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Kcne2 deletion creates a multisystem syndrome predisposing to sudden cardiac death.

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Sudden cardiac death (SCD) is the term given to sudden, unexpected cessation of cardiac function. It is estimated that >1 in 1000 people in developed nations succumb to SCD annually, and it is the leading cause of death worldwide. Distinct from a heart attack, in which the heart continues to beat but blood flow is blocked, in SCD, the heart ceases to beat because of catastrophic, sustained ventricular fibrillation. Without defibrillation within minutes, this type of event is fatal; individuals who survive require an implantable cardiac defibrillator to protect against future SCD incidence. SCD typically occurs without evidence of a myocardial infarction but is considered frequently to require an ischemic substrate or heart failure. Diabetes mellitus is an established risk factor for both myocardial ischemia and SCD, the latter even after adjustment for other risk factors that accompany diabetes mellitus. Dead-in-bed syndrome, the overnight sudden unexplained death of someone with type I diabetes mellitus, may be linked to nocturnal hypoglycemia precipitating lethal ventricular arrhythmias; hypoglycemia linked to tight glycemic control is also associated with and predictive of increased mortality in people with type II diabetes.

Younger victims of SCD may lack detectable ischemic substrates, and in these cases in particular, a genetic electric disorder of cardiac origin is often implicated. To date, >25 genes have been identified, which are linked or associated with ventricular arrhythmias predisposing to SCD. These genes all encode cardiac-expressed ion channel subunits or channel-interacting proteins; their disruption is considered sufficient to cause monogenic, lethal ventricular arrhythmias by direct perturbation of ion currents orchestrating ventricular myocyte excitability. Most arrhythmia-susceptibility genes are not, however, expressed exclusively in the heart, suggesting the possibility that monogenic arrhythmia syndromes are complex, multisystem disorders. Here, we report that deletion of the widely expressed KCNE2 K+ channel β subunit gene creates a multifactorial substrate for SCD that includes diabetes mellitus, dyslipidemia, hyperkalemia, and progressive loss of ventricular repolarization reserve. The findings support the idea of multiplex origins even in monogenic ventricular arrhythmias.

Methods
We generated and genotyped the wild-type, heterozygous, Kcne2−/−, Kcne3−/−, and double-knockout Kcne2−/−Kcne3−/− mice as previously described and housed and used them according to the US National Institutes of Health Guide for the Care and Use of Laboratory

Key Words: arrhythmias, cardiac death, sudden, cardiac ion channels ischemia potassium
Animals. Animal procedures were approved by the Animal Care and Use Committees at Weill Medical College of Cornell University and University of California, Irvine. All adult mice used in this study, aside from breeding males, were female and generated from Kcne2–/– × Kcne2–/– crosses. Except where indicated, 2 age groups of adult mice were used, referred to as 4m-old and 7m-old. For functional studies, the 4m-old group were of mean age when studied: 4.3±0.1 months, n=27 (Kcne2+/–) versus 4.2±0.1 months, n=28 (Kcne2–/–). The 7m-old group were of mean age when studied: 7.4±0.1 months, n=30 (Kcne2–/–) versus 7.4±0.4 months, n=42 (Kcne2+/–). The P21 pups studied for the microarray comparison of maternal versus pup genotype effects were all male and were generated from either Kcne2–/– × Kcne2–/– or Kcne2–/– × Kcne2–/– crosses as indicated.

Briefly, statistical analyses were generally conducted as follows: unpaired Student t test for comparison of 2 groups; 1-way ANOVA followed by Tukey Honest Significant Difference test or Bonferroni test for comparison of multiple groups; repeated measures 2-way ANOVA followed by post hoc Bonferroni correction for ST heights over time. Raw microarray data were analyzed using Partek Express software (Partek, St Louis, MO). Ingenuity Systems iReport software (Qiagen, Hilden, Germany) was used to compare raw microarray data and for pathway and network analysis independently, using default settings. Unless otherwise described, the Kolmogorov–Smirnov test was used to verify the assumption of normal distribution. Statistical significance was assumed with P<0.05. Detailed methods and associated references are described in the Methods in the Data Supplement.

**Results**

**Kcne2 Deletion Causes Maternal Genotype-Dependent and Genotype-Independent Cardiac Remodeling.**

Kcne2–/– pups of Kcne2–/– dams exhibit much more substantial cardiac hypertrophy at P21 than Kcne2–/– pups of Kcne2–/– dams do (Figure 1A), primarily arising from complications of maternal hypothyroidism during gestation and lactation. Specifically, we previously demonstrated that thyroid KCNQ1-KCNE2 potassium channels are required for optimal thyroid hormone biosynthesis; Kcne2 deletion causes hypothyroidism during gestation and lactation in mice but not in nonpregnant/lactating adult mice <12 months of age. The most profound consequences of this are observed preweaning in the pups of Kcne2–/– dams, which exhibit alopecia, stunted growth, and cardiac hypertrophy. These manifestations are closely associated with maternal hypothyroidism because they can be largely prevented by thyroid hormone treatment of the dam during gestation and lactation or by surrogacy with wild-type dams at P1. Conversely, these symptoms can be initiated in wild-type pups by surrogacy with Kcne2–/– dams. One of the main mechanistic explanations for these effects is that maternal hypothyroidism impairs milk ejection.

Here, global whole-transcript microarray analysis revealed differential atrial and ventricular gene network remodeling dependent on pup and maternal Kcne2 genotype (Figure 1B); for all differentially expressed genes, see the Data Supplement. Surprisingly, gene interaction hierarchy analysis of predicted differentially expressed gene interaction networks uncovered AGT, which encodes angiotensinogen, as the most common predicted upstream effector in pup genotype-dependent cardiac remodeling (Figure 1C–1F). Dam genotype-dependent, pup genotype-independent predicted pathways were in contrast, headed by PPARG and PNPLA2 in atria (Figure 1C and 1D) and TLR4 in the ventricles (Figure 1E and 1F); the latter finding is consistent with the previously reported role for this gene in ventricular hypertrophy.

**Kcne2 Deletion Elevates Serum Angiotensin II and Causes Adrenal Dysfunction and Lipid Accumulation.**

Angiotensinogen is cleaved by renin (in response to decreased renal perfusion) to generate angiotensin I, which is converted by angiotensin-converting enzyme to angiotensin II. Cardiac myocyte angiotensinogen expression is increased in an auto-crine loop by angiotensin II. Accordingly here we found that serum angiotensin II concentration in Kcne2–/– mice was twice that of Kcne2+/– littermates (n=10–14; P=0.012; Figure 2A). However, serum aldosterone, which is typically released by the adrenal gland upon angiotensin II stimulation, was unaltered (n=9; P=0.95; Figure 2B). The adrenal unresponsiveness could not be explained by disruption of a direct adrenal role of Kcne2 because it is not expressed in the adrenal glands (Figure 2C). We detected Kcne2 in the lung (Figure 2C), the primary source of angiotensin-converting enzyme, but Kcne2 deletion reduced pulmonary angiotensin-converting enzyme expression (Figure 2D). This is consistent with activation of feedback mechanisms to reduce angiotensin I to II conversion and suggests against the possibility that pulmonary Kcne2 deficiency increased serum angiotensin II by directly increasing angiotensin-converting enzyme expression in the lung.

Microarray analysis of the adrenal transcriptome (Figure 2E) indicated predominantly downregulation, in adult Kcne2–/– mouse adrenals, of expression of genes and gene networks, with PPARG as the most common upstream element (Figure 2F), associated with lipid metabolism and uptake (for all differentially expressed transcripts, see Data Supplement), glucose metabolism disorders and insulin resistance (Figure 2G), and metabolic syndrome (Figure 2H). The data suggested a compensatory response to hyperstimulation or aberrant adrenal lipid accumulation, a diabetic/ hyperlipidemic environment, and a defect in steroidogenesis, in Kcne2–/– adrenals.

Adrenal glands of Kcne2–/– mice did not exhibit macroscopic hypertrophy as would be expected in primary hyperaldosteronism, but Kcne2 deletion caused adrenal cortex vacuolation and lipid accumulation consistent with chronic hyperstimulation as occurs with chronic stimulation by angiotensin II (Figure 2I), also consistent with diabetic dyslipidemia.

**Kcne2 Deletion Causes Dyslipidemia, Diabetes Mellitus, and Anemia.**

Examining potential causes of the adrenal atrophy, we discovered that Kcne2 deletion causes hypercholesterolemia, raising free low-density lipoprotein cholesterol but not altering free high-density lipoprotein cholesterol or cholesteryl esters (Figure 3A). Strikingly, Kcne2–/– mice, but not their Kcne2+/– littermates, also develop diabetes mellitus, characterized by fasting hypoglycemia (Figure 3B) and impaired glucose tolerance (Figure 3C and 3D). We detected Kcne2 expression in mouse pancreas, suggesting that Kcne2 deletion may pathologically impair a pancreatic K+ current (Figure 3E).

In addition, after observing that Kcne2–/– mice often exhibit paler extremities than their Kcne2+/– littermates (Figure 3F), we also found that Kcne2–/– mice exhibit splenomegaly (4.2-fold increased mean body mass-corrected spleen mass; Figure 3G and 3H). One likely cause for these
2 observations is anemia. *Kcne2* deletion causes achlorhydria because the KCNQ1-KCNE2 K⁺ channel is expressed on the apical membrane of parietal cells and is required for gastric acid secretion.9 One consequence of achlorhydria is anemia because of inadequate iron absorption and vitamin B12 deficiency. Here, we quantified blood cell parameters and found that *Kcne2*⁺⁻ mice exhibit anisocytosis and microcytic anemia, specific hallmarks of iron-deficiency anemia; the lowered mean corpuscular hemoglobin was also consistent with this (Figure 3I).

Anemia, hypercholesterolemia, and diabetes mellitus all diminish myocardial oxygen supply, predispose to chronic myocardial ischemia,15 and are associated with increased risk of human SCD.16–18 In addition, fasting-induced hypoglycemia is considered an important risk factor for diabetic SCD in the form of dead-in-bed syndrome.19,20
Kcne2 Deletion Causes Hyperkalemia and QTc Prolongation

In normal circumstances, hyperkalemia stimulates the renin–angiotensin–aldosterone system, elevating angiotensin II and also aldosterone, increasing sodium reabsorption and potassium excretion by the kidneys, increasing blood pressure. Here, we found that Kcne2–/– mice show significant hyperkalemia (8.2±0.44 mmol/L K⁺; n=23) when compared with Kcne2+/+ mice (6.4±0.23 mmol/L K⁺; n=40; P<0.01; Figure 4A). Chronic hyperkalemia would be expected to elevate serum angiotensin II chronically and, in combination with other destructive influences on the adrenal (Figures 2 and 3), lead to impaired aldosterone production (Figure 2B) and inability to restore normokalemia. Interestingly, the high angiotensin II did not elevate blood pressure in Kcne2–/– mice, which was slightly lower than that of age-matched Kcne2+/+ littermates (Figure I in the Data Supplement), possibly reflecting an inability to excrete sufficient K⁺.

KCNQ1-KCNE2 K⁺ channels generate K⁺ recycling currents in gastric parietal cells and other epithelia. KCNE2, in parietal cell apical membrane complexes with KCNQ1, is required to return to the stomach lumen K⁺ ions brought into the cell by the H⁺/K⁺ATPase during gastric acid secretion.9,21 We previously found that Kcne2 deletion results in aberrant parietal cell basolateral targeting of KCNQ1 in complexes with pathologically upregulated KCNE3.10 This could provide a gastric short-circuit current funnelling K⁺ from the stomach through to the blood, robbing the stomach lumen of K⁺ (consistent with the observed achlorhydria in Kcne2–/– mice) and potentially increasing serum K⁺ (Figure 4B). To test this hypothesis, we first quantified serum K⁺ in Kcne3–/– and double-knockout Kcne2–/– Kcne3–/– mice. Although Kcne3–/– mice were normokalemic (n=18), deletion of both Kcne2 and Kcne3 genes caused a statistically nonsignificant trend toward hypokalemia (serum K⁺ of 5.1±0.46 mmol/L; n=24; P>0.05 versus wild-type). Consistent with this hypothesis, although...
not achieving statistical significance when comparing mean slopes between genotypes, using an ex vivo stomach preparation, we found that the \textit{Kcne2}–/– stomach mucosa exhibits a trend toward an increased luminal-to-serosal K+ flux when compared with either wild-type or double-knockout \textit{Kcne2}–/–, \textit{Kcne3}–/– mucosae, as predicted by our model (Figure 4A–4C).

The findings (Figures 1–4) present a picture of a single gene deletion causing interactive disruption of multiple epithelia and consequent cardiac gene network remodeling, creating a multifactorial systemic substrate comprising a panoply of known risk factors for SCD. We next examined potential electrical substrates. Hyperkalemia depolarizes cardiac myocyte membranes, counteracting the effects of repolarizing K+ currents, and is in itself proarrhythmic.\textsuperscript{22} In the mouse ventricular myocardium, \textit{Kcne2} regulates \textit{I}_{\text{to}} and \textit{I}_{\text{K,slow}} by forming complexes with, and augmenting currents through, the Kv4.2 and Kv1.5 Kv α subunits, respectively.\textsuperscript{23} We previously demonstrated that \textit{Kcne2} deletion reduces ventricular myocyte \textit{I}_{\text{to}} and \textit{I}_{\text{K,slow}} density in young adult (3–4 months old) mice. Although it does not alter baseline QT or QTc interval, it compromises ventricular myocyte repolarization sufficiently to predispose mice to drug-induced QTc prolongation.\textsuperscript{23}

Here, modeling in silico the effects on ventricular action potentials of the hyperkalemia in \textit{Kcne2}–/– mice, the hyperkalemia was found to be a significant component in prolonging action potential duration and was predicted to depolarize the resting membrane potential of myocytes in both the ventricular apex and septum by 6.1 mV (from –78.7 to –72.6 mV; Figure 4D and 4E). Next, we recapitulated the previously observed lack of effects on baseline ventricular repolarization in 4m-old mice,\textsuperscript{23} but examination of older mice (7m old) revealed an abnormally high-amplitude T wave and a striking delay in returning of the T wave to baseline (quantified as an 85% increase in heart rate–corrected QT interval (QTc) in \textit{Kcne2}–/– mice when compared with age-matched wild-type littermates (n=8–15; Figure 4G). The age-dependent QTc lengthening cannot readily be explained by a pure electric defect caused solely by loss of KCNE2 from ventricular ion channels and instead is consistent with a more complex pathogenesis involving chronic pathological changes such as...
are observed in the cardiac remodeling associated with diabetes mellitus and hypercholesterolemia in human subjects and mouse models, the molecular underpinnings of which can be detected as early as P21 in $K_{CNE2}^{-/-}$ mice (Figure 1).

**Kcne2 Deletion Generates an Electric Substrate for Postischemic SCD**

The systemic defects reported above would be predicted to generate myocardial ischemia in aging mice or humans and, in combination with the profound QTc prolongation (Figure 4G), would be expected to predispose to dangerous ventricular tachyarrhythmias (VTs). $K_{CNE2}^{-/-}$ mice from heterozygous crosses exhibit hypothyroidism and cardiac hypertrophy at 12 to 15 months, complicating attempts to correlate specific systemic abnormalities with cardiac events at these advanced ages. Therefore, here we instead standardized ischemia using surgery in 7m-old female mice from $K_{CNE2}^{+/+}$ crosses that are euthyroid and do not yet exhibit cardiac hypertrophy (Figure II in the Data Supplement) to compare the role of electric and other perturbations caused by $K_{CNE2}^{-/-}$ deletion in an ischemic context directly but without the pathological structural remodeling that occurs in these mice after 12 months because of hypothyroidism.

ECG analysis during a 10-minute left anterior descending coronary artery ligation revealed similar ST elevation in 7m-old
Kcne2+/− mice when compared with age-matched Kcne2+/+ littermates (Figure 5A and 5B); myocardial extracellular signal-regulated kinase activation measured in hearts isolated after 20 minutes of reperfusion suggested similar ischemic insult in both genotypes (Figure 5C). Although two thirds of Kcne2+/− mice remained in sinus rhythm throughout reperfusion and the remainder exhibited monomorphic VT returning to sinus rhythm within 20 minutes, only 2/13 Kcne2−/− mice remained in sinus rhythm, the rest exhibiting VT. Most strikingly, in 4/13 Kcne2−/− mice, monomorphic VT degenerated into polymorphic VT, ventricular fibrillation, and SCD; this was not observed in Kcne2+/− mice (Figure 5D and 5E). In addition, 2 Kcne2+/− mice died during the ligation period, with ECGs consistent with acute heart failure (no fibrillation). These are not included in the analysis in Figure 5 because they did not reach the reperfusion stage.

**Kcne2 Deletion Causes Fasting-Induced Ischemia, AV Block, and SCD**

Because of the heightened risk of SCD in hypoglycemic diabetics, we repeated the ECG studies in a further cohort of 7m-old female mice that had been fasted overnight. Strikingly, fasted Kcne2+/− mice, but not Kcne2+/+ mice, showed marked ST segment depression (Figure 6A and 6B), a hallmark of myocardial ischemia (an additional Kcne2−/− mouse, but no Kcne2−/− mice, died suddenly during transfer from its cage before an ECG could be recorded). The acute ischemia was caused by overnight fasting because ST depression was not observed in fed Kcne2−/− mice (Figure 5A and 5B). Suggesting against a structural defect, cardiac hypertrophy was not detectable (Figure 6C), contrary to what is observed in Kcne2−/− mice at 12 to 15 months.11 Overnight fasting further increased serum [K+] in Kcne2−/− but not in Kcne2+/− mice (Figure 6D); this would be predicted to prolong the QTc further, but accurate QTc quantification was not possible because of the ST depression.

Although overnight fasting did not alter the outcome of coronary artery ligation in Kcne2+/− mice (Figure 6E and 6F), overnight-fasted Kcne2−/− mice showed significantly depressed ST height when compared with that of Kcne2+/− mice throughout ligation (Figure 6F), despite exhibiting equivalent cardiac extracellular signal-regulated kinase activation (Figure 6G). Kcne2−/− mice also developed severe AV block, which was not observed in the absence of fasting (Figure 6E, 6H, and 6I). This severity of AV block would strongly predispose to syncope and SCD in a human subject.27 Notably, hyperkalemia, which was markedly exacerbated here in Kcne2−/− mice by overnight fasting, is associated with potentially lethal AV block, particularly in human subjects with existing factors causing myocardial ischemia.28 Interestingly, hypoglycemia more typically results in hypokalemia, itself arrhythmogenic,29 highlighting the degree of dysregulation occurring in multiple homeostatic systems because of Kcne2 deletion. Indeed, Kcne2 deletion seems to disrupt the renin–angiotensin–aldosterone system to the extent that normal homeostatic mechanisms are lost, probably because of chronic hyperkalemia in combination with diabetic dyslipidemia.

Summing all observed mortality in 7m-old mice immediately before or during ischemia/reperfusion experiments (30-minute duration) in this study, we observed a significant predisposition to sudden death in Kcne2+/− mice (8/23 Kcne2−/− mice versus 0/16 Kcne2+/+ mice; P=0.008 by 1-tailed Fisher exact test).

**Figure 5.** Kcne2 deletion predisposes to sudden cardiac death (SCD) early in reperfusion. **A,** Representative ECGs recorded during coronary artery ligation of 7m-old female Kcne2+/+ and Kcne2−/− mice (n=8–12). **B,** Mean ST heights from traces as in **A,** P<0.05 between genotypes at all time points (n=8–12). Groups were not significantly different (by repeated measures ANOVA). **C,** Left, Western blots of ventricular phosphorylated extracellular signal-regulated kinase (pERK) and total extracellular signal-regulated kinase (tERK) from mice as in **B,** isolated from control (nonoperated) mice or after ischemia/reperfusion (surgery); right, pERK/tERK protein band density measured from blots on left (n=4). **P<0.01,** **P<0.001 for control (C) vs surgery (S).** **D,** Cardiac arrhythmia incidence and mortality during postischemia reperfusion in 7m-old female Kcne2+/+ (n=9) and Kcne2−/− (n=13) mice. Numbers of animals per category are indicated in parentheses. **P<0.05 between genotypes.** **E,** Exemplar ECGs of the most severe arrhythmias by genotype, recorded during postcoronary artery ligation reperfusion of 7m-old female Kcne2+/+ and Kcne2−/− mice (n=9 to 13). Kcne2−/− mice always returned to sinus rhythm, unlike Kcne2−/− mice. PVT indicates polymorphic VT; Sinus, remained in sinus rhythm; VF, ventricular fibrillation; VT, ventricular tachycardia.
**Discussion**

The current model for monogenic arrhythmogenesis (Figure 6J, i) relies heavily on a myocentric mechanism, but given the new findings for KCNE2, this may be too simplistic a model, which ignores the extracardiac effects of disrupting arrhythmia-susceptibility genes, the large majority of which are also expressed outside the heart. Although extrapolation of mouse models to human disease must be conducted with extreme caution, 35% of *Kcne2*−/− mice in the present study succumbed to sudden death immediately before, during, or after surgery to induce transient ischemia, supporting the hypothesis that more subtle single-allele effects of human KCNE2 mutations could be significant when considering large populations. We suggest a new model for KCNE2-linked arrhythmogenesis in mice, elements of which may be applicable to some human arrhythmias (Figure 6J, ii), and aspects of...
which are likely to apply to other broadly expressed arrhythmia-susceptibility genes, especially KCNQ1, which partners KCNE1, 2, and 3 in a variety of epithelial cell types.7

KCNQ1 gene variants are strongly linked to type II diabetes mellitus,30 yet the mechanism has not been delineated. Nor has a dissection of the potential arrhythmogenic contribution of KCNQ1-linked diabetes mellitus in humans, or systemic effects of Kenq1 deletion in mice, been reported, to our knowledge (although Ken1 disruption has been shown to affect K+ homeostasis in mice, with the suggestion that this could contribute to arrhythmogenesis).31 However, a recent study showed that hypergastrinemia, a marker of parietal cell dysfunction, correlated well with QT prolongation in KCNQ1-linked Jervell and Lange–Nielsen Syndrome.32 Interestingly, we previously found that even single-allele disruption of Ken2 causes achlorhydria in mice, intermediate between wild-type mice and the achlorhydria we found in Ken2−/− mice.8 Furthermore, we previously found that the gastric effects of Ken2 deletion worsened with age,6 providing indirect support for the hypothesis that extracardiac effects of Ken2 disruption could contribute to age-dependent worsening of the cardiac phenotype. KCNQ1 and KCNE1 are also reportedly expressed in neuronal networks and the brain stem, and KCNQ1-linked seizures suggested as being arrhythmogenic, potentially explaining some cases of sudden unexplained death in epilepsy33, an analogous situation was recently reported for Rett syndrome.34

Diabetes mellitus, hypercholesterolemia, and anemia all ultimately reduce myocardial oxygen supply, leading to myocardial ischemia, and are recognized risk factors in SCD, especially in combination. In addition, nocturnal hypoglycemia in diabetics predisposes to SCD; cardiac events in overnight-fasted Ken2−/− mice reported here provide insights into the type of catastrophic cardiac events that might lead to the dead-in-bed syndrome form of SCD in a hypoglycemic diabetic. Particularly striking is that a single gene disruption provides the systemic substrate (diabetes mellitus, hypercholesterolemia, elevated angiotensin II), the electric substrate (impaired ventricular repolarization caused by direct ventricular channel subunit loss, hyperkalemia, and probably remodeling in response to the elements of the ischemic substrate), and also a trigger (hypoglycemia, causing in this case acute ischemia, acute exacerbation of hyperkalemia, and probably AV block).

Although results obtained from knockout mice cannot be directly extrapolated to explain human disease states, the AV block observed in fasted Ken2−/− mice suggests parallels to arrhythmogenesis mechanisms linked to increased mortality in large-scale studies of diabetes mellitus35 and thought to underlie nocturnal SCD in nondiabetics.36 ST depression (as we observed in fasted Ken2−/− mice) was also observed in type 2 diabetics in whom hypoglycemia was induced by insulin infusion.37 The general consensus is that there must be an underlying genetic component involving a ventricular ion channel in dead-in-bed syndrome to provide an electric substrate and reduce the probability of a triggering event. Strategies to recapitulate aspects of human cardiac arrhythmogenesis. This could include enhancing the ability to recognize individuals with an inherited predisposition to SCD, particularly in the context of diabetes mellitus, and to design more effective avoidance, management, and therapy strategies that lessen the overall SCD substrate and reduce the probability of a triggering event. Strategies might involve routine genetic screening of diabetics for pathological single-nucleotide polymorphisms in known monogenic arrhythmia genes (particularly KCNQ1 and KCNE2), especially before embarking on aggressive glycemic control regimens.

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Disclosures
None.

References

CLINICAL PERSPECTIVE

Sudden cardiac death (SCD) is a leading cause of mortality, thought to require both an ischemic and electric substrate and perhaps an additional trigger. Recognizing genetic and environmental risk factors that predispose to SCD will reduce mortality by facilitating early prevention and therapeutic strategies. Genetic variants within genes encoding ion channel subunits (including KCNE2) are known to underlie ventricular arrhythmias that can provide the electric substrate for SCD. The established paradigm is that these gene mutations directly impair the function of ventricular myocyte ion channels, and that other, unrelated substrates or triggers superimposed on this electric substrate can lead to SCD. We now show in a mouse model that genetic disruption in the KCNE2 gene causes a multisytem syndrome that can provide both the electric and ischemic substrates, and the trigger, for SCD. In human populations, polymorphisms in KCNE2 and other ion channel genes predispose to inherited and drug-induced long-QT syndrome, but extracardiacopathologies arising from the same sequence variants, and their potential role in cardiac and extracardiac diseases, have been largely overlooked. Indeed, polymorphisms in the human KCNQ1 locus, which encodes a potassium channel regulated by KCNE2, are strongly linked to both diabetes mellitus and long-QT syndrome, but whether superimposition of multiple KCNQ1-linked disorders predisposes to SCD is not known. Our findings suggest that consideration of the extracardiac pathologies potentially caused by mutations in known arrhythmia genes will lead to a fuller understanding of inherited predisposition to SCD and ultimately to improved early detection and prevention strategies.