

Human Genome Center

Laboratory of Genome Technology

シーケンス技術開発分野

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The major goal of our group is to identify genes of medical importance, and to develop new diagnostic and therapeutic tools. We have been attempting to isolate genes involving in carcinogenesis and also those causing or predisposing to various diseases as well as those related to drug efficacies and adverse reactions. By means of technologies developed through the genome project including a high-resolution SNP map, a large-scale DNA sequencing, and proteome/metabolome analysis, we have isolated a number of biologically and/or medically important genes, and are developing novel diagnostic and therapeutic tools.

1. Functional analysis of p53 signaling pathway Regulation of the innate immune response and gut microbiome by p53

p53 is a key tumor suppressor mutated in half of human cancers. In recent years, p53 was shown to regulate a wide variety of functions. From the transcriptome analysis of 24 tissues of irradiated mice, we identified 553 genes markedly induced by p53. Gene Ontology (GO) enrichment analysis found that the most associated biological process was innate immunity. 16S rRNA-seq analysis revealed that Akkermansia, which has anti-inflammatory properties and is involved in the regulation of intestinal barrier integrity, was decreased in p53-knockout (p53^{-/-}) mice after radiation. p53^{-/-} mice were susceptible to radiation-induced GI toxicity and had a significantly shorter survival time than p53-wild-type (p53^{+/+}) mice following radiation. However, administration of antibiotics resulted in a significant improvement in survival and protection against GI toxicity. Mbl2 and Lcn2, which have antimicrobial activity, were identified to be directly transactivated by p53 and secreted by liver into the circulatory system. We also found the expression of MBL2 and LCN2 was decreased in liver cancer tissues with p53 mutations compared with those without p53 mutations. These results indicate that p53 is involved in shaping the gut microbiome through its

downstream targets related to the innate immune system, thus protecting the intestinal barrier.

2. Analysis of host genetic factors of various diseases

Genotype imputation accuracy and the quality metrics of the minor ancestry in multi-ancestry reference panels

Large-scale imputation reference panels are currently available and have contributed to efficient genome-wide association studies through genotype imputation. However, whether large-size multi-ancestry or small-size population-specific reference panels are the optimal choices for under-represented populations continues to be debated. We imputed genotypes of East Asian (180k Japanese) subjects using the Trans-Omics for Precision Medicine reference panel and found that the standard imputation quality metric (Rsq) overestimated dosage r^2 (squared correlation between imputed dosage and true genotype) particularly in marginal-quality bins. Variance component analysis of Rsq revealed that the increased imputed-genotype certainty (dosages closer to 0, 1 or 2) caused upward bias, indicating some systemic bias in the imputation. Through systematic simulations using different template switching rates (θ value) in the hidden Markov model, we revealed that the lower θ

value increased the imputed-genotype certainty and Rsq; however, dosage r^2 was insensitive to the θ value, thereby causing a deviation. In simulated reference panels with different sizes and ancestral diversities, the θ value estimates from Minimac decreased with the size of a single ancestry and increased with the ancestral diversity. Thus, Rsq could be deviated from dosage r^2 for a subpopulation in the multi-ancestry panel, and the deviation represents different imputed-dosage distributions. Finally, despite the impact of the θ value, distant ancestries in the reference panel contributed only a few additional variants passing a predefined Rsq threshold. We conclude that the θ value substantially impacts the imputed dosage and the imputation quality metric value.

Identification of a novel genetic variant associated with osteoporosis: insights from the Taiwan Biobank Study

Purpose

The purpose of this study was to identify new independent significant SNPs associated with osteoporosis using data from the Taiwan Biobank (TWBB).

Material and Methods

The dataset was divided into discovery (60%) and replication (40%) subsets. Following data quality control, genome-wide association study (GWAS) analysis was performed, adjusting for sex, age, and the top 5 principal components, employing the Scalable and Accurate Implementation of the Generalized mixed model approach. This was followed by a meta-analysis of TWBB1 and TWBB2. The Functional Mapping and Annotation (FUMA) platform was used to identify

osteoporosis-associated loci. Manhattan and quantile-quantile plots were generated using the FUMA platform to visualize the results. Independent significant SNPs were selected based on genome-wide significance ($P < 5 \times 10^{-8}$) and independence from each other ($r^2 < 0.6$) within a 1 Mb window. Positional, eQTL (expression quantitative trait locus), and Chromatin interaction mapping were used to map SNPs to genes.

Results

A total of 29 084 individuals (3154 osteoporosis cases and 25 930 controls) were used for GWAS analysis (TWBB1 data), and 18 918 individuals (1917 cases and 17 001 controls) were utilized for replication studies (TWBB2 data). We identified a new independent significant SNP for osteoporosis in TWBB1, with the lead SNP rs76140829 (minor allele frequency = 0.055, P -value = 1.15×10^{-08}). Replication of the association was performed in TWBB2, yielding a P -value of 6.56×10^{-3} . The meta-analysis of TWBB1 and TWBB2 data demonstrated a highly significant association for SNP rs76140829 (P -value = 7.52×10^{-10}). In the positional mapping of rs76140829, 6 genes (*HABP2*, *RP11-481H12.1*, *RNU7-165P*, *RP11-139 K1.2*, *RP11-57H14.3*, and *RP11-214 N15.5*) were identified through chromatin interaction mapping in mesenchymal stem cells.

Conclusions

Our GWAS analysis using the Taiwan Biobank dataset unveils rs76140829 in the *VTI1A* gene as a key risk variant associated with osteoporosis. This finding expands our understanding of the genetic basis of osteoporosis and highlights the potential regulatory role of this SNP in mesenchymal stem cells.

Publications

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