Consuming alcohol can increase the risk of cancers including those of the head, neck, esophagus, bowel, breast, and liver. This cancer risk after alcohol consumption is increased several-fold for approximately 560 million East-Asian people who carry ALDH2*2 (rs671, E504K) variant in aldehyde dehydrogenase 2 (ALDH2), that limits the metabolism of the alcohol break-down product acetaldehyde. This ALDH2*2 variant is associated with the alcohol flushing syndrome and tachycardia. Whether other missense mutations in the ALDH2 gene exists that causes alcohol flushing and tachycardia remains poorly understood. Here we hypothesized other inactive ALDH2 missense mutations exists that cause acetaldehyde accumulation and alcohol flushing syndrome in humans.

After IRB approval, we used selective ion flow mass spectrometry to quantify acetaldehyde levels for wild-type ALDH2, ALDH2*2, and other ALDH2 missense variants in humans after an alcohol challenge. In addition, we evaluated the activity of these proteins in vitro, and in 3T3 transiently transfected cells. Statistical analysis was performed by ANOVA and Tukey’s post hoc with significance set at $p < 0.05$. All data are presented as mean ± SEM.

We identified humans carrying genetic mutations in ALDH2 including rs671 (E504K) and two novel mutations, rs747096195 (R101G), and rs190764869 (R114W). After subjecting volunteers to an alcohol challenge (0.25g/kg), rs747096195 (R101G) and rs190764869 (R114W) cause facial flushing and 2-fold higher acetaldehyde accumulation, while rs671 causes 9-fold higher acetaldehyde accumulation relative to humans with wild type ALDH2. Further, heart rate changes after alcohol consumption correlate with inefficient acetaldehyde metabolism ($r=0.90$, 95% confidence 0.78-0.95, n=26, $p<0.0001$). Characterization with ALDH2 enzyme expressed in bacterial and cultured 3T3 cells supports that rs747096195 (R101G), rs190764869 (R114W), and rs671 (E504K) genetic variants in ALDH2 result in less efficient acetaldehyde metabolism relative to wild type ALDH2. Cellular reactive oxygen species (ROS) of the wild-type and mutant variants significantly increased by 2-3-fold for cells treated with ethanol compared to untreated cells.

Together, we identified genetic variants in the ALDH2 enzyme besides rs671 that cause inefficient acetaldehyde metabolism and developed a method to non-invasively phenotype differences in acetaldehyde metabolism after an alcohol challenge in humans. This is an important step for developing precision medicine strategies to provide individualized recommendations regarding alcohol use by factoring in how genetics when coupled with phenotype may ultimately influence cancer risk from consuming alcohol.

This work was supported by GM119522 (ERG).