

# Application of Integrated Chromatin Accessibility and Transcriptome Analysis in Atrial Fibrillation Research

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## Abstract

Atrial fibrillation (AF) is a common persistent arrhythmia that affects approximately 33 million people worldwide. The incidence of AF increases sharply with age. Its pathogenesis is extremely complex and mainly involves the interaction between cardiac electrophysiology and structural remodeling, inflammation, fibrosis, and metabolic disorders. Genome-Wide Association Studies (GWAS) have uncovered plenty of risk loci linked to atrial fibrillation; among these loci, PITX2, TBX5, ZFHX3 and PRRX1 represent some of the most well-studied genes. These genes take part in atrial tissue development, myocardial electrical conduction and gene transcriptional regulation. However, most genetic variants do not sit within coding sequences, and researchers still cannot figure out their exact biological functions. As multi-omics research keeps moving forward, increasing experimental evidence suggests that factors influencing AF-related genes mainly fall into two categories: one is inherited genetic variants, and the other covers altered chromatin structure and abnormal gene expression. Epigenetic regulatory patterns include DNA methylation, histone modification, chromatin remodeling and non-coding RNAs; these mechanisms can adjust gene expression without changing the original DNA base sequences. Chromatin accessibility analysis allows researchers to spot activated promoter and enhancer regions, and transcriptome analysis can measure how high or low gene expression levels are. When researchers combine ATAC-seq with RNA-seq, they can build connections between chromatin regulatory regions and gene transcription, so as to screen candidate regulatory segments, transcription factor networks and interactive relationships of genes related to atrial fibrillation. This combined research approach has been adopted in cardiovascular epigenetics experiments, and it helps researchers further interpret how non-coding variants work, as well as sort out internal regulatory networks

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of atrial fibrillation. Results from multiple integrated analyses show that AF-related risk variants mostly lie within cardiac-specific open chromatin regions; after researchers delete one single regulatory segment on the *Tbx5* locus, gene dosage will get altered, and animals will gain higher susceptibility to arrhythmia. Single-cell multi-omics technologies further expand research scope in this field, and they enable researchers to investigate unique regulatory programs inside different cell types, such as cardiomyocytes, fibroblasts, endothelial cells and immune cells. This review sums up practical applications of combined chromatin-accessibility and transcriptome analysis in AF research; it describes disease-related regulatory segments, candidate genes, genetic risk loci, cell-specific functional mechanisms and potential therapeutic targets. Meanwhile, it lists existing research obstacles, including obvious sample heterogeneity, insufficient causal verification and the lack of unified analytical workflows. This paper also discusses future research directions, and technologies like single-cell multi-omics, spatial omics and artificial intelligence may push forward the development of precision medicine for atrial fibrillation.

## Keywords

Atrial Fibrillation, RNA Sequencing, Multi-Omics Analysis

## 1. Introduction

Atrial fibrillation, or AF for short, is a common persistent arrhythmia, and more than 33 million people across the world suffer from this disease; advancing age can greatly raise people's risk of developing AF. AF patients often have typical symptoms such as palpitations, chest tightness and reduced exercise tolerance, and these patients also face higher risks of ischemic stroke, heart failure and cardiovascular-related death [1]. As research on atrial fibrillation continues to progress, catheter ablation, anticoagulation therapies and anti-arrhythmic drugs have achieved great improvements; still, pathological mechanisms of AF are complicated and vary greatly among individuals, and many patients obtain poor treatment effects or experience AF recurrence after clinical intervention. Researchers have not fully clarified the complete pathogenesis of atrial fibrillation, and it is relatively difficult to carry out studies about how genetic variants regulate gene expression. It is of great practical significance to fill this research gap; if relevant studies make major breakthroughs, clinicians can obtain new biomarkers and discover new therapeutic targets for diseases. Traditional research models can hardly explain the complex genetic features behind atrial fibrillation. The onset and continuous progression of AF are affected by many different factors; these factors include atrial electrophysiological remodeling driven by ion channel dysfunction and action potential changes, as well as atrial structural remodeling, tissue fibrosis, massive extracellular-matrix deposition, activated inflammatory responses and disturbed body metabolism. Genome-Wide Association Studies (GWAS) have identified many AF risk loci, including *PITX2*, *TBX5*, *ZFHX3* and *PRRX1*; these

genes participate in atrial development, myocardial signal conduction and transcriptional regulation. Yet most known risk loci are located in non-coding regions, and these sites may affect gene expression by acting on enhancers and promoters [2]. Epigenetic mechanisms such as DNA methylation, histone modification, chromatin remodeling and non-coding RNAs can regulate gene expression without changing DNA sequences, and they further get involved in the occurrence of atrial fibrillation. High-throughput sequencing technologies drive the development of cardiovascular epigenetics; ATAC-seq uses Tn5 transposase to draw genome-wide open-chromatin maps, and this technology can locate promoters, enhancers and transcription-factor-binding sites [3]. RNA-seq is able to detect transcriptome-wide expression changes, and it provides experimental evidence for researchers to analyze disease-related signaling pathways [4]. When researchers use these two sequencing technologies together, they can correlate the open status of regulatory regions with gene expression levels, and they can better reconstruct transcription-factor networks and sort out disease-relevant signaling pathways.

Such multi-omics approaches are being adopted with increasing frequency in complex diseases, and for AF research they supply a regulatory framework. For example, integrated analyses have demonstrated that AF risk variants are enriched in cardiac-specific open chromatin; deleting a single regulatory region at *Tbx5*, for instance, can shift gene dosage and modify arrhythmia susceptibility [5] [6].

This review covers its application in AF research: disease-related regulatory regions, candidate genes, genetic risk loci, cell type-specific mechanisms, and therapeutic targets. It also discusses challenges (sample heterogeneity, data integration, causality) and prospects (single-cell multi-omics, spatial omics, AI) for AF precision medicine. For our literature search, we queried PubMed, Web of Science, and Google Scholar for studies published between January 2015 and September 2026, using the terms: (“atrial fibrillation” OR “AF”) AND (“chromatin accessibility” OR “ATAC-seq” OR “scATAC-seq”) AND (“transcriptome” OR “RNA-seq” OR “scRNA-seq”) AND (“multi-omics” OR “integrative analysis”). Studies were included if they 1) used human or animal atrial tissue, 2) combined chromatin accessibility with transcriptome data, and 3) reported AF-related regulatory mechanisms or targets. Studies using only single-omics or non-cardiac tissues were excluded. We categorized the included studies into paired multi-omics (same nuclei/samples) and independent dataset integration.

## **2. Technical Basis of Integrated Chromatin Accessibility and Transcriptome Analysis**

In eukaryotic cells, DNA is not naked but packaged into chromatin, winding around histone octamers to form nucleosomes. Two principal states are recognized: open euchromatin and closed heterochromatin. The open state tends to be enriched in promoters, enhancers, insulators, and other regulatory elements, which allows transcription factors to bind and activate genes [7]. Shifts between these states lie at the heart of gene expression regulation. In AF, atrial tissue re-

sponds to electrical, mechanical, and inflammatory stress by remodeling its chromatin, a process that alters transcriptional networks and implies that accessibility changes help govern disease-related genes. ATAC-seq takes advantage of a hyperactive Tn5 transposase, which fragments DNA and inserts sequencing adapters into open chromatin at the same time. Because stable nucleosome structures do not exist inside open chromatin areas, the Tn5 enzyme tends to insert itself into these accessible genome segments; once researchers finish the sequencing work, they carry out peak-calling steps to mark out these open genome segments, and scientists can later assign annotations to these marked areas as promoters, enhancers or binding locations for transcription factors [8]. ATAC-seq shows higher detection sensitivity, needs smaller amounts of starting sample material, and follows a more straightforward operating pipeline, if people make comparisons against DNase-seq and FAIRE-seq; many research projects have adopted this technique to find regulatory segments unique to cardiomyocytes, and researchers can also use genetic datasets to build links between non-coding sequence changes and their actual biological roles [9]. Even so, results generated from ATAC-seq only reflect possible regulatory capacity, and this method cannot give direct descriptions for real-world gene expression status, so research teams have to bring in transcription-related datasets, to judge whether one given open genome segment can really change the activity of its downstream target genes. On the other hand, RNA-seq lets investigators track expression shifts over the full set of transcript sequences; researchers can pick out differentially expressed genes (DEGs) by comparing transcript profiles collected under varied experimental settings, and enrichment tests alongside pathway analysis help workers figure out the related biological processes. For atrial-fibrillation-related research, RNA-seq is capable of spotting abnormal signals linked with inflammatory responses, extracellular matrix reconstruction, energy turnover and the contraction performance of heart muscle cells [10] [11]. Higher gene expression values may come from activated enhancer regions, strengthened attachment of transcription factor molecules or other epigenetic control patterns; researchers cannot get direct explanations for upstream controlling factors, if they only make use of RNA-seq outputs, thus transcriptome data on its own is not enough for people to work out complete regulatory networks for complicated illnesses. When researchers use ATAC-seq alongside RNA-seq, they can merge information about how open regulatory segments are together with gene expression records, and this practice builds up connections among regulatory DNA fragments, transcription factor molecules and their corresponding target genes. A genome segment is likely to serve as an active regulatory fragment, when this region gains higher accessibility meanwhile its neighboring genes show elevated expression levels; investigators can further locate disease-promoting molecular networks, once they add motif forecasting, enhancer labeling and risk-site examination into their analytical workflow. This combined analytical plan using ATAC-seq and RNA-seq can therefore not only discover differentially expressed genes (DEGs), it can also show researchers which regulatory DNA regions have

gone through alterations, which transcription factors exert control over these regions, and how these factors alter the expression of illness-relevant genes, allowing people to clarify epigenetic working mechanisms behind atrial fibrillation.

### **3. Application Progress of Integrated Chromatin Accessibility and Transcriptome Analysis in Atrial Fibrillation Research**

#### **3.1. Functional Mechanisms of Non-Coding Variants and Regulatory Networks**

Researchers have found numerous gene positions raising AF disease risk through GWAS work, yet most of these sequence changes sit within non-coding DNA parts whose actual biological roles still remain unclear; non-coding DNA segments hold promoter and enhancer elements, so these sequence changes are able to modify gene output by adjusting chromatin open status or interfering with transcription-related control processes. ATAC-seq technology can locate those open DNA segments with regulatory effects, and when research workers pair this tool with RNA-seq datasets, the combined approach helps build connections between gene variants, functional DNA fragments and their downstream target genes. van Ouwerkerk and his research group collected separately-produced human atrial ATAC-seq datasets, genetic information and enhancer prediction outputs for their analysis; instead of making use of matched multi-omics data obtained from identical specimen materials, they used these resources to mark out AF-relevant risk zones, and their work uncovered several risk gene positions falling inside heart-related open regulatory chromatin [5]. Such experimental observations tell us that AF-related gene variants gather within open chromatin which is specific to heart tissue, and this enrichment situation can be seen most obviously inside cardiomyocytes, with these variant sites sitting close to genes that manage heart growth and heartbeat rhythm control. Bosada and co-workers built mice carrying Tbx5 gene mutations, and they removed certain regulatory DNA segments connected with AF in these experimental animals; this operation brought about moderate rise of Tbx5 gene activity, triggered the expression of genes for tissue growth and ion transportation, extended the action potential recorded from atrial cells, and made these mice more likely to develop rhythm disorders, these results imply that non-coding DNA fragments can affect AF disease risk by acting on transcription factors sensitive to gene dosage levels [12]. When people look closely at this Tbx5-focused mouse experiment, the collected data show that the removal of just one single AF-linked regulatory segment is enough to shift Tbx5 expression amounts, this event will rewrite cellular genetic programs and raise the animals' tendency to suffer arrhythmia episodes; this research work further highlights how important one individual non-coding DNA fragment can be for biological functions. Still, research workers have to keep inter-species differences in mind, when they try to extend these mouse-derived results to human AF cases; such differences cover atrial electrical properties as well as whole sets of gene-

controlling networks between various species. Taken together, all these published studies offer a usable analytical framework, and this framework can connect risk positions discovered from GWAS screening to candidate AF-related genes together with their possible regulatory mechanisms.

### 3.2. Enhancer Regulatory Networks and Candidate Gene Screening

Enhancer elements control gene activity in a tissue-restricted manner, and shifts in enhancer functional status will match the variation levels of chromatin open conditions; for AF illness, mechanical force, inflammatory signals and fibrosis-related triggers are able to modify enhancer performance, and these modifications will further bring about changed gene expression patterns. Researchers can draw full-genome chromatin profiles by applying the ATAC-seq approach, and they may guess possible regulatory molecules from sequencing outputs; when investigators pair this tool with RNA-seq datasets, they are allowed to build linked molecular networks covering enhancer segments, transcription factor proteins and their corresponding target genes. Multiple molecular networks will go wrong during AF-related transcription disturbance, these networks cover heart muscle electrical behaviors, extracellular matrix reorganization, inflammatory reactions and metabolic biochemical events. For atrial fibrotic conditions, unusual chromatin activation may drive modified gene activity inside fibroblasts, and inflammation-associated molecular networks can also push this fibrotic process forward [13]. Several signal transmission pathways take part in enhancer rearrangement observed under AF circumstances; mechanical stretch stress and neurohormone stimulation can trigger the production of transcription factor groups such as TGF- $\beta$ /SMAD, Wnt/ $\beta$ -catenin, and NF- $\kappa$ B. Within left-atrial fibrosis linked to AF illness, TGF- $\beta$ /Smad together with Wnt/ $\beta$ -catenin signal cascades may speed up fibroblast multiplication and raise the output of fibrosis-related protein substances, meanwhile NF- $\kappa$ B signal activity correlates with higher production of inflammatory mediators, and this pathway may take indirect part in left atrial tissue reconstruction [14]. Existing research works have reported that TGF- $\beta$  signals can turn on fibrosis-driving enhancers inside heart-derived fibroblasts, which may lift the expression of extracellular matrix-coding genes, and TNF- $\alpha$  alongside IL-6 can strengthen such biological reactions by switching on enhancers that rely on NF- $\kappa$ B activity; nevertheless, solid experimental proof collected directly from AF-related samples remains quite scarce. Chromatin accessibility datasets offer support for researchers to pick out candidate genes with potential regulatory backgrounds; genes showing abnormal expression, together with altered open status of nearby DNA segments and special transcription-factor binding features, can hint at existing epigenetic control mechanisms. Research workers can rank candidate enhancers and transcription factors for follow-up identification work, once they connect ATAC-seq peak signals with expression values of neighboring genes and combine motif forecasting, enhancer marking and risk-locus examination. Even

though this analytical method helps tell early regulatory incidents apart from later-stage transcriptional shifts, scientists still need to carry out functional laboratory tests, so as to confirm cause-and-effect connections between regulatory events and gene transcription. The combined usage of ATAC-seq and RNA-seq can cut down false-positive outputs that appear when researchers only screen according to gene expression data, and this joint approach assists people in locating critical regulatory molecules. As a result, multi-omics analysis supplies a regulatory reference framework for explaining transcriptional variation and sorting key AF-related regulatory targets, and additional experimental efforts are still required to validate these cause-effect regulatory associations.

### **3.3. Single-Cell Multi-Omics Reveals Cellular Heterogeneity in Atrial Fibrillation**

Researchers collect mixed signals coming from various cell groups when they run sequencing experiments at the whole-tissue level; atrial tissue contains different kinds of cell types including heart muscle cells, fibroblasts, endothelial cells and immune cells, so these bulk-tissue sequencing projects fail to completely uncover regulatory mechanisms that belong to each distinct cell type. Modern technical tools such as single-cell RNA sequencing (scRNA-seq) and ATAC-seq allow investigators to check both gene activity and chromatin open conditions for individual cells, and this testing ability plays an important part for researchers to figure out how different cell groups behave during atrial fibrillation development. Kang and other study members applied matched single-nucleus multi-omics approaches (10× Multiome, this platform completes snRNA-seq and snATAC-seq detection within the very same nucleus simultaneously), the research group noticed that cardiomyocytes isolated from AF patients have activated androgen receptor signaling cascades, meanwhile fibroblasts present noticeable changes inside their NR4A1-associated molecular networks; these experimental outcomes proved that different cell populations carry out their own distinctive regulatory tasks inside disease-affected tissue [15]. Cardiomyocytes and fibroblasts are not the only cell groups that take part in the disease process of atrial fibrillation, other cell populations also contribute to AF development. Endothelial cells are able to modify blood vessel tension and local inflammatory reactions; immune cells including macrophages and T lymphocytes can remodel the microenvironment inside atrial tissue. Researchers can sort out regulatory routines that belong to particular cell types with single-cell multi-omics approaches, and these techniques also make it possible to uncover how these cell groups interact with one another. Scientists can guess about signal exchanges happening between fibroblasts and immune cells, when they run ligand-receptor interaction analysis, and this process allows them to pick out paracrine molecular signals which might keep tissue fibrosis and inflammatory reactions going. When single-cell multi-omics tools are used together with spatial omics technology, researchers can get a clearer picture about how cell physical positions, chromatin conditions, and gene expression lev-

els connect with each other within atrial tissue.

#### 4. Current Challenges and Future Perspectives

Researchers can uncover the disease-causing mechanisms of AF, when they combine chromatin accessibility data together with transcriptome analysis, yet plenty of practical obstacles still exist for present-day research work.

The first problem lies in the heterogeneity of samples, which is the main obstacle. Most studies use human atrial tissues obtained during cardiac surgery, and the sample size is usually small. Meanwhile, patient age, co-existing illnesses, particular forms of atrial fibrillation, and the clinical interventions given to AF patients, can all shape chromatin conditions as well as gene expression profiles, and this situation lowers result repeatability across separate study groups [6] [16]. Besides that, a range of technical variables and biological conditions can create extra disturbance, when researchers carry out comparisons between atrial samples taken from AF subjects and non-AF subjects. Investigators generally collect atrial tissue samples from several common positions, and these positions cover the left atrial wall, right atrial wall and atrial free wall; sample sites will bring about differences in cell make-up, fibrosis severity and chromatin profiles, and such differences will add position-related bias to experimental outputs. For the control subjects included in our research, many of them suffer from other cardiovascular disorders, for instance valvular heart injury and heart failure; these extra health issues are able to alter chromatin states and gene expression on their own. What is more, atrial fibrillation will bring shifts in cellular components as the disease goes on, it will cut down the number of cardiomyocytes, while fibroblasts and immune cells will grow in quantity, and these changes may produce misleading transcription and epigenetic signals for the whole tissue sample. Single-cell and single-nucleus testing tools can ease this trouble to some degree, since these tools allow researchers to separate signals belonging to distinct cell types, yet these approaches still have drawbacks; problems like biased cell separation and unsatisfactory nucleus capture rate will affect final data. The second major difficulty comes from inadequate tests for causal relationships; ATAC-seq and RNA-seq are capable of showing correlations between accessible chromatin segments and gene expression levels, but these observed correlations cannot confirm real causal links. Researchers need to run practical functional tests, such as CRISPR gene editing, chromatin interaction assays including Hi-C and Capture Hi-C, plus in-cell and animal model experiments, so they can confirm whether one certain open chromatin segment really controls its target gene [17]. The third main limitation is the absence of uniform processing pipelines; researchers adopt different peak searching settings, data normalization strategies and data combination algorithms; these differences reduce the comparability among experimental outputs and give rise to conflicting findings.

When research workers make use of single-cell multi-omics tools that contain scATAC-seq and scRNA-seq, they can examine cell-specific regulatory networks

with higher accuracy, and uncover how cardiomyocytes, fibroblasts, endothelial cells together with immune cells work jointly during AF onset and disease progression [6]. Spatial transcriptome and epigenome methods can supply positional data for individual cells, and they help illustrate how cell locations interact with the diseased microenvironment inside atrial tissue. Artificial intelligence alongside machine learning methods gets more frequent use for merging different sets of multi-omics data; deep learning models can combine datasets with large internal differences, and raise the reliability for AF risk evaluation as well as potential target identification [18]. If multi-omics datasets are combined with clinical symptom records, imaging results and electrophysiology measurements, people can build multi-layer prediction models, and such models will boost accuracy for AF diagnosis and patient treatment. To draw a brief conclusion, joint measurement of chromatin accessibility and transcript information has turned into one key way to study molecular mechanisms behind atrial fibrillation; as multi-omics kits, computing algorithms and functional verification tools become more reliable, this analytical method can describe AF-related regulatory networks in a more complete manner, and lay more solid groundwork for early-stage disease detection, biomarker screening and targeted clinical therapy.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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