1. No.
   2019G008

2. Title
   Functional characterization of genetic variants of cytochrome P4 50s involved in metabolic activation of procarcinogens

3. Period
   2019-2021

4. Summary
   Cytochrome P450 1A2 (CYP1A2) is an important P450 isozyme that catalyzes the activation reaction of carcinogenic precursors in tobacco, and functional changes of enzyme proteins due to genetic polymorphisms of CYP1A2 are considered to be one of the factors that explain individual differences in susceptibility to carcinogenesis caused by smoking. In this study, we used the whole genome sequence database of the Japanese population to comprehensively identify the functional changes of variant enzymes derived from low-frequency CYP1A2 gene polymorphisms. We transiently expressed each of 42 recombinant CYP1A2 variant enzymes in 293FT cells using gene polymorphism information extracted from the whole genome database of Tohoku Medical Megabank Organization of Tohoku University. The expressed variant enzymes were reacted with phenacetin, a typical substrate of CYP1A2, and the degree of functional change was evaluated from the quantitative values of metabolites by enzyme reaction kinetics. The results showed a marked decrease in enzymatic reaction kinetic parameters in several variants compared to wild-type CYP1A2. This study has provided fundamental information that allows us to assess with greater accuracy than previously possible which types of CYP1A2 gene polymorphisms cause decreased activation of carcinogenic precursors and to what extent they contribute to genetic diversity in cancer development.