Filling in the Gaps
Deciphering the Function of Noncoding DNA
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Principal Findings
The authors identified more than 6200 candidate enhancer sequences in adult and fetal human hearts. Interestingly, comparison of putative enhancers from human fetal tissue and age-matched mouse myocardium revealed considerable species-specific differences, as only about one-fifth of fetal human heart enhancer candidates coincided with significant peaks at the orthologous site in the mouse genome. Despite the poor sequence conservation between human and mouse enhancers, the top candidates in each species shared a similar collection of transcription factor binding sites, providing a possible explanation for the activity of even poorly conserved human heart enhancers in transgenic mouse assays, which validated 43 of 65 candidate enhancers tested (66%), a significantly larger proportion than what can be expected by chance alone. Additional support that these genomic regions function as enhancers in human myocardial tissue came from statistical enrichment analysis of functional gene annotations that demonstrated that the predicted enhancers were enriched near genes with known cardiac functions. Importantly, more than twice as many putative enhancers (~5000) were found in fetal heart tissue compared with adult myocardium (~2200) and only half of the enhancers identified in adult tissue were concomitantly found in fetal hearts, suggesting considerable developmental-specific regulation.

Testing the hypothesis that genomic variation within the candidate enhancers carries functional significance, the authors identified several SNPs for gene expression in primary human cells. Because functional variants—particularly eQTLs that map far away from their parent genes (trans eQTLs)—commonly operate in a tissue-dependent manner, the authors examined 81 human fetal candidate enhancers located within 50 kb of 30 selected cardiac genes that are associated with various cardiovascular diseases. They found more than 1500 SNPs in these genomic regions; however, in-depth follow-up studies are needed to elucidate the role of these SNPs for the in vivo activity of the cardiac enhancers and for their potential role in disease processes.
Implications
This study has several important implications: First, the genome-wide annotation of the relatively uncharted noncoding genome is expected to aid in the interpretation of GWAS data and facilitate the functional exploration of how noncoding enhancer variants contribute to cardiac disease. Second, this study highlights the dynamic regulatory architecture of the genome and supports a remarkable heterogeneity of enhancers, characterized by profound species-, tissue-, and developmental-specific activity. As an indication of significant species-specific differences in enhancer sequences, neither direct comparison to mouse ChIP-Seq data nor computational methods based on comparative genomics and sequence conservation between mouse and human DNA were able to accurately predict more than 20–30% of human enhancers identified in the present study. This highlights that mouse enhancers may be of limited value to localize human enhancers and underscores the need for sequencing-based experiments directly from human myocardium. In addition, the differences between enhancers in fetal versus adult myocardium also suggest important implications for disease states, as heart failure is commonly characterized by a reversal to a fetal gene expression pattern. Thus, one can only speculate that substantial differences in enhancer activity also exist between the failing and nonfailing myocardium. Deciphering the role of enhancers in nonfailing and failing hearts will be the next step to understand the complexity of gene expression networks in the failing heart.

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Disclosures
None.
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