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## New Gene-Candidate in Atrial Fibrillation Polymorphism of $\beta$ 1-Adrenoreceptor Gene

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### 1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring 1-2% of the general population (European Society of Cardiology, 2010). The lifetime risk of the development of AF at age 40 years has been estimated to be approximately 1 in 4 (Lloyd-Jones et al., 2004). In most cases atrial fibrillation is secondary, i.e. caused by some cardiovascular disease. However, in minimum 1/3 of patients causes of AF are impossible to identify. In these situations idiopathic or lone AF is being the case. It is assumed that a significant number of cases of idiopathic (lone) AF is hereditary inflicted.

Significant influence of heredity on the development of AF was first stated by H. Gould in 1950. He assumed hereditary character of AF in several generations of one family, who had been under observation for 36 years. Most publications on the genealogy of AF were issued in the 1990s. They describe cases of families whose members had AF or atrial flutter. (Bertram et al., 1996; Bharati et al., 1992; Gillor et al., 1992; Girona et al., 1997; Poret et al., 1996). At the same period was published the results of observing the development of AF in two embryos during the 23<sup>rd</sup> and 25<sup>th</sup> weeks of antenatal development. Both children were born with persistent AF (Tikanoja et al., 1998).

Families, where intraventricular conduction disorders alongside with various tachyarrhythmias tended to accumulate, were of special interest for the researchers. There are families described, whose members of several generations had AF and/or atrial flutter combined with block of different branches of His' bundle or atrio-ventricular heart block (Amat-y-Leon et al., 1974; Bertram et al., 1996; M.S.; Friedli, 1993).

There was point out that AF at parents increases the risk of development of atrial fibrillations in posterity. Among 2 243 relatives examined 681 (30%) had at least one parent with the registered AF (Fox et al., 1997). Priority in postulation of the AF autosomal-dominant model belongs to J. Girona. They presented two families where 20 out of 70 examined persons had paroxysmal or permanent form of AF (Girona et al., 1997).

The clinical, electrophysiological and genetic examinations were conducted in three Spanish families with AF. Genetic analysis showed that the gene responsible for the AF in these families was localized on the 10q chromosome in the area 10q22-24. Genetic typing of the patients with AF revealed the locus of the pathologic gene between D10S1694 and D10S1786. The disease is inherited with a high degree of penetrance. The authors suggest

that the candidate genes for this pathology are genes of  $\beta$ -adrenoreceptors (ADRB1),  $\alpha$ -adrenoreceptors (ADRA2) and genes of G-protein coupled receptor-kinase (GPRR5) as localized on the same 10 chromosome, in locus 23-26. In the families studied cardiac fibrillation was found in 21 out of 49 members. Genealogies of these families are shown in Fig. 1. One of the diseased members (II-8) died of stroke at the age of 68. Another one (III-2), who had paroxysmal cardiac fibrillation since he was 20 years old, suddenly died at the age of 36, but autopsy was not performed. Out of 19 alive family members 18 had chronic AF and 1 suffered from paroxysmal form of AF (Brugada et al., 1997).

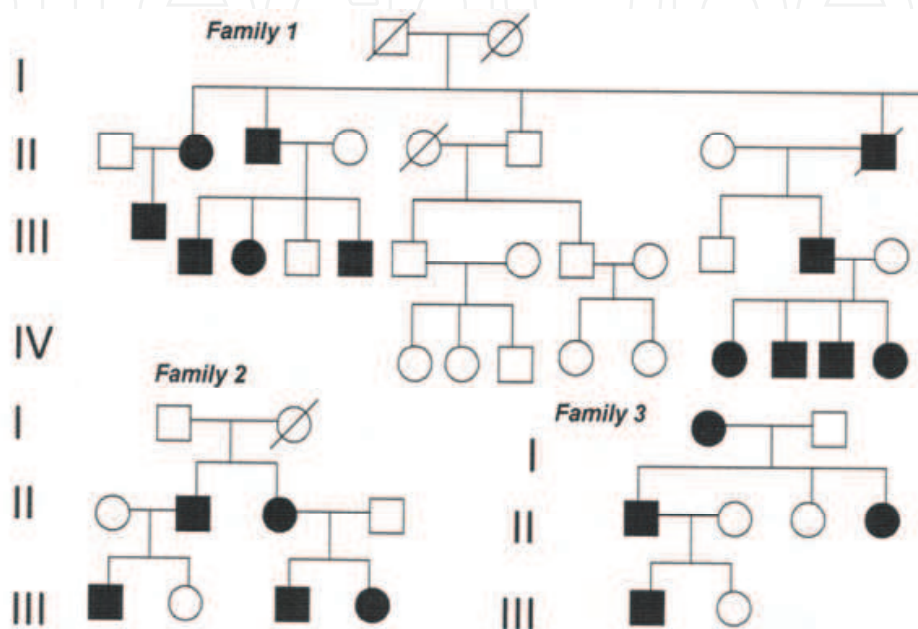


Fig. 1. Genealogy of 3 Spanish families with AF.

The hereditary AF was defined as a monogenic arrhythmia, which suggests, according to the author, that there is a possibility to correct this condition early (Roden, 2004). However, this type of rhythm disorder is characterized by genetic heterogeneity as an identical phenotypic pattern can be seen in mutations in different genetic loci. Along with the AF locus situated in the 10<sup>th</sup> chromosome, investigators mapped AF gene on a proximal long shoulder of 6q 14-16 in the interval between D6S286 and D651021 (Ellinor et al., 2004). In this particular family AF was inherited as Mendelian disease.

Finally, Chinese researchers identified 2 genes responsible for inherited AF (Yang et al., 2004). Those were the genes of myocyte potassium channels' proteins. Specifically, they reported replacement of arginine to cycteine in 27 position of gene KCNE2 on chromosome 21q22.1-22, which codes  $\beta$ -subunit of potassium channels. These mutations were found in 2 out of 28 examined Chinese families with inherited AF. The mutation (S140G) of gene KCNQ1 on chromosome 11p15.5, which codes  $\alpha$ -subunit of cardiac potassium channel was identified. Occurrence of AF in these cases is caused by the fact that the function of respective potassium channels in the genes influenced by the described mutations, increases. This leads to shortening of the action potential and effective atrial refractory period. As was mentioned above, when the function of the described channels decreases, long QT syndrome occurs, thus variants LQT1 and LQT6 take place. It is also worth reminding that one of the leading phenotypic manifestations of a short QT syndrome, when

the function of potassium channels increases, is paroxysmal AF. Thus, the given data of the Chinese researchers prove the suggestion that some of the familial AF variants can be classified as channels pathology (Yang et al., 2004).

There is established a relative association between inherited AF and other genetic disorders: long QT syndrome, dilation cardiomyopathy, hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome. The results of a forty-year long observation over nine generation of one family with cardiomyopathy and AF were reported in 2000. Out of 325 examined persons 106 were found to have AF (Sparks et al., 2000).

The discovery of a missense mutation (D1275N) of sodium channels gene SCN5A in patients with dilatation cardiomyopathy and of a missense mutation (replacement of arginine to histidine in 663 position) in the heavy chain of  $\beta$ -cardiac myosin allowed to suggest it, which caused linked inheritance of hypertrophic cardiomyopathy and AF (Gruver et al., 1999; Olson et al., 2005).

A combination of Wolff-Parkinson-White syndrome and hypertrophic cardiomyopathy caused by the pathology of PRKAG gene, which codes  $\gamma$ 2-subunit of adenosine monophosphate - activated protein kinase was presented in 2001. The 38-44% of patients with a familial form of this syndrome had AF, as opposed to 15-20% with sporadic forms of the disease. The gene of this pathology is mapped on chromosome 7q34-36. Sequence analysis of these patients' DNA showed replacement of arginine to glutamine in position 302 (Gollob et al., 2001).

Recent years' research is aimed to find candidate genes associated with the development of AF. One of such candidate genes is a polymorphous marker of G-protein  $\beta$ 3-subunit gene. (BNB3). Multifunctional G-protein is localized in cell membranes of cardiac hystiocytes, smooth muscular vessel cells, fibroblasts; it can be involved in the processes of cardiac muscle and vessel wall remodeling. The connection between polymorphism (deletion) of mitochondrial DNA and development of lone AF was also proved (Lai et al., 2004). In another study was discovered association of polymorphous C825T marker of BNB3 gene, which codes  $\beta$ -3 subunit of G-protein. As a result of genetic typing the patients fell into the following categories: C-allele homozygotes (CC genotype); heterozygotes (CT genotype) and T-allele homozygotes (TT genotype). The association between TT genotype and decreasing risk of AF was established (Schreieck et al., 2004).

The increasing of connexin 43 in AF was correlated with enlargement of the left atrium. The mutation in gene 1q21.1, which causes connexin 40 decreasing, was found out that contributes to development of aortic arch anomalies with AF (Christiansen et al., 2004).

Morphologic substrate of AF electrogenesis can be genetically determined imperfection of connective tissue development in embryogenesis, which leads to disorder in intertissue interactions and electromechanical instability. It can be proved by the work of Japanese researchers, who showed significantly frequent development of AF through experiments on transgenic mice with atrial fibrosis (Nakajima et al., 2000).

At the 21<sup>st</sup> Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology (2000) there was an interesting report on the fact that myocardial "pump cuffs", which form in embryogenesis around pulmonary veins openings, are morphological substrate of ectopic activity that can cause atrial fibrillation and flutter. Myocytes in these are characterized by spontaneous electric activity, as opposed to cardiac hystiocytes of the left atrium. Clinical features of primary AF, its clinical pathogenetic forms, anatomical and electrophysiological risk factors for this pathology are not studied to a sufficient extent.

Inheritance patterns of this pathology as well as phenotypic predictors of this pathology were not studied in all the details.

## 2. Results

### 2.1 Atrial fibrillation genealogy

In relation to that, during the last five years we have examined 103 probands with the diagnosed AF and 301 members of their families (I, II, III degrees of relation) in our clinic. The probands' families were divided into groups based on the etiology of AF. Thus, we got Group 1, comprising 53 probands with idiopathic AF and 154 members of their families; Group 2 had 50 probands with secondary AF and 147 family members.

The study established the fact of family disease aggregation in the probands' families with AF. Secondary AF aggregation in the families reached 7.31% (22 diseased family members out of 301), which was significantly larger than population frequency (0.4%) of the disease (H. Kulbertus et al., 1982). In the probands' families with AF the biggest percentage of the diseased was among the family members of the first degree of relation. Specifically, the pathology in question was found at 9.86% of the examined family members within the first degree of relation and only 1.16% of the family members within the second degree of relation had it.

According to our data, among the family members of the first degree of relation, the most susceptible to atrial fibrillation are mothers (36.36%), sisters (19.44%) and fathers (16.67%) as shown in Fig.2.

Heritability of susceptibility ( $H^2$ ) was defined within the framework of Falconer's model which postulates normal distribution of susceptibility in a population and among the family members of the first degree of relation. According to this model, regression coefficient of AF susceptibility was:

$$b = \frac{Xq - Xr}{a} = \frac{2,65 - 1,287}{2,962} = 0,460$$

$Xq$  - a threshold point of susceptibility distribution in population;

$Xr$  - a threshold point of susceptibility distribution among family members;

$a$  - average susceptibility of the diseased in a population sample.

The values were taken from the tables - appendix to the formula of regression coefficient calculation. Heritability coefficient:

$$H^2 = \frac{b}{r} = \frac{0,460}{2} = 0,230$$

$r$  - a relation coefficient,  $r = 2$  for the family members of the first degree of relation.

Thus, heritability of AF susceptibility according to Falconer's model was 23%; the rest 77% of AF development cases are caused by the environmental factors.

To conduct the formal genetic analysis of inheritance type Weinberg's method is used for unit registration. The sick siblings in the probands' families with idiopathic AF, where this pathology was traced in several generations were used for the segregation analysis. Taking into account the results received from the sibs and probands' methods of segregation analysis for the families where probands suffer from idiopathic AF, we can assume autosomal-dominant type of this pathology inheritance.

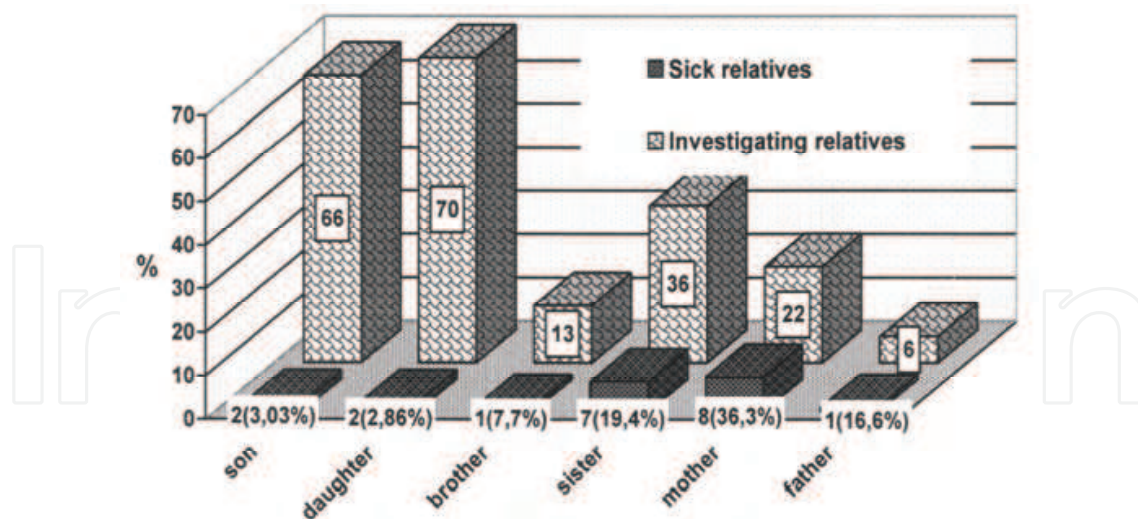


Fig. 2. Family AF aggregation in the probands' families with AF.

## 2.2 Family history

Proband - female, 54 years old, was examined in February, 2002. She complained about fits of unrhythmical heartbeat accompanied by dyspnea; headaches occurring after rise in blood pressure (BP). According to the anamnesis, paroxysmal atrial fibrillation was first diagnosed in 1992. The patient had several examinations in hospital. Amiodaron was administered, but treatment was not regularly. When she stops taking the medication, AF paroxysms recur, usually twice a month, mostly on exertion. Those were terminated with procainamide hydrochloride. In recent two years the blood pressure started to rise. The highest levels were 200/100 mmHg. The blood pressure did not reach with the use of ACE inhibitors. The skin was normal color and moistness. The chest was not deformed. No abnormalities in the precordial area. Apical beat was palpated on the left midclavicular line. Left heart border was dilated within the left midclavicular line. Heart sounds were clear, rhythmical, no murmur. Heart rate was 65 bpm. BP was 140/90 mmHg. No other systems' pathologies were found. In admittance, ECG showed sinus rhythm with the heart rate 65 bpm, axis = +15°, P 0.1", PQ 0.16", QRS 0.08", QT 0.38",  $R_{V5,V6} > R_{V4}$ . Conclusion: signs of the left ventricular hypertrophy. On 20jun2002 ECG showed atrial fibrillation with the ventricular heart rate 100-135 bpm. We revealed hardening of aorta and aortic valve cusps, slight symmetric left ventricular hypertrophy (interventricular septum - 1.1 cm; left ventricle posterior wall - 1.2 cm) by echo. The left atrium size was normal (2.8 cm). Left ventricular ejection fraction (LVEF) was normal. Diagnosis: Idiopathic heart rhythm disorder: paroxysmal atrial fibrillation type. Concomitant disease: Arterial hypertension.

Proband's mother, 75 years old, with complains about unrhythmical heart beat; shortness of breath on slight exertion, sometimes at rest, which worsens in the lying position; heaviness in the right hypochondrium; swollen ankles, constricting retrosternal pain on exertion (walking about 500 m on the level road). Those were stopped by taking nitroglycerine. Further complains include seeing little dots when the BP rises; weakness and dizziness. According to the anamnesis, chronic AF was first diagnosed 17 years ago. Before becoming chronic, paroxysms had been recurring for 10 years. At the age of 60 angina pectoris symptoms started to reveal, the BP began to rise. Maximal BP levels were 220/115 mmHg. Around the same time clinical picture of heart failure was observed. The treatment included cardiac glycosides,  $\beta$ -blockers, ACE inhibitors, diuretics, antithrombotic. The skin was pale, dry. Chest was not deformed. No abnormalities in the precordial area. Apex beat was palpated at 1 cm to the

outside of the left midclavicular line. Left heart border was dilated up to the 1 cm from the left midclavicular line. Heart sounds were muffled, arrhythmical, systolic murmur was heard on the aorta and Botkin-Erb point. Heart rate was 100 bpm; BP was 150/85 mmHg. Respiration was rough, no crackles with breathing rate 20 per minute. Palpatory tenderness in the right hypochondrium. Percussion findings showed the lower end of the liver to be below the edge of the costal margin. Pastosity of the knees was noticed. ECG showed rhythm of atrial fibrillation with the ventricular rate 85-130 bpm, axis = 0°, QRS 0.08", QT 0.36",  $R_{V5,V6} > R_{V4}$ . Signs of the left ventricle hypertrophy were seen. Echo data revealed aorta and aortic valve cusps hardening; severe left ventricle hypertrophic (interventricular septum 1.4 cm, left ventricle back wall is 1.5 cm). The left atrium was dilated (4.6 cm). LVEF was slightly reduced (52%, by Teicholz). Diagnosis: Idiopathic heart rhythm disorder: chronic atrial fibrillation type. Concomitant disease: Arterial hypertension. Coronary heart disease. Angina pectoris.

Proband's son, 17 years old, complained about stabbing pains in the cardiac apex. Irregularities in the cardiac performances were not subjectively noticed. According to the anamnesis, during last 5 years ECG records showed frequent ventricular premature beats. The patient is regularly taking  $\beta$ -adrenergic blockers with no positive antiarrhythmical effect. The skin was slightly hyperemic, of normal moistness, red dermographism. Chest was not deformed. No abnormalities in the precordial area. Apex beat was palpated at 1 cm to the inside of the left midclavicular line. Heart borders were within normal ranges. Heart sounds were clear, arrhythmical, no murmur. Heart rate was 70 bpm, (with frequent extrasystole). BP was 130/85 mmHg. No other systems' pathologies were found. ECG showed sinus rhythm with the heart rate 80 bpm, axis = + 40°, P 0,06", PQ 0,16", QRS 0,08". QT 0,34". Conclusion: Frequent ventricular extrasystole, trigeminy. Bicycle ergometry registered frequent ventricular premature beats at rest; the number of premature beats did not reduce at exertion. Echo did not reveal any pathology. Transesophageal left atrium stimulation results: Wenckebach point - 176 per minute, sinus node recovery time (SNRT) - 1050 msec, corrected sinus node recovery time (SNRTc) - 250 msec. Ultrafrequent stimulation with a short volley of stimuli provoked a paroxysm of atrial fibrillation with the ventricular rate 79-120 bpm. Frequent ventricular premature beats were also registered. Diagnosis: Idiopathic heart rhythm disorder: type of frequent ventricular premature beats and paroxysmal atrial fibrillation.

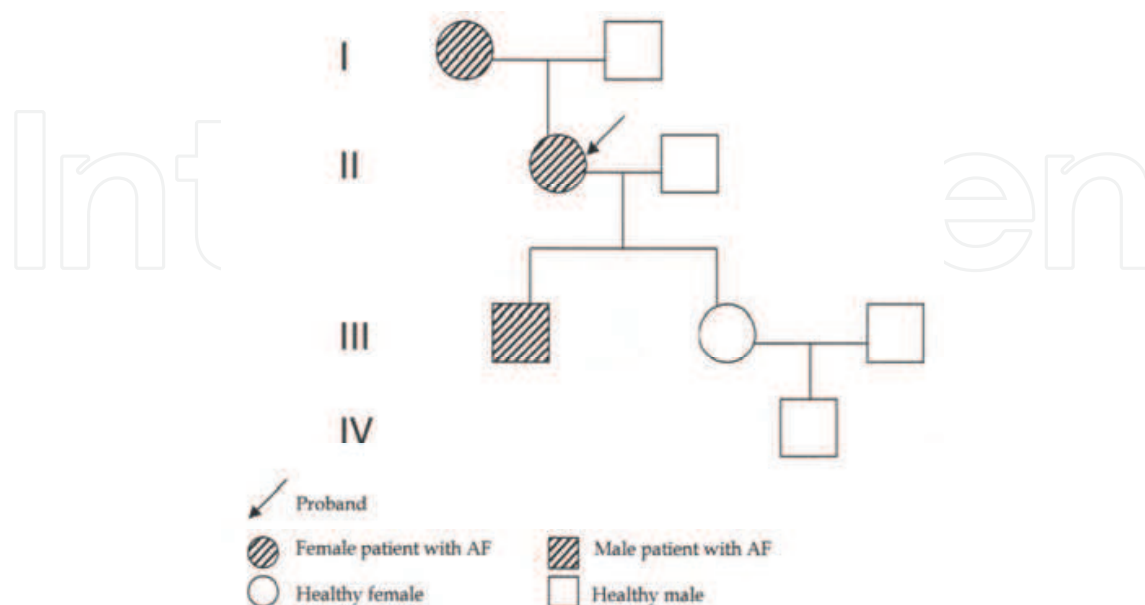


Fig. 3. Genealogy of the family with atrial fibrillation.

Proband's daughter, 35 years old, with complains about stabbing pains in the cardiac apex, feeling of incomplete inhalation, dizziness. The patient can not indicate for sure when the above mentioned symptoms appeared. According to the patient, their possible causes were physical and emotional overstrain. Taking sedatives given positive effect. No irregularities in the cardiac performance were revealed. The skin was normal tone and moistness. Chest was not deformed. No abnormalities in the precordial area. Apex beat was palpated at 1 cm to the inside of the left midclavicular line. Heart borders were within normal ranges. Heart sounds were clear, rhythmical, no murmur. Heart rate was 65 bpm. BP was 120/80 mmHg. No other systems' pathologies were found. ECG showed a sinus rhythm with the heart rate 64 bpm, axis = + 30°, P 0.08", PQ 0.16", QRS 0.08", QT 0.36". Echo did not reveal any abnormalities. Bicycle ergometry revealed no cardiac rhythm disorders. Exertion tolerance is high. No hypertension syndrome. Holter ECG-monitoring registered a sinus rhythm with normal variability. No cardiac rhythm disorders were found during the examination period. Proband's grandson, 13 years old, did not any complains. Cardiac rhythm disorder had never occurred. According to the anamnesis, patient had some minor respiratory diseases and chickenpox. The examination did not reveal any abnormalities. ECG showed a sinus rhythm with the heart rate 76 bpm, axis = + 40°, P 0.06", PQ 0.16", QRS 0.06", QT 0.34". Echo revealed first degree mitral valve prolapse (mitral valve cusps sagging up to 4 mm).

### 2.3 New gene-candidate of atrial fibrillation

We evaluated  $\beta$ 1-adrenoreceptor candidate gene polymorphism in the patients with lone and secondary AF. Genetic study has been performed using DNA extracted from peripheral blood leukocytes (Smith, 1990). Amplification was achieved with PCR. Genetic tests were performed in 30 patients of the 1<sup>st</sup> group (lone AF) and 25 their healthy relatives; and in 30 patients of the 2<sup>nd</sup> group (secondary AF) and 44 their healthy relatives. Besides, 198 patients, who did not have any signs of cardiovascular diseases, were genetically typed (control group).

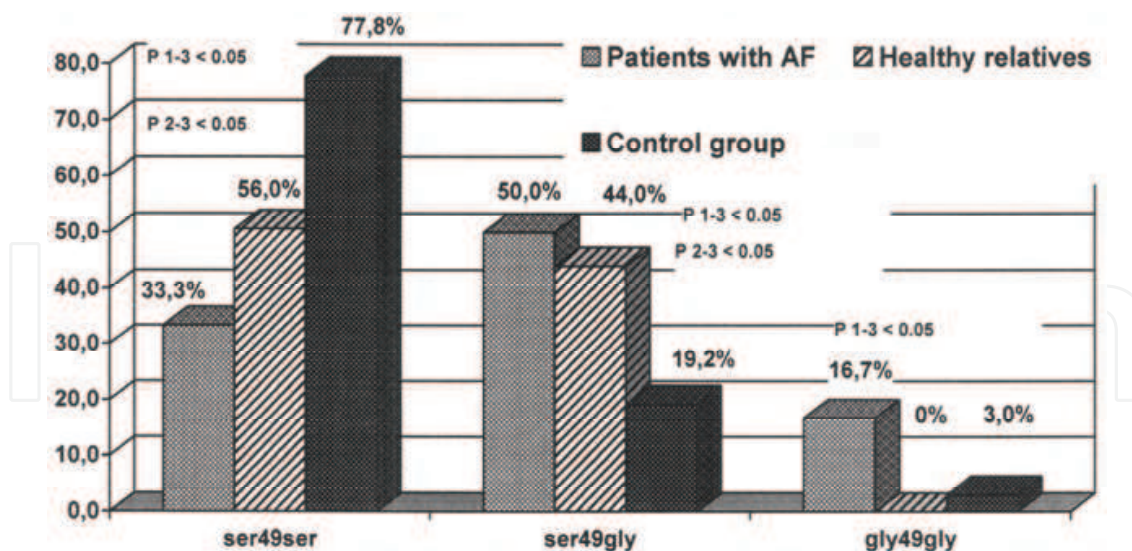


Fig. 4. Polymorphism of  $\beta$ 1 - adrenoreceptors gene among patients with lone AF.

According to own data, probands and their relatives with lone AF had significantly prevailing heterozygous genotype of  $\beta$ 1-adrenoreceptors (Ser49 Glu) in comparison with the control group: 15 probands (50%) and 11 relatives (44%) in comparison with 38 (19.2%) of the control group. The 1<sup>st</sup> group probands also showed domination on the rare allele



(Glu49Glu) in comparison with the control group: 5 (16.7%) and 6 (3.2%) respectively. However, the described genotype was found in none of the healthy relatives of the 1<sup>st</sup> group probands (Fig.4).

The 2<sup>nd</sup> group patients also demonstrated a significant domination of a heterozygous allele (Ser49Glu): 14 (46.7%) in comparison with the control group 38 (19.2%). However, the genotype in question was not significantly predominant in these patients' relatives in comparison with the control group. Frequency of genotype Glu49Glu occurrence in the patients with secondary AF and their relatives was not significantly different from that of the control group (Fig.5).

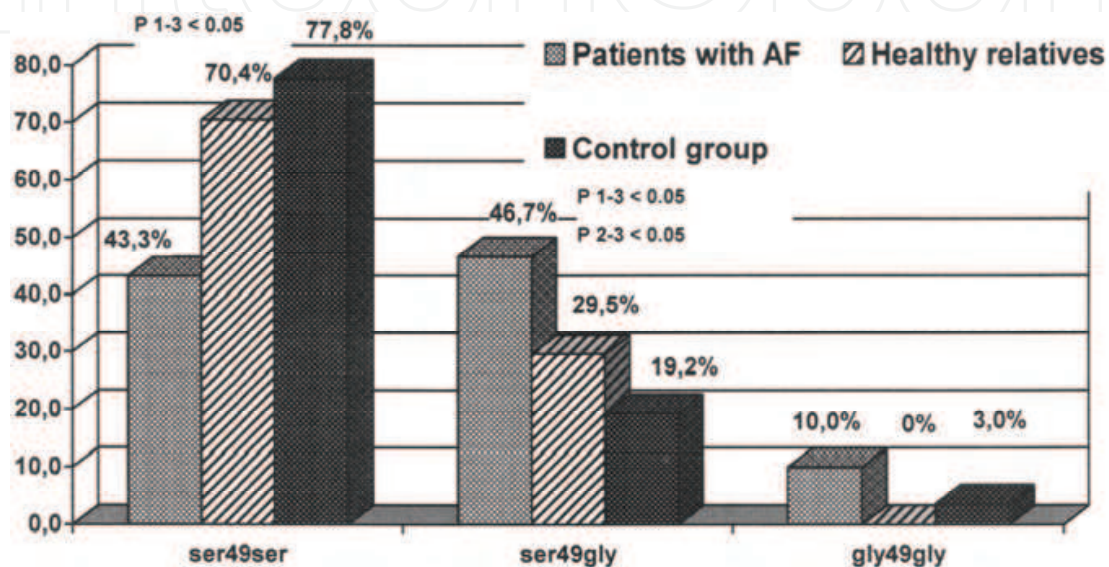


Fig. 5. Polymorphism of  $\beta$ 1-adrenoreceptors gene in patients with secondary atrial fibrillation.

Taking everything presented above into account, heterozygous variant of the genotype of  $\beta$ 1-adrenoreceptors gene Ser49Glu can be considered one of the genetic predictors of both lone and secondary AF. Genotype Ser49Glu can also serve as a predictor of lone AF. Relatives of those probands with the lone AF and Ser49Glu genotype are under the risk of developing this pathology.

### 3. Conclusion

On the whole, analysis of our own data and the data presented in literature shows that AF can be caused by hereditary predisposition. The most obvious manifestation of hereditary predisposition is in the patients with lone AF. Hereditary AF is often associated with other cardiovascular diseases (primary cardiomyopathy, Wolff-Parkinson-White syndrome, long- and short QT syndromes etc.). In some cases hereditary AF is a monogenic disease. However, as seen in many cases, AF is caused by a particular combination of certain genes' polymorphism (candidate genes). Our study of polymorphism of  $\beta$ 1-adrenoreceptors gene in the patients with lone and secondary AF can assist in solution of one of the aspects of this problem. It is also beyond all doubt that further search for candidate genes causing both lone and secondary AF remains urgent. This search's findings can contribute greatly to the prevention of one of the most common and dangerous arrhythmias. As genetic are gradually incorporated into routine clinical practice, classification system may facilitate individualized AF therapy based on pharmacogenomic principles (Roberts & Gollob, 2010).

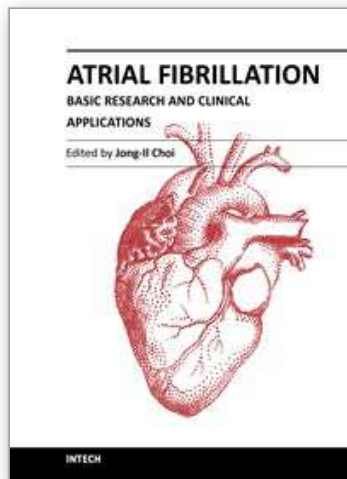
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## **Atrial Fibrillation - Basic Research and Clinical Applications**

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Atrial Fibrillation-Basic Research and Clinical Applications is designed to provide a comprehensive review and to introduce outstanding and novel researches. This book contains 22 polished chapters and consists of five sections: 1. Basic mechanisms of initiation and maintenance of atrial fibrillation and its pathophysiology, 2. Mapping of atrial fibrillation and novel methods of signal detection. 3. Clinical prognostic predictors of atrial fibrillation and remodeling, 4. Systemic reviews of catheter-based/surgical treatment and novel targets for treatment of atrial fibrillation and 5. Atrial fibrillation in specific conditions and its complications. Each chapter updates the knowledge of atrial fibrillation, providing state-of-the art for not only scientists and clinicians who are interested in electrophysiology, but also general cardiologists.

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