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Common and rare genetic
variants in patients with
atrial fibrillation and their
impact on the clinical
course of the disease

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Abbreviations used in the Thesis

AD	Autosomal dominant
AF	Atrial fibrillation
AH	Arterial hypertension
CAD	Coronary artery disease
CIn	Cerebral infarction
CMP	Cardiomyopathy
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiography
ECV	Electrical cardioversion
GWAS	Genome-wide association study
MRI	Magnetic resonance imaging
NGS	Next-generation sequencing
PRS	Polygenic risk score

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adults, and its prevalence continues to rise – over the past fifty years it has increased more than threefold (Schnabel et al., 2015). Furthermore, AF prevalence increases with age: in individuals younger than 59 years it is 0.7%, whereas in those aged 86 years and older it reaches 17.8% (Heeringa et al., 2006). This is attributed both to longer life expectancy and to the increasing prevalence of AF-associated risk factors with advancing age (Staerk et al., 2017).

AF is associated with several complications that can negatively affect a patient's quality of life. One of the most serious is cerebral infarction (CIn). In a patient with AF and no other risk factors, the risk of developing CIn is approximately 2.5%, while AF is identified in 25% of all CIn cases (Christiansen et al., 2016; Marini et al., 2005). Other related complications include heart failure, thromboembolism, dementia, and cognitive impairment (Anter et al., 2009; Ding et al., 2018; Rivard et al., 2022).

Risk factors play an important role in the development of AF, and at least one AF risk factor is present in more than 85% of patients (Kloosterman et al., 2020). Traditional AF risk factors include cardiovascular diseases (coronary artery disease (CAD), valvular pathologies, cardiomyopathies, heart failure, arterial hypertension (AH), and congenital heart defects), extracardiac conditions (diabetes mellitus, chronic kidney disease, thyroid dysfunction (hypo- or hyperthyroidism), chronic pulmonary diseases (bronchial asthma, chronic obstructive pulmonary disease (COPD), sleep apnoea), autoimmune or autoinflammatory diseases, malignancies, and active infections, as well as lifestyle and socio-epidemiological factors (obesity, excessive alcohol consumption, smoking, excessive physical exertion, and sedentary lifestyle) (Hindricks et al., 2021). However, in a subset of AF patients, no known risk factor is identified despite extensive clinical evaluation. This form of AF is sometimes referred to as idiopathic or “lone” atrial fibrillation (Tello-Montoliu et al., 2015). As the accuracy and availability of various diagnostic modalities continue to improve worldwide, the prevalence of idiopathic AF is declining, owing to improved identification of risk factors, including subclinical conditions. This is related to the absence of a universally accepted definition of idiopathic AF and the lack of precise criteria specifying which investigations must be performed in order to conclude that a patient has no AF-associated risk factors and no structural cardiac abnormalities (Hindricks et al., 2021; Wyse et al., 2014). Furthermore, studies on idiopathic AF are not directly comparable, as patient inclusion criteria vary considerably between them (Table 1). Genetic testing is also not listed as one of the mandatory investigations required to confirm a diagnosis of idiopathic AF. In light of all the above, the European Society of Cardiology guidelines do not recommend the use of the term “lone atrial fibrillation” or “idiopathic” AF (Hindricks et al., 2021).

Table 1

Diagnostic Criteria for Idiopathic Atrial Fibrillation Across Different Studies

Age of AF onset	Exclusion criteria	Diagnostic Investigations	Reference
Not defined	The patient has heart disease and thyrotoxicosis	Not defined	(Evans et al., 1954)
< 60 years	Heart failure, hypertension, coronary artery disease, significant valvular pathology, thyroid disease, COPD, hypoxaemia, or other cardiopulmonary diseases, including congenital anomalies	Not defined	(Tran et al., 2013)
Not defined	Any structural heart disease, including CAD, CMP, left ventricular ejection fraction < 45%, etc., hypertension, COPD, recent infection, malignancy, thyroid dysfunction, hepatic or renal failure, CIn or surgery within the last 6 months, trauma or vascular event within the last four weeks, autoimmune disease, use of anti-inflammatory agents, electrolyte imbalance, etc.	Not defined	(Yao et al., 2009)
< 65 years	Cardiovascular, cardiopulmonary, or structural heart disease	Not defined	(Buiatti et al., 2016)
Not defined	Structural heart disease, CAD, hypertension, pulmonary disease, hyperthyroidism, diabetes mellitus, CIn	Medical history, chest X-ray, routine blood biochemistry, echocardiography . CAD excluded based on ECG or stress test results	(Lau et al., 2013)
< 60 years	Hypertension, CAD, left ventricular ejection fraction < 50%, valvular pathology (moderate or severe), hyperthyroidism, obstructive sleep apnoea	Not defined	(Lazarte et al., 2021)

AF – atrial fibrillation, COPD – chronic obstructive pulmonary disease, CAD – coronary artery disease, CMP – cardiomyopathy, CIn – cerebral infarction, ECG – electrocardiography.

The pathogenesis of AF is multifactorial and has not yet been fully elucidated. Studies indicate that fibrosis (Heijman et al., 2016; Li et al., 1999), inflammation (Conen et al., 2010; Rotter et al., 2006), and dysfunction of intercellular connexin gap junction proteins (Jennings et al., 2013; Thibault et al., 2022) play a significant role in the development of the arrhythmia. Pathogenetically, AF can be characterised by the interaction between triggering factors (e.g., ectopic activity at the pulmonary vein ostia in the left atrium) and perpetuating mechanisms, or substrate (e.g., structural cardiac remodelling (Stiles et al., 2009)) (de Groot et al., 2010;

Haïssaguerre et al., 1998). Moreover, in recent years an increasing body of literature has been published on the role of genetic factors in the development of AF. The first data on the association between AF and genetic factors were published in 2003, when Yi-Han Chen and colleagues described a four-generation family with autosomal dominant (AD) inherited AF caused by a loss-of-function variant in the potassium channel-encoding gene *KCNQ1* (Chen et al., 2003). Subsequently, in 2007, data from a genome-wide association study (GWAS) were published, revealing that variants located in the 4q25 region influence the risk of developing AF (Gudbjartsson et al., 2007). Data have also been published showing that in younger AF patients with no identifiable clinical risk factors, genetic testing reveals rare or common genetic variants associated with an increased risk of AF development (Lazarte et al., 2021; Yoneda et al., 2021).

Aim of the Study

To identify genetic risk factors for atrial fibrillation and evaluate their impact on the clinical course of the disease and treatment efficacy.

Objectives of the Study

The following objectives were set to achieve the aim of the dissertation:

- to perform genetic testing of AF patients and control group in Latvia – to determine common variant genotypes (*CAVI* gene rs3807989, *SOX5* rs11047543, *MYH7* rs28631169, *ZFHX3* rs2106261, *KCNN3* rs13376333, *KCNJ5* rs75190942, *PITX2* rs2200733 and rs6828972) and polygenic risk score, and to identify their impact on the risk of AF development;
- to determine the impact of the aforementioned common variant genotypes and polygenic risk score on sinus rhythm maintenance six months following electrical cardioversion;
- to perform genetic variant analysis in genes associated with arrhythmias, cardiomyopathies, and congenital heart defects in young AF patients without risk factors from Latvia and the *UK Biobank*;
- to determine whether young AF patients without risk factors develop structural, morphological, or functional myocardial changes over time.

Hypotheses of the Study

1. Common genetic variants determine the efficacy of rhythm control in AF patients undergoing electrical cardioversion.
2. Young AF patients without risk factors with genetically confirmed AF (monogenic AF) develop morphological myocardial changes or cardiomyopathy.

Novelty of the Study

The study of genetic factors in AF has remained a topic of active research for more than 20 years. Several studies have been published demonstrating an association between the risk of AF development and common genetic variants, with data available both on individual variants and on combinations of multiple variants through polygenic risk scores (PRS) (Choe et al., 2019; Lubitz et al., 2010; O'Sullivan et al., 2022). Furthermore, the role of genetic variants in AF therapy has also been described – results from several studies indicate that the efficacy of catheter ablation is influenced by the patient's genetic profile (Choe et al., 2019; Wong et al., 2020; Chen et al., 2016). Parvez et al. described the efficacy of electrical cardioversion in AF patients in relation to genotype (Parvez et al., 2013); however, to date no data have been published on the association between PRS and the risk of AF recurrence following sinus rhythm restoration by electrical cardioversion (ECV).

As next-generation sequencing (NGS) has advanced and become more widely accessible, new discoveries have emerged in the field of AF genetics – in young patients without clinical risk factors, cardiomyopathy and inherited arrhythmias related rare pathogenic variants are being identified. However, the prevalence of rare variants varies considerably across different study populations (Chalazan et al., 2023; Christophersen et al., 2013; Kandola et al., 2023; Olesen et al., 2014). William R. Goodyer and colleagues, in a small study of 11 young AF patients without risk factors and a proven genetic aetiology, found that 72% of cases demonstrated structural or functional cardiac changes on magnetic resonance imaging (Goodyer et al., 2019). There is a lack of prospective longitudinal data on young AF patients without risk factors, as well as on the dynamics of structural, morphological, and functional changes over time.

This work will help identify the impact of genetic factors on the development of AF and the clinical course of the disease. Furthermore, the study will analyse the association between PRS and the efficacy of ECV which, according to the available literature, has not been investigated to date.

Conclusions

1. The risk allele of the *PITX2* gene variant rs2200733 is statistically significantly associated with the risk of AF development. A PRS > 7 is not statistically significantly associated with the risk of AF development.
2. The risk allele of the *SOX5* gene variant rs11047543 is statistically significantly associated with a lower risk of AF recurrence within six months following ECV, demonstrating a protective effect. In contrast, PRS > 7 is statistically significantly associated with the risk of AF recurrence six months after ECV.
3. Twenty-four percent of young AF patients without risk factors from the Latvian cohort and eight percent from the *UK Biobank* cohort have a molecularly confirmed cause of AF with a proven monogenic form of the disease. All identified rare genetic variants are located in genes associated with cardiomyopathies and congenital heart defects. Two founder variants in the *TTN* gene were identified in the young AF patient group from the Latvian cohort.
4. Seven (54%) patients with monogenic AF demonstrated structural, functional, and morphological cardiac changes on cardiac magnetic resonance imaging (MRI), which developed progressively over time.

Proposals

1. At present, there is no compelling evidence to support the routine use of common genetic variants in AF diagnostics and everyday patient care. Future research should evaluate the impact of individual rare variants and PRS on the efficacy of AF treatment (targeted rhythm control, catheter ablation efficacy). This could potentially allow patients with a genetically predicted low probability of sustained sinus rhythm maintenance to avoid costly procedures and interventions that may carry adverse health consequences (e.g., complications related to catheter ablation or anaesthesia).
2. Molecular genetic testing (sequencing of a cardiac disease-associated gene panel) should be considered in young AF patients in routine clinical practice, in order to identify in a timely manner those at risk of developing cardiomyopathy and to tailor their care accordingly. Particular emphasis should be placed on careful and close patient monitoring in cases where clinically significant variants are identified in genes carrying a very high risk of sudden cardiac death (e.g., *LMNA* and *RBM20*).
3. Given that young AF patients without risk factors develop structural and morphological myocardial changes over time, it is plausible that AF represents an early manifestation of cardiomyopathy rather than a purely electrical cardiac disease. Accordingly, cardiac MRI should be incorporated into routine follow-up in this patient group, with repeated assessment of functional, structural, and morphological cardiac parameters over time, in order to detect the development of cardiomyopathy or chronic heart failure as early as possible.
4. Genetic segregation analysis should be performed in families of young AF patients without risk factors. Clinical screening is recommended for first-degree relatives, including ECG and Holter monitoring to assess cardiac rhythm disturbances, and echocardiography for evaluation of cardiac structure and function. If an asymptomatic relative is found to carry a variant in a gene associated with a high risk of sudden cardiac death (e.g., *LMNA*), cardiac MRI should additionally be performed to assess subclinical morphological myocardial changes. This approach will enable early detection of heritable disease within families and potentially reduce adverse cardiovascular outcomes.
5. Given the wide variation in the prevalence of pathogenic and likely pathogenic rare variants across AF studies, the establishment of an international registry for young AF patients without risk factors is warranted. Unified inclusion criteria and strictly defined risk factors that must be excluded should be adopted. Such data would substantially increase statistical power and enable comparison of disease prevalence and characteristics across different populations, including assessment of the frequency and clinical significance of Latvian founder variants in the broader context of Baltic and Northern European countries.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. **Rudaka, I.**, Vilne, B., Isakova, J., Kalejs, O., Gailite, L., Rots, D. 2023. Genetic Basis of Early Onset Atrial Fibrillation in Patients without Risk Factors. *J Cardiovasc Dev Dis.* 28.02.2023. 10(3):104. doi: 10.3390/jcdd10030104.
2. Vogel, S., **Rudaka, I.**, Rots, D., Isakova, J., Kalējs, O., Viksne, K., Gailite, L. 2021. A Higher Polygenic Risk Score Is Associated with a Higher Recurrence Rate of Atrial Fibrillation in Direct Current Cardioversion-Treated Patients. *Medicina (Kaunas).* 18.11.2021. 18;57(11):1263. doi: 10.3390/medicina57111263.
3. **Rudaka, I.**, Rots, D., Uzars, A., Kalejs, O., Gailite, L. 2020. Association Between 4q25 Variants, Risk of Atrial Fibrillation and Echocardiographic Parameters. Proceedings of the Latvian Academy of Sciences. Section B. *Natural, Exact, and Applied Sciences.*, vol. 74, no. 1, Sciendo, 2020, 1–6. <https://doi.org/10.2478/prolas-2020-0001>.

Reports and theses at international congresses and conferences:

1. **Grike, I.** New Horizons in the Treatment of Hypertrophic Cardiomyopathy. RSU Conference “Knowledge For Use in Practice”. 26–28.03.2025.
2. **Grike, I.** The Role of Genetic Variants Pathogenesis and Clinical Outcomes of Atrial Fibrillation. RSU Conference “Knowledge For Use in Practice”. 26–28.03.2025.
3. **Grike, I.**, Vilne, B., Kalejs, O., Rots, D., Trusinskis, K., Gailite, L. Whole exome sequencing in young atrial fibrillation patients. European Society of Cardiology Cardio Genomics Conference. 6.–7.12.2024.
4. **Rudaka, I.**, Vilne, B., Kalejs, O., Rots, D., Trusinskis, K., Gailite, L. 2024. Whole exome sequencing in young atrial fibrillation patients. European Heart Rhythm Association Congress 2024, 7.–9.04.2024.
5. **Rudaka, I.**, Vilne, B., Isakova, J., Gailite, L., Kalejs, O., Rots, D. Is early onset atrial fibrillation a first manifestation in dilated cardiomyopathy? Evidence from whole exome sequencing. Annual Meeting of ESC Working group on Myocardial and Pericardial Diseases. 7.–8.10.2022.
6. **Rudaka, I.**, Rots, D., Isakova, J., Gailite, L., Kalejs, O. Titin Loss-of-function variants and lone atrial fibrillation: not-a-lone anymore? Congress of the European Cardiac Arrhythmia Society, 5.–7.04.2020, 25.
7. **Rudaka, I.**, Rots, D., Kalejs, O., Gailite, L. Next generation sequencing in lone atrial fibrillation patients. European Heart Rhythm Association Congress 2020, 29.–31.03.2020.
8. **Rudaka, I.**, Rots, D., Kalejs, O., Gailite, L. Prevalence of OBSCN truncating variants in lone atrial fibrillation. American College of Cardiology Congress 2020, 28.–30.03.2020, 451.
9. **Rudaka, I.**, Vasiljevs, A., Rots, D., Kalejs, O., Gailite, L. Interaction of genetic variants and atrial fibrillation risk factors. 16th International Dead Sea Symposium, 24.–26.02.2020, 23.
10. **Rudaka, I.**, Rots, D., Uzars, A., Kalējs, O., Gailite, L. Association between 4q25 variant rs6838973 and atrial fibrillation in the Latvian population. RSU Conference “Knowledge For Use in Practice”. 1.–3.04.2019
11. **Rudaka, I.**, Rots, D., Uzars, A., Kalējs, O., Gailite, L. Rare variants in OBSN gene in lone atrial fibrillation and arrhythmogenic right ventricular cardiomyopathy. Congress of the European Cardiac Arrhythmia Society. 16.–18.06.2019
12. **Rudaka, I.**, Rots, D., Uzars, A., Kalējs, O., Gailite, L. Occurrence of cardiomyopathy-related genetic variants in lone atrial fibrillation patients: a case series. Annual Meeting of ESC Working group on Myocardial and Pericardial Diseases. 03.–05.10.2019

13. **Rudaka, I.,** Rots, D., Uzars, A., Kalējs, O., Audže, I., Gailite, L. PITX2 gēna variāciju asociācija ar kreisā priekškambara tilpuma indeksu pacientiem ar mirdzaritmiju. RSU Zinātniska konference 22.–23.03.2018.
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15. **Rudaka, I.,** Rots, D., Uzars, A., Kalējs, O., Gailite, L. Association of 4q25 variants and echocardiographic parameters in patients with atrial fibrillation. VII Baltic Genetics Congress. 24.–27.10.2018

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