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# Discordance of somatic mutations between Asian and Caucasian patient populations with gastric cancer

**Feifei Jia**[1,2], **Jamie K. Teer**[3], **Todd C. Knepper**[2], **Jae K. Lee**[3], **Hong-Hao Zhou**[1], **Yi-Jing He**[1,2], and **Howard L. McLeod**[1,2]

[1]Institute for Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha, China

[2]DeBartolo Family Personalized Medicine Institute, Moffitt Cancer Center

[3]Department of Biostatistics and Bioinformatics, Moffitt Cancer Center

## Abstract

**Background—**Differences in response to cancer treatments have been observed among racially and ethnically diverse gastric cancer patient populations. In the era of targeted therapy, mutation profiling of cancer is a crucial aspect of making therapeutic decisions. Mapping driver gene mutations for the gastric cancer patient population as a whole has significant potential to advance precision therapy.

**Methods—**Gastric cancer patient cases with sequencing data (total n=473) were obtained from The Cancer Genome Atlas (TCGA; n=295), Moffitt Cancer Center Total Cancer Care™ (TCC; n=33), and three published studies (n=145). Relevant somatic mutation frequency data were obtained from cBioPortal, TCC database and in-house analysis tool, and relevant publication

**Results—**We have found somatic mutation rates of several driver genes significantly vary between gastric cancer patients of Asian and Caucasian descent, with substantial variation across different geographic regions. Non-parametric statistical tests were performed to examine significant differences in protein-altering somatic mutations between Asian and Caucasian gastric cancer patient groups. Frequencies of somatic mutations of 5 genes were APC(Asian: Caucasian 6.06% vs. 14.40%, p=0.0076) ARIDIA(20.7% vs. 32.1%, p=0.01) KMT2A(4.04% vs. 12.35%,

Correspondence Author: Dr. Howard L. McLeod, Medical Director Personalized Medicine Institute, Division of Population Science, Moffitt Cancer Center. Howard.McLeod@moffitt.org, Phone: 813-745-8435, Fax: 813-745-6525.

Compliance with Ethical Standards

*Conflict of interest:* The authors (FJ, JT, TK, JL YL & HM) declare that they have no competing interests.

*Ethnical approval and informed consent:* All patients declared informed consent and the studies were approved by Moffitt Cancer Center.

**Authors' Contributions**

**Conception and design**: Howard L. McLeod, Jae K. Lee, Jamie K. Teer, Yi-jing He

**Development of methodology:** Feifei Jia, Jae K. Lee, Jamie K. Teer, Todd C. Knepper

**Acquisition of data:** Feifei Jia, Jamie K. Teer, Todd C. Knepper

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** Feifei Jia, Jamie K. Teer, Jae K. Lee, Howard L. McLeod

**Writing, review, and/or revision of the manuscript:** Feifei Jia, Howard L. McLeod, Jamie K. Teer, Jae K. Lee, Hong-hao Zhou, Todd C. Knepper, Yi-jing He

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** Feifei Jia, Yi-jing He, Todd C. Knepper

**Study supervision:** Howard L. McLeod, Jae K. Lee, Jamie K. Teer, Hong-hao Zhou, Yi-Jing He

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p=0.003) PIK3CA(9.6% vs. 18.52%, p=0.01) PTEN(2.52% vs. 9.05%, p=0.008), showing significant differences between Asian and Caucasian gastric cancer patients.

**Conclusions—**Our study has found significant differences in protein-altering somatic mutation frequencies in diverse geographic populations. In particular, we found that the somatic patterns may offer better insight and important opportunities for both targeted drug development and precision therapeutic strategies between Asian and Caucasian gastric cancer patients.

## 1. Introduction

Nearly one million new cases of gastric cancer (GC) are estimated to occur each year, making it the fifth most common malignancy in the world. (GLOBOCAN 2012)(1). There is substantial geographic variation in the incidence of gastric cancer, with the highest rates in East Asian and the lowest in North American populations(2). Certain environmental factors such as *H. pylori* infection, dietary factors, and smoking patterns may contribute to these disparities (3–5). The study of the genetic basis of gastric cancer, including host genetic susceptibility, has improved understanding of the pathogenesis of this disease and has highlighted the role of infection and chronic inflammation in gastric cancer.

Precision therapy research has opened up opportunities for cancer treatments, commercialization, and personal understanding on highly heterogeneous human tumors. Advances in high-throughput cancer genome sequencing and profiling technologies are rapidly transforming the development and approval of targeted agents, paving the way for a more precise therapeutic selection for individual patients. Multiple signaling pathways have been identified as key drivers of cancer patient outcome and therapeutic response through genetic and epigenetic aberrations, allowing for the expansion of gastric cancer classification from epidemiology to molecular disease biology.

Given the power and throughput of next generation sequencing, the application of this technology is driving the development of new therapies by targeting the most frequently occurring molecular abnormalities. However, much of our knowledge of somatic mutations have been obtained from tumors of Western Caucasian patient populations, while the greatest burden of gastric cancer is among Eastern Asian patient populations. This raises the question of whether gastric cancers from Asian- and Caucasian-descended patients exhibit different somatic genomic alterations, leading to an inadvertent disparity in development and application of new therapies.

## 2. Materials and Methods

### 2.1 Integrating multi-country sequencing somatic mutation data from TCGA

Mutation data of Hong Kong cases (N=100) (6) and Japanese cases (N=30) (7) were identified in genes relevant to gastric cancer (Table 1) using cBioPortal. Singapore (N=15) cases were obtained from the published study (8).

TCGA stomach adenocarcinoma (STAD) cases (N=295) were obtained with relevant clinical and somatic mutation (Level 2) data from the TCGA web portal (tcga-data.nci.nih.gov;June, 2014). These TCGA cases were further filtered with 1000 Genomes and re-annotated as

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described below. Mutation rates were calculated among patient groups defined by country of origin. TCGA identifier was used as a linker to clinical and genomic data. Finally, Germany (N=38), Poland (N=32), Russia (N=80), South Korea (N=31), Ukraine (N=38), U.S (N=22) and Vietnam (N=22) gastric cancer samples were obtained with mutation frequencies across relevant genes (Figure 1) (supplementary table 1).

### 2.2 Patients and tissues, DNA extraction and quantification at Moffitt Cancer Center

Gastric cancer samples were identified at H. Lee Moffitt Cancer Center as part of a large population based study acquiring nearly 20,000 snap frozen, clinically characterized cancer specimens(9, 10). Gastric adenocarcinoma and signet-ring cell carcinoma (Supplementary Table 3) were all included.

Primary and metastatic samples from 33 gastric cancer patients (self-identified race = “white”) were available for analysis. In all cases, tissue and clinical data were collected on patients under institutional review board approval as part of the Total Cancer Care (TCC) project(9). Approval from Moffitt Cancer Center IRB was obtained to analyze clinical data for this study (Supplementary Table 2) from patients who consented to the TCC protocol and whose tumors were profiled with targeted sequencing.

All tumors were collected from curative survival resections and snap frozen in liquid nitrogen within 15–20 min of extirpation. Tumors then underwent a macro dissection quality control process to ensure >80% tumor was present in the specimen that underwent sequence analysis. DNA was then extracted from 33 gastric cancer specimens, followed by targeted sequencing using a custom designed Agilent Sure Select Capture, Agilent Technologies, Inc., Santa Clara, CA. 1,321 cancer-associated genes were selected by a joint committee (Merck Co., Inc. & Moffitt Cancer Center) for hybrid capture and sequencing. Capture probes for the 1,321 genes were based on the Agilent 50 MB Sure Select capture.

### 2.3 Targeted exome sequencing workflow and analysis at Moffitt Cancer Center

Tumor samples from Total Cancer Care were subjected to genomic capture (performed by BGI, Shenzhen using Sure Select custom designs targeting 1,321 genes, Agilent Technologies, Inc., Santa Clara, CA) and massively parallel sequencing (performed by BGI, Shenzhen using GAIIx, Illumina, Inc., San Diego, CA). Sequences were aligned to the hs37d5 human reference with the Burrows-Wheeler Aligner (BWA)(11). Insertion/deletion realignment, quality score recalibration, and variant identification were performed with the Genome Analysis ToolKit (GATK) (12). Sequence variants were annotated with ANNOVAR(13). Additional contextual information was incorporated, including allele frequency from the 1000 Genomes Project and the NHLBI Exome Sequence Project, in silico functional impact predictions, and observations from the Collection of Somatic Mutations in Cancer (COSMIC). Somatic mutations were enriched by filtering out variants observed in the 1000 Genomes Project and observed at >5% in an internal normal sample dataset (supplementary table 2).

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### 2.4 Statistical analysis comparing Asian and Caucasian gastric cancer patient populations

We selected gastric cancer patients from Hong Kong, Vietnam, South Korea, Japan as Asian group (n=198), while gastric cancer patients from US, Germany, Poland, Russia, Ukraine and TCC were included in the Caucasian group (n=243). Somatic mutation frequency was calculated as GC patients bearing mutation for each gene divided by total number in each ethnic group (198 for Asian and 243 for Caucasian). We used exact binominal test to examine statistically significant differences in somatic mutation frequencies for 11 genes (supplementary table 4). Statistical analysis were performed using open source statistical software R (v3.1.0), and world maps were also drawn using R packages “rworldmap” and “rgdal”.

## 3. Results

Assessment of WES/WGS studies in Asian patients identified 11 genes that were consistently mutated in GC. Somatic mutation frequencies of five of those genes *APC*, *ARID1A*, *KMT2A*, *PIK3CA*, and *PTEN*, were significantly different between the Asian and Caucasian geographic populations (Table 1) (Supplementary figures). The mean frequency was higher in Caucasians compared to Asian patient populations for five genes. More detailed information for these genes and their somatic mutations is described below.

The mean frequency of *APC* alteration was more than twice as high in Caucasian than Asian patients (Figure 2), with the highest frequency in German patients and lowest in patients from Singapore. Within patients from Asian regions, the frequency was the highest in South Korea (16.1%) and lowest in Singapore (0%), whereas in Europe the frequency was the highest in Germany (26.3%) and lowest in Ukraine (5.3%).

19 of 198 (9.6%) Asian gastric cancer patients had *PIK3CA* mutations, compared to 45 of 243 (18.5%) in Caucasian population (p=0.01). Amongst Asian countries, South Korea GC patients harbored the highest alteration frequency of *APC*, *ARID1A*, *GLI3*, *PIK3CA* and *KMT2A* (Figure 3). Further, *PIK3CA*, *GLI3* and *ARID1A* mutation frequency are higher than any accessed cohorts. Chinese (Hong Kong) has the highest mutation rates of *ACVR2A* (8%) and *PTEN* (4%) amongst Asian countries, compared to the Asian means of 4% for *ACVR2A* and 2.5% for *PTEN*. Interestingly, other than China (Hong Kong), no other Asian GC patients harbored *ACVR2A* alterations. Although *PTEN* alterations were relatively frequent in Chinese patients compared to other Asian countries, it was altered less often than Caucasian patients (9.1%). Contrasting with the relatively high frequency of *ACVR2A* and *PTEN*, Chinese GC patients harbored the lowest frequency of *KMT2A* (2%) and *PIK3CA* (2%) alterations.

Japanese GC patients harbored the lowest *CTNNB1*, *GLI3*, *PTEN*, *SMAD4*, and *TP53* alterations (3%, 3%, 0%, 3% and 37% respectively) among Asian countries, compared to the mean values of 5.6%, 11.1%, 2.5%, 6.6% and 51.5% respectively, across the Asian region. Singapore GC patients’ alterations in *ACVR2A*, *APC*, *CDH1* and *PTEN* were absent. Alterations in *ARID1A* were lowest among Asian countries (13.3% vs. Asian mean 21.7%). On the other hand, *CTNNB1* alteration rates in Singapore GC patients were the highest among Asian GC patients (13.3% vs. Asian mean 5.6%).

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Significant heterogeneity was seen across the Caucasian cohorts. However, consistent patterns could not be detected. German patients had the highest frequency of *APC* and *KMT2A* alterations, but lowest for *CDH1*. Polish GC patients harbored the highest *CDH1* alteration rates while the lowest *KMT2A* and *SMAD4* alteration rates; Ukrainian GC patients have the highest *SMAD4*, *PIK3CA*, *GLI3* and lowest *TP53*, *APC* alteration rates. Caucasian patient population has larger variation of *KMT2A* alteration compared Asian group, ranging 3.1% to 18.4%, compared to 2% to 9.7% in Asian population. The mean *KMT2A* mutational frequency was three times higher in Caucasian compared to Asian GC patients (p=0.003) (Figure 3).

Dramatic differences were seen in *PTEN* gene, the mutation rates were 13.8% and 13.6% for Russia and American GC patients, while *PTEN* alterations were absent in Vietnamese, Singaporean and Japanese GC patients. *PTEN* mutation rates are higher among Caucasian gastric cancer patients compared to Asian cases. (p=0.008) (Figure 4).

## 4. Discussion

Understanding geographic differences in somatic mutation frequency is more than an academic interest and is important for rational global introduction of targeted cancer drugs due to the highly heterogeneous therapeutic responses in their worldwide applications. For example, from recent Phase II and III trials suggested that epidermal growth factor receptor (EGFR) inhibitors were more effective for Asian cancer patients than patients in other ethnicities, a characteristic that parallels a much higher incidence of EGFR-activating mutations among Asian patient populations (14–17). Consequently, clinical studies focusing on EGFR-targeted therapies have rapidly advanced based on the fact that Asian patients harboring the EGFR somatic mutation account for 30–40% of total patients, significantly higher than that of patients from European descents (18–21).

It has been observed thus far that ethnic factors are likely to contribute to the disappointing results in advanced gastric cancer, so these factors should be carefully taken into account when conducing global clinical trials across different ethnic populations (22–25). Stratified analysis by race/ethnicity may need to be performed in such global studies in order to maximize benefits of alternative precision therapeutic modalities. For instance, the phase III GRANITE-1, first global gastric antitumor trial with everolimus (NCT00879333), did not show a significant survival benefit from everolimus beyond BSC (best supportive care) for the worldwide cohort of advanced gastric cancer patients whose disease relapsed after one or two lines of systemic chemotherapy(22). However, when ethnic subgroups were examined, a 15% reduced risk of death was seen for Caucasian patients (U.S., Canada, Israel, Russia, Mexico, Colombia, Brazil, Venezuela, Australia and New Zealand) compared to patients in Asia (China, Hong Kong, Japan, Korea, Taiwan and Thailand) (22). Di Nicolantonio and colleagues have demonstrated that *PIK3CA* mutations can sensitize cancer cells to everolimus (26). Interestingly, our study demonstrated *PIK3CA* mutation rates is almost twice as high in Caucasian gastric cancer patients as they are Asian cases (18.5% vs. 9.6%, p= 0.012). This suggests a mechanistic basis behind the differential response to everolimus in Caucasian gastric cancer patients. Even if Asian patients with *PIK3CA* mutations might also have been more likely to respond to the drug, the effect could have been masked in the

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overall analysis by a low mutation frequency among Asian patients. Initial investigations on biomarkers in the PI3K/Akt/mTOR pathway are ongoing and its results are being eagerly awaited (22).

Unfortunately, in-depth understanding of the molecular underpinnings of gastric cancer is currently lagging compared to many other cancers of similar incidence and morbidity. Thanks to recent advance in NGS technology, common somatic alterations (*PTEN*, *PIK3CA*, and *TP53*) are rapidly being discovered, some of which are being pursued clinically. For instance, a multination Phase I study (US, Germany, Japan, South Korea, Switzerland and Taiwan) of PIK3CA inhibitor BYL719 in combination with the HSP90 inhibitor AUY922 in advanced gastric cancer patients carrying either a molecular alteration of PIK3CA or an amplification of HER2 (NCT01613950). Also, a Phase II trial of AZD5363 (Akt inhibitor) plus paclitaxel/AZD2014 (mTOR inhibitor) plus paclitaxel in biomarker negative (PIK3CA/MEK/RAS/TP53/MET) advanced gastric adenocarcinoma patients as second-line chemotherapy are currently enrolling patients (NCT02449655). A single-arm phase II study of AZD1775 (Wee1 G2 checkpoint serine/threonine protein kinase inhibitor) in combination with paclitaxel in patients with advanced gastric adenocarcinoma harboring *TP53* mutation as a second-line chemotherapy (NCT02448329) is also currently recruiting participants. These studies should yield greater understanding of the translational impact of mutated biological pathways, in addition to the anticipated therapeutic benefits.

Many novel somatic gene targets (*CDH1*, *ARID1A*, *KMT2A*, *ACVR2A*, *CTNNB1*, *GLI3*, *SMAD4*, and *APC*) have also been identified to be of great interest (6–8). Our study demonstrated that Caucasian gastric cancer patients have higher mutation rates of *APC*, *ARID1A*, *KMT2A*, *PIK3CA*, and *PTEN* genes than Asian patients. The mechanism responsible for the high frequency of these mutations in Caucasian patients will be a subject of great interest. In the near future considerably larger Asian clinical trials will need to understand ethnic differences in these biomarkers and their somatic mutation frequencies. If frequencies of such biomarkers are lower in Asian populations (as we have shown for mutation rates in five genes), more patients may need to be screened for eligibility to complete sufficiently powered biomarker-driven trials.

Global gastric cancer drug development is largely performed in Western countries whilst considerable somatic based prognostic indicator models of gastric cancer were identified and developed in Asian countries. Tan et al. identified two major intrinsic genomic subtypes as a statistically significant covariate which is associated with survival time following adjuvant, 5-fluorouracil-based therapy (27). Cho et al. (28) identified and validated robust prognostic markers (*CTNNB1*, *EXOSC3*, *TOP2A*, *LBA1*, *LZTR1* and *CCL5*) in Korean gastric cancer patients and developed a prognostic risk score that can be easily translated into clinic. Lei Z et al. identified three subtypes of gastric adenocarcinoma: proliferative, metabolic, and mesenchymal based on gene expression patterns (29). Results from detailed molecular and/or pathological GC studies from Asian populations are promising, but it remains questionable whether they can be fully extrapolated to Caucasian populations. Our study has shown that there can be significant biomarker frequency differences across populations, suggesting that the potential clinical impact of a biomarker may also vary across

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populations. Although personalized research into these differences has just begun, molecular models should be carefully considered when transforming into clinic.

The traditional approach of one-size fits all clinical trials and attempting to find a single optimal therapy to apply across gastric cancer has likely contributed to a slow progress on treating this disease with novel targeted drugs. The study from TCGA has enlightened understanding of this highly heterogeneous disease by cataloging genomic characteristics across a spectrum of gastric cancer patients from large international groups(30). Our analyses utilizing TCGA and other databases have found discordance of somatic mutations in specific clinically relevant genes between the two ethnic groups. Differences were also observed among countries with similar ethnic populations, suggesting that it also be important to consider local-regional differences as well as national/ethnic diversities.

There are several limitations in our current study. First, differences in mutation rates between different ethnic groups may also be due to different depths or other technologic aspects of sequencing methods. Also, although TCGA used similar sequencing and analysis methods for each sample, sample sizes and representative countries of Asian patient populations were limited. Despite these limitations, comparisons within TCGA showed the same trends as our overall analysis, which, at least partially confirmed the observations and analysis results obtained in our global comparison. It remains important for future large molecular cancer studies to include diverse patient populations in proportions that allow conclusions to be drawn. We believe that our findings help to understand the multifaceted nature of gastric cancer, underscore the importance of molecular-guided personalized medicine, and provide practical implications for further study and future personalized gastric cancer treatments.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Key points

The aim of the study was to find substantial ethnic and geographic variation of somatic mutations among Asian and Caucasian gastric cancer patients.

Our findings suggest that gastric cancer from Asian- and Caucasian-descended patients exhibit different somatic genomic alterations and help to understand multifaceted nature of gastric cancer, underlying the importance of molecular-guided precision medicine and provide practical clinical implications for further study in gastric cancer treatments.

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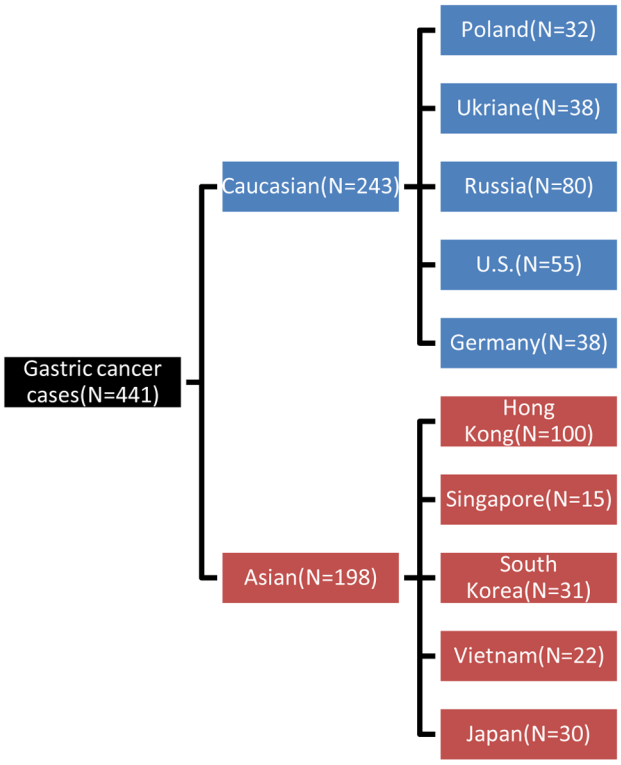


**Fig. 1.**

Gastric cancer cases from diverse countries. *U.S. data are from TCGA U.S. and TCC cohort.

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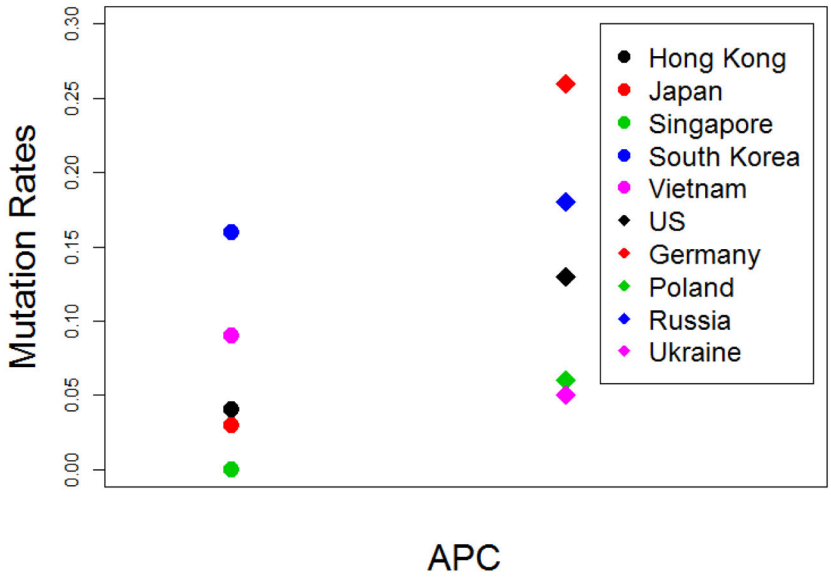


**Fig. 2.**

*APC* mutation rates across diverse geographic area. Circles represent Asian countries while diamonds represent Caucasian countries.

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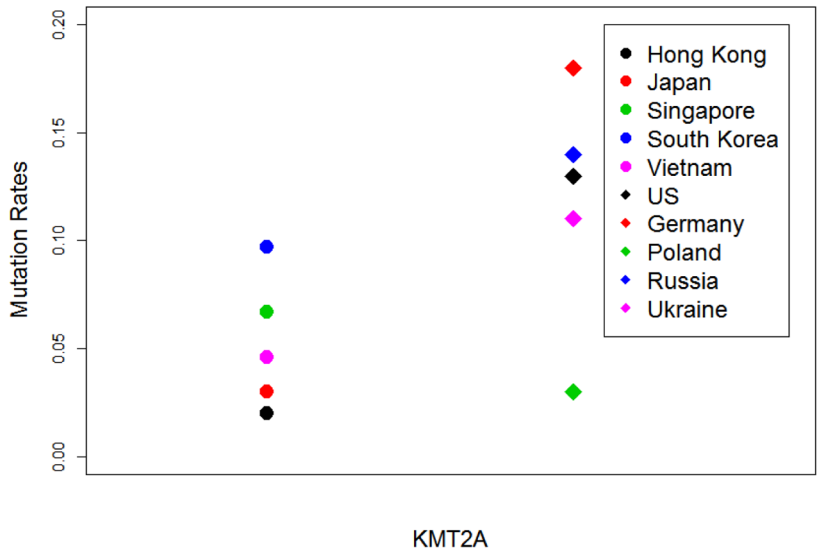


**Fig. 3.**

*KMT2A* mutation rates across diverse geographic area. Circles represent Asian countries while diamonds represent Caucasian countries.

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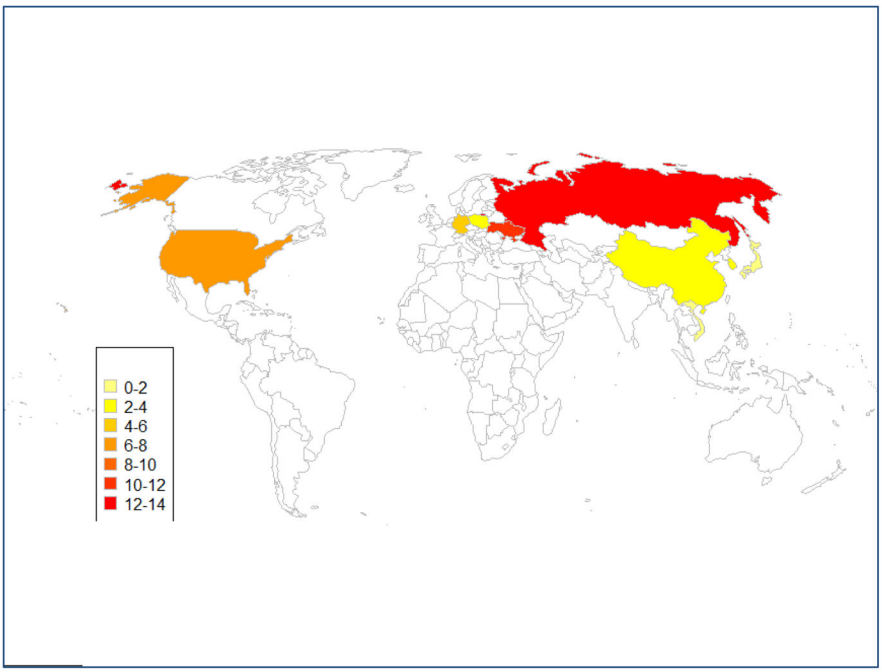


**Fig. 4.**

*PTEN* mutation rates shown on the world map. Numbers on the left side of the figure indicate PTEN alteration rates.

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**Table 1**

Similarities and differences between Asian and Caucasian gastric cancer patients. Shown are the mutation rates for 11 genes of interests to in each ethnicity.

| Gene | Asian (Alteration rates) | Caucasian (Alteration rates) | P-value |
|---|---|---|---|
| ***ACVR2A*** | 4.0% | 6.2% | 0.06 |
| ***APC*** | 6.0% | 14.4% | 0.007* |
| ***ARID1A*** | 20.0% | 32.1% | 0.01* |
| ***CDH1*** | 13.1% | 10.7% | 0.52 |
| ***CTNNB1*** | 5.5% | 8.2% | 0.37 |
| ***GLI3*** | 11.1% | 13.2% | 0.61 |
| ***KMT2A*** | 4.0% | 12.4% | 0.003* |
| ***PIK3CA*** | 9.6% | 18.5% | 0.012* |
| ***PTEN*** | 2.5% | 9.1% | 0.008* |
| ***SMAD4*** | 6.5% | 7.8% | 0.75 |
| ***TP53*** | 51.5% | 44.4% | 0.17 |