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Molecular and Genomic Mechanisms Underlying the Pathophysiology of Atrial Fibrillation

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Abstract:

- ***Background:***

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and a major cause of cardiovascular morbidity and mortality. Despite major therapeutic advances, the molecular determinants of AF initiation and persistence remain incompletely defined.

- ***Methods:***

Current genomic and functional evidence were synthesised from large-scale genome-wide association studies (GWAS), transcriptomic, proteomic, and epigenomic investigations. Key molecular pathways implicated in calcium handling, fibrosis, and transcriptional regulation were reviewed with reference to translational models.

- ***Results:***

Over one hundred AF-associated loci have been identified, most located within non-coding regulatory regions. The 4q25 locus near PITX2 shows the strongest and most reproducible association. Variants at this site influence calcium-handling proteins (SERCA2, RyR2) and modulate atrial electrophysiology. Integrative multi-omic analyses reveal disturbed Wnt, Notch, and BMP signalling, enhanced atrial fibrosis, and altered metabolic gene expression. Polygenic risk scores improve AF prediction beyond traditional risk factors.

- ***Conclusions:***

AF results from the interaction of genetic predisposition and environmental stressors that converge on shared molecular pathways controlling calcium flux, structural remodelling, and inflammation. Translational integration of genomic and physiological data offers a pathway towards precision-based prevention and therapy.

Keywords: *Atrial fibrillation; Genomics; PITX2; Calcium Signalling; Polygenic Risk; Fibrosis; Precision Cardiology.*

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I. INTRODUCTION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by chaotic atrial electrical activity and irregular ventricular responses. On the surface electrocardiogram, AF manifests as fibrillatory waves replacing discrete P-waves, together with variable RR intervals, indicating loss of coordinated atrial contraction [1]. Prevalence rises steeply with age, affecting 1–2 % of adults and nearly 8 % of those aged ≥ 80 years [2]. The global burden continues to grow owing to demographic ageing and the increasing prevalence of hypertension, diabetes, and obesity [3].

AF carries significant clinical consequences, including a five-fold higher risk of stroke, a three-fold risk of heart failure, and substantial healthcare costs [4]. Its management integrates stroke prevention through anticoagulation, rate or rhythm control with pharmacological or ablative strategies, and modification of reversible risk factors [5].

- *Pathophysiological Overview*

AF develops when electrical triggers interact with a vulnerable atrial substrate. Ectopic foci, particularly within the pulmonary veins, initiate arrhythmia through abnormal automaticity or triggered activity. Maintenance requires a permissive substrate of slowed conduction, shortened refractoriness, and structural heterogeneity. Chronic atrial stretch, inflammation, and fibrosis accentuate conduction anisotropy and promote multiple re-entrant wavelets [6].

- *Genetic Predisposition*

Familial clustering of AF indicates a heritable component; heritability estimates range from 20 % to 60 %. Rare, high-impact mutations have been identified in genes encoding ion-channel subunits (*KCNQ1*, *SCN5A*, *NPPA*) and

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connexins, whereas common low-penetrance variants have been mapped through GWAS [7–9]. To date, more than one hundred independent loci have been associated with AF, implicating genes involved in cardiac development, electrophysiology, and structural maintenance. The locus on chromosome 4q25 adjacent to *PITX2* remains the most robust finding [10].

➢ *Molecular Basis*

The *PITX2* transcription factor directs left–right cardiac asymmetry and modulates atrial ion-channel expression. Reduced *PITX2* expression alters calcium-handling dynamics and increases vulnerability to delayed after-depolarisations [11]. Understanding how *PITX2* and other regulatory elements interact with environmental influences—such as hypertension, oxidative stress, and ageing—is central to explaining AF heterogeneity.

➢ *Purpose of the Present Study*

This paper synthesises current genomic and molecular insights into AF pathophysiology, with emphasis on how non-coding genetic variation, transcriptional regulation, and cellular signalling converge to produce arrhythmogenic substrates. Evidence from GWAS, functional models, and integrative omic analyses is reviewed to outline a translational framework linking genotype to phenotype.

➢ *Molecular Pathophysiology of Atrial Fibrillation*

AF originates from a dynamic interplay between electrical triggers, mechanical stress, and a structurally remodelled atrial substrate. The arrhythmia is therefore both an electrical and a structural disease.

➢ *Trigger–Substrate Interactions*

The pulmonary veins are the principal source of ectopic firing. Myocardial sleeves extending into these veins possess distinctive electrophysiological properties that favour spontaneous depolarisation. Adrenergic and vagal fluctuations further shorten atrial refractoriness, permitting the initiation of re-entry. On a cellular level, abnormal calcium cycling within the sarcoplasmic reticulum—through increased ryanodine receptor (RyR2) leak or impaired sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2) re-uptake—creates delayed after-depolarisations which trigger ectopic beats.

Atrial fibrosis disrupts cell-to-cell conduction by separating myocardial bundles with collagen and altering connexin expression. The resultant conduction heterogeneity sustains multiple re-entrant wavelets, perpetuating AF. These electrophysiological and structural changes collectively constitute the arrhythmogenic substrate [12].

II. GENOMIC INSIGHTS

➢ *Genome-Wide Association Studies*

Genome-wide association studies (GWAS) have revealed over one hundred loci associated with AF risk, with most variants residing in non-coding regions that regulate gene expression rather than alter protein sequence. Integrative analyses consistently implicate calcium handling, cardiac development, and fibrotic pathways as central themes [13].

➢ *The 4q25 PITX2 Locus*

The 4q25 region adjacent to *PITX2* remains the most significant and reproducible GWAS signal. *PITX2* encodes a paired-like homeodomain transcription factor critical for left–right cardiac patterning and atrial morphogenesis. Risk alleles such as rs2200733 (T) and rs13143308 (T) increase AF susceptibility by modulating enhancer activity and *PITX2* expression. Reduced *PITX2* activity alters expression of ion-channel genes and calcium-handling proteins, enhancing RyR2 phosphorylation and SR calcium leak [14–16]. Functional studies demonstrate that this translates to heightened calcium spark frequency and spontaneous action potentials within atrial cardiomyocytes.

➢ *Additional AF-Associated Loci*

Other validated loci include *ZFHX3* (16q22), *KCNN3* (1q21), *PRRX1* (1q24), *CAV1* (9q22), and *HCN4* (15q24). These genes encode regulators of ion-channel transcription, small-conductance calcium-activated potassium channels, and pacemaker current components, underscoring the multifaceted molecular basis of AF [17–19].

Table 1 Selected Loci Associated with Atrial Fibrillation.

Chromosome / Gene	Lead Variant	Risk Allele	p-Value
4q25 (*PITX2*)	rs2200733	T	3×10^{-41}
16q22 (*ZFHX3*)	rs2106261	T	2×10^{-16}
1q21 (*KCNN3*)	rs13376333	T	1×10^{-9}
1q24 (*PRRX1*)	rs3903239	C	2×10^{-12}
15q24 (*HCN4*)	rs7164883	C	4×10^{-9}
9q22 (*CAV1*)	rs3807989	A	6×10^{-12}

➢ *Pathway-Level Integration*

Multi-omic integration has connected these genomic findings to perturbed cellular pathways. Variants affecting *PITX2*, *KCNN3*, and *ZFHX3* converge on dysregulated calcium flux, Wnt/Notch signalling, and transcriptional control of ion-channel genes [20]. Enhanced NFAT and calcineurin activation promotes electrical remodelling, while profibrotic cascades driven by TGF-β and connective-tissue growth factor (CTGF) remodel the atrial matrix. Together, these molecular derangements explain the coexistence of conduction abnormalities and fibrosis that typify AF.

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III. RISK FACTORS AND PREDICTION

➢ *Clinical and Environmental Determinants*

AF develops through the convergence of genetic predisposition and acquired stressors. Advancing age is the most powerful non-genetic determinant, reflecting progressive atrial fibrosis, oxidative stress, and ion-channel remodelling. Hypertension, coronary artery disease, obesity, diabetes, and obstructive sleep apnoea contribute to atrial stretch and inflammatory activation [21]. Lifestyle factors—alcohol excess, sedentary behaviour, and high endurance exercise—can modulate autonomic tone and structural remodelling. Men exhibit higher incidence, whereas women face greater thrombo-embolic risk once AF develops [22]. Ethnic disparities reflect both sociobiological and genetic variation in allele frequencies at key loci such as *PITX2* and *KCNN3* [23].

➢ *Polygenic Risk Prediction*

The advent of GWAS has enabled construction of polygenic risk scores (PRS) summarising the cumulative effect of thousands of common variants. In large cohorts, PRS improve discrimination beyond clinical variables such as CHA_2DS_2-VASc or BMI. Individuals in the top decile of PRS carry a two- to three-fold greater lifetime risk of AF than those in the lowest decile [24]. However, predictive accuracy diminishes when PRS trained in European populations are applied to non-European ancestries, emphasising the need for cross-ancestry calibration [25].

Table 2 Representative Studies Assessing Polygenic Risk Scores for Atrial Fibrillation.

Study	Cohort	Method	Main Finding	Clinical Implication
Ayoub 2022	UK Biobank	6.7 M SNP PRS	Improved early prediction	Supports proactive monitoring
Kullo 2022	Multi-ethnic	Cross-ancestry PRS	Enhanced generalisability	Reduces ancestry bias
Ahn 2025	< 60 yrs AF	PRS + clinical	Predicts HF risk	Guides prevention
Choi 2021	East Asian	Ethnicity-specific PRS	Detects silent AF	Tailored screening

Integration of PRS with electronic health records and wearable-device monitoring could permit population-level screening and targeted intervention. Ethical frameworks are required to ensure equitable implementation and data protection [26].

IV. COMPLICATIONS OF ATRIAL FIBRILLATION

➢ *Stroke and Thrombo-Embolism*

AF increases the risk of ischaemic stroke five-fold. Loss of atrial contraction causes stasis in the left atrial appendage, promoting thrombus formation and subsequent cerebral embolism. Anticoagulation with vitamin-K antagonists or direct oral anticoagulants reduces stroke by two-thirds, but balancing efficacy against bleeding risk remains crucial. Risk stratification using CHA_2DS_2-VASc and HAS-BLED scores informs treatment decisions [27].

➢ *Heart Failure*

Rapid and irregular ventricular rates in AF precipitate tachycardia-induced cardiomyopathy. Impaired diastolic filling reduces stroke volume and elevates filling pressures, leading to pulmonary congestion and reduced cardiac output. Rate control or restoration of sinus rhythm can reverse left-ventricular dysfunction in many cases [28]. AF also worsens pre-existing heart failure through neurohormonal activation and structural remodelling [29].

➢ *Chronic Kidney Disease*

AF and chronic kidney disease (CKD) share risk factors including hypertension, diabetes, and vascular ageing. AF reduces renal perfusion, promotes micro-infarction, and triggers renin–angiotensin–aldosterone activation, accelerating CKD progression. Conversely, CKD predisposes to AF through electrolyte imbalance and myocardial fibrosis. Observational studies report a two-fold increased risk of incident CKD among AF patients [30].

➢ *Cognitive Decline and Dementia*

AF is associated with cognitive impairment independent of overt stroke. Mechanisms include micro-embolism, cerebral hypoperfusion, and systemic inflammation. Chronic irregularity of cardiac output leads to white-matter injury and neurodegeneration. Early anticoagulation and optimal vascular-risk management may mitigate this effect [31].

V. GENOMIC AND MOLECULAR MECHANISMS

➢ *The Role of PITX2 and the 4q25 Locus*

The transcription factor *PITX2* occupies a central position in the molecular pathophysiology of AF. It regulates left–right cardiac patterning and maintains the electrical and structural identity of the left atrium. Reduced *PITX2* expression, whether from genetic variants or epigenetic silencing, disrupts ion-channel transcription, alters connexin distribution, and impairs conduction [32].

Variants such as rs13143308T at 4q25 are associated with enhanced sarcoplasmic reticulum calcium release via increased phosphorylation of *RyR2* and upregulation of *SERCA2*. This leads to spontaneous calcium sparks, delayed after-depolarisations, and ectopic activity. Chromatin-looping studies show that these variants alter enhancer–promoter interactions controlling *PITX2* expression [33, 34].

➢ *Other Gene Loci and Mechanistic Insights*

Variants in *KCNN3* influence small-conductance calcium-activated potassium (SK) channels, modulating repolarisation. *ZFHX3* encodes a zinc-finger homeobox protein that interacts with STAT3 to regulate atrial remodelling. *CAV1* modulates caveolae-mediated signalling and calcium-channel localisation, whereas *HCN4* variants perturb pacemaker current (I_f), influencing sinus-node activity. Collectively, these findings show that AF

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susceptibility arises from perturbations in developmental, electrical, and structural pathways [35, 36].

VI. FUNCTIONAL INTERPRETATION AND MODEL ORGANISMS

➢ *Induced Pluripotent Stem Cell Models*

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) provide a human-specific platform for investigating variant function. Cells carrying *KCNN3* or *PITX2* risk alleles display shortened action-potential duration, increased calcium transient amplitude, and altered gene-expression profiles consistent with clinical AF phenotypes [37]. These models enable testing of antiarrhythmic compounds and facilitate genotype-specific therapeutic screening.

➢ *Animal Models*

Conditional knockout of *PITX2* in mice recapitulates AF features, including ectopic atrial activity, fibrosis, and slowed conduction. Chronic atrial tachypacing in canine models induces electrical and structural remodelling similar to persistent AF, providing a translational bridge between molecular findings and clinical arrhythmogenesis [38].

Table 3 Representative Models Used for AF Mechanistic Investigation.

Model	Phenotype	Advantages	Limitations
Mouse *PITX2* KO	Ectopy, fibrosis	Genetic precision	Species differences
hiPSC-CM	Ca^{2+} handling defects	Human genotype	Immature cells
Canine tachypacing	Electrical remodelling	Physiological relevance	High cost
Computational	Wave propagation	Controlled testing	Simplified tissue

➢ *Computational Modelling*

Mathematical models simulate how ion-channel kinetics, fibrosis density, or conduction velocity contribute to arrhythmia maintenance. Integrating patient-derived data allows personalised prediction of ablation outcomes and drug effects [39]. Machine-learning frameworks combining ECG, imaging, and genomic data have begun to predict AF recurrence with notable accuracy [40].

VII. PROTEOMIC, TRANSCRIPTOMIC, AND EPIGENOMIC INTEGRATION

➢ *Transcriptomic Changes*

High-throughput sequencing demonstrates widespread dysregulation of genes involved in calcium handling, oxidative stress, and extracellular-matrix turnover. Single-cell analyses reveal upregulation of *BMP10* and other developmental regulators in *PITX2*-deficient atrial cardiomyocytes [41]. Differential expression of inflammatory mediators and collagen-synthesis genes reflects ongoing structural remodelling.

➢ *Proteomic Profiles*

Proteomic analysis of atrial tissue highlights enrichment of inflammatory and fibrotic proteins—particularly matrix metalloproteinases (MMP2, MMP9), collagens, and complement components. Altered energy metabolism is evident, with reduced oxidative-phosphorylation proteins and increased glycolytic enzymes [42]. These findings point to a metabolic shift accompanying electrical and structural remodelling.

➢ *Epigenomic Mechanisms*

Epigenetic modifications—DNA methylation, histone acetylation, and non-coding RNA regulation—link environmental stress to sustained molecular change. ATAC-seq profiling demonstrates enhanced chromatin accessibility at promoters of fibrotic and inflammatory genes and repression of oxidative-metabolism loci [43]. MicroRNAs such as miR-21 and miR-150 correlate with fibrosis and electrical remodelling and show potential as circulating biomarkers [44].

Epigenetic therapies, including HDAC inhibitors and targeted miRNA modulation, offer promising future interventions but require careful evaluation of specificity and safety [45].

VIII. CONCLUSION

Atrial fibrillation is a multifactorial arrhythmia that reflects a convergence of genetic predisposition, environmental stressors, and complex molecular interactions within the atrial myocardium. Insights from genome-wide association and multi-omic studies have identified *PITX2* and its regulatory network as central to the pathogenesis of AF, linking developmental biology with adult cardiac electrophysiology. Variants affecting calcium handling, ion-channel expression, and fibrotic pathways combine to create the electrical and structural substrates required for arrhythmia initiation and maintenance.

Emerging tools—including polygenic risk scoring, induced pluripotent stem-cell models, and integrative computational analyses—are redefining AF as a disorder that can be predicted, prevented, and potentially corrected through precision medicine. Translating these molecular discoveries into clinical benefit will depend on equitable implementation of genomic screening, development of targeted modulators of calcium and transcriptional pathways, and continued refinement of rhythm-control strategies.

Ultimately, integration of genomics with electrophysiological and clinical data promises a future in which AF management moves from reactive treatment to proactive prevention based on each patient's molecular profile.

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