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Large-scale identification of tissue-specific enhancers *in vivo*

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Regulatory sequences that control gene expression in time and space play important roles in evolution, phenotypic variation and human disease, but their systematic identification and functional characterization remains a largely unresolved quest. Distant-acting transcriptional enhancers are particularly challenging to uncover because they are scattered among the vast non- coding portion of the genome. We and others have previously used extreme evolutionary conservation to identify human candidate enhancer sequences. Large-scale transgenic mouse assays revealed that many extremely constrained non-coding sequences are tissue-specific transcriptional enhancers active during embryonic development. However, comparative genomic methods fail to predict the spatiotemporal activity patterns of individual enhancers. To address this limitation, we used chromatin immunoprecipitation with the enhancer-associated protein p300, followed by massively parallel sequencing (ChIP-seq) to identify more than 17,000 *in vivo* binding sites of p300 in eight different embryonic mouse tissues. Using a transgenic mouse reporter assay, we determined the embryonic *in vivo* activities of more than 130 of these sequences and show that tissue-specific p300 binding accurately predicts not only the genomic location of tissue-specific enhancers, but also the tissues in which they are active. Our high-confidence predictions of tissue-specific distant-acting enhancers add an important layer of functional annotation to the non-coding portion of the human genome, and we expect them to enable genome-wide studies of the role of enhancers in vertebrate development, human disease and regulatory evolution.

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