



HEpD: A database describing epigenetic differences between Thoroughbred and Jeju horses



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ABSTRACT

With the advent of next-generation sequencing technology, genome-wide maps of DNA methylation are now available. The Thoroughbred horse is bred for racing, while the Jeju horse is a traditional Korean horse bred for racing or food. The methylation profiles of equine organs may provide genomic clues underlying their athletic traits. We have developed a database to elucidate genome-wide DNA methylation patterns of the cerebrum, lung, heart, and skeletal muscle from Thoroughbred and Jeju horses. Using MeDIP-Seq, our database provides information regarding significantly enriched methylated regions beyond a threshold, methylation density of a specific region, and differentially methylated regions (DMRs) for tissues from two equine breeds. It provided methylation patterns at 784 gene regions in the equine genome. This database can potentially help researchers identify DMRs in the tissues of these horse species and investigate the differences between the Thoroughbred and Jeju horse breeds.

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1. Introduction

DNA methylation at the cytosine of CpG dinucleotides is a biochemical modification that regulates gene expression in eukaryotic genomes. It is involved in many biological processes like genomic imprinting, development, and cell differentiation by epigenetic modification. Abnormal DNA methylation has been implicated in diseases including cancer (Bird, 2002; Robertson, 2005; Klose and Bird, 2006; Illingworth et al., 2008). With the advent of next generation sequencing (NGS) technologies, genome-wide DNA methylation data is now publicly available in many human disease samples. The ENCODE project provided researchers with the function of each human and mouse genomic region. In other species including economic animals, raw genome-wide DNA

methylation data has been provided (Li et al., 2011; Sati et al., 2012), but these data are difficult to analyze and information is scattered across a wide number of sources. In order to overcome this deficiency, we have developed a DNA methylation database for Thoroughbred and Jeju horse cerebrum, lung, heart, and skeletal muscle tissues. The Horse Epigenetic Database (HEpD) provides the methylation peaks of each genomic region, and differentially methylated regions (DMRs) in four tissues of the two horse breeds.

Many bioinformatics tools provide methylation patterns for each genomic region in humans. Abnormal methylation patterns were confirmed by many databases based on the results of whole-genome methylation analysis (He et al., 2008; Hackenberg et al., 2011; Lv et al., 2012). Tissue-specific methylation patterns were also provided in humans (Xin et al., 2012; James et al., 2013). However, these databases concentrated solely on the human genome. Although genome-wide DNA methylation data in organisms, besides humans and plants, have been made accessible to the public, there have been few freely available databases until now.

Thoroughbred horses are intentionally selected for speed, stamina, and agility. Therefore, Thoroughbred horses have many specific genetic characteristics related to horse economic traits, like genotype, SNPs, and

Abbreviations: HEpD, Horse Epigenetic Database; DMR, differentially methylated region; NGS, next generation sequencing; ENCODE, encyclopedia of DNA elements; SNP, single nucleotide polymorphism; TE, transposable element; MeDIP-Seq, Methylated DNA ImmunoPrecipitation Sequencing.

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transcripts (McGivney et al., 2009; Hill et al., 2010a; Hill et al., 2010b; Park et al., 2012). Jeju horses are the descendants of 160 Mongolian horses that have inhabited and been bred since 1276 on Jeju Island, South Korea (Nam, 1969). Compared to the Thoroughbred, the Jeju horse is hardy, small, and often used for racing or as a food source. Analysis of the Jeju horse is valuable for identifying Jeju-specific traits and conservation of the Korean genetic resource. This study is to provide information about DMRs between four tissues as well as between two different horse breeds.

Transposable elements (TEs) make up approximately 30–50% of the mammalian genome. The expression of TEs induces genome instability, thus the host genome maintains DNA methylation in order to inhibit TE expression (Carnell and Goodman, 2003; Girardot et al., 2006). Variation of DNA methylation state in TE regions could induce a change in the genome defense system. Comparing DMRs between the TEs could provide interesting research topics. This database provides TE location and insertion direction along with their DNA methylation state.

Providing genomic information and constructing a web-based database of DNA methylation patterns is generally useful for performing further functional studies as well as for elucidating tissue-specific or breed-specific traits. This database provides the relatively highly-methylated regions in the whole genome, and an additional selection option helps to compare the methylation of two equine breeds in four tissues. We also provide the 'Gene index' option for easily comparing gene regions between tissues of the two equine breeds. In order to enhance the further studies of database users, we have linked our results pages to the related UCSC Genome Browser and Ensembl database for each genomic region. Results are presented as a web page or in Microsoft Excel format. The HEpD will provide insight for the functional study of methylation and potential roles for finding tissue-specific and breed-specific methylation patterns.

2. Material and methods

2.1. Sample information

We performed methylated DNA immunoprecipitation followed by next-generation sequencing (MeDIP-Seq) in four tissues (cerebrum,

lung, heart, and skeletal muscle) derived from genomic DNA from each individual of Thoroughbred and Jeju horses (Lee et al., 2014) (Table S1). All animal protocols (ethical procedures and scientific care) used in this study were reviewed and approved by the Pusan National University-Institutional Animal Care and Use Committee (PNU-IACUC; Approval Number PNU-2013-0411).

2.2. Data source generation of datasets

A total of eight genomic DNA were extracted from tissues, then sonicated and immunoprecipitated for MeDIP-Seq analysis. The DNA libraries were constructed by paired-end sequencing with a lead length of 50 bp via the Illumina HiSeq 2000. Sequence data were aligned to the horse reference genome (equCab2) by using the SOPAligner ver. 2.21 (Li et al., 2009). The information on data production and alignment was indicated in Table S2, and genome coverage variation with sequence read depth was analyzed (Table S3). The peak scanning was carried out by MACS (version 1.4.2) with a cutoff P-value of 1×10^{-4} (Zhang et al., 2008).

2.3. Identity methylation states

The location of a methylation peak was converted to a *.csv file and then stored in a MySQL database. The genomic regions and their corresponding methylation values were stored. Each methylation peak resolution is 50 bp. As shown in Fig. 1, we classified the methylation peak values into three categories for subsequent studies. First, Type I provides the methylation values and coordinates of peaks that pass a certain threshold set by the user (Fig. 1A). Second, the user can input a specific region in the horse genome; The Type II category will return the methylation peak values in the user-specified region (Fig. 1B). Lastly, the Type III search will identify regions with differential methylation between the Thoroughbred and Jeju horses. The degree of difference can be specified by the user. To compare the methylation peak values between two breeds, the Type III search is recommended (Fig. 1C).

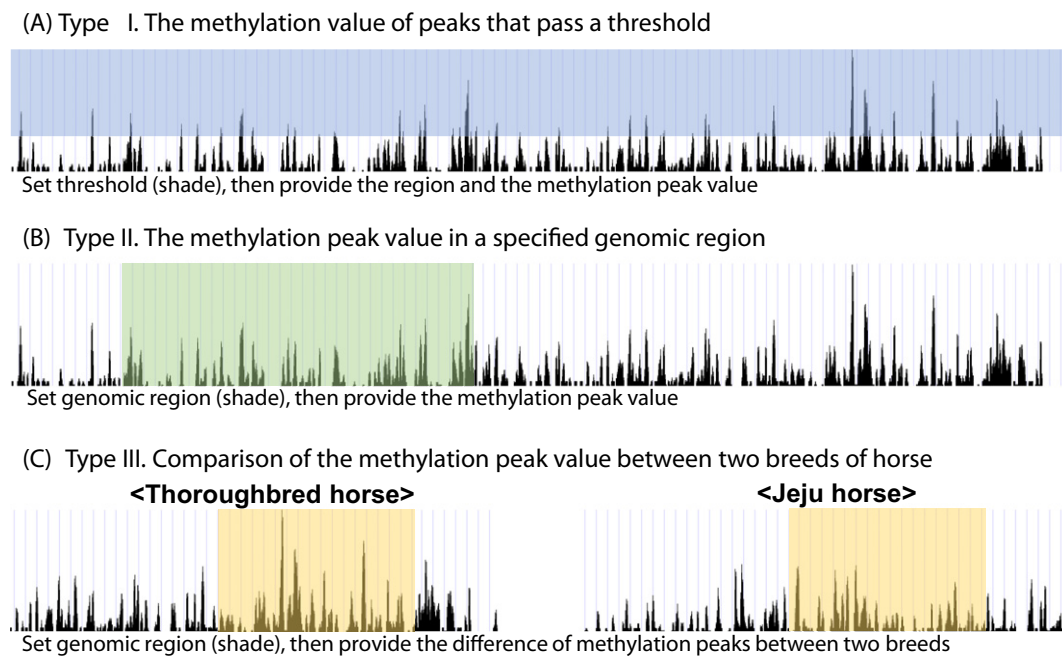


Fig. 1. The three strategies used by HEpD for finding methylated regions. (A) This strategy provides the methylation peak values that pass a user-set threshold (Type I). (B) This strategy displays methylation peak values within a specified genomic region (Type II). (C) This strategy displays the differentially methylated peak values that pass a user-set threshold (Type III) of the Thoroughbred and Jeju horses.

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