RNA-seq profiling of the atrial transcriptome reveals gender-specific patterns and interactions with atrial fibrillation and heart failure

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Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with heart failure (HF) and stroke. Clinical and experimental data from previous studies suggest gender differences in mechanisms and phenotypes of AF: women may have more atrial fibrosis, worse outcomes after catheter ablation, and some women carry a higher risk for thromboembolic complications than men. The molecular mechanisms underlying these differences are still poorly understood.

Methods: Gender-based transcriptional patterns were assessed using paired-end, directional RNA sequencing data generated from atrial tissue biopsies in 199 patients either in sinus rhythm or with paroxysmal or persistent AF as part of the CATCH-ME project. Transcript counts were compared between genders separately in the left and right atria using the DESeq2 package in R. The models were adjusted for potential sources of confounding (age, atrial fibrillation status, heart failure status and sequencing batch). Interaction models were implemented using DESeq2 to compare gender*morbidity interactions for persistent AF and HF. Significance was assessed using likelihood ratio tests comparing models with and without the interaction terms. Results with an adjusted P-value 0.05 were considered significant and utilized for subsequent downstream assessments. Differentially expressed (DE) genes were tested for enrichment of gene ontology (GO) terms and KEGG pathways using the WebGestalt toolkit.

Results: Transcriptome-wide profiling across the cohort identified 33 sex-differentiated genes in the left atria and 51 in the right atrial samples, with 21 of these showing bilateral differences. Interestingly, 36 (44%) of the results from these analyses were comprised of non-coding transcripts, including long non-coding RNAs (lncRNAs), antisense RNAs and pseudogenes. GO and pathway enrichment analyses for these genes revealed their involvement in critical pathways such as the complement and coagulation cascades and RNA transport. Interaction analyses between gender and AF identified two genes (MPP2 & GNAS-AS1) that were differentially transcribed in the right atria and one gene (MYL2) that was DE in the left atria by gender in persistent AF samples. A similar analysis comparing gender*HF morbidity also revealed evidence of DE. Four transcripts (HLA-DQB1-AS1, EIF1AY, UTY and ZFY-AS1) showed gender-specific differences in expression by HF status in left atria, while HLA-DQB1-AS1 was differentially regulated by gender and HF status in right atrial samples.

Conclusions: These RNA-seq analyses provide novel insights into gender-related differences in the transcriptional landscape of right and left adult human atrial appendages. Moreover, interaction analyses identified three genes DE in female atria in persistent AF and four DE genes in female atria in heart failure, providing a molecular anchor for the observed differences in atrial diseases phenotypes between men and women.