Decoding the Genetic Puzzle: Unravelling HLA & KIR Association with complex diseases

Seik-Soon Khor

Genome Medical Science Project
National Center for Global Health and Medicine, Japan

Abstract

Human leukocyte antigen (HLA) and killer cell immunoglobulin-like receptors (KIR) has been reported to be associated with various diseases and traits. Natural killer (NK) cells are essential in innate immunity as well as playing a role in antigen-specific responses. NK cell function is based on a myriad of complex interactions mediated by membrane-bound and soluble gene products. Among that collective, NK cell activity is genetically modulated by differential expression of inhibitory and activating killer cell immunoglobulin-like receptors (KIR) that recognize HLA class I ligands. The high level of both allelic and gene copy number polymorphism of KIR may have resulted from selection pressure driven by exposure to a wide variety of diseases, possibly in parallel with or causally related to selection pressure underlying HLA polymorphism. Indeed, coordinated KIR-HLA associations have been detected with HIV infection, hepatitis C infection, human papilloma virus (HPV) induced cervical cancer, psoriatic arthritis and type 1 diabetes. With the recent advancement of next generation sequencing (NGS) technology, KIR can now be characterized to high resolution including KIR gene copy number (CP), KIR haplotypes and KIR allele types. However, KIR gene detection is currently very limited when examining genome wide SNP data from GWAS studies using conventional computational methods, despite the high-density SNP coverage. Thus, we developed a new methodology named HIBAG (HLA Genotype Imputation with Attribute Bagging) and KIBAG (KIR Genotype Imputation with Attribute Bagging) which enables a rapid and inexpensive way to determine HLA & KIR genotypes from a GWAS dataset. HLA typing of the samples used in this study are performed by ALLtype NGS kit (Thermofisher). KIR typing of 726 Japanese (JPN), 367 Africans (AFR), 278 Admixed American (AMR), 507 East Asians (EAS), 406 Europeans (EUR) and 108 South Asians (SAS) were performed using the Scisco Genetics KIR typing kit. SNPs information of these samples were determined using Affymetrix Axiom Japonica V2 for Japanese samples and Illumina Omni 2.5 for the remaining samples. HLA & KIR reference types were generated by the attribute bagging method applied in HIBAG & KIBAG. HLA alleles imputation average reached

an average of 98% in Japanese population, KIR CP imputation average accuracies of 98.6% (JPN), 91.1%(AFR), 96.8%(AMR), 98.4%(EAS), 98.2%(EUR) and 94.2%(SAS) were obtained respectively across 16 KIR genes. This work is part of the project of HKimpNet (HLA & KIR Imputation Network) and 18th International HLA & Immunogenetics Workshop (IHIWS) with the aim of providing population-specific HLA & KIR imputation systems to the research community.