**Supplementary Methods**

**Date of retrieval or release version of accessed data/ software**

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| **Accessed data/ software** | **Version or date of access** |
| PharmGKB | January 23, 2020 |
| CPIC | April 1, 2020 |
| PharmVar | December 27, 2019 |
| dbSNP | Build 140 |
| 1000 Genomes Project | Phase 3 data |
| gnomAD (gnomad.broadinstitute.org) | Version 2.1.1 |
| Chinese Genomic Variation Database (https://bigd.big.ac.cn/cgvd/) | Version 1.0 |
| ClinVar | Version 20190305 |
| Ensembl | Release 99 |
| Reference genome | UCSC hg19 reference genome assembly |
| Genome analysis toolkit (GATK) | Version 3.4 |
| Burrows-Wheeler Aligner | Version 0.7.8 |
| Picard | Version 1.79 |
| HLA-HD | Version 1.2.0 |
| Variant Tools (vtools) | Version 2.7.0 |
| wANNOVAR | Build 20200223 |
| R | Version 3.6.0 |

**Subject recruitment, exome sequencing and bioinformatics analysis**

The raw exome sequencing data of 1141 samples were processed by pipeline based on GATK.[1] Reads were aligned to the University of California Santa Cruz (UCSC) hg19 reference genome assembly by Burrows-Wheeler Aligner and duplicated reads were removed by Picard.[2] Local realignment around indels, base quality score recalibration, and cohort-based multi-sample variant calling were performed using the GATK toolset. HLA typing for the targeted HLA genes (*HLA-A* and *HLA-B*) was performed using HLA-HD.[3]

Stringent quality control (QC) procedures were performed on the exome sequencing dataset. Multiple QC steps at sample levels were performed. First, all samples were verified to have a FREEMIX score of < 0.05 (mean = 0.001794, median = 0.0008) using VerifyBamID to detect sample contamination.[4] Second, a sample check was performed using Peddy and 17 duplicated or related samples were identified and subsequently removed from further analysis. Third, principal component analysis was performed using Peddy to compare with 1000 Genomes Project reference data.[4],[5] Samples not clustering with the East Asian population (n = 8) were removed from analysis (Fig 1). At variant level QC, variants failing any of the following filters were removed from downstream analysis by KGGSeq: genotyping quality <20, read depth <8X, and Hardy-Weinberg test P-value ≤ 1×10-5.[6] Finally, all variants also needed to pass Variant Quality Score Recalibration (VQSR) annotated by GATK with the SNP tranche sensitivity threshold of 99.5% and INDEL tranche sensitivity threshold of 99.0%.

Variants passing the QC were loaded into our in-house genome database powered by Variant Tools (vtools).[7] Variants of the108 high-confidence pharmacogenes were extracted from vtools and annotated by wANNOVAR,[8] including data from dbSNP, the gnomAD dataset, the Clinvar database, and the Chinese Genomic Variation Database.[9],[10]

Variants were categorized into four classes according to their allele frequency (AF): common (>5%), low frequency (1% to 5%), rare (0.1% to 1%), and very rare (<0.1%) based on the global AF of the gnomAD database. In this study, a rare variant was defined as a variant having a gnomAD global AF <1%. Currently, the pharmacogenetics community has not reached a consensus on standardized methodology to evaluate the functional impact of rare variants. In this study, CADD, REVEL, and PREDICT were used to predict the consequence of missense variants identified in the 108 high-confidence pharmacogenes.[11],[12],[13] A missense variant was considered deleterious when it had a Phred-scaled CADD score >20, REVEL score >0.7, or PREDICT score >0.6. For loss-of-function (LoF) variants, CADD and LOFTEE were used to examine the deleterious effect, and an LoF variant was considered deleterious when it had a Phred-scaled CADD score >20 or LOFTEE of “high-confidence.” The gene lengths of the 108 pharmacogenes were retrieved from Ensembl based on the UCSC hg19 reference genome assembly.[14]

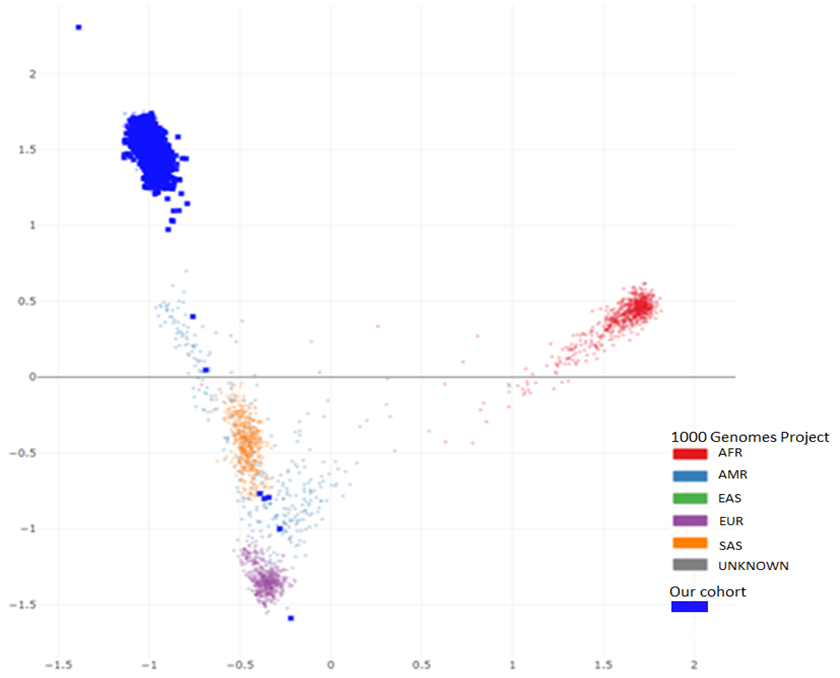
**Projected prescription impact analysis**

In the case of a drug affected by more than one pharmacogene, the actionable phenotype frequency is calculated as follows to avoid double-counting individuals who have an actionable phenotype in more than one gene.

Where and refers to the actionable phenotype frequency of gene A and gene B respectively.

**Figures**

Fig 1 - Principal component analysis to evaluate the ethnicity of the exome sequencing data



Principal component analysis shows that 1116 of our samples clustered with the East Asian samples from the 1000 Genome project (in the top left corner), and eight samples were removed from the final dataset as they clustered with other populations.  
AFR, African; AMR, Ad Mixed American; EAS, East Asian; EUR, European; SAS, South Asian

**Supplementary References**

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