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An Integrated Genetic Analysis of Disease

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STANDFIRST

A recent GWAS of quantitative traits (clinical lab measurements) was performed and incorporated with additional GWAS of a variety of complex diseases in Japanese subjects. Together, the data demonstrated pleiotropy, genetic correlation, and cell type specificity in regard to quantitative disease traits as predictors of multiple complex diseases.

Clinical laboratory measurements are valuable intermediate phenotypes that are used to diagnose and monitor the progression of disease. These intermediate phenotypes, or quantitative traits, have been the basis of many genome wide association studies (GWAS) (1). The present study by Kanai and colleagues (2) incorporated the results of a GWAS of a number of commonly-obtained clinical lab measurements, as quantitative traits, with a GWAS of a number of complex diseases in Japanese subjects. Together, the data demonstrated pleiotropy, genetic correlation, and cell type specificity in regard to quantitative traits as predictors of multiple complex diseases. The results of this study indicate that clinical lab measurements can provide important insight into the genetics and etiology of complex disease.

Kanai and colleagues initially examined the association between autosomal and X-chromosomal variants and quantitative traits in over 160,000 Japanese subjects from the Bio Bank Japan Project (2,3,4). The 58 quantitative traits included blood pressure and echocardiography-related phenotypes in addition to the results of blood tests pertaining to metabolic function, serum proteins and electrolytes, kidney-related metabolites, liver-related metabolites, and hematological indices. The GWAS identified 1,407 trait-associated loci for 53 of the quantitative traits. Interestingly, pleiotropy, the sharing of risk alleles across multiple traits (5), was observed for 88 loci for traits across multiple traits (intercategorical) and 225 loci across traits in a single category. Among genetic loci demonstrating the greatest pleiotropy between traits were *ALDH2* which was associated with 21 traits in seven categories (including metabolic-, kidney-, and blood pressure-related phenotypes); *GCKR* which associated with 18 traits in seven categories (including kidney-related phenotypes); *ABO* which associated with 15 traits in six categories; and *RGS12* which associated with nine traits in six categories (including kidney-related traits). A subsequent analysis was then undertaken to estimate polygenic correlations across 57 of the original traits in addition to body mass index (BMI) and adult height. Over 170 genetic correlations with 100

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intercategorical correlations were observed between traits. The greatest number of significant correlations was observed with BMI, which correlated with 22 traits in seven categories including blood pressure, total protein in the blood, and body height. The observed pleiotropic associations and correlations across quantitative traits indicate that these traits share common genetic pathways.

To explore the correlations between the intermediate phenotypes and disease, the above GWAS were incorporated with 30 case-control GWAS results for complex diseases in Japanese subjects. The disease categories included: metabolic disease, cardiovascular disease, allergic disease, autoimmune disease, infectious disease, hematological disease, psychiatric disorders, musculoskeletal disease, cancer, and other complex diseases. A pairwise analysis demonstrated 68 significant genetic correlations between the quantitative traits and the complex diseases. Interestingly, over 75% of the correlations involved cardiometabolic diseases (type 2 diabetes, ischemic stroke, cerebral aneurysm, myocardial infarction, peripheral artery disease, and atrial fibrillation) which correlated with traits in seven of the measured categories including measured indices in the metabolic-, blood pressure-, and echocardiographic-related categories. While many of the associations were predictable, notable correlations were also observed between ischemic stroke and uric acid, between myocardial infarction and the plasma albumin to globulin ratio, between urolithiasis and systolic blood pressure, and between asthma and systolic blood pressure. The authors then constructed a network from the matrix of the genetic correlations which demonstrated distinctive clusters of biologically-related phenotypes and a close interrelationship between cardiometabolic diseases and biomarkers which were interconnected with kidney- and liver-related as well as hematological traits. These observations provide insight into expected and somewhat surprising relationships between genetic loci, quantitative traits, and disease.

Finally, the results from the quantitative trait and the disease GWAS were used along with cell-type specific annotations for histone modifications to assess the cell-type specificity of human traits and diseases on the basis of heritability enrichment (2,6,7). The initial analysis demonstrated heritability enrichments in cell-type groups consistent with known biology (e.g. kidney cell type groups were enriched for estimated glomerular filtration rate). A subsequent analysis of individual cell types identified 384 significant heritability enrichments for 50 quantitative traits and diseases. A clustering analysis then demonstrated that distinct clusters comprised related traits and cell types with the most distinct cluster involving immune and hematopoietic cell types enriched in immune-related diseases and traits. A network matrix was then constructed to highlight shared cell types involved traits and disease. The largest network was composed of clusters associated with WBC count, lymphocyte count, and height.

The present study provides potentially important insight into the relationships between genetic loci, intermediate phenotypes, and diseases. As depicted in Figure 1, genetic loci harbor variants that are associated with multiple, sometimes distinct, quantitative traits. Similarly, associations were drawn between genetic variants and complex diseases. The correlations observed between the GWAS of the traits and diseases supports the biological relevance between clinical traits and diseases and provides an opportunity for further study to determine cause and effect relationships. While many of the correlations drawn between

the GWAS of traits and diseases would appear to have a similar biological origin (i.e. the observed correlations between cerebral aneurysm and myocardial infarction with blood pressure-related quantitative traits), other correlations are less obvious (e.g. urolithiasis and blood pressure-related traits), have not been extensively studied or described (8), and provide the opportunity to examine potential causative relationships. The GWAS results identify potentially important genetic loci, but it is important to note that these studies, by design, only identify associations and do not yield a particular gene target or mechanism (1); subsequent study will be necessary to directly connect alterations in genetic sequence with differences in quantitative traits. Finally, DNA sequence alone is unlikely to fully explain common and complex diseases as environmental factors can lead to epigenetic modifications of the DNA, and alterations in profiles of RNA, proteins, and metabolites with resulting changes in physiological function (9).

In summary, Kanai et al conducted a large GWAS on non-European subjects to identify previously described and novel genetic loci for quantitative traits in Japanese individuals. A further incorporation of GWAS for complex diseases permitted the identification of pleiotropic loci, genetic correlations, and cell-type specificity. Together, these results confirm previous observations and provide novel information and insight into disease biology.

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Biography

Dr. David Mattson's laboratory examines the normal and pathophysiological regulation of renal function and arterial blood pressure. Particular emphasis is placed on the paracrine, autocrine, and hormonal regulation of renal tubular and vascular function. Additional studies are geared toward an understanding of the genetic basis of hypertension and renal disease.

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Figure 1.

GWASs demonstrated genetic associations with intermediate phenotypes and diseases in Japanese subjects. A further analysis of the GWAS data indicated that similar loci associate with both intermediate phenotypes and diseases providing additional biological insight. The correlations between phenotypes and disease may provide predictive power and serve as the basis for further study to investigate disease.