Epigenomic data facilitate genetic studies for osteoporosis in post-GWAS era

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Osteoporosis is a highly prevalent skeletal disease characterized by reduced bone mass and micro-architectural alterations. Similar to breast cancer and stroke, the rate of mortality related to osteoporotic fractures ranges from 15% to 30% (1). Bone mineral density (BMD) is the golden standard in diagnosing osteoporosis and genome-wide association studies (GWASs) have identified many genetic loci for BMD. However, missing heritability is still a problem since current known susceptibility loci can only explain a relatively small fraction of estimated heritability for osteoporosis (2). True association signals may be missed due to the stringent statistical significance thresholds of GWASs. The effectiveness of finding missing heritability by increasing sample size is limited (2).

Recently, the Encyclopedia of DNA Elements (ENCODE) (3) and Epigenome Roadmap projects (4) have released abundant epigenomic data for genome annotation. With these data, most of the GWASs SNPs were found to be located near or within epigenomic elements (3,5), reminding us that known susceptibility genes associated with BMD may share common regulatory characteristics. We carried out enrichment analyses (6) and found that these genes were tended to be affected by repressive or inactive epigenomic marks, such as EZH2 and H3K27me3. The epigenomic character we summarized provided possible clues for further studies which aimed to explore the action pathways of the susceptibility genes.

We further hypothesized that enriched regulatory characteristics for known BMD genes may be used to predict novel susceptibility genes. Our analyses and subsequent functional experiments (6) results did support our hypothesis and *BDNF* was identified as a novel *BMD* gene. Our study opened a new avenue to address the missing heritability problem for complex diseases. In addition, since epigenomic information was considered in the analysis process, the novel genes we identified are likely to be functional. Consistently, we performed short interfering RNA (siRNA) knock-down experiments for *BDNF* and the results showed that inhibition of *BDNF* may disrupt bone formation.

The aim of genetic studies for complex diseases is to find susceptibility genes and offer targets for therapeutic studies. During the past decade, GWASs have offered a large amount of potential markers. However, the mechanisms of the identified variants are mostly unclear, especially for the non-coding variants. Public epigenomic data facilitate our understanding of the GWASs signals (7). Our study (6) provided a guide pipeline for integrating epigenomic elements and GWASs results. Studies on other complex diseases using the same strategy are encouraged.

Limitations of our study should be acknowledged. Firstly, as mentioned by Dr. Morris (8), the SNPs (rs11030119 and rs7124442) we validated successfully have a relatively low minor allele frequencies (MAFs). As it might be expected, the MAFs of our sample were similar to that of the East Asian population in the 1,000 Genome project. Replication study with larger sample size in East Asian or in other ethnic populations is needed to confirm their associations with fracture. Secondly, as it also mentioned by Dr. Morris (8), we only used data from ENCODE and

some cell lines we used were not directly relevant to bone. We didn't exclude any cell lines because osteoporosis is a typical complex disease, involving various biological and metabolism processes (9). We started our project right before the release of Roadmap data (4). So we didn't use the epigenomic data from primary tissues in the Roadmap project (4). Data directly from bone tissues are still unavailable currently. We believed that the interpretation of GWAS results would be more precise once these data are accessible. Lastly, we only focused on the promoter regions, which might neglect potential epigenomic information from other genetic regions. However, integrating all SNPs and epigenomic data would generate a large amount of data with excessive computational demands. New analysis strategy is needed to handle such abundant data.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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