Genetically Based Atrial Fibrillation: Current Considerations for Diagnosis and Management

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January 10, 2022

Abstract

Atrial fibrillation (AF) is the most common atrial arrhythmia and is subcategorized into numerous clinical phenotypes. Given its heterogeneity, investigations into the genetic mechanisms underlying AF have been pursued in recent decades, with predominant analyses focusing on early onset or lone AF. Linkage analyses, genome wide association studies (GWAS), and single gene analyses have led to the identification of rare and common genetic variants associated with AF risk. Significant overlap with genetic variants implicated in dilated cardiomyopathy syndromes, including truncating variants of the sarcomere protein titin, have been identified through these analyses, in addition to other genes associated with cardiac structure and function. Despite this, widespread utilization of genetic testing in AF remains hindered by the unclear impact of genetic risk identification on clinical outcomes and the high prevalence of variants of unknown significance (VUS). However, genetic testing is a reasonable option for patients with early onset AF and in those with significant family history of arrhythmia. While many knowledge gaps remain, emerging data support genotyping to inform selection of AF therapeutics. In this review we highlight the current understanding of the complex genetic basis of AF and explore the overlap of AF with inherited cardiomyopathy syndromes. We propose a set of criteria for clinical genetic testing in AF patients and outline future steps for the integration of genetics into AF care.

INTRODUCTION

Atrial fibrillation (AF) is the most common atrial arrhythmia and confers increased risk of cardiovascular morbidity and mortality. AF carries a significantly increased risk of incident and recurrent ischemic stroke[1,2], myocardial infarction, heart failure[3], and all-cause mortality.[4]In addition, AF directly impacts patient outcomes and quality of life, and, over the past few decades, multiple randomized trials have been aimed at evaluating the effects of various antiarrhythmic drugs (AAD) and procedural interventions to affect these outcomes.[5-10] However, there is significant heterogeneity in the clinical phenotype of, as well as management strategies for, AF.[11-13] Given the rising prevalence[14] of and significant public health burden incurred by AF and its associated heterogeneity, recent work has focused on the genetic underpinnings of AF and its implications on diagnosis and treatment-specific outcomes.[15]

Genetic analysis has largely been focused on the clinical subgroup of 'early onset AF' or 'lone AF,' typically defined as clinically recognized AF in a patient <66 years old and in the absence of structural heart disease.[16] This work has resulted in the identification of multiple genes in familial forms of AF and single nucleotide polymorphisms (SNPs) associated with the development of this clinical sub-phenotype of AF[17,18]; additionally, many of the same genetic loci have been identified as modulators of clinical response to AF therapeutics. Despite these advances, contemporary guidelines do not support the routine use of genetic testing in AF patients.[19] Herein, we describe the current understanding of the association between genetic susceptibility and AF, review challenges related to patient selection for genetic testing, and describe the

outcomes of AAD and catheter interventions for genetically mediated AF. Further, we propose potential next steps in the understanding and integration of genetics into clinical AF care.

GENETIC BASIS OF AF

Linkage Analysis in AF

It is well-documented that AF is a highly heritable[20,21] condition. A study using monozygotic twins revealed a heritability estimate of 62%[22], while population based estimates using common genetic variants in a European cohort indicated 22.1% heritability among patients with AF, irrespective of age at AF onset and sex.[23] Given this, multiple inquiries into the genetic basis of AF have been developed and have focused on a variety of analytic techniques, including gene linkage among families with autosomal dominant AF, genome-wide association studies (GWAS), and single gene variant analyses, which highlight the complex contribution of genetics to AF development (**Figure 1**).[17] Multiple rare single gene gain-of-function (GOF) and loss-of-function (LOF) variants in genes encoding ion channels relevant to the cardiac conduction cycle, transcription factors,[24] and structural proteins, including those involved in the myocardial sarcomere[25-27], have been identified in linkage studies which identify recombination events between genetic markers and trait loci in generally large, multi-generational families. One such gene, *KCNQ1* , encodes a portion of the I_{ks} channel involved in cardiac myocyte repolarization and is associated with long QT syndrome type 1; GOF mutations in this gene have also been associated with early onset AF, a normal correct QT interval, and left ventricular dilation.[28]

AF Genome Wide Association Analysis

Notably, the identification of mutations derived from linkage analyses is relatively uncommon, and most often found in patients with early-onset lone AF (<40-45 years of age at AF onset) and have a relatively small impact on population-level AF.[29,30]To interrogate more common variants that contribute to AF, GWAS studies compare patients with AF and unaffected controls and have identified SNPs that associate with increased risk of AF development. To date, over 100 loci have been identified to have genome-wide significance in AF risk, the majority of which have been studied in large populations of patients predominantly of European ancestry. Large cohort studies have revealed that European ancestry subjects have an increased risk of AF when compared to African, Asian, and Hispanic ancestry subjects, which suggests that these populations have different risk alleles or that the frequency of risk alleles differs significantly between groups.[31-34] The largest multi-ethnic meta-analysis of GWAS for AF to-date had 84% European ancestry and identified 97 loci associated with AF, including 67 that were novel in a combined ancestry analysis and 3 that were European-specific.[29] The region that was most significantly associated with AF across ancestries was 4q25, upstream of the *PITX2* gene. Effect estimates were similar for the top associations, suggesting that genetic susceptibility for AF is relatively constant across ancestries. However, this meta-analysis with more than half a million participants only included 43,000 non-European subjects, with Asian ancestry most represented and Hispanic the least. Asian ancestry-specific GWAS have replicated some of these loci including *PITX2* , *TBX5* (which is associated with fibroblast differentiation)[35] and *ZFHX3* (a zinc finger-encoding gene associated with cellular differentiation located at 16q22), were found to be associated with early onset AF.[36,37] However, in a small Hispanic/Latino cohort, of the 9 AF risk SNPs examined, only *PITX2* replicated, highlighting the complex heterogeneity in AF genetics.[38] There is a pressing need to improve diversity in studies of AF. Many loci are similar across ancestries, but prevalence and outcomes differ suggesting that shared loci may provide general disease mechanisms and unique loci may modify disease based on diverse genetic backgrounds or environmental effects. Efforts are underway to improve diversity in genetic studies including expansion of biobanks in China and Africa. In the US, programs such as the National Heart, Lung, and Blood Institute's TOPMed Program, the Million Veteran Program, and the All of Us Research Program are trying to address these disparities in genetic studies.

Despite this, GWAS analyses have identified multiple genes associated with increased AF risk that are implicated in various aspects of cardiac myocyte function. SNPs located in genes encoding ion channels, including*KCNQ1* [39,40], and the angiotensinogen gene (*AGT*)[411] have been associated with increased risk

of AF. Additionally, the 4q25 locus has consistently been strongly associated with AF risk in all-comers[42], lone AF[43], and new AF after coronary artery bypass surgery.[44] The 4q25 locus is an inter-codon region near the gene for transcription factor *PITX2* . This gene is known to regulate right-left differentiation in embryonic cardiac development.[45] Additionally, *PITX2*overexpression leads to modification of L-type calcium and delayed rectifier potassium current, resulting in increased AF susceptibility through multiple pathways.[46] Presence of multiple alleles in 4q25 is associated with a risk gradient for AF development[47] and has been demonstrated to increase the likelihood of AF development in family members with rare genetic AF-associated variants.[48] This suggests that other identified AF-associated SNPs may modulate AF development in those with rare, AF-associated mutations.

Single Gene Analyses, TTN Cardiomyopathy, and Polygenic Risk

The variety of mutations and SNPs identified in familial AF and by GWAS has led to comparative analyses of single genes and SNPs between AF and controls. In patients with early-onset AF, approximately 10% have an identifiable variant that is associated with either an inherited arrhythmia or cardiomyopathy syndrome, with the odds of carrying a disease-associated variant increasing by 25% per decade at earlier time of AF diagnosis.[49] One such gene that has garnered significant attention is *SCN5A* , which encodes the sodium channel that controls inward sodium current as part of atrial depolarization.[50] *SCN5A* mutations have been described in long QT syndrome type 3, Brugada syndrome[51], familial dilated cardiomyopathy (DCM).[52,53] Mutations in *SCN5A* have been suggested through single gene analyses to be associated with AF development in both lone AF and AF in the context of structural heart disease.[54,55]

Importantly, there is a growing understanding of the overlap between AF and genetic DCM. The most prominent example is that of *TTN*cardiomyopathy. *TTN* encodes the largest human protein, and truncating variants in *TTN* (*TTNtv*) have previously been implicated in 25% of familial cases of DCM[56] and linked to increased risk of ventricular arrhythmias.[57]Patients with *TTN* DCM are known to have high rates of AF[58] and be more likely to develop persistent AF.[57] *TTNtv* also appear to lead to increased risk of AF[59], even when controlling for cardiomyopathy status.[60] In one population of familial AF, *TTNtv* were associated with AF onset at median age of 26, and all variants were in the cardiac isoforms of *TTN* . Of interest, in this analysis, *TTNtv* carriers did not have echocardiographic evidence of left ventricular (LV) structural dysfunction and had normal left atrial (LA) and LV dimensions at time of diagnosis or at follow-up multiple years later.[61] LOF variants in *TTN* are more common among patients with early-onset AF compared to healthy controls[62], with a higher proportion of variants seen in younger patients at time of AF diagnosis.[63]Additionally, when compared to all patients with AF, early-onset AF *TTNtv* carriers are at increased risk of reduction in left ventricular ejection fraction and left atrial late gadolinium enhancement on cardiac magnetic resonance imaging, a marker of atrial fibrosis.[64]

The success of GWAS at identifying SNPs significantly associated with AF sparked interest in using polygenic risk scores (PRS) in the clinic. PRS is calculated by summing over the risk alleles an individual carries, weighted by the effect size derived from a GWAS, and has been established for prediction of AF development.[65] An analysis of the FinnGenn biobank, which utilizes patients in a large Finnish database, showed that the top 2.5% of scorers in an AF PRS system have a predicted 61% lifetime risk of AF.[66]Another PRS in a largely European, United Kingdom population demonstrated that a higher PRS modifies a patient's risk of AF development in addition to the risk that is predicted by traditional AF risk factors (including hypertension, diabetes, obesity, and smoking).[59] This finding was replicated in the Framingham cohort, where clinical risk factors were shown to further modify AF risk within individual PRS subgroups.[67]Finally, a higher PRS is also associated with higher risk of AF in *TTN* LOF variant carriers.[68] However, there are no current models combining SNPs and clinical risk factors to predict long-term outcomes of patients with AF.

CLINICAL TESTING CONSIDERATIONS

Despite the plethora of data supporting genetic risk analysis for the prediction of AF and increasingly available commercial genetic tests, contemporary guidelines do not recommend routine genetic testing for all-comers with AF. The 2014 American Heart Association, American College of Cardiology, and the Heart

Rhythm Society guidelines provide a class IIb recommendation for consideration of genetic testing in patients with AF and multigenerational familial AF.[19]This is clarified in the Heart Rhythm Society and the European Heart Rhythm Association consensus statement by citing a lack of actionable evidence on how genetic analyses, which have largely focused on AF prediction, will impact clinical AF outcomes.[69]

Challenges of Genetic Testing

Genetic testing in all-comers with AF remains challenging for several reasons, in part due to logistic issues with genetic testing, including lack of universal access and high financial cost.[70]Additionally, there are several AF-specific factors that limit universal genetic testing among patients with AF, in addition to lack of clinical outcome data to support its use. Foremost, widespread genetic testing in AF is limited by an unknown prevalence of rare, potentially pathogenic variants in all-comers with AF. In patients with very early-onset lone AF only 15% may carry a recognized pathologic mutation in a panel of genetic mutations, including various ion channel genes, associated with AF development[30]; this finding has been replicated in broader context of all lone-AF patients.[49] These rates are similar in very-early onset AF patients with regards to *TTN*mutations, with a prevalence of 16%.[71] These estimates are much lower when considering genes associated with long-QT syndrome[72] and laminopathies (which are associated with mutations in Lamin A/C, nuclear membrane filaments)[73], which are associated with higher rates of AF.[74,75] Additionally, discovery of carrier status of these genes in family members does not imply 100% penetrance.[17,76]

Widespread genetic testing in AF has the potential to uncover multiple variants of uncertain significance (VUS). Yoneda et al. found that in a cohort of 1,293 early onset AF subjects, 812 (63%) carried a VUS in an inherited cardiomyopathy or arrhythmia syndrome gene.[49] Universal genetic testing would likely lead to a high number of VUS detected, and, currently, there is limited data to adjudicate how these variants affect disease state, which is also a problem for other inherited cardiomyopathy syndromes.[77]Additionally, widespread genetic testing may be limited by the ability of positive AF family history in predicting AF occurrence in unaffected family members and in outcomes for patients with AF. Positive family history of AF confers an approximate 2-fold relative risk of developing AF in unaffected family members.[78] Family history of AF is also more commonly seen in patients with early-onset lone AF.[79] Additionally, a positive family history of AF diagnosed in a first-degree relative at [?]65 years old is associated with an increased risk of atrial arrhythmia recurrence in drug-refractory AF post-ablation.[80] Similarly, patients with a positive family history of AF occurring in a first-degree relative [?]65 years old are more likely to receive a permanent pacemaker or implantable cardioverter-defibrillator (ICD).[81] Taken together, this stresses the importance of gathering a thorough family history in patients that are newly diagnosed with AF.

Recommendations for Genetic Testing

Genetic testing in AF carries multiple potential benefits, including early identification of patients who are at high risk for developing an associated cardiomyopathy and in whom intensified surveillance may be warranted.[82] Based on the current available data, we suggest consideration of genetic testing in selected subsets of the AF population (Figure 2):

1. Patients with lone AF, defined as <66 years of age at time of AF diagnosis and in the absence of structural heart disease
2. Patients without clinical risk factors for AF, such as hypertension, chronic kidney disease, or diabetes
3. Patients with AF and family history of ICD implantation
4. Patients with AF and family history of sudden cardiac death
5. Patients with AF and who have multigenerational family history of AF[83]

CLINICAL MANAGEMENT CONSIDERATIONS

Given the growing repository of causative rare genes and linked SNPs with AF, multiple studies have analyzed the role of specific genetic variants on outcomes by AF management strategy (rate vs rhythm control; AAD trial vs ablation). However, outcomes remain variable by variant analyzed (**Table 1**). Additionally, many published studies on this topic are retrospective, observational studies, and there is a dearth of prospective,

randomized controlled trials to inform the universal utility of genetic testing and to inform AF care. For example, there is a paucity of data for surgical treatment in genetically linked AF. Given lone AF is a well-established clinical phenotype, multiple studies have analyzed post-operative rhythm-free survival after Cox-Maze surgery in this population.[84,85] Among these patients, Cox-Maze is associated with durable freedom from AF without the use of AAD.[86] Although there is a strong genetic association with lone AF, there have been no direct analyses of genetic variants on outcomes in surgical AF management.

In contrast, there are some emerging data for the effect of genetic variation on AF pharmacotherapy response. In acute AF with rapid ventricular response, it is currently recommended to utilize atrioventricular nodal blocking agents for symptomatic and heart rate management.[86] Only one analysis has evaluated the response to intravenous diltiazem in rapid ventricular response in European patients with AF. However, multiple AF susceptibility SNPs combined into a susceptibility score, including those at 4q25, did not appear to alter response to acute rate control methods in an emergency room AF population.[87] In contrast, the Vanderbilt AF Registry identified that the wildtype SNP rs10033464 at 4q25 was associated with a favorable response to anti-arrhythmic drug therapy, compared to matched controls with a variant allele.[88]

More supporting evidence has identified that genetic variability influences outcomes after AF catheter ablation. A variety of SNPs associated with AF susceptibility have been shown to be associated with modulation of response to catheter ablation.[89-93]Additionally, SNPs associated with electrical remodeling in lone AF have also been associated with AF recurrence post ablation,[94] and there is some emerging data concerning the effects of atrial cardiomyopathy[95] and DCM related variants on post-ablation outcomes.[96] By far, SNPs at locus 4q25 have consistently been associated with AF susceptibility, and there are a number of analyses indicating this locus' role in response to AF therapy. The SNP rs2200733, which was one of the first SNPs associated with increased AF susceptibility at 4q25 has been demonstrated to lead to decreased likelihood of arrhythmia-free survival and increased likelihood of AAD therapy post catheter ablation, possibly due to altered left atrial conduction patterns.[97-99]However, other SNPs, including rs10033464 (which is associated with increased left atrial diameter)[100], at this locus have not been consistently associated with AF recurrence post-ablation, including in a predominantly Turkish-based population[101] and in meta-analysis.[102] There is some conflicting data in another European population the rs10033464 SNP was associated with AF recurrence post ablation[103] and in meta-analysis.[100,104] This variability may be explained in part by variation in increased levels of circulating biomarkers of myocardial fibrosis in patients with paroxysmal AF.[105] Of note, there is emerging evidence that other SNPs at 4q25 may increase left atrial scar formation and increase non-pulmonary vein triggers for AF recurrence, which may help inform future risk stratification when selecting patients for catheter ablation.[106] However, prospective analyses of these and other SNPs are still needed.

While most studies in this space rely on observational data, the Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Metoprolol Succinate for Prevention of Symptomatic Atrial Fibrillation/Atrial Flutter (AFL) in Patients with Heart Failure (GENETIC-AF) trial was one of the first trials to interrogate the genotype-outcome relationship. This trial investigated the role of genotype-guided use of bucindolol versus metoprolol succinate in reducing the recurrence of symptomatic AF/AFL events and/or mortality in a population of heart failure with reduced ejection fraction. This trial was founded on the principle that bucindolol is a non-selective beta-blocker with particular efficacy in patients with *ADRB1*Arg389Arg genotype.[107] Patients managed with bucindolol had 55% reduction in AF burden compared to metoprolol and a 32% reduction in necessity of rhythm control strategies for those with recurrent AF/AFL.[108] This trial represents a major advance in the use of genotyping to inform therapy selection in AF/AFL patients and may help inform further trial design surrounding AF outcomes and other genetic variants.

FUTURE DIRECTIONS IN GENETIC AF

As medical care continues to move towards a personalized, precision-based approach, genetic testing and recognition of genetically mediated disease processes will rise to the forefront in medical diagnosis, treatment, and prognosis. This too includes the recognition that a sizable proportion of the AF population manifests a genetically mediated form of AF, and this paradigm is even more true for patients with early onset or lone AF in the absence of structural heart disease. While this paradigm shift is in its relative infancy, research is

emerging that will support enhanced recognition and care of these patients.

At this time, there remains heterogeneity across medical centers as it relates to which patients are referred for genetic testing.[109] The future of this field will rely on the development of risk stratification models for AF based on genetic profile, family history, and patient phenotype information; effective treatment plans based on a patient's genetic profile (including rate control strategy, medical rhythm control and ablation therapy)[110]; and evaluation for long-term progression of disease based on, likely, a combination of genetic and environmental factors.[111] It may bear to reason, as well, that there are subsets of the AF population that may be at differential risk for thromboembolic events and stroke when compared to the AF population at large. While there is emerging data to suggest that AF PRS[112, 113] may predict cardioembolic stroke risk, future prospective studies in this space are needed. Creating a genetic profile using both common and rare variation is becoming increasingly affordable with even whole genome sequence data nearly within reach for many patients. As these costs continue to come down, the medical community must be prepared to utilize these data. While new research programs seek to sequence more diverse cohorts, these data are often completely deidentified with little to no phenotype data. Additional cohorts with phenotype information are needed to provide fine-tuned associations across detailed phenotypes. Medical biobanks that incorporate a subject's complete medical record and genomic profile, provide a fertile space for medical research and require further investment.

Among patients with AF as part of a greater cardiomyopathic process, such as those with *TTN* and Lamin A/C mutations, recognition of an underlying genetic etiology should heighten awareness and screening for ventricular tachyarrhythmias and ventricular dysfunction.[114] These patients are at increased risk of not only AF but also non-sustained ventricular tachycardia and atrioventricular block and would likely benefit from more frequent arrhythmia monitoring.[115] If a genetic cardiomyopathy is suspected, patients should be referred to genetic counseling and, if appropriate, a cardiologist with experience caring for patients with genetically mediated cardiomyopathies. Early recognition is important for future screening in the index patient, as well as for relevant family screening for arrhythmia and LV dysfunction. The growth of our understanding of genetic cardiomyopathies and their interaction with AF presents an exciting new challenge in the care of these patients. As the field continues to learn more about this subset of patients, we anticipate the development of diagnostic and therapeutic plans based in part on a patient's genetic profile.

REFERENCES

1. Marini C, De Santis F, Sacco S, et al. Contribution of Atrial Fibrillation to Incidence and Outcome of Ischemic Stroke: Results from a Population-Based Study. *Stroke* . 2005;36(6):1115-1119.
2. Pistoia F, Sacco S, Tiseo C, et al. The Epidemiology of Atrial Fibrillation and Stroke. *Cardiol Clin* . 2016;34(2):255-268.
3. Dries DL, Exner DV, Gersh BJ, et al. Atrial Fibrillation is Associated with an Increased Risk for Mortality and Heart Failure Progression in Patients with Asymptomatic and Symptomatic Left Ventricular Systolic Dysfunction: A Retrospective Analysis of the SOLVD Trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* . 1998;32(3):695-703.
4. Ruddox V, Sandven I, Munkhaugen J, et al. Atrial Fibrillation and the Risk of Myocardial Infarction, All-Cause Mortality and Heart Failure: A Systematic Review and Meta-Analysis. *Eur J Prev Cardiol* . 2017;24(14):1555-1566.
5. Turagam MK, Garg J, Whang W, et al. Catheter Ablation of Atrial Fibrillation in Patients with Heart Failure: A Meta-Analysis of Randomized Controlled Trials. *Ann Intern Med* . 2019;170(1):41-50.
6. Kuck KH, Furnkranz A, Chun KRJ, et al. Cryoballoon or Radiofrequency Ablation for Symptomatic Paroxysmal Atrial Fibrillation: Reintervention, Rehospitalization, and Quality-of-Life Outcomes in the FIRE AND ICE Trial. *Eur Heart J* . 2016;37(38):2858-2865.
7. Mark DB, Anstrom KJ, Sheng S, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients with Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* . 2019;321(13):1275-1285.
8. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of Catheter Ablation vs Antiarrhyth-

mic Medication on Quality of Life in Patients with Atrial Fibrillation: The CAPTAF Randomized Controlled Trial. *JAMA* . 2019;321(11):1059-1068.

9. Weiner MM, Baron EL, Joshi K, et al. Catheter Versus Surgical Ablation of Atrial Fibrillation: An Analysis of Outcomes. *J Cardiothorac Vasc Anesth* . 2018;32(5):2435-2443.
10. Chen C, Zhou X, Zhu M, et al. Catheter Ablation Versus Medical Therapy for Patients with Persistent Atrial Fibrillation: A Systematic Review and Meta-Analysis of Evidence from Randomized Controlled Trials.*J Interv Card Electrophysiol* . 2018;52(1):9-18.
11. Inohara T, Shrader P, Pieper K, et al. Association of Atrial Fibrillation Clinical Phenotypes with Treatment Patterns and Outcomes: A Multicenter Registry Study. *JAMA Cardiol* . 2018;3(1):54-63.
12. Margulescu AD, Mont L. Persistent Atrial Fibrillation vs Paroxysmal Atrial Fibrillation: Differences in Management. *Expert Rev Cardiovasc Ther* . 2017;15(8):601-618.
13. Darrat YH, Shah J, Elayi C-S, et al. Regional Lack of Consistency in the Management of Atrial Fibrillation (from the RECORD-AF Trial).*Am J Cardiol* . 2017;119(1):47-51.
14. Schnabel RB, Yin X, Gona P, et al. 50 Year Trends in Atrial Fibrillation Prevalence, Incidence, Risk Factors, and Mortality in the Framingham Heart Study: A Cohort Study. *Lancet* . 2015;386(9989):154-162.
15. Campbell HM, Wehrens XHT. Genetics of Atrial Fibrillation: An Update.*Curr Opin Cardiol* . 2018;33(3):304-310.
16. Chalazon B, Mol D, Darbar FA, et al. Association of Rare Genetic Variants and Early-Onset Atrial Fibrillation in Ethnic Minority Individuals. *JAMA Cardiol* . 2021;6(7):811-819.
17. Roselli C, Rienstra M, Ellinor PT. Genetics of Atrial Fibrillation in 2020: GWAS, Genome Sequencing, Polygenic Risk, and Beyond. *Circ Res.* 2020;127(1):21-33.
18. Fatkin D, Santiago CF, Huttner IG, et al. Genetics of Atrial Fibrillation: State of the Art in 2017. *Heart Lung Circ* . 2017;26(9):894-901.
19. January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.*Circulation* . 2014;130(23):e199-e267.
20. Darbar D, Herron KJ, Ballew JD, et al. Familial Atrial Fibrillation is a Genetically Heterogeneous Disorder. *J Am Coll Cardiol* . 2003;41(12):2185-2192.
21. Fox CS, Parise H, D'Agostino RB, et al. Parental Atrial Fibrillation as a Risk Factor for Atrial Fibrillation in Offspring. *JAMA* . 2004;291(23):2851-2855.
22. Christophersen IE, Ravn LS, Budtz-Joergensen E, et al. Familial Aggregation of Atrial Fibrillation: A Study in Danish Twins.*Circ Arrhythm Electrophysiol* . 2009;2(4):378-383.
23. Weng LC, Choi SH, Klarin D, et al. Heritability of Atrial Fibrillation. *Circ Cardiovasc Genet* . 2017;10(6):e001838.
24. Postma AV, van der Meerakker JBA, Mathijssen IB, et al. A Gain-of-Function TBX5 Mutation is Associated with Atypical Holt-Oram Syndrome and Paroxysmal Atrial Fibrillation. *Circ Res.*2008;102(11):1433-1442.
25. Gudbjartsson DF, Holm H, Sulem P, et al. A Frameshift Deletion in the Sarcomere Gene MYL4 Causes Early-Onset Familial Atrial Fibrillation.*Eur Heart J* . 2017;38(1):27-34.
26. Li RG, Xu YJ, Ye WG, et al. Connexin45 (GJC1) Loss-of-Function Mutation Contributes to Familial Atrial Fibrillation and Conduction Disease. *Heart Rhythm* . 2021;18(5):684-693.
27. Orr N, Arnaout R, Gula LJ, et al. A Mutation in the Atrial-Specific Myosin Light Chain Gene (MYL4) Causes Familial Atrial Fibrillation.*Nat Commun* . 2016;7:11303.
28. Das S, Makino S, Melman YF, et al. A Mutation in the S3 Segment of KCNQ1 Results in Familial Lone Atrial Fibrillation. *Heart Rhythm* . 2009;6(8):1146-1153.
29. Roselli C, Chaffin MD, Weng LC, et al. Multi-Ethnic Genome-Wide Association Study for Atrial Fibrillation. *Nat Genet* . 2018;50(9):1225-1233.
30. Olesen MS, Andreasen L, Jabbari J, et a. Very Early-Onset Lone Atrial Fibrillation Patients Have a High Prevalence of Rare Variants in Genes Previously Associated with Atrial Fibrillation. *Heart Rhythm* . 2014;11(2):246-251.

31. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident Atrial Fibrillation Among Asians, Hispanics, Blacks, and Whites.*Circulation* . 2013;128(23):2470-2477.
32. Magnani JW, Norby FL, Agarwal SK, et al. Racial Differences in Atrial Fibrillation-Related Cardiovascular Disease and Mortality: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Cardiol* . 2016;1(4):433-441.
33. Marcus GM, Olgin JE, Whooley M, et al. Racial Differences in Atrial Fibrillation Prevalence and Left Atrial Size. *Am J Med* . 2010;123(4):e1-7.
34. Nielsen JB, Thorolfsdottir RB, Fritsche LG, et al. Biobank-Driven Genomic Discovery Yields New Insight into Atrial Fibrillation Biology.*Nat Genet* . 2018;50(9):1234-1239.
35. Song K, Nam YJ, Luo X, et al. Heart Repair by Reprogramming Non-Myocytes with Cardiac Transcription Factors. *Nature* . 2012;485(7400):599-604.
36. Lee JY, Kim TH, Yang PS, et al. Korean Atrial Fibrillation Network Genome-Wide Association Study for Early-Onset Atrial Fibrillation Identifies Novel Susceptibility Loci. *Eur Heart J* . 2017;38(34):2586-2594.
37. Low SK, Takahaski A, Ebana Y, et al. Identification of Six New Genetic Loci Associated with Atrial Fibrillation in the Japanese Population.*Nat Genet* . 2017;49(6):953-958.
38. Chalazan B, Mol D, Sridhar A, et al. Genetic Modulation of Atrial Fibrillation Risk in Hispanic/Latino Cohort. *PLoS One* . 2018;13(4):e0194480.
39. Christophersen IE, Rienstra M, Roselli C, et al. Large-Scale Analyses of Common and Rare Variants Identify 12 New Loci Associated with Atrial Fibrillation. *Nat Genet* . 2017;49(6):946-952.
40. Chu HM, Feng MJ, Li YG, et al. Polymorphisms but Not Mutations of the KCNQ1 Gene Are Associated with Lone Atrial Fibrillation in the Chinese Han Population. *ScientificWorldJournal* . 2013;373454.
41. Wang H, Teng Y, Wang K, et al. The M235T Polymorphism in the Angiotensinogen Gene and Atrial Fibrillation: A Meta-Analysis. *J Renin Angiotensin Aldosterone Syst* . 2015;16(3):647-652.
42. Ebana Y, Ozaki K, Liu L, et al. Clinical Utility and Functional Analysis of Variants in Atrial Fibrillation-Associated Locus 4q25.*J Cardiol* . 2017;70(4):366-373.
43. Olesen MS, Holst AG, Jabbari J, et al. Genetic Loci on Chromosomes 4q25, 7p31, and 12p12 Are Associated with Lone Atrial Fibrillation Before the Age of 40 Years. *Can J Cardiol* . 2012;28(2):191-195.
44. Body SC, Collard CD, Sherman SK, et al. Variation in the 4q25 Chromosomal Locus Predicts Atrial Fibrillation After Coronary Artery Bypass Graft Surgery. *Circ Cardiovasc Genet* . 2009;2(5):499-506.
45. Ryan AK, Blumberg B, Rodriguez-Esteban C, et al. PITX2 Determines Left-Right Asymmetry of Internal Organs in Vertebrates. *Nature* . 1998;394(6693):545-551.
46. Bai J, Lu Y, Lo A, et al. PITX2 Upregulation Increases the Risk of Chronic Atrial Fibrillation in a Dose-Dependent Manner By ModulatingI_{Ks} and I_{CaL} - Insights from Human Atrial Modelling. *Ann Transl Med* . 2020;8(5):191.
47. Lubitz SA, Lunetta KL, Lin H, et al. Novel Genetic Markers Associate with Atrial Fibrillation Risk in Europeans and Japanese. *J Am Coll Cardiol* . 2014;63(12):1200-1210.
48. Ritchie MD, Rowan S, Kucera G, et al. Chromosome 4q25 Variants Are Genetic Modifiers of Rare Ion Channel Mutations Associated with Familial Atrial Fibrillation. *J Am Coll Cardiol* . 2012;60(13):1173-1181.
49. Yoneda ZT, Anderson KC, Quintana JA, et al. Early-Onset Atrial Fibrillation and the Prevalence of Rare Variants in Cardiomyopathy and Arrhythmia Genes. *JAMA Cardiol* . 2021;6(12):1371-1379.
50. Savio-Galimberti E, Darbar D. Atrial Fibrillation and *SCN5A*Variants. *Card Electrophysiol Clin* . 2014;6(4):741-748.
51. Wilde AAM, Amin AS. Clinical Spectrum of SCN5A Mutations: Long QT Syndrome, Brugada Syndrome, and Cardiomyopathy. *JACC Clin Electrophysiol* . 2018;4(5):569-579.
52. McNair WP, Ku L, Taylor MRG, et al. *SCN5A* Mutation Associated with Dilated Cardiomyopathy, Conduction Disorder, and Arrhythmia.*Circulation* . 2004;110(15):2163-2167.
53. Olson TM, Michels VV, Ballew JD, et al. Sodium Channel Mutations and Susceptibility to Heart

Failure and Atrial Fibrillation. *JAMA* . 2005;293(4):447-454.
54. Darbar D, Kannankeril PJ, Donahue BS, et al. Cardiac Sodium Channel (*SCN5A*) Variants Associated with Atrial Fibrillation.*Circulation* . 2008;117(15):1927-1935.
55. Ilkhanoff L, Arking DE, Lemaitre RN, et al. A Common SCN5A Variant is Associated with PR Interval and Atrial Fibrillation Among African Americans. *J Cardiovasc Electrophysiol* . 2014;25(11):1150-1157.
56. Herman DS, Lam L, Taylor MRG, et al. Truncations of Titin Causing Dilated Cardiomyopathy. *N Engl J Med* . 2012;366(7):619-628.
57. Corden B, Jarman J, Whiffin N, et al. Association of Titin-Truncating Genetic Variants with Life-Threatening Cardiac Arrhythmias in Patients with Dilated Cardiomyopathy and Implanted Defibrillators. *JAMA Netw Open* . 2019;2(6):e196520.
58. Akhtar MM, Lorenzini M, Cicerchia M, et al. Clinical Phenotypes and Prognosis of Dilated Cardiomyopathy Caused by Truncating Variants in the *TTN* Gene. *Circ Heart Fail* . 2020;13(10):e006832.
59. Huang K, Trinder M, Roston TM, et al. The Interplay Between Titin, Polygenic Risk, and Modifiable Cardiovascular Risk Factors in Atrial Fibrillation. *Can J Cardiol* . 2021;37(6):848-856.
60. Haggerty CM, Damrauer SM, Levin MG, et al. Genomics-First Evaluation of Heart Disease Associated with Titin-Truncating Variants.*Circulation* . 2019;140(1):42-54.
61. Ahlberg G, Refsgaard L, Lundegaard PR, et al. Rare Truncating Variants in the Sarcomeric Protein Titin Associate with Familial and Early-Onset Atrial Fibrillation. *Nat Commun* . 2018;9(1):4316.
62. Lazarte J, Laksman ZW, Wang J, et al. Enrichment of Loss-of-Function and Copy Number Variants in Ventricular Cardiomyopathy Genes in 'Lone' Atrial Fibrillation. *Europace* . 2021;23(6):844-850.
63. Choi SH, Weng LC, Roselli C, et al. Association Between Titin Loss-of-Function Variants and Early-Onset Atrial Fibrillation.*JAMA* . 2018;320(22):2354-2364.
64. Andreasen L, Bertelsen L, Ghouse J, et al. Early-Onset Atrial Fibrillation Patients Show Reduced Left Ventricular Ejection Fraction and Increased Atrial Fibrosis. *Sci Rep* . 2020;10:10039.
65. Khera AV, Chaffin M, Aragam KG, et al. Genome-Wide Polygenic Risk Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations. *Nat Genet* . 2018;50:1219-1224.
66. Mars N, Koskela JT, Ripatti P, et al. Polygenic and Clinical Risk Scores and Their Impact on Age at Onset and Prediction of Cardiometabolic Diseases and Common Cancers. *Nat Med* . 2020;26:549-557.
67. Weng LC, Preis SR, Hulme OL, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation.*Circulation* . 2018;137(10):1027-1038.
68. Choi SH, Jurgens SJ, Weng LC, et al. Monogenic and Polygenic Contributions to Atrial Fibrillation Risk: Results from a National Biobank. *Circ Res.* 2020;126(2):200-209.
69. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies. *Heart Rhythm* . 2011;8(8):1308-1339.
70. Ingles J, Macciocca I, Morales A, Thomson K. Genetic Testing in Inherited Heart Diseases. *Heart Lung Circ* . 2020;29(4):505-511.
71. Goodyear WR, Dunn K, Caleshu C, et al. Broad Genetic Testing in a Clinical Setting Uncovers a High Prevalence of Titin Loss-of-Function Variants in Very Early Onset Atrial Fibrillation. *Circ Genom Precis Med* . 2019;12(11):e002713.
72. Olesen MS, Yuan L, Liang B, et al. High Prevalence of Long QT Syndrome-Associated *SCN5A* Variants in Patients with Early-Onset Lone Atrial Fibrillation. *Circ Cardiovasc Genet* . 2012;5(4):450-459.
73. Brauch KM, Chen LY, Olson TM. Comprehensive Mutation Scanning of*LMNA* in 268 Patients with Lone Atrial Fibrillation. *Am J Cardiol* . 2009;103(10):1426-1428.
74. Taylor MRG, Fain PR, Sinagra G, et al. Natural History of Dilated Cardiomyopathy Due to Lamin A/C Gene Mutations. *J Am Coll Caridol* . 2003;41(5):771-780.
75. Yeung C, Enriquez A, Suarez-Fuster L, Baranchuk A. Atrial Fibrillation in Patients with Inherited Cardiomyopathies. *Europace* . 2019;21(1):22-32.
76. Olesen MS, Nielsen MW, Haunsø S, Svendsen JH. Atrial Fibrillation: The Role of Common and Rare Genetic Variants. *Eur J Hum Genet* . 2014;22(3):297-306.
77. Hershberger RE, Givertz MM, Ho CY, et al. Genetic Evaluation of Cardiomyopathy - A Heart Failure

Society of America Practice Guideline. *J Card Fail* . 2018;24(5):281-302.
78. Chang SH, Kuo CF, Chou IJ, et al. Association of a Family History of Atrial Fibrillation with Incidence and Outcomes of Atrial Fibrillation: A Population-Based Family Cohort Study. *JAMA Cardiol* . 2017;2(8):863-867.
79. Alzahrani Z, Ornelas-Loredo A, Darbar SD, et al. Association Between Family History and Early-Onset Atrial Fibrillation Across Racial and Ethnic Groups. *JAMA Netw Open* . 2018;1(5):e182497.
80. Wu Z, Jiang C, Li J, et al. Effect of Family History of Atrial Fibrillation on Recurrence After Atrial Fibrillation Ablation: A Report from the Chinese Atrial Fibrillation Registry Study. *J Cardiovasc Electrophysiol* . 2021;32(3):678-685.
81. Heidarali M, Bakhshandeh H, Fazelifar A, Haghjoo M. Clinical Profile and Outcome of Familial Versus Non-Familial Atrial Fibrillation.*Int J Cardiol* . 2020;314:70-74.
82. Girolami F, Frisso G, Benelli M, et al. Contemporary Genetic Testing in Inherited Cardiac Disease: Tools, Ethical Issues, and Clinical Applications. *J Cardiovasc Med* . 2018;19(1):1-11.
83. Wilson BD, Wasmund SL, Sachse FB, et al. Evidence for a Heritable Contribution to Atrial Fibrillation Associated with Fibrosis.*JACC Clin Electrophysiol* . 2019;5(4):493-500.
84. Jessurun ER, van Hemel NM, Defauw JA, et al. Results of Maze Surgery for Lone Paroxysmal Atrial Fibrillation. *Circulation* . 2000;101(13):1559-1567.
85. Weimar T, Schena S, Bailey MS, et al. The Cox-Maze Procedure for Lone Atrial Fibrillation: A Single-Center Experience Over 2 Decades.*Circ Arrhythm Electrophysiol* . 2012;5(1):8-14.
86. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* . 2021;42(5):373-498.
87. Barrett TW, Self WH, Darbar D, et al. Association of Atrial Fibrillation Risk Alleles and Response to Acute Rate Control Therapy.*Am J Emerg Med* . 2016;34(4):735-740.
88. Parvez B, Vaglio J, Rowan S, et al. Symptomatic Response to Antiarrhythmic Drug Therapy is Modulated by a Common Single Nucleotide Polymorphism in Atrial Fibrillation. *J Am Coll Cardiol* . 2012;60(6):539-545.
89. Wu G, Cheng M, Huang H, et al. A Variant of IL6R is Associated with the Recurrence of Atrial Fibrillation After Catheter Ablation in a Chinese Han Population. *PLoS One* . 2014;9(6):e99623.
90. Cao H, Xu W, Chen X, et al. Functional Promoter -1816C>G Variant of RANKL Predicts Risk and Prognosis of Lone Atrial Fibrillation. *Heart Vessels* . 2019;34(1):151-158.
91. Choi EK, Park JH, Lee JY, et al. Korean Atrial Fibrillation (AF) Network: Genetic Variants for AF Do Not Predict Ablation Success.*J Am Heart Assoc.* 2015;4(8):e002046.
92. Park JK, Lee JY, Yang PS, et al. Good Responders to Catheter Ablation for Long-Standing Persistent Atrial Fibrillation: Clinical and Genetic Characteristics. *J Cardiol* . 2017;69(3):584-590.
93. Wu H, Xu J, Chen S, et al. Association of *SCN10A* Polymorphisms with the Recurrence of Atrial Fibrillation After Catheter Ablation in a Chinese Han Population. *Sci Rep* . 2017;7:44003.
94. Ueberham L, Bollmann A, Shoemaker MB, et al. Genetic ACE I/D Polymorphism and Recurrence of Atrial Fibrillation After Catheter Ablation. *Circ Arrhythm Electrophysiol.* 2013;6(4):732-737.
95. Zhong Y, Tang K, Li H, et al. Rs4968309 in Myosin Light Chain 4 (MYL4) Associated with Atrial Fibrillation Onset and Predicts Clinical Outcomes After Catheter Ablation in Atrial Fibrillation Patients Without Structural Heart Disease. *Circ J.*2019;83(10):1994-2001.
96. Rahm AK, Lugenbiel P, Ochs M, et al. Pulmonary Vein Isolation Treats Symptomatic AF in a Patient with Lamin A/C Mutation: Case Report and Review of the Literature. *Clin Res Cardiol* . 2020;109(8):1070-1075.
97. Wong GR, Nalliah CJ, Lee G, et al. Genetic Susceptibility to Atrial Fibrillation is Associated with Atrial Electrical Remodeling and Adverse Post-Ablation Outcome. *JACC Clin Electrophysiol* . 2020;6(12):1509-1521.
98. Shoemaker MB, Muhammad R, Parvez B, et al. Common Atrial Fibrillation Risk Alleles at 4q25 Predict

Recurrence After Catheter-Based Atrial Fibrillation Ablation. *Heart Rhythm* . 2013;10(3):394-400.
99. Zhao LQ, Zhang GB, Wen ZJ, et al. Common Variants Predict Recurrence After Nonfamilial Atrial Fibrillation Ablation in Chinese Han Population. *Int J Cardiol* . 2017;227:360-366.
100. Hu Z, Zou D. Genotype-Phenotype Associations in Atrial Fibrillation: A Meta-Analysis. *J Interv Card Electrophysiol* . 2019;54(3):283-288.
101. Ulus T, Dural M, Mese P, et al. Genetic Variants Associated with Atrial Fibrillation and Long-Term Recurrence After Catheter Ablation for Atrial Fibrillation in Turkish Patients. *Anatol J Cardiol* . 2021;25(2):129-138.
102. Shoemaker MB, Bollmann A, Lubitz SA, et al. Common Genetic Variants and Response to Atrial Fibrillation Ablation. *Circ Arrhythm Electrophysiol* . 2015;8(2):296-302.
103. Husser D, Adams V, Piorkowski C, et al. Chromosome 4q25 and Atrial Fibrillation Recurrence After Catheter Ablation. *J Am Coll Cardiol* . 2010;55(8):747-753.
104. He J, Zhu W, Yu Y, et al. Variant rs2200733 and rs10033464 on Chromosome 4q25 Are Associated with Increased Risk of Atrial Fibrillation After Catheter Ablation: Evidence from a Meta-Analysis.*Cardiol J* . 2018;25(5):628-638.
105. Choi JI, Baek YS, Roh SY, et al. Chromosome 4q25 Variants and Biomarkers of Myocardial Fibrosis in Patients with Atrial Fibrillation. *J Cardiovasc Electrophysiol* . 2019;30(10):1904-1913.
106. Mohanty S, Hall AW, Mohanty P, et al. Novel Association of Polymorphic Genetic Variants with Predictors of Outcome of Catheter Ablation in Atrial Fibrillation: New Directions from a Prospective Study (DECAF).*J Interv Card Electrophysiol* . 2016;45(1):7-17.
107. Piccini JP, Connolly SJ, Abraham WT, et al. A Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Metoprolol Succinate for Prevention of Symptomatic Atrial Fibrillation/Atrial Flutter in Patients with Heart Failure: Rationale and Design of the GENETIC-AF Trial. *Am Heart J* . 2018;199:51-58.
108. Piccini JP, Dufton C, Carroll IA, et al. Bucindolol Decreases Atrial Fibrillation Burden in Patients with Heart Failure and the*ADRB1* Arg389Arg Genotype. *Circ Arrhythm Electrophysiol* . 2021;14(8):e009591.
109. Pison L, Hocini M, Potpara TS, et al. Work-Up and Management of Lone Atrial Fibrillation: Results of the European Heart Rhythm Association Survey. *Europace* . 2014;16(10):1521-1523.
110. Kirchhof P, Breithardt G, Bax J, et al. A Roadmap to Improve the Quality of Atrial Fibrillation Management: Proceedings from the Fifth Atrial Fibrillation Network/European Heart Rhythm Association Consensus Conference. *Europace* . 2016;18(1):37-50.
111. Hall JL, Barac A, Benjamin EJ. Genetic Mutations as Risk Predictors of Atrial Fibrillation Recurrence After Catheter Ablation? *J Am Coll Cardiol* . 2010;55(8):754-757.
112. Lubitz SA, Parsons OE, Anderson CD, et al. Atrial Fibrillation Genetic Risk and Ischemic Stroke Mechanisms. *Stroke* . 2017;48(6):1451-1456.
113. Pulit SL, Weng LC, McArdle PF, et al. Atrial Fibrillation Genetic Risk Differentiates Cardioembolic Stroke from Other Stroke Subtypes.*Neurol Genet* . 2018;4(6):e293.
114. Kumar S, Baldinger SH, Gandjbakhch E, et al. Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers. *J Am Coll Cardiol* . 2016;68(21):2299-2307.
115. Verdonschot JAJ, Hazebroek MR, Karpels IPC, et al. Implications of Genetic Testing in Dilated Cardiomyopathy. *Circ Genom Precis Med* . 2020;13(5):476-487.

Table 1: Summary of evidence of influence of genetics on outcomes in AF catheter ablation

Citation	Variant in Gene/Locus	Study Population	Outcome Analyzed	Result
Wu G, et al.[89]	*IL6R*	AAD-refractory AF, Chinese population	Early (within 1 month) and late (within 1 year) recurrence after catheter ablation	Early: OR 1.84 (95% CI 1.31-2.59, p=4.10x10^{-4}) Late: OR 1.92 (95% CI 1.30-2.81, p=0.001)

Citation	Variant in Gene/Locus	Study Population	Outcome Analyzed	Result
Cao H, et al.[90]	*RANKL*	Lone AF, Chinese population	Recurrence after first-time catheter ablation	HR 1.62 (95% CI 1.37-1.96, p<0.001) for CG/CC vs GG genotype
Wu H, et al.[93]	*SCN10A*	AAD-refractory AF, Chinese population	Recurrence after RFCA	OR 0.36 (95% CI 0.22-0.60, p=7.04x10^{-5}) for rs6795970; other 14 SNPs not significant
Choi EK, et al.[91]	4q25, 16q22, 1q21	AF without structural heart disease or prior ablation, Korean population	Recurrence after RFCA	No significant associations
Park JK, et al.[92]	4q25, 16q22, 1q21	Long-standing persistent AF, Korean population	Recurrence after RFCA	OR 2.70 (95% CI 1.41-5.14, p=0.003) for rs2106216 of *ZFHX3*; other SNPs not significant
Wong GR, et al.[97]	4q25 rs2200733	AF without structural heart disease, Predominantly European cohort	Recurrence after RFCA	HR 0.35 (95% 0.17-0.73, p=0.005) for arrhythmia-free survival in variant carriers
Shoemaker MB, et al.[98]	4q25 rs2200733, rs10033464	AF without prior surgical ablation, Vanderbilt AF Registry	Any atrial arrhythmia after catheter ablation	Survival time ratio 0.76 (95% CI 0.60-0.95, p=0.016) for rs2200733
Husser D, et al.[103]	4q25 rs2200733, rs10033464	Persistent or AAD-refractory AF, Caucasian population	Early (within 1 week of ablation) and late AF recurrence (within 6 months) after catheter ablation	Early OR 2.08 (95% CI 1.09-3.99, p=0.027) Late OR 2.88 (95% CI 1.25-6.63, p=0.013) rs2200733 also significant
Zhao LQ, et al.[99]	8 SNPs in 4q25, 16q22 and NAAP, KCNJ5, and IL6R genes	Non-lone AF, Chinese population	Any atrial arrhythmia >3 months after catheter ablation	HR 1.77 (95% CI 1.06-2.94, p=0.028) for homozygous rs2200733

Citation	Variant in Gene/Locus	Study Population	Outcome Analyzed	Result
Ulus T, et al.[101]	11 SNPs in *PITX2, ZFHX3, EPHX2, CAV1, TBX5, TGF-1, and SCN10A*	AF without severe structural heart disease, Turkish population	Any atrial arrhythmia after cryoballoon ablation	OR 4.50 (95% CI 1.04-19.31, p=0.043) for rs3807989_G in *CAV1*

***Abbreviations:** AF, atrial fibrillation; AAD, antiarrhythmic drug; OR, odds ratio; CI, confidence interval; RFCA, radiofrequency catheter ablation; SNP, single nucleotide polymorphism

Figure 1: Summary list of select single genes and SNPs implicated in genetic AF

Legend: Orange: select single genes (including ion channel genes) associated with AF in familial and single gene analyses; Green: select loci associated with AF in GWAS; Blue: cardiomyopathy genes associated with AF risk in multiple study designs. Of note, each gene may be identified by multiple different genetic analysis types.

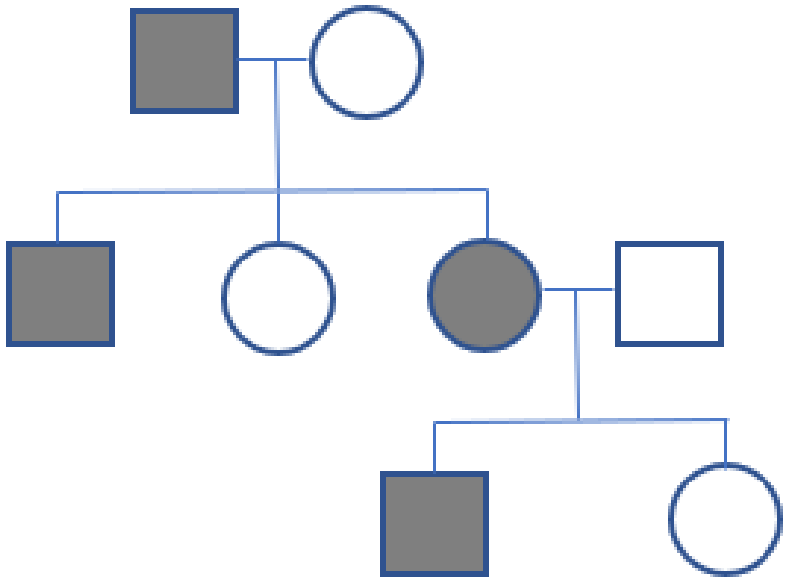

Figure 2: Suggested algorithm for genetic testing in AF

Legend: Stepwise approach to diagnosis and management of genetic AF. In addition to traditional one-time or ambulatory electrocardiogram and transthoracic echocardiogram, patients with newly diagnosed AF should have a detailed family history of AF (including time of onset), sudden cardiac death, and ICD taken. Patients with significant personal or family history should undergo genetic testing, and, if positive, be referred for further counseling by a cardiologist specializing in genetics.