SCN5A mutations and polymorphisms in patients with ventricular fibrillation during acute myocardial infarction

TIM BOEHRINGER[1,2], PETER BUGERT[1,2], MARTIN BORGGREFE[2,3] and ELIF ELMAS[2,3]

[1]Institute of Transfusion Medicine and Immunology, German Red Cross Blood Service Baden-Württemberg, Hessen 68167; [2]Medical Faculty Mannheim, Heidelberg University; [3]First Department of Medicine, University Medical Centre Mannheim, Heidelberg University, Mannheim 68167, Germany

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Abstract. Mutations in the *SCN5A* gene encoding the $Na_v1.5$ channel α-subunit are known to be risk factors of arrhythmia, including Brugada Syndrome and Long QT syndrome subtype 3. The present study focused on the role of *SCN5A* variants in the development of ventricular fibrillation (VF) during acute myocardial infarction (AMI). Since VF during AMI is the major cause of sudden death in the Western world, *SCN5A* mutations represent genetic risk factors for sudden death. By exon re-sequencing, the entire coding region and flanking intron regions were sequenced in 46 AMI/VF$^+$ patients. In total, nine single nucleotide variants were identified of which four represented common single nucleotide polymorphisms (SNPs; 87G>A, 1673A>G, IVS16-6C>T and 5457T>A). Only five rare variants were identified, each in only one patient. Only two of the rare variants represented missense mutations (3578G>A and 4786T>A). The common SNPs and the missense mutations were also genotyped using polymerase chain reaction methods in 79 AMI/VF$^-$ patients and 480 healthy controls. The SNPs did not demonstrate significant differences in allele and genotype frequencies between the study groups. The 3578G>A mutation was identified in one out of the 480 controls, whereas the 4786T>A mutation was not present in AMI/VF$^-$ patients and controls. In conclusion, the majority of AMI/VF$^+$ patients demonstrated a wild type sequence or common SNPs in *SCN5A*. Only two out of 46 (4.3%) AMI/VF$^+$ patients revealed mutations that may be involved in Nav1.5 dysfunction and VF. However, this requires further functional validation.

Correspondence to: Professor Elif Elmas, First Department of Medicine, University Medical Centre Mannheim, Heidelberg University, 1-3 Theodor-Kutzer-Ufer, Mannheim 68167, Germany
E-mail: elif.elmas@umm.de

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Introduction

In the Western world ventricular fibrillation (VF) during acute myocardial infarction (AMI) is the major cause of sudden cardiac death (SCD) (1). VF occurs in 10% of cases within the first hours following the symptoms of an AMI (2,3). In addition to established risk factors for VF, a significant genetic component may be detected using extensive observational population studies (4-7). In primary electrical heart diseases, including Long QT syndrome (LQTS), Short QT syndrome and Brugada syndrome, genes encoding ion channels are mutated.

The *SCN5A* gene encodes the major cardiac voltage-gated sodium channel α-subunit $Na_v1.5$ and is located on chromosome 3p21-24 (8). Exons 2-28 contain the protein-coding sequence and several splice variants have been described (9). The major role of the sodium channel is the rapid depolarization at the beginning of an action potential and the transmission of electrical impulses in the heart myocardia (8,10). Mutations in *SCN5A* may affect different mechanisms, including channel activation, inactivation and reactivation or may lead to complete loss of function (11). Mutations were identified in different types of arrhythmias (12-15), i.e. in 10-20% of patients with Brugada syndrome and in 6% of patients with Long QT syndrome subtype 3 (LQTS3). Common polymorphisms in *SCN5A* modulate the biophysical defects of *SCN5A* mutations (16-19) or may be associated with an increased risk of SCD (20). The potential association of *SCN5A* variants with VF during AMI remains unclear. Among a small cohort of 19 patients suffering from VF during AMI, only one demonstrated a missense mutation in *SCN5A* (21). In our previous study on 240 AMI patients, including 73 patients with primary VF an association of the *SCN5A*-H558R polymorphism with the risk of VF or AMI was not identified (22).

The present study aimed to investigate the role of *SCN5A* mutations and polymorphisms in the development of VF during AMI. Screening for DNA sequence variation in the coding region of *SCN5A* was performed by exon re-sequencing in patients suffering from VF during AMI (AMI/VF$^+$). For common single nucleotide polymorphisms (SNPs) and rare mutations identified in the AMI/VF$^+$ patients polymerase chain reaction with sequence-specific primers (PCR-SSP) was developed. In order to estimate the role of these gene variants

Table I. Baseline characteristics of patients and controls.

Characteristic	AMI/VF$^+$ patients (n=49)	AMI/VF$^-$ patients (n=74)	Controls (n=480)	Significance (P-value)[a]
No. of males (%)	44 (91.8)	53 (71.6)	288 (60.0)	0.045[a] <0.001[b]
Age (mean ± SD)	60.7±10.0	61.0±12.0	57.3±6.7	0.903[a] 0.001[b]
CAD, n (%)				
1-vessel disease	28 (57.1)	27 (36.5)	-	0.028[a]
2-vessel disease	18 (36.7)	22 (29.7)	-	0.438[a]
3-vessel disease	3 (6.1)	25 (33.8)	-	<0.001[a]
No. of patients with hypertension (%)	27 (55.1)	40 (54.1)	-	0.909[a]
No. of patients with hyperlipoproteinemia (%)	26 (53.1)	47 (63.5)	-	0.266[a]
No. of smokers (%)	26 (53.1)	38 (51.4)	-	0.853[a]
No. of patients with diabetes mellitus (%)	11 (22.4)	17 (23.0)	-	0.946[a]
No. of patients with a family history of myocardial infarction (%)	12 (24.5)	17 (23.0)	-	0.830[a]

[a]AMI/VF$^+$ vs. AMI/VF$^-$; [b]AMI vs. controls. AMI, acute myocardial infarction; VF, ventricular fibrillation; CAD, coronary artery disease; SD, standard deviation.

as risk factors for VF or AMI, the present study additionally genotyped AMI/VF$^-$ patients and healthy controls.

Materials and methods

Patients and controls. Patients were recruited from the First Department of Medicine (Cardiology), University Medical Centre (Mannheim, Germany). The controls were recruited at the Institute of Transfusion Medicine and Immunology, German Red Cross Blood Service (Mannheim, Germany). In total 49 Patients who suffered from VF during AMI (AMI/VF$^+$) and 74 AMI patients without VF (AMI/VF$^-$) were included. Additionally, a control group of 480 healthy blood donors was analyzed. The baseline characteristics of the study individuals are summarized in Table I. All patients and controls provided written consent to use biological material for molecular genetic research purposes. The study was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University (Mannheim, Germany). DNA was extracted from EDTA blood samples of all study individuals using commercial kits (QIAamp® DNA Blood Mini kit; Qiagen, Hilden, Germany).

Mutation screening and genotyping. *SCN5A* exons 2-28 were amplified from genomic DNA using flanking intron primers (Table II). Sequencing was performed on the two strands with the use of the amplification primers.

For the single nucleotide variations (mutations and SNPs) identified by mutation screening PCR-SSP methods were established according to standard protocols (23) and the primers are provided in Table III. In addition, PCR-SSP methods were developed for *SCN5A* variants 1062T>C, 354G>C, 287C>T and 1199G>C, which were associated with arrhythmia in previous studies (21,24). All patients and controls were genotyped for the *SCN5A* variants using PCR-SSP.

Statistical analysis. Fisher exact and χ^2 tests were performed to investigate differences between the study cohorts in the baseline characteristics as well as allele and genotype frequencies of the *SCN5A* polymorphisms. SPSS statistical software version 12.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis.

Results and Discussion

Screening for *SCN5A* sequence variations in the entire coding region and flanking intron regions was achieved by exon re-sequencing in 46 AMI/VF$^+$ patients. In total, nine single nucleotide variations were identified and were all listed in the Single Nucleotide Polymorphism Database and LQTS gene Leiden Open Variation Database (25) (Table IV). Four variants (87G>A, 1673A>G, IVS16-6C>T and 5457T>A) represented common SNPs of which only 1673A>G (His558Arg) was a missense variant. However, all SNPs have previously been described as normal variants without an association with arrhythmia (26-31).

The 630G>A variant is rare and was found in exon 6b of one AMI/VF$^+$ patient. The amino acids encoded by exon 6b are present in the major 'adult' SCN5A isoform, whereas exon 6a is alternatively spliced in the 'neonatal' isoform (9). However, the nucleotide change 630G>A does not alter the encoded amino acid and no effect on protein function was assumed. The variants 3183G>A and 4509C>T also represent rare and silent variants, each found in only one AMI/VF$^+$ patient. The rare and silent variants were not further investigated in the present study.

Table II. Primers for amplification and re-sequencing of *SCN5A* exons 2-28.

Target	Binding region	Direction	Sequence (5'-3')	Final $MgCl_2$ conc. (mM)	Size (bp)
Exon 2	Intron 1	Sense	ctgtccctgggcatagaatc	3.5	188
(part I)	Exon 2	Antisense	ttctctgccatgcgcttctc		
Exon 2	Exon 2	Sense	cagcttccgcaggttcacac	2.0	288
(part II)	Intron 2	Antisense	ggagttgcacagaagggtag		
Exon 3	Intron 2	Sense	tctacacaagggcctaatgctac	2.0	274
	Intron 3	Antisense	agggaatcagcgctactctc		
Exon 4	Intron 3	Sense	cccatgctgctcagctttcc	2.0	152
	Intron 4	Antisense	gtggagaagaggccctgaag		
Exon 5	Intron 4	Sense	acgtaaggaacctggagaacc	3.5	306
	Intron 5	Antisense	agggaggaagccagaaagag		
Exon 6	Intron 5	Sense	caggcggtggttctgctttg	2.0	424
	Intron 6	Antisense	aaggcccaggcatatccctc		
Exon 7	Intron 6	Sense	cgtgcttgttcttgccttcc	3.5	299
	Intron 7	Antisense	gctggtctcacaaagtcttc		
Exon 8	Intron 7	Sense	cctggatgcaaggcggaaac	2.0	274
	Intron 8	Antisense	gaagggtcctggcaggtaag		
Exon 9	Intron 8	Sense	tggcactaggtttgtgaagc	2.0	325
	Intron 9	Antisense	ctgagcccacacttgctgtc		
Exon 10	Intron 9	Sense	cctggcacaactagactagg	3.5	332
	Intron 10	Antisense	agtcaggtgagggcttagag		
Exon 11	Intron 10	Sense	ggctgcacaaagtctcaatg	2.0	348
	Intron 11	Antisense	aaacaggaagcgcagagatg		
Exon 12	Intron 11	Sense	ccctctcctcatgcccttag	2.0	425
	Intron 12	Antisense	tgctgtggtgcctgcatctc		
Exon 13	Intron 12	Sense	cccaggctgacgcaaatctc	2.0	242
	Intron 13	Antisense	tgggtcaggctgggataaag		
Exon 14	Intron 13	Sense	gtcatctcccagagcaagtc	2.0	379
	Intron 14	Antisense	caggatgcccatttgagagc		
Exon 15	Intron 14	Sense	ggccagggagtctttccatc	2.0	283
	Intron 15	Antisense	ttgggttgtgccgagccttc		
Exon 16	Intron 15	Sense	ccagagcccttcacaaggtc	2.0	442
	Intron 16	Antisense	gctgggtagatgagtggatg		
Exon 18	Intron 17	Sense	gcatgggcagggtctgaaac	3.5	284
	Intron 18	Antisense	gctggcttcagggacaaagg		
Exon 21	Intron 20	Sense	ggcttcatgtccaccttgtc	2.0	256
	Intron 21	Antisense	cggcaatgggtttctccttc		
Exon 22	Intron 21	Sense	cccatttctactttgcctccc	3.5	172
	Intron 22	Antisense	tgggaaggcagccacctc		
Exon 23	Intron 22	Sense	aaagggcatgtgctctgg	2.0	378
	Intron 23	Antisense	ccattgggaggaaggaagtc		
Exon 24	Intron 23	Sense	gaagctcaagcgaggtacag	2.0	229
	Intron 24	Antisense	acgagatcttgcccttgtgg		
Exon 26	Intron 25	Sense	ggttggtgccttctctttgc	3.5	244
	Intron 26	Antisense	ctcaggctgggctgaaagac		
Exon 27	Intron 26	Sense	gggatgagaggcagcaacag	2.0	373
	Intron 27	Antisense	gtccagctgacttgtatacc		
Exon 28	Intron 27	Sense	gacagaggtgccaccagtag	3.5	450
(Part I)	Exon 28	Antisense	cccgagagccattgctgttg		
Exon 28	Exon 28	Sense	acccatccaagatctcctac	3.5	494
(Part II)	Exon 28	Antisense	tggtggtgatgggctcgtag		

Table III. Primers for PCR-SSP typing of *SCN5A* variants.

SCN5A variation	Gene region	Direction	Specificity	Sequence (5'-3')	Size (bp)
-1062T>C	Promoter	Sense	1062T	ccccataggtcctgggcat	127
		Sense	1062C	ccccataggtcctgggcac	127
		Antisense		cagagcctggagtcacatac	
-354G>C	Promoter	Sense	-354G	ccgcggacagacagacatag	138
		Sense	-354C	gtatactctggcgggtgctgg	138
		Antisense		gtatactctggcgggtgctgc	
287C>T	Intron 1	Sense	287C	gtccctgcgtgctcctcc	145
		Sense	287T	gtccctgcgtgctcctct	145
		Antisense	Generic	ggcgcacggtgtttagagac	
87G>A	Exon 2	Sense	87G	catcgagaagcgcatggcg	168
		Sense	87A	catcgagaagcgcatggca	168
		Antisense	Generic	ggctctccgatgagctcttg	
1199G>C	Exon 10	Sense	Generic	cctggcacaactagactagg	
(G400A)		Antisense	1199G	gttcaccaggtagaaggacc	166
		Antisense	1199C	gttcaccaggtagaaggacg	166
1673A>G	Exon 12	Sense	1673A	ggagagcgagagccacca	139
(H558R)		Sense	1673G	ggagagcgagagccaccg	139
		Antisense	Generic	ttgcagtccacagtgctgttc	
IVS16C>T	Intron 16	Sense	IVS16-6C	gtgagcctgacccattatctc	
		Sense	IVS16-6T	gtgagcctgacccattatct	299
		Antisense	Generic	tggtggtgatgggctcgtag	299
3578G>A	Exon 20	Sense	3578G	agggaaggtctggtggcg	304
(R1193Q)		Sense	3578A	agggaaggtctggtggca	304
		Antisense	Generic	tcctgctctggcctccatac	
4786T>A	Exon 27	Sense	4786T	caacagctggaatatcttcgact	148
(F1596I)		Sense	4786A	caacagctggaatatcttcgaca	148
		Antisense	Generic	gaagctagggttgtacatgg	
5457T>A	Exon 28	Sense	5457T	tcctgtctgactttgccgat	180
		Sense	5457A	tcctgtctgactttgccgac	180
		Antisense	Generic	tcttcagggcgtccatctcc	

PCR-SSP, polymerase chain reaction with sequence-specific primers.

In one AMI/VF$^+$ patient (79 year old, male) the missense mutation 3578G>A (R1193Q) was identified. The mutation was described as a normal variant with a frequency of 0.3% in Caucasians (32). However, the mutation conducts a longer QT-time and an association with LQTS has been discussed (33,34). Associations have also been described with Brugada syndrome, progressive cardiac conduction defect (PCCD) and sudden infant death syndrome (30,34,35). Recently, the R1193Q variant was described in a young Korean patient (3 year old, male) with LQTS (36).

The missense mutation 4786T>A (F1596I) in exon 27 was found in one AMI/VF$^+$ patient (54 year old, male). In a previous study the mutation was found in two out of 2,500 LQTS patients; however, not in the 1,300 individuals of the control group (37). An association with primary atrial fibrillation has been discussed; however, no evidence for an effect of the mutation on the channel function has been described (38).

In order to evaluate allele and genotype frequencies, the common SNPs (87G>A, 1673A>G, IVS16-6C>T and 5457T>A) were genotyped by PCR-SSP in all patients (49 AMI/VF$^+$ and 74 AMI/VF$^-$) and controls (480 healthy blood donors). The differences in allele and genotype frequencies between the study groups were not identified to be statistically significant (Table V). The rare missense mutations (3578G>A and 4786T>A) were screened by PCR-SSP in AMI/VF$^-$ patients and controls. None of the AMI/VF$^-$ 74 patients were positive for the two mutations, whereas, one

Table IV. Single nucleotide variants identified in the *SCN5A* gene of AMI/VF$^+$ patients.

Gene region	Occurence[a]	Nucleotide change	Amino acid change	dbSNP[b]
Exon 2	Common	87G>A	None	rs6599230
Exon 6b	Rare	630G>A	None	rs193922727
Exon 12	Common	1673A>G	His558Arg	rs1805124
Intron 16	Common	IVS16-6C>T	Unknown	rs41260344
Exon 17	Rare	3183G>A	None	rs7430407
Exon 20	Rare	3578G>A	Arg1193Glu	rs41261344
Exon 26	Rare	4509C>T	None	rs45548237
Exon 27	Rare	4786T>A	Phe1596Ile	rs199473278
Exon 28	Common	5457T>A	None	rs1805126

[a]Each rare variant was found in only one of the 46 analyzed AMI/VF$^+$ patients. AMI, acute myocardial infarction; VF, ventricular fibrillation; single nucleotide polymorphism database (dbSNP); [b]dbSNP reference number.

Table V. Genotype frequency of *SCN5A* variants.

Variant	Genotype[a]	AMI/VF$^+$ n (%)	AMI/VF$^-$ n (%)	Controls n (%)	Significance (P-value)
-1062T>C	TT	49 (100)	74 (100)	480 (100)	-
-354G>C	GG	49 (100)	74 (100)	480 (100)	-
287C>T	CC	49 (100)	74 (100)	480 (100)	-
87G>A	GG	31 (68.9)	50 (69.4)	294 (63.0)	0.188[b]
	GA	12 (26.7)	22 (30.6)	158 (33.8)	0.568[c]
	AA	2 (4.4)	0 (0)	15 (3.2)	0.378[d]
1199G>C	GG	49 (100)	74 (100)	480 (100)	-
1673A>G	AA	34 (69.4)	46 (62.2)	283 (59.3)	0.712[b]
	AG	14 (28.6)	26 (35.1)	168 (35.2)	0.345[c]
	GG	1 (2.0)	2 (2.7)	26 (5.5)	0.277[d]
IVS16-6C>T	CC	45 (93.9)	-	444 (92.7)	-
	CT	3 (6.1)	-	34 (7.1)	0.919[c]
	TT	0 (0)	-	1 (0.2)	-
3578G>A	GG	48 (98.0)	74 (100)	479 (99.8)	-
	GA	1 (2.0)	0 (0)	1 (0.2)	0.046[c]
	AA	0 (0)	0 (0)	0 (0)	-
4786T>A	TT	48 (98.0)	74 (100)	480 (100)	-
	TA	1 (2.0)	0 (0)	0 (0)	-
	AA	0 (0)	0 (0)	0 (0)	-
5457T>A	TT	20 (42.6)	30 (44.8)	208 (44.3)	0.669[b]
	TA	20 (42.6)	32 (47.8)	209 (44.6)	0.801[c]
	AA	7 (14.8)	5 (7.4)	52 (11.1)	0.973[d]

[a]Genotypes: homozygous major allele, heterozygous, homozygous minor allele; [b]P1: AMI/VF$^+$ vs. AMI/VF$^-$; [c]P2: AMI/VF$^+$ vs. controls; [d]P3: AMI vs. controls. AMI, acute myocardial infarction; VF, ventricular fibrillation.

of the 480 controls was positive for the 3578G>A mutation. All study individuals were also screened for the *SCN5A* variants (1062T>C, 354G>C, 287C>T and 1199G>C) that were associated with arrhythmia in previous studies (21,24). However, none of the patients or controls were positive for these variants.

In conclusion, mutations in the *SCN5A* gene are relatively uncommon in AMI/VF$^+$ patients. In the present study only

two out of 49 AMI/VF$^+$ patients (4.1%) demonstrated *SCN5A* variants that may be the cause of VF.

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