ABSTRACT

BACKGROUND: Drug efficacy can be affected by numerous factors including gene-drug and drug-drug interactions. CYP2D6 is an important enzyme for drug metabolism that catalyses the production of endoxifen from tamoxifen. The African-specific *CYP2D6*17* allele causes a reduced function effect on the CYP2D6 enzyme by decreasing substrate affinity. Various methods have been employed to study enzyme function in a physiologically relevant in vitro model. Recently, iPSCs have been used to develop cellular models for liver-like tissue and to study individual differences in drug metabolism and toxicity. **AIM:** The study aimed to assess the frequency of the *CYP2D6*17* variant in African populations and to evaluate its enzyme activity in activation of tamoxifen to endoxifen in iPSC-derived hepatocyte-like cells (SC-HLCs). **METHODS:** *CYP2D6* data was downloaded from the 1000 Genomes Project (KGP), African Genome Variation Project (AGVP) and PharmVar databases to establish haplotype and diplotype frequencies of reduced function variants, including *CYP2D6*17*, in African populations. SNP rs28371706, as a proxy for *CYP2D6*17*, was genotyped and sequenced to identify homozygotes. Skin samples were collected from homozygotes to isolate dermal fibroblasts for the development of induced pluripotent stem cell (iPSC) lines. iPSC lines were used for the creation of stem-cell-derived hepatocyte-like cell (SC-HLC) 3D spheroid models. HepG2 cells were cultured in 3D as spheroids and *CYP3A4* induction was performed using rifampicin incubations for 24-, 48- and 72-hour time periods. CYP3A4 enzyme activity was measured using a CYP3A4 luciferase assay. **RESULTS:** *CYP2D6*17* average haplotype frequencies from KGP, AGVP and PharmVar data for African populations were 20.70%, 19.95% and 20.0% respectively, and *CYP2D6*17* average homozygous diplotype frequencies for KGP, AGVP and PharmVar were 4.28%, 3.98% and 7.81% respectively. Sequencing identified five individuals with a C/C genotype, two were T/T, two were T/C heterozygote, and one was A/C at the rs28371704 SNP locus. HepG2 3D spheroids showed a 7.70% (1.08-fold) (Rifampicin2.5 µM) and a 2.87% (1.03-fold) (Rifampicin 25 µM) increase for the 24-hour normalised enzyme activity readings for *CYP3A4* rifampicin induction. The 72-hour *CYP3A4* rifampicin induction normalised enzyme activity readings showed a 12.62% (0.13-fold) (Rifampicin 2.5 µM) and a 92.64% (0.93-fold) (Rifampicin 25 µM) decrease in CYP3A4 activity. **DISCUSSION:** The distribution of the *CYP2D6*17* variant is likely due to early African population migratory patterns. This may have implications for tamoxifen treatment in patients with breast cancer and other drugs that are metabolised by CYP2D6 in African populations. This research has established the first step in generating iPSC lines that have the *CYP2D6*17* variant. The next steps for this research are to establish cellular models for other *CYP* gene variants common in Africans to assess their effects on drug metabolism.