Original Article

Systems-Level in Silico Bioinformatic Profiling Identifies Key Hub Genes and Potential Therapeutic Targets in Atrial Fibrillation without Overt Comorbidity

Fadhlan Abdur Rahman [1*], Suryono Suryono [2,3], Aditha Satria Maulana [3], Pipiet Wulandari [2,3]

[1] Citra Husada Hospital, Jember, Indonesia.
[2] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Jember University, Jember, Indonesia.
[3] Dr. Soebandi General Hospital, Jember, Indonesia.

Citation: Abdur Rahman F, Suryono S, Satria Maulana A, Wulandari P. Systems-Level in Silico Bioinformatic Profiling Identifies Key Hub Genes and Potential Therapeutic Targets in Atrial Fibrillation without Overt Comorbidity. Res Heart Yield Transl Med 2026; 21(1):40-49.

https://doi.org/10.18502/jthc.v21i1.21282

Highlights

- Systems-level bioinformatics delineates the molecular architecture of AF without overt comorbidity.
- Network analysis reveals a highly interconnected ion-channel–centered interactome.
- DMNC topology prioritizes 10 mechanistically relevant hub genes governing atrial electrophysiology.
- Sodium and potassium channel modulators emerge as dominant drivers of arrhythmogenic susceptibility.
- These findings establish a molecular framework for precision stratification in isolated AF.

Article info:

Received: 10 Nov. 2025
Revised: 17 Dec. 2025
Accepted: 28 Dec. 2025

*** Corresponding Author:**
Fadhlan Abdur Rahman
Citra Husada Hospital, Jember, East Java, Indonesia. 68191.
Tel: +62 8515 6271 811
Email: fadhlanabdurrahman@gmail.com

ABSTRACT

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with substantial morbidity and mortality. AF occurring in individuals without structural heart disease or conventional risk factors, currently referred to as AF without overt comorbidity, remains poorly understood. Genetic susceptibility is thought to contribute, but the underlying molecular mechanisms are incompletely defined. This study aimed to identify key genes and biological processes associated with AF without overt comorbidity using an in-silico bioinformatics approach.

Methods: Genes associated with AF without overt comorbidity were retrieved from the GeneCards database using a knowledge-based, database-driven strategy. Functional enrichment analysis of Gene Ontology biological processes was performed using WebGestalt. Protein-protein interaction (PPI) analysis was conducted using STRING and visualized in Cytoscape. Hub genes were identified exclusively using the Density of Maximum Neighborhood Component (DMNC) algorithm via the CytoHubba plugin. Three-dimensional protein structures of selected hub genes were modeled using SWISS-MODEL and evaluated using PROCHECK for exploratory structural characterization.

Results: Eighty-one genes associated with AF without overt comorbidity were identified. PPI analysis demonstrated significant interaction enrichment ($P<1.0\times10^{-16}$), indicating a nonrandom and biologically coherent network. Functional enrichment analysis revealed cardiac muscle cell action potential and cardiac muscle contraction as the most significantly enriched biological processes. Ten hub genes were identified based on DMNC ranking. Among these, GPD1L, SCN1B, SCN4B, and KCNE2 showed central network positions and acceptable stereochemical quality in exploratory structural evaluation.

Conclusion: This in silico study identifies candidate genes and biological processes potentially involved in AF without overt comorbidity. The findings are hypothesis generating and warrant further functional and clinical validation.

Keywords: Bioinformatics; In Silico; Atrial Fibrillation without Overt Comorbidity; Hub Genes; Protein–Protein Interaction

RHYTHM
Research in Heart Yield and Translational Medicine

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias worldwide and poses a major health burden because of its association with stroke, cardiovascular complications, and increased mortality.

Its incidence continues to rise.[1] AF frequently coexists with cardiovascular and systemic conditions such as hypertension, valvular heart disease, and thyroid dysfunction, all independently linked to AF risk.[2-4]

In some individuals, AF occurs without identifiable risk factors or structural heart disease. This phenotype, hereafter referred to as AF without overt comorbidity, is predominantly observed in younger adults (aged<60y).[5] Reported prevalence varies from 1.6% to 30%, depending on the population studied.[6] Although previously considered relatively benign, AF without overt comorbidity can impair quality of life and progress to persistent AF, increasing the risk of stroke, heart failure, and mortality.[7] Current guidelines provide limited recommendations for imaging or ancillary testing to exclude underlying cardiac pathology in this subgroup.

Advances over the past 2 decades have improved understanding of AF electrophysiological and structural mechanisms; nonetheless, the pathophysiology of AF without overt comorbidity remains incompletely defined.[8] Regional studies highlight associations between perceived stress and AF, suggesting additional contextual contributors.9 Emerging evidence also points to a genetic component, including variants in ion channels, gap junction proteins, and accessory subunits.[10]

This study aimed to identify key genes and biological processes associated with AF without overt comorbidity and explore candidate molecular pathways using in silico bioinformatics.

Methods

Gene Retrieval and Data Collection

Gene selection was conducted using a knowledge-based, database-driven approach rather than a primary transcriptomic or sequencing data set. AF–associated genes were retrieved exclusively from the GeneCards database (https://www.genecards.org).[11]

The search term “lone atrial fibrillation” was used to retrieve gene-disease associations, as this term remains commonly indexed in biomedical databases. For reporting and interpretation purposes, and in accordance with current clinical guidelines, this phenotype is referred to throughout the manuscript as AF without overt comorbidity.

Genes were ranked according to the GeneCards relevance score, and those with a relevance score of 10 or greater were retained. The top 100-ranked genes were selected for downstream analyses. Duplicate entries and non–protein-coding genes were excluded.

Because no primary gene expression data set was analyzed, no differential expression analysis or multiple testing correction was applied. The resulting gene list was subsequently used for functional enrichment analysis, protein-protein interaction (PPI) network construction, and network-based hub gene prioritization.

Functional Enrichment Analysis

Functional annotation of the identified genes was performed to explore biological processes implicated in the pathogenesis of AF without overt comorbidity. Kyoto Encyclopedia of Genes and Genomes pathways and Gene Ontology terms were analyzed using Overrepresentation Enrichment Analysis via WebGestalt 2019 (http://www.webgestalt.org).[12] A false discovery rate (FDR<0.05) was applied as the statistical significance threshold. For clarity and interpretability, only the top 10 most significant biological processes (lowest FDR) were visualized.

PPI Network Construction and Hub Gene Identification

PPI among the candidate genes was evaluated using the STRING database (version 11.0b) (https://string-db.org).[13] A PPI network was constructed using a high-confidence interaction threshold (confidence score>0.7) to minimize spurious associations.

The resulting PPI network was imported into Cytoscape for visualization and network analysis.[14] Hub genes were identified using the CytoHubba plugin, exclusively based on the Density of Maximum Neighborhood Component algorithm. The DMNC algorithm was selected because it prioritizes nodes with high local connectivity within densely interacting network modules, rather than relying solely on the number of connections. Degree centrality was not used for hub gene selection in this study. The top 10 genes ranked by DMNC score were designated as hub genes for subsequent analyses. Because hub gene identification was based solely on network topology and a single topological algorithm, these genes were considered candidate hub genes. Accordingly, the findings should be interpreted as hypothesis generating, and no direct inference regarding therapeutic relevance can be made without further functional or clinical validation.

Protein Structure Modeling

Three-dimensional structures of the proteins encoded by the top 10 hub genes were modeled using the SWISS-MODEL server (https://swissmodel.expasy.org). Protein sequences in FASTA format were obtained from the NCBI RefSeq Protein Database. Template selection was based on the highest available Global Model Quality Estimate and QMEAN scores derived from the Protein Data Bank.[15]

Structural Validation and Quality Assessment

Protein structural models were evaluated using PROCHECK through the SAVES v6.0 platform (UCLA–DOE Institute for Genomics and Proteomics) to assess stereochemical quality, including backbone dihedral angle distributions visualized by Ramachandran plots.[16] Validation was conducted solely for exploratory assessment, without implications for druggability or ligand-binding potential.

Results

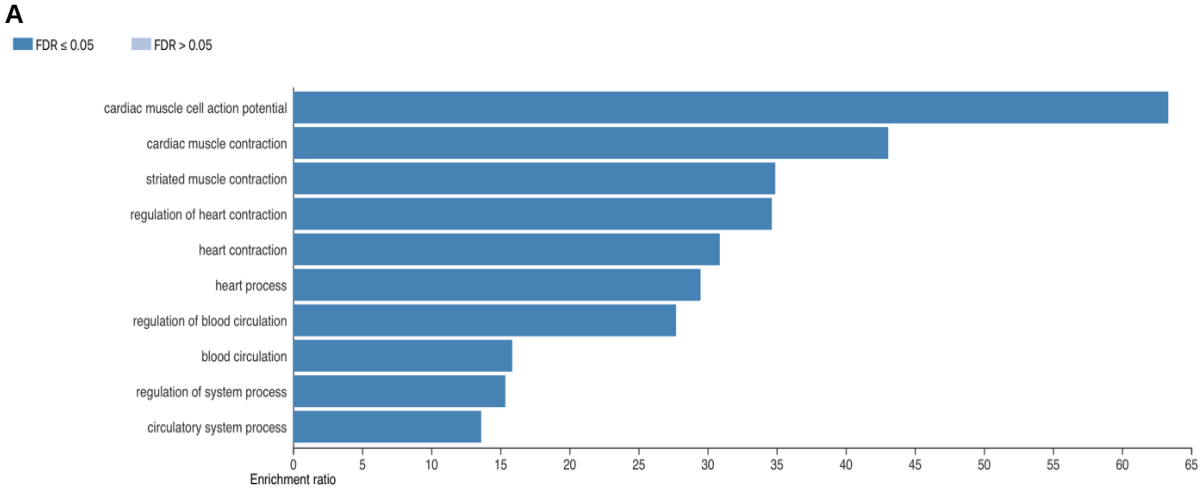
Identification of Genes Associated with AF Without Overt Comorbidity

The GeneCards search identified 81 genes associated with AF without overt comorbidity. These genes were used for functional enrichment and network analyses.

Functional Enrichment Analysis

Functional enrichment analysis was performed using WebGestalt to identify biological processes associated with AF without overt comorbidity. Based on overrepresentation analysis results with an FDR of less than 0.05, the top 10 significantly enriched biological processes were identified (Figure 1A).

The 2 most prominent biological processes were cardiac muscle cell action potential (25 genes) and cardiac muscle contraction (31 genes) (Figure 1B). An enrichment volcano plot is provided to illustrate the overall distribution of enrichment significance across biological processes (Figure 1C).



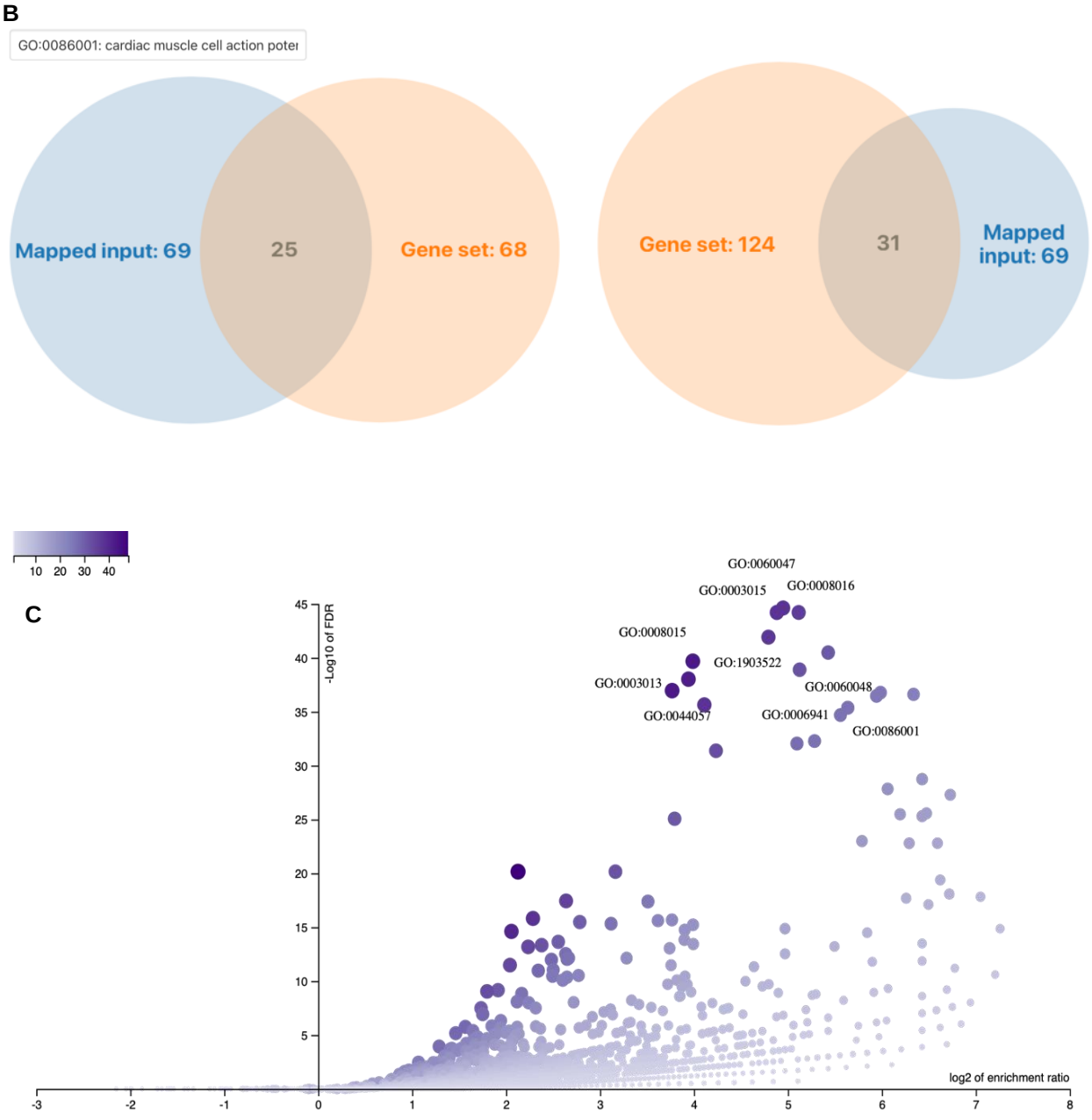


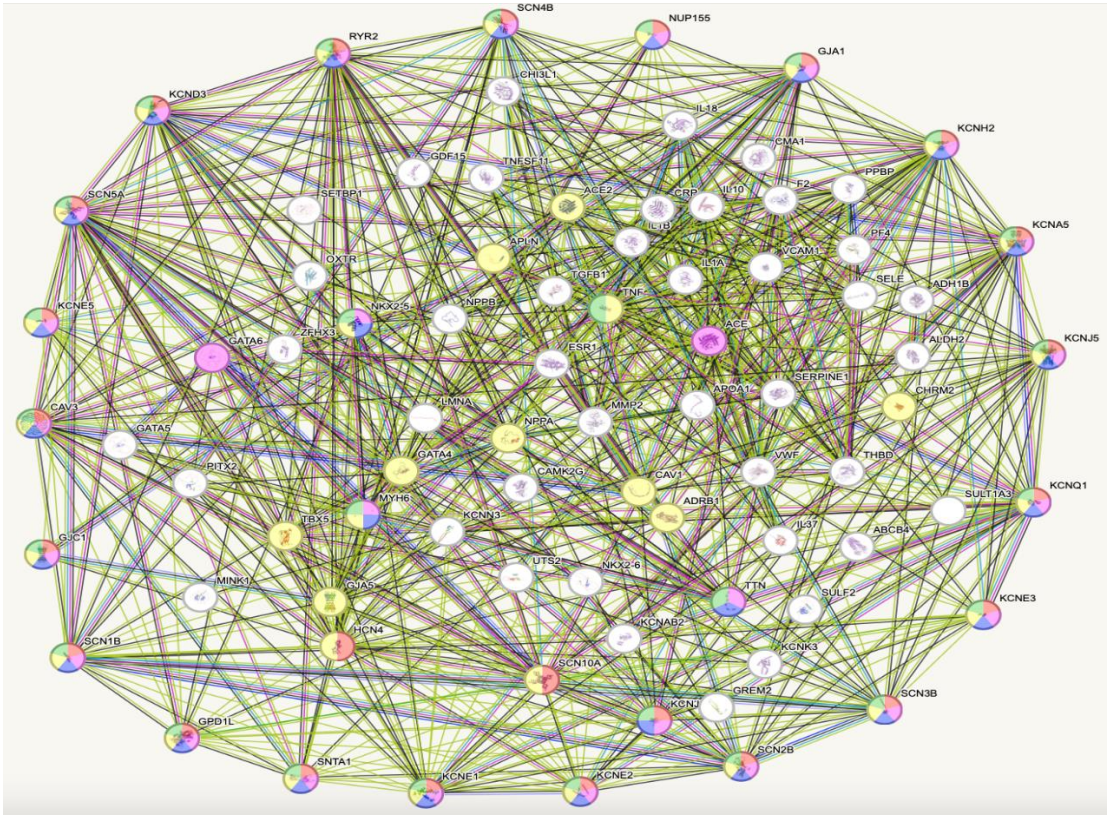
Figure 1. Functional enrichment analysis of genes associated with atrial fibrillation (AF) without overt comorbidity using WebGestalt. **A**, Bar plot showing the top 10 significantly enriched Gene Ontology (GO) biological processes identified by overrepresentation analysis (FDR<0.05). **B**, Gene set overlap visualization illustrating the intersection between the input gene list and genes annotated to the most significant biological process. **C**, Volcano plot displaying enrichment significance (−log10 FDR) vs log2 enrichment ratio for enriched biological processes; selected GO terms are annotated to highlight the most significant results.

Construction of the PPI Network

All 81 high-relevance genes were incorporated into a PPI network using the STRING database. The resulting network demonstrated a PPI enrichment *P* value less than 1.0×10^{-16}, indicating that the observed interactions were significantly more frequent than expected by chance and formed a biologically meaningful interaction network related to AF without overt comorbidity (Figure 2).

Functional categories were visualized using color-coded nodes:

- Red: cardiac muscle cell action potential
- Pink: heart contraction
- Blue: cardiac muscle contraction
- Yellow: regulation of heart contraction
- Green: striated muscle contraction



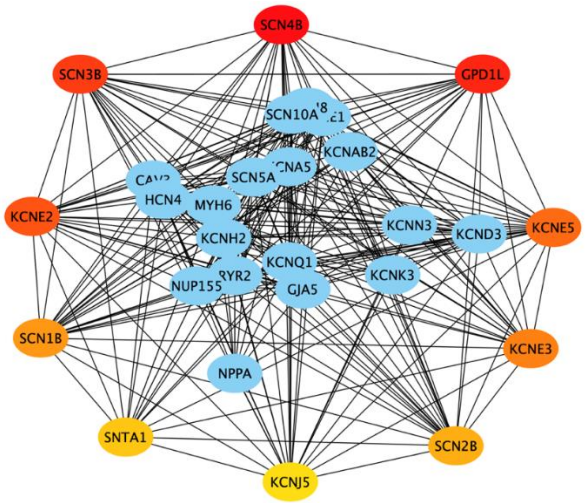
number of nodes: 81
number of edges: 671
average node degree: 16.6
avg. local clustering coefficient: 0.666

expected number of edges: 110
PPI enrichment p-value: < 1.0e-16
your network has significantly more interactions than expected (what does that mean?)

Figure 2. STRING-based protein–protein interaction (PPI) network of atrial fibrillation (AF)-associated genes. The network includes 81 genes and demonstrates significant interaction enrichment (P<1.0 × 10^−16), indicating a biologically nonrandom network. Nodes are color-coded based on enriched biological processes: red, cardiac muscle cell action potential; pink, heart contraction; blue, cardiac muscle contraction; yellow, regulation of heart contraction. Unclassified genes are shown in white.

Identification of Hub Genes Using CytoHubba-DMNC

CytoHubba DMNC analysis identified 10 candidate hub genes: SCN4B, GPD1L, SCN3B, KCNE2, KCNE5, KCNE3, SCN1B, SCN2B, SNTA1, and KCNJ5 (Figure 3). These genes encode ion channel subunits or regulatory proteins involved in cardiac conduction.



Ranking Method
DMNC

Rank	Node
1	SCN4B
2	GPD1L
3	SCN3B
4	KCNE2
5	KCNE5
6	KCNE3
7	SCN1B
8	SCN2B
9	SNTA1
10	KCNJ5

Figure 3. Hub gene identification using the CytoHubba DMNC algorithm. Hub genes were ranked exclusively according to DMNC scores derived from the STRING-based PPI network. Node color intensity reflects relative DMNC ranking, with darker colors indicating higher local connectivity. The top 10-ranked genes were selected as candidate hub genes for subsequent analyses.

RHYTHM
Research in Heart Yield and Translational Medicine

Protein Structure Modeling and Quality Validation

Three-dimensional structural models of proteins encoded by the 10 hub genes were generated using SWISS-MODEL based on protein sequences obtained from the NCBI database (Figure 4). Structural quality was evaluated using PROCHECK by assessing residue distribution within favored and allowed regions of the Ramachandran plot. (See the figure below.)

Ramachandran plot analysis showed that most residues in the predicted protein models were located within favored and allowed regions, indicating acceptable stereochemical quality of the modeled structures.

Several protein models, including *SCN4B*, *GPD1L*, *KCNE2*, and *SCN1B*, exhibited a higher proportion of residues in favored regions (>90%), whereas others showed moderate stereochemical quality based on PROCHECK assessment (Table 1).

Table 1. PROCHECK analysis of modeled protein structures showing the percentage of residues located in the most favored regions of the Ramachandran plot

Gene	Most Favoured Region (%)
SCN4B	94.9
GPD1L	93.6
SCN3B	87.7
KCNE2	92.3
KCNE5	74.4
KCNE3	85.4
SCN1B	93.7
SCN2B	85.8
SNTA1	87.7
KCNJ5	88.1

Note: Percentages indicate the proportion of residues located in the most favored regions of the Ramachandran plot based on PROCHECK analysis and reflect stereochemical plausibility of the predicted models.

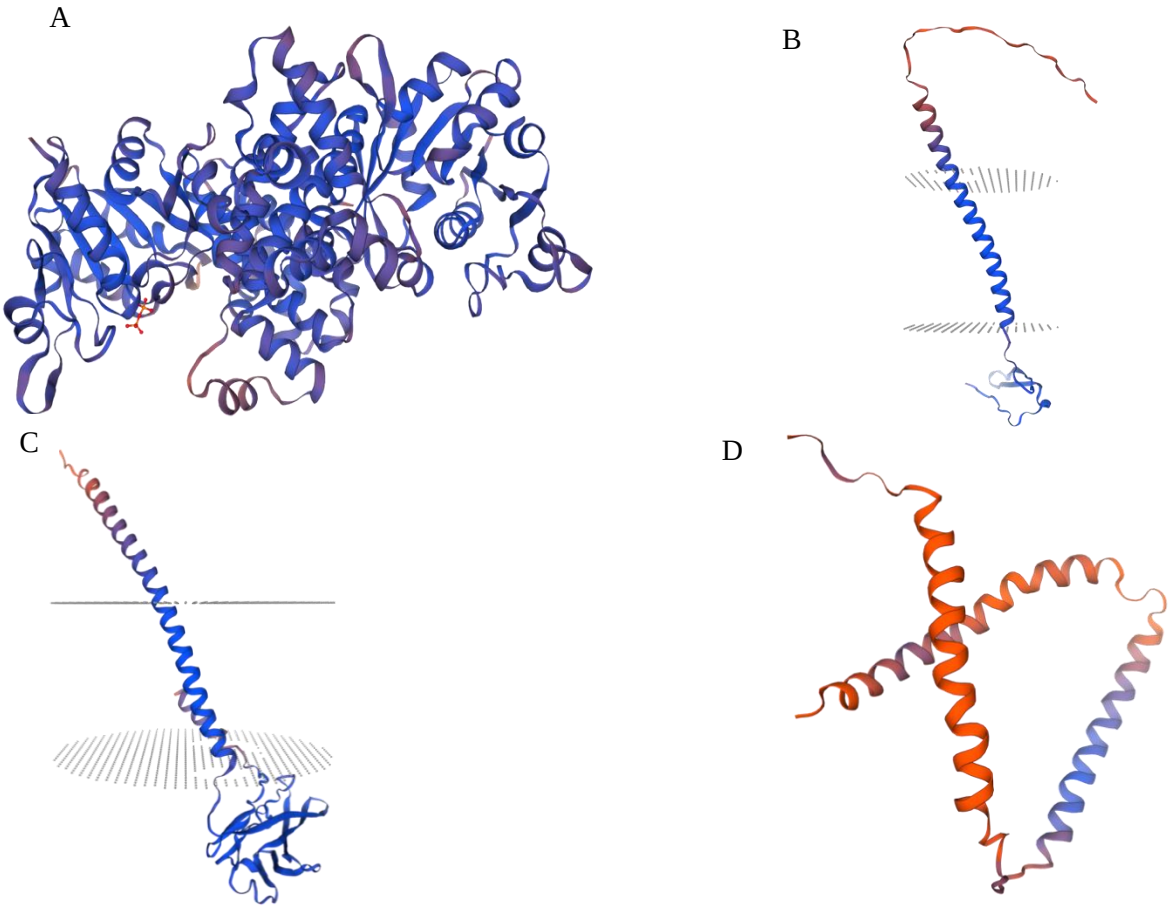


Figure 4. Three-dimensional structural models of selected hub proteins were generated using SWISS-MODEL. A, GPD1L. B, SCN1B. C, SCN4B. D, KCNE2. Models were constructed based on the highest-quality available templates from the Protein Data Bank and are presented for exploratory structural characterization.

Discussion

Genetic Architecture of AF Without Overt Comorbidity

AF occurring in the absence of overt clinical risk factors, historically referred to as AF without overt comorbidity, has increasingly been recognized as a genetically enriched subtype of AF. Compared with common AF in the general population, AF without overt comorbidity demonstrates a stronger heritable component, as numerous studies have highlighted genetic variants associated with ion channel dysfunction, abnormal electrical conduction, and dysregulated gene expression.[17] These findings collectively underscore the complex molecular mechanisms driving susceptibility to this phenotype.

Genetic and Epigenetic Contributions

Epigenetic processes exert substantial influence over AF predisposition. Deoxyribonucleic acid methylation, transcriptional and translational regulation by noncoding RNAs, and chromatin remodeling through histone modification can substantially alter the expression of genes critical for atrial electrophysiology and structural homeostasis.[18] Such regulatory shifts establish a proarrhythmic molecular environment, even in the absence of overt structural heart disease.

Electrophysiological Mechanisms Underlying AF Without Overt Comorbidity

The development of AF involves two principal electrophysiologic pathways: atrial reentry and ectopic atrial firing. Although AF without overt comorbidity typically lacks gross structural abnormalities, subtle yet clinically relevant electrophysiologic substrates frequently exist.[18] These include the following:

- Ion channel variations that shorten the atrial effective refractory period
- Microscopic atrial fibrosis
- Impaired gap junction connectivity

Together, these abnormalities generate conduction heterogeneity, predisposing atrial tissue to multiple reentry circuits despite otherwise normal anatomic findings.[19]

Disrupted Calcium Handling

Abnormal intracellular calcium dynamics represent another central mechanism contributing to AF without overt comorbidity. Reduced L-type Ca^{2+} channel current, combined with increased spontaneous sarcoplasmic reticulum Ca^{2+} release, enhances Na^{+} influx via the Na^{+}-Ca^{2+} exchanger. This process promotes calcium waves and delayed afterdepolarizations, which serve as potent triggers of atrial arrhythmogenesis. Concurrent gap junction remodeling further impairs intercellular conduction, amplifying tissue-level electrical instability.[20]

Sarcomeric and Structural Remodeling

Genetic variants associated with AF without overt comorbidity are also known to affect sarcomeric and cytoskeletal integrity. Mutations in titin, desmin, LMNA, and EMD disrupt contractile mechanics, nuclear lamina structure, and conduction velocity. These structural perturbations promote atrial myopathy and facilitate both the initiation and perpetuation of AF, reinforcing the pivotal role of molecular remodeling in this phenotype.[21]

In Silico Genomic Findings

Gene Identification and Functional Enrichment

Using the GeneCards database, the present study identified 81 genes associated with AF without overt comorbidity. Functional enrichment analysis revealed two dominant biological processes:

1. **Cardiac muscle cell action potential** (25 genes), reflecting electrophysiological abnormalities such as shortened action potential duration, impaired rate adaptation, reduced L-type Ca^{2+} channel expression, altered K^{+} currents, and dysfunctional calcium handling.
2. **Cardiac muscle contraction** (31 genes), highlighting structural and mechanical contributors including defects in sarcomeric proteins (eg, titin and desmin), cytoskeletal abnormalities (LMNA and EMD), and impaired intercellular communication via connexin dysfunction (eg, *GJA5*).

These processes align closely with previously described mechanisms underlying AF without overt comorbidity, supporting the biological relevance of the identified gene set.[21]

PPI Network and Hub Gene Determination

STRING network analysis demonstrated a highly significant protein–protein interaction enrichment ($P<1.0\times10^{-16}$), indicating extensive functional interconnectivity among the 81 genes. The network highlighted multiple central nodes involved in pathways regulating cardiac electrophysiology and contraction, including SCN3B, SCN2B, KCNE2, KCNE1, SNTA1, GPD1L, SCN1B, GJC1, CAV3, KCNE5, and SCN5A.

Using CytoHubba with the DMNC algorithm, 10 candidate hub genes were identified: SCN4B, GPD1L, SCN3B, KCNE2, KCNE5, KCNE3, SCN1B, SCN2B, SNTA1, and KCNJ5.

Mechanistic Insights into Hub Genes

Each hub gene contributes to arrhythmogenic pathways via distinct mechanisms.[22–28]

- **SCN4B:** alters sodium channel gating, creating a proarrhythmic substrate.
- **GPD1L:** modulates Nav1.5 activity; dysfunction reduces sodium current and impairs depolarization.
- **SCN3B, SCN1B, SCN2B:** encode auxiliary sodium channel subunits; mutations reduce channel density, disrupt gating, or impair activation kinetics.
- **KCNE2, KCNE5, KCNE3:** regulate potassium channels; gain- or loss-of-function variants modify repolarization and shorten action potential duration, facilitating reentry.
- **SNTA1:** stabilizes ion channel complexes; disruption reduces atrial excitability.
- **KCNJ5:** alters GIRK4-mediated parasympathetic potassium current, enhancing arrhythmogenesis.

Protein Structure Validation

PROCHECK-based structural evaluation demonstrated that several predicted protein models, including GPD1L, SCN1B, SCN4B, and KCNE2, exhibited a high proportion (>90%) of residues located within favored regions of the Ramachandran plot. This finding reflects acceptable geometric plausibility and stereochemical consistency of the modeled structures.

Nevertheless, PROCHECK analysis provides information on geometric quality only and does not inform on functional activity, ligand-binding affinity, or pharmacologic druggability. Accordingly, the structural findings should be interpreted as preliminary and descriptive, serving as a foundation for future docking analyses or experimental structural studies rather than as evidence of therapeutic relevance.

Limitations

This study has several limitations. First, the analyses were conducted entirely using in silico and database-driven approaches, without incorporation of primary transcriptomic, proteomic, or sequencing data sets. Consequently, the findings should be interpreted as exploratory and hypothesis generating, rather than confirmatory.

Second, gene selection relied on curated database evidence and network-based analyses rather than direct measurement of gene expression or causal inference. As a result, the identified genes and pathways reflect reported associations and topological importance within interaction networks, which may not directly correspond to biologic activity in atrial tissue. Third, hub genes were identified based on topological ranking algorithms without functional perturbation experiments, longitudinal clinical correlation, or external cohort validation. Therefore, conclusions regarding biologic significance or therapeutic relevance remain preliminary.

Fourth, structural analyses were limited to stereochemical quality assessment using PROCHECK and Ramachandran plot evaluation. These analyses do not provide information on ligand-binding affinity, druggability, or pharmacologic interactions, and should not be interpreted as evidence of therapeutic targeting potential.

Finally, the absence of experimental validation

(eg, in vitro or in vivo studies) and clinical validation in patient cohorts limits the translational applicability of the findings. Future studies integrating multi-omics data sets, functional experiments, and clinical data will be necessary to confirm and extend the results of this work.

Conclusion

AF without overt comorbidity occurs in individuals without identifiable structural heart disease. Genetic factors may, however, still contribute to disease susceptibility. The findings of the current study suggest that several genes, including *GPD1L*, *SCN1B*, *SCN4B*, and *KCNE2*, may be associated with molecular pathways relevant to atrial electrophysiology in AF without overt comorbidity. These genes should be considered candidate molecular contributors and may provide a basis for future functional studies aimed at improving the understanding and stratification of AF without overt comorbidity.

Supplementary Information

Additional file 1: Supplementary Data 1. GeneCards Search Results—AF Without Overt Comorbidity

Additional file 2: Supplementary Data 2. Supplementary Figures

Declarations:

Ethical Approval

Ethical approval was not required for conducting this research.

Funding

The authors did not receive financial support for the research, authorship, or publication of this article.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgments

The authors have no acknowledgement to disclose.

References

1. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. Circulation. 2024;149(1):e1-156.
2. Antoun I, Layton GR, Nizam A, Barker J, Abdelrazik A, Eldesouky M, et al. Hypertension and Atrial Fibrillation: Bridging the Gap Between Mechanisms, Risk, and Therapy. Medicina (Kaunas). 2025;61(2):362.
3. Lancellotti P, Miraglia V. Valvular heart disease and atrial fibrillation: advances in mechanisms, risk stratification, and therapeutic approaches. Acta Cardiol. 2025;80(6):535-40.
4. Zhang Y, Dedkov EI, Teplitsky D, Weltman NY, Pol CJ, Rajagopalan V, et al. Both hypothyroidism and hyperthyroidism increase atrial fibrillation inducibility in rats. Circ Arrhythm Electrophysiol. 2013; 6(5):952-9.
5. Kim EJ, Yin X, Fontes JD, Magnani JW, Lubitz SA, McManus DD, et al. Atrial fibrillation without comorbidities: prevalence, incidence and prognosis (from the Framingham Heart Study). Am Heart J. 2016 Jul;177:138-44.
6. Potpara TS, Lip GY. Lone atrial fibrillation: what is known and what is to come. Int J Clin Pract. 2011;65(4):446-57.
7. Thomas V, Schulein S, Millar RNS, Mayosi BM. Clinical characteristics and outcome of lone atrial fibrillation at a tertiary referral centre: the Groote Schuur Hospital experience. Cardiovasc J Afr. 2018;29(5):268-72.
8. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, et al. Lone atrial fibrillation: does it exist? J Am Coll Cardiol. 2014;63(17):1715-23.
9. Khaleghparast S, Maleki M, Rafiee F, Karimian S, Sari L, Mazloomzadeh S. The Association of Perceived Stress and Atrial Fibrillation. Res Heart Yield Transl Med 2025; 20(3):185-192.
10. Andreasen L, Nielsen JB, Olesen MS. Genetic aspects of lone atrial fibrillation: what do we know? Curr Pharm Des. 2015;21(5):667-78.

11. GeneCards. The Human Gene Database. Available from: https://www.genecards.org. Accessed Oct 2025.
12. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B. WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs. Nucleic Acids Res. 2019;47(W1):W199-205.
13. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein–protein association networks with increased coverage. Nucleic Acids Res. 2019;47(D1):D607-13.
14. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated biomolecular interaction networks. Genome Res. 2003;13(11):2498-504.
15. Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, et al. SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic Acids Res. 2018;46(W1):W296-303.
16. UCLA–DOE Institute for Genomics and Proteomics. SAVES v6.0: Structure Analysis and Verification Server. Available from: https://saves.mbi.ucla.edu/.
17. Roberts JD, Gollob MH. Impact of Genetic Discoveries on the Classification of Lone Atrial Fibrillation. J Am Coll Cardiol. 2010;55(8):705-12.
18. Andersen JH, Andreasen L, Olesen MS. Atrial fibrillation—a complex polygenetic disease. Eur J Hum Genet. 2021;29(7):1051-60.
19. Huang Z, Luo C, Wu Z, Zheng B. Electrophysiological Mechanisms and Therapeutic Potential of Calcium Channels in Atrial Fibrillation. Rev Cardiovasc Med. 2025;26(6):33507.
20. Ahlberg G, Refsgaard L, Lundegaard PR, Andreasen L, Ranthe MF, Linscheid N, et al. Rare truncating variants in the sarcomeric protein titin associate with familial and early-onset atrial fibrillation. Nat Commun. 2018; 9(1):4316.
21. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002;54(2):230-46.
22. Li RG, Wang Q, Xu YJ, Zhang M, Qu XK, Liu X, et al. Mutations of the SCN4B-encoded sodium channel β4 subunit in familial atrial fibrillation. Per Med. 2018;15(2):93-102.
23. Denti F, Paludan-Müller C, Olesen SP, Haunsø S, Svendsen JH, Olesen MS, et al. Functional consequences of genetic variation in sodium channel modifiers in early onset lone atrial fibrillation. Int J Mol Med. 2013;32(1):144-50.
24. Olesen MS, Jespersen T, Nielsen JB, Liang B, Møller DV, Hedley P, et al. Mutations in sodium channel β-subunit SCN3B are associated with early-onset lone atrial fibrillation. Cardiovasc Res. 2011;89(4):786-93.
25. Nielsen JB, Bentzen BH, Olesen MS, David JP, Olesen SP, Haunsø S, et al. Gain-of-function mutations in potassium channel subunit KCNE2 associated with early-onset lone atrial fibrillation. Biomark Med. 2014;8(4):557-70.
26. Lundby A, Ravn LS, Svendsen JH, Haunsø S, Olesen SP, Schmitt N. KCNE3 mutation V17M identified in a patient with lone atrial fibrillation. Cell Physiol Biochem. 2008;21(1-3):47-54.
27. Watanabe H, Darbar D, Kaiser DW, Jiramongkolchai K, Chopra S, Donahue BS, et al. Mutations in sodium channel β1- and β2-subunits associated with atrial fibrillation. Circ Arrhythm Electrophysiol. 2009;2(3):268-75.
28. Jabbari J, Olesen MS, Holst AG, Nielsen JB, Haunso S, Svendsen JH. Common polymorphisms in KCNJ5 are associated with early-onset lone atrial fibrillation in Caucasians. Cardiology. 2011;118(2):116-20.