

Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases

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Clinical measurements can be viewed as useful intermediate phenotypes to promote understanding of complex human diseases. To acquire comprehensive insights into the underlying genetics, here we conducted a genome-wide association study (GWAS) of 58 quantitative traits in 162,255 Japanese individuals. Overall, we identified 1,407 trait-associated loci ($P < 5.0 \times 10^{-8}$), 679 of which were novel. By incorporating 32 additional GWAS results for complex diseases and traits in Japanese individuals, we further highlighted pleiotropy, genetic correlations, and cell-type specificity across quantitative traits and diseases, which substantially expands the current understanding of the associated genetics and biology. This study identified both shared polygenic effects and cell-type specificity, represented by the genetic links among clinical measurements, complex diseases, and relevant cell types. Our findings demonstrate that even without prior biological knowledge of cross-phenotype relationships, genetics corresponding to clinical measurements successfully recapture those measurements' relevance to diseases, and thus can contribute to the elucidation of unknown etiology and pathogenesis.

Clinical laboratory measurements (e.g., blood test results) are powerful intermediate phenotypes that can be used to diagnose and monitor human diseases. Elucidation of the underlying genetics, as well as inference of genetic relationships to diseases and implicated cell types, can provide clues about disease biology. To this end, GWASs have been conducted to investigate various quantitative traits, including anthropometric^{1–3}, metabolic^{4–6}, kidney-related⁷, hematological^{8–10}, and blood pressure traits^{11–13}. The interplay between the genetics of quantitative traits and diseases has been assessed by several approaches, such as pleiotropy^{14–16}, genetic correlation^{17–19}, and Mendelian randomization²⁰. For example, recent large-scale studies of body mass index (BMI), a key measure for assessing obesity, revealed shared genetic effects on metabolic traits and the involvement of the central nervous system¹ and immune cells² in obesity susceptibility. However, previous studies primarily examined subjects of European ancestry, and each study separately focused on few quantitative traits. For the creation of a comprehensive landscape, additional studies of non-European populations are warranted that simultaneously investigate a wide range of clinical measurements and extensively interrogate their relevance to complex diseases.

Here we report a GWAS of 58 quantitative traits in 162,255 Japanese individuals from the BioBank Japan Project (BBJ)^{21,22}, one of the largest non-European single-descent biobanks with detailed phenotypes, to broaden the current knowledge and understanding

of the genetics and biology of these traits. Moreover, we incorporated additional GWASs of complex diseases and traits in Japanese subjects, and evaluated pleiotropy, genetic correlation, and cell-type specificity with respect to the quantitative traits. Our study provides many insights into the genetic basis of various quantitative traits and illuminates the complex genetic links among clinical measurements, complex diseases, and relevant cell types.

Results

Genome-wide association analysis of 58 quantitative traits. We tested 5,961,600 autosomal variants and 147,353 X-chromosome variants (imputed with 1000 Genomes Project Phase 1²³; Methods) for association with 58 quantitative traits in 162,255 Japanese individuals. The studied traits covered a wide range of clinical measurements, grouped into nine distinct categories (Table 1): metabolic ($n=8$), serum protein ($n=4$), kidney-related ($n=4$), electrolyte ($n=5$), liver-related ($n=6$), other biochemical ($n=6$), hematological ($n=15$), blood pressure ($n=4$), and echocardiographic ($n=9$). The study design is illustrated in Supplementary Fig. 1, and the detailed characteristics of the subjects, phenotype source, and exclusion criteria are described in Supplementary Tables 1 and 2.

Overall, we identified 1,407 trait-associated loci for 53 quantitative traits that satisfied a genome-wide significance threshold of $P=5.0 \times 10^{-8}$ (Methods). Of these, 679 loci were novel (Table 1 and Supplementary Table 3). When we applied multiple-testing

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Genetic Analysis Of Quantitative Traits

G Thomas



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Table of Contents Genetic Analysis Of Quantitative Traits

1. Understanding the eBook Genetic Analysis Of Quantitative Traits
 - The Rise of Digital Reading Genetic Analysis Of Quantitative Traits
 - Advantages of eBooks Over Traditional Books
2. Identifying Genetic Analysis Of Quantitative Traits
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Genetic Analysis Of Quantitative Traits
 - User-Friendly Interface
4. Exploring eBook Recommendations from Genetic Analysis Of Quantitative Traits
 - Personalized Recommendations
 - Genetic Analysis Of Quantitative Traits User Reviews and Ratings
 - Genetic Analysis Of Quantitative Traits and Bestseller Lists
5. Accessing Genetic Analysis Of Quantitative Traits Free and Paid eBooks
 - Genetic Analysis Of Quantitative Traits Public Domain eBooks
 - Genetic Analysis Of Quantitative Traits eBook Subscription Services
 - Genetic Analysis Of Quantitative Traits Budget-Friendly Options
6. Navigating Genetic Analysis Of Quantitative Traits eBook Formats
 - ePub, PDF, MOBI, and More
 - Genetic Analysis Of Quantitative Traits Compatibility with Devices
 - Genetic Analysis Of Quantitative Traits Enhanced eBook Features
7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Genetic Analysis Of Quantitative Traits
 - Highlighting and Note-Taking Genetic Analysis Of Quantitative Traits
 - Interactive Elements Genetic Analysis Of Quantitative Traits

8. Staying Engaged with Genetic Analysis Of Quantitative Traits
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Genetic Analysis Of Quantitative Traits
9. Balancing eBooks and Physical Books Genetic Analysis Of Quantitative Traits
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Genetic Analysis Of Quantitative Traits
10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
11. Cultivating a Reading Routine Genetic Analysis Of Quantitative Traits
 - Setting Reading Goals Genetic Analysis Of Quantitative Traits
 - Carving Out Dedicated Reading Time
12. Sourcing Reliable Information of Genetic Analysis Of Quantitative Traits
 - Fact-Checking eBook Content of Genetic Analysis Of Quantitative Traits
 - Distinguishing Credible Sources
13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
14. Embracing eBook Trends
 - Integration of Multimedia Elements
 - Interactive and Gamified eBooks

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