Atrial fibrillation in the presence and absence of heart failure enhances expression of genes involved in cardiomyocyte structure, conduction properties, fibrosis, inflammation, and endothelial dysfunction

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BACKGROUND  Little is known about genome-wide changes in the atrial transcriptome as a cause or consequence of atrial fibrillation (AF), and the effect of its common and clinically relevant comorbidity—heart failure (HF).

OBJECTIVE  The purpose of this study was to explore candidate disease processes for AF by investigating gene expression changes in atrial tissue samples from patients with and without AF, stratified by HF.

METHODS  RNA sequencing was performed in right and left atrial appendage tissue in 195 patients undergoing open heart surgery from centers participating in the CATCH-ME consortium (no history of AF, n = 91; paroxysmal AF, n = 53; persistent/permanent AF, n = 51). Analyses were stratified into patients with/without HF (n = 75/120) and adjusted for age, sex, atrial side, and a combination of clinical characteristics.

RESULTS  We identified 35 genes associated with persistent AF compared to patients without a history of AF, both in the presence or absence of HF (false discovery rate <0.05). These were mostly novel associations, including 13 long noncoding RNAs. Genes were involved in regulation of cardiomyocyte structure, conduction properties, fibrosis, inflammation, and endothelial dysfunction. Gene set enrichment analysis identified mainly inflammatory gene sets to be enriched in AF patients without HF, and gene sets involved in cellular respiration in AF patients with HF.

CONCLUSION  Analysis of atrial gene expression profiles identified numerous novel genes associated with persistent AF, in the presence or absence of HF. Interestingly, no consistent transcriptional changes were associated with paroxysmal AF, suggesting that AF-induced changes in gene expression predominate other changes.

KEYWORDS  Atrial fibrillation; Atrial tissue samples; Gene expression; Heart failure; RNA sequencing

Introduction
Atrial fibrillation (AF) induces functional and structural changes in the atria, which are attributed to the high and irregular atrial rate during AF and to multiple risk factors including age, hypertension, and other heart diseases, but also to genetic variants associated with AF.1 Although altered gene expression is a major adaptive mechanism to these factors, transcriptome-wide expression changes associated with AF and relevant comorbidities have not been systematically studied in human atria.

Quantification of gene expression in atrial tissue may reveal changes in gene expression associated with AF itself and with its comorbidities. Comparing the atrial transcriptome in patients with and without AF using next-generation RNA sequencing (RNA-Seq) is a critical step toward this goal.2

Ventricular dysfunction or heart failure (HF) also may induce proarrhythmic functional and structural changes in the atria in the absence of AF, such as shortening of the effective refractory period,3 action potential duration prolongation,4 changes in Ca2+ handling, and an increase in profibrotic markers.5 In the Framingham Heart Study, 37% of patients with new-onset AF had a pre-existing diagnosis of HF, and 56% of new HF patients suffered from AF.6 In addition to AF, HF induces profound changes in atrial gene expression. In a canine model, the number of expression changes associated with HF seemed larger than those associated with AF.7

To characterize gene expression changes associated with AF in patients with and without HF, we sequenced 195 atrial biopsies from a large multicenter cohort of open heart surgery patients, enabling the transcriptome-wide discovery of differentially expressed transcripts, including protein-coding and noncoding transcripts.

Methods
Patient characteristics and atrial tissue samples
Tissue samples from the left atrial appendage (LAA) and right atrial appendage (RAA) were collected from 5 participating centers in the CATCH ME (Characterizing Atrial fibrillation by Translating its Causes into Health Modifiers in the Elderly) consortium (www.catch-me.info). Samples were collected during surgery and flash-frozen in liquid nitrogen to prevent RNA degradation. The investigation complied with the principles outlined in the Declaration of Helsinki. Individual, written informed consent was obtained from each patient, and the Medical Ethics Committee of each center approved sample collection. Centralized processing and analysis were performed under CATCH ME consortium-wide Data Sharing and Material Transfer Agreements.

Transcriptomic analyses
Total RNA was extracted from atrial tissue at the Core Facility Genomics of the Medical Faculty, University of Muenster, Germany. A detailed description of the RNA sequencing is available in the Supplemental Material.

Differentially expressed transcripts associated with AF were determined stratified by HF and adjusted for age, sex, and atrial tissue location. Adjustment for remaining sources of significant variation in clinical characteristics was performed using principal component analysis. The number of significant components was selected using the Auer-Gervini method.8 Technical confounders (eg, sequencing batch and center effects) were modeled by surrogate variables,9 controlling for atrial rhythm, HF, age, sex, clinical principal components, and atrial tissue location.
Expression analysis was performed using DESeq2 (https://bioconductor.org/packages/DESeq2). Differential exon usage was assessed using DEXSeq (https://bioconductor.org/packages/DEXSeq). False discovery rate was set at 5% using the Benjamini-Hochberg procedure.

Gene ontology enrichment, KEGG pathway, and gene set enrichment analysis were performed using clusterProfiler (https://bioconductor.org/packages/clusterProfiler) and DOSE (https://bioconductor.org/packages/DOSE). Protein–protein networks were constructed using STRING (string-db.org). Individual gene function was explored by searching for gene identifiers in OMIM (Online Mendelian Inheritance in Man).

Statistical analysis
Patient characteristics were compared using 1-way analysis of variance for continuous data (Kruskal-Wallis for non-normally distributed data) and χ² tests for categorical data. Spearman correlation matrices between expression levels of transcripts were calculated using the “Hmisc” (https://hbiostat.org/R/Hmisc) package for R. Differences were tested using the Striger test (R-package “psych”) (https://personality-project.org/r/psych).

Results
Tissue sample selection and patient characteristics
Tissue sample selection and analysis workflow are depicted in Figure 1. Patient rhythm status was classified as no history of AF (SR) (n = 91); paroxysmal AF (PAF) (n = 53); or persistent/permanent AF (PersAF) (n = 51). There were between-group differences in age, sex, history of coronary artery disease, and previous myocardial infarction (Table 1). Principal component analysis of clinical characteristics revealed that patients with HF (n = 75) represented a distinct, younger population of patients (Supplemental Figure 1). To account for remaining variations in clinical characteristics and center-associated variation (Supplemental Table 1), 2 clinical principal components were included in transcriptomic analyses, together accounting for >35% of variation (Supplemental Table 2). Two surrogate variables were identified, accounting for technical confounders in gene expression profiles (Supplemental Figures 2, 3, and 4).

Differentially expressed genes associated with AF in the presence or absence of HF
In total, 222 transcripts were differentially expressed between samples from SR and PersAF patients without HF (AF/HF−) and 125 in HF patients (AF/HF+). No genes were associated with PAF compared to SR in either group. Only in patients without HF, 18 genes were identified between PAF and PersAF (Supplemental Tables 3, 4, and 5). Thirty-five transcripts were differentially expressed between SR and PersAF patients in both strata with concordant direction of effect (Figures 2A and 2B, and Supplemental Table 6). Of these, 18 were protein-coding (Table 2), 13 long non-coding RNAs, 1 pseudo-gene, and 3 unclassified. Expression differences associated with PersAF compared to SR were similar in patients with/without HF; 93% of differentially expressed genes in 1 comparison had a (non-)significant concordant fold-change in the other. A strong increase in expression in PersAF compared to SR
was observed for genes MDM1 (Mouse Double-Minute 1) and EAF1 (Ell-Associated Factor 1). Six of 35 AF genes were also differentially expressed between PAF and PersAF in HF– but not in HF+ patients (Figure 2A), including MDM1 (Figure 2C).

Combining all samples, we found no evidence supporting interaction between PAF and HF or PersAF and HF on gene expression. Notably, the main effect of AF was preserved in this combined analysis, with 163 genes independently associated with PersAF, including 24 of 35 genes identified in the stratified analysis (Figure 3A). When stratified by side (LAA/RAA) and corrected for presence of HF, gene expression differences between PersAF and SR remained consistent (31/28 of 35 for LAA/RAA, respectively) (Figure 3A).

Although significant gene expression differences were predominantly observed between PersAF and SR patients, transcripts often showed identical direction of effect in other comparisons (Figure 3B).

### Enrichment analyses

Gene ontology–term enrichment analysis of differentially expressed transcripts in the AF/HF– comparison indicated enrichment of genes within the terms “sarcomere”, “contractile fiber part”, and “myofibril” (P<.002), whereas differentially expressed transcripts in AF/HF+ were enriched in “cell-cell adhesion mediator activity” and “rhabdomyosarcoma” (P<.002). KEGG pathway enrichment analysis revealed enrichment in “oocyte meiosis” (P<.001) and “oxytocin signaling” (P<.01) in AF/HF– and no enrichment in AF/HF+ (Supplemental Tables 7, 8, and 9).

Gene set enrichment analysis of all expression differences, including nonsignificant changes, revealed many enriched gene sets (Figure 4). In AF/HF–, both PAF and PersAF gene expression were enriched in immune response–related gene ontology terms, whereas in AF/HF+, PAF and PersAF gene expression were enriched for gene sets associated with cellular respiration.
The extended protein–protein interaction network of the 18 protein-coding AF genes (confidence level threshold 0.7) identified CDC42 (Cell Division Control Protein 42 Homolog) as a hub gene (Figure 2D), linking AF genes TNK2 (Tyrosine Kinase Nonreceptor 2) and PPP1CA (Protein Phosphatase 1). Furthermore, the interaction network illustrates the connection of the cytokine interferon-γ (encoded by the differentially expressed IFNG [Interferon-γ] gene) to the JAK-STAT signaling pathway.

**Differential exon usage**
Analysis revealed 41 cases of differential exon usage in 30 genes in AF/HF− and 437 cases in 156 genes in AF/HF+ (Supplemental Tables 10 and 11). No differences in exon usage were found in other comparisons. Concordant differential exon usage associated with PersAF in patients with/without HF was found for MAPK10 (Mitogen-Activated Protein Kinase 10, last exon) and for EAF1 (first/last exons), correcting for expression differences between rhythm status (Table 3).

**AF gene locus expression correlation**
Near each of the 35 AF genes (±500,000 base pairs), correlations between gene expression were computed. Correlation matrices were constructed separately for SR and PersAF. Striking differences were observed for the locus containing both MDM1 and IFNG, which in PersAF formed a tightly
correlated group together with IL22/IL26 (Interleukin 22/26). This correlation was absent in SR (Figure 5).

Discussion

Careful analysis of RNA-Seq transcription profiles in atrial tissue from the CATCH ME consortium identified 35 transcripts that were differentially expressed in patients with PersAF compared to patients without a history of AF, including both protein-coding and noncoding transcripts. These differences were observed in patients with and without HF. Interestingly, no consistent changes were associated with PAF, suggesting that PAF patients do not

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Fold-change (HF-/HF+)</th>
<th>P_adj (HF-/HF+)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM1</td>
<td>6.1/3.7</td>
<td>2.6e-13/1.4e-03</td>
<td>Negative regulator of centriole duplication</td>
</tr>
<tr>
<td>RALGPS1</td>
<td>2.8/2.6</td>
<td>1.9e-08/8.3e-03</td>
<td>Activation of small GTPase RALA of the Ras family</td>
</tr>
<tr>
<td>EAF1</td>
<td>2.3/2.0</td>
<td>1.5e-06/2.9e-03</td>
<td>Glutamate-mediated synaptic signaling</td>
</tr>
<tr>
<td>GRMB</td>
<td>5.7/5.3</td>
<td>1.8e-06/4.0e-02</td>
<td>Cytokine involved in immune response</td>
</tr>
<tr>
<td>IFNG</td>
<td>5.3/3.2</td>
<td>1.0e-03/3.9e-03</td>
<td>Implicated in autophagy regulation</td>
</tr>
<tr>
<td>WDR41</td>
<td>1.6/1.9</td>
<td>1.0e-03/9.6e-03</td>
<td>Activated CDC42 kinase, implicated in cell spreading and migration</td>
</tr>
<tr>
<td>TNK2</td>
<td>2.0/2.8</td>
<td>2.2e-03/2.9e-02</td>
<td>Regulates B-type natriuretic peptide (BNP) production</td>
</tr>
<tr>
<td>CHGB</td>
<td>0.4/0.2</td>
<td>2.5e-03/1.1e-02</td>
<td>Deubiquitinase</td>
</tr>
<tr>
<td>DBI</td>
<td>1.4/1.5</td>
<td>3.0e-03/2.1e-02</td>
<td>Diazepam binding inhibitor</td>
</tr>
<tr>
<td>ST7L</td>
<td>0.7/0.6</td>
<td>6.2e-03/4.0e-02</td>
<td>Suppression of tumorigenicity</td>
</tr>
<tr>
<td>CCNB1</td>
<td>0.4/0.3</td>
<td>6.2e-03/1.2e-02</td>
<td>May negatively regulate cell cycle progression</td>
</tr>
<tr>
<td>DDX25</td>
<td>0.3/0.1</td>
<td>1.5e-02/7.8e-03</td>
<td>ATP-dependent RNA helicase</td>
</tr>
<tr>
<td>TMEM176A</td>
<td>0.6/0.5</td>
<td>1.9e-02/5.0e-02</td>
<td>Transmembrane protein</td>
</tr>
<tr>
<td>PPI1CA</td>
<td>0.7/0.6</td>
<td>2.2e-02/3.5e-02</td>
<td>Involved in cell division, regulation of glycogen metabolism and muscle contractility</td>
</tr>
<tr>
<td>MARK4</td>
<td>1.5/1.7</td>
<td>2.6e-02/5.0e-02</td>
<td>Involved in regulation of the microtubule network and cell cycle progression</td>
</tr>
<tr>
<td>BLMH</td>
<td>0.5/0.4</td>
<td>3.3e-02/3.0e-02</td>
<td>Bleomycin hydrolase</td>
</tr>
<tr>
<td>CRLS1</td>
<td>0.4/0.2</td>
<td>4.8e-02/1.2e-03</td>
<td>Important in maintaining the functional integrity and dynamics of mitochondria</td>
</tr>
</tbody>
</table>

HF-/HF+ = no heart failure/heart failure; P_adj = adjusted P value; PersAF = persistent/permanent atrial fibrillation.

HF–/HF+ (no heart failure/heart failure)
exhibit a specific molecular phenotype, and that most transcriptional changes observed in PersAF are a consequence of AF, rather than a cause. Although in contrast with results from a canine model of early stage AF, this is consistent with previous findings showing absence of AF-induced electrical remodeling in isolated atrial cardiomyocytes from PAF patients.

AF genes are associated with cell cycle, cardiomyocyte structure, and inflammation
Although some of the 35 identified AF genes have no known links with cardiac rhythm, others are involved in pathways linking AF to cardiomyocyte structure, conduction properties, fibrosis, inflammation, molecule trafficking, and endothelial dysfunction. MDM1 and MARK4 (Map/Microtubule

Table 3 Robust differential exon usage associated with PersAF

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon</th>
<th>HF− Fold-change</th>
<th>PersAF− Fold-change</th>
<th>P_adj</th>
<th>HF+ Fold-change</th>
<th>PersAF+ Fold-change</th>
<th>P_adj</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPK10</td>
<td>E330</td>
<td>0.7</td>
<td>0.5</td>
<td>4.6e-02</td>
<td>0.3</td>
<td>0.2</td>
<td>1.1e-02</td>
</tr>
<tr>
<td>EAF1</td>
<td>E001</td>
<td>0.8</td>
<td>0.7</td>
<td>1.4e-02</td>
<td>0.8</td>
<td>0.6</td>
<td>1.6e-03</td>
</tr>
<tr>
<td>EAF1</td>
<td>E011</td>
<td>1.4</td>
<td>1.6</td>
<td>3.3e-02</td>
<td>1.5</td>
<td>1.6</td>
<td>2.1e-02</td>
</tr>
</tbody>
</table>

HF−/HF+ = no heart failure/heart failure; P_adj = adjusted P value; PAF = paroxysmal atrial fibrillation; PersAF = persistent/permanent atrial fibrillation; SR = no history of atrial fibrillation.
Affinity-Regulating Kinase 4) are associated with microtubule organization and play a role in the cell cycle, as do TNK2, CCNDBP1 (Cyclin D-Type-Binding Protein 1), and PPP1CA. MDM1 is a microtubule-binding protein that negatively regulates centriole duplication.\(^20\)

At first glance, the link between upregulated MDM1 expression and AF pathophysiology is not obvious. However, previous studies demonstrated that atrial cardiomyocyte cell cycle stimulation partly prevents fibrosis,\(^21\) suggesting that MDM1 upregulation might be involved in cell cycle inhibition and the formation of fibrosis.

MDM1 is also connected to MDM2, which controls p53, and is relevant for premature aging including early cardiovascular death.\(^22\)

**Figure 5** Gene expression correlation between patients without a history of atrial fibrillation (SR) and persistent/permanent atrial fibrillation (PersAF) in the region around MDM1/IFNG. Top: Correlation matrix for SR (below diagonal) and PersAF (above diagonal). Correlations marked with “x” indicate nonsignificant correlations. Bottom: Close-up of correlations in the region IFNG/IL26/MDM1. Numbers in colored squares indicate significant correlations. IFNG = Interferon-γ; IL26 = Interleukin 26; MDM1 = Mouse Double-Minute 1.

AF patients with and without HF exhibit subtle differences in expression profile enrichment

Expression differences associated with AF were generally comparable between AF/HF− and AF/HF+. However, gene set enrichment analyses suggested subtle differences in pathway and gene ontology enrichment between AF patients with and without HF, highlighting overexpression of genes involved in the (response of the) immune system in AF/HF− patients. In AF/HF+ patients, immune system enrichment was less pronounced. Instead, we found enriched gene sets linked to cellular respiration and cardiac muscle contraction, which may be driven by Ca\(^{2+}\) handling abnormalities associated with HF.\(^5\)

**Differential exon usage highlights the role of EAF1**

Differences in exon usage were observed for MAPK10 and EAF1 in both AF/HF− and AF/HF+. MAPK10 is activated in ischemic tissue; however, neural MAPK10 deficiency may activate pathways involved in promoting blood flow recovery to ischemic limb tissue.\(^30\)

**Correlation analysis suggests differences in transcriptional regulation around MDM1/IFNG**

We found potential coregulation of expression of neighboring transcripts for adjacent AF-related genes IFNG/IL26/MDM1, which were strongly coexpressed in PersAF but not in SR. This may be an example of cross-talk.
among neighboring genes, or it indicate a common regulator, as demonstrated for AF-related genes PITX2c and EN-PEP. IFNG/IL26/IL22/MDM1 were all upregulated in PersAF patients, in line with the role of inflammation in AF pathophysiology.

**Study limitations**

Atrial tissue was obtained during open heart surgery. No information was available on atrial rhythm during surgery, which limited our ability to detect gene expression changes directly affected by heart rhythm. Patients with HF formed a distinct subset (younger patients without hypertension), whereas characteristics of patients with different rhythm statuses were more comparable. Therefore, we performed analyses stratified by HF status. Because no information was available to discern between HF with reduced or preserved ejection fraction, we did not perform an in-depth analysis of gene expression associated with HF, prioritizing the robust detection of AF genes.

**Conclusion**

Using RNA-Seq, we identified novel genes associated with PersAF, irrespective of the presence of HF. Differential exon usage and expression correlation analysis suggested EAF1 and MDM1/IFNG to be important players in the altered transcriptional regulation and response to inflammation in atrial tissue of patients with PersAF. Our findings inform future mechanistic research of AF genes and on novel therapeutic targets in AF patients. Future studies using single nuclei sequencing may disentangle the contribution of distinct cell populations to the pathogenesis of AF and further improve patient stratification based on clinical and genomic data using artificial intelligence approaches.

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**Appendix Supplementary data**

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jhrthm.2022.08.019.

**References**


