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Lineage-specific DNA hypomethylation impacts on complex traits in Human

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Introduction

The cross-species characterization of evolutionary changes in the functional genome can facilitate the translation of genetic findings across species and the interpretation of the evolutionary basis underlying complex phenotypes. A better understanding of the evolutionary divergence in DNA methylation in humans will enable us to unveil the regulatory mechanisms underlying humans-specific molecular and complex phenotypes.

Materials and Methods

To investigate the evolutionary features of DNA methylation and their impacts on gene expression , we integrated 160 whole-genome bisulfite sequencing and RNA sequencing datasets from three somatic tissues (i.e., brain, liver, and skeletal muscle) and sperm, representing all three germ layers and germline cells across seven mammals, including humans, mice, pigs, dog, sheep, goats and cattle. We explored phylogeny-specific and tissue-specific variations in epigenomic marks and their potential functional implications. Finally, we explored the impact of HMR evolution on gene expression and complex traits by examining large GWAS summary statistics and gene expression eQTLs in humans.

Results and Discussion

We systematically characterized the evolutionary dynamics of DNA methylation and gene expression in three somatic tissues and sperm across seven mammalian species, including humans, mice, pigs, dog, sheep, goats and cattle. We observed the evolutionary characteristic of DNA hypomethylation in a tissue-type dependent manner. Furthermore, by integrating multi-tissue gene expression quantitative trait loci (eQTLs) and genome-wide association studies (GWAS) of 57 human traits, we provided novel insights into the genetic and evolutionary basis of gene expression and complex phenotypes. Compared with species-specific HMRs, conserved HMRs exhibited a greater enrichment for lead eQTL and heritability of most of complex traits in humans. In addition, human-specific HMRs in three somatic tissues and sperm showed significant enrichment for some complex traits, even though the number of enriched traits was much smaller than that for conserved HMRs. Collectively, these results suggest that HMRs with different evolutionary constraints contribute disproportionately to complex traits and diseases in humans.

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