Abstract: 699

Side-specific differences in atrial tissue expression are associated with atrial fibrillation and heart failure: the CATCH ME Consortium

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Background/Introduction: The human left (LA) and right atrium (RA) differ substantially in terms of development, structure and function. These differences have implications for both atrial function and pathophysiology; however, on the molecular level, they are poorly understood. RNA sequencing provides an opportunity to explore the atrial transcriptional landscape underpinning this laterality.

Purpose: In the large, well-characterized CATCH ME tissue bank, RNA from human atrial samples was sequenced to assess expression differences between RA and LA and their relationship with atrial fibrillation and heart failure.

Methods: Samples from LA and/or RA appendages were obtained from 199 patients during cardiac surgery. At that time, detailed medical histories, including atrial fibrillation and heart failure status, were determined. Poly-A tailed RNA was extracted from these samples and directional, paired-end libraries were prepared and sequenced. A two-stage study design was implemented. In the first stage, expression differences between LA and RA were assessed in paired samples from the same patients (n=32 patients). The use of paired samples eliminated the possibility of confounding due to comorbidities, medication usage, environmental exposures, surgical indication and other sources. In the independent second stage (n=98 LA and 69 RA samples), differential expression models were adjusted for potential sources of confounding (age, gender, atrial fibrillation status, heart failure, and sequencing batch). Results were significant when they reached transcriptome-wide significance (false discovery rate=0.05) in both stages with a concordant direction of effect.

Results: These analyses identified 714 differentially expressed transcripts, 96% of them previously unobserved. At a false discovery rate=0.05, 3 of these transcripts showed evidence of interaction with atrial fibrillation diagnosis (PRCP, SLC9C1, and SLC52A2), and 7 with heart failure diagnosis (BMP10, ADIPOQ, ATP5S, ADIPOQ-AS1, PITX2, SLN, and SYN2). Both interaction analyses yielded evidence for an enrichment of nominal significance (54 of 714, Phenomial=3.3x10-3 for atrial fibrillation and 86 of 714, Phenomial=1.2x10-13, for heart failure), suggesting other identified transcripts may play a role in these diseases. Differential exon usage was observed for 55 transcripts, suggesting side-specific differences in isoform expression. Some notable genes identified in this analysis included ENPEP (in very close proximity to PITX2), which was also a top hit in the differential expression analyses, GJA5 (somatic mutations in this gene, coding Cx40, have been associated with atrial fibrillation), and OBSCN (interacts with titin and plays a role in myofibrillogenesis).

Conclusion: These results greatly expand our knowledge of the transcriptional differences between adult human
LA and RA and identify a number of transcripts that either cause, or result from, atrial fibrillation and heart
disease.