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(54) Title: METHODS FOR DETECTING BRUGADA SYNDROME

(57) Abstract: The invention provides a method of identifying a presence of Brugada Syndrome in a subject. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant which encodes a truncated SCN5A protein, (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) identifying the presence of Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.



METHODS FOR DETECTING BRUGADA SYNDROME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. 61/786,882, filed March 15, 2013, the contents of which are incorporated herein by reference in its entirety.

STATEMENT OF U.S. GOVERNMENTAL INTEREST

[0002] This invention was made with U.S. government support under National Institutes of Health (NIH) Grant No. R01 HL085558, R01 HL072742, R01 HL106592, R01 HL104025, R01 HL 085369, R32 HL072742, and P01 HL058000. The government has certain rights in this invention.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0003] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: 2 megabytes ASCII (Text) file named "47508A_SeqListing.txt," created on March 11, 2014."

BACKGROUND

[0004] Brugada Syndrome (Phenotype MIM #601144; also known as BRGDA1, Right Bundle Branch Block, ST Segment Elevation, Sudden Death Syndrome, Sudden Unexplained Nocturnal Death Syndrome; SUNDS) is an inherited sudden death condition caused mostly by reductions in cardiac sodium current. According to OMIM, it is characterized by an ST-segment elevation in the right precordial electrocardiogram leads (so-called type 1 ECG) and a high incidence of sudden death in patients with structurally normal hearts. The syndrome typically manifests during adulthood, with a mean age of sudden death of 41 +/- 15 years, but occurs in infants and children (summary by Antzelevitch et al., *Circulation* 111: 659-670 (2005)). The exact prevalence of Brugada syndrome is unknown, although it is estimated to affect 5 in 10,000 people worldwide and approximately 155,000 people in the United States. While relatively rare, Brugada Syndrome is a major cause of sudden unexplained death syndrome (SUDS) and is the most common cause of sudden death in young men without known underlying cardiac disease. This condition occurs much more frequently in people of Asian ancestry, particularly in Japanese and Southeast Asian populations. Although Brugada syndrome affects both men and women, the condition appears to be 8 to

10 times more common in men. Researchers suspect that testosterone, a sex hormone present at much higher levels in men, may be responsible for this difference.

[0005] Brugada syndrome is usually diagnosed by an electrocardiogram (ECG) and physical examination. In a report from the second consensus conference on Brugada syndrome, Antzelevitch et al. (2005), *supra* stated that a definitive diagnosis can be made when a type 1 ST-segment elevation is observed in greater than 1 right precordial lead (V1 to V3) in the presence or absence of a sodium channel-blocking agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at less than 45 years of age, coved-type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration. They noted that confounding factors that could account for the ECG abnormality or syncope, including arrhythmogenic right ventricular dysplasia should be excluded.

[0006] Evidence shows that Brugada syndrome-1 (BRGDA1) is caused by heterozygous mutation in the SCN5A gene on chromosome 3p22. Related syndromes are also caused by mutations but in genes other than the SCN5A gene. For example, Brugada syndrome-2 (Phenotype MIM #611777) is caused by mutation in the GPD1L gene. Brugada syndrome-3 (Phenotype MIM #611875) and Brugada syndrome-4 (Phenotype MIM #611876), the phenotypes of which include a shortened QT interval on ECG, are caused by mutation in the CACNA1C and CACNB2 genes, respectively. Brugada syndrome-5 (Phenotype MIM #612838) is caused by mutation in the SCN1B gene. Brugada syndrome-6 (Phenotype MIM #613119) is caused by mutation in the KCNE3 gene. Brugada syndrome-7 (Phenotype MIM #613120) is caused by mutation in the SCN3B gene. Brugada syndrome-8 (Phenotype MIM #613123) is caused by mutation in the HCN4 gene. Accordingly, genetic testing may be used to confirm a clinical diagnosis of Brugada Syndrome.

[0007] However, approximately 80% of patients with Brugada Syndrome do not have a mutation in one of the genes known to cause Brugada Syndrome. Even for the ~20% who can be diagnosed through genetic testing, the cost of the test is about \$4000. In view of the foregoing, there is a need for a more time-, energy-, and cost-efficient means for diagnosing Brugada Syndrome.

SUMMARY

[0008] Based at least in part on the data presented herein for the first time, blood samples obtained from patients diagnosed with Brugada Syndrome exhibited a decreased level of SCN5A messenger RNA (mRNA), including full-length SCN5A mRNA and SCN5A splice variant mRNA (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). An increased level of mRNA encoded by SCN5A splicing factor genes and a decreased level of mRNA encoded by a gene of a major component of the unfolded protein response (UPR) were also observed in the blood samples of the Brugada Syndrome patients.

[0009] Accordingly, the invention provides a method of identifying a presence of Brugada Syndrome in a subject. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) identifying the presence of Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0010] The invention also provides a method of determining a subject's need for therapy for Brugada Syndrome (BS). In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) determining the subject as needing therapy for Brugada Syndrome, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0011] Further provided is a method of treating a subject for Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a

SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) providing a therapy for Brugada Syndrome to the subject when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0012] In exemplary embodiments of the method of treating a subject for Brugada Syndrome, the subject is one which has been analyzed for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). In exemplary aspects, a biological sample obtained from the subject was analyzed for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). In such embodiments, the method comprises the step of providing a therapy for Brugada Syndrome to the subject exhibiting a reduced level of (a), (b), and/or (d), relative to a control level, and/or an increased level of (c), relative to a control level.

[0013] Undiagnosed and/or untreated Brugada Syndrome can lead to syncope and sudden cardiac death. The invention furthermore provides a method of reducing risk for syncope and/or sudden cardiac death in a subject. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) providing a therapy for Brugada Syndrome to the subject when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level. In exemplary embodiments, the subject is one which has been analyzed for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing

factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). In exemplary aspects, a biological sample obtained from the subject was analyzed for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). In such embodiments, the method comprises the step of providing a therapy for Brugada Syndrome to the subject exhibiting a reduced level of (a), (b), and/or (d), relative to a control level, and/or an increased level of (c), relative to a control level.

[0014] The invention additionally provides a method for monitoring progression or regression of Brugada Syndrome in a subject diagnosed with Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject at a timepoint occurring before the time at which the second biological sample is obtained from the subject, and (iii) determining progression of the Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining regression of the Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[0015] The invention furthermore provides methods of monitoring a subject's risk for syncope and/or sudden cardiac death. In exemplary embodiments, the method comprises the

steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject at a timepoint occurring before the time at which the second biological sample is obtained from the subject, and (iii) determining an increased risk for syncope and/or sudden cardiac death in the subject, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining a decreased risk for syncope and/or sudden cardiac death in the subject, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[0016] Further provided are methods of determining the efficacy of a test compound or test therapy for treating Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein) (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject before administration of the test compound or

test therapy and the second biological sample is obtained from the subject after administration of the test compound or test therapy, and (iii) determining the test compound or test therapy as ineffective for treating Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining the test compound or test therapy as effective for treating Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[0017] The invention provides related kits for diagnosing Brugada Syndrome. In exemplary embodiments, the kit comprises a binding agent which binds to a gene product encoded by the *PERK* gene, a binding agent which binds to a full-length a gene product encoded by the *SCN5A* gene, a binding agent which binds to a gene product encoded by the *Luc7A* gene, a binding agent which binds to a gene product encoded by the *RBM25* gene, a binding agent which binds to a gene product encoded by the *PRP40* gene, a binding agent which binds to an *SCN5A* E28C splice variant mRNA transcript, or a protein product encoded thereby, and/or a binding agent which binds to an *SCN5A* E28D splice variant mRNA transcript, or a protein product encoded thereby. In exemplary aspects, the gene product is an mRNA and the binding agent is a nucleic acid probe. In exemplary aspects, the gene product is protein and the binding agent is an antibody or an antigen-binding fragment thereof.

[0018] Also provided are systems, computer-readable storage media, and methods implemented by a computer processor which can be used in methods described herein. In exemplary aspects, the inventive systems, computer-readable storage media, methods implemented by a processor in a computer, kits, or a combination thereof, each of which described below, may be utilized in any of the methods of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 is a schematic representation of the splice variants identified in the 5' end of the human *SCN5A* gene. The map shows the genomic structure of *SCN5A* with untranslated (open bars) or translated (closed bars) transcribed sequences and nontranscribed sequences (lines). Splicing patterns for each of the three exon 1 isoforms are identified.

[0020] Figure 2 provides cDNA sequences for E1A , E1B1, E1B2, E1B3, E1B4, E2A, E2B1 and E2B2.

[0021] Figure 3 is a schematic representation of the splice variants identified in the 3' end of the human SCN5A gene. Above the map shows the genomic structure of SCN5A with untranslated (open bars) or translated (closed bars) transcribed sequences and nontranscribed sequences (lines). Splicing patterns for each of the four exon 28 isoforms are identified.

[0022] Figure 4 provides cDNA sequences for E28A (Figure 4A and 4B), E28B (Figure 4C), E28C (Figure 4D), and E28D (Figure 4E).

[0023] Figures 5 and 6 demonstrate a correlation of cardiac tissue and WBC mRNA abundances of SCN5A variants VC and VD. Figure 5 shows tissue levels of the variant VC as a function of WBC levels measured in the same patient. Figure 6 shows tissue levels of the variant VD as a function of WBC levels measured in the same patient. The best-fit linear regression is displayed as a solid black line. Grey lines represent the 95% confidence intervals.

[0024] Figures 7 to 13 represent a collection of graphs depicting the relative level of full-length mRNA encoded by the SCN5A gene (Figure 7), mRNA encoded by the SCN5A Variant E28C (Figure 8), mRNA encoded by the SCN5A Variant E28D (Figure 9), mRNA encoded by the RBM25 gene (Figure 10), mRNA encoded by the Luc7A gene (Figure 11), mRNA encoded by the PRP40 gene (Figure 12), and mRNA encoded by the PERK gene (Figure 13) of blood samples obtained from patients diagnosed with Brugada Syndrome as described in Example 2. Each control level was set to 1 and the level of mRNA was relative to the control level.

[0025] Figure 14 is a schematic of an exemplary embodiment 101 of a system 100 for assessing a subject's need for an implanted cardiac defibrillator (ICD).

[0026] Figure 15 represents a flow chart depicting an exemplary computer-readable method resulting in an output diagnosis of Brugada Syndrome.

DETAILED DESCRIPTION

[0027] *Method of identifying presence of Brugada Syndrome*

[0028] The invention provides a method of identifying a presence of Brugada Syndrome in a subject. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA

(mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) identifying the presence of Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0029] *Method of determining need for therapy for Brugada Syndrome*

[0030] The invention also provides a method of determining a subject's need for therapy for Brugada Syndrome (BS). In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) determining the subject as needing therapy for Brugada Syndrome, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0031] *Method of monitoring Brugada Syndrome*

[0032] The invention additionally provides a method for monitoring progression or regression of Brugada Syndrome in a subject diagnosed with Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject at a timepoint occurring before the time at which the second biological sample is

obtained from the subject, and (iii) determining progression of the Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining regression of the Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[0033] The invention additionally provides a method for monitoring a subject's risk for Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject at a timepoint occurring before the time at which the second biological sample is obtained from the subject, and (iii) determining the subject has having an increased risk for Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining the subject as having a decreased risk for Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[0034] *Analysis of biological samples*

[0035] In exemplary embodiments, the methods of the invention comprise analyzing a biological sample obtained from a subject for (a) a level of full-length messenger RNA

(mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR).

[0036] In exemplary aspects, the biological sample is analyzed for (a), (b), (c), and/or (d) by measuring the level, concentration or amount of said mRNA in the biological sample. In this regard, the methods of the invention may comprise measuring (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR) of the biological sample. Levels of mRNA may be measured by any technique known in the art, including but not limited to northern blotting or reverse transcription followed by real-time quantitative PCR (RT-qPCR). Alternatively, "tag based" technologies, such as Serial analysis of gene expression (SAGE) and RNA-Seq, may be carried out to provide a relative measure of the cellular concentration of different mRNAs.

[0037] In alternative or additional aspects, the biological sample is analyzed for (a), (b), (c), and/or (d) by measuring the level, concentration or amount of the protein product encoded by the mRNA in the biological sample. In this regard, the methods of the invention may comprise analyzing a biological sample obtained from a subject for (a) a level of a protein product encoded by a full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of a protein product encoded by an mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of a protein product encoded by mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of a protein product encoded by mRNA encoded by a gene of the unfolded protein response (UPR). In some aspects, the level, concentration or amount of protein product is determined by an immunoassay, e.g., Western blotting, an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay (RIA), an immunohistochemical assay, which methods are known in the art.

[0038] In some aspects, the level of protein product is represented by a level of the protein product's biological activity, e.g., enzymatic activity. In exemplary aspects, the protein level is reflected by the levels of the substrate or product of the enzymatic reaction catalyzed by the

protein product. Methods of assaying for the level of biological activity, e.g., enzymatic activity, are known in the art.

[0039] In some aspects, the protein level is represented by the level of biological activity of a related protein, e.g., a protein which acts upstream or downstream of the marker. For example, if the marker is a phosphorylated protein in the active state, then, in some embodiments, the marker level is represented by the activity level of the kinase which phosphorylates the marker. In other aspects, if the marker is a transcription factor which activates expression of a gene, then, in some embodiments, the marker level is represented by the expression levels of the gene activated by the marker.

[0040] *SCN5A transcripts*

[0041] As described herein and in the art (e.g., U.S. Application Publication No. 2007/0212723 A1), analysis in or near the promoter and 5' and 3' untranslated regions (UTRs) of the *SCN5A* gene led to identification of multiple specific 5' and 3' mRNA splice variants. As shown in Figures 1 to 4, the splice variants include Exon 1 splice variants: E1B1 (SEQ ID NO. 1), E1B2 (SEQ ID NO. 2), E1B3 (SEQ ID NO. 3), and E1B4 (SEQ ID NO. 4), and also include Exon 2 splice variants: E2B1 (SEQ ID NO. 5), E2B2 (SEQ ID NO. 6), and furthermore include Exon 28 splice variants E28B (SEQ ID NO. 7), E28C (SEQ ID NO. 8), or E28D (SEQ ID NO. 9).

[0042] The E1B1, E1B2, E1B3, E1B4, E2B1, and E2B2 splice variants are from the 5' region, the locations of which in the *SCN5A* gene and mRNA are depicted in FIG. 1. The nucleic acid sequences for E1B1, E1B2, E1B3, E1B4, E2B1, and E2B2 are shown in FIG. 2. E1A (SEQ ID NO. 10) is the wild-type (or full-length) isoform in and/or near the 5'UTR of exon 1, while E1B1, E1B2, E1B3, E1B4 are its various spliced (or truncated) variants. Similarly, E2A (SEQ ID NO. 11) is the wild-type (full-length) isoform in and/or near the 5'UTR of exon 2, while E2B1, and E2B2 are its various variants.

[0043] The E28B, E28C, or E28D splice variants are from or near the 3' untranslated region, the locations of which in the *SCN5A* mRNA are depicted in FIG. 3. The nucleic acid sequences for E28B, E28C, and E28D are set forth in SEQ ID NOs: 7-9, respectively. Each of E28B, E28C, and E28D is a truncated splice variant encoding shortened, dysfunctional channels. Both E28B and E28C contains untranslated and translated regions while E28D contains only translated region of exon 28. The physiological significance of the E28B, E28C and E28D splice variants is supported by a premature stop codon in exon 28 of one of

the two SCN5A alleles, resulting in an 86% reduction in the Na⁺ current (Shang et al., *Circ. Res.*, 101:1146-1154, 2007).

[0044] The E28A splice variant is another isoform of the 3' region of SCN5A Exon 28. There are two isoforms of the E28A: E28A-short (E28A-S) (SEQ ID NO. 12) and E28A-long (E28A-L) (SEQ ID NO. 13). Both isoforms of E28A contains 1239 base pairs in the translated region. The difference between E28-L and E28-S resides in the UTR where E28A-L contains 2295 base pairs of the 3'UTR, while E28A-S contains 834 base pairs of the 3'UTR. E28A-S contains only the first 834 base pairs of the 3'UTR. E28A-L represents the wild-type (WT) isoform. For purposes herein, outside of this paragraph, recitation of "E28A" refers to E28A-S, and E28A-L will be referred to as wild-type or WT.

[0045] As used herein, the term "truncated SCN5A Exon 28 transcript" refers to a transcript comprising a shortened or truncated translated region of Exon 28 of the SCN5A gene. In exemplary aspects, the truncated SCN5A Exon 28 transcript is a transcript comprising an E28B transcript, E28C transcript, or E28D transcript, which may be referred to herein as "E28B," "E28C," and "E28D," respectively. In exemplary aspects, the truncated SCN5A Exon 28 transcript is a transcript comprising one of an E28C transcript or E28D transcript.

[0046] As used herein, the term "full length SCN5A Exon 28 transcript" refers to a transcript comprising the full length translated region of Exon 28 of the SCN5A gene. In exemplary aspects, the full length SCN5A Exon 28 transcript is a WT SCN5A Exon 28 transcript. In exemplary aspects, the full length SCN5A Exon 28 transcript is a spliced transcript which is shortened or truncated, as compared to WT SCN5A Exon 28 transcript, yet the spliced transcript still comprises the full length translated region of SCN5A Exon 28. In exemplary aspects, the full length SCN5A Exon 28 transcript is a transcript comprising an E28A transcript (E28A-S).

[0047] In exemplary aspects of the methods of the invention, the biological sample is analyzed by measuring the level, concentration or amount of full length mRNA in the biological sample wherein the full length mRNA are encoded by the SCN5A gene. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of an SCN5A splice variant, (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). The SCN5A splice variant can be any of those taught herein. For example, the SCN5A splice variant may be any of Exon 1 splice variants: E1B1

(SEQ ID NO. 1), E1B2 (SEQ ID NO. 2), E1B3 (SEQ ID NO. 3), and E1B4 (SEQ ID NO. 4). For example, the SCN5A splice variant may be any of Exon 2 splice variants: E2B1 (SEQ ID NO. 5), E2B2 (SEQ ID NO. 6). For example, the SCN5A splice variant may be any of Exon 28 splice variants: E28B (SEQ ID NO. 7), E28C (SEQ ID NO. 8), or E28D (SEQ ID NO. 9). In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of E28A-S and/or E28A-L. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of a truncated SCN5A Exon 28 transcript. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of a full length SCN5A Exon 28 transcript. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of all transcripts encoded by either a full length mRNA encoded by the SCN5A gene or by an SCN5A splice variant. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of a truncated SCN5A Exon 28 transcript and/or a full length SCN5A Exon 28 transcript. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the SCN5A Exon 28 splice variant, E28C and/or E28D, each of which encode a truncated SCN5A protein. In exemplary aspects of the invention, the biological sample is analyzed by measuring all mRNA, including both full-length and truncated mRNA, encoded by the SCN5A gene. Suitable methods of determining expression levels of nucleic acids (e.g., mRNA) are known in the art and include quantitative polymerase chain reaction (qPCR), including, but not limited to, real time PCR, Northern blotting and Southern blotting. See, e.g., U.S. Patent Application Publication No. 2007/0212723 A1, Shang et al., *Circulation Research* 101: 1146-1154 (2007); and International Patent Application Publication Nos. WO/2012/094651 and WO/2010/129964. An exemplary method is described herein the EXAMPLES.

[0048] In exemplary aspects of the methods of the invention, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by the full length mRNA in the biological sample wherein the full length mRNA are encoded by the SCN5A gene. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by an SCN5A splice variant, (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). The SCN5A splice variant can be any of those taught herein. For example, the SCN5A splice variant may be any of Exon 1 splice variants: E1B1 (SEQ ID NO. 1), E1B2 (SEQ ID NO. 2), E1B3 (SEQ ID NO. 3), and E1B4 (SEQ ID NO. 4). For example, the SCN5A splice variant

may be any of Exon 2 splice variants: E2B1 (SEQ ID NO. 5), E2B2 (SEQ ID NO. 6). For example, the SCN5A splice variant may be any of Exon 28 splice variants: E28B (SEQ ID NO. 7), E28C (SEQ ID NO. 8), or E28D (SEQ ID NO. 9). In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by the E28A-S and/or E28A-L. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by a truncated SCN5A Exon 28 transcript. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by a full length SCN5A Exon 28 transcript. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of all the protein products encoded by all the transcripts encoded by either a full length mRNA encoded by the SCN5A gene or by an SCN5A splice variant. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by the a truncated SCN5A Exon 28 transcript and/or a full length SCN5A Exon 28 transcript. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of the protein product encoded by the SCN5A Exon 28 splice variant, E28C and/or E28D, each of which encode a truncated SCN5A protein. In exemplary aspects of the invention, the biological sample is analyzed by measuring all protein products encoded by SCN5A mRNA, including both full-length and truncated mRNA.

[0049] In aspects, wherein the level of a protein product encoded by a truncated SCN5A Exon 28 splice variant is analyzed, the level in exemplary aspects, is determined by measuring a first level using a first antibody which specifically binds to the full length SCN5A protein product wherein the antibody binds to an epitope within the C-terminal portion of the full length SCN5A protein product, which epitope is not present in the truncated SCN5A protein product, by measuring a second level using a second antibody which binds to an epitope within the N-terminal portion of the full length SCN5A protein product, which epitope is present in the truncated SCN5A protein product, and subtracting the first level from the second level in order to determine the level of the truncated Exon 28 splice variant.

[0050] Suitable methods of determining expression levels of protein products are known in the art and include immunoassays (e.g., Western blotting, an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay (RIA), and immunohistochemical assay. See, e.g., U.S. Patent Application Publication No. 2007/0212723 A1, Shang et al., *Circulation Research*

101: 1146-1154 (2007); and International Patent Application Publication Nos. WO/2012/094651 and WO/2010/129964.

[0051] *Splicing Factors and Components Related the Unfolded Protein Response (UPR)*

[0052] In exemplary aspects of the methods of the invention, the biological sample is analyzed for a level of mRNA encoded by a SCN5A splicing factor gene or by a gene of the unfolded protein response (UPR). In exemplary aspects, the splicing factor gene is hLuc7A, PRP40, or RBM25. In exemplary aspects, the gene of the UPR is a transducer of the UPR, for example, PERK. Accordingly, the methods may comprises measuring mRNA of splicing factor hLuc7a, splicing factor PRP40, splicing factor RBM25 and/or PERK. The methods may additionally or alternatively comprise measuring the protein product(s) encoded by one or more of the mRNA of splicing factor hLuc7a, splicing factor PRP40, splicing factor RBM25 and/or PERK. Accordingly, in exemplary aspects, the methods described herein may comprise measuring a level of splicing factor hLuc7a protein, splicing factor PRP40 protein, splicing factor RBM25 protein and/or PERK protein or, a splicing factor hLuc7a mRNA, splicing factor PRP40 mRNA, splicing factor RBM25 mRNA and/or PERK mRNA.

[0053] Luc7A (NCBI Gene ID No. 51747) is also known as LUC7L3; LUC7-like 3; CRA; CROP; LUC7A; hLuc7A; CREAP-1; and OA48-18. Exemplary mRNA sequences of hLuc7A are set forth herein as SEQ ID NOs: 34 and 35 but may also found in the NCBI's nucleotide database as Accession No. NM_006107.3 and as Accession No. NM_016424.4. Exemplary amino acid sequences of hLuc7A are set forth herein as SEQ ID NOs: 36 and 37 but may also be found in the NCBI's Protein database as Accession No. NP_006098.2 and as Accession No. NP_057508.2.

[0054] PRP40 (NCBI Gene ID No. 55660) is also known as PRP40A, PRP40 pre-mRNA processing factor 40 homolog A (*S. cerevisiae*), HYPA; FBP11; FLAF1; FBNP3; HIP10; Prp40; FBP-11; HIP-10; and NY-REN-6. An exemplary mRNA sequence of PRP40 is set forth herein as SEQ ID NO: 663 but may be found in the NCBI's nucleotide database as Accession No. NM_017892. An exemplary amino acid sequence of RBM25 is set forth herein as SEQ ID NO: 664 but may be found in the NCBI's Protein database as Accession No. NP_060362.

[0055] RBM25 (NCBI Gene ID No. 58517) is also known as RNA binding motif protein 25; S164; NET52; RNPC7; Snu71; RED120; fSAP94; MGC105088; and MGC117168. An exemplary mRNA sequence of RBM25 is set forth herein as SEQ ID NO: 38 but may be

found in the NCBI's nucleotide database as Accession No. NM_021239.2. An exemplary amino acid sequence of RBM25 is set forth herein as SEQ ID NO: 39 but may be found in the NCBI's Protein database as Accession No. NP_067062.1.

[0056] PERK (NCBI Gene ID No. 9451) is also known as eukaryotic translation initiation factor 2-alpha kinase 3, EIF2AK3, protein kinase R-like endoplasmic reticulum kinase, PKR-like ER kinase; PEK; WRS; and DKFZp781H1925. An exemplary mRNA sequence of PERK is set forth herein as SEQ ID NO: 40 but may also be found on the NCBI's nucleotide database as Accession No. NM_004836.5. An exemplary amino acid sequence of PERK is set forth herein as SEQ ID NO: 41 but may also be found on the NCBI's Protein database as Accession No. NP_004827.4.

[0057] In exemplary aspects, wherein the biological sample is analyzed for a level of mRNA encoded by a SCN5A splicing factor gene or by a gene of the unfolded protein response (UPR), the biological sample is analyzed by measuring the level, concentration or amount of mRNA encoded by the SCN5A splicing factor gene or by the gene of the UPR in the biological sample. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of mRNA encoded by the RBM25 gene, the Luc7A gene, the PRP40, gene, or the PERK gene. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of mRNA encoded by the RBM25 gene, the Luc7A gene, the PRP40, gene, and the PERK gene. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of mRNA encoded by the RBM25 gene, the Luc7A gene, the PRP40, gene, and the PERK gene, in addition to measuring the level, concentration or amount of mRNA encoded by the SCN5A gene (e.g., but not limited to the full length mRNA encoded by the SCN5A gene and/or SCN5A splice variant mRNA encoding a truncated protein product (e.g., but not limited to E28C and E28D)). Suitable methods of determining expression levels of nucleic acids (e.g., mRNA) are known in the art and include quantitative polymerase chain reaction (qPCR), including, but not limited to, real time PCR, Northern blotting and Southern blotting. See, e.g., U.S. Patent Application Publication No. 2007/0212723 A1, Shang et al., *Circulation Research* 101: 1146-1154 (2007); and International Patent Application Publication Nos. WO/2012/094651 and WO/2010/129964. An exemplary method is described herein the EXAMPLES.

[0058] In exemplary aspects, wherein the biological sample is analyzed for a level of mRNA encoded by a SCN5A splicing factor gene or by a gene of the unfolded protein

response (UPR), the biological sample is analyzed by measuring the level, concentration or amount of a protein product encoded by an mRNA encoded by the SCN5A splicing factor gene or by the gene of the UPR in the biological sample. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of a protein product encoded by an mRNA encoded by the RBM25 gene, the Luc7A gene, the PRP40, gene, or the PERK gene. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of a protein product encoded by an mRNA encoded by the RBM25 gene, the Luc7A gene, the PRP40, gene, and the PERK gene. In exemplary aspects, the biological sample is analyzed by measuring the level, concentration or amount of a protein product encoded by an mRNA encoded by the RBM25 gene, the Luc7A gene, the PRP40, gene, and the PERK gene, in addition to measuring the level, concentration or amount of a protein product encoded by an mRNA encoded by the SCN5A gene (e.g., but not limited to the full length mRNA encoded by the SCN5A gene and/or SCN5A splice variant mRNA encoding a truncated protein product (e.g., but not limited to E28C and E28D)). Suitable methods of determining expression levels of protein products are known in the art and include immunoassays (e.g., Western blotting, an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay (RIA), and immunohistochemical assay. See, e.g., U.S. Patent Application Publication No. 2007/0212723 A1, Shang et al., *Circulation Research* 101: 1146-1154 (2007); and International Patent Application Publication Nos. WO/2012/094651 and WO/2010/129964.

[0059] *Interpretation of Biological Sample Analysis*

[0060] The methods of the invention comprise a further step wherein the presence of Brugada Syndrome in the subject is identified, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level. In a related aspect, the methods of the invention comprise a further step of determining the subject as needing therapy for Brugada Syndrome, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0061] With regard to the above-monitoring methods, the methods further comprise determining the subject has having an increased risk for Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or

determining the subject as having a decreased risk for Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample, or determining progression of the Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining regression of the Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[0062] Relative to a control level or the level of the first biological sample, the level that is determined may an increased level. As used herein, the term “increased” with respect to level refers to any % increase above a control level. The increased level may be at least or about a 10% increase, at least or about a 15% increase, at least or about a 20% increase, at least or about a 25% increase, at least or about a 30% increase, at least or about a 35% increase, at least or about a 40% increase, at least or about a 45% increase, at least or about a 50% increase, at least or about a 55% increase, at least or about a 60% increase, at least or about a 65% increase, at least or about a 70% increase, at least or about a 75% increase, at least or about a 80% increase, at least or about a 85% increase, at least or about a 90% increase, at least or about a 95% increase, relative to a control level.

[0063] Relative to a control level or the level of the first biological sample, the level that is determined may a decreased level. As used herein, the term “decreased” with respect to level refers to any % decrease below a control level. The decreased level may be at least or about a 10% decrease, at least or about a 15% decrease, at least or about a 20% decrease, at least or about a 25% decrease, at least or about a 30% decrease, at least or about a 35% decrease, at least or about a 40% decrease, at least or about a 45% decrease, at least or about a 50% decrease, at least or about a 55% decrease, at least or about a 60% decrease, at least or about a 65% decrease, at least or about a 70% decrease, at least or about a 75% decrease, at least or about a 80% decrease, at least or about a 85% decrease, at least or about a 90% decrease, at least or about a 95% decrease, relative to a control level.

[0064] In exemplary aspects, each of the referenced levels is normalized to a housekeeping gene, such as, the β -actin gene. The levels may be normalized to another housekeeping gene, such as any of those described herein.

[0065] *Additional Steps*

[0066] With regard to any of the methods of the invention, the methods may include additional steps. For example, the method may include repeating one or more of the recited step(s) of the method. Accordingly, in exemplary aspects, the method comprises re-analyzing the subject for (a) a level of full length mRNA encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). In exemplary aspects, the method comprises re-analyzing the subject every 6 to 12 months, wherein the analysis is based on a different biological sample obtained from the same subject. In some aspects, the method comprises obtaining a biological sample from the subject every 6 to 12 months and determining the level of (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); of each biological sample obtained.

[0067] In exemplary aspects, the method comprises analyzing the biological sample for (a) a level of full length mRNA encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR) in more than one way. For example, the method in some aspects comprises analyzing the biological sample for both mRNA levels and protein products.

[0068] In exemplary aspects, the method comprises analyzing the biological sample for only one of: (a) a level of full length mRNA encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, or (d) a level of mRNA encoded by a gene of the unfolded protein response

(UPR). In exemplary aspects, the method comprises analyzing the biological sample for only (a) a level of full length mRNA encoded by the SCN5A gene and (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, the method comprises analyzing the biological sample for only (a) a level of full length mRNA encoded by the SCN5A gene and (b) a level of mRNA of the SCN5A splice variant E28C and/or E28D. In exemplary aspects, the method comprises analyzing all levels of mRNA of the SCN5A gene. In exemplary aspects, the method comprises analyzing all levels of mRNA of the SCN5A gene and the biological sample is blood, or a fraction thereof. In exemplary aspects, the method comprises analyzing the biological sample for all of (a) a level of full length mRNA encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR) in more than one way. In exemplary aspects, the method comprises analyzing the biological sample for either mRNA or the protein product encoded thereby of only the SCN5A gene, an SCN5A splicing factor gene and/or a gene of the UPR, and the method does not include analyzing the biological sample for mRNA or a protein product encoded thereby of any other gene.

[0069] In exemplary embodiments, the method comprises further steps for diagnosing Brugada Syndrome in a subject. Diagnostic criteria for Brugada Syndrome are described in Wilde et al., *Eur Heart J.* 23: 1648-1654 (2002); Antzelevitch et al., *Circulation* 111: 659-670 (2005); and Richter et al., *Eur Heart J* 31: 1357-1364 (2010). For instance, the method further comprises performing an electrocardiogram on the subject. In exemplary embodiments, the method further comprises examining the subject for a structural defect of the heart. The method in exemplary aspects, includes analyzing the subject's medical record and/or medical history. In exemplary aspects, the subject's medical record is analyzed for any occurrence of aborted sudden cardiac death, treatment for sudden death, recent occurrences or frequent occurrences of unexplained syncope (i.e., loss of consciousness) or dizziness. In exemplary aspects, the subject's medical history is analyzed for any family member dying due to sudden cardiac death and/or any family member being diagnosed with Brugada Syndrome. In additional or alternative aspects, the method further comprises performing a genetic test on the subject, whereupon the presence or absence of one or more

of the known genetic mutations associated with Brugada Syndrome is determined. Genetic mutations associated with Brugada Syndrome are described below.

[0070] In exemplary aspects, the method further comprises administering a therapeutic agent or device once the need therefor or a risk has been determined. For example, the methods described herein may optionally comprise a step of providing an appropriate therapy (administering a pharmaceutical agent or implementing a standard of care) to the subject determined to have a need therefor. In exemplary aspects, the methods of the invention comprise one or more steps related to providing the appropriate therapy. The methods may, for example, comprise a step of implanting an ICD into a subject, or administering to the subject an agent which increases sodium channel current. The agent which increases sodium channel current may be any one known in the art, some of which are described herein. The agent which increases sodium channel current may be administered to the subject by any suitable route of administration known in the art, some routes of which are described herein below.

[0071] Any and all possible combinations of the steps described herein are contemplated for purposes of the inventive methods.

[0072] *Genetic Screening*

[0073] Genetic mutations associated with Brugada Syndrome are known in the art and are catalogued at the website maintained by the Molecular Cardiology Laboratories IRCCS Fondazione Salvatore Maugeri having the URL <http://www.fsm.it/cardmoc>. According to this website, the mutations associated with Brugada Syndrome 1 occur in the SCN5A gene and include those shown in Table 1:

TABLE 1

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
G3A	M1I	Missense	N-term	BrS	Kapplinger et al., <i>Heart Rhythm</i> 7(1): 33-46 (2010)
G53A	R18Q	Missense	N-term	BrS	Kapplinger et al. 2010
G80A	R27H	Missense	N-term	BrS	Priori et al., <i>Circulation</i> 105(11): 1342-1347 (2002)

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>191_193delTGC</i>	L64del	In-frame deletion	N-term	BrS	Kapplinger et al. 2010
<i>T210G</i>	N70K	Missense	N-term	BrS	Kapplinger et al. 2010
<i>C217T</i>	Q73X	Nonsense	N-term	BrS	Kapplinger et al. 2010
<i>G250A</i>	D84N	Missense	N-term	BrS	Kapplinger et al. 2010
G253A	G35S	Missense	N-term	BrS (footnote 1)	Levy-Nissenbaum et al, <i>Genet Test</i> 5(4): 331-334 (2001)
<i>T278C</i>	F93S	Missense	N-term	BrS	Kapplinger et al. 2010
<i>T281G</i>	I94S	Missense	N-term	BrS	Kapplinger et al. 2010
G283	V95I	Missense	N-term	BrS	Linag et al. 2006
<i>C310T</i>	R104W	Missense	N-term	BrS	Kapplinger et al. 2010
<i>G311A</i>	R104Q	Missense	N-term	BrS	Kapplinger et al. 2010
<i>C327A</i>	N109K	Missense	N-term	BrS	Kapplinger et al. 2010
<i>C361T</i>	R121W	Missense	N-term	BrS	Kapplinger et al. 2010
<i>G362A</i>	R121Q	Missense	N-term	BrS	Kapplinger et al. 2010
<i>A376G</i>	K126E	Missense	N-term	BrS	Kapplinger et al. 2010
<i>381dupT</i>	L128SfsX44	Frame Shift	DI-S1	BrS	Kapplinger et al. 2010
<i>C393 -5A*</i>	-	Splice Site	DI-S1	BrS	Kapplinger et al. 2010
<i>T407C</i>	L136P	Missense	DI-S1	BrS	Kapplinger et al. 2010
<i>410_418dupTCATGTGCA</i>	I137_C139dup	In-frame insertion	DI-S1	BrS	Kapplinger et al. 2010
<i>G436A</i>	V146M	Missense	DI-S1	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
G461A	R104Q	Missense	N-term	BrS(1)	Levy-Nissenmaum 2001
G468A	W156X	Nonsense	DI-S1/S2	BrS	Kapplinger et al. 2010
T477A	Y159X	Nonsense	DI-S2	BrS	Kapplinger et al. 2010
G481C	E161Q	Missense	DI-S2	BrS	Kapplinger et al. 2010
G481A	E161K	Missense	DI-S2	BrS	Kapplinger et al. 2010
486delC	Y162XfsX1	Frame shift	DI-S2	BrS	Kapplinger et al. 2010
-	K126E	Missense	DI/S1	BrS	Vatta et al. 2002
n.a.	E161K (see also)	Missense	DI/S1-S2	BrS	Smits et al. 2002
G525C	K175N	Missense	DI-S2	BrS	Kapplinger et al. 2010
C533G	A178G	Missense	DI-S2	BrS	Kapplinger et al. 2010
C535T	R179X	Nonsense	DI-S2/S3	BrS	Kapplinger et al. 2010
T544C	C182R	Missense	DI-S2/S3	BrS	Kapplinger et al. 2010
C554T	A185V	Missense	DI-S2/S3	BrS	Kapplinger et al. 2010
C559T	T187I	Missense		BrS+SSS	Makiyama et al. 2005
G579A	W193X	Nonsense	DI-S3	BrS	Kapplinger et al. 2010
C611T	A204V	Missense	DI-S3	BrS	Kapplinger et al. 2010
G611+1A*	-	Slice site	DI-S3	BrS	Kapplinger et al. 2010
611+3_611+4dupAA	-	Splice site	DI-S3	BrS	Kapplinger et al. 2010
A612 -2G*	-	Splice site	DI-S3	BrS	Kapplinger et al. 2010
T635A	L212Q	Missense	DI-S3/S4	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
T635C	L212P	Missense	DI/S3-S4	Atrial standstill	Makita et al 2005
656_657insATTCA	T220FfsX10	Frame shift	DI-S4	BrS	Kapplinger et al. 2010
C659T	T220I	Missense	DI-S4	BrS -DCM	Kapplinger et al. 2010
C664T	R222X	Nonsense	DI-S4	BrS	Kapplinger et al. 2010
G665A	R222Q	Missense	DI-S4	BrS	Kapplinger et al. 2010
G667C	V223L	Missense	DI-S4	BrS	Kapplinger et al. 2010
C673T	R225W	Missense	DI-S4	BrS	Kapplinger et al. 2010
C677T	A226V	Missense	DI/S4	BrS	Priori et al 2002
A688G	I230V	Missense	DI/S4	BrS	Priori et al 2002
G694A	V232I	Missense	DI-S4	BrS	Kapplinger et al. 2010
Ins AAint 7	IVS7DS+4	Splice error	DI/S5-S6	BrS	Chen et al. 1998
G718A	V240M	Missense	DI-S4/S5	BrS	Kapplinger et al. 2010
A745T	K249X	Nonsense	DI-S4/S5	BrS	Kapplinger et al. 2010
C808A	Q270K	Missense	DI-S5	BrS	Kapplinger et al. 2010
T827A	L276Q	Missense	DI-S5	BrS	Kapplinger et al. 2010
C832G	H278D	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
C844T	R282C	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
G845A	R282H	Missense	DI/S5-S6	BrS	Priori et al 2002; Itoh et al 2005
G874A	G292S	Missense	DI/S5-S6	BrS	Niimura et al 2004
G880A	V294M	Missense	DI/S5-S6	BrS	Priori et al 2002

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
G898A	V300I	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
-	K317N	Missense	DI/S5-S6	BrS	Yi et al. 2003
G934+1A*	-	Splice site	DI-S5/S6	BrS	Kapplinger et al. 2010
C934+4T*	-	Splice site	DI-S5/S6	BrS	Kapplinger et al. 2010
T944C	L315P	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
C959A	T320N	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
G995A	G319S	Missense	DI/S5-S6	BrS	Priori et al. 2000
G998+1A*	-	Splice site	DI-S5/S6	BrS	Kapplinger et al. 2010
C1007T	P336L(8)	Missense	DI/S5-S6	BrS	Cordeiro et al. 2006
T974G	L325R	Missense	DI/S5-S6	BrS	Keller et al. 2005
G1036T	E346X	Nonsense	DI-S5/S6	BrS	Kapplinger et al. 2010
G1052A	G351D	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
-(G1052T? in Kapplinger et al.)	G351V	Missense	DI/S5-S6	BrS	Vatta et al. 2002
C1058T	T353I	Missense	DI/S5-S6	BrS	Pfahnl et al. 2007
G1066A	D356N	Missense	DI/S5-S6	BrS+CCD	Makiyama et al. 2005
C1099T	R367C	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
G1100A	R367H	Missense	DI/S5-S6	SUNDS/BrS /Atrial standstill ^(2, 3)	Vatta et al. 2002; Takehara et al, 2004
G1100T	R367L	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
T1106A	M369K	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>T1120G</i>	W374G	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
n.a.	R367C	Missense	DI/S5-S6	BrS + ARVC	Smits et al. 2002
n.a.	M369K	Missense	DI/S5-S6	BrS	Smits et al. 2002
G1127A	R376H	Missense	DI/S5-S6	BrS	Rossenbacker et al 2004; Frustaci et al 2005
<i>G1156A</i>	G386R	Missense	DI-S5/S6	BrS	Kapplinger et al. 2010
<i>G1157A</i>	G386E	Missense	DI-S5/S6	Brs	Kapplinger et al. 2010
1177-1179del	393delF	Deletion	DI/S6	BrS	Priori et al 2002
<i>G1186C</i>	V396L	Missense	DI-S6	BrS	Kapplinger et al. 2010
<i>T1187C</i>	V396A	Missense	DI-S6	BrS	Kapplinger et al. 2010
A1217G	N406S	Missense	DI/S6	BrS	Itoh H 2005
<i>C1255T</i>	Q419X	Nonsense	DI-DII	BrS	Kapplinger et al. 2010
<i>G1315A</i>	E439K	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>T1338+2A*</i>	-	Splice site	DI-DII	BrS	Kapplinger et al. 2010
<i>1428_1431delCAAG</i>	S476RfsX30	Frame shift	DI-DII	BrS	Kapplinger et al. 2010
<i>1479del</i>	K493	Deletion	DI-DII	BrS	Smits et al. 2002
<i>A1502G</i>	D501G	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>1537delC</i>	R513VfsX8	Frame shift	DI-DII	BrS	Kapplinger et al. 2010
<i>1562delA</i>	K521SfsX102	Frame shift	DI-DII	BrS	Kapplinger et al. 2010
<i>G1577A</i>	R526H	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>T1595G</i>	F532C	Missense	DI-DII	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>C7603T</i>	R535X	Nonsense	DI-DII	BrS	Kapplinger et al. 2010
<i>T1629A</i>	F543L	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>G1651A</i>	A551T	Missense	DI-DII	BrS	Lai et al. 2005
<i>G1654A</i>	G552R	Missense	DI-DII	BrS	Kapplinger et al. 2010
n.a.	R535X	Nonsense	DI-DII	BrS	Smits et al. 2002
<i>G1663A</i>	E555K	Missense	DI-DII	BrS	Takahata et al. 2003
<i>T1700A</i>	L567Q	Missense	DI-DII	BrS-SIDS(4)	Priori et al. 2000
<i>C1717T</i>	Q573X	Nonsense	DI-DII	BrS	Kapplinger et al. 2010
<i>1721delG</i>	G574DfsX49	Frame shift	DI-DII	BrS	Kapplinger et al. 2010
n.a.	del AL 586-587	Deletion	DI-DII	SIDS	Arnestad et al 2007
<i>G1844A</i>	G615E	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>C1855T</i>	L619F	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>C1858T</i>	R620C	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>G1890A</i>	T630T	Silent/Splice site	DI-DII	BrS	Kapplinger et al. 2010
<i>G1890+5A*</i>	-	Splice site	DI-DII	BrS	Kapplinger et al. 2010
<i>C1895T</i>	T632M	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>C1918G</i>	P640A	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>1936delC</i>	Q646RfsX5	Frame shift	DI-DII	BrS	Kapplinger et al. 2010
<i>C1940A</i>	A647D	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>C1943T</i>	P648L	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>1950_1953delAGAT</i>	D651AfsX25	Frame shift	DI-DII	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>C1981T</i>	R661W	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>1983_1993dupGGCCCTCAGCG</i>	A665GfsX16	Frame shift	DI-DII	BrS	Kapplinger et al. 2010
<i>2024_2025delAG</i>	E675VfsX45	Frame shift/splice	DI-DII	BrS	Kapplinger et al. 2010
A2042C	H681P	Missense	DI-DII	BrS	Priori et al 2002
<i>T2047G</i>	C683G	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>G2092T</i>	E698X	Nonsense	DI-DII	BrS	Kapplinger et al. 2010
<i>C2102T</i>	P701L	Missense	DI-DII	BrS	Kapplinger et al. 2010
<i>C2150T</i>	P717L	Missense	DII-S1	BrS	Kapplinger et al. 2010
<i>2201dupT</i>	M734lfsX11	Frame shift	DII-S1	BrS	Kapplinger et al. 2010
n.a.	A735V	Missense	DI/S1	SUNDS(3)	Vatta et al. 2002
<i>C2204T</i>	A735V	Missense	DII-S1		Kapplinger et al. 2010
C2204A	A735E	Missense	DI/S1	BrS	Priori et al.2000
<i>G2236A</i>	E746K	Missense	DII-S1/S2	BrS	Kapplinger et al. 2010
<i>G2254A</i>	G752R	Missense	DII-S2	BrS	Kapplinger et al. 2010
<i>G2273A</i>	G758E	Missense	DII-S2	BrS	Kapplinger et al. 2010
<i>2274delG</i>	I759FfsX6	Frame shift	DII-S2	BrS	Kapplinger et al. 2010
<i>T2291G</i>	M764R	Missense	DII-S2	BrS	Kapplinger et al. 2010
<i>G2314A</i>	D772N	Missense	DII-S2/S3	BrS	Kapplinger et al. 2010
<i>C2317T</i>	P773S	Missense	DII-S2/S3	BrS	Kapplinger et al. 2010
<i>2320delT</i>	Y774TfsX28	Frame shift	DII-S2/S3	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
IVS14-1G>C		Splice Error	DII/S2	BrS	Priori et al 2000
n.a.	G752R	Missense	DII/S2	BrS	Smits et al. 2002
2326_2328delTAC	Y776del	In-frame deletion	DII-S2/S3	BrS	Kapplinger et al. 2010
G2365A	V789I	Missense	DII-S3	BrS	Kapplinger et al. 2010
G2423C	R808P	Missense	DII-S4	BrS	Kapplinger et al. 2010
2435_2436+3delTGGTAins CGCCT	L812P	Indel/splice site	DII-S4	BrS	Kapplinger et al. 2010
G2465A	W822X	Nonsense	DII-S4	BrS	Kapplinger et al. 2010
G2466A	W822X	Missense	DII/S4	BrS	Keller et al 2005
C2504T	S835L	Missense	DII/S4-S5	BrS	Niimura et al 2004
T2516C	L839P	Missense	DII-S4/S5	BrS	Kapplinger et al. 2010
2533delG	V845CfsX2	Frame shift	DII-S5	BrS	Kapplinger et al. 2010
2549_2550insTG	F851GfsX19	Frame shift	DII-S5	BrS	Kapplinger et al. 2010
2550_2551dupGT	F851CfsX19	Frame shift	DII-S5	BrS	Kapplinger et al. 2010
T2552C	F851L	Missense	DIII/S5	BrS	Priori et al 2002
C2553A	F851L	Missense	DII-S5	BrS	Kapplinger et al. 2010
2581-2582delTT	F861fs951X	Frameshift	DIII/S5	BrS+CCD	Schulze-Bahr 2003
2582_2583delTT	F861WfxX90	Frame shift	DII-S5	BrS	Kapplinger et al. 2010
G2599C	E867Q	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
2602delC	L867X	Nonsense	DIII/S5	BrS+CCD	Smits et al. 2002; Schulze-Bahr 2003
2602delC	L868X	Frame shift	DII-S5/S6	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
2613delC	S871fs+9X	Frameshift	DIII/S5-S6	BrS	Priori et al 2002
<i>C2632T</i>	R878C	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
<i>G2633A</i>	R878H	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
<i>A2657C</i>	H886P	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
T2674A	F891I	Missense	DII/S5-S6	BrS	Priori et al.2000
<i>C2677T</i>	R893C	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
<i>G2678A</i>	R893H	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
T2686A	C896S	Missense	DIII/S5-S6	BrS	Priori et al 2002
<i>G2701A</i>	E901K	Missense	DII-S5/S6	BrS	Kapplinger et al. 2010
C2729T	S910L	Missense	DIII/S5-S6	BrS	Priori et al 2002
<i>T2743C</i>	C915R	Missense	DII-S6	BrS	Kapplinger et al. 2010
<i>T2750G</i>	L917R	Missense	DII-S6	BrS	Kapplinger et al. 2010
<i>A2780G</i>	N927S	Missense	DII-S6	BrS	Kapplinger et al. 2010
<i>T2783C</i>	L928P	Missense	DII-S6	BrS	Kapplinger et al. 2010
<i>T2804C</i>	L935P	Missense	DII-S6	BrS	Kapplinger et al. 2010
<i>2850delT</i>	D951MfsX6	Frame shift	DII/DII I	BrS	Kapplinger et al. 2010
n.a.	D951X	Nonsense	DII-DIII	BrS	Smits et al 2002
C2893T	R965C	Missense	DII-DIII	BrS	Priori et al.2000
<i>G2894A</i>	R965H	Missense	DII/DII I	BrS	Kapplinger et al. 2010
<i>2914_2923delTTTGTCAAGC</i>	F972GfsX170	Frame shift	DII/DII I	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>G2989A</i>	A997T	Missense	DII/DII I	BrS	Kapplinger et al. 2010
<i>3140_3141dupTG</i>	P1048CfsX98	Frame shift	DII/DII I	BrS	Kapplinger et al. 2010
<i>G3157A</i>	E1053K	Missense	DII-DIII	BrS	Priori et al.2000
<i>A3164G</i>	D1055G	Missense	DII-DIII	BrS	Kapplinger et al. 2010
<i>3171_3172delTGinsA</i>	D1057EfsX88	Insertion/deletion	DII/DII I	BrS	Kapplinger et al. 2010
<i>3228+2delT*</i>	-	Splice site	DII/DII I	BrS	Kapplinger et al. 2010
<i>C3236A</i>	S1079Y	Missense	DII/DII I	BrS	Kapplinger et al. 2010
<i>G3340A</i>	D1114N	Missense	DII-DIII	BrS and RW(5)	Splawski et al.; Priori et al.;
<i>C3338T</i>	A1113V	Missense	DII/DII I	BrS	Kapplinger et al. 2010
<i>G3345A</i>	W1115X	Nonsense	DII/DII I	BrS	Kapplinger et al. 2010
<i>C3352T</i>	Q1118X	Nonsense	DII-DIII	BrS	Priori et al 2002
<i>G3068A</i>	R1023H	Missense	DII-DIII	BrS+ ARVC	Frustaci et al 2005
<i>G3419C</i>	S1140T	Missense	DII-DIII	BrS	Kapplinger et al. 2010
<i>3553_3554delCA</i>	Q1185GfsX55	Frame Shift	DII-DIII	BrS	Kapplinger et al. 2010
<i>G3573A</i>	W1191X	Nonsense	DII-DIII	RrS	Shin et al, 2006
<i>G3576A</i>	W1192X	Nonsense	DII-DIII	BrS	Kapplinger et al. 2010
<i>G3622T</i>	E1208X	Nonsense	DIII-S1	BrS	Kapplinger et al. 2010
<i>3634_3636delATC</i>	I1212del	In-frame del	DIII-S1	BrS	Kapplinger et al. 2010
<i>G3656A</i>	S1219N	Missense	DIII-S1	BrS	Kapplinger et al. 2010
<i>3666delG</i>	A1223PfsX7	Frame shift/splice	DIII-S1	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>G3673A</i>	E1225K	Missense	DIII-S1/S2	BrS	Kapplinger et al. 2010
<i>G3676A</i>	E1225K	Missense	DIII/S1	BrS+CCD (see also here)	Smits et al. 2002; Schulze-Bahr 2003
<i>T3682C</i>	Y1228H	Missense	DIII-S1/S2	BrS	Kapplinger et al. 2010
<i>C3694T</i>	R1232W	Missense	DIII-S1/S2	BrS	Kapplinger et al. 2010
-	R1232W	Missense	DIII/S1-S2	BrS	Chen et al. 1998
<i>G3695A</i>	R1232Q	Missense	DIII-S1/S2	BrS	Kapplinger et al. 2010
<i>G3708T</i>	K1236N	Missense	DIII/S1-S2	BrS	Priori et al 2002
<i>T3716C</i>	L1239P	Missense	DIII/S2	BrS	Kapplinger et al. 2010
<i>G3718C</i>	E1240Q	Missense	DIII/S2	BrS	Priori et al 2002
<i>G3727A</i>	D1243N	Missense	DIII/S2	BrS	Kapplinger et al. 2010
<i>T3746A</i>	V1249D	Missense	DIII/S2	BrS	Kapplinger et al. 2010
<i>A3758G</i>	E1253G	Missense	DIII/S2	BrS	Kapplinger et al. 2010
<i>G3784A</i>	G1262S	Missense	DIII/S2	BrS	Kapplinger et al. 2010
<i>G3813C</i>	W1271C	Missense	DIII/S3	BrS	Kapplinger et al. 2010
delG3816	n.a.	Frameshift	DIII/S2	BrS	Smits et al. 2002
<i>G3823A</i>	D1275N	Missense	DIII/S3	BrS -DCM	Kapplinger et al. 2010
<i>G3840+1A</i>	-	Splice Site	DIII/S3	BrS	Kapplinger et al. 2010
<i>C3863G</i>	A1288G	Missense	DIII/S3	BrS	Kapplinger et al. 2010
<i>3894delC</i>	I1299SfsX13	Frame Shift	DIII/S4	BrS	Kapplinger et al. 2010
<i>T3932C</i>	L1311P	Missense	DIII/S4	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
G3934A	G1262S	Missense	DIII/S 2	BrS	Shin et al 2004
T3878C	F1293S	Missense	DIII/S 3-S4	BrS	Priori et al 2002
<i>G3956T</i>	G1319V	Missense	DIII/S 4-S5	BrS	Kapplinger et al. 2010
n.a.	G1319V	Missense	DIII/S 4-S5	BrS	Smits et al. 2002
<i>A3963+4G*</i>	-	Splice Site	DIII/S 4-S5	BrS	Kapplinger et al. 2010
<i>T3963+2C</i>	-	Splice Site	DIII/S 4-S5	BrS	Kapplinger et al. 2010
<i>T3968G</i>	V1323G	Missense	DIII/S 4-S5	BrS	Kapplinger et al. 2010
<i>C3995T</i>	P1332L	Missense	DIII/S 4-S5	BrS	Kapplinger et al. 2010
<i>G4018A</i>	V1340I	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
<i>T4030C</i>	F1344L	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
T4031C	F1344S	Missense	DIII/S 5	BrS	Keller et al 2006
<i>C4036A</i>	L1346I	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
<i>T4037C</i>	L1346P	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
<i>T4052G</i>	M1351R	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
<i>G4057A</i>	V1353M	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
<i>G4072T</i>	G1358W	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
<i>G4077T</i>	K1359N	Missense	DIII/S 5	BrS	Kapplinger et al. 2010
n.a.	S1382I	Missense	DIII/S 5-S6	BrS	Smits et al. 2002
<i>T4079G</i>	F1360C	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4088A</i>	C1363Y	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>T4118A</i>	L1373X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4145T</i>	S1382I	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>C4147T</i>	Q1383X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>T4178A</i>	L1393X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>C4182G</i>	Y1394X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
4189delT	n.a.	Frameshift	DIII/S 5-S6	BrS	Glatzer KA 2004
del A4190	V1398X	Nonsense	DIII/S 5-S6	BrS	Chen et al. 1998
<i>del A4190</i>	K1397RfsX2	Frame Shift	DIII/S 5-S6	BrS	Kapplinger et al. 2010
n.a.	V1405L	Missense	DIII/S 5-S6	BrS	Smits et al. 2002
<i>G4213A</i>	V1405M	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4213C</i>	V4105L	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4216C</i>	G1406R	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4217A</i>	G1406E	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4222A</i>	G1408R	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>A4226G</i>	Y1409C	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>C4227G</i>	Y1409X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>C4234T</i>	L1412F	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>A4255G</i>	K1419E	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4258C</i>	G1420R	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4279T</i>	A1427S	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>C4283T</i>	A1428V	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>A4294G</i>	R1432G	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4296C</i>	R1432S	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4298T</i>	G1433V	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4299A</i>	G1433G	Silent/Splice site	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4299+1T*</i>	-	Splice site	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>4299+1delG*</i>	-	Splice Site	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4300-1A*</i>	-	Splice site	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>T4302G</i>	Y1434X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>C4313T</i>	P1438L	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4320A</i>	W1440X	Nonsense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>G4321C</i>	E1441Q	Missense	DIII/S 5-S6	BrS	Kapplinger et al. 2010
<i>A4342C</i>	I1448L	Missense	DIII/S 6	BrS	Kapplinger et al. 2010
<i>T4343C</i>	I1448T	Missense	DIII/S 6	BrS	Kapplinger et al. 2010
<i>A4346G</i>	Y1449C	Missense	DIII/S 6	BrS	Kapplinger et al. 2010
<i>T4352A</i>	V1451D	Missense	DIII/S 6	BrS	Kapplinger et al. 2010
<i>G4372T</i>	G1406R ⁽⁶⁾	Missense	DIII/S 5-S6	BrS+CCD(6)	Kindt et al. 2001
<i>4376_4379delTCTT</i>	F1459SfsX3	Frame shift	DIII/S 6	BrS	Kapplinger et al. 2010
<i>A4387T</i>	N1463Y	Missense	DIII/S 6	BrS	Kapplinger et al. 2010
<i>4389_4396delCCTCTTTA</i>	L1464WfsX5	Frame shift	DIII/S 6	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
A1294G	R1432G	Missense	DIIIS5-S6	BrS	Deschennes et al. 2000
G4402T	V1468F	Missense	DIII/S6	BrS	Kapplinger et al. 2010
4402-4406del	G1467fs+13X	Frameshift	DIII/S6	BrS	Priori et al 2002
C4426T	Q1476X	Nonsense	DIII/DIV	BrS	Kapplinger et al. 2010
4435-4437delAAG	K1479del	Deletion	DIII-DIV	BrS	Smits et al 2002; Schulze-Bahr 2003
G4437+5A*	-	Splice site	DIII/DIV	BrS	Kapplinger et al. 2010
4477_4479delAAG	K1493del	In-frame del	DIII/DIV	BrS	Kapplinger et al. 2010
A4477T	K1493X	Nonsense	DIII/DIV	BrS	Kapplinger et al. 2010
-	Y1494N	Missense	DIII/DIV	BrS	Tian et al 2007
4498-4500del	K1500del	Deletion	DIII-DIV	BrS+RW+CD	Priori et al 2002
C4501G	L1501V	Missense	DIII/DIV	BrS	Kapplinger et al. 2010
n.a.	G1502S	Missense	DIII-DIV	BrS	Smits et al. 2002
C4534T	R1512W	Missense	DIII-DIV	BrS	Deschennes et al. 2000
T4562A	I1521K	Missense	DIII/DIV	BrS	Kapplinger et al. 2010
G4573A	V1525M	Missense	DIV/S1	BrS	Kapplinger et al. 2010
A4580G	K1527R ⁽⁷⁾	Missense	DIII-DIV	BrS	Yokoi et al. 2005
G4642A	E1548K	Missense	DIV/S1-S2	BrS	Kapplinger et al. 2010
G4705C	A1569P ⁽⁷⁾	Missense	DIV/S1	BrS	Yokoi et al. 2005
4708_4710dupATC	I1570dup	In-frame insertion	DIV/S2	BrS	Kapplinger et al. 2010
T4712G	F1571C	Missense	DIV/S2	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>G4720A</i>	E1574K	Missense	DIV/S 2	BrS	Kapplinger et al. 2010
4729ins aa	K1578fs+52X	Frameshift	DIV/S 2	BrS+SSS	Makiyama et al. 2005
<i>T4745C</i>	L1582P	Missense	DIV/S 2	BrS	Kapplinger et al. 2010
<i>C4747T</i>	R1583C	Missense	DIV/S 2-S3	BrS	Kapplinger et al. 2010
<i>G4748A</i>	R1583H	Missense	DIV/S 2-S3	BrS	Kapplinger et al. 2010
<i>G4773A</i>	W1591X	Nonsense	DIV/S 3	BrS	Kapplinger et al. 2010
<i>G4783C</i>	D1595H	Missense	DIV/S 3	DCM	Olson E et al. 2005
<i>G4810A</i>	V1604M	Missense	DIV/S 3	BrS	Kapplinger et al. 2010
c.4810+3_4810+6dupGGGT	-	Splice error	DIV/S 3-S4	BrS	Rossenbacker et al. 2005
4813+5insTGGG	V1604sp	Splice error	DIV/S 3-S4	BrS	Hong K et al 2005
<i>4813+2_4813+5dupTGGG</i>	-	Splice site	DIV/S 3	BrS	Kapplinger et al. 2010
<i>A4838T</i>	Q1613L	Missense	DIV/S 3-S4	BrS	Kapplinger et al. 2010
<i>C4845A</i>	Y1615X	Nonsense	DIV/S 3-S4	BrS	Kapplinger et al. 2010
4849delTCT	F1617del	Deletion	DIV/S 3-S4	BrS	Linag et al. 2006
<i>4856delC</i>	P1619RfsX12	Frame shift	DIV/S 3-S4	BrS	Kapplinger et al. 2010
<i>C4858T</i>	T1620M	Missense	DIV/S 3-S4		Chen et al. 1998
<i>C4859T</i>	T1620M	Missense	DIV/S 3-S4	BrS	Kapplinger et al. 2010
<i>C4864T</i>	R1623X	Nonesense	DIV/S 4	BrS+SSS	Makiyama et al. 2005
<i>C4867T</i>	R1623X	Nonsense	DIV/S 4	BrS	Kapplinger et al. 2010
<i>G4868A</i>	R1623Q	Missense	DIV/S 4	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
<i>C4885T</i>	R1629X	Nonsense	DIV/S4	BrS	Kapplinger et al. 2010
<i>G4886A</i>	R1629Q	Missense	DIV/S4	BrS	Kapplinger et al. 2010
<i>C4912T</i>	R1638X	Nonsense	DIV/S4	BrS	Kapplinger et al. 2010
<i>G4925A</i>	G1642E	Missense	DIV/S4	BrS	Kapplinger et al. 2010
<i>C4946A</i>	A1649V	Missense	DIVS4-/S5	BrS	Linag et al. 2006
<i>A4975G</i>	I1660V(8)	Missense	DIV/S5	BrS+AVblock	Cordeiro et al. 2006
<i>A4978G</i>	I1660V	Missense	DIV/S5	BrS	Kapplinger et al. 2010
<i>G4981A</i>	G1661R	Missense	DIV/S5	BrS	Kapplinger et al. 2010
<i>G4981C</i>	G1661R	Missense	DIV/S5	BrS	Kapplinger et al. 2010
<i>G4999A</i>	V1667I	Missense	DIV/S5	BrS	Kapplinger et al. 2010
<i>C5015A</i>	S1672Y	Missense	DIV/S5	BrS	Kapplinger et al. 2010
<i>G5038A</i>	A1680T	Missense	DIV/S5	BrS	Kapplinger et al. 2010
<i>5068_5070delGA</i>	D1690HfsX98	Frame shift	DIV/S5-S6	BrS	Kapplinger et al. 2010
<i>C5083T</i>	Q1695X	Nonsense	DIV/S5-S6	BrS	Kapplinger et al. 2010
<i>G5092A</i>	A1698T	Missense	DIV/S5-S6	BrS	Kapplinger et al. 2010
-	S1710L	Missense	DIV/S5-S6	IVF(9)	Akai et al.2000
<i>5124_5126delCAC</i>	T1709del	In-frame del	DIV/S5-S6	BrS	Kapplinger et al. 2010
<i>C5126T</i>	T1709M	Missense	DIV/S5-S6	BrS	Kapplinger et al. 2010
<i>C5126G</i>	T1709R	Missense	DIV/S5-S6	BrS	Kapplinger et al. 2010
<i>G5134A</i>	G1712S	Missense	DIV/S5-S6	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
A5141G	D1714G	Missense	DIV/S 5-S6	BrS	Amin et al 2005
5157delC	I1720SfsX67	Frame shift	DIV/S 5-S6	BrS	Kapplinger et al. 2010
A5165G	N1722D	Missense	DIV/S 5-S6	BrS	Kapplinger et al. 2010
T5182C	C1728R	Missense	DIV/S 5-S6	BrS	Kapplinger et al. 2010
C5184G	C1728W	Missense	DIV/S 5-S6	BrS	Kapplinger et al. 2010
IVS21+1G>A	-	Splice error		BrS	Smits et al. 2002
G5218A	G1740R	Missense	DIV/S 5-S6	BrS	Priori et al 2002
n.a.	G1743E	Missense	DIV/S 6	BrS	Smits et al. 2002
G5227A	G1743R	Missense	DIV/S 6	BrS	Takahata et al. 2003
G5228A	G1743E	Missense	DIV/S 5-S6	BrS	Kapplinger et al. 2010
5290delG	V1764SfsX23	Frame shift	DIV/S 6	BrS	Kapplinger et al. 2010
G5290T	V1764F	Missense	DIV/S 6	BrS	Kapplinger et al. 2010
C5336T	T1779M	Missense	c-term	BrS	Kapplinger et al. 2010
G5350A	E1784K	Missense	c-term	BrS	Priori et al 2002
5356_5357delCT	L1786EfsX2	Frame shift	c-term	BrS	Kapplinger et al. 2010
5387_5388insTGA	1795_1796insD	In-frame ins	c-term	BrS	Kapplinger et al. 2010
5420dupA	F1808IfsX3	Frame shift	c-term	BrS	Kapplinger et al. 2010
C5435A	S1812X	Nonsense	c-term	BrS	Kapplinger et al. 2010
5464_5467delTCTG	E1823HfsX10	Frame shift	c-term	BrS	Kapplinger et al. 2010
C5494G	Q1832E	Missense	c-term	BrS	Kapplinger et al. 2010

Nucleotide Change	Aminoacid Change	Mutation Type	Region	Phenotype	Reference
Ins TGA 5537	1795 insD	Insertion	c-term	BrS + RW(10)	Bezzina et al. 1999
5577_5578dupAA	R1860KfsX13	Frame shift	c-term	BrS	Kapplinger et al. 2010
G5581A	V1861I	Missense	c-term	BrS	Kapplinger et al. 2010
T5383C	Y1795H	Missense	c-term	BrS	Priori et al. 2000
C5425A	S1812X	Nonsense	c-term	BrS+CCD	Schulze-Bahr 2003
n.a.	A1924T	Missense	c-term	BrS	Smits et al. 2002
G5616C	K1872N	Missense	c-term	BrS	Kapplinger et al. 2010
G5707C	S1904L	Missense	c-term	BrS	Kapplinger et al. 2010
G5770A	A1924T	Missense	c-term	BrS	Kapplinger et al. 2010
G5803A	G1935S	Missense	c-term	BrS	Kapplinger et al. 2010
G5812A	E1938K	Missense	c-term	BrS	Kapplinger et al. 2010
6010_6012dupTTC	F2004dup	In-frame ins	c-term	BrS	Kapplinger et al. 2010
T6010G	F2004V	Missense	c-term	BrS	Kapplinger et al. 2010
-	V1951L	Missense	c-term	SIDS	Arnestad et al 2007

Amino acid numbering in “Amino Acid Change” is based on Gene Bank cDNA:
NM_000335 (which is provided herein as SEQ ID NO: 659)

n.a. = not available; ARVC= arrhythmogenic right ventricular cardiomyopathy; SSS= sinus node disease; CCD= Cardiac Conduction Defect; RW = Romano-Ward (long QT) phenotype

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37. Yi et al., *Di Yi Jun Yi Da Xue Xue Bao* 23(11): 1139-1142 (2003)
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Footnotes of Table 1:

- (1) This mutation was associated with mild phenotype and low penetrance; expression studies were not performed
- (2) Atrial standstill occurred during procainamide administration and was associated with a Brugada syndrome phenotype (Takehara et al, 2004).
- (3) SUNDS = Sudden Unexplained Nocturnal Death Syndrome, alternative name for Brugada syndrome described in far east countries.
- (4) SIDS=Sudden Infant Death Syndrome;
- (5) BrS phenotype reported by Priori et al; RW phenotype reported by Splawski et al;
- (6) CCD= Cardiac Conduction Defect; The nucleotide and amino acid coding of G1406R has been reported as described in the paper.
- (7) K1527R and A1569P were found on the same allele in an asymptomatic subject with BrS pattern.
- (8) This mutation was found as compound heterozygous with P336L.

(9) Idiopathic Ventricular Fibrillation in the absence of the typical Brugada syndrome pattern;
 (10) BS + RW (Romano Ward)=Brugada Syndrome and Long QT syndrome is present in the same family.

[0074] Also, according to this website, the mutations associated with Brugada Syndrome 4 occur in the CACNA1c gene and include those shown in Table 2:

TABLE 2

Nucleotide Change	Amino Acid Change	Mutation Type	Localization	Phenotype	Functional Effect	Notes	References
109 G>A	G37R	sSNP	N-term (exon 2)	-			Burashnikov et al 2010
116 C>T	A39V	Missense	N-term (exon 2)	Brugada/short QT	Loss of function	found in association with SNP KCNH2 K897T	Burashnikov et al 2010 ; Antzelevitch et al. 2007
-	G402S	Missense	DI/S6 (exon 8)	Timothy (LQT8)	Gain of function		Splawski et al 2005
1216 G>A	G406R	Missense	DI/S6 (exon 8A)	Timothy (LQT8)	Gain of function		Splawski et al 2004; Antzelevitch et al. 2007
1468 G>A	G490R	Missense	DI/DII (exon 10)	Brugada/short QT	Loss of function	found in association with SNP SCN5A-H558R and SCN5A-S1103Y	Burashnikov et al 2010
2449 C>T	P817S	cSNP	DI/DII (exon 17)	-			Burashnikov et al 2010
2548-550del GAG	E850 del	Deletion	DII/DIII (exon 19)	Early repolarization			Burashnikov et al 2010
3343 G>A	E1115K	Missense	DIII-S5/S6 (exon 43)	Brugada	-	found in association with SNP KCNH2 K897T	Burashnikov et al 2010
5150 C>G	.A1717G	cSNP	C-term (exon 42)	-			Burashnikov et al 2010
5360 C>T	T1787M	cSNP	C-term (exon 42)	-			Burashnikov et al 2010
-	P1820L	cSNP	C-term				Antzelevitch et al. 2007
-	V1821M	cSNP	C-term				Antzelevitch et al. 2007

Nucleotide Change	Amino Acid Change	Mutation Type	Localization	Phenotype	Functional Effect	Notes	References
5485_5499 dup15	E1829_Q1833 dup	Duplication	C-term (exon 44)	Brugada			Burashnikov et al 2010
5510 G>A	C1837Y	Missense	C-term (exon 42/43)	C-term		Found in association with SNP SCN5A P1090L	Burashnikov et al 2010
5639 G>A	R1880Q	Missense	C-term (exon 44)	Brugada		found in association with SNP KCNH2 K897T and CACNA1c R1973Q	Burashnikov et al 2010
5918 G>A	R1973Q	cSNP	C-term (exon 46)	-			Burashnikov et al 2010
6040 G>A	V2014I	Missense	C-term (exon 46)	Brugada		found in association with SNP CACNB2B D601E and SCN5A H558R	Burashnikov et al 2010
6388 G>A	D2130N	Missense	C-term (exon 47)	Brugada		found in association with SNP KCNE2 T10M and CACNA1C A1717G	Burashnikov et al 2010

Reference sequence in Burashnikov et al: NM_000219, NM_201590, NM_000722.2 which are provided herein as SEQ ID NOs: 660-662, respectively. Burashnikov et al., *Heart Rhythm* 7(12): 1872-1882 (2010); Antzelevitch et al., *Circulation* 115(4): 442-449 (2007); Splawski et al., *PNAS* 102(23): 8089-8096 (2005); Splawski et al., *Cell* 119(1): 19-31 (2004)

[0075] *Biological Samples*

[0076] With regard to the methods disclosed herein, in some embodiments, the biological sample obtained from the subject comprises a bodily fluid, including, but not limited to, blood, plasma, serum, lymph, breast milk, saliva, mucous, semen, vaginal secretions, cellular extracts, inflammatory fluids, cerebrospinal fluid, feces, vitreous humor, or urine obtained from the subject. In some aspects, the sample is a composite panel of at least two of the foregoing biological samples. In some aspects, the biological sample is a composite panel of at least two of a blood sample, a plasma sample, a serum sample, and a urine sample. In

exemplary aspects, the biological sample comprises blood or a fraction thereof (e.g., plasma, serum, fraction obtained via leukopheresis). In exemplary aspects, the biological sample comprises white blood cells obtained from the subject. In exemplary aspects, the biological sample comprises only white blood cells. In exemplary aspects, the biological sample is muscle tissue (e.g., skeletal muscle tissue). In exemplary aspects, the biological sample is cardiac tissue (e.g., cardiac muscle tissue).

[0077] *Subjects*

[0078] With regard to the methods disclosed herein, the subject in exemplary aspects is a mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits, mammals from the order Carnivora, including Felines (cats) and Canines (dogs), mammals from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). In some aspects, the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). In some aspects, the mammal is a human.

[0079] In exemplary embodiments, the subject is a male human. In exemplary embodiments, the subject is about 40 years old or younger. In exemplary aspects, the subject is about 39 years old or younger, about 38 years old or younger, about 37 years old or younger, about 36 years old or younger, about 35 years old or younger, about 34 years old or younger, about 33 years old or younger, about 32 years old or younger, about 31 years old or younger, about 30 years old or younger, about 29 years old or younger, about 28 years old or younger, about 27 years old or younger, about 26 years old or younger, about 25 years old or younger, about 24 years old or younger, about 23 years old or younger, about 22 years old or younger, about 21 years old or younger, or about 20 years old or younger.

[0080] In exemplary aspects, the subject's medical record is analyzed for any occurrence of aborted sudden cardiac death or treatment for sudden death. In exemplary embodiments, the subject has a medical record including a recent (e.g., but not limited to, within the last 30-60 days) or frequent occurrences of syncope or dizziness. In exemplary embodiments, the subject has a medical history of a family member dying due to sudden cardiac death and/or any family member being diagnosed with Brugada Syndrome. In additional or alternative aspects, the subject is one who has been screened for genetic mutations associated with Brugada Syndrome. In exemplary aspects, the subject does not have a genetic mutation in

the open reading frame of the SCN5A gene. In exemplary aspects, the subject does not have a genetic mutation in the CACNA1c gene or in the GPD1-L gene. In exemplary aspects, the subject does not have any of the genetic mutations listed in Table 1 or 2.

[0081] In exemplary embodiments, the subject does not have a structural defect of the heart or a structural heart disease. By “structural heart disease” is meant any disease that affects the heart muscle or changes the architecture of the heart, and is synonymous with “structural defect of the heart.” In some aspects, the structural defect of the heart is ischemic heart disease, chronic stable angina, or chronic angina. In some aspects, the structural defect of the heart is hypertrophic cardiomyopathy, ischemia, ischemia-reperfusion or coronary artery occlusion-reperfusion, ischemic heart disease, myocardial injury, myocardial toxicity, myocardial infarction, congenital heart lesion, valvular stenosis or valvular regurgitation, coronary artery disease, chronic angina, chronic stable angina, arrhythmias. In some aspects, the structural defect of the heart is a myocardial trauma or a myocardial toxicity.

[0082] In exemplary embodiments, the subject is not exhibiting any signs or symptoms of heart failure and/or is not experiencing heart failure. In exemplary embodiments, the subject is not exhibiting any of dyspnea, fatigue, exercise intolerance, jugular venous distension, pulmonary rales, peripheral edema, pulmonary vascular redistribution, interstitial edema, and pleural effusions.

[0083] *Controls*

[0084] In the methods described herein, the level that is determined (e.g., the level of full-length mRNA encoded by the SCN5A gene, the level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), the level of mRNA encoded by a SCN5A splicing factor gene, and/or the level of mRNA encoded by a gene of the UPR) may be the same as a control level or a cut off level or a threshold level, or may be increased or decreased relative to a control level or a cut off level or a threshold level. In some aspects, the control subject is a matched control of the same species, gender, ethnicity, age group, smoking status, BMI, current therapeutic regimen status, medical history, or a combination thereof, but differs from the subject being diagnosed in that the control does not suffer from Brugada Syndrome and/or is not at risk for Brugada Syndrome and/or is not or has not been clinically diagnosed for Brugada Syndrome and/or does not have a medical history including a family member who has been diagnosed with Brugada Syndrome. In exemplary aspects, the control subject does not have a medical

history including syncope and/or dizziness. In exemplary aspects, the control subject has not been treated for sudden cardiac death or does not have a family history of sudden cardiac death. In exemplary aspects, the control, does not have a structural defect of the heart, is not suffering from or has not had heart failure or arrhythmias. In exemplary embodiments, the control subject is not exhibiting any signs or symptoms of heart failure and/or is not experiencing heart failure. In exemplary aspects, the control subject does not have an ICD.

[0085] *Housekeeping Genes*

[0086] In the methods described herein, the level that is determined (e.g., the level of full-length mRNA encoded by the SCN5A gene, the level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), the level of mRNA encoded by a SCN5A splicing factor gene, and/or the level of mRNA encoded by a gene of the UPR) may be normalized or calibrated to a level of a housekeeping gene. The housekeeping gene in some aspects is β -actin or GAPDH. In exemplary aspects, the housekeeping gene is any one of those set forth in the sequence listing as SEQ ID NOs: 60-635 or any one of those set forth in Table 3 below.

TABLE 3

Accession No.	Name	SEQ ID NO
NM_001101	Actin, beta (ACTB)	60
NM_000034	aldolase A, fructose-bisphosphate (ALDOA)	61
NM_002046	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	62
NM_000291	Phosphoglycerate kinase 1 (PGK1)	63
NM_005566	Lactate dehydrogenase A (LDHA)	64
NM_002954	Ribosomal protein S27a (RPS27A)	65
NM_000981	Ribosomal protein L19 (RPL19)	66
NM_000975	Ribosomal protein L11 (RPL11)	67
NM_007363	Non-POU domain containing, octamer-binding (NONO)	68
NM_004309	Rho GDP dissociation inhibitor (GDI) alpha (ARHGDIA)	69
NM_000994	Ribosomal protein L32 (RPL32)	70
NM_022551	Ribosomal protein S18 (RPS18)	71
NM_007355	heat shock protein 90kDa alpha (cytosolic), class B member 1 (HSP90AB1)	72
NM_004515	Interleukin enhancer binding factor 2, 45kDa (ILF2)	73
NM_004651	Ubiquitin specific peptidase 11 (USP11)	74
NM_004888	ATPase, H ⁺ transporting, lysosomal 13kDa, V1 subunit G1 (ATP6V1G1)	75
NM_003334	Ubiquitin-like modifier activating enzyme 1 (UBA1)	76
NM_001320	Casein kinase 2, beta polypeptide (CSNK2B)	77
NM_003915	Copine I (CPNE1)	78
NM_001250	CD40 molecule, TNF receptor superfamily member 5 (CD40)	79
NM_001904	Catenin (cadherin-associated protein), beta 1, 88kDa (CTNNB1)	80
NM_003753	Eukaryotic translation initiation factor 3, subunit D (EIF3D)	81
NM_004541	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa (NDUFA1)	82
NM_001654	V-raf murine sarcoma 3611 viral oncogene homolog (ARAF)	83
NM_002967	Scaffold attachment factor B (SAFB)	84
NM_001183	H ⁺ transporting, lysosomal accessory protein 1 (ATP6AP1)	85
NM_003526	Histone cluster 1, H2bc (HIST1H2BC)	86
NM_004718	Cytochrome c oxidase subunit VIIa polypeptide 2 like (COX7A2L)	87
NM_004436	Endosulfine alpha (ENSA)	88

Accession No.	Name	SEQ ID NO
NM_001207	Basic transcription factor 3 (BTF3)	89
NM_004907	Immediate early response 2 (IER2)	90
NM_004889	ATP synthase, H ⁺ transporting, mitochondrial Fo complex, subunit F2 (ATP5J2)	91
NM_003769	Serine/arginine-rich splicing factor 9 (SRSF9)	92
NM_003910	BUD31 homolog (S. cerevisiae) (BUD31)	93
NM_000100	Cystatin B (stefin B) (CSTB)	94
NM_004785	Solute carrier family 9 (sodium/hydrogen exchanger), member 3 regulator 2 (SLC9A3R2)	95
NM_001120	Major facilitator superfamily domain containing 10 (MFSD10)	96
NM_000182	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (HADHA)	97
NM_003377	Vascular endothelial growth factor B (VEGFB)	98
NM_003576	Serine/threonine kinase 24 (STK24)	99
NM_000918	Prolyl 4-hydroxylase, beta polypeptide (P4HB),	100
NM_004584	RAD9 homolog A (S. pombe) (RAD9A)	101
NM_004952	Ephrin-A3 (EFNA3)	102
NM_004308	Rho GTPase activating protein 1 (ARHGAP1)	103
NM_003190	TAP binding protein (tapasin) (TAPBP)	104
NM_004640	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B (DDX39B)	105
NM_001064	Transketolase (TKT)	106
NM_002117	Major histocompatibility complex, class I, C (HLA-C)	107
NM_004161	RAB1A, member RAS oncogene family (RAB1A)	108
NM_003339	Ubiquitin-conjugating enzyme E2D 2 (UBE2D2)	109
NM_003969	Ubiquitin-conjugating enzyme E2M (UBE2M)	110
NM_000516	GNAS complex locus (GNAS)	111
NM_002819	Polypyrimidine tract binding protein 1 (PTBP1)	112
NM_001001	Ribosomal protein L36a-like (RPL36AL)	113
NM_004649	Chromosome 21 open reading frame 33 (C21orf33), nuclear gene encoding mitochondrial protein	114
NM_000175	Glucose-6-phosphate isomerase (GPI)	115
NM_001867	Cytochrome c oxidase subunit VIIc (COX7C)	116
NM_001967	Eukaryotic translation initiation factor 4A2 (EIF4A2)	117
NM_001863	Cytochrome c oxidase subunit VIb polypeptide 1 (ubiquitous) (COX6B1)	118
NM_001997	Finkel-Biskis-Reilly murine sarcoma virus (FBR-MuSV) ubiquitously expressed (FAU)	119
NM_002088	Glutamate receptor, ionotropic, kainate 5 (GRIK5)	120
NM_001862	Cytochrome c oxidase subunit Vb (COX5B)	121
NM_004255	Cytochrome c oxidase subunit Va (COX5A)	122
NM_001788	Septin 7 (SEPT7)	123
NM_004781	Vesicle-associated membrane protein 3 (cellubrevin) (VAMP3)	124
NM_003801	Glycosylphosphatidylinositol anchor attachment protein 1 homolog (yeast) (GPAA1)	125
NM_004643	Poly(A) binding protein, nuclear 1 (PABPN1)	126
NM_001537	Heat shock factor binding protein 1 (HSBP1)	127
NM_003680	Tyrosyl-tRNA synthetase (YARS)	128
NM_003345	Ubiquitin-conjugating enzyme E2I (UBE2I)	129
NM_002568	Poly(A) binding protein, cytoplasmic 1 (PABPC1)	130
NM_001487	Biogenesis of lysosomal organelles complex-1, subunit 1 (BLOC1S1)	131
NM_001861	Cytochrome c oxidase subunit IV isoform 1 (COX4I1)	132
NM_004890	Sperm associated antigen 7 (SPAG7)	133
NM_002812	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 8 (PSMD8)	134
NM_004926	Zinc finger protein 36, C3H type-like 1 (ZFP36L1)	135
NM_002539	Ornithine decarboxylase 1 (ODC1)	136
NM_000979	Ribosomal protein L18 (RPL18)	137
NM_000977	Ribosomal protein L13 (RPL13)	138
NM_001015	Ribosomal protein S11 (RPS11)	139
NM_001760	Cyclin D3 (CCND3)	140
NM_003973	Ribosomal protein L14 (RPL14)	141
NM_002815	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 11 (PSMD11)	142
NM_000367	Thiopurine S-methyltransferase (TPMT)	143
NM_000973	Ribosomal protein L8 (RPL8)	144
NM_004689	Metastasis associated 1 (MTA1),	145
NM_001848	Collagen, type VI, alpha 1 (COL6A1)	146
NM_004068	Adaptor-related protein complex 2, mu 1 subunit (AP2M1)	147

Accession No.	Name	SEQ ID NO
NM_001687	ATP synthase, H ⁺ transporting, mitochondrial F1 complex, delta subunit (ATP5D)	148
NM_004197	Serine/threonine kinase 19 (STK19)	149
NM_001028	Ribosomal protein S25 (RPS25)	150
NM_001022	Ribosomal protein S19 (RPS19)	151
NM_004759	Mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2)	152
NM_001623	Allograft inflammatory factor 1 (AIF1)	153
NM_004894	Chromosome 14 open reading frame 2 (C14orf2)	154
NM_002375	Microtubule-associated protein 4 (MAP4)	155
NM_001013	Ribosomal protein S9 (RPS9)	156
NM_003779	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 3 (B4GALT3)	157
NM_001296	Chemokine binding protein 2 (CCBP2)	158
NM_001009	Ribosomal protein S5 (RPS5)	159
NM_003021	Small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha (SGTA)	160
NM_004285	Hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase) (H6PD),	161
NM_004142	Matrix metalloproteinase-like 1 (MMPL1)	162
NM_001950	E2F transcription factor 4, p107/p130-binding (E2F4)	163
NM_003815	ADAM metalloproteinase domain 15 (ADAM15)	164
NM_001119	Adducin 1 (alpha) (ADD1)	165
NM_001111	Adenosine deaminase, RNA-specific (ADAR)	166
NM_003466	Paired box 8 (PAX8)	167
NM_001155	Annexin A6 (ANXA6)	168
NM_003465	Chitinase 1 (chitotriosidase) (CHIT1)	169
NM_003186	Transgelin (TAGLN)	170
NM_000802	Folate receptor 1 (adult) (FOLR1),	171
NM_004924	Actinin, alpha 4 (ACTN4)	172
NM_002931	Ring finger protein 1 (RING1)	173
NM_000020	Activin A receptor type II-like 1 (ACVRL1),	174
NM_001785	Cytidine deaminase (CDA)	175
NM_004339	Pituitary tumor-transforming 1 interacting protein (PTTG1IP)	176
NM_003860	Barrier to autointegration factor 1 (BANF1)	177
NM_000214	Jagged 1 (JAG1)	178
NM_002167	Inhibitor of DNA binding 3, dominant negative helix-loop-helix protein (ID3)	179
NM_001664	Ras homolog gene family, member A (RHOA)	180
NM_003166	Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3 (SULT1A3)	181
NM_001746	Calnexin (CANX)	182
NM_001662	ADP-ribosylation factor 5 (ARF5)	183
NM_001660	ADP-ribosylation factor 4 (ARF4)	184
NM_001658	ADP-ribosylation factor 1 (ARF1)	185
NM_003313	Tissue specific transplantation antigen P35B (TSTA3)	186
NM_001494	GDP dissociation inhibitor 2 (GDI2)	187
NM_003145	Signal sequence receptor, beta (translocon-associated protein beta) (SSR2)	188
NM_001619	Adrenergic, beta, receptor kinase 1 (ADRBK1)	189
NM_001420	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 3 (Hu antigen C) (ELAVL3)	190
NM_004930	Capping protein (actin filament) muscle Z-line, beta (CAPZB)	191
NM_004596	Small nuclear ribonucleoprotein polypeptide A (SNRPA)	192
NM_004168	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp) (SDHA)	193
NM_004156	Protein phosphatase 2 (formerly 2A)	194
NM_004910	Phosphatidylinositol transfer protein, membrane-associated 1 (PITPNM1)	195
NM_004517	Integrin-linked kinase (ILK)	196
NM_004494	Hepatoma-derived growth factor (HDGF)	197
NM_004121	Gamma-glutamyltransferase 5 (GGT5)	198
NM_004404	Septin 2 (SEPT2)	199
NM_004394	Death-associated protein (DAP)	200
NM_004383	c-src tyrosine kinase (CSK)	201
NM_004074	Cytochrome c oxidase subunit VIIIA (ubiquitous) (COX8A)	202
NM_004039	Annexin A2 (ANXA2)	203
NM_001053	Somatostatin receptor 5 (SSTR5)	204
NM_001328	C-terminal binding protein 1 (CTBP1)	205
NM_001273	Chromodomain helicase DNA binding protein 4 (CHD4)	206
NM_003430	Zinc finger protein 91 (ZNF91)	207
NM_003314	Tetratricopeptide repeat domain 1 (TTC1)	208
NM_003217	Transmembrane BAX inhibitor motif containing 6 (TMBIM6)	209

Accession No.	Name	SEQ ID NO
NM_003132	Spermidine synthase (SRM)	210
NM_000199	N-sulfoglucosamine sulfohydrolase (SGSH)	211
NM_002818	Proteasome (prosome, macropain) activator subunit 2 (PA28 beta) (PSME2)	212
NM_002733	Protein kinase, AMP-activated, gamma 1 non-catalytic subunit (PRKAG1)	213
NM_002631	Phosphogluconate dehydrogenase (PGD)	214
NM_002574	Peroxiredoxin 1 (PRDX1)	215
NM_002512	Non-metastatic cells 2, protein (NM23B) expressed in (NME2)	216
NM_002455	Metaxin 1 (MTX1)	217
NM_002444	Moesin (MSN)	218
NM_000529	Melanocortin 2 receptor (adrenocorticotrophic hormone) (MC2R)	219
NM_003573	latent transforming growth factor beta binding protein 4 (LTBP4)	220
NM_002315	LIM domain only 1 (rhombotin 1) (LMO1)	221
NM_000884	IMP (inosine 5'-monophosphate) dehydrogenase 2 (IMPDH2)	222
NM_003641	Interferon induced transmembrane protein 1 (9-27) (IFITM1)	223
NM_000841	Glutamate receptor, metabotropic 4 (GRM4)	224
NM_002070	Guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2 (GNAI2)	225
NM_001493	GDP dissociation inhibitor 1 (GDI1)	226
NM_002048	Growth arrest-specific 1 (GAS1)	227
NM_002032	Ferritin, heavy polypeptide 1 (FTH1)	228
NM_001418	Eukaryotic translation initiation factor 4 gamma, 2 (EIF4G2)	229
NM_001350	Death-domain associated protein (DAXX)	230
NM_001843	Contactin 1 (CNTN1)	231
NM_001728	basigin (Ok blood group) (BSG)	232
NM_001667	ADP-ribosylation factor-like 2 (ARL2)	233
NM_001659	ADP-ribosylation factor 3 (ARF3)	234
NM_003746	Dynein, light chain, LC8-type 1 (DYNLL1)	235
NM_002127	Major histocompatibility complex, class I, G (HLA-G)	236
NM_004712	Hepatocyte growth factor-regulated tyrosine kinase substrate (HGS)	237
NM_003475	Ras association (RalGDS/AF-6) domain family (N-terminal) member 7 (RASSF7)	238
NM_004046	ATP synthase, H ⁺ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle (ATP5A1)	239
NM_001894	Casein kinase 1, epsilon (CSNK1E)	240
NM_003795	Sorting nexin 3 (SNX3)	241
NM_001909	Cathepsin D (CTSD)	242
NM_002792	Proteasome (prosome, macropain) subunit, alpha type, 7 (PSMA7)	243
NM_002799	Proteasome (prosome, macropain) subunit, beta type, 7 (PSMB7)	244
NM_002300	Lactate dehydrogenase B (LDHB)	245
NM_004176	Sterol regulatory element binding transcription factor 1 (SREBF1)	246
NM_002796	Proteasome (prosome, macropain) subunit, beta type, 4 (PSMB4)	247
NM_002794	Proteasome (prosome, macropain) subunit, beta type, 2 (PSMB2)	248
NM_002793	Proteasome (prosome, macropain) subunit, beta type, 1 (PSMB1)	249
NM_002473	Myosin, heavy chain 9, non-muscle (MYH9)	250
NM_001810	centromere protein B, 80kDa (CENPB)	251
NM_002624	Prefoldin subunit 5 (PFDN5)	252
NM_004710	Synaptogyrin 2 (SYNGR2)	253
NM_001127	Adaptor-related protein complex 1, beta 1 subunit (AP1B1)	254
NM_002107	H3 histone, family 3A (H3F3A)	255
NM_003899	Rho guanine nucleotide exchange factor (GEF) 7 (ARHGEF7)	256
NM_003406	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (YWHAZ)	257
NM_002419	Mitogen-activated protein kinase kinase kinase 11 (MAP3K11)	258
NM_001130	Amino-terminal enhancer of split (AES)	259
NM_003379	Ezrin (EZR)	260
NM_002636	PHD finger protein 1 (PHF1)	261
NM_002622	Prefoldin subunit 1 (PFDN1)	262
NM_001823	Creatine kinase, brain (CKB)	263
NM_003405	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (YWHAH)	264
NM_002939	Ribonuclease/angiogenin inhibitor 1 (RNH1)	265
NM_003562	Solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 (SLC25A11)	266
NM_001916	Cytochrome c-1 (CYC1)	267
NM_002823	Prothymosin, alpha (PTMA)	268

Accession No.	Name	SEQ ID NO
NM_003096	Small nuclear ribonucleoprotein polypeptide G (SNRPG)	269
NM_003321	Tu translation elongation factor, mitochondrial (TUFM)	270
NM_003404	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (YWHAB)	271
NM_002946	Replication protein A2, 32kDa (RPA2)	272
NM_004356	CD81 molecule (CD81)	273
NM_001743	Calmodulin 2 (phosphorylase kinase, delta) (CALM2)	274
NM_004231	ATPase, H ⁺ transporting, lysosomal 14kDa, V1 subunit F (ATP6V1F)	275
NM_004893	H2A histone family, member Y (H2AFY)	276
NM_004146	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa (NDUFB7)	277
NM_002128	High mobility group box 1 (HMGB1)	278
NM_002002	Fc fragment of IgE, low affinity II, receptor for (CD23) (FCER2)	279
NM_000858	Guanylate kinase 1 (GUK1)	280
NM_001469	X-ray repair complementing defective repair in Chinese hamster cells 6 (XRCC6)	281
NM_003766	Beclin 1, autophagy related (BECN1)	282
NM_003906	Minichromosome maintenance complex component 3 associated protein (MCM3AP)	283
NM_000757	Colony stimulating factor 1 (macrophage) (CSF1)	284
NM_002149	Hippocalcin-like 1 (HPCAL1)	285
NM_001694	H ⁺ transporting, lysosomal 16kDa, V0 subunit c (ATP6V0C)	286
NM_004047	H ⁺ transporting, lysosomal 21kDa, V0 subunit b (ATP6V0B)	287
NM_001696	ATPase, H ⁺ transporting, lysosomal 31kDa, V1 subunit E1 (ATP6V1E1)	288
NM_001865	Cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2)	289
NM_004373	Cytochrome c oxidase subunit VIa polypeptide 1 (COX6A1)	290
NM_000801	FK506 binding protein 1A	291
NM_000992	Ribosomal protein L29 (RPL29)	292
NM_000988	Ribosomal protein L27 (RPL27)	293
NM_001004	ribosomal protein, large, P2 (RPLP2)	294
NM_001003	Ribosomal protein, large, P1 (RPLP1)	295
NM_000405	GM2 ganglioside activator (GM2A)	296
NM_000967	Ribosomal protein L3 (RPL3)	297
NM_001428	Enolase 1, (alpha) (ENO1)	298
NM_000999	Ribosomal protein L38 (RPL38)	299
NM_000997	Ribosomal protein L37 (RPL37)	300
NM_000995	Ribosomal protein L34 (RPL34)	301
NM_002948	Ribosomal protein L15 (RPL15)	302
NM_002952	Ribosomal protein S2 (RPS2)	303
NM_001026	Ribosomal protein S24 (RPS24)	304
NM_001020	Ribosomal protein S16 (RPS16)	305
NM_001018	Ribosomal protein S15 (RPS15)	306
NM_001017	Ribosomal protein S13 (RPS13)	307
NM_000969	Ribosomal protein L5 (RPL5)	308
NM_000985	Ribosomal protein L17 (RPL17)	309
NM_000937	Polymerase (RNA) II (DNA directed) polypeptide A, 220kDa (POLR2A)	310
NM_001016	Ribosomal protein S12 (RPS12)	311
NM_002140	Heterogeneous nuclear ribonucleoprotein K (HNRNPK)	312
NM_002138	Heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa) (HNRNPD)	313
NM_004499	Heterogeneous nuclear ribonucleoprotein A/B (HNRNPAB)	314
NM_001014	Ribosomal protein S10 (RPS10)	315
NM_002383	MYC-associated zinc finger protein (purine-binding transcription factor) (MAZ)	316
NM_002467	V-myc myelocytomatosis viral oncogene homolog (avian) (MYC)	317
NM_001436	Fibrillarin (FBL)	318
NM_004069	Adaptor-related protein complex 2, sigma 1 subunit (AP2S1)	319
NM_001614	Actin, gamma 1 (ACTG1)	320
NM_002355	Mannose-6-phosphate receptor (cation dependent) (M6PR)	321
NM_004597	Small nuclear ribonucleoprotein D2 polypeptide 16.5kDa (SNRPD2)	322
NM_002308	Lectin, galactoside-binding, soluble, 9 (LGALS9)	323
NM_000398	Cytochrome b5 reductase 3 (CYB5R3)	324
NM_000754	Catechol-O-methyltransferase (COMT)	325
NM_002406	Mannosyl (alpha-1,3-)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase (MGAT1)	326
NM_003752	Eukaryotic translation initiation factor 3, subunit C (EIF3C)	327
NM_001355	D-dopachrome tautomerase (DDT)	328

Accession No.	Name	SEQ ID NO
NM_004960	Fused in sarcoma (FUS)	329
NM_004729	Zinc finger, BED-type containing 1 (ZBED1)	330
NM_004587	Ribosome binding protein 1 homolog 180kDa (dog) (RRBP1)	331
NM_004552	NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa (NADH-coenzyme Q reductase) (NDUFS5)	332
NM_004450	Enhancer of rudimentary homolog (Drosophila) (ERH)	333
NM_004048	Beta-2-microglobulin (B2M)	334
NM_000239	Lysozyme (LYZ)	335
NM_000269	Non-metastatic cells 1, protein (NM23A) expressed in (NME1)	336
NM_000431	Mevalonate kinase (MVK)	337
NM_001247	Ectonucleoside triphosphate diphosphohydrolase 6 (putative) (ENTPD6)	338
NM_003365	Ubiquinol-cytochrome c reductase core protein I (UQCRC1)	339
NM_003329	Thioredoxin (TXN)	340
NM_001069	Tubulin, beta 2A class IIa (TUBB2A)	341
NM_000356	Treacher Collins-Franceschetti syndrome 1 (TCOF1)	342
NM_003134	Signal recognition particle 14kDa (homologous Alu RNA binding protein) (SRP14)	343
NM_003131	Serum response factor (c-fos serum response element-binding transcription factor) (SRF)	344
NM_000454	Superoxide dismutase 1	345
NM_003091	Small nuclear ribonucleoprotein polypeptides B and B1 (SNRNPB)	346
NM_003089	Small nuclear ribonucleoprotein 70kDa (U1) (SNRNP70)	347
NM_003016	Serine/arginine-rich splicing factor 2 (SRSF2)	348
NM_003952	Ribosomal protein S6 kinase, 70kDa, polypeptide 2 (RPS6KB2)	349
NM_002950	Ribophorin I (RPN1)	350
NM_002743	Protein kinase C substrate 80K-H (PRKCSH)	351
NM_002686	Phenylethanolamine N-methyltransferase (PNMT)	352
NM_002654	Pyruvate kinase, muscle (PKM2)	353
NM_002648	Pim-1 oncogene (PIM1)	354
NM_002635	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3 (SLC25A3)	355
NM_002494	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 1, 6kDa (NDUFC1)	356
NM_002488	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa (NDUFA2)	357
NM_002434	N-methylpurine-DNA glycosylase (MPG)	358
NM_002415	Macrophage migration inhibitory factor (glycosylation-inhibiting factor) (MIF)	359
NM_002227	Janus kinase 1 (JAK1)	360
NM_001536	Arginine methyltransferase 1 (PRMT1)	361
NM_000183	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (HADHB)	362
NM_002085	Glutathione peroxidase 4 (phospholipid hydroperoxidase) (GPX4)	363
NM_001502	Glycoprotein 2 (zymogen granule membrane) (GP2)	364
NM_002080	Glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2) (GOT2)	365
NM_001440	Exostoses (multiple)-like 3 (EXTL3)	366
NM_003754	Eukaryotic translation initiation factor 3, subunit F (EIF3F)	367
NM_003755	Eukaryotic translation initiation factor 3, subunit G (EIF3G)	368
NM_003757	Eukaryotic translation initiation factor 3, subunit I (EIF3I)	369
NM_001360	7-dehydrocholesterol reductase (DHCR7)	370
NM_001344	Defender against cell death 1 (DAD1)	371
NM_001914	Cytochrome b5 type A (microsomal) (CYB5A)	372
NM_001834	Clathrin, light chain B (CLTB)	373
NM_001833	Clathrin, light chain A (CLTA)	374
NM_001281	Tubulin folding cofactor B (TBCB)	375
NM_001749	Calpain, small subunit 1 (CAPNS1)	376
NM_001697	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit (ATP5O)	377
NM_001689	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit C3 (subunit 9) (ATP5G3)	378
NM_001675	Activating transcription factor 4 (tax-responsive enhancer element B67) (ATF4)	379
NM_001642	Amyloid beta (A4) precursor-like protein 2 (APLP2)	380
NM_014724	Zinc finger protein 96 (ZNF96)	381
NM_005494	DnaJ (Hsp40) homolog, subfamily B, member 6 (DNAJB6)	382
NM_006597	Heat shock 70kDa protein 8 (HSPA8)	383
NM_006623	Phosphoglycerate dehydrogenase (PHGDH)	384

Accession No.	Name	SEQ ID NO
NM_015646	RAP1B, member of RAS oncogene family (RAP1B)	385
NM_016532	Inositol polyphosphate-5-phosphatase K (INPP5K)	386
NM_015292	extended synaptotagmin-like protein 1 (ESYT1)	387
NM_005870	Sin3A-associated protein, 18kDa (SAP18)	388
NM_006833	COP9 constitutive photomorphogenic homolog subunit 6 (Arabidopsis) (COPS6)	389
NM_005718	Actin related protein 2/3 complex, subunit 4, 20kDa (ARPC4)	390
NM_005719	Actin related protein 2/3 complex, subunit 3, 21kDa (ARPC3)	391
NM_006372	Synaptotagmin binding, cytoplasmic RNA interacting protein (SYNCRIP)	392
NM_005180	BMI1 polycomb ring finger oncogene (BMI1)	393
NM_018975	Telomeric repeat binding factor 2, interacting protein (TERF2IP)	394
NM_005731	Actin related protein 2/3 complex, subunit 2, 34kDa (ARPC2)	395
NM_020151	StAR-related lipid transfer (START) domain containing 7 (STARD7)	396
NM_005103	Fasciculation and elongation protein zeta 1 (zygin I) (FEZ1)	397
NM_012179	F-box protein 7 (FBXO7)	398
NM_020360	phospholipid scramblase 3 (PLSCR3)	399
NM_014891	PDGFA associated protein 1 (PDAP1)	400
NM_005745	B-cell receptor-associated protein 31 (BCAP31)	401
NM_005418	suppression of tumorigenicity 5 (ST5)	402
NM_006262	Peripherin (PRPH)	403
NM_133476	Zinc finger protein 384 (ZNF384)	404
NM_006570	Ras-related GTP binding A (RRAGA)	405
NM_006333	C1D nuclear receptor corepressor (C1D)	406
NM_007285	GABA(A) receptor-associated protein-like 2 (GABARAPL2)	407
NM_006354	Transcriptional adaptor 3 (TADA3)	408
NM_014302	Sec61 gamma subunit (SEC61G)	409
NM_006118	HCLS1 associated protein X-1 (HAX1)	410
NM_012100	Aspartyl aminopeptidase (DNPEP)	411
NM_015680	Cyclin Pas1/PHO80 domain containing 1 (CNPPD1)	412
NM_030796	Vesicular, overexpressed in cancer, prosurvival protein 1 (VOPP1)	413
NM_024069	KxDL motif containing 1 (KXD1)	414
NM_013234	Eukaryotic translation initiation factor 3, subunit K (EIF3K)	415
NM_013310	Chromosome 2 open reading frame 27A (C2orf27A)	416
NM_018507	Hypothetical protein PRO1843 (PRO1843)	417
NM_017670	OTU domain, ubiquitin aldehyde binding 1 (OTUB1)	418
NM_016292	TNF receptor-associated protein 1 (TRAP1)	419
NM_014916	Lemur tyrosine kinase 2 (LMTK2)	420
NM_014696	G protein regulated inducer of neurite outgrowth 2 (GPRIN2)	421
NM_014630	Zinc finger protein 592 (ZNF592)	422
NM_014761	Increased sodium tolerance 1 homolog (yeast) (IST1)	423
NM_007286	Synaptopodin (SYNPO)	424
NM_007263	Coatamer protein complex, subunit epsilon (COPE)	425
NM_006349	Zinc finger, HIT-type containing 1 (ZNHIT1)	426
NM_006004	Ubiquinol-cytochrome c reductase hinge protein (UQCRH)	427
NM_005787	Asparagine-linked glycosylation 3, alpha-1,3- mannosyltransferase homolog (S. cerevisiae) (ALG3)	428
NM_012412	H2A histone family, member V (H2AFV)	429
NM_012401	Plexin B2 (PLXNB2)	430
NM_007262	Parkinson protein 7 (PARK7)	431
NM_007273	Prohibitin 2 (PHB2)	432
NM_021009	Ubiquitin C (UBC)	433
NM_023009	MARCKS-like 1 (MARCKSL1)	434
NM_015456	Cofactor of BRCA1 (COBRA1)	435
NM_005053	RAD23 homolog A (S. cerevisiae) (RAD23A)	436
NM_006830	Ubiquinol-cytochrome c reductase, complex III subunit XI (UQCR11),	437
NM_005682	G protein-coupled receptor 56 (GPR56)	438
NM_012102	Arginine-glutamic acid dipeptide (RE) repeats (RERE)	439
NM_005550	Kinesin family member C3 (KIFC3)	440
NM_021960	Myeloid cell leukemia sequence 1 (BCL2-related) (MCL1)	441
NM_021959	Protein phosphatase 1, regulatory (inhibitor) subunit 11 (PPP1R11)	442
NM_014730	Malectin (MLEC)	443
NM_014402	Ubiquinol-cytochrome c reductase, complex III subunit VII, 9.5kDa (UQCRCQ)	444
NM_007067	K(lysine) acetyltransferase 7 (KAT7)	445

Accession No.	Name	SEQ ID NO
NM_006086	Tubulin, beta 3 class III (TUBB3)	446
NM_014972	Transcription factor 25 (basic helix-loop-helix) (TCF25)	447
NM_024092	Transmembrane protein 109 (TMEM109)	448
NM_021983	Major histocompatibility complex, class II, DR beta 4 (HLA-DRB4)	449
NM_006510	Tripartite motif containing 27 (TRIM27)	450
NM_006711	RNA binding protein S1, serine-rich domain (RNPS1)	451
NM_006145	DnaJ (Hsp40) homolog, subfamily B, member 1 (DNAJB1)	452
NM_033142	Chorionic gonadotropin, beta polypeptide 7 (CGB7)	453
NM_006351	Translocase of inner mitochondrial membrane 44 homolog (yeast) (TIMM44)	454
NM_014281	Poly-U binding splicing factor 60KDa (PUF60)	455
NM_012106	ADP-ribosylation factor-like 2 binding protein (ARL2BP)	456
NM_021975	V-rel reticuloendotheliosis viral oncogene homolog A (avian) (RELA),	457
NM_014874	Mitofusin 2 (MFN2)	458
NM_006796	AFG3 ATPase family gene 3-like 2 (S. cerevisiae)(AFG3L2)	459
NM_006666	RuvB-like 2 (E. coli) (RUVBL2)	460
NM_005219	Diaphanous homolog 1 (Drosophila) (DIAPH1)	461
NM_033546	Myosin, light chain 12B, regulatory (MYL12B)	462
NM_032348	Matrix-remodelling associated 8 (MXRA8)	463
NM_024798	Sorting nexin 22 (SNX22)	464
NM_021103	Thymosin beta 10 (TMSB10)	465
NM_020195	Short chain dehydrogenase/reductase family 39U, member 1 (SDR39U1)	466
NM_017432	Prostate tumor overexpressed 1 (PTOV1)	467
NM_014901	Ring finger protein 44 (RNF44)	468
NM_014694	ADAMTS-like 2 (ADAMTSL2)	469
NM_007369	G protein-coupled receptor 161 (GPR161)	470
NM_006156	Neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)	471
NM_006429	chaperonin containing TCP1, subunit 7 (eta) (CCT7)	472
NM_006513	Seryl-tRNA synthetase (SARS)	473
NM_005022	Profilin 1 (PFN1)	474
NM_014654	Syndecan 3 (SDC3)	475
NM_007209	Ribosomal protein L35 (RPL35)	476
NM_006082	Tubulin, alpha 1b (TUBA1B)	477
NM_006362	Nuclear RNA export factor 1 (NXF1)	478
NM_014228	Solute carrier family 6 (neurotransmitter transporter, L-proline), member 7 (SLC6A7)	479
NM_006411	1-acylglycerol-3-phosphate O-acyltransferase 1 (AGPAT1)	480
NM_021134	Mitochondrial ribosomal protein L23 (MRPL23)	481
NM_021974	Polymerase (RNA) II (DNA directed) polypeptide F (POLR2F)	482
NM_006808	Sec61 beta subunit (SEC61B)	483
NM_005617	Ribosomal protein S14 (RPS14)	484
NM_005520	Heterogeneous nuclear ribonucleoprotein H1 (H) (HNRNPH1)	485
NM_006755	Transaldolase 1 (TALDO1)	486
NM_006010	Mesencephalic astrocyte-derived neurotrophic factor (MANF)	487
NM_005088	A kinase (PRKA) anchor protein 17A (AKAP17A)	488
NM_014754	Phosphatidylserine synthase 1 (PTDSS1)	489
NM_021953	Forkhead box M1 (FOXO1),	490
NM_006908	RAS-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1) (RAC1)	491
NM_014231	Vesicle-associated membrane protein 1 (synaptobrevin 1) (VAMP1)	492
NM_014833	KIAA0618 gene product (KIAA0618)	493
NM_005157	c-abl oncogene 1, non-receptor tyrosine kinase (ABL1)	494
NM_006325	RAN, member RAS oncogene family (RAN)	495
NM_007245	Ataxin 2-like (ATXN2L)	496
NM_007008	Reticulon 4 (RTN4)	497
NM_006782	Zinc finger protein-like 1 (ZFPL1)	498
NM_006694	Jumping translocation breakpoint (JTB)	499
NM_006703	Nudix (nucleoside diphosphate linked moiety X)-type motif 3 (NUDT3),	500
NM_006032	Copine VI (neuronal) (CPNE6)	501
NM_012227	GTP binding protein 6 (putative) (GTPBP6)	502
NM_014604	Tax1 (human T-cell leukemia virus type I) binding protein 3 (TAX1BP3),	503
NM_021642	Fc fragment of IgG, low affinity IIa, receptor (CD32) (FCGR2A)	504
NM_005354	Jun D proto-oncogene (JUND),	505
NM_020529	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	506

Accession No.	Name	SEQ ID NO
	(NFKBIA)	
NM_005561	Lysosomal-associated membrane protein 1 (LAMP1)	507
NM_014774	KIAA0494	508
NM_014390	Staphylococcal nuclease and tudor domain containing 1 (SND1)	509
NM_014623	Male-enhanced antigen 1 (MEA1)	510
NM_014453	Charged multivesicular body protein 2A (CHMP2A)	511
NM_012127	CDKN1A interacting zinc finger protein 1 (CIZ1)	512
NM_012099	CD3e molecule, epsilon associated protein (CD3EAP)	513
NM_006888	Calmodulin 1 (phosphorylase kinase, delta) (CALM1)	514
NM_006867	RNA binding protein with multiple splicing (RBPMS)	515
NM_006743	Complement component 1, q subcomponent-like 1 (C1QL1)	516
NM_006688	Tubulin, gamma complex associated protein 2 (TUBGCP2)	517
NM_006295	Valyl-tRNA synthetase (VARS)	518
NM_006283	Transforming, acidic coiled-coil containing protein 1 (TACC1)	519
NM_006221	Peptidylprolyl cis/trans isomerase, NIMA-interacting 1 (PIN1)	520
NM_006148	LIM and SH3 protein 1 (LASP1)	521
NM_005954	Metallothionein 3 (MT3)	522
NM_006003	Ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1 (UQCRCF1)	523
NM_005998	Chaperonin containing TCP1, subunit 3 (gamma) (CCT3)	524
NM_005997	Vacuolar protein sorting 72 homolog (S. cerevisiae) (VPS72)	525
NM_005629	Solute carrier family 6 (neurotransmitter transporter, creatine)	526
NM_005548	Lysyl-tRNA synthetase (KARS)	527
NM_005545	Immunoglobulin superfamily containing leucine-rich repeat (ISLR)	528
NM_005507	Cofilin 1 (non-muscle) (CFL1)	529
NM_005381	Nucleolin (NCL)	530
NM_005439	Myeloid leukemia factor 2 (MLF2)	541
NM_006445	PRP8 pre-mRNA processing factor 8 homolog (S. cerevisiae) (PRPF8)	542
NM_019059	translocase of outer mitochondrial membrane 7 homolog (yeast) (TOMM7)	543
NM_006039	Mannose receptor, C type 2 (MRC2)	544
NM_006066	Aldo-keto reductase family 1, member A1 (aldehyde reductase) (AKR1A1)	545
NM_013318	Proline-rich coiled-coil 2B (PRRC2B)	546
NM_006098	Guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1 (GNB2L1),	547
NM_007359	Cancer susceptibility candidate 3 (CASC3)	548
NM_017510	Transmembrane emp24 protein transport domain containing 9 (TMED9),	549
NM_015399	Breast cancer metastasis suppressor 1 (BRMS1)	550
NM_014508	Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C (APOBEC3C)	551
NM_018955	Ubiquitin B (UBB)	552
NM_006368	cAMP responsive element binding protein 3 (CREB3)	553
NM_015024	Exportin 7 (XPO7)	554
NM_031420	Mitochondrial ribosomal protein L9 (MRPL9)	555
NM_013232	Programmed cell death 6 (PDCD6)	556
NM_005917	Malate dehydrogenase 1, NAD (soluble) (MDH1)	557
NM_032801	Junctional adhesion molecule 3 (JAM3)	558
NM_030662	Mitogen-activated protein kinase kinase 2 (MAP2K2)	559
NM_006268	D4, zinc and double PHD fingers family 2 (DPF2)	560
NM_006826	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (YWHAQ)	561
NM_144582	Testis expressed 261 (TEX261)	562
NM_144565	Dual oxidase maturation factor 1 (DUOXA1)	563
NM_005984	Solute carrier family 25 (mitochondrial carrier; citrate transporter), member 1 (SLC25A1)	564
NM_017828	COMM domain containing 4 (COMMD4)	565
NM_020150	SAR1 homolog A (S. cerevisiae) (SAR1A)	566
NM_014610	Glucosidase, alpha; neutral AB (GANAB)	567
NM_014225	Protein phosphatase 2, regulatory subunit A, alpha (PPP2R1A)	568
NM_006937	SMT3 suppressor of mif two 3 homolog 2 (S. cerevisiae) (SUMO2)	569
NM_005726	Ts translation elongation factor, mitochondrial (TSFM)	570
NM_005347	Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa) (HSPA5)	571
NM_014255	Canopy 2 homolog (zebrafish) (CNPY2)	572
NM_006815	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1 (KDELRL1)	573
NM_005456	Mitogen-activated protein kinase 8 interacting protein	574
NM_005273	Guanine nucleotide binding protein (G protein), beta polypeptide 2 (GNB2)	575
NM_007260	Lysophospholipase II (LYPLA2)	576

Accession No.	Name	SEQ ID NO
NM_007103	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa (NDUFV1)	577
NM_017797	BTB (POZ) domain containing 2 (BTBD2)	578
NM_016237	Anaphase promoting complex subunit 5 (ANAPC5)	579
NM_005801	Eukaryotic translation initiation factor 1 (EIF1)	580
NM_005216	Dolichyl-diphosphooligosaccharide—protein glycosyltransferase (DDOST)	581
NM_016457	Protein kinase D2 (PRKD2)	582
NM_006442	DR1-associated protein 1 (negative cofactor 2 alpha) (DRAP1)	583
NM_021019	Myosin, light chain 6, alkali, smooth muscle and non-muscle (MYL6)	584
NM_005112	WD repeat domain 1 (WDR1)	585
NM_005370	RAB8A, member RAS oncogene family (RAB8A)	586
NM_006289	Talin 1 (TLN1)	587
NM_005698	Secretory carrier membrane protein 3 (SCAMP3)	588
NM_024011	Cyclin-dependent kinase 11A (CDK11A)	589
NM_005105	RNA binding motif protein 8A (RBM8A)	590
NM_006013	Ribosomal protein L10 (RPL10)	591
NM_005786	Teashirt zinc finger homeobox 1 (TSHZ1)	592
NM_007104	Ribosomal protein L10a (RPL10A)	593
NM_005762	Tripartite motif containing 28 (TRIM28)	594
NM_012138	Apoptosis antagonizing transcription factor (AATF)	595
NM_015318	Rho/Rac guanine nucleotide exchange factor (GEF) 18 (ARHGEF18)	596
NM_012423	Ribosomal protein L13a (RPL13A)	597
NM_021128	Polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa (POLR2L)	598
NM_032635	Transmembrane protein 147 (TMEM147)	599
NM_005080	X-box binding protein 1 (XBP1)	600
NM_006389	Hypoxia up-regulated 1 (HYOU1)	601
NM_024112	Chromosome 9 open reading frame 16 (C9orf16)	602
NM_006817	Transmembrane emp24 domain trafficking protein 2 (TMED2)	603
NM_022830	Terminal uridylyl transferase 1, U6 snRNA-specific (TUT1)	604
NM_019884	Glycogen synthase kinase 3 alpha (GSK3A)	605
NM_021107	Mitochondrial ribosomal protein S12 (MRPS12)	606
NM_021074	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa (NDUFV2)	607
NM_014944	Calsyntenin 1 (CLSTN1)	608
NM_014764	DAZ associated protein 2 (DAZAP2)	609
NM_015343	CTD nuclear envelope phosphatase 1 (CTDNEP1)	610
NM_014420	Dickkopf homolog 4 (<i>Xenopus laevis</i>) (DKK4)	611
NM_005884	p21 protein (Cdc42/Rac)-activated kinase 4 (PAK4)	612
NM_012407	Protein interacting with PRKCA 1 (PICK1)	613
NM_012111	AHA1, activator of heat shock 90kDa protein ATPase homolog 1 (yeast) (AHSA1)	614
NM_007144	Polycomb group ring finger 2 (PCGF2)	615
NM_007108	Transcription elongation factor B (SIII), polypeptide 2 (18kDa, elongin B) (TCEB2)	616
NM_007278	GABA(A) receptor-associated protein (GABARAP)	617
NM_007100	ATP synthase, H ⁺ transporting, mitochondrial Fo complex, subunit E (ATP5I)	618
NM_006936	SMT3 suppressor of mif two 3 homolog 3 (<i>S. cerevisiae</i>) (SUMO3)	619
NM_006899	Isocitrate dehydrogenase 3 (NAD ⁺) beta (IDH3B), nuclear gene encoding mitochondrial protein	620
NM_006801	RNA binding motif (RNP1, RRM) protein 3 (RBM3)	621
NM_006612	Kinesin family member 1C (KIF1C)	622
NM_006659	Tubulin, gamma complex associated protein 2 (TUBGCP2)	623
NM_006595	Apoptosis inhibitor 5 (API5)	624
NM_006401	Acidic (leucine-rich) nuclear phosphoprotein 32 family, member B (ANP32B),	625
NM_006423	Rab acceptor 1 (prenylated) (RABAC1)	626
NM_006460	Hexamethylene bis-acetamide inducible 1 (HEXIM1)	627
NM_006356	ATP synthase, H ⁺ transporting, mitochondrial Fo complex, subunit d (ATP5H)	628
NM_005891	Acetyl-CoA acetyltransferase 2 (ACAT2)	629
NM_005839	Serine/arginine repetitive matrix 1 (SRRM1)	630
NM_005594	Nascent polypeptide-associated complex alpha subunit (NACA)	631
NM_005340	Histidine triad nucleotide binding protein 1 (HINT1)	632
NM_005175	ATP synthase, H ⁺ transporting, mitochondrial Fo complex, subunit C1 (subunit 9) (ATP5G1)	633
NM_005165	Aldolase C, fructose-bisphosphate (ALDOC)	634
NM_005001	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7, 14.5kDa (NDUFA7)	635

[0087] *Treatment of Brugada Syndrome*

[0088] Further provided herein is a method of treating a subject for Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) providing a therapy for Brugada Syndrome to the subject when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0089] The invention additionally provides a method of treating a subject for Brugada Syndrome wherein the subject is one who has been analyzed for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). The method comprises the step of providing a therapy for Brugada Syndrome to the subject when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[0090] With regards to the methods of treatment, the therapy may be any therapy for Brugada Syndrome. In some aspects, the therapy is an implanted cardiac defibrillator (ICD). As used herein, the term “Implanted Cardiac Defibrillator” or “ICD” is synonymous with “implantable cardiac defibrillator” or “implanted cardiac device” or “implantable cardiac device” or “implantable cardioverter-defibrillator device” and refers to a small battery-powered electrical impulse generator that is programmed to deliver a jolt of electricity, when a cardiac arrhythmia is detected.

[0091] The therapy may be an agent which increases sodium current (e.g., sodium channel current). The therapy may be a mitochondrially-targeted antioxidant (e.g., but not limited to MitoQ), a mitochondria electron transport re-coupling agent, a Protein Kinase A Activator (e.g., but not limited to NAD⁺), a Protein Kinase C Inhibitor, a c-Src Inhibitor (e.g., but not limited to, 4-amino-5-(4-methylphenyl)-7-(t-butyl)pyrazolo-d-3,4-pyrimidine (PP1)), an anion transporter inhibitor, e.g., but not limited to 4,4'-Di-isothiocyanatostilbene-2,2'-

disulfonic acid (DIDS), an inner-membrane anion channels (IMAC) modulator (e.g., but not limited to, N-butan-2-yl-1-(2-chlorophenyl)-N-methylisoquinoline-3-carboxamide (PK11195)), an NADPH oxidase inhibitor (e.g., but not limited to apocynin, a.k.a., acetovanillone), a Protein Kinase G Activator (e.g., but not limited to 8-Bromoguanosine 3',5'-cyclic monophosphate (8-Br-cGMP)). Mitochondrially-targeted antioxidants are discussed in Smith and Murphy, *Discovery Medicine* 11(57): 106-114 (2011) and International Patent Application Publication No. WO/1999/056954. In exemplary aspects, the therapy for Brugada Syndrome is nicotinamide adenine dinucleotide (NAD⁺), PP1, pelargonidin, forskolin, chelerythrine, deltaV1-1, superoxide dismutase (SOD), mitoTEMPO, malonate, DIDS, PK11195, 4-CD, apocynin applied intracellularly (not extracellularly), adenylyl imidodiphosphate (AMPPNP), KT5823 (CAS Number 126643-37-6), or 8-Br-cGMP. Additional agents that increase sodium current include, but are not limited to, nerve growth factor (NGF), nitric oxide, isoprenaline, apelin, aldosterone, and brevetoxin 3. Alternatively, the therapy is selected from tedisamil, isoproterenol, orciprenaline, or cilostazol.

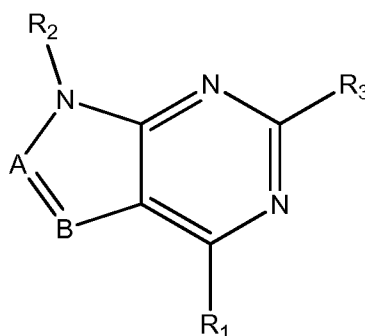
[0092] *c-Src Inhibitors*

[0093] In exemplary embodiments of any of the methods of the invention, the c-Src inhibitor is a compound which inhibits c-Src from binding to another protein. In exemplary aspects, the c-Src inhibitor is a compound which inhibits a protein binding to c-Src via the SH2 domain of c-Src, the SH3 domain of c-Src, or the substrate binding domain of c-Src.

[0094] In exemplary embodiments of any of the methods of the invention, the c-Src inhibitor is a compound which inhibits c-Src tyrosine kinase activity. In exemplary aspects, the c-Src inhibitor exhibits an IC₅₀ which is about 100 μM or less, e.g., about 50 μM or less, about 25 μM or less, about 20 μM or less, about 15 μM or less, about 10 μM or less, about 5 μM or less, about 2 μM or less, about 1 μM or less. In exemplary aspects, the c-Src inhibitor exhibits an IC₅₀ which is about 100 nM or less, e.g., about 50 nM or less, about 25 nM or less, about 20 nM or less, about 15 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, about 1 nM or less.

[0095] In exemplary aspects, the c-Src inhibitor is a heterocyclic adenosine triphosphate (ATP) analog. In exemplary aspects, the c-Src inhibitor is selected from the group consisting of: (i) a pyrazolo-[2,3-d]pyrimidine, (ii) pyrrolo-[2,3-d] pyrimidine, (iii), pyrido-[2,3-

d]pyrimidine, (iv) quinoline carbonitrile, or (v) olomucine. In exemplary aspects, the c-Src inhibitor comprises a structure of Formula I:



[Formula I]

wherein (i) A is a nitrogen atom and B is a carbon atom; (ii) A is a carbon atom and B is a nitrogen atom; or (iii) each of A and B is a carbon atom,

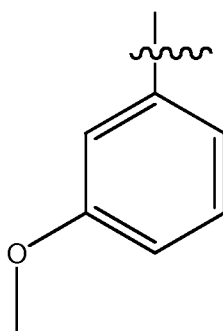
wherein, when B is a carbon atom, B is attached to H, a C1-C4 alkyl, aryl, or a substituted aryl, and R₃ is H;

wherein, when B is a nitrogen atom, R₃ is -NHR₄, wherein R₄ is a C1-C6 alcohol;

wherein R₁ is a -NH₂ or -NHR₅; wherein R₅ is aryl or substituted aryl; and

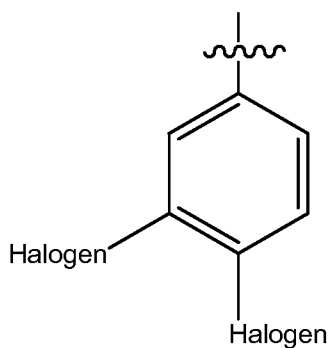
wherein R₂ is an H, alkyl, aryl, or a substituted aryl.

[0096] In exemplary aspects, each of A and B is a carbon atom, B is attached to a substituted aryl, R₁ is a -NH₂, R₂ is a substituted aryl, and R₃ is H. In exemplary aspects, B is attached to a substituted aryl of Structure A or B:



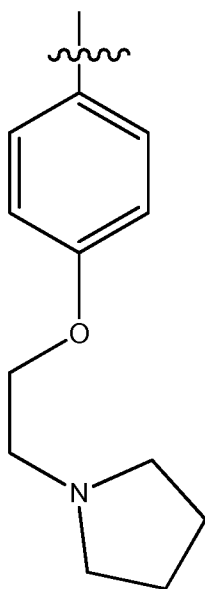
[Structure A]

or

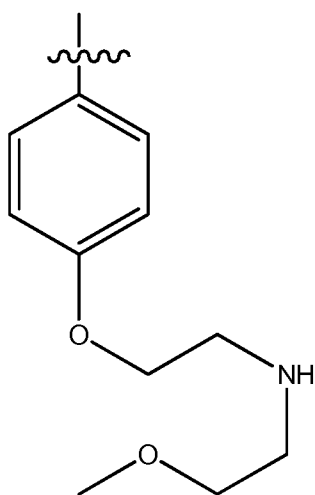


[Structure B]

wherein “Halogen” is selected from a group consisting of Cl, F, I, and Br. In exemplary aspects, the halogen is F. In exemplary aspects, R₂ is a substituted aryl of Structure C or D:



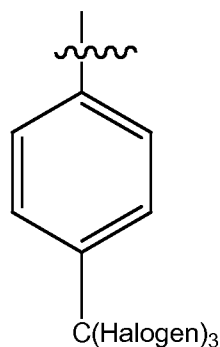
[Structure C]



[Structure D].

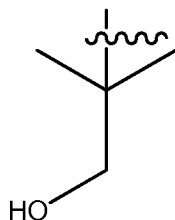
[0097] In exemplary aspects, A is a nitrogen atom, B is a carbon atom attached to an aryl, R₁ is -NH₂, R₂ is C(CH₂)₃, and R₃ is H.

[0098] In exemplary aspects, A is a carbon atom, B is a nitrogen atom, R₁ is NHR₅; wherein R₅ is a substituted aryl, R₂ is -CH₂CH₃, and R₃ is -NHR₄, wherein R₄ is a C1-C6 alcohol. In exemplary aspects, R₅ is a substituted aryl of Structure D or E:

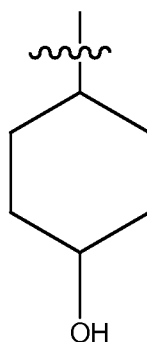


[Structure E]

wherein “Halogen” is selected from a group consisting of Cl, F, I, and Br. In exemplary aspects, the halogen is F. In exemplary aspects, R₄ is an alcohol of Structure F or G:

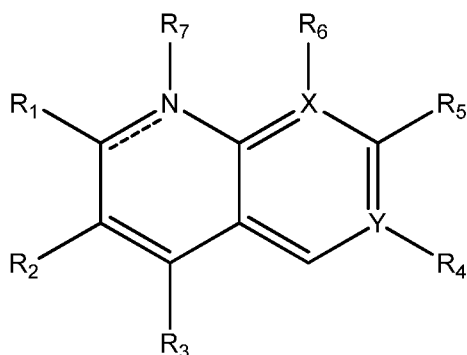


[Structure F]



[Structure G].

[0099] In exemplary aspects, the c-Src inhibitor comprises a structure of Formula II:



[Formula II]

wherein each of X and Y is independently a carbon atom or a nitrogen atom, wherein:

when X is a nitrogen atom, R6 is absent,

when X is a carbon atom, R6 is H, a C1-C4 alkyl, or $-O(C1-C4alkyl)$;

when Y is a nitrogen atom, R4 is absent,

when Y is a carbon atom, R4 is H, C1-C4 alkyl, or $-O(C1-C4alkyl)$;

wherein ----- represents a single or double bond, wherein:

when R1 is H, ----- represents a double bond,

when R1 is a double bonded oxygen atom, ----- represents a single bond; and

wherein:

R2 is $-CN$ or a substituted aryl,

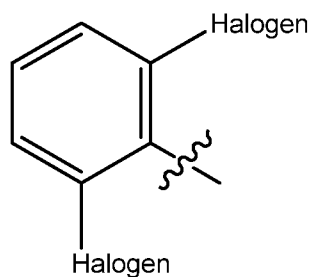
R3 is H or $-(CH_2)_{0-4}$ aryl, or $-(NH)aryl$, optionally, wherein “aryl” is a substituted aryl,

R5 is $-NHR_8$ or a substituted alkoxyl,

R7 is absent, H or a C1-C4 alkyl, and

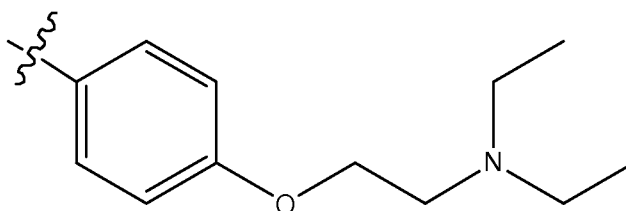
R8 is a substituted aryl.

[00100] In exemplary aspects, each of X and Y is a nitrogen atom. In exemplary aspects, R1 is a double bonded oxygen atom, R2 is a substituted aryl, R3 is H, each of R4 and R6 is absent, R5 is NHR_8 , and R7 is a C1-C4 alkyl. In exemplary aspects, R2 is a substituted aryl of Structure H:



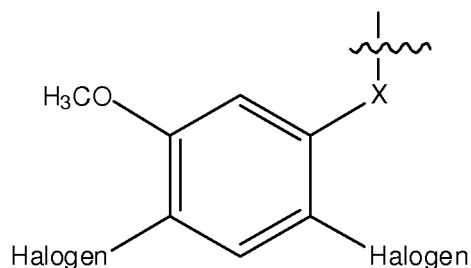
[Structure H],

wherein each “Halogen” is as defined herein. In exemplary aspects, each “Halogen” is a chlorine atom. In exemplary aspects, R8 is a substituted aryl of Structure I:



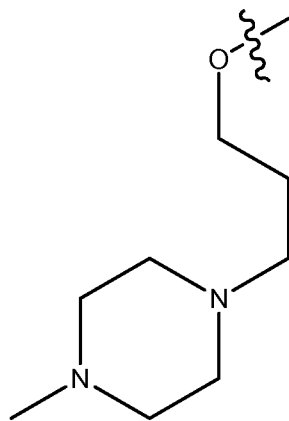
[Structure I].

[00101] In exemplary aspects, each of X and Y is a carbon atom. In exemplary aspects, R1 is H, R2 is -CN, R3 is -(CH₂)_naryl or -(NH)_naryl, wherein “aryl” is a substituted aryl, R4 is -O(C1-C4alkyl), R5 is a substituted alkoxy, R6 is H, and R7 is absent. In exemplary aspects, R3 comprises Structure J:



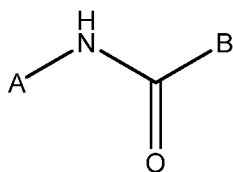
[Structure J],

wherein each “Halogen” is as defined herein and X is -(CH₂)₀₋₄ or -NH. In exemplary aspects, each “Halogen” is a chlorine atom. In exemplary aspects, R4 is -OCH₃. In exemplary aspects, R5 is a substituted alkoxy comprising the structure of Structure K:



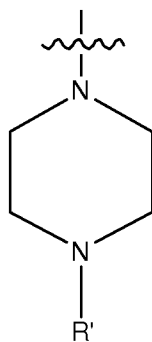
[Structure K].

[00102] In exemplary embodiments, the c-Src inhibitor comprises a structure of Formula III:



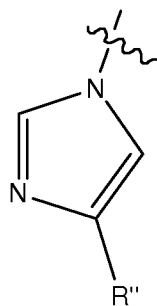
[Formula III]

wherein A is an aryl or a substituted aryl, B is a substituted aryl in which at least one of the substitutions comprises (i) a moiety comprising a structure of Structure L:



[Structure L]

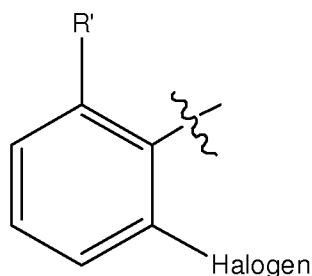
wherein R' is an alkyl or alkoxy, e.g., a C1-C4 alkyl or C1-C4 alkoxy,
or (ii) a moiety comprising a structure of Structure M:



[Structure M]

wherein R'' is an alkyl or alkoxy, e.g., a C1-C4 alkyl or C1-C4 alkoxy.

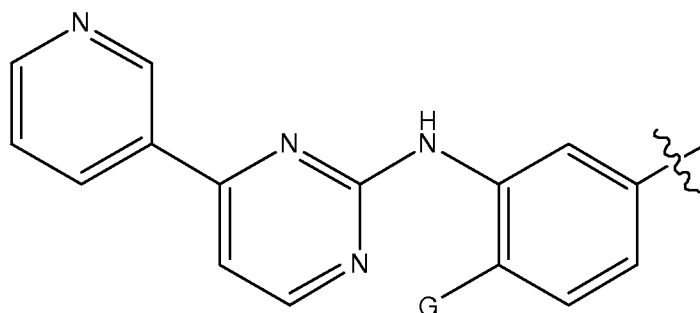
[00103] In exemplary embodiments, A of Formula III is a substituted aryl comprising the structure of Structure N:



[Structure N]

wherein R' is a C1-C4 alkyl and "halogen" is as described herein. In exemplary embodiments, the halogen is a chlorine atom.

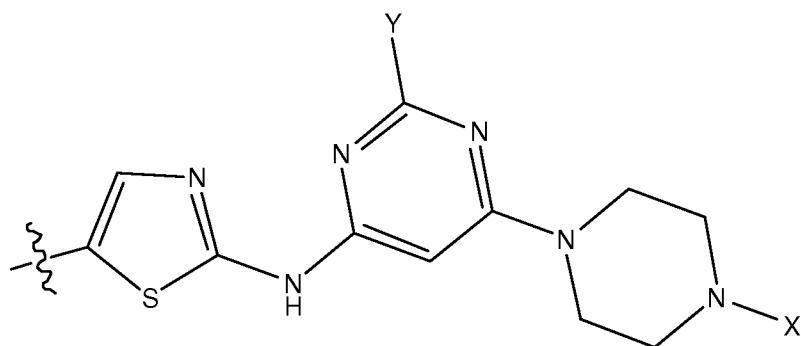
[00104] In alternative embodiments, A of Formula III is a substituted aryl comprising Structure O



[Structure O]

wherein G is $-(CH_2)_{0-4}CH_3$.

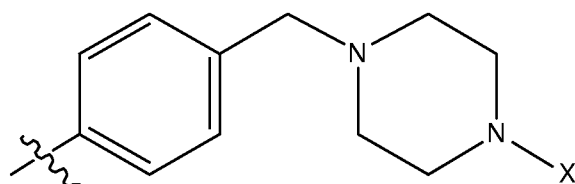
[00105] In exemplary aspects, B of Formula III is a substituted aryl comprising the structure of Structure P:



[Structure P]

wherein X is $-(CH_2)_{0-4}OH$ and Y is $-(CH_2)_{0-4}CH_3$.

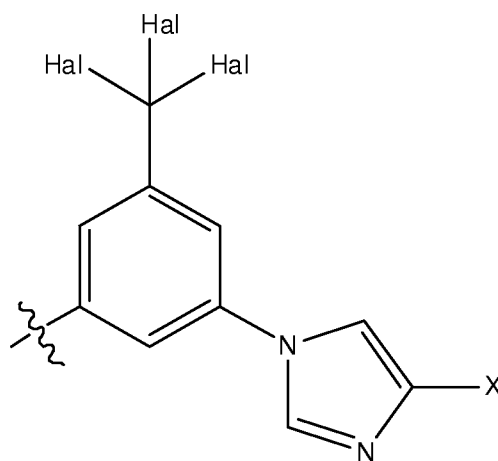
[00106] In exemplary aspects, B of Formula III is a substituted aryl comprising the structure of Structure Q:



[Structure Q]

wherein X is $-(CH_2)_{0-4}CH_3$.

[00107] In exemplary aspects, B of Formula III is a substituted aryl comprising the structure of Structure R:

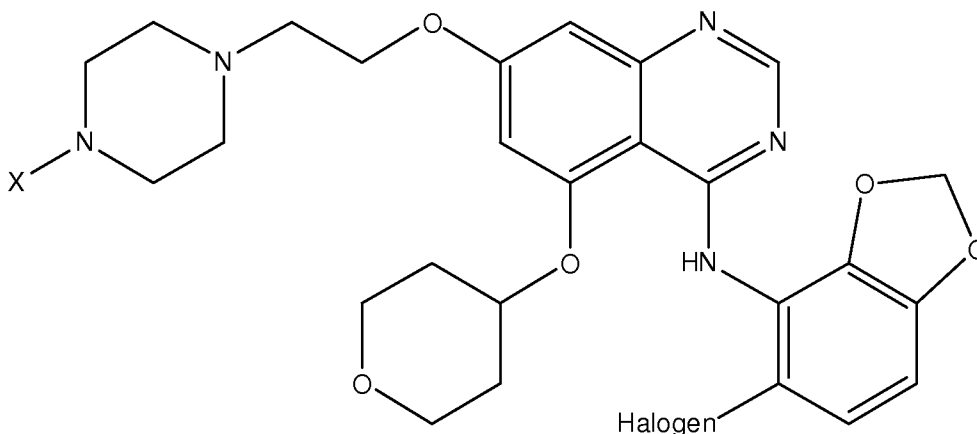


[Structure R]

wherein "Hal" is a halogen as described herein and X is $-(CH_2)_{0-4}CH_3$. In exemplary aspects, each "Hal" of Structure R is a fluorine atom.

[00108] In exemplary embodiments, the c-Src inhibitor comprising a structure of Formula III is selected from the group consisting of imatinib, dasatinib, and nilotinib.

[00109] In exemplary aspects, the c-Src inhibitor comprises a structure of Formula IV:



[Formula IV]

wherein X is $(\text{CH}_2)_{0-4}\text{CH}_3$ and "Halogen" is as described herein, e.g., a chlorine atom. In exemplary aspects, the c-Src inhibitor comprising a structure of Formula IV is saracatinib.

[00110] In exemplary aspects, the c-Src inhibitor is selected from the group consisting of: PP1, PP2, CGP76030, CGP77675, PD166285, PD173955, PD180970, SKI606, NVP-AAK980, CDP79883, AZD0530, S135, S140, AZM475271, AP23464, AP23451, AP22408, AP23236, dasatinib, bosutinib, and saracatinib.

[00111] In exemplary aspects, the c-Src inhibitor is not a compound selected from the group consisting of: PP2, herbimycin A, Src siRNA, 4-amino-5-(4-chlorophenyl)-7-(-(t-butyl)pyraxolo[3,4-D]pyrimidine.

[00112] The term "treat" as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment. Rather, there are varying degrees of treatment of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment in a subject. Furthermore, the treatment can include treatment or prevention of one or more conditions or symptoms of the disease being treated. Also, for purposes herein, "treatment" can encompass prophylactic treatment, wherein the onset of the disease, or a symptom or condition thereof, is delayed.

[00113] *Syncope and Sudden Cardiac Death and Methods Relating Thereto*

[00114] Sudden cardiac death (SCD) accounts for approximately 325,000 deaths per year in the United States, which number is higher than the number of deaths attributed to lung cancer, breast cancer, or acquired immune deficiency syndrome (AIDS). SCD is responsible for about 50% of deaths from heart failure and often is the first expression of coronary disease. See, Sovari et al., “Sudden Cardiac Death,” *e-medicine Cardiology*, article 151907, updated November 4, 2010; and Zheng et al., *Circulation* 104: 2158-2163 (2001). A common cause of SCD is ventricular arrhythmia, including, for example, ventricular tachycardia (VT), in which the resting heart rate is faster than normal, ventricular fibrillation (VF), in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart, making the muscles quiver rather than contract properly, or an arrhythmic condition in which both VT and VF are present. See, Wedro, B., “Sudden Cardiac Arrest (Sudden Cardiac Death),” *medicine.net*, Kulick and Soppler, eds. Current methods of treating ventricular fibrillation include defibrillation via an electrical defibrillator or a precordial thump.

[00115] As used herein the term “syncope” refers to the transient loss of consciousness and postural tone, characterized by rapid onset, short duration, and spontaneous recovery due to global cerebral hypoperfusion (low blood flow to the brain) that most often results from hypotension (low blood pressure). Syncope is distinct from epileptic seizures, concussion, cerebrovascular accident, and coma. In exemplary aspects, the syncope is preceded by a prodromal state that may include one or more of dizziness, loss of vision, loss of hearing, loss of pain and feeling, nausea, abdominal discomfort, weakness, sweating, a feeling of heat, palpitations. There are three types of syncope: cardiogenic, reflex, and orthostatic hypotension. In exemplary aspects, the syncope referenced herein means cardiogenic syncope. In exemplary aspects, the syncope is neither vasovagal syncope nor deglutition syncope.

[00116] Undiagnosed and/or untreated Brugada Syndrome may lead to sudden cardiac death and/or syncope. The invention also provides methods of reducing a subject’s risk for syncope or sudden cardiac death. In exemplary embodiments, the method comprises the steps of (i) analyzing a biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene,

and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); and (ii) providing a therapy for Brugada Syndrome to the subject when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[00117] The invention additionally provides methods of reducing a subject's risk for syncope or sudden cardiac death, and the subject is one who has been analyzed for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR). The method comprises the step of providing a therapy for Brugada Syndrome to the subject when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

[00118] The invention provides methods of monitoring a subject's risk for syncope and/or sudden cardiac death. In exemplary embodiments, the method comprises the steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject at a timepoint occurring before the time at which the second biological sample is obtained from the subject, and (iii) determining an increased risk for syncope and/or sudden cardiac death in the subject, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining a decreased risk for syncope and/or sudden cardiac death in the subject, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b),

and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[00119] *Screening Methods for new Brugada Syndrome Therapy*

[00120] Further provided are methods of determining the efficacy of a test compound or test therapy for treating Brugada Syndrome. In exemplary embodiments, the method comprises the steps of (i) analyzing a first biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR); (ii) analyzing a second biological sample obtained from the subject for (a) a level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, (b) a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), (c) a level of mRNA encoded by a SCN5A splicing factor gene, and/or (d) a level of mRNA encoded by a gene of the unfolded protein response (UPR), wherein the first biological sample is obtained from the subject before administration of the test compound or test therapy and the second biological sample is obtained from the subject after administration of the test compound or test therapy, and (iii) determining the test compound or test therapy as ineffective for treating Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is reduced, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is increased, relative to the level of (c) of the first biological sample; or determining the test compound or test therapy as effective for treating Brugada Syndrome, when the level of (a), (b), and/or (d) of the second biological sample is increased, relative to the level of (a), (b), and/or (d) of the first biological sample, and/or when the level of (c) of the second biological sample is reduced, relative to the level of (c) of the first biological sample.

[00121] *Routes of Administration*

[00122] With regard to the methods comprising providing therapy for Brugada Syndrome, the therapy may be administered through any suitable means. The following discussion on routes of administration is merely provided to illustrate exemplary embodiments and should not be construed as limiting the scope in any way.

[00123] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the therapy dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and other pharmacologically compatible excipients. Lozenge forms can comprise the therapy in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the therapy in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to, such excipients as are known in the art.

[00124] The therapy, alone or in combination with other suitable components, can be delivered via pulmonary administration and can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations also may be used to spray mucosa. In some embodiments, the therapy is formulated into a powder blend or into microparticles or nanoparticles. Suitable pulmonary formulations are known in the art. See, e.g., Qian et al., *Int J Pharm* 366: 218-220 (2009); Adjei and Garren, *Pharmaceutical Research*, 7(6): 565-569 (1990); Kawashima et al., *J Controlled Release* 62(1-2): 279-287 (1999); Liu et al., *Pharm Res* 10(2): 228-232 (1993); International Patent Application Publication Nos. WO 2007/133747 and WO 2007/141411.

[00125] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended

recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The term, "parenteral" means not through the alimentary canal but by some other route such as subcutaneous, intramuscular, intraspinal, or intravenous. The therapy can be administered with a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol or hexadecyl alcohol, a glycol, such as propylene glycol or polyethylene glycol, dimethylsulfoxide, glycerol, ketals such as 2,2- dimethyl-1,3-dioxolane-4-methanol, ethers, poly(ethyleneglycol) 400, oils, fatty acids, fatty acid esters or glycerides, or acetylated fatty acid glycerides with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[00126] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[00127] Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl- β -aminopropionates, and 2-alkyl -imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[00128] The parenteral formulations will typically contain from about 0.5% to about 25% by weight of the therapy in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5% to about 15% by weight. Suitable surfactants include polyethylene glycol sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide

with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[00129] Injectable formulations are in accordance with the invention. The requirements for effective pharmaceutical carriers for injectable compositions are well-known to those of ordinary skill in the art (see, e.g., *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986)).

[00130] Additionally, the therapy can be made into suppositories for rectal administration by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[00131] It will be appreciated by one of skill in the art that, in addition to the above-described pharmaceutical compositions, the therapy can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes.

[00132] *Kits*

[00133] The invention provides related kits for diagnosing Brugada Syndrome. In exemplary embodiments, the kit comprises a binding agent which binds to a gene product encoded by the PERK gene, a binding agent which binds to a full-length gene product encoded by the SCN5A gene, a binding agent which binds to a gene product encoded by the *Luc7A* gene, a binding agent which binds to a gene product encoded by the *RBM25* gene, a binding agent which binds to a gene product encoded by the *PRP40* gene, a binding agent which binds to an *SCN5A* E28C splice variant mRNA transcript, or a protein product encoded thereby, and/or a binding agent which binds to an *SCN5A* E28D splice variant mRNA transcript, or a protein product encoded thereby. In exemplary aspects, the gene product is an mRNA and the binding agent is a nucleic acid probe. In exemplary aspects, the gene product is protein and the binding agent is an antibody or an antigen-binding fragment thereof.

[00134] In exemplary aspects, the only binding agents in the kit are binding agents which bind to full-length gene products encoded by the SCN5A gene and binding agents which bind to truncated gene products encoded by the SCN5A gene and the use of the kit achieves a measurement of all SCN5A gene products in a biological sample. In exemplary aspects, the binding agents are nucleic acid probes. In exemplary aspects, the binding agents are antibodies or antigen binding fragments thereof. In exemplary aspects, the kit comprises both nucleic acid probes and antibodies, or antigen binding fragments thereof, which bind to SCN5A mRNA (truncated or full-length) or SCN5A protein products encoded thereby. In exemplary aspects, the biological sample is a blood sample and the kit comprises a container suitable for holding a blood sample. In exemplary aspects, the kit comprises a vial, a tube, a microtiter plate, a dish, a flask, or the like. In exemplary aspects, the container holds about 5 mL of fluid, or less. In exemplary aspects, the kit comprises heparin to prevent the blood from clotting. In exemplary aspects, the kit comprises a skin pricking device, e.g., a finger-prick device. In exemplary aspects, the kit comprises a filter or a paper onto which blood is absorbed. In exemplary aspects, the kit comprises reagents suitable for isolating white blood cells from the blood sample. In exemplary aspects, the kit comprises reagents suitable for isolating RNA or proteins from white blood cells. In exemplary aspects, the kit comprises reagents suitable for reverse transcribing the RNA into complementary DNA (cDNA) and for amplification of the cDNA.

[00135] In some aspects, the kits further comprise instructions for use, e.g., instructions for diagnosing Brugada Syndrome. In some aspects, the instructions are provided as a paper copy of instructions, an electronic copy of instructions, e.g., a compact disc, a flash drive, or other electronic medium. In some aspects, the instructions are provided by way of providing directions to an internet site at which the instructions may be accessed by the user.

[00136] In exemplary aspects, the kits further comprise information relating to a control level, wherein the control level is the comparator against which the level of the subject is compared. In exemplary aspects, the kits further comprise directions to or the address of an internet site at which the user may access the information relating to the control level. In exemplary aspects, the kits further comprise directions to or the address of an internet site at which the user is prompted to enter the level of full-length messenger RNA (mRNA) encoded by the SCN5A gene, level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), level of mRNA encoded by a SCN5A splicing factor gene, and/or level of mRNA encoded by a gene of the UPR.

Input of this information results in a comparison of the level to a control level and the display of an output relating to the presence or absence of Brugada Syndrome. In exemplary aspects, the input of the level of full-length messenger RNA (mRNA) encoded by the SCN5A gene and/or the level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), must be at least or about 1.5-fold reduced relative to the control level, in order to have an output of the presence of Brugada Syndrome displayed. In exemplary aspects, the input of the level of full length mRNA encoded by the SCN5A gene and the level of SCN5A splice variants must be at least or about 1.5-fold reduced relative to the control level, in order to have an output of the presence of Brugada Syndrome displayed.

[00137] *Systems, Computer-Readable Storage Media, and Methods Implemented by a Computer Processor*

[00138] Fig. 34 illustrates an exemplary embodiment 101 of a system 100 for detecting the presence of Brugada Syndrome for a subject. Generally, the system 100 may include one or more client devices 102, a network 104, and a database 108. Each client device 102 may be communicatively coupled to the network 104 by one or more wired or wireless network connections 112, which may be, for example, a connection complying with a standard such as one of the IEEE 802.11 standards (“Wi-Fi”), the Ethernet standard, or any other appropriate network connection. Similarly, the database 108 may be communicatively coupled to the network 104 via one or more connections 114. (Of course, the database could alternatively be internal to one or more of the client devices 102.) The database 108 may store data related to the determination of the presence of Brugada Syndrome in a subject including, but not limited to, data of a biological sample obtained from the subject, data of a biological sample obtained from a control or test population, etc. The data of the biological samples may be, for example, related to one or more of a level of a full-length mRNA encoded by the SCN5A gene, a level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein), a level of a truncated SCN5A Exon 28 transcript, a level of a full length SCN5A Exon 28 transcript, a level of multiple SCN5A Exon 28 transcripts, a level of mRNA encoded by a SCN5A splicing factor gene (e.g., but not limited to, RBM25, PRP40, Luc7A), a level of mRNA encoded by a gene of the UPR (e.g., but not limited to PERK), etc., as described in greater detail below.

[00139] As will be understood, the network 104 may be a local area network (LAN) or a wide-area network (WAN). That is, network 104 may include only local (e.g., intra-

organization) connections or, alternatively, the network 104 may include connections extending beyond the organization and onto one or more public networks (e.g., the Internet). In some embodiments, for example, the client device 102 and the database 108 may be within the network operated by a single company (Company A). In other embodiments, for example, the client device(s) 102 may be on a network operated by Company A, while the database 108 may be on a network operated by a second company (Company B), and the networks of Company A and Company B may be coupled by a third network such as, for example, the Internet.

[00140] Referring still to Fig. 34, the client device 102 includes a processor 128 (CPU), a RAM 130, and a non-volatile memory 132. The non-volatile memory 132 may be any appropriate memory device including, by way of example and not limitation, a magnetic disk (e.g., a hard disk drive), a solid state drive (e.g., a flash memory), etc. Additionally, it will be understood that, at least with regard to Fig. 34, the database 108 need not be separate from the client device 102. Instead, in some embodiments, the database 108 is part of the non-volatile memory 132 and the data 122, 124, 126 may be stored as data within the memory 132. For example, the data 122 may be included as data in a spreadsheet file stored in the memory 132, instead of as data in the database 108. In addition to storing the records of the database 108 (in some embodiments), the memory 132 stores program data and other data necessary to analyze data of one or more sample and/or control populations, determine a mean of the data, determine a threshold against which data of the subject may be compared, and/or determine the presence of Brugada Syndrome for a subject. For example, in an embodiment, the memory 132 stores a first routine 134, a second routine 136, and a third routine 138. The first routine 134 may receive data values related to one or more sample and/or control populations, and determine a mean of the data values received by the routine 134. The second routine 136 may compute one or more statistical parameters of the data collected by the first routine 134, such as determining a mean value, a standard deviation value, etc. Additionally and/or alternatively, the second routine 136 may set a first threshold against which data from one or more subjects may be compared in order to determine the presence of Brugada Syndrome for a subject. The third routine 138 may, for example, receive data for one or more subjects, compare the data of the one or more subjects to the threshold value(s) determined by the second routine 136, and/or determine the presence of Brugada Syndrome for a subject according to the comparison of the subject's data to the threshold value. Regardless, each of the routines is executable by the processor 128 and

comprises a series of compiled or compilable machine-readable instructions stored in the memory 132. Additionally, the memory 132 may store generated reports or records of data output by one of the routines 134 or 136. Alternatively, the reports or records may be output to the database 108. One or more display/output devices 140 (e.g., printer, display, etc.) and one or more input devices 142 (e.g., mouse, keyboard, tablet, touch-sensitive interface, etc.) may also be coupled to the client device 102, as is generally known.

[00141] As will be understood, although individual operations of one or more methods are illustrated and described as separate operations, one or more of the individual operations may be performed concurrently, and nothing requires that the operations be performed in the order illustrated. Structures and functionality presented as separate components in example configurations may be implemented as a combined structure or component. Similarly, structures and functionality presented as a single component may be implemented as separate components. These and other variations, modifications, additions, and improvements fall within the scope of the subject matter herein.

[00142] For example, the network 104 may include but is not limited to any combination of a LAN, a MAN, a WAN, a mobile, a wired or wireless network, a private network, or a virtual private network. Moreover, while only two clients 102 are illustrated in Fig. 34 to simplify and clarify the description, it is understood that any number of client computers are supported and can be in communication with one or more servers (not shown).

[00143] Fig. 35 depicts an exemplary embodiment of a Brugada Syndrome detection method 200 that may be utilized for any appropriate gene, such as SCN5A mRNA, PERK mRNA, RBM25 mRNA, Luc7A mRNA, PRP40 mRNA, etc implemented by the system 100. Generally speaking, the detection method 200 includes determining whether a mean value, μ , is a predetermined value (block 205). If the system 100 determines that μ is predetermined, then the system 100 transfers control to a block 220 (discussed below.) If the system 100 determines that μ is not predetermined, then the system 100 receives a plurality of data values relating to a control level of a gene (e.g., SCN5A mRNA) from a biological sample from a test subject (block 210). Using these received data values, the system 100 determines a mean value, μ , (block 215), and receives a specific data value, α , (e.g., α_{SCN5A}) relating to a test level of the gene from the biological sample from the test subject. Moreover, the method 200 includes determining whether α is less than or equal to $(\mu - (0.5\mu))$ (block 225) and displaying the diagnosis of Brugada Syndrome in the case that α is less than or equal to

$(\mu - (0.5\mu))$ (block 230). If α is not less than or equal to $(\mu - (0.5\mu))$, the system 100 may transfer control back to the block 205.

[00144] Additionally, certain embodiments are described herein as including logic or a number of routines. Routines may constitute either software routines (e.g., code embodied on a machine-readable medium or in a transmission signal) or hardware routines. A hardware routine is tangible unit capable of performing certain operations and may be configured or arranged in a certain manner. In example embodiments, one or more computer systems (e.g., a standalone, client or server computer system) or one or more hardware routines of a computer system (e.g., a processor or a group of processors) may be configured by software (e.g., an application or application portion) as a hardware routine that operates to perform certain operations as described herein.

[00145] Similarly, the methods or routines described herein may be at least partially processor-implemented. For example, at least some of the operations of a method may be performed by one or processors or processor-implemented hardware modules. The performance of certain of the operations may be distributed among the one or more processors, not only residing within a single machine, but deployed across a number of machines. In some example embodiments, the processor or processors may be located in a single location (e.g., within a home environment, an office environment or as a server farm), while in other embodiments the processors may be distributed across a number of locations.

[00146] The performance of certain of the operations may be distributed among the one or more processors, not only residing within a single machine, but deployed across a number of machines. In some example embodiments, the one or more processors or processor-implemented modules may be located in a single geographic location (e.g., within a home environment, an office environment, or a server farm). In other example embodiments, the one or more processors or processor-implemented modules may be distributed across a number of geographic locations.

[00147] Some embodiments may be described using the expression “coupled” and “connected” along with their derivatives. For example, some embodiments may be described using the term “coupled” to indicate that two or more elements are in direct physical or electrical contact. The term “coupled,” however, may also mean that two or more elements are not in direct contact with each other, but yet still co-operate or interact with each other. The embodiments are not limited in this context.

[00148] As used herein, the terms “comprises,” “comprising,” “includes,” “including,” “has,” “having” or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such process, method, article, or apparatus. Further, unless expressly stated to the contrary, “or” refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[00149] In addition, use of the “a” or “an” are employed to describe elements and components of the embodiments herein. This is done merely for convenience and to give a general sense of the description. This description should be read to include one or at least one and the singular also includes the plural unless it is obvious that it is meant otherwise.

[00150] The invention provides systems comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device. In exemplary embodiments, the machine readable instructions that, when executed by the processor, cause the processor to (i) receive a plurality of data values relating to a control level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a control subject, (ii) determine a mean value, μ , of the data values of (i), (iii) receive a data value, α , relating to a test level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a test subject, (iv) display an output diagnosis relating to Brugada Syndrome, when α is less than or equal to a threshold, T, which is $(\mu - (X\mu))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00151] In exemplary embodiments, the machine readable instructions that, when executed by the processor, cause the processor to (i) receive a data value, α , relating to a test level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a test subject and (ii) display an output diagnosis relating to Brugada Syndrome, when α is less than or equal to a threshold, T, which is $(\mu - (X\mu))$, wherein X is a number between 0.35 and 0.75 and μ is a predetermined mean value of a plurality of data values relating to a control level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a control subject. In exemplary aspects, X

of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00152] In exemplary aspects of the systems herein, α is the level of full length mRNA encoded by the SCN5A gene or the level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, α is the sum of the level of full length mRNA encoded by the SCN5A gene and the level of the SCN5A splice variant mRNA (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, α is the level of full length SCN5A Exon 28 mRNA or the level of a truncated SCN5A Exon28 mRNA. In exemplary aspects, α is the sum of the level of full length SCN5A Exon 28 mRNA and the level of a truncated SCN5A Exon28 mRNA. In any of these aspects, the truncated SCN5A Exon28 mRNA may be the mRNA of SCN5A Exon 28 Variant C (E28C) or the mRNA of SCN5A Exon 28 Variant D (E28D). In exemplary aspects, the truncated SCN5A Exon28 mRNA may be a sum of the mRNA of E28C and the mRNA of E28D.

[00153] In exemplary aspects, the output diagnosis is (a) an identification of the presence of Brugada Syndrome, (b) a determination of the subject needing therapy for Brugada Syndrome, (c) a determination of progression of Brugada Syndrome, (d) a determination of an increased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as ineffective as a therapy for Brugada Syndrome. In exemplary aspects, the system comprises additional machine readable instructions. For instance, the system may comprise instructions that, when executed by the processor, cause the processor to display a negative output diagnosis relating to Brugada Syndrome, when α is greater than $(\mu - (X\mu))$, wherein the negative output diagnosis is (a) an identification of the absence of Brugada Syndrome, (b) a determination of the subject not needing therapy for Brugada Syndrome, (c) a determination of regression of Brugada Syndrome, (d) a determination of a decreased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as effective as a therapy for Brugada Syndrome.

[00154] In additional or alternative embodiments, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, (ii) determine a mean value, μ_{PERK} , for the PERK mRNA received in (i), (iii) receive a data value, α_{PERK} , relating to a test level of the PERK mRNA from a biological sample obtained from a test subject, (iv) display an output diagnosis

relating to Brugada Syndrome, when α_{PERK} is less than or equal to a threshold T_{PERK} , which is $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00155] In exemplary aspects, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and (ii) display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to a threshold T_{PERK} , which is $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein μ_{PERK} is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject and wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00156] In additional or alternative embodiments, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, (ii) determine a mean value, μ_{RBM25} , for the RBM25 mRNA received in (i), (iii) receive a data value, α_{RBM25} , relating to a test level of the RBM25 mRNA from a biological sample obtained from a test subject, (iv) display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to a threshold T_{RBM25} , which is $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00157] In exemplary aspects, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and (ii) display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to a threshold T_{RBM25} , which is $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ_{RBM25} is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject and X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00158] In additional or alternative embodiments, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a plurality of data values relating to a control level of Luc7A mRNA from a biological sample obtained from a control subject, (ii) determine a mean value, μ_{LUC7A} , for the Luc7A mRNA received in (i), (iii) receive a data value, α_{LUC7A} , relating to a test level of the Luc7A mRNA from a biological sample obtained from a test subject, (iv) display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to a threshold T_{LUC7A} , which is $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00159] In exemplary aspects, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a data value, α_{LUC7A} , relating to a test level of Luc7A mRNA from a biological sample obtained from a test subject and (ii) display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to a threshold T_{LUC7A} , which is $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein μ_{LUC7A} is a predetermined mean value of a plurality of data values relating to a control level of Luc7A mRNA from a biological sample obtained from a control subject and X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00160] In additional or alternative embodiments, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, (ii) determine a mean value, μ_{PRP40} , for the PRP40 mRNA received in (i), (iii) receive a data value, α_{PRP40} , relating to a test level of the PRP40 mRNA from a biological sample obtained from a test subject, (iv) display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to a threshold T_{PRP40} , which is $(\mu_{\text{PRP40}} + (X\mu_{\text{PRP40}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00161] In exemplary aspects, the system comprises machine readable instructions that, when executed by the processor, cause the processor to (i) receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and (ii)

display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to a threshold T_{PRP40} , which is $(\mu_{PRP40} + (X\mu_{PRP40}))$, wherein μ_{PRP40} is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, and X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00162] Also provided herein are computer-readable storage media having stored thereon machine-readable instructions executable by a processor. In exemplary embodiments, the instructions comprise: (i) instructions for causing the processor to receive a plurality of data values relating to a control level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a control subject, (ii) instructions for causing the processor to determine a mean value, μ , of the data values of (i), (iii) instructions for causing the processor to receive a data value, α , relating to a test level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a test subject, and (iv) instructions for causing the processor to display an output diagnosis relating to Brugada Syndrome, when α is less than or equal to a threshold T, which is $(\mu - (X\mu))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00163] In exemplary aspects, the instructions comprise (i) instructions for receiving a data value, α , relating to a test level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a test subject and (ii) instructions for displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to a threshold T, which is $(\mu - (X\mu))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00164] In exemplary aspects of the storage media herein, α is the level of full length mRNA encoded by the SCN5A gene or the level of mRNA of an SCN5A splice variant (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, α is the sum of the level of full length mRNA encoded by the SCN5A

gene and the level of the SCN5A splice variant mRNA (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, α is the level of full length SCN5A Exon 28 mRNA or the level of a truncated SCN5A Exon28 mRNA. In exemplary aspects, α is the sum of the level of full length SCN5A Exon 28 mRNA and the level of a truncated SCN5A Exon28 mRNA. In any of these aspects, the truncated SCN5A Exon28 mRNA may be the mRNA of SCN5A Exon 28 Variant C (E28C) or the mRNA of SCN5A Exon 28 Variant D (E28D). In exemplary aspects, the truncated SCN5A Exon28 mRNA may be a sum of the mRNA of E28C and the mRNA of E28D.

[00165] In exemplary aspects, the output diagnosis is (a) an identification of the presence of Brugada Syndrome, (b) a determination of the subject needing therapy for Brugada Syndrome, (c) a determination of progression of Brugada Syndrome, (d) a determination of an increased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as ineffective as a therapy for Brugada Syndrome. In exemplary aspects, the system comprises additional machine readable instructions. For instance, the system may comprise instructions that, when executed by the processor, cause the processor to display a negative output diagnosis relating to Brugada Syndrome, when α is greater than $(\mu - (X\mu))$, wherein the negative output diagnosis is (a) an identification of the absence of Brugada Syndrome, (b) a determination of the subject not needing therapy for Brugada Syndrome, (c) a determination of regression of Brugada Syndrome, (d) a determination of a decreased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as effective as a therapy for Brugada Syndrome.

[00166] In additional or alternative embodiments, the instructions comprise: (i) instructions for causing the processor to receive a plurality of data values relating to a control level of mRNA encoded by the PERK gene from a biological sample obtained from a control subject, (ii) instructions for causing the processor to determine a mean value, μ_{PERK} , of the data values of (i), (iii) instructions for causing the processor to receive a data value, α_{PERK} , relating to a test level of mRNA encoded by the PERK gene from a biological sample obtained from a test subject, and (iv) instructions for causing the processor to display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to a threshold T_{PERK} , which is $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00167] In exemplary aspects, the instructions comprise (i) instructions for receiving a data value, α_{PERK} , relating to a test level of mRNA encoded by the PERK gene from a biological sample obtained from a test subject and (ii) instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to a threshold T_{PERK} , which is $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein μ_{PERK} is a predetermined mean value of a plurality of data values relating to a control level of mRNA encoded by the PERK gene from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00168] In additional or alternative embodiments, the instructions comprise: (i) instructions for causing the processor to receive a plurality of data values relating to a control level of mRNA encoded by the RBM25 gene from a biological sample obtained from a control subject, (ii) instructions for causing the processor to determine a mean value, μ_{RBM25} , of the data values of (i), (iii) instructions for causing the processor to receive a data value, α_{RBM25} , relating to a test level of mRNA encoded by the RBM25 gene from a biological sample obtained from a test subject, and (iv) instructions for causing the processor to display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to a threshold T_{RBM25} , which is $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00169] In exemplary aspects, the instructions comprise (i) instructions for receiving a data value, α_{RBM25} , relating to a test level of mRNA encoded by the RBM25 gene from a biological sample obtained from a test subject and (ii) instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to a threshold T_{RBM25} , which is $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ_{RBM25} is a predetermined mean value of a plurality of data values relating to a control level of mRNA encoded by the RBM25 gene from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00170] In additional or alternative embodiments, the instructions comprise: (i) instructions for causing the processor to receive a plurality of data values relating to a control level of mRNA encoded by the LUC7A gene from a biological sample obtained from a control subject, (ii) instructions for causing the processor to determine a mean value, μ_{LUC7A} , of the data values of (i), (iii) instructions for causing the processor to receive a data value, α_{LUC7A} , relating to a test level of mRNA encoded by the LUC7A gene from a biological sample obtained from a test subject, and (iv) instructions for causing the processor to display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to a threshold T_{LUC7A} , which is $(\mu_{LUC7A} + (X\mu_{LUC7A}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00171] In exemplary aspects, the instructions comprise (i) instructions for receiving a data value, α_{LUC7A} , relating to a test level of mRNA encoded by the LUC7A gene from a biological sample obtained from a test subject and (ii) instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to a threshold T_{LUC7A} , which is $(\mu_{LUC7A} + (X\mu_{LUC7A}))$, wherein μ_{LUC7A} is a predetermined mean value of a plurality of data values relating to a control level of mRNA encoded by the LUC7A gene from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00172] In additional or alternative embodiments, the instructions comprise: (i) instructions for causing the processor to receive a plurality of data values relating to a control level of mRNA encoded by the PRP40 gene from a biological sample obtained from a control subject, (ii) instructions for causing the processor to determine a mean value, μ_{PRP40} , of the data values of (i), (iii) instructions for causing the processor to receive a data value, α_{PRP40} , relating to a test level of mRNA encoded by the PRP40 gene from a biological sample obtained from a test subject, and (iv) instructions for causing the processor to display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to a threshold T_{PRP40} , which is $(\mu_{PRP40} + (X\mu_{PRP40}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00173] In exemplary aspects, the instructions comprise (i) instructions for receiving a data value, α_{PRP40} , relating to a test level of mRNA encoded by the PRP40 gene from a biological sample obtained from a test subject and (ii) instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to a threshold T_{PRP40} , which is $(\mu_{PRP40} + (X\mu_{PRP40}))$, wherein μ_{PRP40} is a predetermined mean value of a plurality of data values relating to a control level of mRNA encoded by the PRP40 gene from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00174] Further provided herein are methods implemented by a processor in a computer. In exemplary embodiments, the method comprises the steps of: (i) receiving a plurality of data values relating to a control level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a control subject, (ii) determining a mean value, μ , of the data values received in (i), (iii) receiving a data value, α , relating to a test level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a test subject, (iv) displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to a threshold T, which is $(\mu - (X\mu))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00175] In exemplary embodiments, the method comprises the steps of (i) receiving a data value, α , relating to a test level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a test subject and (ii) displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to a threshold T, which is $(\mu - (X\mu))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of SCN5A mRNA (either or both full length mRNA or truncated) from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00176] In exemplary aspects of the methods herein, α is the level of full length mRNA encoded by the SCN5A gene or the level of mRNA of an SCN5A splice variant (e.g., but not

limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, α is the sum of the level of full length mRNA encoded by the SCN5A gene and the level of the SCN5A splice variant mRNA (e.g., but not limited to a SCN5A splice variant which encodes a truncated SCN5A protein). In exemplary aspects, α is the level of full length SCN5A Exon 28 mRNA or the level of a truncated SCN5A Exon28 mRNA. In exemplary aspects, α is the sum of the level of full length SCN5A Exon 28 mRNA and the level of a truncated SCN5A Exon28 mRNA. In any of these aspects, the truncated SCN5A Exon28 mRNA may be the mRNA of SCN5A Exon 28 Variant C (E28C) or the mRNA of SCN5A Exon 28 Variant D (E28D). In exemplary aspects, the truncated SCN5A Exon28 mRNA may be a sum of the mRNA of E28C and the mRNA of E28D.

[00177] In exemplary aspects, the output diagnosis is (a) an identification of the presence of Brugada Syndrome, (b) a determination of the subject needing therapy for Brugada Syndrome, (c) a determination of progression of Brugada Syndrome, (d) a determination of an increased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as ineffective as a therapy for Brugada Syndrome. In exemplary aspects, the system comprises additional machine readable instructions. For instance, the system may comprise instructions that, when executed by the processor, cause the processor to display a negative output diagnosis relating to Brugada Syndrome, when α is greater than $(\mu - (X\mu))$, wherein the negative output diagnosis is (a) an identification of the absence of Brugada Syndrome, (b) a determination of the subject not needing therapy for Brugada Syndrome, (c) a determination of regression of Brugada Syndrome, (d) a determination of a decreased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as effective as a therapy for Brugada Syndrome.

[00178] In additional or alternative embodiments, the method comprises the steps of (i) receiving a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, (ii) determining a mean value, μ_{PERK} , for the PERK mRNA received in (i), (iii) receiving a data value, α_{PERK} , relating to a test level of the PERK mRNA from a biological sample obtained from a test subject, (iv) displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to a threshold T_{PERK} , which is $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00179] In exemplary aspects, the method comprises steps of (i) receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and (ii) displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to a threshold T_{PERK} , which is $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein μ_{PERK} is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject and wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00180] In additional or alternative embodiments, the method comprises the steps of (i) receiving a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, (ii) determining a mean value, μ_{RBM25} , for the RBM25 mRNA received in (i), (iii) receiving a data value, α_{RBM25} , relating to a test level of the RBM25 mRNA from a biological sample obtained from a test subject, (iv) displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to a threshold T_{RBM25} , which is $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00181] In exemplary aspects, the method comprises the steps of (i) receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and (ii) displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to a threshold T_{RBM25} , which is $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ_{RBM25} is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject and X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00182] In additional or alternative embodiments, the method comprises the step of (i) receiving a plurality of data values relating to a control level of Luc7A mRNA from a biological sample obtained from a control subject, (ii) determining a mean value, μ_{LUC7A} , for the Luc7A mRNA received in (i), (iii) receiving a data value, α_{LUC7A} , relating to a test level of the Luc7A mRNA from a biological sample obtained from a test subject, (iv) displaying an

output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to a threshold T_{LUC7A} which is $(\mu_{LUC7A} + (X\mu_{LUC7A}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00183] In exemplary aspects, the method comprises the steps of (i) receiving a data value, α_{LUC7A} , relating to a test level of Luc7A mRNA from a biological sample obtained from a test subject and (ii) displaying an output diagnosis of Brugada Syndrome, when α_{LUC7A} is greater than or equal to a threshold T_{LUC7A} which is $(\mu_{LUC7A} + (X\mu_{LUC7A}))$, wherein μ_{LUC7A} is a predetermined mean value of a plurality of data values relating to a control level of Luc7A mRNA from a biological sample obtained from a control subject and X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50..

[00184] In additional or alternative embodiments, the method comprises the steps of (i) receiving a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, (ii) determining a mean value, μ_{PRP40} , for the PRP40 mRNA received in (i), (iii) receiving a data value, α_{PRP40} , relating to a test level of the PRP40 mRNA from a biological sample obtained from a test subject, (iv) displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to a threshold T_{PRP40} which is $(\mu_{PRP40} + (X\mu_{PRP40}))$, wherein X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00185] In exemplary aspects, the method comprises the steps of (i) receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and (ii) displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to a threshold T_{PRP40} which is $(\mu_{PRP40} + (X\mu_{PRP40}))$, wherein μ_{PRP40} is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject and X is a number between 0.35 and 0.75. In exemplary aspects, X of the threshold is a number between 0.40 and 0.60. In exemplary aspects, X is a number between 0.45 and 0.55. In exemplary aspects, X is about 0.50.

[00186] In exemplary aspects, the output diagnosis is (a) an identification of the presence of Brugada Syndrome, (b) a determination of the subject needing therapy for Brugada Syndrome, (c) a determination of progression of Brugada Syndrome, (d) a determination of an increased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as ineffective as a therapy for Brugada Syndrome. In exemplary aspects, the system comprises additional machine readable instructions. For instance, the system may comprise instructions that, when executed by the processor, cause the processor to display a negative output diagnosis relating to Brugada Syndrome, when α_{PERK} is greater than $(\mu_{PERK} - (X\mu_{PERK}))$ or α_{RMB25} is less than $(\mu_{RMB25} - (X\mu_{RMB25}))$ or α_{LUC7A} is less than $(\mu_{LUC7A} - (X\mu_{LUC7A}))$ or α_{PRP40} is less than $(\mu_{PRP40} - (X\mu_{PRP40}))$ or, wherein the negative output diagnosis is (a) an identification of the absence of Brugada Syndrome, (b) a determination of the subject not needing therapy for Brugada Syndrome, (c) a determination of regression of Brugada Syndrome, (d) a determination of a decreased risk for syncope or sudden cardiac death, or (e) a determination of a test compound as effective as a therapy for Brugada Syndrome.

[00187] The following examples serve only to illustrate the invention or provide background information relating to the invention. The following examples are not intended to limit the scope of the invention in any way.

EXAMPLES

EXAMPLE 1

[00188] This example demonstrates a correlation of cardiac tissue and blood abundances of SCN5A Exon 28 Variant C (E28C) and SCN5A Exon 28 Variant D (E28D).

[00189] In order to show that white blood cell (WBC) SCN5A variants might be an acceptable surrogate for the physiologically relevant levels of variants in heart, we designed paired analysis of WBC and ventricular tissue variants from the same patient. A total 14 paired blood and heart tissue samples were collected. More specifically, heart tissue samples were obtained from residual cores removed after left ventricular assist device (LVAD) placement at our affiliate, Christ Advocate Hospital. Eligible patients were over 18 years of age, had a LVEF of <35% documented in the last year, and had a need for LVAD implantation. Paired blood samples were collected simultaneously from patients undergoing LVAD placement. The blood samples were collected in PAX tubes (Fisher Scientific, Pittsburgh, PA) following the manufacturer's procedure. Samples were stored for up to three days at room temperature or five days at 2–8°C.

[00190] Total RNA from blood samples was isolated using the PAXgene Blood RNA isolation kit. Total RNA was isolated from WBCs and human heart tissue with the RNeasy Mini and RNeasy Lipid Tissue Mini Kits, respectively (Qiagen, Valencia, CA) and then converted to cDNA using the High Capacity cDNA Reverse Transcription Kit (Qiagen). Quantitative RT-PCR was done using iQ™ SYBR® Green Supermix. The primer sequences used were as shown in Table 4:

TABLE 4

Target	Primers
SCN5A (full length)	Forward: 5'-TTACGCACCTTCCGAGTCCTCC-3' (SEQ ID NO: 665) Reverse: 5'-GATGAGGGCAAAGACGCTGAGG-3' (SEQ ID NO: 666)
Human SCN5A E28C	Forward: 5'-TTACGCACCTTCCGAGTCCTCC-3' (SEQ ID NO: 667) Reverse: 5'-TCTCTTCTCCCCTCCTGCTGGTCA-3' (SEQ ID NO: 668)
Human SCN5A E28D	Forward: 5'-TTACGCACCTTCCGAGTCCTCC-3' (SEQ ID NO: 669) Reverse: 5'-GGAAGAGCGTCGCGGAGAGAAGAAGTA-3' (SEQ ID NO: 670)

[00191] Quantitative reverse transcription polymerase chain reaction (qRT-PCR) thermal cycling conditions were an initial uracil-N-glycosylase incubation at 50°C for two minutes. iTaq™ DNA polymerase was activated with an initial denaturation step at 95°C for five minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds, and annealing and extension at 60°C for one minute. Each sample was measured for the target gene SCN5A, E28C, E28D, and β -actin. Variants levels were expressed as a percentage of the variant with respect to the total Na⁺ channel mRNA to correct for differences in WBC SCN5A expression between subjects.

[00192] The correlation between blood and tissue variants levels is shown for E28C and E28D in Figure 5 and 6, respectively. The coefficients of determination, r^2 , were 0.60 and 0.57 and the correlation coefficients, r , were 0.78 and 0.75 for variants E28C and E28D, respectively, demonstrating the high degree of correlation of tissue and blood SCN5A variants.

EXAMPLE 2

[00193] This example demonstrates that decreased mRNA transcript levels of SCN5A (including full length transcripts and variant transcripts (e.g., E28C and E28D)), relative to control levels, correlate with the presence of Brugada Syndrome.

[00194] Peripheral blood samples from patients diagnosed with Brugada Syndrome were obtained from the Molecular Cardiology IRCCS Fondazione Maugeri (Pavia, Italy). The diagnosis of Brugada Syndrome in the patients was based on the presence of a "spontaneous" or of a "Class IC antiarrhythmic drug induced" type I ECG pattern. The DNA of each patient was screened for mutations in the opening reading frame of the SCN5A gene and no mutations were identified in any of the patients. The peripheral blood samples (3 ml per sample) were stored in PAXgene™ Blood RNA tubes (Qiagen) as essentially described in Example 1.

[00195] Total RNA was extracted from the white blood cells of the peripheral blood using the Trizol reagent (Invitrogen, Carlsbad, CA) and/or the PAXgene blood kit. RNA was then converted into cDNA using the High Capacity cDNA Reverse Transcription Kit (Qiagen). Quantitative RT-PCR was done using iQ™ SYBR® Green Supermix under the following conditions: a holding stage of 95°C for 20 min and 40 cycles at 95°C for 30 s and 60°C for 60 s. The primer sequences used were as shown in Table 5:

TABLE 5

Targeted Gene	Primer Sequence
SCN5A	Forward: 5'-TTACGCACCTTCCGAGTCCTCC-3' (SEQ ID NO: 671) Reverse: 5'-GATGAGGGCAAAGACGCTGAGG-3' (SEQ ID NO: 672)
SCN5A variant	Forward: 5'-TTACGCACCTTCCGAGTCCTCC-3' (SEQ ID NO: 671)

E28C	673) Reverse: 5'-TCTCTTCTCCCCTCCTGCTGGTCA-3' (SEQ ID NO: 674)
SCN5A variant E28D	Forward: 5'-TTACGCACCTTCCGAGTCCTCC-3' (SEQ ID NO: 675) Reverse: 5'GGAAGAGCGTCGGGGAGAAGAAGTA-3' (SEQ ID NO: 676)
PERK	Forward: 5'- AGTCTCTGCTGGAGTCTTCATGACACTGTGTCTCAGACTCTT (SEQ ID NO: 677) Reverse: TGACACTGTGTCTCAGACTCTT (SEQ ID NO: 678)
RBM25	Forward: 5'-TGTCTTTTCCACCTCATTGAATCG-3' (SEQ ID NO: 679) Reverse: 5'-ATTGGTACAGGAATCATTGGGGT-3' (SEQ ID NO: 680)
LUC7L3	Forward: 5'-GGACCAAGATCAGAACGTGTATTTG-3' (SEQ ID NO: 681) Reverse: 5'-CAGTTGTTGGATGAGTTAATGGGC-3' (SEQ ID NO: 682)
PRP40	Forward:GACAGCGATCAGAGTCTCGTTC (SEQ ID NO: 683) Reverse:TCGCTCAGCATCGGATTCTGGA (SEQ ID NO: 684)
β -actin	Forward: 5'-GGATCGGCGGCTCCAT (SEQ ID NO: 685) Reverse: 5'CATACTCCTGCTTGCTGATCCA (SEQ ID NO: 686)

[00196] Data were analyzed using the threshold cycle (CT) relative quantification method and normalized to beta actin. For each transcript, the normalized values were then expressed relative to the mean of the control.

[00197] Full-length SCN5A mRNA transcripts were reduced in 17 of 20 patients. In those with reduced SCN5A mRNA prevalence, the reduction was $47 \pm 9\%$ of control ($p < 0.001$),

suggesting that reduced transcription, rather than point mutations, causes Brugada Syndrome in a majority of patients.

[00198] As shown in Figures 8 and 9, the level of SCN5A E28C mRNA transcripts and the level of SCN5A E28D mRNA transcripts decreased (relative to control levels) in 80% of the patients tested. The mRNA transcript levels of splicing factor genes, RBM25, Luc7A, and PRP40, increased (relative to control). See, Figures 10-12. Also, the level of PERK, a major component of the unfolded protein response (UPR), decreased, relative to control (Figure 13).

[00199] There was evidence of SCN5A transcription dysregulation in most patients with Brugada Syndrome and no defined gene defect. These data suggest that the levels of SCN5A mRNA transcripts (full length SCN5A, E28C and E28D) in white blood cells may be a useful tool to determine the presence of Brugada Syndrome in patients. These data also suggest that increased mRNA transcript levels of splicing factor genes correlate with the presence of Brugada Syndrome. These data furthermore suggest that decreased mRNA transcript levels of a major component of the UPR correlate with the presence of Brugada Syndrome.

EXAMPLE 3

[00200] This example demonstrates a clinical validation study.

[00201] Peripheral blood samples from patients diagnosed with Brugada Syndrome based on clinical criteria (see, e.g., Wilde et al., *Eur Heart J.* 23: 1648-1654 (2002); Antzelevitch et al., *Circulation* 111: 659-670 (2005); and Richter et al., *Eur Heart J* 31: 1357-1364 (2010)) are obtained from the Molecular Cardiology IRCCS Fondazione Maugeri (Pavia, Italy). The diagnosis of Brugada Syndrome in the patients was based on the presence of a "spontaneous" or of a "Class IC antiarrhythmic drug induced" type I ECG pattern. Peripheral blood samples from healthy control patients not diagnosed with Brugada Syndrome are obtained from a blood bank. The peripheral blood samples (3 ml per sample) are stored in PAXgene™ Blood RNA tubes (Qiagen) as essentially described in Example 1. Total RNA is extracted from the white blood cells of the peripheral blood and then converted into cDNA using the High Capacity cDNA Reverse Transcription Kit (Qiagen), as essentially described in Example 2. Quantitative RT-PCR is carried out using iQ™ SYBR® Green Supermix under the following conditions: a holding stage of 95°C for 20 min and 40 cycles at 95°C for 30 s and 60°C for 60 s. The primer sequences used are those shown in Table 5.

[00202] The levels of mRNA encoded by the SCN5A gene, PERK gene, RBM25 gene, PRP40 gene, and the Luc7A gene are determined. It is expected that the full length and truncated mRNA of the SCN5A gene and the mRNA of the PERK gene are decreased in blood samples obtained from Brugada Syndrome patients, relative to those obtained from healthy control patients. It is also expected that the mRNA of the RBM25 gene, PRP40 gene, and Luc7A gene are increased in blood samples obtained from Brugada Syndrome patients, relative to those obtained from healthy control patients.

[00203] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[00204] The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted.

[00205] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range and each endpoint, unless otherwise indicated herein, and each separate value and endpoint is incorporated into the specification as if it were individually recited herein.

[00206] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[00207] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as

appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

WHAT IS CLAIMED:

1. A method of identifying a presence of Brugada Syndrome in a subject, comprising (i) analyzing a biological sample obtained from the subject for

a. a level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene,

b. a level of mRNA of an *SCN5A* splice variant which encodes a truncated *SCN5A* protein,

c. a level of mRNA encoded by a *SCN5A* splicing factor gene, and/or

d. a level of mRNA encoded by a gene of the unfolded protein response (UPR);

and (ii) identifying the presence of Brugada Syndrome in the subject, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

2. The method of claim 1, comprising analyzing the biological sample obtained from the subject for a full length *SCN5A* Exon 28 transcript and/or a truncated *SCN5A* Exon 28 transcript.

3. The method of claim 1 or 2, wherein the *SCN5A* splice variant is *SCN5A* Exon 28 Splice Variant C (E28C) or *SCN5A* Exon 28 Splice Variant D (E28D).

4. The method of claim 3, comprising analyzing the biological sample for both the level of mRNA of the E28C *SCN5A* splice variant and the level of mRNA of the E28D *SCN5A* splice variant.

5. The method of any one of claims 1 to 4, comprising analyzing the biological sample for (a).

6. The method of any one of claims 1 to 5, wherein the *SCN5A* splicing factor gene is *RBM25*, *Luc7A*, *PRP40*, or.

7. The method of claim 6, comprising analyzing the biological sample for the level of mRNA encoded by two or all of *RBM25*, *Luc7A*, and *PRP40*.
8. The method of any one of claims 1 to 7, wherein gene of the UPR is *PERK*.
9. The method of any one of claims 1 to 8, wherein each of the level of mRNA and the control level is normalized to the level of mRNA encoded by a housekeeping gene of the biological sample.
10. The method of claim 9, wherein the housekeeping gene is the β -actin gene.
11. The method of any one of the preceding claims, wherein the level of mRNA is determined by real-time RT-PCR analysis.
12. The method of any one of the preceding claims, wherein the level of full-length mRNA encoded by the *SCN5A* gene is reduced by at least 50%, relative to a control level.
13. The method of any one of claims 1 to 12, wherein the biological sample comprises heart cells or white blood cells.
14. The method of claim 13, wherein the biological sample comprises white blood cells.
15. The method of claim 14, wherein the biological sample is blood or a fraction thereof.
16. The method of any one of the preceding claims, wherein the subject is male.
17. The method of any one of claims 1 to 16, wherein the subject is about 40 years old or younger.
18. The method of any one of claims 1 to 17, wherein the subject has a medical history including syncope and/or dizziness.

19. The subject of any one of claims 1 to 18, wherein the subject has been treated for and survived sudden cardiac death or has a family history of sudden cardiac death.

20. The method of any one of claims 1 to 19, wherein the subject does not have any structural defect of the heart.

21. The method of any one of claims 1 to 20, further comprising performing a genetic test on the subject, optionally, wherein the genetic test analyzes the sequence of the *SCN5A* gene, the *CACNA1c* gene, and/or the *GPD1-L* gene.

22. The method of any one of claims 1 to 21, wherein the subject does not have a genetic mutation in the open reading frame of *SCN5A* gene.

23. The method of any one of claims 1 to 22, wherein the subject does not have a genetic mutation in the *CACNA1c* gene or in the *GPD1-L* gene.

24. The method of any one of claims 1 to 23, wherein the subject does not have any of the mutations listed in Table 1 or Table 2.

25. The method of any one of claims 1 to 24, further comprising performing an electrocardiogram on the subject.

26. The method of any one of the preceding claims, further comprising providing to the subject a therapy for Brugada Syndrome, when the presence of Brugada Syndrome has been identified in the subject.

27. The method of claim 26, wherein the therapy comprises an implantable cardioverter-defibrillator (ICD).

28. The method of claim 26 or 27, wherein the therapy comprises nicotinamide adenine dinucleotide (NAD⁺).

29. A method of determining a subject's need for therapy for Brugada Syndrome (BS), comprising the step of (i) analyzing a biological sample obtained from the subject for

- a. a level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene,
- b. a level of mRNA of an *SCN5A* splice variant which encodes a truncated SCN5A protein,
- c. a level of mRNA encoded by a *SCN5A* splicing factor gene, and/or
- d. a level of mRNA encoded by a gene of the unfolded protein response (UPR);

and (ii) determining the subject as needing therapy for Brugada Syndrome, when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

30. The method of claim 29, wherein the therapy is an ICD, a mitochondrially-targeted antioxidant, a mitochondria electron transport re-coupling agent, a Protein Kinase A Activator, a Protein Kinase C Inhibitor, a c-Src Inhibitor, an anion transporter inhibitor, an inner-membrane anion channels (IMAC) modulator, an NADPH oxidase inhibitor, or a Protein Kinase G Activator.

31. The method of claim 30, wherein the therapy is an ICD and wherein the level of mRNA of an *SCN5A* splice variant which encodes a truncated SCN5A protein is not a level relative to the level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene.

32. The method of any one of claims 29 to 31, comprising analyzing the biological sample obtained from the subject for a full length SCN5A Exon 28 transcript and/or a truncated SCN5A Exon 28 transcript.

33. The method of any one of claims 29 to 32, wherein the *SCN5A* splice variant is *SCN5A* Exon 28 Splice Variant C (E28C) or *SCN5A* Exon 28 Splice Variant D (E28D).

34. The method of claim 33, comprising analyzing the biological sample for both the level of mRNA of the E28C *SCN5A* splice variant and the level of mRNA of the E28D *SCN5A* splice variant.

35. The method of any one of claims 29 to 34, comprising analyzing the biological sample for (a) and/or (b).

36. The method of any one of claims 29 to 35, wherein the *SCN5A* splicing factor gene is *RBM25*, *Luc7A*, *PRP40*, or.

37. The method of claim 36, comprising analyzing the biological sample for the level of mRNA encoded by two or all of *RBM25*, *Luc7A*, and *PRP40*.

38. The method of any one of claims 29 to 38, wherein gene of the UPR is *PERK*.

39. The method of any one of claims 29 to 38, wherein each of the level of mRNA and the control level is normalized to the level of mRNA encoded by a housekeeping gene of the biological sample.

40. The method of claim 39, wherein the housekeeping gene is the β -actin gene.

41. The method of any one of claims 29 to 40, wherein the level of mRNA is determined by real-time RT-PCR analysis.

42. The method of any one of claims 29 to 41, wherein the level of full-length mRNA encoded by the *SCN5A* gene is reduced by at least 50%, relative to a control level.

43. The method of any one of claims 29 to 42, wherein the biological sample comprises heart cells or white blood cells.

44. The method of claim 43, wherein the biological sample comprises white blood cells.

45. The method of claim 44, wherein the biological sample is blood or a fraction thereof.

46. The method of any one of claims 29 to 45, wherein the subject is male.
47. The method of any one of claims 29 to 46, wherein the subject is about 40 years old or younger.
48. The method of any one of claims 29 to 47, wherein the subject has a medical history including syncope and/or dizziness.
49. The subject of any one of claims 29 to 48, wherein the subject has been treated for and survived sudden cardiac death or has a family history of sudden cardiac death.
50. The method of any one of claims 29 to 49, wherein the subject does not have any structural defect of the heart.
51. The method of any one of claims 29 to 50, further comprising performing a genetic test on the subject, optionally, wherein the genetic test analyzes the sequence of the *SCN5A* gene, the *CACNA1c* gene, and/or the *GPD1-L* gene.
52. The method of any one of claims 29 to 51, wherein the subject does not have a genetic mutation in the open reading frame of *SCN5A* gene.
53. The method of any one of claims 29 to 52, wherein the subject does not have a genetic mutation in the *CACNA1c* gene or in the *GPD1-L* gene.
54. The method of any one of claims 29 to 53, wherein the subject does not have any of the mutations listed in Table 1 or Table 2.
55. A method of treating a subject for Brugada Syndrome, comprising the step of (i) analyzing a biological sample obtained from the subject for
- a. a level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene,
 - b. a level of mRNA of an *SCN5A* splice variant which encodes a truncated *SCN5A* protein,
 - c. a level of mRNA encoded by a *SCN5A* splicing factor gene,
- and/or

d. a level of mRNA encoded by a gene of the unfolded protein response (UPR);

and (ii) providing to the subject a therapy for Brugada Syndrome when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

56. A method of reducing risk for syncope and/or sudden cardiac death by ventricular fibrillation in a subject, comprising the step of (i) analyzing a biological sample obtained from the subject for

a. a level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene,

b. a level of mRNA of an *SCN5A* splice variant which encodes a truncated *SCN5A* protein,

c. a level of mRNA encoded by a *SCN5A* splicing factor gene, and/or

d. a level of mRNA encoded by a gene of the unfolded protein response (UPR);

and (ii) providing to the subject a therapy for Brugada Syndrome when the level of (a), (b), and/or (d) are reduced, relative to a control level, and/or when the level of (c) is increased, relative to a control level.

57. A method of treating Brugada Syndrome in a subject from which a biological sample was obtained and the biological sample was analyzed for

a. a level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene,

b. a level of mRNA of an *SCN5A* splice variant which encodes a truncated *SCN5A* protein,

c. a level of mRNA encoded by a *SCN5A* splicing factor gene, and/or

d. a level of mRNA encoded by a gene of the unfolded protein response (UPR);

comprising the step of providing to the subject a therapy for Brugada Syndrome in an amount effective to treat the Brugada Syndrome.

58. The method of any one of the preceding claims wherein the level of mRNA is determined by measuring the level of protein encoded by the mRNA transcripts.

59. The method of claim 58, wherein the level of protein is measured by an immunoassay.

60. The method of claim 58 or 59, wherein the level of protein is normalized to the protein level encoded by a housekeeping gene, optionally, wherein the housekeeping gene is β -actin.

61. The method of any one of claims 55 to 60, wherein the therapy is an ICD, a mitochondrially-targeted antioxidant, a mitochondria electron transport re-coupling agent, a Protein Kinase A Activator, a Protein Kinase C Inhibitor, a c-Src Inhibitor, an anion transporter inhibitor, an inner-membrane anion channels (IMAC) modulator, an NADPH oxidase inhibitor, or a Protein Kinase G Activator.

62. The method of claim 61, wherein the therapy is an ICD and wherein the level of mRNA of an *SCN5A* splice variant which encodes a truncated *SCN5A* protein is not a level relative to the level of full-length messenger RNA (mRNA) encoded by the *SCN5A* gene.

63. The method of any one of claims 55 to 62, wherein the method comprises analyzing the biological sample obtained from the subject for a full length *SCN5A* Exon 28 transcript and/or a truncated *SCN5A* Exon 28 transcript, or wherein the subject has been analyzed for a full length *SCN5A* Exon 28 transcript and/or a truncated *SCN5A* Exon 28 transcript.

64. The method of any one of claims 55 to 63, wherein the *SCN5A* splice variant is *SCN5A* Exon 28 Splice Variant C (E28C) or *SCN5A* Exon 28 Splice Variant D (E28D).

65. The method of claim 64, wherein the method comprises analyzing the biological sample for both the level of mRNA of the E28C *SCN5A* splice variant and the level of mRNA of the E28D *SCN5A* splice variant, or wherein the subject has been analyzed for both the level of mRNA of the E28C *SCN5A* splice variant and the level of mRNA of the E28D *SCN5A* splice variant.

66. The method of any one of claims 55 to 65, wherein the method comprises analyzing the biological sample for (a) and/or (b) or wherein the subject has been analyzed for (a) and/or (b).

67. The method of any one of claims 55 to 66, wherein the *SCN5A* splicing factor gene is *RBM25*, *Luc7A*, or *PRP40*.

68. The method of claim 67, wherein the method comprises analyzing the biological sample for the level of mRNA encoded by two or all of *RBM25*, *Luc7A*, and *PRP40* or the subject has been analyzed for the level of mRNA encoded by two or all of *RBM25*, *Luc7A*, and *PRP40*.

69. The method of any one of claims 55 to 68, wherein the gene of the UPR is *PERK*.

70. The method of any one of claims 55 to 69, wherein each of the level of mRNA and the control level is or was normalized to the level of mRNA encoded by a housekeeping gene of the biological sample.

71. The method of claim 70, wherein the housekeeping gene is the β -actin gene.

72. The method of any one of claims 55 to 71, wherein the level of mRNA is or was determined by real-time RT-PCR analysis.

73. The method of any one of claims 55 to 72, wherein the level of full-length mRNA encoded by the *SCN5A* gene is or was reduced by at least 50%, relative to a control level.

74. The method of any one of claims 55 to 73, wherein the biological sample comprises or comprised heart cells or white blood cells.

75. The method of claim 74, wherein the biological sample comprises or comprised white blood cells.

76. The method of claim 75, wherein the biological sample is or was blood or a fraction thereof.

77. The method of any one of claims 55 to 76, wherein the subject is male.

78. The method of any one of claims 55 to 77, wherein the subject is about 40 years old or younger.

79. The method of any one of claims 55 to 78, wherein the subject has a medical history including syncope and/or dizziness.

80. The subject of any one of claims 55 to 79, wherein the subject has been treated for and survived sudden cardiac death or has a family history of sudden cardiac death.

81. The method of any one of claims 55 to 80, wherein the subject does not have any structural defect of the heart.

82. The method of any one of claims 55 to 81, wherein the method further comprises performing a genetic test on the subject, optionally, wherein the genetic test analyzes the sequence of the *SCN5A* gene, the *CACNA1c* gene, and/or the *GPD1-L* gene.

83. The method of any one of claims 55 to 82, wherein the subject does not have a genetic mutation in the open reading frame of *SCN5A* gene.

84. The method of any one of claims 55 to 83, wherein the subject does not have a genetic mutation in the *CACNA1c* gene or in the *GPD1-L* gene.

85. The method of any one of claims 55 to 84, wherein the subject does not have any of the mutations listed in Table 1 or Table 2.

86. A Brugada Syndrome diagnostic kit comprising (i) a binding agent which binds to a full-length mRNA transcript encoded by the *SCN5A* gene or a protein product encoded by the full-length mRNA transcript, (ii) a binding agent which binds to an mRNA of an *SCN5A* splice variant or to a protein product encoded by the *SCN5A* splice

variant, (iii) a binding agent which binds to an mRNA encoded by a gene of the UPR or a protein product encoded by the gene of the UPR, (iv) a binding agent which binds to an mRNA encoded by a SCN5A splicing factor gene or a protein product encoded by the SCN5A splicing factor gene.

87. The Brugada Syndrome diagnostic kit of claim 86, wherein the gene of the UPR is *PERK*.

88. The Brugada Syndrome diagnostic kit of claim 86 or 87, wherein the SCN5A splicing factor gene is *RBM25*, *Luc7A*, or *PRP40*.

89. The Brugada Syndrome diagnostic kit of any one of claims 86 to 88, comprising a binding agent which binds to a full length SCN5A Exon 28 transcript and/or a truncated SCN5A Exon 28 transcript, and/or a protein product encoded by the full length SCN5A Exon 28 transcript and/or the truncated SCN5A Exon 28 transcript.

90. The Brugada Syndrome diagnostic kit of claim 89, wherein the truncated SCN5A Exon 28 transcript is E28C or E28D.

91. The Brugada Syndrome diagnostic kit of any one of claims 86 to 90, wherein the kit is intended for use in a method of any one of claims 1 to 85.

92. The Brugada Syndrome diagnostic kit of any one of claims 86 to 91, comprising a nucleic acid probe.

93. The Brugada Syndrome diagnostic kit of claim 92, wherein the nucleic acid probe comprises the sequence of any one of SEQ ID NOs: 665-686.

94. The Brugada Syndrome diagnostic kit of any one of claims 86 to 93, comprising an antibody which specifically binds to the protein product of (i), (ii), (iii), or (iv).

95. The Brugada Syndrome diagnostic kit of claim 94, comprising an antibody which specifically binds to a full length or truncated SCN5A protein product, a PERK protein product, an RBM25 protein product, a LUC7A protein product, a PRP40 protein product.

96. The Brugada Syndrome diagnostic kit of claim 95, wherein the antibody which specifically binds to the full length SCN5A protein product binds to an epitope within the C-terminal portion of the full length SCN5A protein product, which epitope is not present in the truncated SCN5A protein product.

97. The Brugada Syndrome diagnostic kit of claim 95, wherein the antibody binds to an epitope within the N-terminal portion of the full length SCN5A protein product, which epitope is present in the truncated SCN5A protein product.

98. The Brugada Syndrome diagnostic kit of any one of claims 86 to 97, comprising a container suitable for collecting blood.

99. The Brugada Syndrome diagnostic kit of claim 98, wherein the container comprises heparin.

100. The Brugada Syndrome diagnostic kit of any one of claims 86 to 99, comprising a skin pricking device, optionally, a finger prick device.

101. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a plurality of data values relating to a control level of SCN5A mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ , of the data values of (i);
- iii. receive a data value, α , relating to a test level of SCN5A mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α is less than or equal to $(\mu - (0.X\mu))$, wherein X is 0.35-0.75.

102. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a data value, α , relating to a test level of SCN5A mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α is less than or equal to $(\mu - (0.5\mu))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of SCN5A mRNA from a biological sample obtained from a control subject.

103. The system of claim 101 or 102, wherein α is the level of full length mRNA encoded by the SCN5A gene.

104. The system of claim 101 or 102, wherein α is the level of mRNA of an SCN5A splice variant.

105. The system of claim 104, wherein the SCN5A splice variant encodes a truncated SCN5A protein product.

106. The system of claim 101 or 102, wherein α is the sum of the level of full length mRNA encoded by the SCN5A gene and the level of the SCN5A splice variant mRNA which encodes a truncated protein.

107. The system of claim 101 or 102, wherein α is the level of full length SCN5A Exon 28 mRNA.

108. The system of claim 101 or 102, wherein α is the level of a truncated SCN5A Exon28 mRNA.

109. The system of claim 101 or 102, wherein α is the sum of the level of full length SCN5A Exon 28 mRNA and the level of a truncated SCN5A Exon28 mRNA.

110. The system of claim 109, wherein the truncated SCN5A Exon28 mRNA is (a) the mRNA of SCN5A Exon 28 Variant C, (b) the mRNA of SCN5A Exon 28 Variant D, or both (a) and (b).

111. The system of any one of claims 101 to 110, wherein X is 0.4 to 0.6.

112. The system of claim 111, wherein X is 0.45 to 0.55.

113. The system of claim 112, wherein X is about 0.50.

114. The system of any one of claims 101 to 113, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{PERK} , of the data values of (i);
- iii. receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (0.X\mu_{\text{PERK}}))$, wherein X is 0.35-0.75.

115. The system of any one of claims 101 to 114, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{RBM25} , of the data values of (i);
- iii. receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (0.X\mu_{\text{RBM25}}))$, wherein X is 0.35-0.75.

116. The system of any one of claims 101 to 115, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{LUC7A} , of the data values of (i);

- iii. receive a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{LUC7A} + (0.X\mu_{LUC7A}))$, wherein X is 0.35-0.75.

117. The system of any one of claims 101 to 116, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{PRP40} , of the data values of (i);
- iii. receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{PRP40} + (0.X\mu_{PRP40}))$, wherein X is 0.35-0.75.

118. The system of any one of claims 101 to 117, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{PERK} - (X\mu_{PERK}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

119. The system of any one of claims 101 to 118, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

120. The system of any one of claims 101 to 119, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

121. The system of any one of claims 101 to 120, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (X\mu_{\text{PRP40}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

122. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising:

- i. instructions for receiving a plurality of data values relating to a control level of SCN5A mRNA from a biological sample obtained from a control subject;
- ii. instructions for determining a mean value, μ , of the data values of (i);
- iii. instructions for receiving a data value, α , relating to a test level of SCN5A mRNA from a biological sample obtained from a test subject; and
- iv. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to $(\mu - (0.X\mu))$, wherein X is 0.35-0.75.

123. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising:

- iii. instructions for receiving a data value, α , relating to a test level of SCN5A mRNA from a biological sample obtained from a test subject and
- iv. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to $(\mu - (0.5\mu))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of SCN5A mRNA from a biological sample obtained from a control subject.

124. The computer-readable storage medium of claim 122 or 123, wherein α is the level of full length mRNA encoded by the SCN5A gene.

125. The computer-readable storage medium of claim 122 or 123, wherein α is the level of mRNA of an SCN5A splice variant.

126. The computer-readable storage medium of claim 125, wherein the SCN5A splice variant encodes a truncated SCN5A protein product.

127. The computer-readable storage medium of claim 122 or 123, wherein α is the sum of the level of full length mRNA encoded by the SCN5A gene and the level of the SCN5A splice variant mRNA which encodes a truncated protein.

128. The computer-readable storage medium of claim 122 or 123, wherein α is the level of full length SCN5A Exon 28 mRNA.

129. The computer-readable storage medium of claim 122 or 123, wherein α is the level of a truncated SCN5A Exon28 mRNA.

130. The computer-readable storage medium of claim 122 or 123, wherein α is the sum of the level of full length SCN5A Exon 28 mRNA and the level of a truncated SCN5A Exon28 mRNA.

131. The computer-readable storage medium of claim 130, wherein the truncated SCN5A Exon28 mRNA is (a) the mRNA of SCN5A Exon 28 Variant C, (b) the mRNA of SCN5A Exon 28 Variant D, or both (a) and (b).

132. The computer-readable storage medium of any one of claims 122 to 123, wherein X is 0.4 to 0.6.

133. The computer-readable storage medium of claim 132, wherein X is 0.45 to 0.55.

134. The computer-readable storage medium of claim 133, wherein X is about 0.50.

135. The computer-readable storage medium of any one of claims 122 to 134, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{PERK} , of the data values of (i);

- iii. receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (0.X\mu_{\text{PERK}}))$, wherein X is 0.35-0.75.

136. The computer-readable storage medium of any one of claims 122 to 135, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{RBM25} , of the data values of (i);
- iii. receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (0.X\mu_{\text{RBM25}}))$, wherein X is 0.35-0.75.

137. The computer-readable storage medium of any one of claims 122 to 136, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{LUC7A} , of the data values of (i);
- iii. receive a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject; and

- iv. display an output diagnosis relating to Brugada Syndrome, when α_{LUX7A} is greater than or equal to $(\mu_{LUC7A} + (0.X\mu_{LUC7A}))$, wherein X is 0.35-0.75.

138. The computer-readable storage medium of any one of claims 122 to 137, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{PRP40} , of the data values of (i);
- iii. receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{PRP40} + (0.X\mu_{PRP40}))$, wherein X is 0.35-0.75.

139. The computer-readable storage medium of any one of claims 122 to 138, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{PERK} - (X\mu_{PERK}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

140. The computer-readable storage medium of any one of claims 122 to 139, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

141. The computer-readable storage medium of any one of claims 122 to 140, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

142. The computer-readable storage medium of any one of claims 122 to 141, comprising machine readable instructions that, when executed by the processor, cause the processor to

- i. receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (X\mu_{\text{PRP40}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained

from a control subject, wherein X is a number between 0.35 and 0.75.

143. A computer-implemented method relating to Brugada Syndrome comprising:

- i. receiving a plurality of data values relating to a control level of SCN5A mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ , of the data values of (i);
- iii. receiving a data value, α , relating to a test level of SCN5A mRNA from a biological sample obtained from a test subject; and
- iv. displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to $(\mu - (0.X\mu))$, wherein X is 0.35-0.75.

144. A computer-implemented method relating to Brugada Syndrome comprising:

- i. receiving a data value, α , relating to a test level of SCN5A mRNA from a biological sample obtained from a test subject and
- ii. displaying an output diagnosis relating to Brugada Syndrome, when α is less than or equal to $(\mu - (0.5\mu))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of SCN5A mRNA from a biological sample obtained from a control subject.

145. The computer-implemented method of claim 143 or 144, wherein α is the level of full length mRNA encoded by the SCN5A gene.

146. The computer-implemented method of claim 143 or 144, wherein α is the level of mRNA of an SCN5A splice variant.

147. The computer-implemented method of claim 146, wherein the SCN5A splice variant encodes a truncated SCN5A protein product.

148. The computer-implemented method of claim 143 or 144, wherein α is the sum of the level of full length mRNA encoded by the SCN5A gene and the level of the SCN5A splice variant mRNA which encodes a truncated protein.

149. The computer-implemented method of claim 143 or 144, wherein α is the level of full length SCN5A Exon 28 mRNA.

150. The computer-implemented method of claim 143 or 144, wherein α is the level of a truncated SCN5A Exon28 mRNA.

151. The computer-implemented method of claim 143 or 144, wherein α is the sum of the level of full length SCN5A Exon 28 mRNA and the level of a truncated SCN5A Exon28 mRNA.

152. The computer-implemented method of claim 151, wherein the truncated SCN5A Exon28 mRNA is (a) the mRNA of SCN5A Exon 28 Variant C, (b) the mRNA of SCN5A Exon 28 Variant D, or both (a) and (b).

153. The computer-implemented method of any one of claims 143 to 144, wherein X is 0.4 to 0.6.

154. The computer-implemented method of claim 153, wherein X is 0.45 to 0.55.

155. The computer-implemented method of claim 154, wherein X is about 0.50.

156. The computer-implemented method of any one of claims 143 to 155, comprising

- i. receiving a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{PERK} , of the data values of (i);

- iii. receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject; and
- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (0.X\mu_{\text{PERK}}))$, wherein X is 0.35-0.75.

157. The computer-implemented method of any one of claims 143 to 156, comprising

- i. receiving a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{RBM25} , of the data values of (i);
- iii. receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject; and
- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (0.X\mu_{\text{RBM25}}))$, wherein X is 0.35-0.75.

158. The computer-implemented method of any one of claims 143 to 157, comprising

- i. receiving a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{LUC7A} , of the data values of (i);
- iii. receiving a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject; and

- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{LUX7A} is greater than or equal to $(\mu_{LUC7A} + (0.X\mu_{LUC7A}))$, wherein X is 0.35-0.75.

159. The computer-implemented method of any one of claims 143 to 158, comprising

- i. receiving a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{PRP40} , of the data values of (i);
- iii. receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject; and
- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{PRP40} + (0.X\mu_{PRP40}))$, wherein X is 0.35-0.75.

160. The computer-implemented method of any one of claims 143 to 159, comprising

- i. receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and
- ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{PERK} - (X\mu_{PERK}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

161. The computer-implemented method of any one of claims 143 to 160, comprising

- i. receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and

- ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.
- 162. The computer-implemented method of any one of claims 143 to 161, comprising
 - i. receiving a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject and
 - ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.
- 163. The computer-readable storage medium of any one of claims 143 to 162, comprising
 - i. receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and
 - ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (X\mu_{\text{PRP40}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.
- 164. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{PERK} , of the data values of (i);
- iii. receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (0.X\mu_{\text{PERK}}))$, wherein X is 0.35-0.75.

165. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{RBM25} , of the data values of (i);
- iii. receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (0.X\mu_{\text{RBM25}}))$, wherein X is 0.35-0.75.

166. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{LUC7A} , of the data values of (i);

- iii. receive a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{LUC7A} + (0.X\mu_{LUC7A}))$, wherein X is 0.35-0.75.

167. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject;
- ii. determine a mean value, μ_{PRP40} , of the data values of (i);
- iii. receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject; and
- iv. display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{PRP40} + (0.X\mu_{PRP40}))$, wherein X is 0.35-0.75.

168. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{PERK} - (X\mu_{PERK}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

169. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

170. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

171. A system comprising: a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, wherein the machine readable instructions, when executed by the processor, cause the processor to:

- i. receive a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and
- ii. display an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (X\mu_{\text{PRP40}}))$, wherein μ is a

predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

172. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject;
- ii. instructions for determining a mean value, μ_{PERK} , of the data values of (i);
- iii. instructions for receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject; and
- iv. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (0.X\mu_{\text{PERK}}))$, wherein X is 0.35-0.75.

173. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject;
- ii. instructions for determining a mean value, μ_{RBM25} , of the data values of (i);
- iii. instructions for receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject; and

- iv. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (0.X\mu_{\text{RBM25}}))$, wherein X is 0.35-0.75.

174. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject;
- ii. instructions for determining a mean value, μ_{LUC7A} , of the data values of (i);
- iii. instructions for receiving a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject; and
- iv. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (0.X\mu_{\text{LUC7A}}))$, wherein X is 0.35-0.75.

175. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject;
- ii. instructions for determining a mean value, μ_{PRP40} , of the data values of (i);
- iii. instructions for receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject; and

- iv. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (0.X\mu_{\text{PRP40}}))$, wherein X is 0.35-0.75.

176. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and
- ii. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

177. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and
- ii. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

178. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject and
- ii. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (X\mu_{\text{LUC7A}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

179. A computer-readable storage medium having stored thereon a set of instructions, executable by a processor, the instructions comprising

- i. instructions for receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and
- ii. instructions for displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (X\mu_{\text{PRP40}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

180. A computer-implemented method, comprising

- i. receiving a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{PERK} , of the data values of (i);
- iii. receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject; and

- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (0.X\mu_{\text{PERK}}))$, wherein X is 0.35-0.75.

181. A computer-implemented method comprising

- i. receiving a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{RBM25} , of the data values of (i);
- iii. receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject; and
- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (0.X\mu_{\text{RBM25}}))$, wherein X is 0.35-0.75.

182. A computer-implemented method comprising

- i. receiving a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject;
- ii. determining a mean value, μ_{LUC7A} , of the data values of (i);
- iii. receiving a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject; and
- iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{\text{LUC7A}} + (0.X\mu_{\text{LUC7A}}))$, wherein X is 0.35-0.75.

183. A computer-implemented method comprising

- i. receiving a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject;

- ii. determining a mean value, μ_{PRP40} , of the data values of (i);
 - iii. receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject; and
 - iv. displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{\text{PRP40}} + (0.X\mu_{\text{PRP40}}))$, wherein X is 0.35-0.75.
184. A computer-implemented method comprising
- i. receiving a data value, α_{PERK} , relating to a test level of PERK mRNA from a biological sample obtained from a test subject and
 - ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{PERK} is less than or equal to $(\mu_{\text{PERK}} - (X\mu_{\text{PERK}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PERK mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.
185. A computer-implemented method comprising
- i. receiving a data value, α_{RBM25} , relating to a test level of RBM25 mRNA from a biological sample obtained from a test subject and
 - ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{RBM25} is greater than or equal to $(\mu_{\text{RBM25}} + (X\mu_{\text{RBM25}}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of RBM25 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.
186. A computer-implemented method comprising
- i. receiving a data value, α_{LUC7A} , relating to a test level of LUC7A mRNA from a biological sample obtained from a test subject and

- ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{LUC7A} is greater than or equal to $(\mu_{LUC7A} + (X\mu_{LUC7A}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of LUC7A mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.
187. A computer-readable storage medium comprising
- i. receiving a data value, α_{PRP40} , relating to a test level of PRP40 mRNA from a biological sample obtained from a test subject and
 - ii. displaying an output diagnosis relating to Brugada Syndrome, when α_{PRP40} is greater than or equal to $(\mu_{PRP40} + (X\mu_{PRP40}))$, wherein μ is a predetermined mean value of a plurality of data values relating to a control level of PRP40 mRNA from a biological sample obtained from a control subject, wherein X is a number between 0.35 and 0.75.

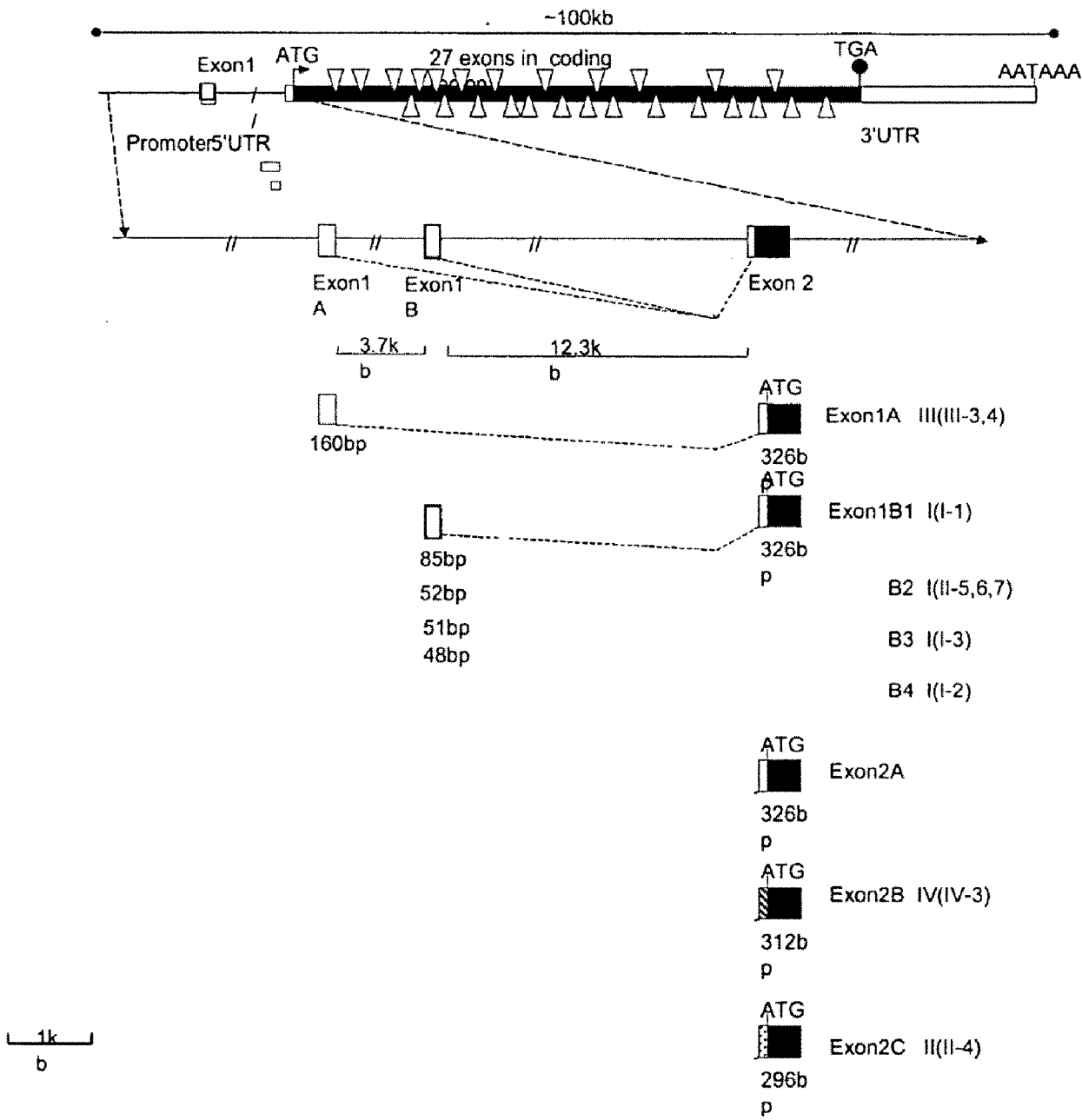
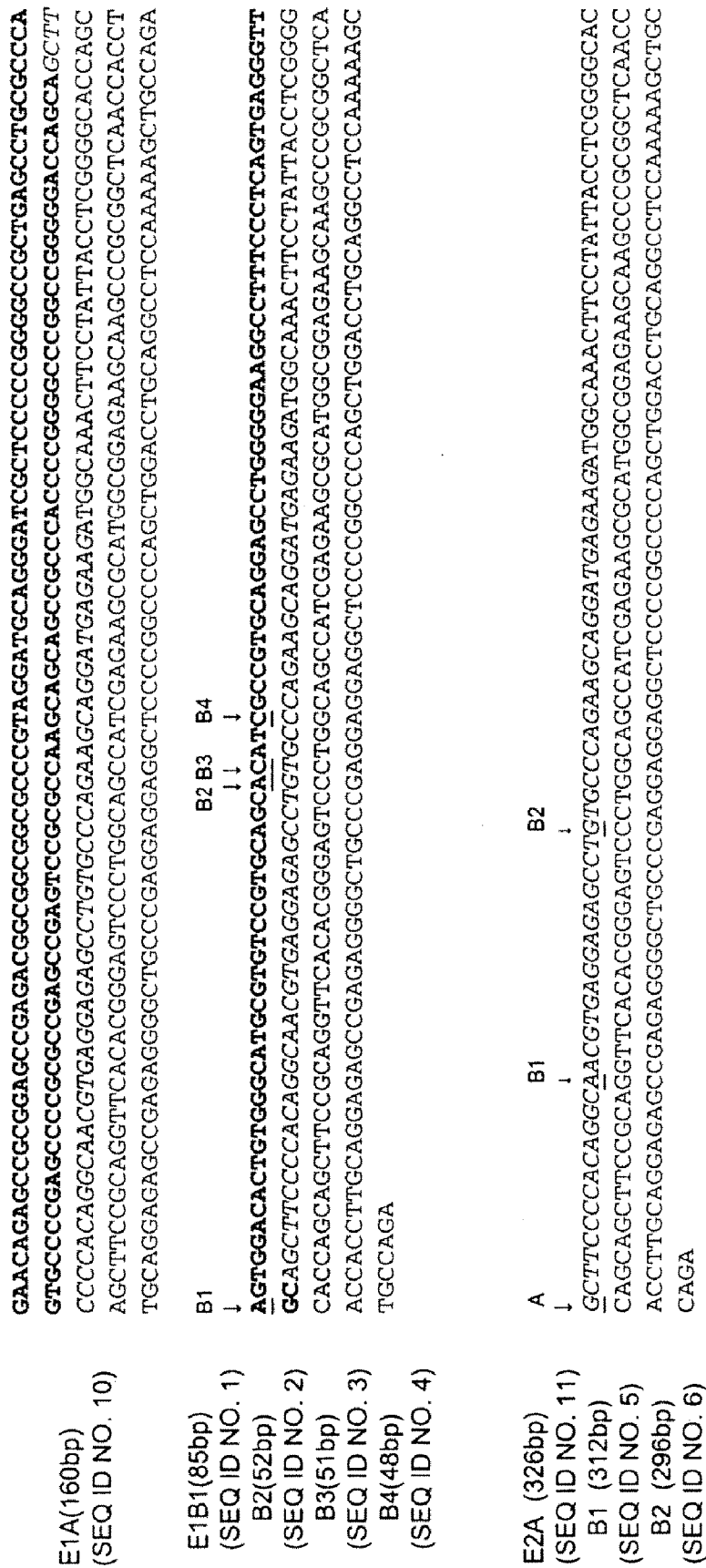


FIG. 1



Bold: Exon 1, Italics: UTR of Exon 2, Regular: Exon 2,

Arrow and underlined base indicate the first base of the isoform indicated above the arrow

FIG. 2

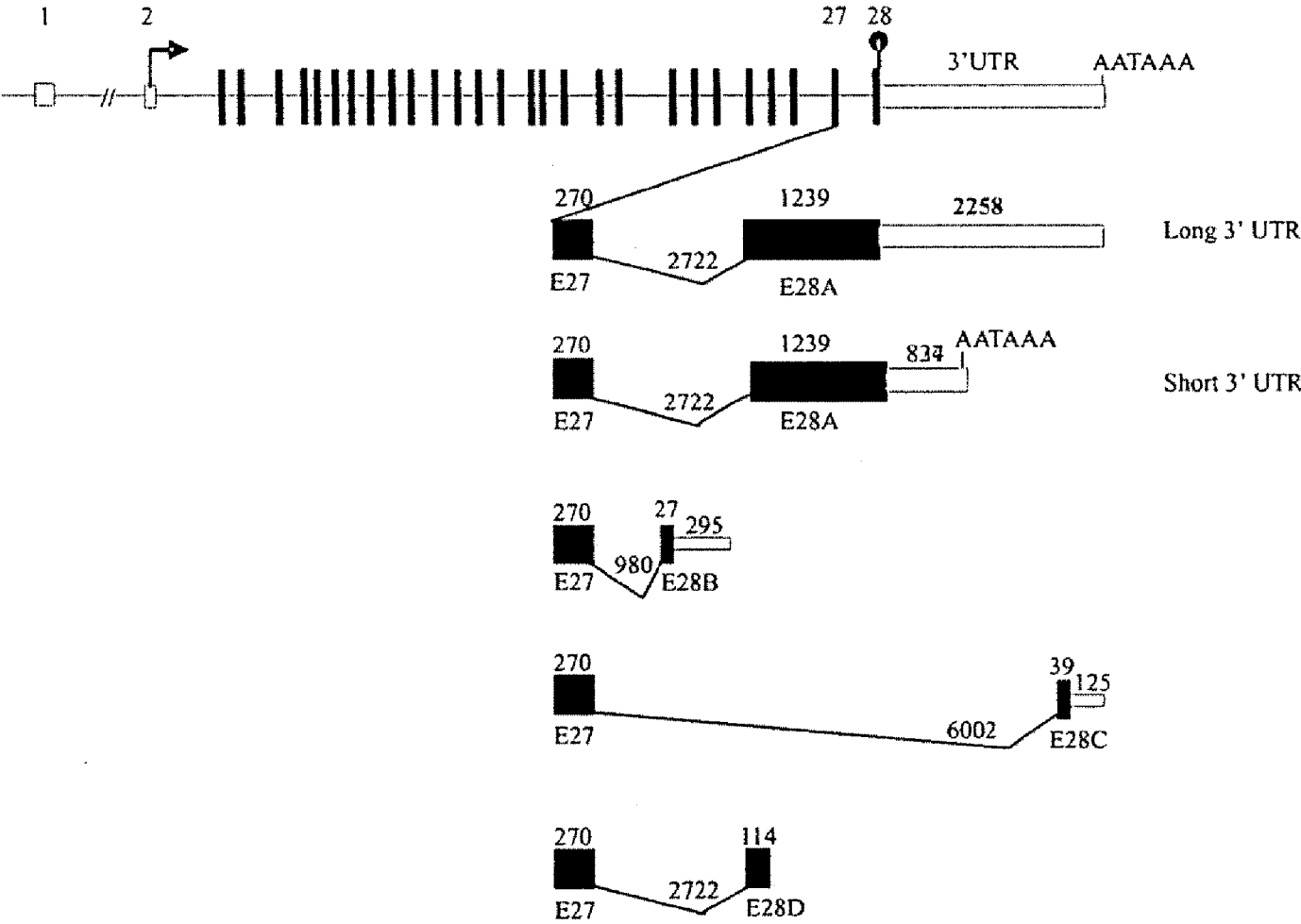


FIG. 3

E28A translated region (1239bp intrantranslated region (codon))

DNA (Nucleic Acid Nos. 1-1239 of SEQ ID NOS. 12 and 13) :

GGCACTGTGCTCTCGGACATCATCCAGAAGTACTTCTCTCCCGACGCTCTCCGAGTCATCCGCTGCGCCGAATAGGCC
GCATCCTCAGACTGATCCGAGGGGCCAAGGGATCCGACGCTGCTCTTGGCCCTCATGATGCCCTGCCCTCTTCA
ACATCGGGCTGCTGCTCTTCTCGTCATGTTTCATCTACTCCATCTTGGCATGGCCAACTTCGCTTATGTCAAGTGGAGGCT
GGCATCGACGACATGTTCAACTTCCAGACCTTGGCCAAACAGCATGCTGTGCTCTTCCAGATCACCACTCGGCGGCTGG
GATGGCTCCTCAGCCCCATCCTCAACACTGGGCGCCCTACTGCGACCCCACTCTGCCCAACAGCAATGGCTCTCGGGGG
GACTCGGGAGCCGAGCGGTGGCATCCTCTTCTTACCACCTACATCATCTCCTTCTCATCTGTTGTTCAACATGTACA
TTGCCATCATCCTGGAACTTCAGCGTGGCCACGGAGAGACCGAGCCCTGAGTGAGGACGACTTCGATATGTTCT
ATGAGATCTGGGAGAAATTTGACCCAGAGGCCACTCAGTTTATTGAGTATTCGGTCTGTCTGACTTTGCCGACGCCCTGTCT
GAGCCACTCCGTATCGCCAGCCCAACCCAGATAAGCCTCATCAACATGGACCTGCCATGGTGTAGTGGGACCGCATCCAT
TGCAATGGACATCTCTTTGCCTTACCAAAGGTCCTGGGGAGTCTGGGAGATGGACGCCCTGAAGATCCAGATGGAG
GAGAAGTTCATGCGAGCCACCCATCCAAAGATCTCTACGAGCCCATCACCACTCCGGCGCAAGCACGAAGAGGTG
TCGGCCATGGTTATCCAGAGAGCCTTCCGAGGACCTGCTGCAACGCTCTTTGAAGCATGCCCTCCTTCCCTCCGTCAGC
AGGCGGGCAGCGCCTCTCCGAAGAGGATGCCCTGAGCGAGAGGGCCTCATCGCCTACGTGATGATGAGAACTTCTCC
CGACCCCTTGCCCCACCTCCAGCTCCTCCATCTCCTCCACTTCTTCCACCTCCTATGACAGTGTCACTAGAGCCACCA
GCGATAACCTCCAGGTGCGGGGTCTGACTACAGCCACAGTGAAGATCTCGCCGACTTCCCCCTTCTCCGGACAGGGACC
GTGAGTCCATCGTGTGA

Deduced Protein^{*} (SEQ ID NO: 14)

GTVLSDIQKYFFSPTLFRVIRLARIGRILRLIRGAKGIRTLFALMMSLPALFNIGLLFLVMFIYSIFGMANFAYVKWEAGIDDMFNQF
FANSMCLCFQITTSAGWDGLLSPILNTGPPYCDPTLPNSNGSRGDCGSPAVGILFFTYYIIISFLIVNMYYIAILENFSVATEESTEPLS
EDDFDMFYEWKFDPEATQFIEYSVLSDFADALSEPLRIAKPNQISLINMDLPMVSGDRIHCMDILFAFTKRVLGESGEMDALKIQM
EEKFMAANPSKISYEPITTLRRKHEEVSAMVIQRAFRHLLQRSLKHASFLFRQQAGSGLSEEDAPEREGLIAYVMSENFSTRPLGP
PSSSSISSTSFPPSYDSVTRATSDNLQVRGSDYSHSEDLADFPPSPDRDRRESIV

^{*}Protein translated from codon region

FIG. 4A

E28A Untranslated region (3'UTR) sequences:

3'UTR-L (2295bp) (Nucleic Acid Nos. 1240-3497 of SEQ ID NO. 13)

3'UTR-S (834bp) (Bold only) (Nucleic Acid Nos. 1240-2066 of SEQ ID NO. 12)

gctcggcctggctggccaggacacactgaaaaggcagccttttccaccatggcaaacctaaatgcagtcagtcacaaaaccagcctggggccttccctgg
 ctttgggagtaagaaatgggctcagccccgcggatcaaccaggcagagttctgtggcgccgctggacagcggagcagttggcctgtgttgggagg
 cctcagatagacctgtacctgtgtcaggaatgcccctgcggctctgaaagcaacttcacccagctgctgagggcgaatatataaactgagac
 tgtatatgtgtgaatgggctttcataaattattatatattgatattttttacttgagcaagaactaaggatttttccatggacatgggcagcaat
 tcacgctgtctcttccaccctgaacaagagtgctatggagcagccgggaagtctgttctcaagcagaagtggatccagtggtggctccacaggt
 cttcaactgcccagggtcgaaatggggtccccctccacttgacctgagatgctgggagggtgaacccccactcacacaagcacacacacagtcct
 cacacaggaggccagacacaggccgtggaccaggctccagcctaaggagacaggccttccccgcggccccccaaagatgggggttcttgttcc
 acggggtcacctcgtggccccctattgtctcgaaggctccattttccccctgtgttttcacgcaggtcatattgtcagtcctacaaaaataaaaaggctt
 ccagaggagagtgccctgggtcccagggtggccctaggcactgatagttgccttttctccccctcctgttaagagtattacaaaaaccacaaaggacaca
 agggtgcaagccccattcacggcctggcatgcagcttgtccttgctcctggaaacctggcaggccccctggccagccagccatcgggaagagggtgagc
 catgggggtttggggctaaagaagttcacaggccctgagccatggcgccctcagcctgcctgaagagaggaactggcgatctcccagggtctctctg
 gaccatacgcggaggagttttctgtgtgttctccagctcctctccagacacagagacatgggagtggygagcggagcttyggccctgcgccctgtgcag
 ggaaagggtatggtcagggcccgagttctcgtgccccttagaggggaatgaaccatggcacctttgagagagggggcactgtggtcagggccagcctctctg
 gctcagcccggtatcctgatggcaccacacacagaggacctctttggggcaagatccagggtgtccccataggtcttgtgaaaaggcttttccagggaaa
 aatattttactagtcacatcacccccaggacctcttcagctgctgacaaatcctatttagcatatgcaaatcttttaacatagagaactgtcacccctga
 ggtaacagggtcaactggcgaagcctgagcaggcagggttggctgccccattccagctctcccatggagccccctccacgggcgcagtgccctccag
 gccacctcagttcacctgccggctctgggctggctccttaacctacctcggcagctgtcggagggtggacatttbtggcagtgctgaaggggg
 cattgccggcgagtaagattatgtttcttctgtcacccccagttcccttgggtggcaacccacagaccacccatgccccctgacagatctagtcttc
 ttctcctgtgttccctttgagtcagtggtggacacggtttaactgtcccagcgacatttctccaagtggaaatcctattttttagatctccatgct
 ttgtctctcaaggcttggagaggtatgtgccccctcctgggtgctcacggcctgtctacacaggcaggaatgcggttgggaggcaggtcgggctgccagcc
 cagctggccggaaggagactgtgggtttttgtgtgtgtggacagccccgggagctttgagacaggtgcctggggctggctgcagacgggtgtggttggggg
 tgggaggtgagctagaccccaaccccttagcttttagcctggctgtcacctttttaatttccagaactgcacaatgaccagcagggagggaaggacagaca
 tcaagtgccagatgtgtctgaactaatcgagcacttctcaccaacttcatgtataataaaatcacatatttttaaaacaaaccacaaatggctta
 catg

FIG. 4B

E28B (total 321bp, 27bp in codon, 295bp UTR)

DNA (SEQ ID NO. 7) :

GGAGCCCTCCTAGTGAGTATGAAGTGATATCTCACTGAGGTTTTGGTTTGCAAAAGCAAAATGACTGATGACTAACGAT
GCAGGACATCTTTCCATGTGCATGTTGGTCATTTATATATCTTCCCTTGGAGAAATCTCTATTGAGATCCTTAGCTCATT
TTAATTGGGTTATTTCTCTCTCTCTGTTGAGTTGTAGAGTTCTTTACATATTCTGGATCACAGTCTCTTATCAGATATA
TGATTTAAAAATATTTTCTCCTAGTCTGTGAGTTTTTTCATTTCTAGTGTGTCATTAAAGCACAAAAGTTTTACATGT
T

Deduced Protein ^{*} (SEQ ID NO: 15)**GALLVSMK**

*Protein translated from codon region
Bold=translated region

FIG. 4C

E28C (total 164bp, 39bp in codon, 125p UTR)

DNA (SEQ ID NO. 8) :

GAAGTGCACAATGACCAGCAGGAGGGAGAGAGTAGGAAAAAGGAGGGAAGGACAGACATCAAGTGCC
AGATGTTGTCTGAACTAATCGAGCACCTTCACCAAACCTTCATGTATAAATAACATATTTTAAAAACAAACCA
ATAAATGGCTTACATG

Deduced protein ^{*} (SEQ ID NO: 16)**ELHNDQQEGRRE**

^{*}Protein translated from codon region
Bold=translated region

FIG. 4D

E28D(114bp in codon)

DNA

AACAAGTACCAGGGCTTCATATTCGACATGTGACCAAGCAGGCCCTTTGACGTCACCATCATGTTTCTGATCTGCTTGAATATG
GTGACCATGATGGTGGAGACAGATGACCAAAGTCCTGAGAAAATCAACATCTTGGCCAAGATCAACCTGCTCTTTGTGGCCATC
TTCACAGGCGAGTGTATTGTCAAGCTGGCTGCCCTGGGCCACTACTACTTCACCAACAGCTGGAATATCTTCGACTTCGTGGTT
GTCATCCTCTCCATCGTGGGCACTGTGCTCTCGGACATCATCCAGAACTACTTCTTCTCCCCGACGCTCTTCCGAGTCATCCGC
CTGGCCCGAATAGGCCGCATCCTCAGACTGATCCGAGGGGCCAAGGG

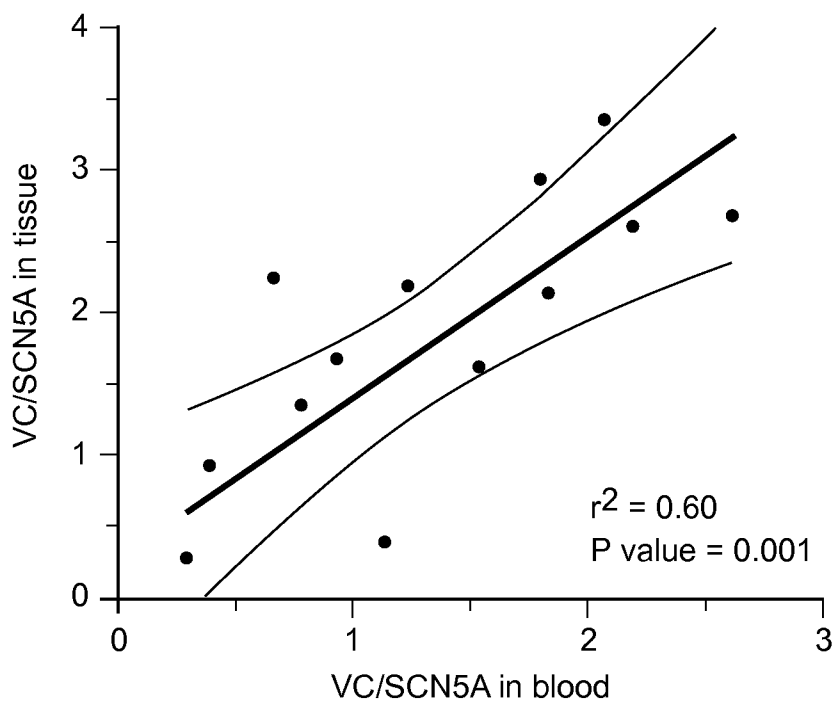
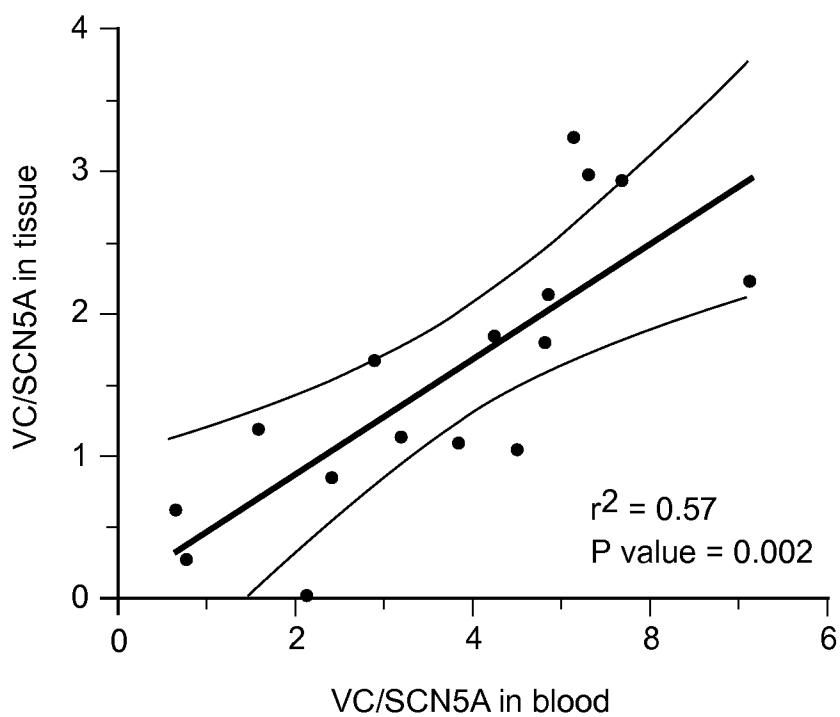
(SEQ ID NO: 9)

Protein

NKYQGFIFDIVTKQAFDVTTIMFLICLNMVTMMVETDDQSPEKINILAKINLLEFVAIFTGECIVKLAALRHHYFTNSWNIFDFVV
VILSIVGTVLSDIIQKYFFSPTLFRVIRLARIGRILRLIRGAKG

(SEQ ID NO: 17)

FIG. 4E

**FIG. 5****FIG. 6**

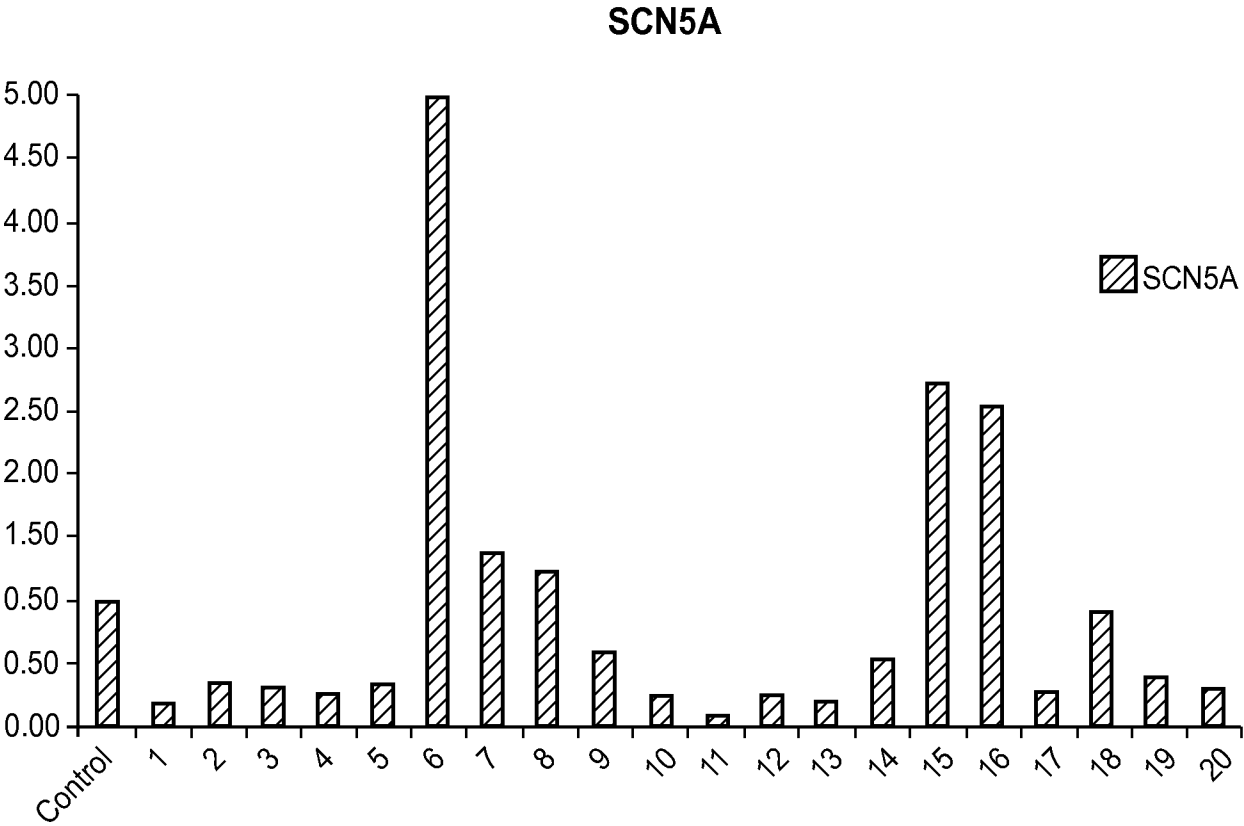


FIG. 7

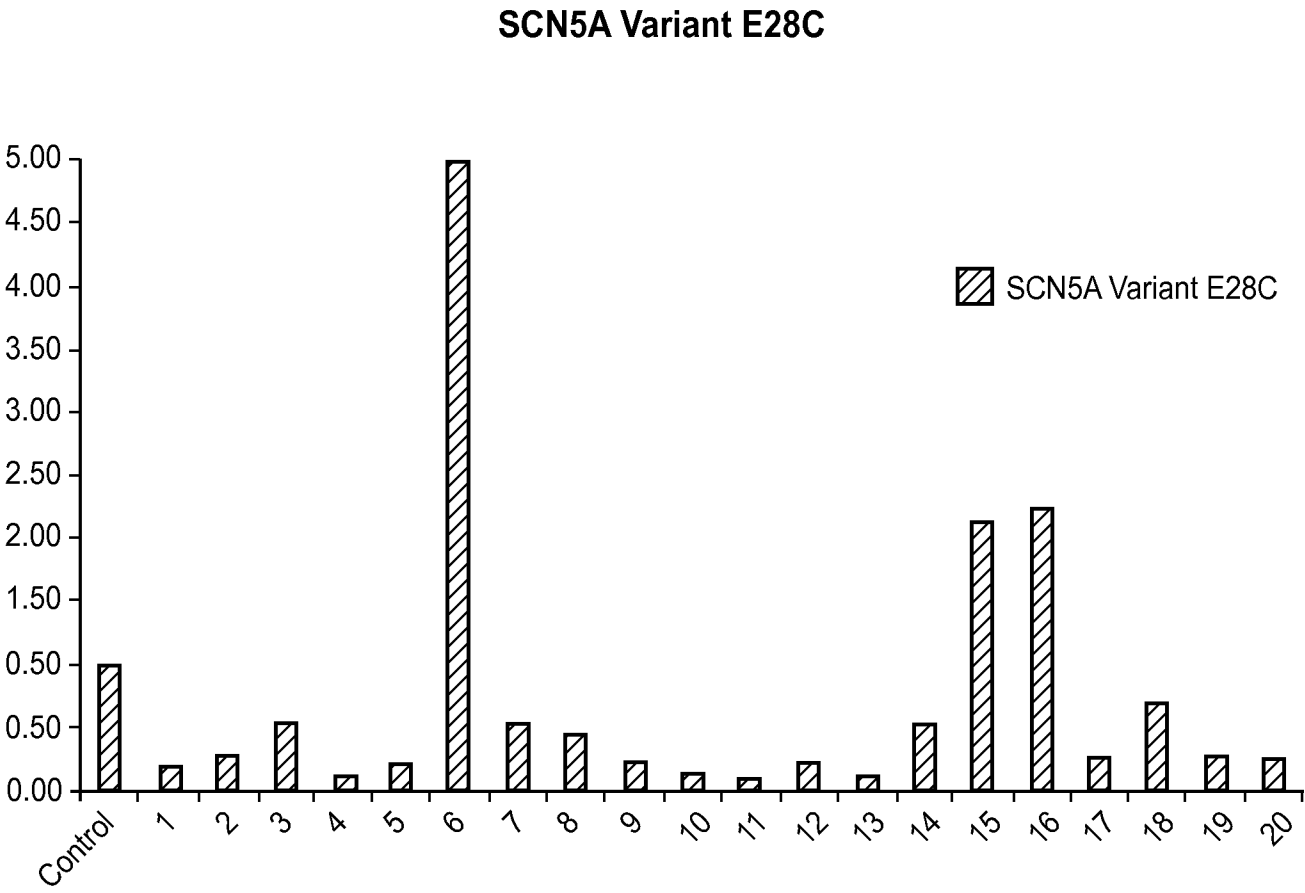
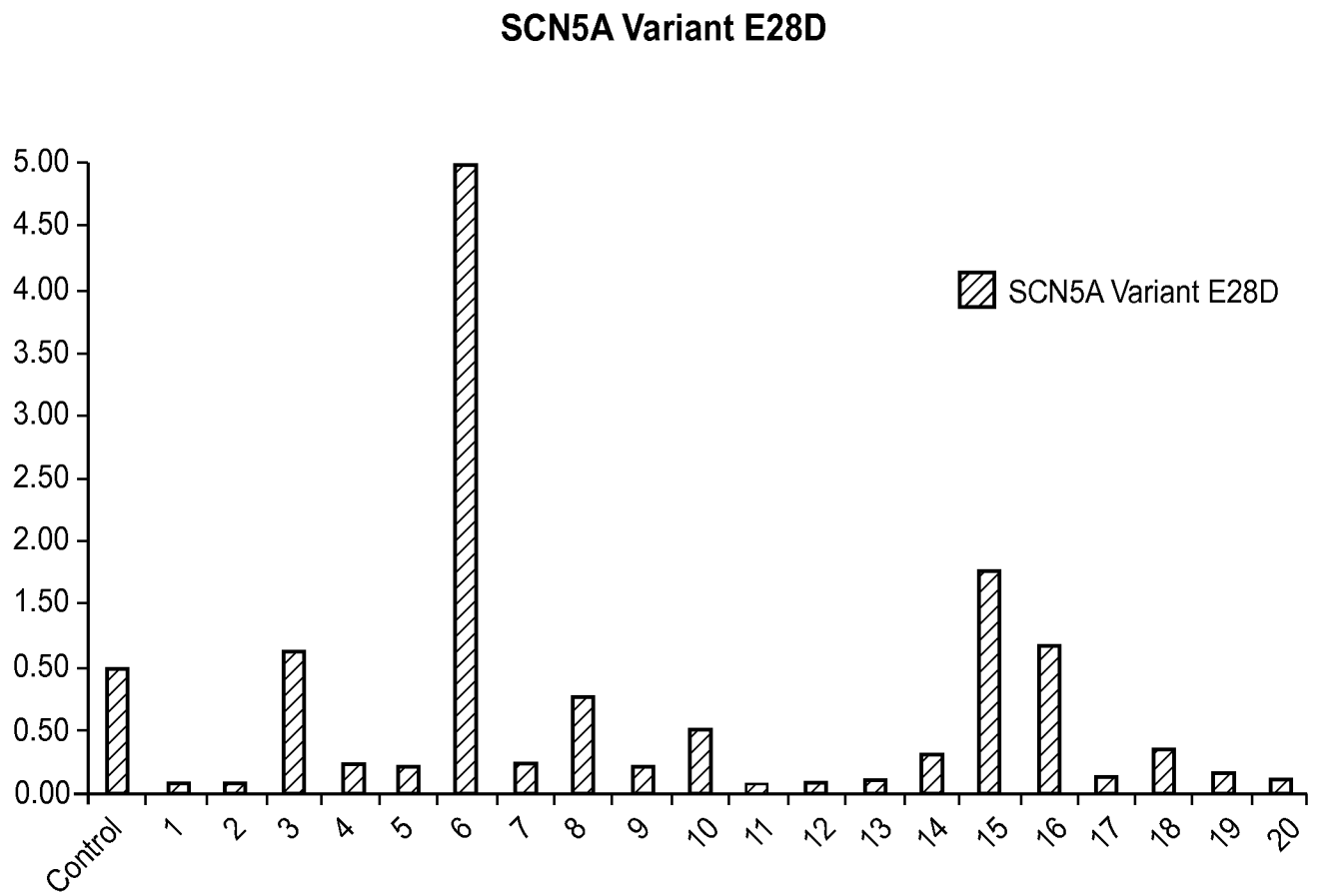
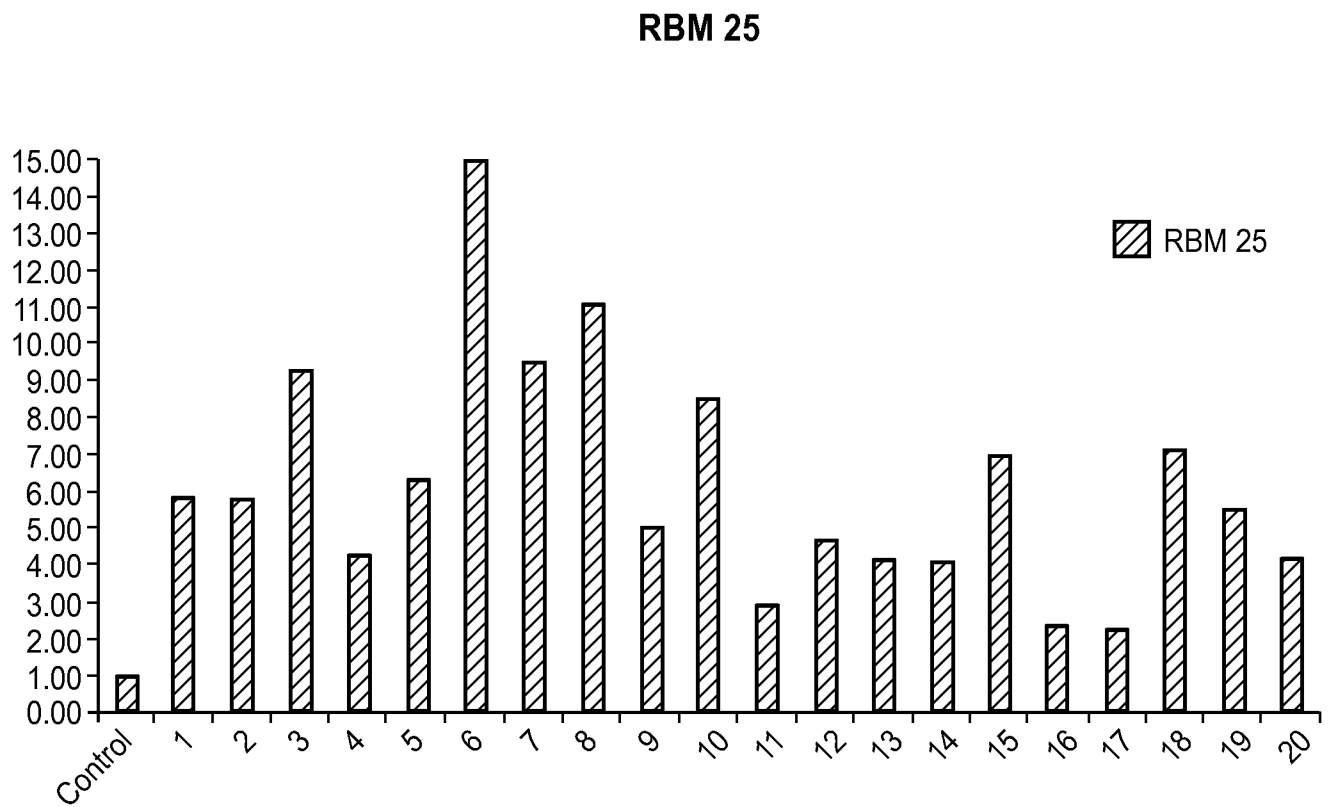
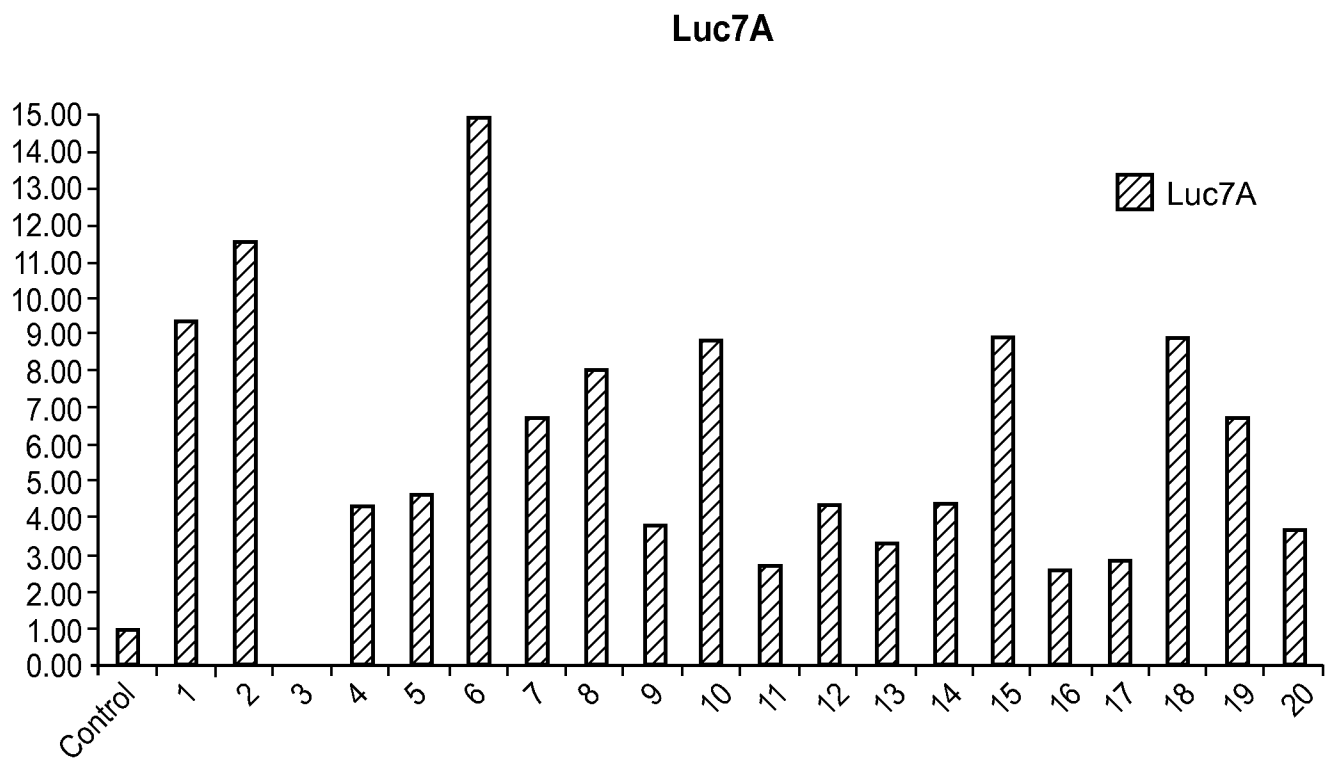
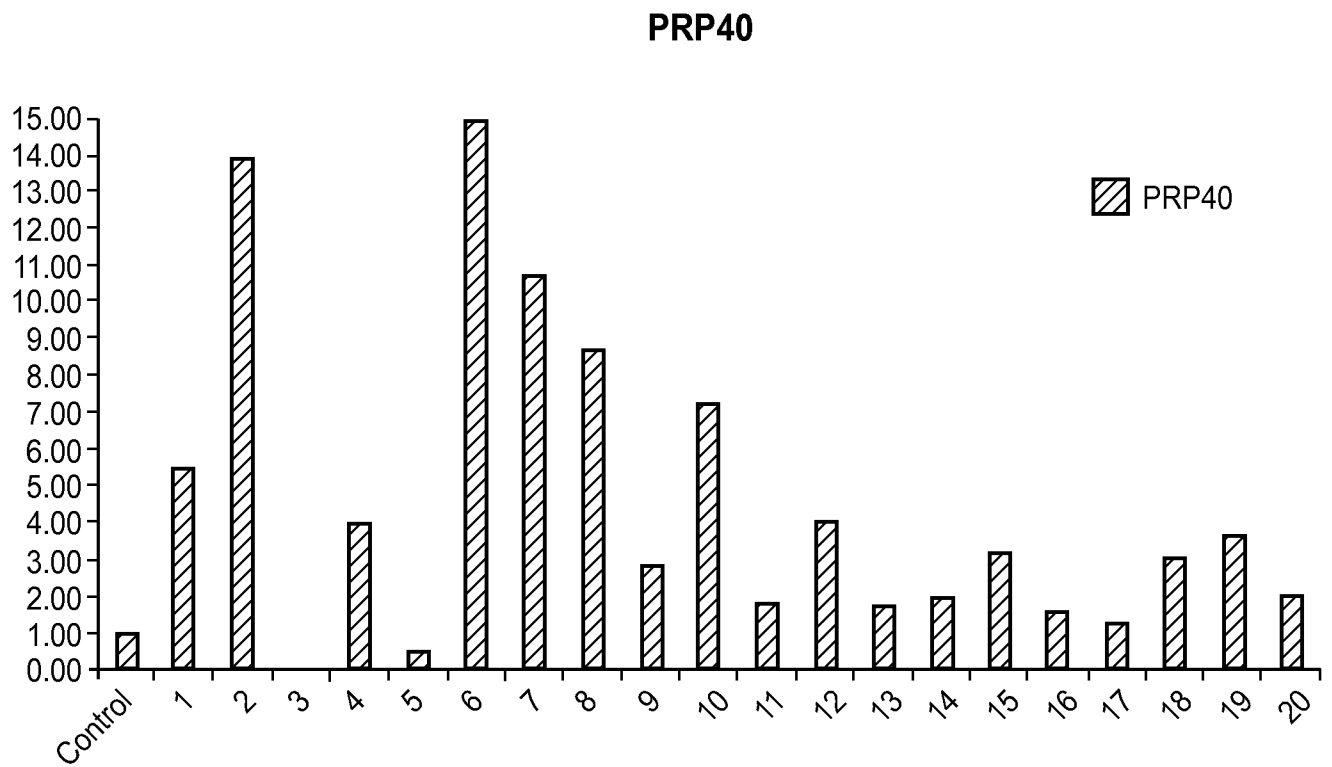


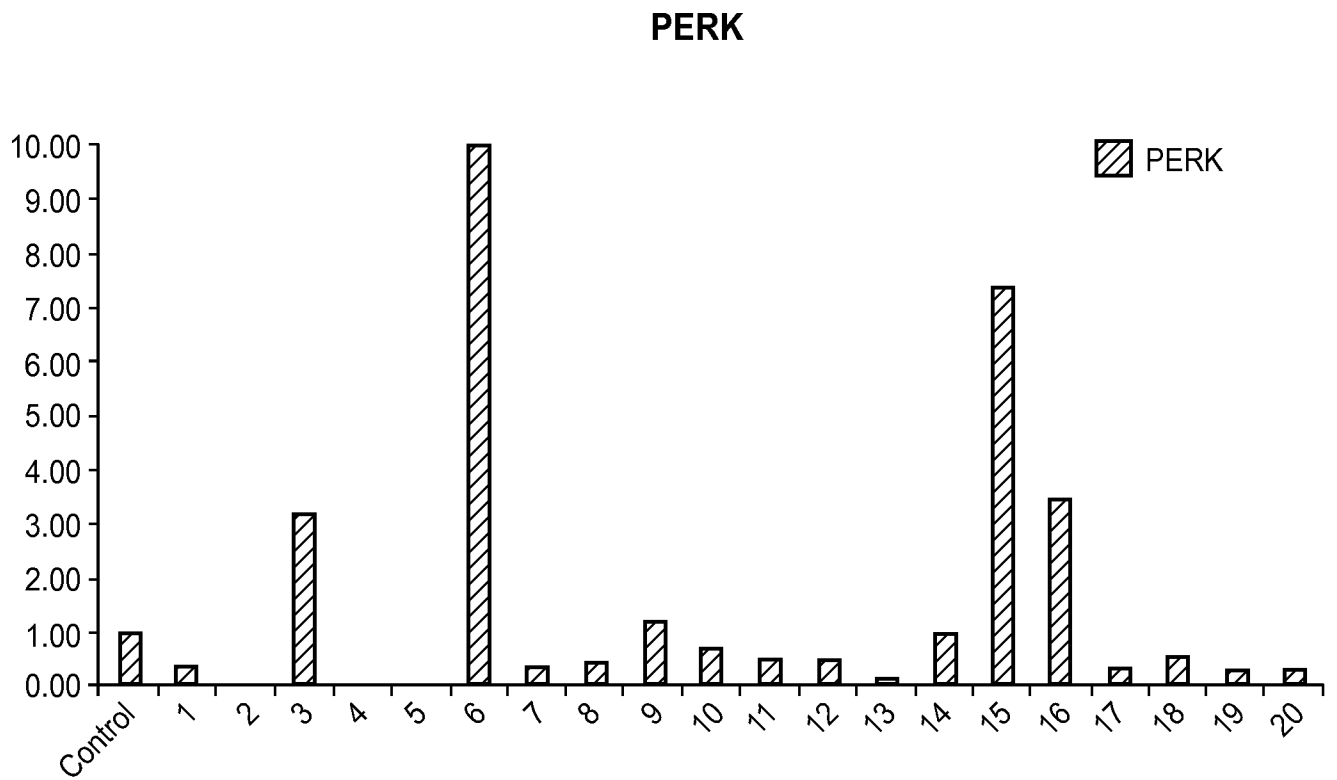
FIG. 8

**FIG. 9**

**FIG. 10**

**FIG. 11**

**FIG. 12**

**FIG. 13**

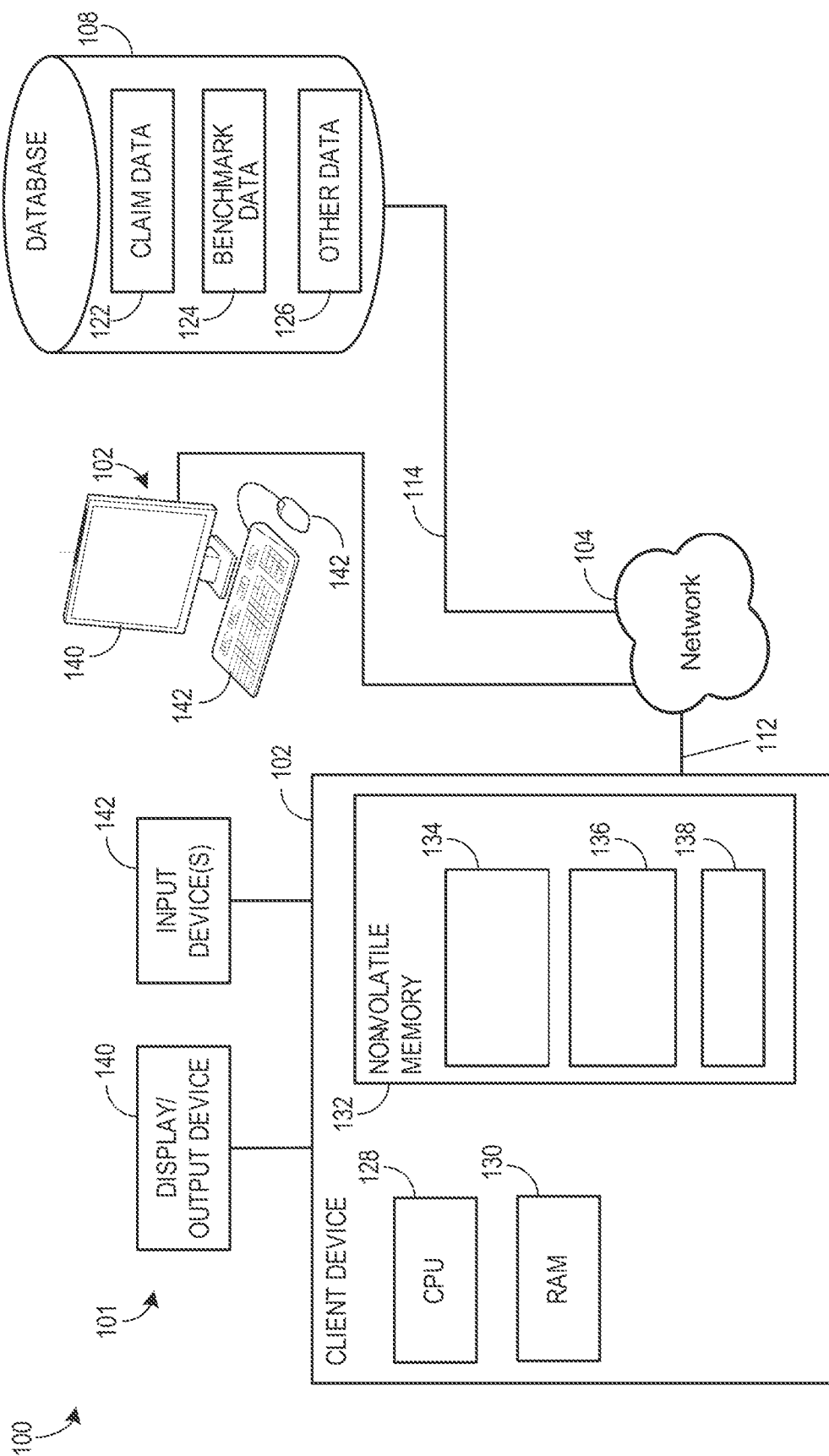


FIG. 14

200 →

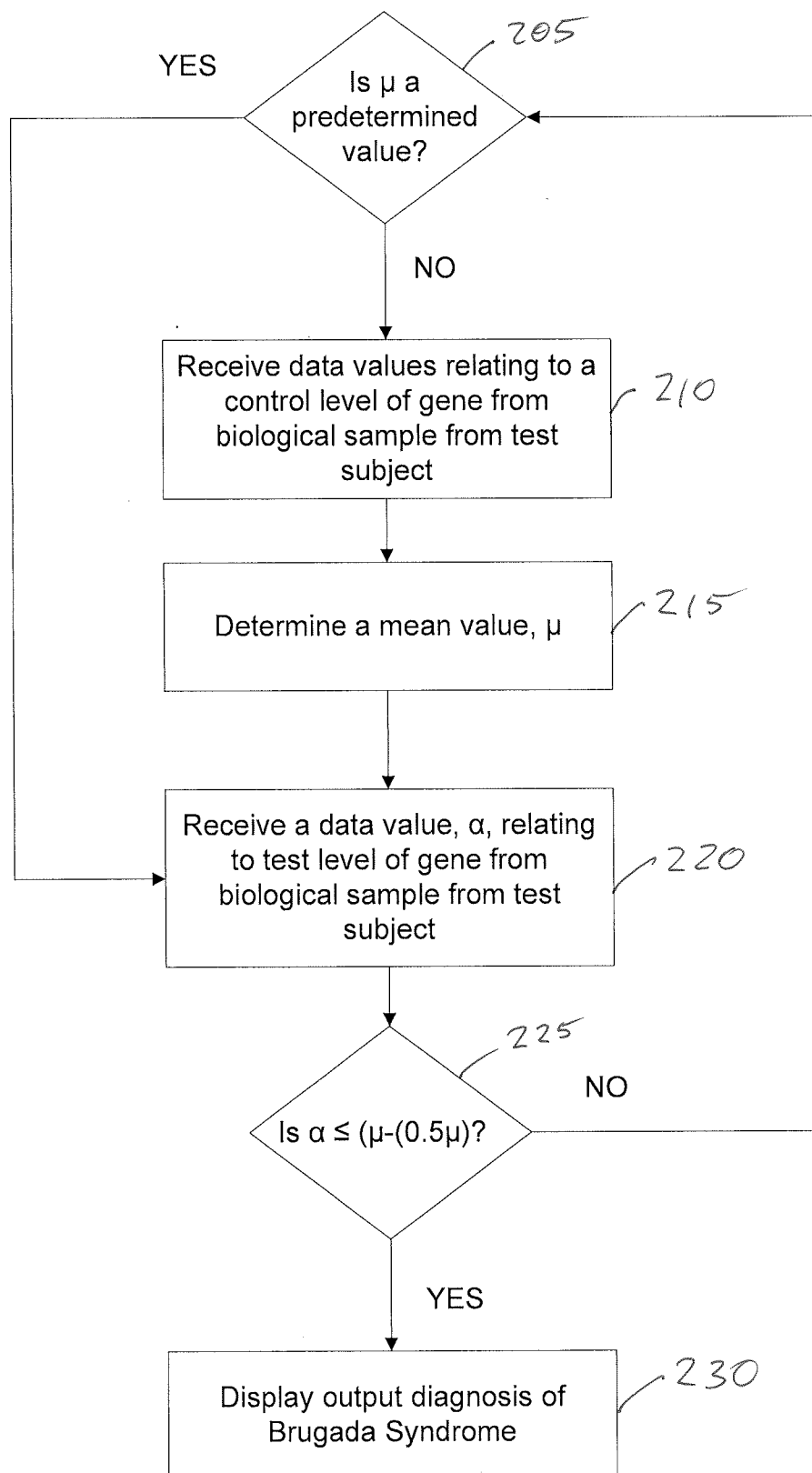


FIG. 15