Association mapping of the xMHC in the risk of childhood acute lymphoblastic leukemia in Japanese

Abstract

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease, where immature lymphoid cells in the bone marrow, peripheral blood, and other organs are proliferated. The extended major histocompatibility complex (xMHC) is the candidate genomic region in this study that spans approximately 7.6 megabases (Mb) on the short arm of chromosome 6 (6p21.3). The xMHC is a unique region of the genome that contains a large number of densely populated genes important in human immunity. A case-control study conducted previously in the US showed a significant increased risk associated with the single nucleotide polymorphism (SNP) rs9296968 located in proximity to *HLA-DOA*. In this study, we conducted an association mapping analysis across an approximately 5 Mb regions of the xMHC comprising childhood ALL patients from Tokyo Children's Cancer Study Group (n=540) and controls from a subset of adult participants enrolled in the Nagahama Study, a community-based prospective cohort study, and Aichi Cancer Center Study, hospital-based cohort of non-cancer outpatient visitors (n=3715). The association analysis between xMHC SNPs and risk of childhood ALL was performed using multivariable logistic regression analysis examining 2,126 SNPs adjusted for population substructure by including principal components estimates derived from a genome-wide panel of SNPs. In addition, the analysis was performed based on three genetic models of inheritance. The permutation method for controlling the false-positive rate due to multiple testing was performed. After accounting for multiple comparisons, rs975195 showed statistically significant association with childhood ALL risk (OR=0.73, 95% CI=0.62-0.85, nominal p-value=5.2×10^{-5}, corrected p-value=0.036). SNP rs2074505 (OR= 0.73, 95% CI=0.63-0.86, p-value=7.7×10^{-5}) is in strong linkage disequilibrium (LD) with rs975195 (R^2=0.98) which is a synonymous variant located in the *GNL1* gene. Another SNP in strong LD (R^2=0.77) is rs2516647 (OR= 0.78, 95% CI=0.67-0.90, p-value=7.2×10^{-4}) and is an intronic variant located in the *PRR3* gene. These findings were not reported in the previous study in California and have a potential to be Japanese specific SNPs that is associated with childhood ALL. Further investigation with imputation and fine-mapping as well as specification of proximity genes is warranted.