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ASSOCIATION BETWEEN 4q25 VARIANTS, RISK OF ATRIAL FIBRILLATION AND ECHOCARDIOGRAPHIC PARAMETERS

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Atrial fibrillation (AF), the most common type of arrhythmia, has a heritable component. Variants at locus 4q25 are best associated with the risk of AF development in genome-wide association studies. Left atrial volume is an independent predictor of recurrence of AF after successful sinus rhythm restoration. The aim of our study was to investigate potential association between genetic variants at 4q25 locus and the risk of AF and echocardiographic parameters. We included 241 AF patients and 119 control individuals into the study. Left ventricle ejection fraction (LVEF, %) and left atrial volume index (LAVI, ml/m^2) were assessed by transthoracic echocardiography during outpatient visits. We selected five 4q25 genetic variants (rs6825911, rs1126483, rs10004516, rs6838973, rs2200733) for the analysis. Variant rs6838973 was found to be associated with reduced risk of AF in additive (CCTT) and dominant (CC vs. CT+TT) models of inheritance. On the other hand, additive (CC<CT<TT) and dominant (CC vs. CT+TT) models of rs2200733 were associated with greater risk of AF. The same variations were found to be associated with age of AF onset. Median LAVI was 39.0 ml/m^2 (IQR = 10.0) and median LVEF was 56.0% (IQR = 13.0). Statistically significant association was observed only between LAVI and variant rs1126483 in the dominant model of inheritance (median LAVI in CC vs. CT+TT – 38 ml/m^2 vs. 40 ml/m^2, U *= 1602.5,* p *= 0.032). No significant association was found for LVEF and the analysed genotypes.*

Key words: *arrhythmia, common genetic variants, echocardiography,* PITX2, ENPEP.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, with overall prevalence of 2%, and it has progressively increased worldwide (Chugh Sumeet *et al*., 2014). It is estimated that in 2030 in Europe there will be 14–17 million AF patients (Zoni-Berisso *et al*., 2014). Pathogenesis of AF is related to many cardiac and extracardiac risk factors, such as hypertension, coronary heart disease, thyroid dysfunction, excessive alcohol consumption and many others (Kirchhof *et al*., 2016). Furthermore, specific echocardiographic parameters are associated with increased risk of AF. Among them there are parameters of diastolic dysfunction, dilated left atrium, and left ventricular hypertrophy (O'Neal *et al*., 2017; Lee and Jang, 2018; Morsy *et al*., 2018). During the last decade the association of AF and genetic factors has raised interest. The largest AF GWASs to date identified more than 100 related genetic loci. However, the 4q25 locus was found to be the most significantly associated (Nielsen *et al*., 2018; Roselli *et al*., 2018). Therefore, variants in this locus were selected for analysis in the current study. It is known that the risk of AF occurrence increases with each decade of age above 60 years (Schnabel *et al*., 2015). Previous studies highlighted linkage between genetic factors and time of AF onset (Gudbjartsson *et al*., 2007; Liu *et al*., 2017).

The aim of the study was to investigate association of 4q25 variants with risk of AF, age of onset of AF and association, and with echocardiographic parameters.

MATERIALS AND METHODS

The study included 241 patients with persistent and long-standing persistent AF. All patients were admitted to the Latvian Cardiology Centre, Pauls Stradiņš Clinical Univer-

Table 1. Genetic variants selected for the study

Genetic variants	Localisation	Changes of nucleotides	Consequence	Method of genotyping
rs6825911	*ENPEP* gene intronic variant	C>T	Intron variant, influence on *ENPEP* expression in various tissues (https://gtexportal.org/home/snp/rs6825911)	TaqMan assay C_29321008_10
rs1126483	*ENPEP* gene, exon 2	T>C	Missense	HRM
rs10004516	*ENPEP*, exon 1	A>G	Missense	RFLP – SchI (MlyI)
rs6838973	intergenic	C>T	Change of *PITX2* and *ENPEP* enhancer activity (Aguirre *et al*., 2015; Ye *et al*., 2016)	HRM
rs2200733	intergenic	C>T	Change of *PITX2* and *ENPEP* enhancer activity (Aguirre *et al*., 2015; Ye *et al*., 2016)	HRM

RFLP, Restriction Fragment Length Polymorphism Analysis (primer sequences available upon request); HRM, High-Resolution Melting Analysis (primer sequences available upon request)

sity Hospital, for direct current cardioversion in order to restore sinus rhythm. All participants signed informed consent before enrolment.

Data on transthoratic echocardiohgraphy examination was available for 137 AF patients. Investigation was performed in an outpatient clinic and was carried out according to a standard protocol accepted by the Latvian Society of Cardiology. For the study two echocardiographic parameters (left atrial volume index (LAVI, ml/m^2) and ejection fraction (EF, %)) were used.

The control group included 119 healthy individuals from general practitioner's practice and Internal Disease Department in Madona Hospital. Peripheral blood samples for DNA extraction were obtained from all study participants. DNA was extracted using the commercial kit, innuPREP Blood DNA Mini Kit (Analytik Jena AG, Germany). Five 4q25 genetic variants were selected for the analysis; their description including the genotyping method is given in Table 1. Selection of variants was based on minor allele frequency in Europeans (MAF >10%) from the 1000 Genome Database (http://phase3browser.1000genomes.org) and reports of possible pathogenic implication in AF development (Campione *et al*., 1999; Kathiriya and Srivastava, 2000). Only variants lacking strong linkage disequilibrium between themselves were selected. The results of genotyping for all variants were confirmed by bidirectional automated sequencing (using BigDye Terminator kit v3.1 according to manufacturer guidelines (ThermoFisherScientific, USA) for 5 to 10 randomly selected samples for each variant with different genotypes; in all cases the genotypes were identical.

Statistical analysis was performed in SPSS v.23.0. Continuous variables were expressed in two ways. Normally distributed variables were expressed as mean value ± standard deviation (SD). Non-normally distributed variables were expressed as median and interquartile range in parentheses. The Sharipo-Wilk test and histograms were used to assess normality of continuous variables.

For analysis of association between genetic variants and outcome variables several statistical tests were used. For normally distributed data the independent samples t-test and one-way ANOVA were used. For non-normally distributed data the Mann-Whitney U test and Kruskal-Wallis H tests were applied. The effect on the outcome of minor allele of each variant was assessed in three models of inheritance — additive, dominant, and recessive.

The study was approved by the Latvian Central Medical Ethics Committee (Nr. 1/16-05-09) and was carried out in accordance with the requirements set out in the Declaration of Helsinki.

RESULTS

Basic characteristics of patients are shown in Table 2. Duration of AF varied between 1 month and 5 years with mean duration 44 months. Mean values of included echocardiografic parameters were within normal ranges.

Among the included genetic variants, two were associated with AF (Table 3). Variant rs6838973 was found to be associated with reduced risk of AF in additive (CC<CT<TT) and dominant (CC vs. CT+TT) models of inheritance. In contrast, additive (CC<CT<TT) and dominant (CC vs. CT+TT) models of rs2200733 were associated with greater risk of AF. The same variants were found to be associated with age of AF onset: variant rs6838973 in additive (median age of onset CC vs. CT vs. TT = 59 vs. 62 vs. 62.5 years, Chi square = 6.076, p = 0.048) and dominant models (CC vs. CT+TT = 59 vs. 62 years, U = 4915.5, p = 0.014), and variant rs2200733 in additive (CC vs. CT vs. TT = 62

Table 2. Basic characteristics of the study group

Men, n (%)	151 (62.7)
Age, years	63.94 ± 10.01
Duration of AF, months	43.88 (65.1)
Age of AF onset, years	65.45 (14)
Lone AF, n (%)	21 (8.7)
EDD, mm	52.85 ± 6.9
ESD, mm	35 (10)
LAVI, ml/m^2	39 (10)
EF, %	56 (12)

EDD, end diastolic diameter; ESD, end systolic diameter; LAVI, left atrial volume index; EF, ejection fraction

Table 3. Association of genetic variants and atrial fibrillation

Variation	Model of inheritance	Odds ratio (OR)	95% Confidence interval (CI)	*p* value
rs6825911	Additive	0.672	0.618 – 1.363	0.672
	Dominant	0.876	0.561 – 1.367	0.559
	Recessive	1.246	0.317 – 4.904	0.753
rs1126483	Additive	0.893	0.671 – 1.189	0.440
	Dominant	0.661	0.402 – 1.086	0.102
	Recessive	1.088	0.674 – 1.754	0.730
rs10004516	Additive	0.878	0.586 – 1.315	0.528
	Dominant	0.821	0.517 – 1.305	0.405
	Recessive	1.246	0.317 – 4.904	0.753
rs6838973	Additive	0.694	0.513 – 0.940	**0.018**
	Dominant	0.608	0.375 – 0.987	**0.044**
	Recessive	0.617	0.371 – 1.029	0.064
rs2200733	Additive	1.688	1.136 – 2.510	**0.010**
	Dominant	1.961	1.227 – 3.133	**0.005**
	Recessive	1.517	0.534 – 4.311	0.434

vs. 61 vs. 52.5 years, Chi square = 7.324, $p = 0.026$) and recessive (CC +CT vs. TT = 62 vs. 52.5 years, $U = 895.5$, $p = 0.01$) models.

Regarding association between variants and echocardiographic parameters, a statistically significant association was observed only between LAVI and variant rs1126483 in the dominant model of inheritance (Figs. 1 and 2) (median LAVI in CC vs. CT+TT – 38 ml/m^2 vs. 40 ml/m^2, $U = 1602.5$, $p = 0.032$). No significant association was found for left ventricle EF and the analysed genotypes (not shown).

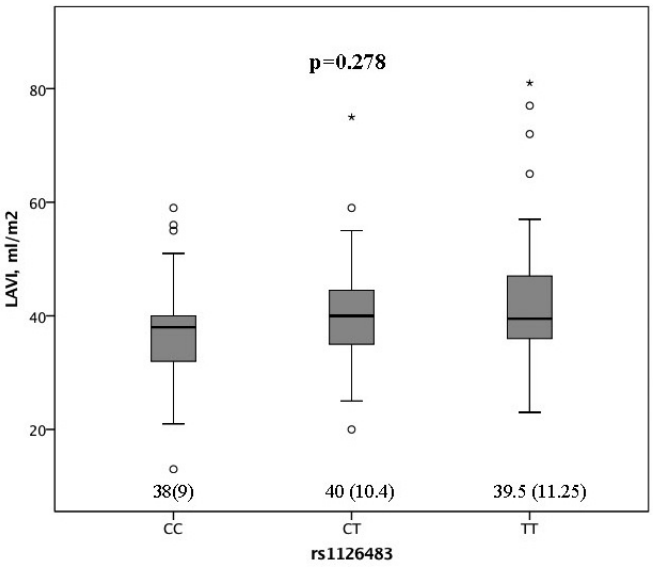

Fig. 1. Association of LAVI and rs1126483 in the additive model of inheritance

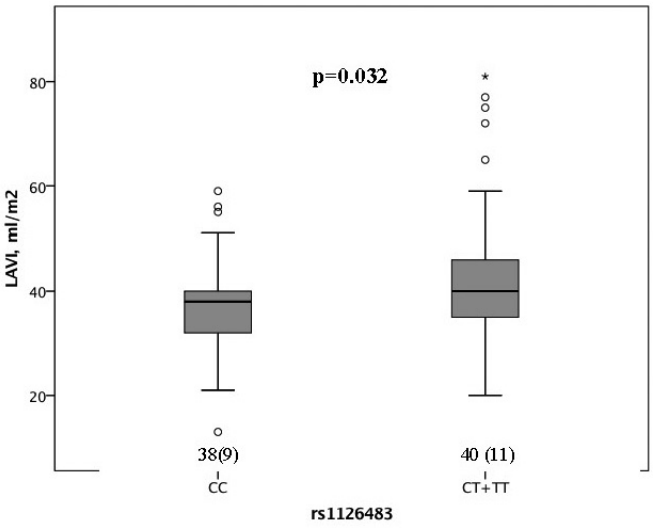

Fig. 2. Association of LAVI and rs1126483 in the dominant model of inheritance

DISCUSSION

Both 4q25 variants showing significant association with AF in our study (rs6838973 and rs2200733) were previously described to be associated with AF in the literature (Lee *et al*., 2010; Kiliszek *et al*., 2011; Ferrán *et al*., 2014). Our data show that these variants are also associated with age of AF onset. Data from the first AF related GWAS revealed a correlation between T allele of rs2200733 and earlier age of onset in the Icelandic population — AF was diagnosed 2.8 years earlier per each T allele (Gudbjartsson *et al*., 2007). To the best of our knowledge, no association between rs6838973 and age of AF onset has been previously described.

GWAS identified multiple AF associated variants at 4q25, which is a non-coding region (Ellinor *et al*., 2012; Lubitz *et al*., 2014). The closest protein encoding gene is *PITX2*, located 150 kb centromeric to 4q25 (Gudbjartsson *et al*., 2007). The next closest gene is *ENPEP* (Aguirre *et al*., 2015). It is hypothesised that variants at 4q25 regulate the function of the proximity genes (Aguirre *et al*., 2015; Ye *et al*., 2016). *PITX2* has an essential role in cardiac morphogenesis, providing asymmetric cardiac development (Campione *et al*., 1999; Kathiriya and Srivastava, 2000), and its expression continues in adult heart (Kahr *et al*., 2011; Kirchhof *et al*., 2011). In an adult mice model it was shown that expression of *Pitx2* decreased with ageing (Wang *et al*., 2010). The postnatal function of *Pitx2* is regulation of genes encoding ion transport proteins, intercalated discs and various transcription factors (Tao *et al*., 2014). However Gore-Panter *et al.* (2014) showed that *PITX2* expression in adult human left atrial appendage is not associated with the genotype located at 4q25, and thus the molecular mechanism of linkage between 4q25 and *PITX2* remains unknown. One of the most significant drivers of AF is the cardiac muscle sleeve around one or more pulmonary veins (Iwasaki *et al*., 2011). An animal experiment revealed that *Pitx2*-deficient mice do not develop a pulmonary myocardium sleeve (Mommersteeg *et al*., 2007). Therefore, we may presume that patients with different AF-related genotypes may have different pulmonary vein morphology. Evidence supporting this hypothesis was provided in a recent study in an AF patients' population, which showed that homozygous carriers

of T allele at rs2200733 had greater diameter of pulmonary veins (Kiliszek *et al*., 2011). Indirect support of this is given by the observation that 4q25 variants, particularly rs2200733, are associated with AF recurrence after successful AF ablation (Husser *et al*., 2010; Chen *et al*., 2016; Shoemaker *et al*., 2013; 2015). Therefore, different morphology of pulmonary veins, mediated by genotype, can lead to earlier AF onset age independently of other risk factors.

Our study showed that the presence of at least one risk allele (T) of variant rs1126483 was associated with greater LAVI in patients with AF. This finding may provide additional explanation and implication of common genetic variants in the pathogenesis of AF.

Left atrial volume is an independent predictor of an incident AF in the whole population and recurrence after successful catheter ablation (Kathiriya and Srivastava, 2000; Lee *et al*., 2010; Olsen *et al*., 2018; Tanabe *et al*., 2007). Interestingly, South Asians have lower prevalence of AF than Caucasians. O'Neill and colleagues showed that this could be due to morphologic characteristics of the heart and a smaller left atrium in particular (O'Neill *et al*., 2018).

However left atrial dilation is also a consequence of AF, as persistence of AF was observed to be associated with both left and right atrial enlargement (Sanfilippo *et al*., 1990). Predictors of greater left atrial dimensions other than AF are age, body mass index, competitive sport, epicardial adipose tissue, habitual alcohol consumption, and chronic kidney failure (Nistri *et al*., 2011; Mancio *et al*., 2018; Plawecki *et al*., 2018; Voskoboinik *et al*., 2018).

Increased atrial diameter and volume are correlated with the degree of atrial fibrosis (Knackstedt *et al*., 2008). Atrial fibrosis plays an important role in pathogenesis of AF. It increases cardiac wavelength and therefore affects re-entry circulation of electrical impulse (Cochet *et al*., 2018; Saha *et al*., 2018). Furthermore, atrial fibrosis affects maintenance of AF and progression of a paroxysmal form to persistent (Morgan *et al*., 2016).

Genetic predisposition of AF is known for more than a decade and ongoing studies reveal new evidence (Gudbjartsson *et al*., 2007; Nielsen *et al*., 2018). Both rare and common genetic variants are associated with AF risk (Feghaly *et al*., 2018). However, the pathogenic mechanism explaining this association is still under investigation and genome-wide association studies are ongoing. Recently, an association was observed between left atrial dimensions and genetic variations. A risk allele of rs10033464, located near *PITX2*, was found to be associated with increased left atrial volume (Feghaly *et al*., 2018). In the present study, association of rs1126483 and LAVI was observed. This variant is located in the *ENPEP* gene, which encodes enzyme glutamylaminopeptidase A (GAPA). Another genetic variant in the *ENPEP* gene was previously described in association with risk of AF (Aguirre *et al*., 2015). GAPA converts angiotensin II into angiotensin III, major components of the renin-angiotensin-aldosterone system (RAAS) (Mizutani *et al*., 2008). Angiotensin III acts as a central blood pressure regulator by interacting with angiotensin I receptors (AT1). This results in increased blood pressure, salt ingestion and drinking behaviour changes and release of arginine vasopressin (Bodineau *et al*., 2008). RAAS is well known as a contributor of cardiac fibrosis. This is primarily due to interaction of angiotensin II with AT1, increase in transforming growth factor-beta 1 (TGF-beta 1) and induction of collagen synthesis by cardiac fibroblasts (Lijnen *et al*., 2000). Although there are no studies showing interaction between angiotensin III and augmentation of fibrosis, the affinity of angiotensin III towards AT1 may also lead to increased production of fibrotic tissue and development of cardiac fibrosis. Thus, a possible linkage of variation in the *ENPEP* gene and greater LAVI could probably be due to atrial fibrosis.

The study has several limitations. The sample size was small and underpowered; therefore, the findings of the study may be false-positive results. The assessment of left atrial dimension by transthoracic echocardiography may not be efficient enough. More sensitive imaging methods, such as cardiac magnetic resonance imaging, should probably be used.

Our results will need to be confirmed in future studies. As well as a possible mechanism for the association of variant rs1126483 and LAVI should be investigated.

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ASOCIĀCIJA STARP 4Q25 VARIANTIEM, ĀTRIJU FIBRILĀCIJAS RISKU UN EHOKARDIOGRĀFISKIEM PARAMETRIEM

Ātriju fibrilācija (ĀF) ir visbiežāk sastopamais aritmiju veids. ĀF ir zināma ģenētiska predispozīcija. Ģenētiskiem variantiem, kas lokalizēti 4q25 lokusā, ir visciešākā saistība ar ĀF attīstības risku. Šī saistība tika aprakstīta vairākos genoma-plašos asociācijas pētījumos. Kreisā priekškambara tilpums ir neatkarīgs prognostiskais faktors ĀF recidīvu attīstībai pēc sinusa ritma atjaunošanas. Pētījuma mērķis bija noskaidrot asociāciju starp 4q25 ģenētiskām variācijām, ĀF risku un ehokardiogrāfiskiem parametriem. Pētījumā tika iekļauts 241 ĀF pacients un 119 kontroles indivīdi. Kreisā kambara izsviedes frakcija (LVEF, %) un kreisā priekškambara tilpuma indekss tika noteikti, veicot transtorakālo ehokardiogrāfiju ambulatori. Saistības analīzei tika izvēlētas piecas 4q25 variācijas (rs6825911, rs1126483, rs10004516, rs6838973, rs2200733). Variants rs6838973 ir asociēts ar zemāku ĀF risku additīvajā (CC<CT<TT) un dominantajā (CC pret CT+TT genotipiem) iedzimšanas modelī. Tāpat arī rs2200733 additīvais un dominantais modelis arī ir statistiski nozīmīgi saistīti ar lielāku ĀF risku. LAVI mediāna ir 39,0 ml/m^2 (IQR = 10,0), bet LVEF — 56,0% (IQR = 13,0). Šīs variācijas ir saistītas arī ar vecumu, kurā pirmreizēji manifestējas ĀF. LAVI mediāna 39,0 ml/m^2 (IQR = 10,0) un EF mediāna 56,0% (IQR = 13,0). Statistiski nozīmīga saistība ir starp LAVI un variācijas rs1126483 dominanto iedzimšanas modeli (LAVI mediāna CCpret CT+TT – attiecīgi 38 ml/m^2 un 40 ml/m^2, U = 1602,5, p = 0,032). Asociāciju starp LVEF un analizētiem genotipiem nenovēro.