【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project : Establishment of a novel strategy for pathological analysis of multifactorial diseases using genetic risk variants

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Research Project Number : 18H05285 Researcher Number : 80191394
Keyword : multifactorial disease, genome-wide association study, risk variants

【Purpose and Background of the Research】

The purpose of this study is to establish a method for identifying causal intermediate phenotypes in the research of human multifactorial diseases based on the principle that genomic factors clearly indicate causality to disease. Recent findings have indicated that the majority of disease risk variants in multifactorial diseases affect gene expression or splicing. In our study, we will focus on immune diseases. Using genetic information, factors having a causal relationship with diseases will be identified from intermediate phenotypes, such as gene expression, epigenetic changes, protein expression, and cellular alterations, among others. These data will enable the pathogenesis of diseases to be more clearly understood, and facilitate the development of new therapies. Once our method has been established, it could also be applied to multifactorial diseases other than immune diseases.

【Research Methods】

The effects of risk variants, such as single nucleotide polymorphisms (SNP), which are identified in genome-wide association study (GWAS), can be elucidated by combining and analyzing various cellular phenotypes and risk variants. Therefore, we will construct datasets of the relationships between gene expression and genetic variants in subsets of immunocompetent cells. To avoid the influence of diseases or treatments, and to obtain clear causal relationships between the genetic variants and intermediate phenotypes, peripheral blood of healthy individuals will be mainly analyzed. After separating cells into approximately 20 different cell subsets with a cell sorter, gene expression analysis and epigenetic analyses will be carried out. We will then combine and analyze the disease risk variants in each subset according to gene expression, splicing, and epigenetic alternations

【Expected Research Achievements and Scientific Significance】

Many diseases have been studied using animal models, but the differences between humans and these animal models remain a major obstacle for clinical application. With human studies, data can be obtained for some intermediate phenotypes, but the identification of causal factors remains difficult. Data without a demonstrated causal relationship is less useful for subsequent research. Therefore, our system for identifying causal factors of diseases will enable us to gain more information to better understand the exact pathogenesis of diseases for developing new therapies.

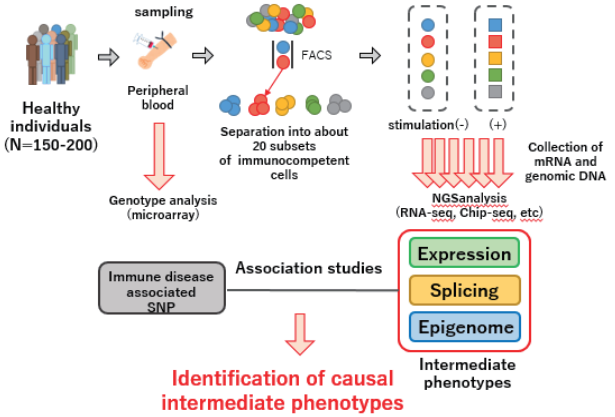

Figure: Novel analysis of multifactorial diseases with risk variants

【Publications Relevant to the Project】

・Ishigaki K, Kochi Y, Suzuki A, et al. and Yamamoto K. Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis. **Nat Genet**, 2017;49;1120-1125
・Okada Y, Wu D, Trynka G, (+94), Matsuda F, Yamamoto K, and Plenge RM. Genetics of rheumatoid arthritis contributes to biology and drug discovery, et al. **Nature**. 2014; 506:376-81

【Term of Project】 FY2018-2022

【Budget Allocation】 148,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.riken.jp/research/labs/ims/autoimmun_dis/