# So fragile, so human: A comparative view of noncoding DNA regions involved in the evolution of the human mind and in its genetic disorders

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**Abstract**:
The development of the human mind, with its complex cognitive abilities and emotional depth, begins with the precise regulation of gene expression during embryogenesis. This regulation involves both coding DNA (which produces proteins) and non-coding DNA elements that fine-tune gene expression in space and time. The unique features of the human brain (such as the number of neurons, the complexity of neuronal connections, and the diversity of brain regions) distinguish humans from other species, including great apes.
This study focuses on non-coding DNA sequence variants (DSVs) linked to neurodevelopmental and psychiatric disorders, such as autism, schizophrenia, bipolar disorder, and major depression. We compare these DSVs with non-coding DNA sequences that exhibit human-accelerated evolution (Human Accelerated Regions, HARs; Human Gained Enhancers, HGEs), believed to be key drivers in the evolution of human-specific brain and cognitive characteristics. We highlight significant overlaps and note that these sequences are located within regions with epigenetic signatures typical of transcriptional enhancers. We use long-range interaction maps (RNApolII-ChIA-PET) to link these enhancers to specific genes through enhancer-promoter interactions. We will experimentally validate the activity of selected enhancers in zebrafish brain. This model provides a means to explore the roles of these enhancers and associated genes in brain development, neuronal differentiation, and function.
We propose that these non-coding DNA elements are essential for orchestrating the spatial and temporal patterns of gene expression that are critical for brain development and function. Variations in these elements can either enhance gene regulation, promoting normal brain function, or disrupt gene expression, contributing to mental health disorders. Our findings underscore how small but impactful changes in non-coding DNA can influence brain development, mental health, and the evolution of human cognition.
By identifying and studying these regions, we aim to provide novel insights into the molecular foundations of the evolution of the human mind and the genetic factors that influence mental health.