HLA-class II and other gene loci associated with susceptibility to *EGFR*-mutated lung adenocarcinoma

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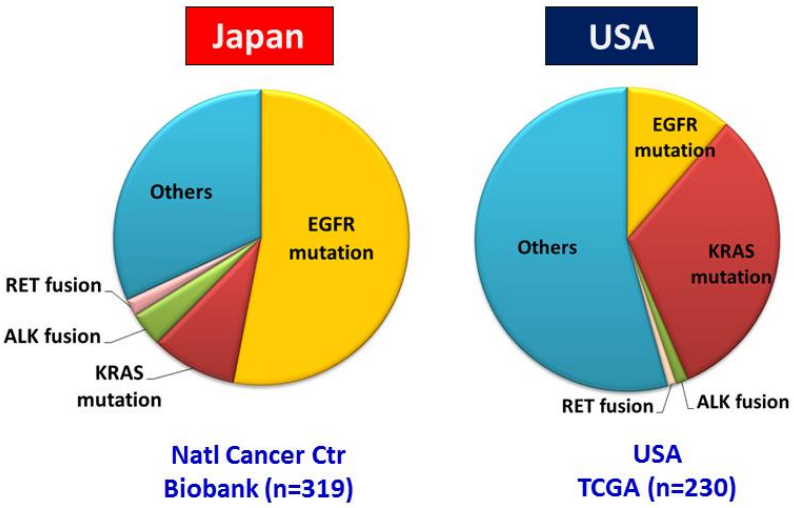
TOKYO, Japan (August 9, 2016) –The National Cancer Center, RIKEN, and other institutions today announced identification of gene loci associated with susceptibility to *EGFR*-mutated lung adenocarcinoma (LADC).

LADC is the most common type of lung cancer worldwide, with incidence and mortality rates increasing in both Asian and Western countries. LADC driven by somatic *EGFR* (epidermal growth factor receptor) mutations is more prevalent in East Asians (30-50%) than in European/Americans (10-20%). A high proportion of patients with *EGFR* mutation-positive LADC are never-smokers and females, making the development of a preventive method critical. Therefore, understanding the genetic factors underlying such LADC is required to identify effective methods of prevention and to elucidate disease etiology.

A Nation-wide collaborating group, including National Cancer Center (Drs. Takashi Kohno and Kouya Shiraishi) and other institutions, investigated genetic factors underlying the risk of this disease by conducting a genome-wide association study, followed by two validation studies, in 3,173 Japanese patients with *EGFR* mutation-positive lung adenocarcinoma and 15,158 controls. Four loci, 5p15.33 (*TERT*), 6p21.3 (*BTNL2*, *HLA-class II*), 3q28 (*TP63*) and 17q24.2 (*BPTF*), previously shown to be strongly associated with overall lung adenocarcinoma risk in East Asians, were re-discovered as loci associated with a higher susceptibility to *EGFR* mutation-positive lung adenocarcinoma. In addition, two additional loci, HLA-class II at 6p21.32 and 6p21.1 (*FOXP4*) were newly identified as loci associated with EGFR mutation-positive lung adenocarcinoma.

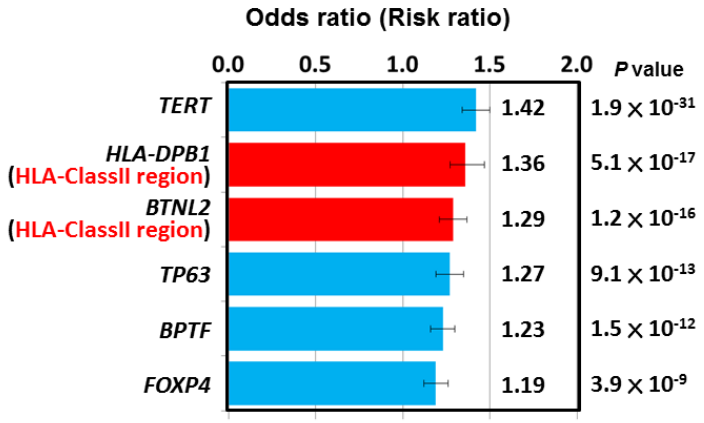
This study indicates that multiple genetic factors, including an immunologic one, underlie the risk of lung adenocarcinomas with *EGFR* mutations. They will help greatly in clarifying the disease etiology and in identifying high-risk individuals for targeted screening and/or prevention based on a combination of genetic and environmental factors.

Somatic Driver Oncogene Mutations in Lung Adenocarcinoma



EGFR mutation frequency is different between Japanese and Caucasian

Five Loci Associated with Risk of Lung Adenocarcinoma with *EGFR* Mutation



***EGFR* mutation**

Recent genome studies have subdivided LADC into several categories, with mutually exclusive activations of responsible oncogenes. One subset of LADC is characterized by mutations in the gene encoding epidermal growth factor receptor (*EGFR*). Advanced LADCs with *EGFR* mutations are often inoperable and are treated with tyrosine kinase inhibitors; however, these tumors frequently become drug resistant, leading to disease progress and death. Thus, understanding the genetic factors underlying the development of

LADC with *EGFR* mutation is required to elucidate disease etiology and to identify effective methods of prevention.

HLA gene
The human leukocyte antigen (HLA) genes encode the major histocompatibility complex (MHC) proteins in humans. These proteins regulate the immune system in humans. HLA genes are highly polymorphic with many alleles whose distributions are different among populations.

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Press release
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