HNF4A Transcription Factor Binding Sequences are Widespread in Alu Repeats.

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Abstract

Background: Alu repeats, which account for ~10% of the human genome, were originally considered to be junk DNA. Recent studies, however, suggest that they may play a role in regulating gene expression by providing a platform for transcription factor binding. **Results:** In this study, we show that binding sites for a highly conserved member of the nuclear receptor superfamily of ligand-dependent transcription factors, hepatocyte nuclear factor 4alpha (HNF4a, NR2A1), are highly prevalent in Alu elements. We employ high throughput protein binding microarrays (PBMs) to show that HNF4a binds >66 unique sequences in Alu elements that are present in >1.3 million locations in the human genome. We use chromatin immunoprecipitation (ChIP) to demonstrate that HNF4a binds Alu repeats in the promoters of target genes (*ABCC3, APOA4, APOM, ATPIF1, CANX, FEMT1A, GSTM4, IL32, IP6K2, PRLR, PRODH2, SOCS2, TTR*) and luciferase assays to show that at least some of those Alu elements can modulate HNF4a-mediated transactivation *in vivo* (*APOM, PRODH2, TTR*). Finally, we perform a comparative genomics analysis to shed light on the evolution of HNF4a binding sites in Alu elements. **Conclusions:** Our findings indicate that HNF4a, in addition to regulating gene expression via binding its classical high affinity sites, can also modulate the expression of genes via low affinity sites in Alu. Since those sites are highly redundant in the human genome, the cumulative effect may be quite large and have an impact on the HNF4a transcriptome.