Original article

MinK gene polymorphism in the pathogenesis of lone atrial fibrillation

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Abstract

Introduction: Atrial fibrillation (AF) is the most common type of complex arrhythmia found in everyday clinical practice. Lone AF is a particular form occurring in 2% to 31% of patients with confirmed AF. Genetic factors may underline this arrhythmia.

Aim: To determine the relationship between G38S polymorphism in the MinK gene and the incidence of lone AF, and to evaluate this polymorphism as a genetic marker of susceptibility to AF.

Methods: The study involved 69 patients with lone AF and 60 control healthy subjects. Both groups included patients aged up to 65 years without cardiovascular or thyroid disease. MinK genotype was determined with PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism). The MinK gene was present in two allelic forms: G and S.

Results: The MinK G allele was found significantly more often in patients with AF (62.32%) compared to control subjects (41.80%) (p=0.009). In the AF group GS occurred more frequently (55.07%) than GG (34.78%) and SS genotypes (10.14%). In a logistic regression model the presence of G variant was associated with increase of AF risk in the study population (OR 2.39; 95% CI 0.88-6.54; p=0.084). Presence of GG genotype was associated with significant, over 10-fold, increase of AF risk. Presence of S allele of the MinK gene met criteria of protective factor against AF in the study population.

Conclusions: 1. G38S polymorphism in the MinK gene seems to be associated with incidence of lone AF in the study population. 2. GG genotype carrier state may significantly relate to increased risk of AF in the study group. 3. G38S polymorphism in the MinK gene could be used as a genetic marker of risk of lone AF.

Key words: atrial fibrillation, genetics, MinK gene polymorphism

Introduction

Atrial fibrillation (AF) is the most commonly diagnosed type of arrhythmia in clinical practice, responsible for approximately 1/3 of hospitalisations for cardiac arrhythmias. Prevalence of AF is about 0.4% of the entire population and increases with age. Cross-sectional studies indicated that it was <1% in patients below 60 years of age and >6% in subjects over 80 years old [1]. Lone AF is one of the forms of AF. The Framingham Heart Study showed that lone AF occurred in 3% to 15% of all AF patients [2]. The term "lone AF" refers to AF originating at younger age (below 65 years) in the absence of any clinical or echocardiographic signs of heart, thyroid and pulmonary disease [3]. Patients with lone AF may "move" to different categories with aging or progression of abnormalities such as enlargement of left atrium and/or left ventricle.

Lone AF is strictly associated with familiar form of AF [4]. William L. Gould in 1957 described a tendency to familiar occurrence of AF [5]. In a 113-person family of Jewish immigrants from Russia, 22 subjects suffered from AF over 5 years. Brugada et al. worked on identification of the genetic locus of familial type of AF [6]. They found a family in Spain in which AF was inherited as an autosomal dominant trait. The family consisted of 26 living members, including 10 suffering from this type of

arrhythmia. Patients were free of other causes of AF such as arterial hypertension, valvular heart disease and hyperthyroidism. DNA pools of AF subjects and healthy members of the family were compared. Genetic analysis showed that the locus responsible for AF is located on the long arm of chromosome 10 (region 10q22-q24), in proximity to β- and α-adrenergic receptors loci. Close location of genes responsible for AF and genes of α- and β-adrenergic receptors may prove an essential role of the autonomic system in AF pathology.

In 2003 an article was published describing another AF-related locus located on chromosome 6 (6q14-16) [7]. The study involved a 34-member family in which AF was diagnosed in 8 members. The locus responsible for AF was determined using linkage analysis. The above-mentioned region contains candidate genes coding the following: connexin 62, 5-hydroxytryptamine receptor, thyroid protein receptor TR1P7, and α-polypeptide TSH. These genes may play a role in the pathogenesis of AF. Regions in chromosome 6q and 10q22 for AF overlap the locus implicated in the development of hypertrophic cardiomyopathy and thus may explain the relation between AF and this disease.

Potassium channels play an essential role in normal electrical function of the myocardium. Recently, the importance of genes coding subunits of potassium channels in the pathogenesis of AF was highlighted.

The aim of this study was to:
 1) determine the relationship between G38S polymorphism of the MinK gene and the incidence of lone AF in the study population
 2) assess this polymorphism as a genetic marker of susceptibility to AF.

Methods

Patients

The study involved 69 patients (mean age 55±10 years; all <65 years) with lone paroxysmal AF. Patients with a history of at least two paroxysms of AF were included. Arrhythmia usually resolved spontaneously. Patients with permanent AF, cardiovascular and thyroid diseases were excluded. All patients had 12-lead ECG during AF and on recovery of sinus rhythm. ECG allowed patients with atrioventricular and bundle branch blocks to be excluded.

All patients also had arterial blood pressure measured in sitting position and laboratory tests (complete blood count, potassium, sodium, TSH, FT_4 and FT_3 levels) done. Patients were enrolled if their blood pressure was below 140/80 mmHg in two consecutive measurements. Diabetes mellitus was

another exclusion criterion. Additionally, detailed medical history was investigated with respect to family history of AF events and smoking.

Control group

The control group comprised 60 healthy individuals aged below 65 years old (mean 53.1±9) in whom thyroid and cardiovascular diseases were excluded. All patients were Caucasians and were hospitalised at the Chair and Department of Internal Disease of the Medical Academy in Lublin between 2000 and 2004 for various causes.

Echocardiography

Transthoracic echocardiography was performed using Hitachi EUB-450 device. Patients were examined in supine position or when on the left side. Following probe positioning in the III, IV intercostal space at the left side of the sternum, 2D parasternal long axis view was obtained. Subsequently, heart structures were measured in M-mode using accepted rules. M-mode parasternal long axis view was used to record:
 1) left ventricular end-diastolic diameter (LVEDD)
 2) posterior wall diastolic diameter (PWDD)
 3) shortening fraction (FS)
 4) ejection fraction (using Teicholz model) (EF)
 5) left ventricular end-diastolic volume (using Teicholz model) (LVEDV)
 6) left atrium diameter (LAD).

Additionally, function of heart chambers was assessed to exclude possible contractility impairment. After M-mode and 2D imaging, pulse wave Doppler echocardiography was performed. This method was applied to assess aortic, pulmonary, tricuspid and mitral blood flow. It aided identification of silent valvular heart disease.

Thus, patients were excluded from the study if valvular heart disease, regional contractility impairment (following past myocardial infarction), hypertrophic cardiomyopathy or atrial and ventricular enlargement were confirmed on echocardiography.

Comparison of clinical and demographic characteristics of studied groups is shown in Table I. The only significant difference was found for diastolic pressure, which was higher in AF patients.

Human DNA isolation

DNA was isolated from 10-20 ml whole blood samples drawn from the radial vein. For this reason Madisen's method was used [8] involving DNA extraction from cellular lysate using phenol, and subsequent precipitation with ethylene alcohol. Sediment containing DNA was

Table I. Comparison of clinical and demographic characteristics of AF patients and control group

Variable	Control group	AF group	p
Age (years)	53±9	55±10	0.234
Gender (F/M)	32.8%/67.2% (20/40)	46.4%/53.6% (32/37)	0.114
Weight (kg)	76±12	78±13	0.298
Height (cm)	168±8	167±9	0.471
BMI (kg/m²)	26.90±4.84	28.07±4.63	0.161
SBP (mmHg)	124.43±17.95	127.74±10.62	0.197
DBP (mmHg)	75.31 ±9.86	78.62±7.74	0.034
TSH µIU/ml	1.51 ±1.29	1.29±1.35	0.352
Smoking	31.1%	33.3%	0.790

SBP – systolic blood pressure, DBP – diastolic blood pressure, TSH – thyroid stimulating hormone

dissolved in 300 µl TE buffer (1 mM EDTA, 10 mM TRIS). DNA samples were stored at 4°C.

Polymorphism analysis with DNA amplification method

Polymorphism of the studied genes was analysed using PCR – RFLP evolved by Mullis. PCRs were performed in 50 µl volume in PTC-200 MJ Research thermocycler. Polymorphism of the MinK gene was detected after fragment amplification in polymerase chain reaction. The following reaction mixture and amplification conditions were prepared: 2 µl of tested DNA, 40 µl buffer, 24 µl $MgCl_2$, 1.6 µl dNTP (dATP, dCTP, dGTP, dTTP), 1.6 µl of each starter, and 10 U polymerase Taq (MBI Fermentas).

Primer sequences: sense – 5´- gTg ggA TCC TAA TgC CCA ggA TgA TC, anti-sense – 5´- gTg gTC gAC TTC ATg ggg AAg gCT TC [9]. Reaction conditions: initial denaturation of DNA at 95°C for 5 minutes, 35 cycles of proper reaction: denaturation at 95°C for 1 minute 30 seconds, at 57°C for 2 minutes – annealing, at 73°C for 1 minute 30 seconds – extending step (elongation), and final incubation at 72°C for 7 minutes. Amplification products were cleaved with restrictive enzyme HindIII (MBI Fermentas) at 37°C for 9-12 hours (conditions recommended by manufacturer) using 1 U enzyme for 20 µl of amplification product. Digestion product was evaluated in 1% agarose gel electrophoresis after staining the gel with ethidium bromide (0.8 µg/1 ml) and under UV light of 366 nm wavelength. Separation time was 30-50 min with voltage of 140 V. Size of digestion products (restriction fragments) was determined by comparing to the size of a known fragment.

This study determined polymorphism of the MinK gene. It involves presence of two MinK alleles, a longer one of 500 base pairs (bp) (S) and a shorter one of 300 bp (G). Three possible genotypes may be observed on electrophoretic separation of HindIII digested product of MinK amplification: GG with one stripe of 300 bp,

GS with two stripes of 300 bp and 500 bp, and SS with one stripe of 500 bp. Genotypes are illustrated in Figure 1.

Statistical analysis

Statistical analysis was performed using Statistica 6.0 software. Differences in frequency of alleles and genotypes between studied groups were analysed using χ^2 test. Significance of between-group differences was evaluated with Student's *t*-test. Characteristics of the study population with respect to determined genotype was carried out with analysis of variance (ANOVA). Odds ratio of AF for individual genotypes was calculated using a logistic regression model. Differences were found statistically significant when p <0.05.

Results

Analysis of the results showed that the MinK G allele was significantly more often found in patients with AF (62.32%) compared to the control group (41.80%) (p=0.0094). Incidence rate of MinK alleles and genotypes in patients is presented in Tables II and III.
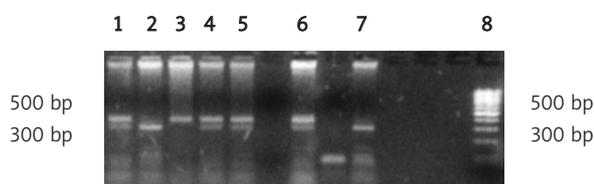

Figure 1. MinK gene restriction fragment length polymorphism. 1% agarose gel electrophoresis, U=140 V, t=40 min. Traces 1, 4, 5, 6 – GS genotype, traces 2, 7 – GG genotype, trace 3 – SS genotype, trace 8 – *DNA Ladder Gene Ruler 100 bp Fermentas marker*

Table II. Frequency of MinK alleles in AF patients and control group

Group	Number of subjects	Number of alleles	G allele	S allele
AF group	69	138	86 (62.32%)	52 (37.68%)
Control group	61	122	51 (41.80%)	71 (58.20%)

$\chi^2=10.93$, df=1, p=0.0094

Table III. Frequency of genotypes in AF and control groups

Group	Number of subjects	GG genotype	GS genotype	SS genotype
AF group	69	24 (34.78%)	38 (55.07%)	7 (10.14%)
Control group	61	3 (4.92%)	45 (73.77%)	13 (21.31%)

$\chi^2=18.30$, df=2, p=0.0001

GS genotype was the most common in patients with AF (55%). GG genotype was more often found in the AF group (34.78 %) compared to controls (4.92%) (p=0.001), whereas SS genotype was more frequent in healthy individuals (21.31%) compared to AF patients (10.14%) (p=0.0001). The results are detailed in Table III.

Patients with AF were divided with respect to their genotype into three subgroups: with GG, GS or SS genotype. Subsequently, respective groups were compared regarding measured clinical parameters. Statistical differences between parameters were calculated for GG and GS groups due to the small number of patients in group SS (7 subjects). Patients with GG and GS genotypes did not differ with respect to analysed parameters. The results are shown in Table IV.

In the logistic regression model presence of G variant (GG+GS genotypes) was associated with increase of AF risk in the study population (OR 2.398; 95% CI 0.88–6.54; p=0.084). Presence of GG genotype was however associated with significant, over 10-fold, increase of AF risk. In the analysed model, carrier state of S variant of the MinK gene (GS+SS genotypes) met criteria of protecting factor against AF in the study population. The results are presented in Figure 2 and Table V.

Discussion

Atrial fibrillation is the most common atrial tachycardia and its pathogenesis was documented to involve genetic factors. Following analysis of the Framingham Heart Study,

Table IV. Characteristics of AF group with respect to genotype

Variable	GG genotype	GS genotype	SS genotype	p*
Number	24	38	7	
Age (years)	59.54±10	54.95±11	59.43±4	0.112
Gender (F/M)	12/12	19/19	1/6	0.603
Weight (kg)	79±16	77±13	81±10	0.675
Height (cm)	168±9	165±9	171±8	0.310
SBP (mmHg)	128.08±10.48	126.32±11.13	134.29±5.35	0.536
DBP (mmHg)	77.13±8.85	78.79±7.26	82.88±4.88	0.423
Potassium$^+$ (mmol/l)	4.19±0.42	4.40±0.51	4.32±0.47	0.097
TSH (μIU/ml)	1.26±1.92	1.24±0.80	1.71±1.52	0.952
LVEDD (mm)	53.49±3.75	50.97±5.52	56.79±6.49	0.054
LVEDV (ml)	104.96±23.33	104.71±21.71	135.00±42.36	0.966
PWDD (mm)	10.59±1.32	10.18±1.42	11.03±2.44	0.260
EF (%)	58.36±5.92	59.71±7.33	53.57±10.56	0.449
LAD (mm)	42.05±4.57	41.75±4.52	43.39±8.83	0.803
Smoking	38%	34%	14%	0.501

LVEDD – left ventricular end-diastolic diameter, LVEDV – left ventricular end-diastolic volume, PWDD – left ventricular posterior wall diameter, EF – left ventricular ejection fraction, LAD – left atrium diameter, p* – statistical significance between GG and G genotypes. For other abbreviations, please see Table I.
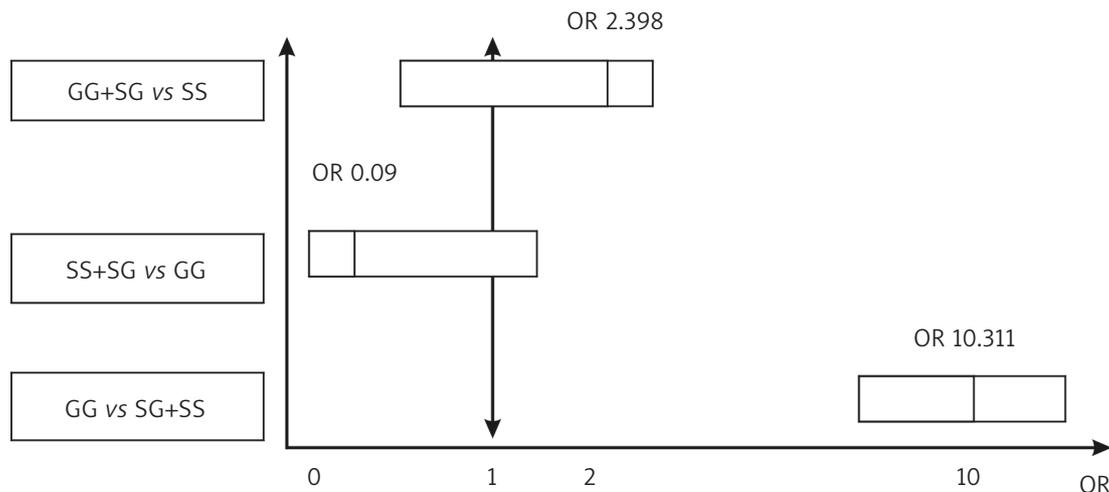
Figure 2. Diagram model of logistic regression for individual alleles and genotypes

Fox et al. concluded that patients whose parents suffered from AF were more susceptible to develop this arrhythmia compared to children of AF-free parents. In this study, 30% of AF subjects had at least one parent with documented AF [10].

Genes that may influence AF incidence are likely to be numerous. One method of identifying these genes is comparative analysis of candidate genes between AF patients and control group matched for age. Using such analysis great attention must be paid to adequately match the study and control groups. Our control group comprised healthy individuals without symptoms suggesting paroxysmal AF. On the other hand, in the light of the CARAF trial, in 21% of patients AF was asymptomatic and resolved spontaneously in 50% of patients within 24-48 hours [11]. However, all efforts were made in our study to exclude from the control group patients with cardiac arrhythmia or other conditions known to coexist with AF.

The MinK gene was selected for the analysis. The MinK gene encodes the β-subunit of the cardiac I_{Ks} channel. There are two types of potassium channels: rapid I_{Ks} and slow I_{Kr}. Subunits of potassium channels are encoded by four genes: KCNQ1 encodes α-subunit of I_{Ks} potassium ion channel; KCNH2, also known as HERG, encodes α-subunit of potassium ion channel, which together with β MinK-related peptide 1 (MiRP-1) forms the I_{Kr} channel that hastens cardiac repolarisation current; KCNE1 (i.e. MinK) and KCNE2 encode β-subunits of potassium channels. The SCN5A gene encodes a subunit that forms the sodium channel responsible for initiating the cardiac action potential. Mutations in SCN5A have been implicated in numerous familial forms of cardiac arrhythmia, including long QT

Table V. Odds ratio for atrial fibrillation with respect to allele and genotype

Alleles and genotypes	Odds ratio; 95% CI; p
G variant: (SG+GG *vs* SS)	OR 2.398; 95% CI 0.88-6.54; p=0.084
S variant: (SS+GS *vs* GG)	OR 0.096; 95% CI 0.027-0.346; p=0.0003
GG genotype: (GG *vs* GS+SS)	OR 10.311; 95% CI 2.884-36.86; p=0.0001

syndrome, idiopathic ventricular fibrillation and conduction disorders.

Our study demonstrated a relationship between MinK GG genotype and occurrence of paroxysmal AF. Presence of G allele of the MinK gene most likely affects function of the potassium ion channel, i.e. excessive shortening of action potential of the atrial tissue. This produces a substrate for AF. This hypothesis requires however further genetic and electrophysiological testing in larger populations.

The MinK gene is located on the long arm of chromosome 21 (21q22.1–22.2) [12]. It incorporates no introns. The gene comprises 390 base pairs and encodes a small protein that forms a single transmembrane domain [9]. MinK polymorphism involves presence of two G and S alleles: 38G allele of the MinK gene encodes a protein with Gly at position 38, whereas 38S allele encodes a protein with Ser in this position. MinK gene expression in the atrial myocardium was confirmed by finding the presence of mRNA and protein of the analysed potassium ion channel [13].

Results of MinK polymorphism studies in European (Caucasian) populations have not been published so

far, which makes the interpretation of our results more difficult. The report published in 2001 evaluated relations between AF and MinK gene polymorphism in an Asian population. Incidence of G allele in AF patients was 76%, whereas in the control group it was 63%. In AF patients GG genotype was found in 59%, and in 42% of healthy individuals. Differences between groups reached statistical significance. The odds ratio for AF in patients with one G allele was 2.16 (95% CI 0.81–5.74) compared to patients without this allele. However, in patients with GG genotype, the odds ratio for AF was 3.58 (95% CI 1.38-9.27) [14]. The results of our study suggest that presence of GG genotype of the MinK gene may serve as a genetic marker of AF threat.

The undoubted limitation of our study is the relatively small size of the study population. Case-control studies are associated with the risk of false positive results. The results require verification in a larger group of Caucasian patients. We noted a small number of subjects with GG genotype in the control group, which diverges from the one observed in the Asian population [14]. This finding should be confirmed in Caucasian population studies.

The MinK gene is located on a chromosome close to other genes that are involved in the pathogenesis of AF [15]. These genes include minK-related protein (MiRP), which is located on chromosome 21. Abbott et al. documented that MiRP is involved in the pathogenesis of cardiac arrhythmias [16]. The best approach would be simultaneous determination of a range of genes in the study patients. Analysis of the number of genes associated with development of AF will increase the chance of adequate working out of this condition. Additionally, occurrence of AF is influenced by many environmental factors such as infection, toxic factors, drugs, alcohol and stress. It would be difficult to totally exclude their influence on AF paroxysms in the studied patients.

Genetic studies of AF will certainly allow faster diagnosis and management of this condition with respect to the determined genetic marker. It seems that progress in AF pharmacogenetics, allowing physicians to make rational decisions regarding selection and dosing of drugs, may considerably contribute to improvement of the state of the art through decrease of drug side effects and doses. All together this should lead to an increased number of patients complying with the prescribed therapy and thus an increased number of successfully treated subjects as well as reduction of costs and complications.

Conclusions

1. G38S polymorphism in the MinK gene seems to be associated with incidence of lone AF in the study population.

2. GG genotype carrier state may significantly relate to increased risk of AF in the study group.

3. G38S polymorphism in the MinK gene could be used as a genetic marker of risk of lone AF.

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Polimorfizm genu MinK w patogenezie samoistnego migotania przedsionków

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Streszczenie

Wstęp: Migotanie przedsionków (AF) jest najczęstszą postacią złożonych zaburzeń rytmu serca stwierdzanych w codziennej praktyce klinicznej. Szczególną postać stanowi samoistne AF występujące u 2–31% chorych ze stwierdzaną arytmią. U podłoża tej arytmii mogą leżeć czynniki genetyczne.

Cel: Określenie związku polimorfizmu G38S genu MinK z występowaniem samoistnego AF i ocena powyższego polimorfizmu jako genetycznego markera podatności na AF.

Metody: Badaniem objęto grupę 69 pacjentów z samoistnym AF oraz 60 osób bez tej arytmii jako grupę kontrolną. Do obu grup zakwalifikowano osoby w wieku do 65. roku życia, u których nie stwierdzono chorób układu sercowo-naczyniowego i chorób tarczycy. Genotyp MinK określono metodą PCR RFLP (łańcuchowa reakcja polimeryzacji polimorfizmu długości fragmentów restrykcyjnych). Gen MinK występował w dwóch formach allelicznych G i S.

Wyniki: Allel G genu MinK istotnie częściej występował w grupie osób z AF (62,32%) w porównaniu z grupą kontrolną (41,80%) (p=0,009). W grupie osób z AF najczęściej występował genotyp GS (55,07%), następnie GG (34,78%) i najrzadziej genotyp SS (10,14%). W modelu regresji logistycznej fakt nosicielstwa wariantu G nie wiązał się z istotnym statystycznie zwiększeniem ryzyka AF w badanej populacji (OR 2,39; 95% CI 0,88–6,54; p=0,084). Natomiast obecność genotypu GG wiązała się z istotnym, ponad 10-krotnym, wzrostem zagrożenia wystąpieniem AF. Obecność allelu S genu MinK spełniała kryteria czynnika ochronnego przed wystąpieniem tej arytmii w badanej populacji.

Wnioski: 1. Polimorfizm G38S genu MinK wydaje się związany z samoistnym AF w badanej populacji. 2. Nosicielstwo genotypu GG może się wiązać z istotnie zwiększonym ryzykiem wystąpienia AF w badanej grupie. 3. Polimorfizm G38S genu MinK mógłby zostać zastosowany jako genetyczny marker zagrożenia wystąpieniem samoistnego AF.

Słowa kluczowe: migotanie przedsionków, genetyka, polimorfizm genu MinK

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