cardiac cellular environment for testing the molecular and cellular phenotype of putative disease-causing SCN5A mutations.

The present study by Bowers et al. (8) shares the limitations of most such studies of molecular phenotype, including limited genetic background (for example, the mutation was studied in only 1 background splice variant clone) and generation of data in a non–muscle cell environment. Nonetheless, the pathogenetically important condition of acidosis was studied and, despite these limitations, a plausible pathogenetic link to the clinical phenotype of SIDS that was not found in earlier studies under standard conditions (6, 7) was described. Future studies of the molecular phenotype of putative disease-causing SCN5A mutations may increasingly involve more complete and complex genetic backgrounds and environmental conditions in human cellular models.

Arrhythmia, genetics, and SIDS

How much of SIDS etiology may be explained by a genetic-based predisposition to fatal arrhythmia? As mentioned above, population-based studies found mutations in *SCN5A* in 2 of 93 SIDS victims (5) with a molecular phenotype consistent with LQT3, and along with other studies of sporadic cases (4, 8), this has established mutations in *SCN5A* as a mechanism for SIDS. It is important to note that loss-of-function mutations such as those that cause Brugada syndrome may also play a role (15). In addition, other ion channel genes, such as those coding for the slow (16) and rapid delayed (17) rectifier potassium current (*LQT1* and *LQT2*, respectively), have been implicated in SIDS. Another study found a mutation in the LQT1-associated gene *KCNQ1* in 1 of 41 SIDS victims (18), but in that case the molecular phenotype was no different than wild type. In light of the present study (8), it would be interesting to assess the effects of acidosis or other environmental factors on that particular mutation to see if an LQT1 phenotype could be induced. These 2 population-based studies (5, 18) suggest that arrhythmia-inducing gene mutations underlie less than 10% of SIDS cases. But these studies only addressed the handful of genes in which mutations are known to induce arrhythmias, and mutations in these genes do not account for all cases of clinically obvious inherited arrhythmia syndromes, let alone a possible predisposition to acquired arrhythmia. Ion channels are macromolecular complexes, and the associated proteins and regulatory proteins of SCN5A, as well as other ion channels (reviewed in ref. 13), are also candidate genes for arrhythmia predisposition and SIDS. To assess the full impact of genetic predisposition to arrhythmia on SIDS, new genes will need to be examined, and the resulting molecular phenotype of any mutations will need to be characterized (keeping in mind not only the importance of environment as illustrated by the present study, but also the knowledge of the genetic background of the individuals at risk), and improved and more complete experimental models will need to be used.

For families of SIDS victims, a clear delineation of risk factors, both genetic and environmental, will be instrumental in identifying children who may benefit from therapeutic intervention. Bowers et al. (8) make cogent suggestions for further study and possible screening for this particular genetic risk factor in select populations. It is likely that uncovering mutations in SCN5A and other ion channels will be just the beginning of determining the complex genetic basis for SIDS, and in the years ahead other genetic abnormalities may also be linked to SIDS. Current thinking emphasizes a brain stem neural network maldevelopment hypothesis for this syndrome (19). It is likely that the etiology of SIDS is heterogeneous and may result from the interaction of a number of genetic and environmental factors. It remains to be determined how many cases of SIDS may eventually be linked to mutations predisposing the carrier to cardiac arrhythmia.

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Gastrointestinal motility and glycemic control in diabetes: the chicken and the egg revisited?

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Upper gastrointestinal dysfunction occurs frequently in diabetes and potentially contributes to both abdominal symptoms and impaired glycemic control; conversely, variations in blood glucose concentration reversibly affect gut motility in humans. In this issue of the *JCI*, Anitha et al. report apoptosis of rodent enteric neurons under hyperglycemic conditions, both in vitro and in vivo, associated with impaired PI3K activity and preventable by glial cell line–derived neurotrophic factor (see the related article beginning on page 344). These observations add to recent insights gained from animal models regarding the etiology of diabetic gastrointestinal dysfunction, but investigators must strive to translate animal data to human diabetes.

Nonstandard abbreviations used: GDNF, glial cell line–derived neurotrophic factor; GLP-1, glucagon-like peptide 1; ICC, interstitial cell of Cajal; STZ, streptozotocin.

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It is now recognized that disordered gastrointestinal motor and sensory function occur frequently in diabetes mellitus and that this has substantial implications for the morbidity and effective management of patients with this condition. For example, gastric emptying is abnormally delayed in 30–50% of outpatients with long-standing type 1 or type 2 diabetes, with potential consequences of gastrointestinal symptoms, impaired nutrition, poor glycemic control, and delayed absorption of oral medications (1). However, the magnitude of the delay in gastric emptying is variable and in many cases modest (2). While diabetic gastroparesis is often associated with symptoms such as nausea, vomiting, postprandial fullness, and bloating, the relationship of symptoms to disordered emptying is relatively weak, and some patients are asymptomatic (2). Intestinal transit is also often disturbed in diabetes (rapid or slow) (3), and symptoms such as diarrhea and constipation occur more frequently than in the general population (4).

Disordered gastrointestinal motility in human diabetes has traditionally been