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# Genetic variation in the parasympathetic signaling pathway in patients with reflex syncope

**H.N. Holmegard[1], M. Benn[2], J. Mehlsen[3] and S. Haunsø[1,4]**

[1]Laboratory of Molecular Cardiology, Rigshospitalet,
Copenhagen University Hospital, Faculty of Health Sciences,
University of Copenhagen, Copenhagen, Denmark
[2]Department of Clinical Biochemistry, Herlev Hospital,
Copenhagen University Hospital, Faculty of Health Sciences,
University of Copenhagen, Copenhagen, Denmark
[3]Coordinating Research Center, Frederiksberg Hospital,
Copenhagen University Hospital, Faculty of Health Sciences,
University of Copenhagen, Copenhagen, Denmark
[4]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital,
Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Corresponding author: M. Benn
E-mail: mben0092@geh.regionh.dk

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**ABSTRACT.** Reflex syncope is defined by a self-terminating transient loss of consciousness associated with an exaggerated response of the vagal reflexes upon orthostatic challenges. A hereditary component has previously been suggested. We hypothesized that variations in genes encoding proteins mediating the vagal signaling in the heart may be involved in reflex syncope pathogenesis. We systematically resequenced the entire coding regions and flanking intron sequences in 5 genes in the cardiac post-synaptic parasympathetic signaling pathway [muscarinic acetylcholine receptor M2 (*CHRM2*); G-protein beta-1 subunit (*GNB1*); G-protein gamma-2 subunit (*GNG2*); potassium inwardly rectifying channel, subfamily J, member 3 (*KCNJ3*); and potassium inwardly

 

rectifying channel, subfamily J, member 5 (*KCNJ5*)] in 74 patients with well-characterized reflex syncope of either cardioinhibitory [Vasovagal Syncope International Study (VASIS-IIB), N = 38] or vasodepressor (VASIS-III, N = 36) type. We identified 2 novel genetic variants (*CHRM2* c.1114C>G and *GNG2* c.87+34G>A) and several known variants (*GNB1*: c.267+14G>A, c.267+19C>T, and c.738C>T; *KCNJ3:* c.119A>G, c.591C>T, c.1038T>C, and c.1494T>C; *KCNJ5*: c. 171T>C, c.810T>G, c.834T>C, c.844C>G, c.938+7C>T, and c.938-10G>A). The minor allele frequency of the *KCNJ5* c.938+7C>T variant was significantly lower in patients than in the control group (0.014 versus 0.089, P = 0.001), and the frequency of heterozygosity and homozygosity was lower in cardioinhibitory patients compared to controls. Genetic variations in genes responsible for the vagal signaling in the heart, including *CHRM2*, *GNB1*, *GNG2*, *KCNJ3*, and *KCNJ5*, are not major contributors to the pathogenesis of reflex syncope of vasodepressor or cardioinhibitory types.

**Key words:** Reflex syncope; Parasympathetic; Vagal signaling; Genetics; Translational medicine

## INTRODUCTION

Recurrence of syncope of unknown etiology is a common health problem affecting 27-30% of the general population (Savage et al., 1985). It is associated with reduced quality of life to a degree similar to that reported in chronic illnesses, and patients frequently suffer from anxiety, somatization, and depression (Rose, et al., 2000; van Dijk et al., 2007). Presumably, most incidents of unexplainable syncope are reflex syncope, also known as vasovagal syncope. Several studies have reported familial occurrence of reflex syncope, suggesting a genetic component in the pathogenesis of this disease (Camfield and Camfield, 1990; Mathias et al., 1998; Bizios and Sheldon, 2009).

As reflex syncope is associated with altered cardiac and vascular functionality, genetic variation in proteins involved in the control of the cardiac rhythm and contractility could play a role in its pathogenesis. Few studies have investigated genetic variations as potential pathogenic contributors (Newton et al., 2005; Marquez et al., 2007; Lelonek et al., 2007, 2008, 2009; Sorrentino et al., 2010); however, these studies have screened known single nucleotide polymorphisms (SNPs) and have not resequenced complete candidate genes, thus limiting the studies to common known variation and excluding so far unknown and rare variants.

Reflex syncope is a complex and heterogeneous disease and a precise diagnostic classification is vital to decrease heterogeneity and increase the ability to identify potential causal genetic variants. In the present study, we therefore only included patients with well-defined cardioinhibitory or vasodepressor types of reflex syncope.

The dysregulation of the cardiovascular function in patients with reflex syncope is thought to be due to an exaggerated vagal signaling response, normally mediated via the muscarinic acetylcholine $M_2$ receptor, encoded by muscarinic acetylcholine receptor M2 (*CHRM2*). Upon vagal stimulation, the $M_2$ receptor releases a G-protein complex consisting of the guanine nucleotide-binding protein subunits beta-1, $G\beta_1$, and gamma-2, $G\gamma_2$, encoded by *GNB1* and *GNG2*, respectively, which then directly activates the inwardly rectifying potassium

channels, G-protein activated inward rectifier potassium channel (GIRK)1/GIRK4 complexes, encoded by potassium inwardly rectifying channel, subfamily J, member 3 (*KCNJ3*), and potassium inwardly rectifying channel, subfamily J, member 5 (*KCNJ5*) genes, respectively, resulting in a reduction in heart rate (Figure 1).

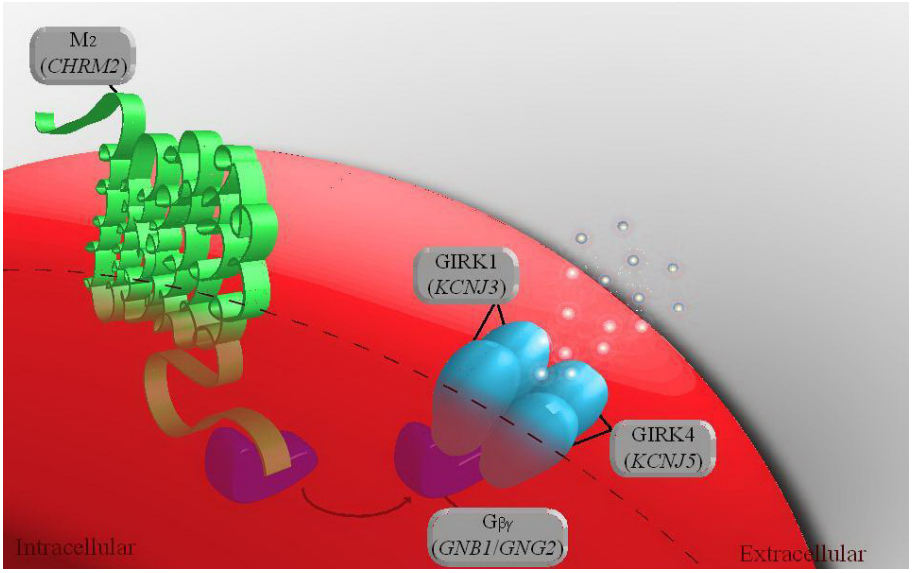


**Figure 1.** Cardiomyocyte signalling. Vagal stimulation of the $M_2$ receptor results in direct activation of inwardly rectifying potassium channels (GIRK1/4 complex) via the $G_{\beta\gamma}$ complex, inducing an efflux of potassium ions and a hyperpolarization of the membrane, in turn resulting in a prolongation of the action potential refractory period and slower heart rate. Gene names are given in parentheses.

We hypothesized that elements of this cardiac vagal signaling cascade may be compromised in patients with reflex syncope. In the present study, we therefore resequenced the coding regions and flanking intron sequences of genes encoding major proteins within the cardiac post-synaptic parasympathetic pathway, including *CHRM2*, *GNB1*, *GNG2*, *KCNJ3*, and *KCNJ5*.

## MATERIAL AND METHODS

### Population

All patients referred to the Coordinating Research Center in Frederiksberg Hospital for confirmation of suspected reflex syncope during the period of February 2004 through June 2009 were subjected to a head-up tilt test (see below). Tilt responses were categorized according to the modified Vasovagal Syncope International Study (VASIS) classification (Brignole et al., 2000), and only patients strictly fulfilling the criteria of cardioinhibition (VASIS-IIB; asystole for more than 3 s coinciding or preceding a drop in blood pressure; N = 38) or vasodepression (VASIS-III; sudden drop in blood pressure and a reduction in heart rate of less than 10% from its peak value at the time of syncope; N = 36) were included in the study. All pa-

tients were free of cardiac, endocrine, and neurological disorders, and gave written informed consent to participate. The study was conducted according to the Declaration of Helsinki II and approved by the Regional Ethics Committee (No. HA-2008-020).

## Head-up tilt test protocol

The head-up tilt testing was performed according to the Italian protocol (Bartoletti et al., 2000). In brief, patients were rested in the supine position for 10 min before head-up tilted to a 60° angle with footboard and leg fixation. If syncope and/or pre-syncope did not occur within 20 min of passive tilting, a reaction was provoked with 400 µg sublingual nitroglycerine and the test was continued for a maximum of 15 min. All patients were rapidly returned to the supine position once reproduction of syncope/pre-syncope was evident. Heart rate and blood pressure were measured continuously from 1 precordial electrocardiogram -lead and photoplethysmography, respectively. Data were sampled at 1.0 kHz and analyzed using Chart 5.59 (AD Instruments Inc., Colorado Springs, CO, USA).

## Genetic screening of patients

Genomic DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and primers for coding exons and flanking intron sequences of *CHRM2* [National Center for Biotechnology Information (NCBI) reference sequence NC_000007.13], *GNB1* (NC_000001.10), *GNG2* (NC_000014.8), *KCNJ3* (NC_000002.11), and *KCNJ5* (NC_000011.9) were designed using the Oligo 6 Primer Analysis software (Molecular Biology Insights, Cascade, CO, USA).

Fragments were examined for variations using high-resolution melting curve analysis (Light Scanner, Idaho Technology, UT, USA). Fragments with melting curves differing from wild-type curves were purified and directly sequenced using an ABI PRISM 3700 DNA analyzer (Applied Biosystems, Foster City, CA, USA). Identified variants were verified by resequencing of a 2nd PCR product and by subsequent genotyping (see below). Primers and PCR conditions are available upon request.

## Genotyping

A control group of 208 disease-free Danish blood donors were genotyped using TaqMan genotyping assays (ABI Prism 7900HT Sequence Detection System, Applied Biosystems) for all variants identified in the patient population.

## Bioinformatics

All variants were searched in public databases (www.ncbi.nlm.nih.gov/pubmed, www.ensembl.org, and www.1000genomes.org). Potential functional effects of all novel and previously reported missense variants were evaluated by *in silico* prediction using the Polymorphism Phenotyping (PolyPhen; Ramensky et al., 2002), Protein Analysis Through Evolutionary Relationships (PANTHER; Thomas, 2003), and Sorting Intolerant From Tolerant (SIFT; Ng and Henikoff, 2003) online programs, using standard parameters and cutoff values.

## Statistical analysis

For baseline characteristics, continuous variables were tested using the independent Student *t*-test and categorical variables were assessed by the $\chi^2$ test. Genotypic and allelic frequency distributions were compared by the Fisher exact test with a corrected $P < 0.003$ considered significant due to multiple tests. Deviations from the Hardy-Weinberg equilibrium were calculated using the Fisher exact test ($P < 0.05$). All statistical tests were performed using the Stata11.0 software (StataCorp. 2009, Stata Statistical Software: Release 11, StataCorp LP, College Station, TX, USA).

## RESULTS

We included 74 patients with either a cardioinhibitory (VASIS-IIB; N = 38) or vasodepressor (VASIS-III; N = 36) type of reflex syncope (72% women, mean age of 32 ± 11 years) in the present study. Patient characteristics are summarized in Table 1. Groups did not differ with respect to time to syncope during head-up tilt or resting heart rate and diastolic blood pressure, although a higher systolic blood pressure was observed in cardioinhibitory compared to vasodepressor patients.

**Table 1.** Patient characteristics.

| | Total (N = 74) | Cardioinhibitory (N = 38) | Vasodepressor (N = 36) | P |
|---|---|---|---|---|
| Age at diagnosis (years, mean ± SD) | 32.0 ± 11.3 | 33.0 ± 11.5 | 30.9 ± 11.1 | 0.49 |
| Women [N (%)] | 53 (71.6) | 27 (71.1) | 26 (72.2) | 0.91 |
| Body mass index [kg/m², mean (SD)][a] | 24.4 (4.3) | 23.5 (2.8) | 25.3 (5.4) | 0.24 |
| Time to syncope [min, mean (SD)] | - | 16.5 (9.3) | 19.4 (8.8) | 0.10 |
| Resting heart rate [bpm, mean (SD)][b] | - | 67.1 (9.9) | 67.2 (9.1) | 0.44 |
| Resting systolic blood pressure [mmHg, mean (SD)][b] | - | 117.8 (15.7) | 109.1 (15.3) | <0.001 |
| Resting diastolic blood pressure [mmHg, mean (SD)][b] | - | 59.1 (10.0) | 57.4 (11.0) | 0.23 |

[a]One vasodepressor woman became unwell and weight and height were not noted for this patient. [b]Average values over the resting period during head-up tilt test. SD = standard deviation.

### *CHRM2*

Re-sequencing of *CHRM2* revealed 1 novel variant in exon 6, *CHRM2* c.1114C>G, as the only variant found in this gene (Table 2). All cardioinhibitory patients were non-carriers (CC), whereas 1 vasodepressor and 3 controls were heterozygous (CG); however, the minor allele frequency did not differ between the groups (Table 3). The C>G nucleotide substitution resulted in an amino acid substitution from proline to alanine (P382A), which was considered "possibly damaging" by *in silico* prediction (PolyPhen; Table 4).

### *GNB1*

We identified 2 intronic and 1 exonic variants in the *GNB1* gene, located in positions +14 and +19 after exon 2 and in exon 6, respectively. All variants have previously been reported and the distribution frequencies for all 3 variants were similar in patients and controls (Tables 2 and 3).

**Table 2.** Variants and minor allele frequencies identified by re-sequencing.

| Gene | Nucleotide position | Rs-number | Major > minor allele[a] | Minor allele frequency | | P patients *vs* controls |
|---|---|---|---|---|---|---|
| | | | | Patients | Controls | |
| *CHRM2* | c.1114 | NA | C > G | 0.007 | 0.007 | 1.00 |
| *GNB1* | c.267+14 | rs17363334 | G > A | 0.054 | 0.103 | 0.09 |
| | c.267+19 | rs77354509 | C > T | 0.054 | 0.103 | 0.09 |
| | c.738 | rs79516120 | C > T | 0.007 | 0.005 | 1.00 |
| *GNG2* | c.87+34 | NA | G > A | 0.007 | 0.000 | 0.27 |
| *KCNJ3* | c.119 | rs16838016 | A > G | 0.007 | 0.012 | 1.00 |
| | c.591 | rs3111033 | C > T | 0.004 | 0.024 | 0.56 |
| | c.1038 | rs17642086 | T > C | 0.304 | 0.345 | 0.42 |
| | c.1494 | rs80085601 | T > C | 0.014 | 0.010 | 0.66 |
| *KCNJ5* | c.171 | rs6590357 | C > T | 0.194 | 0.191 | 0.90 |
| | c.810 | rs7118824 | G > T | 0.189 | 0.186 | 1.00 |
| | c.834 | rs7118833 | C > T | 0.196 | 0.159 | 0.31 |
| | c.844 | rs7102584 | G > C | 0.027 | 0.024 | 0.77 |
| | c.937+7 | rs45516097 | C > T | 0.014 | 0.089 | 0.001 |
| | c.938-10 | rs4937391 | A > G | 0.336 | 0.256 | 0.07 |

[a]The major allele corresponds to the ancestral nucleotide present in the reference sequence (see Material and Methods section). NA = not applicable.

**Table 3.** Genotype frequency among cardioinhibitory and vasodepressor patients and controls.

| Gene | Nucleotide position | Genotype | Cardioinhibitory (%) | Vasodepressor (%) | Controls (%) | Total | P | Hardy-Weinberg P |
|---|---|---|---|---|---|---|---|---|
| *CHRM2* | c.1114 | CC | 38 (100) | 35 (97) | 204 (99) | 277 | 0.49 | 0.90 |
| | | GC | 0 (0) | 1 (3) | 3 (1) | 4 | | |
| *GNB1* | c.267+14 | GG | 36 (95) | 30 (83) | 167 (80) | 233 | 0.23 | 0.83 |
| | | GA | 2 (5) | 6 (17) | 39 (19) | 47 | | |
| | | AA | 0 (0) | 0 (0) | 2 (1) | 2 | | |
| | c.267+19 | CC | 36 (95) | 30 (83) | 167 (80) | 233 | 0.23 | 0.83 |
| | | CT | 2 (5) | 6 (17) | 39 (19) | 47 | | |
| | | TT | 0 (0) | 0 (0) | 2 (1) | 2 | | |
| | c.738 | CC | 37 (97) | 36 (100) | 205 (99) | 278 | 0.60 | 0.93 |
| | | CT | 1 (3) | 0 (0) | 2 (1) | 3 | | |
| *GNG2* | c.87+34 | GG | 38 (100) | 35 (98) | 202 (100) | 275 | 0.13 | 0.98 |
| | | GA | 0 (0) | 1 (3) | 0 (0) | 1 | | |
| *KCNJ3* | c.119 | AA | 37 (97) | 36 (100) | 203 (98) | 276 | 1.00 | 0.86 |
| | | GA | 1 (3) | 0 (0) | 5 (2) | 6 | | |
| | c.591 | CC | 37 (97) | 32 (89) | 196 (95) | 265 | 0.23 | 0.65 |
| | | CT | 1 (3) | 4 (11) | 10 (5) | 15 | | |
| | c.1038 | TT | 19 (50) | 15 (42) | 79 (40) | 113 | 0.46 | 0.02[a] |
| | | CT | 15 (40) | 20 (56) | 104 (52) | 139 | | |
| | | CC | 4 (11) | 1 (3) | 17 (9) | 22 | | |
| | c.1494 | TT | 37 (97) | 35 (97) | 203 (98) | 275 | 0.66 | 0.86 |
| | | CT | 1 (3) | 1 (3) | 4 (2) | 6 | | |
| *KCNJ5* | c.171 | CC | 22 (61) | 23 (64) | 134 (66) | 179 | 0.67 | 0.98 |
| | | CT | 14 (39) | 12 (33) | 59 (29) | 85 | | |
| | | TT | 0 (0) | 1 (3) | 9 (5) | 10 | | |
| | c.810 | GG | 24 (63) | 24 (67) | 140 (68) | 188 | 0.92 | 0.39 |
| | | GT | 13 (34) | 11 (31) | 57 (28) | 81 | | |
| | | TT | 1 (3) | 1 (3) | 10 (5) | 12 | | |
| | c.834 | CC | 23 (61) | 24 (67) | 150 (73) | 197 | 0.44 | 0.21 |
| | | CT | 14 (37) | 11 (31) | 48 (23) | 73 | | |
| | | TT | 1 (3) | 1 (3) | 9 (4) | 11 | | |
| | c.844 | GG | 36 (95) | 34 (94) | 197 (95) | 267 | 0.91 | 0.67 |
| | | GC | 2 (5) | 2 (6) | 10 (5) | 14 | | |
| | c.937+7 | CC | 38 (100) | 34 (94) | 171 (82) | 243 | 0.001[b] | 0.21 |
| | | CT | 0 (0) | 2 (6) | 37 (18) | 39 | | |
| | c.938-10 | AA | 13 (38) | 11 (31) | 117 (57) | 141 | 0.01 | 0.46 |
| | | GA | 20 (59) | 23 (64) | 74 (36) | 117 | | |
| | | GG | 1 (3) | 2 (6) | 16 (8) | 19 | | |

[a]Controls not in Hardy-Weinberg equilibrium. [b]Cardioinhibitory versus control group is significant with P = 0.002.

**Table 4.** Functional prediction of identified variants.

| Gene | Nucleotide position | Amino acid substitution | Domain | Function | PANTHER | PolyPhen | SIFT |
|---|---|---|---|---|---|---|---|
| *CHRM2* | c.1114 | P372A | Exon 6 | Missense | Benign | Possibly damaging | Tolerated |
| *GNB1* | c.267+14 | NA | Intron | NA | NA | NA | NA |
| | c.267+19 | NA | Intron | NA | NA | NA | NA |
| | c.738 | D246D | Exon 6 | Synonymous | NA | NA | NA |
| *GNG2* | c.87+34 | NA | Intron | NA | NA | NA | NA |
| *KCNJ3* | c.119 | K40R | Exon 1 | Missense | Benign | Benign | Tolerated |
| | c.591 | S197S | Exon 1 | Synonymous | NA | NA | NA |
| | c.1038 | H346H | Exon 3 | Synonymous | NA | NA | NA |
| | c.1494 | D498D | Exon 3 | Synonymous | NA | NA | NA |
| *KCNJ5* | c.171 | S57S | Exon 2 | Synonymous | NA | NA | NA |
| | c.810 | L270L | Exon 2 | Synonymous | NA | NA | NA |
| | c.834 | H278H | Exon 2 | Synonymous | NA | NA | NA |
| | c.844 | Q282E | Exon 2 | Missense | Benign[a] | Benign | Tolerated |
| | c.937+7 | NA | Intron | NA | NA | NA | NA |
| | c.938-10 | NA | Intron | NA | NA | NA | NA |

[a]The substituted position does not align to the hidden Markov model used by PANTHER as it does not appear in most related sequences. It is therefore most likely to be benign. NA = not applicable.

## *GNG2*

In one vasodepressor patient, a novel variant in the *GNG2* gene, *GNG2* c.87+34G>A, was identified. This variant was not observed in cardioinhibitory patients or controls; however, both allele and genotype frequencies did not differ between the groups (Table 3).

## *KCNJ3*

In the *KCNJ3* gene, we identified two known variants in exon 1 and two in exon 3; all of these variants exhibited similar minor allele and genotype distribution among patients and controls (Tables 2 and 3). Of these, the *KCNJ3* c.119A>G variant in exon 1 caused an amino acid substitution from lysine to arginine (K40R), whereas the others were synonymous variants (Tables 2 and 4). This variant was absent in the vasodepressor patients and was predicted to be "benign" by all 3 *in silico* programs (Table 4). The *KCNJ3* c.1038T>C variant did not fulfill the Hardy-Weinberg expectations in the control group (P = 0.033), and the variant was excluded from further analysis.

## *KCNJ5*

We identified 6 known variants in the *KCNJ5* gene (Table 2). Four of these were located in exon 2, one immediately after exon 2 (*KCNJ5* c.937+7C>T), and one before exon 3 (of *KCNJ5* c.938-10A>G; Table 3). Only *KCNJ5* c.844G>C resulted in an amino acid substitution (glutamine to glutamate, Q282E), whereas the other coding variants were synonymous. The Q282E variant was predicted to be "benign" by all of the *in silico* prediction programs (Table 4). The *KCNJ5* c.937+7C>T variant was more common in controls compared to patients with cardioinhibitory and vasodepressor syncope (Tables 2 and 3). The distribution did not differ between cardioinhibitory and vasodepressor patients (data not shown), although the variant was not observed in cardioinhibitory patients and the frequencies were significantly different compared to controls (P = 0.002; Table 3).

## DISCUSSION

In the present study, we identified 2 novel genetic variants, *CHRM2* c.1114C>G and *GNG2* c.87+34G>A, and 13 known variants in patients with reflex syncope. The frequency of a known *KCNJ5* variant, c.938+7C>T, was lower in cardioinhibitory patients relative to that of controls.

Most genetic studies in patients with reflex syncope have focused on the sympathetic pathway. Despite this, only 2 studies have identified potentially causal genetic variants. Lelonek et al. (2008) found that a T>C mutation in the *GNAS1* gene (encoding a guanine nucleotide-binding protein alpha subunit) was more common among patients with a positive head-up tilt test. An association was also found between an arginine to glycine amino acid substitution (R389G) in the beta-1 adrenergic receptor gene and positive head-up tilt test in a Mexican population (Marquez et al., 2007). In contrast, a recent study failed to find association of several SNPs in genes in the sympathetic pathway and in patients with reflex syncope (Sorrentino et al., 2010).

It has been suggested that the autonomic dysregulation leading to bradycardia and hypotension is due to a hyperreactive vagal reflex (Rea and Thames, 1993; van Lieshout et al., 1997). In the present study, we identified a novel genetic variant in the muscarinic acetylcholine receptor, $M_2$, (encoded by *CHRM2*) at position c.1114, located in the cytoplasmic domain, between the 5th and 6th transmembrane domains. This variant causes an amino acid substitution from proline to alanine (P372A); these are both structurally different non-polar amino acids, as proline is rigid and bulges due to a cyclic sidechain and alanine has a non-reactive methyl group sidechain. This may be the explanation as to why this missense mutation is predicted to be "possibly damaging" by PolyPhen, whereas PANTHER and SIFT predict it to be "benign". However, the frequency of the variant is similar in patients and controls in the present study, suggesting that it is not likely a causative variant.

The coupling of the $M_2$ receptor to the intracellular signaling pathways is conducted via G-proteins. Upon activation of the $M_2$ receptor, the $\alpha$-$\beta\gamma$ G-protein complex dissociates into a G$\alpha$ and a G$\beta\gamma$ complex. G$\beta\gamma$ subunits containing either $\beta_1$ or $\beta_2$ with multiple G$\gamma$ subunits have been shown to activate the inward rectifying potassium channels (GIRK channels, encoded by the *KCNJ* genes; Wickman et al., 1994; Wickman and Clapham, 1995; Dascal, 1997; Hurowitz et al., 2000), and it has been shown that potassium currents are directly stimulated by the mammalian G$\beta_1\gamma_2$ complex (Logothetis et al., 1987; Reuveny et al., 1994). A novel variant, the intronic *GNG2* c.87+34G>A, was found in a single vasodepressor patient in the present study, but not in cardioinhibitory patients or controls. Most SNPs are considered functionally neutral, but may affect gene expression, trafficking, or protein function, thereby conferring individual differences. Although a transcription factor binding site for the aryl hydrocarbon/dioxin receptor is located at the c.87+34 position of *GNG2*, the guanine at this position is not conserved among species and this receptor is mostly known for its role in xenobiotic metabolism (Hoffman et al., 1991); therefore it is not likely to have functional importance with regard to cardiac functionality.

Inward rectifying potassium channels are abundant in the atrial and sinoatrial node cells (Mark and Herlitze, 2000). Each channel is formed by 2 GIRK1 and 2 GIRK4 subunits (encoded by *KCNJ3* and *KCNJ5*, respectively; Corey et al., 1998). Knockout mouse models of *KCNJ3* and *KCNJ5* show a reduced regulation of heart rate and resistance to vagal stimuli (Kovoor et al., 2001; Bettahi et al., 2002). In the present study, we identified several known variants in these genes, i.e., the K40R in *KCNJ3* and Q282E in *KCNJ5*. Although these are missense variants, both were predicted to be "benign" by *in silico* prediction. One variant,

*KCNJ5* c.937+7C>T, located in a hepatocyte nuclear factor 4 transcription factor binding site, was more common among controls compared to patients (0.014 *vs* 0.089, respectively, P = 0.001) and was absent in cardioinhibitory patients.

In conclusion, the present study suggests that genetic variation in the proteins in the vagal G-protein coupled pathway of cardiac signaling is not a major contributor to the pathogenesis of cardioinhibitory and vasodepressor reflex syncope.

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