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Pharmacogenetics of Efavirenz and Neuropsychiatric Side Effects in Asian Populations

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PHARMACOGENETICS OF EFAVIRENZ AND NEUROPSYCHIATRIC SIDE EFFECTS IN ASIAN POPULATIONS

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Chapter I

Abstract

Efavirenz (EFV), a common antiretroviral drug, was the recommended first-line therapy for the treatment for human immunodeficiency virus infection until 2018. Though many high-income countries have transitioned to newer drugs due to their improved efficacy and low toxicity, EFV is still common in many low- and middle-income countries due to the high cost of alternatives. EFV is believed to cause central nervous system (CNS) toxicity and has been linked with neuropsychiatric side effects such as insomnia, hallucinations, headache, depression, and suicidality, though the causal relationship for depression and suicidality is controversial. Several single nucleotide polymorphisms (SNPs) in CYP2B6 — the gene that encodes the enzyme that metabolizes EFV— have been linked with elevated plasma EFV levels that may lead to neurotoxicity and subsequent side effects. This suggests a great inter-individual genetic variability that may put patients with certain variations at a greater risk of these side effects. Two prominent polymorphisms CYP2B6*6 (516 G>T and 785 A>G) and CYP2B6*9 (516 G>T) are more common in Asians and Africans than in Europeans. The minor allele frequencies for CYP2B6*6 and CYP2B6*9 and genotype frequencies for CYP2B6*6 were analyzed to identify countries in Asia and surrounding regions with high prevalence of these genetic variations. The use of EFV, transition to alternative drugs, and the prevalence of CNS side effects in these countries were characterized. Countries with large occurrence of these SNPs were hypothesized to report frequent CNS adverse effects. These SNPs were the most prevalent in Papua New Guinea, India, Indonesia, and Pakistan, though EFV-induced CNS effects in those with these SNPs were found only in Papua New Guinea and India. Studies that incorporate both genetic and external factors may shed light on the pharmacological outcomes of EFV.

Chapter II

Introduction

Efavirenz

Efavirenz is a common antiviral drug used as a first-line therapy for the treatment of human immunodeficiency virus (HIV) infection and is often prescribed in combination with other antiviral drugs such as nevirapine and tenofovir (Apostolova et al., 2015). Newer drugs have challenged the dominance of efavirenz-containing regimens as preferred HIV treatments due to their lower toxicity and viral resistance, increased tolerance, and improved patient adherence. As a result, EFV is no longer recommended as the first-line treatment by the World Health Organization (2018) and in several countries, including the United States (Apostolova et al., 2015; Department of Human Health, n.d). A low-dose formulation of EFV is still an alternative first-line option, and the regular dosage is recommended only in special circumstances. EFV-based treatment has not been discontinued worldwide due to its greater efficiency in decreasing viral overload than most alternatives, and has been sidelined only recently due to the approval of dolutegravir, which has shown improved (Tongtong et al., 2022) or relatively the same efficiency (NAMSAL ANRS 12313 Study Group, 2019) in viral suppression without EFV-associated toxicity. However, EFV continues to be favored in many low- and middle-income countries as it is far more economically accessible due to the introduction of affordable generic versions (Apostolova et al., 2015; Costa & Vale, 2023).

Efavirenz and Neuropsychological Side Effects

Central nervous system (CNS) toxicity is the most frequent side effect of EFV. About 40-60% of patients report CNS side effects such as headache, dizziness, irritability, abnormal dreams, insomnia and fatigue, while a smaller, inconsistent percentage of patients experience a

range of side effects such as hallucinations, anxiety, depression, suicidality, aggressive behavior, paranoia, and psychosis (Gutierrez et al., 2005; Costa & Vale, 2023; Department of Human Health, n.d). Majority of these symptoms resolve in a few weeks or months, though they can persist for a long time. Additionally, neurotoxicities such as encephalopathy and ataxia can also occur years after the initiation of EFV treatment (Department of Human Health, n.d). These CNS side effects are the primary reason that cause patients to discontinue EFV-based treatments, though these rates of discontinuation are still lower than that of other antiviral regimens (Apostolova et al., 2015).

The inconsistency in the proportion of patients experiencing depression and sucidality is due to the disagreement of findings over whether efavirenz causes these side effects. Efavirenz has previously been shown to induce depressive-like behaviors, increased susceptibility to stress, and spatial memory deficits in rats (po, 10 mg/kg, 34 days) (O'Mahony et al., 2005). Bristol-Myers Squibb (2019), the manufacturer of the brand name Sustiva© under which EFV is commonly sold, recognizes the risk of depression and suicidality on their package inserts. Several studies have identified a high prevalence of depression among patients on EFV-based regimens (Spire et al., 2004; Lochet et al., 2003), and high plasma concentrations of EFV have been significantly correlated with CNS side effects and toxicity (Marzolini et al., 2001; Csajka et al., 2003). Further, Mollan et al. (2014) report a two-fold increase in the risk of suicide ideation and attempted and completed suicide in the EFV patients compared to those on non-efavirenz regimens. A randomized trial by Arenas-Pinto et al. (2018) implicates the initiation of EFV as opposed to other antiretroviral therapies in increasing the risk of suicidality in all patients, with those with a history of psychiatric disorders being at a greater risk.

Other studies point to factors unrelated to EFV use as the cause of the risk of depression and suicidality. For instance, a retrospective cohort study of Taiwanese HIV patients found that having a history of psychiatric disorders, living in less-developed southern Taiwan, and low insurance premiums were correlated with the development of depression, not EFV use (Li et al., 2021). Another study identified age and history of depressive disorders as the risk factors for depression in HIV patients unrelated to efavirenz treatment (Journot et al., 2006). Further, according to an analysis of a multi-cohort trial data, EFV use did not correlate with higher rates of suicide completion (Smith et al., 2014). Napoli et al. (2014) also report an insignificant association between EFV and suicidality after screening the Food and Drug Administration's Adverse Event Reporting System database for reports of suicidality in patients on EFV-based regimens, though this database may suffer from underreporting. Both prospective (Chang et al., 2018) and retrospective (Nkhoma et al., 2016) cohort studies have found no significant association between EFV treatment and risk of suicidality, with the former reporting a decrease in the risk of depression from EFV.

One point of resolution for this controversy is that inter-individual differences may account for the variability observed in the results of these studies. Studies have found large interpatient variability and low intrapatient variability in how much EFV is available in the bloodstream to have an active effect (Marzolini et al., 2001; Csajka et al., 2003). This suggests that the inconsistency of study results may be due to inter-individual differences in the EFV pharmacokinetic pathway, and as high EFV concentrations in the blood have been linked with CNS toxicity, individuals with genetic predispositions that result in higher plasma levels of EFV may be more susceptible to developing neuropsychiatric side effects. This hypothesis is supported by a study conducted by Mollan et al. (2017), which found that genotypes resulting in

elevated plasma EFV levels are linked with higher risk of suicidality. Further, as having a history of psychiatric disorders is a common factor in these studies, psychiatric disorders along with interpatient genetic variability may increase the risk of developing severe CNS symptoms such as depression and suicidality from efavirenz. However, as HIV is a socially stigmatized infection and often differentially affects socially and economically disadvantaged groups, factors such as young age, social deprivation, income, and access to resources cannot be completely ruled out in the development of depression and/or suicidality.

Efavirenz Metabolism and CNS Toxicity

About 90% of efavirenz ingested is cleared through the enzymes of the cytochrome P450 system in the liver. Efavirenz is mostly metabolized into 8-hydroxyefavirenz by the CYP2B6 enzyme. Other minor metabolites include 7-hydroxyefavirenz, 8,14-dihydroxyefavirenz, and 7,8-dihydroxyefavirenz, which are broken down by other cytochrome P450 enzymes such as CYP2A6 and CYP3A4 (except 8,14-dihydroxyefavirenz, which results from CYP2B6-catalyzed conversion of 8-hydroxyefavirenz). Though none of the metabolites of EFV contribute to any pharmacological activity against HIV, the metabolite 8-hydroxyefavirenz is significantly more neurotoxic than efavirenz or any of its other metabolites, though its neurotoxicity may be lowered due to its further conversion into 8,14-dihydroxyefavirenz (Apostolova et al., 2015; Wang et al., 2019).

Though the exact process behind how elevated EFV causes CNS toxicity and side effects is yet to be determined and studies examining this relationship are scarce, some animal and *in vitro* studies have proposed several mechanisms. First, in a study conducted by O'Mahony et al. (2005), rats showed an up-regulated production of pro-inflammatory cytokines (IL-1b and TNF-a) in the blood in response to 10 mg/kg of efavirenz. This inflammatory response and

depressive-like behavior were ameliorated after a selective serotonin reuptake inhibitor paroxetine was administered. As the inflammatory action of pro-inflammatory cytokines has been linked to the development of depressive symptoms in humans (Apostolova et al., 2015), this suggests that EFV may cause CNS symptoms like depression by triggering an inflammatory response.

Another mechanism through which efavirenz can cause neuropsychiatric complications is through imbalancing energy homeostasis in the brain. A study in EFV-treated mice found significant reduction in creatine kinase activity, an enzyme important for ATP production, in the cerebral cortex, cerebellum, hippocampus, and the striatum (Streck et al., 2008). Efavirenz and its metabolites have also been shown to diminish mitochondrial function in mouse cortex, hippocampus, and striatum (Streck et al., 2011) and in human and rat cultures of cortical neurons and glial cells (Brandmann et al., 2013; Funes et al., 2014). Moreover, this bioenergetic stress due to diminished creatine kinase activity and mitochondrial dysfunction have been linked to neurodegenerative diseases such as Alzhiemer's (Aksenov et al., 2000; Brown et al., 2014). So, it possible that EFV diminishes energy production in the brain which may be responsible for fatigue and some of its severe side effects. However, EFV has not been directly correlated with cognitive impairment.

Lastly, a study in both *in vitro* and *in vivo* (rats and mice) models found that efavirenz acts as a partial agonist of serotonin receptors 5-HT_{2A} and 5-HT_{2C} which suggests that efavirenz may cause psychoactivity similar to lysergic acid diethylamide (LSD) (Gatch et al,, 2013). In mice, EFV (ip, 15mg/kg) induced head-twitching similar in response to LSD. Further, rats (po, 8.6 mg/kg, 30 days) showed degeneration in the lateral geniculate body, the part of the intracranial visual relay center of the brain which plays an important role in normal visual

processing. These observations may help in explaining the milder, more prevalent CNS side effects of efavirenz, such as hallucinations, dizziness, and headaches. However, the potential mechanism behind other side effects such as insomnia have not been examined.

Though the mechanism behind CNS side effects of efavirenz have not been fully elucidated, there is strong evidence that implicates higher EFV levels in the blood in the etiology of these effects. One mechanism that can result in the observed increase in EFV plasma concentrations and the associated toxicity is through a version of CYP2B6 enzyme less efficient in metabolizing EFV, which may cause EFV to build up in the bloodstream (Damle et al., 2008; Desta et al., 2016). Indeed, the CYP2B6 gene, which codes for this enzyme, is highly polymorphic and several of its polymorphisms have been strongly associated with high plasma EFV concentration, longer plasma half-life, and severe CNS toxicity (Gouden et al., 2010; Kwara et al., 2009; Mollan et al, 2017; Rotger et al., 2005). Further, as Haas et al. (2018) found that polymorphism in other hypothesized genes, such as those that encode transporters or receptors for neurotransmitters (SLC6A2, SLC6A3, NR3C3, HTR2A, HTR2B, HTR2C, HTR6, NR3C4), were not significantly related to EFV-induced severe side effects, it can be assumed that genetic differences in genes primarily expressed in the brain may not play a significant role here. Hence, this project focuses on genetic polymorphisms in CYP2B6 as this enzyme is a major determinant of the metabolism and plasma exposure of EFV and may determine the predisposition to developing CNS side effects.

Major CYP2B6 Polymorphisms

Genetic polymorphisms in the CYP2B6 gene appear to be responsible for the wide range of inter-individual variations in the pharmacokinetics of efavirenz and the resulting neuropsychological and clinical outcomes. To date, at least 49 variant alleles for CYP2B6 have

been identified (Pharmvar, n.d.) and, out of these, many have been associated with altered gene expression and/or enzyme activity, namely CYP2B6*4 (785 A>G), CYP2B6*5 (1459 C>T), CYP2B6*6 (516 G>T and 785 A>G), and CYP2B6*9 (516 G>T) (Lamba et al., 2003; Lang et al., 2001). The most significant variant is the G516T single nucleotide polymorphism (SNP), a point mutation at position 516 of exon 4 which changes the nucleotide G to T, which results in a much less efficient metabolizing enzyme for efavirenz (Apostolova et al., 2015). Individuals homozygous (TT) or heterozygous (GT) for this mutation produce a less efficient metabolizer and hence have significantly longer half-life and higher blood plasma concentrations of efavirenz than those with the wild-type (GG) allele. This SNP has also been associated with severe CNS toxicity (Haas et al., 2004; Gounden et al., 2010; Mathiesen et al., 2006).

The G516T polymorphism occurs in two alleles, CYP2B6*9 and CYP2B6*6, where the latter contains another point mutation (A785G) that changes A to G at position 785 of exon 5 which imparts an increase in the CYP2B6 enzyme activity. However, this increase is not enough to overcome the reduction in enzyme activity produced by the G516T SNP (Ariyoshi et al., 2001; Desta et al., 2007). Another polymorphism T983C occuring CYP2B6*16 and CYP2B6*18 has also been associated with diminished enzyme activity, though this SNP is signficantly rarer than G516T (Wang et al., 2019).

Prevalence of CYP2B6 Polymorphism

The frequency of G516T polymorphism appears to vary with ethnicity. This SNP has been found to be more common in Africans than in Europeans, Hispanics, or Asians (Klein et al., 2005; Colic et al., 2014). However, the Asian sample considered in these studies consists only of East Asians (Japanese, Korean, and Taiwanese). The Asian continent comprises of many ethnically diverse countries underrepresented in genetic studies, and many regional studies do

not take into account the genetic differences between ethnic groups within their geographical area (Wall et al., 2019). Moreover, a study on cytochrome P450 genes by Zhou & Lauschke (2022) found that the CYP2B6*6 allele is more common in Africans, South Asians, and West Asians, and the CYP2B6*9 allele occurs more frequently among South Asians and West Asians, than in Europeans and East Asians. So, a large demographic has been excluded from the study of EFV-related CNS adverse effects. Moreover, neuropsychiatric side effects are widespread among HIV patients in the Asia-Pacific region, where better alternatives such as dolutegravir tend to be comparatively expensive (Sim & Hill, 2018), and thus have fewer affordable options. Therefore, this project focuses on the frequency of the G516T SNP in various ethnic groups in Asia and surrounding populations in Africa and Eastern Europe due to geographical proximity, and shared history and/or ancestory. The hypothesis predicts that HIV patients with countries and ethnic groups with highest prevalence of the alleles carrying the G516T SNP report greater incidences of neuropsychiatric side effects. Particularly, those homozygous recessive TT (and GT, though to a lesser extent) for this polymorphism are hypothesized to show higher levels of EFV in blood plasma and more frequent experience of neuropsychiatric side effects.

Chapter III

Methods

Data Acquisition

The minor allele frequencies for CYP2B6*9 were obtained from the GenomeAsia 100K project (Wall et al., 2019) containing 66 different ethnic groups spanning across Asia, Africa, West Eurasia, and Oceania. Genotype frequencies for the *9 allele was not collected as this information was not included in the GenomeAsia 100K project. The polymorphism data for CYP2B6*6 allele were compiled from multiple studies summarized in the Supplementary Information section. This dataset contains genotypic (GG, GT, TT) and minor allele frequencies for 44 ethnic groups in Asia, Eastern Europe/Western Asia, North Eastern and Western Africa, and Oceania. The criteria for inclusion of allele and genotype frequencies were identification of ethnic groups in the study and significant p-values. Both datasets include polymorphism data for healthy, adult participants wherever possible.

Data Analysis

As the focus of this study is on Asian ethnic groups and past research suggests that these polymorphisms are less common among Europeans, the Western European samples (labeled as West Eurasian) were dropped from the CYP2B6*9 dataset, although some Eurasian, African, and Oceanian populations were included due to close geopolitical proximity and shared ancestry. Ethnic groups with the highest allele and genotype frequencies were identified. An allele frequency was considered significantly large if it existed in at least 40% (0.40) of the population. The prevalence of CNS side effects in HIV patients on efavirenz regimen and transition to alternative regimens in the identified populations were characterized.

Chapter IV

Results

Countries and ethnic groups with the highest minor allele and genotype frequencies for CYP2B6*6 (516 G>T and 785 A>G) and CYP2B6*9 (516 G>T) were identified. Allele frequencies for *6 and *9 are reported in Figures 1 and 2 and frequencies of GG, GT, and TT genotypes for the *6 allele are summarized in Figure 3. Figure 4 depicts a complete list of populations with an allelic prevalence of 40% and above. The prevalence of neuropsychiatric side effects and transition to alternative regimens in the identified populations have been summarized in Table 1.

CYP2B6*6

The population group with the highest CYP2B6*6 frequency of 0.620 (62%) was the Papuan sample from Papua New Guinea. However, the genotypic frequencies for this population were not found. Several Pakistani ethnic groups had relatively large allele frequencies, such as Punjabis (54.2%), Pathans (48.0%), and Balochs (47.1%) (Fig. 3). Of these, the Baloch (27.8%) and Punjabi (25.0%) groups also had the highest genotype frequencies of TT which indicates a large presence of the least efficient metabolizer of the three genotypes for the *6 polymorphism (Fig. 4). In Indonesia, the *6 allele was prevalent in 51.1% and 41.7% of Javan and Timorian samples respectively. The Timorian group, native to East Nusa Tenggara, had a TT frequency of 22.9%, while the Javan sample interestingly had the largest GT frequency at 88.8% but very low occurrences of the homozygosity (GG 4.5%, TT 6.7%).

Other populations such as Esan (41.4%, GT 54.4%, TT 14.1%) and Yoruba (40.3%, GT 50.9%, TT 14.8%) from Nigeria and Gujarati (40.3%, GT 41.7%, TT 19.4%) from India also had a large prevalence of the 516 G>T and 785 A>G polymorphism. Though Wa emerged as the

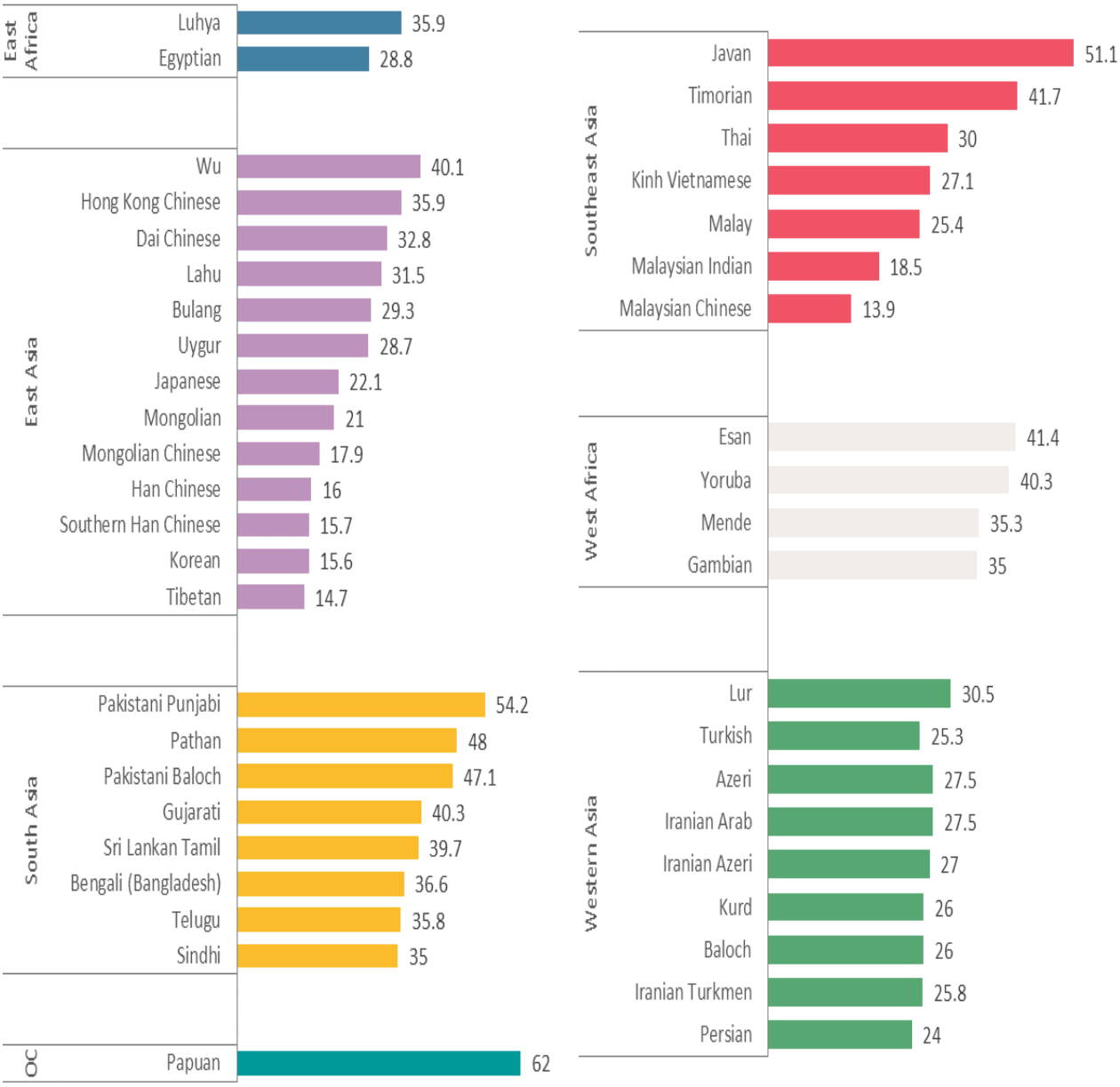

Figure 1. CYP2B6*6 allele frequencies of various ethnic groups found in geographical regions of Asia and surrounding sub-regions. OC = Oceania.

ethnic group with the largest allele frequency in China (40.1%), Hong Kong Chinese (23.1%) had greater TT occurrence than Wu Chinese (15.8%). Though not reported in Figure 4, the allele frequency (39.7%) in the Sri Lankan Tamil sample was very close to the 40% mark, and the GT

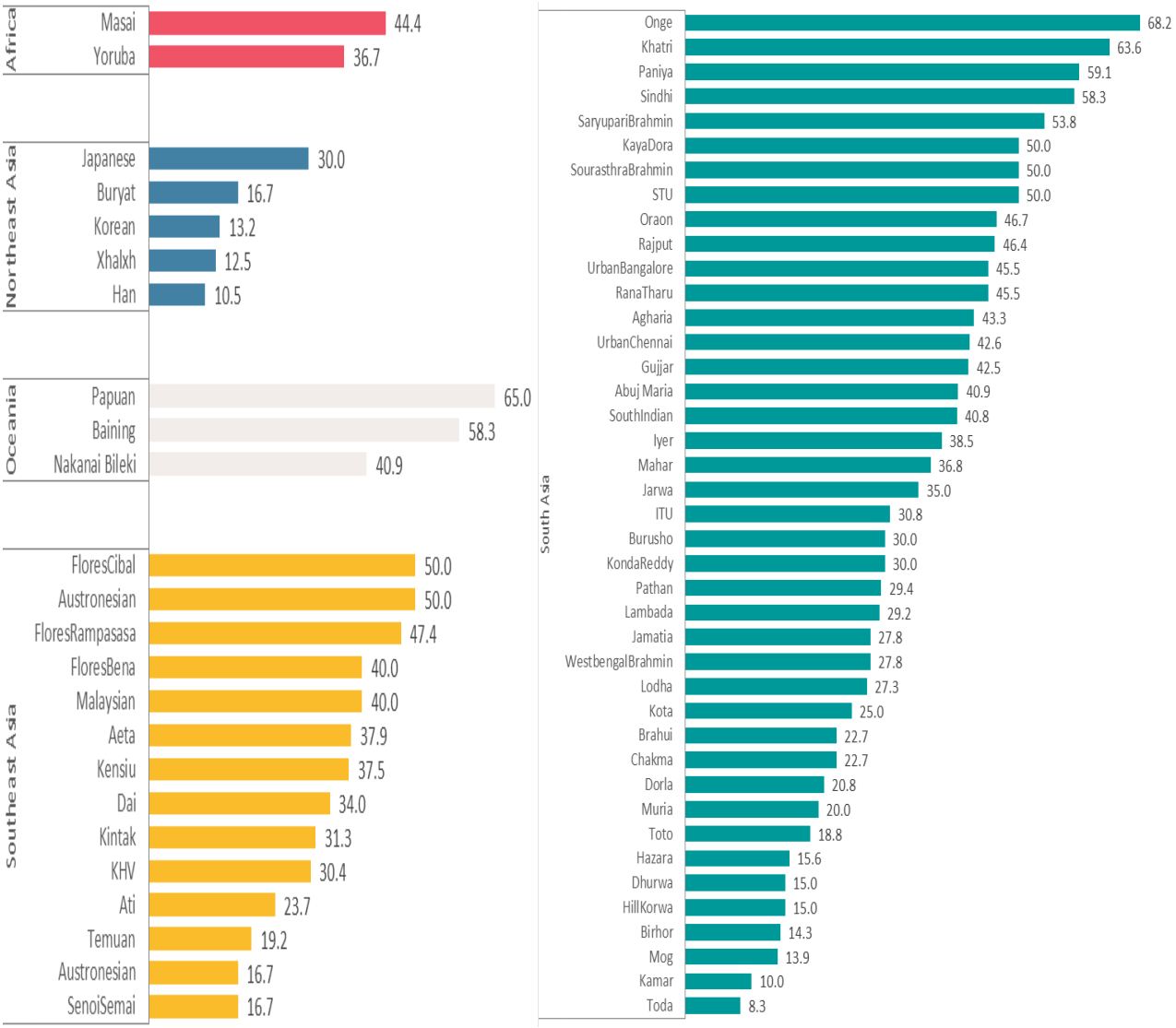

Figure 2. CYP2B6*9 allele frequencies of various ethnic groups found in geographical regions of Asia and surrounding sub-regions.

and TT frequencies (50.0% and 14.7% respectively) were comparable to those in Esan and Yoruba population groups.

CYP2B6*9

The Onge, native to the Andaman Islands of India, had the highest frequency of the *9 allele at 68.2% (Fig. 4). Around 12 other Indian ethnic groups had allele frequencies greater than 0.40, such as Khatri (63.6%), Paniya (59.1%), Saryupari Brahmin (53.8%), etc., perhaps due to

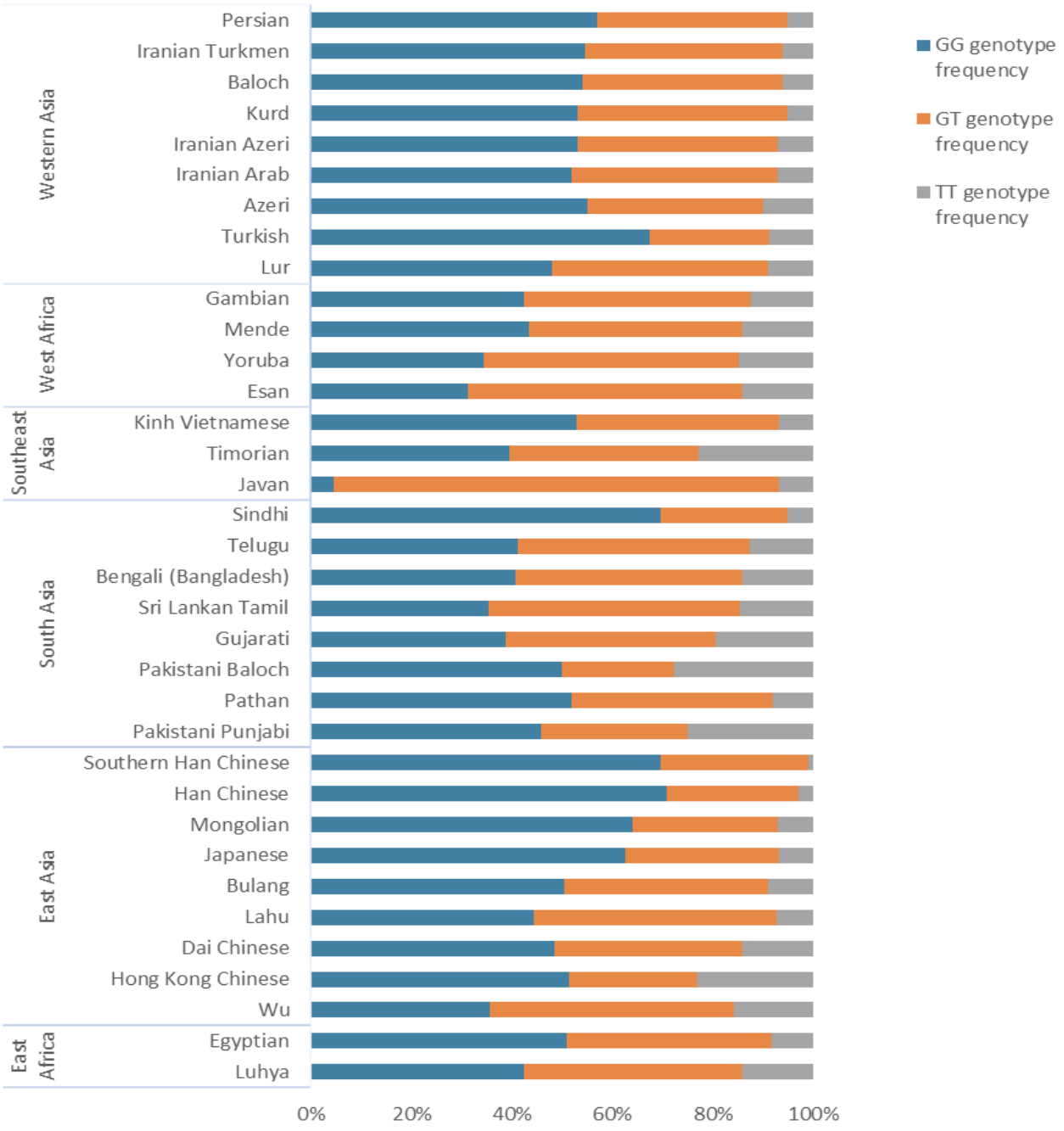

Figure 3. The CYP2B6*6 genotype frequencies for various ethnic groups found in geographical regions of Asia and surrounding sub-regions.

the large representation of ethnic groups from India comprising half of the dataset. The Papuan sample (65%) had the second highest prevalence of *9 allele, similar to its *6 allele frequency. The Baining, another ethnic group from Papua New Guinea not represented in *6 data, also had

one of the largest observed allele frequencies (58.3%). In contrast to the ethnic groups from Pakistan identified to be relevant to CYP2B6*6, the Sindhi, Rajput, and Gujjar samples had an occurrence of greater than 40%, where the latter two were not represented in the *6 data and the Sindhi population had relatively lower allele and genotype frequencies of *6 (35%, GT 25.2%, 5.1%) (Fig. 1). Though the *9 allele frequencies for Javan and Timorian groups were not included, many related Indonesian populations such as the Austronesians (50.0%), and the Cibal (50.0%), Rampasasa (47.4%), and Bena (40.0%) peoples from the island of Flores had relatively high prevalence of the G516T polymorphism. The prevalence of *9 in the Sri Lankan Tamil sample was slightly higher (50.0%) than that of *6 allele.

Countries with High Prevalence of CYP2B6*6 and CYP2B6*9

The use of efavirenz-containing regimens, reports of neuropsychiatric side effects, and HIV burden, and the transition to and cost-effectiveness of alternative regimens such as dolutegravir (DTG) in countries with highest allele and/or genotype frequencies were analyzed.

Papua New Guinea

Though Papuans were the only population group from Papua New Guinea represented in the data collected for CYP2B6*6, Papuans comprise of the largest ethnic and ancestral group in Papua New Guinea (Standish & Jackson, 2023) and their samples had one of the highest observed allele frequencies for both CYP2B6*6 and CYP2B6*9 at 62% and 65% respectively. As the reported estimates of genotypic frequencies for *6 were not found, the relative prevalence of homozygous recessive and heterozygous genotypes for this allele could not be examined.

Papua New Guinea has the largest ongoing HIV epidemic in the Pacific region, with at least 51,000 people living with HIV as of 2019 (UNAIDS, 2020). Andriguetti et al. (2021) reported the genotype frequencies of CYP2B6*9 as 25% GG, 45% GT, and 30% TT in a sample

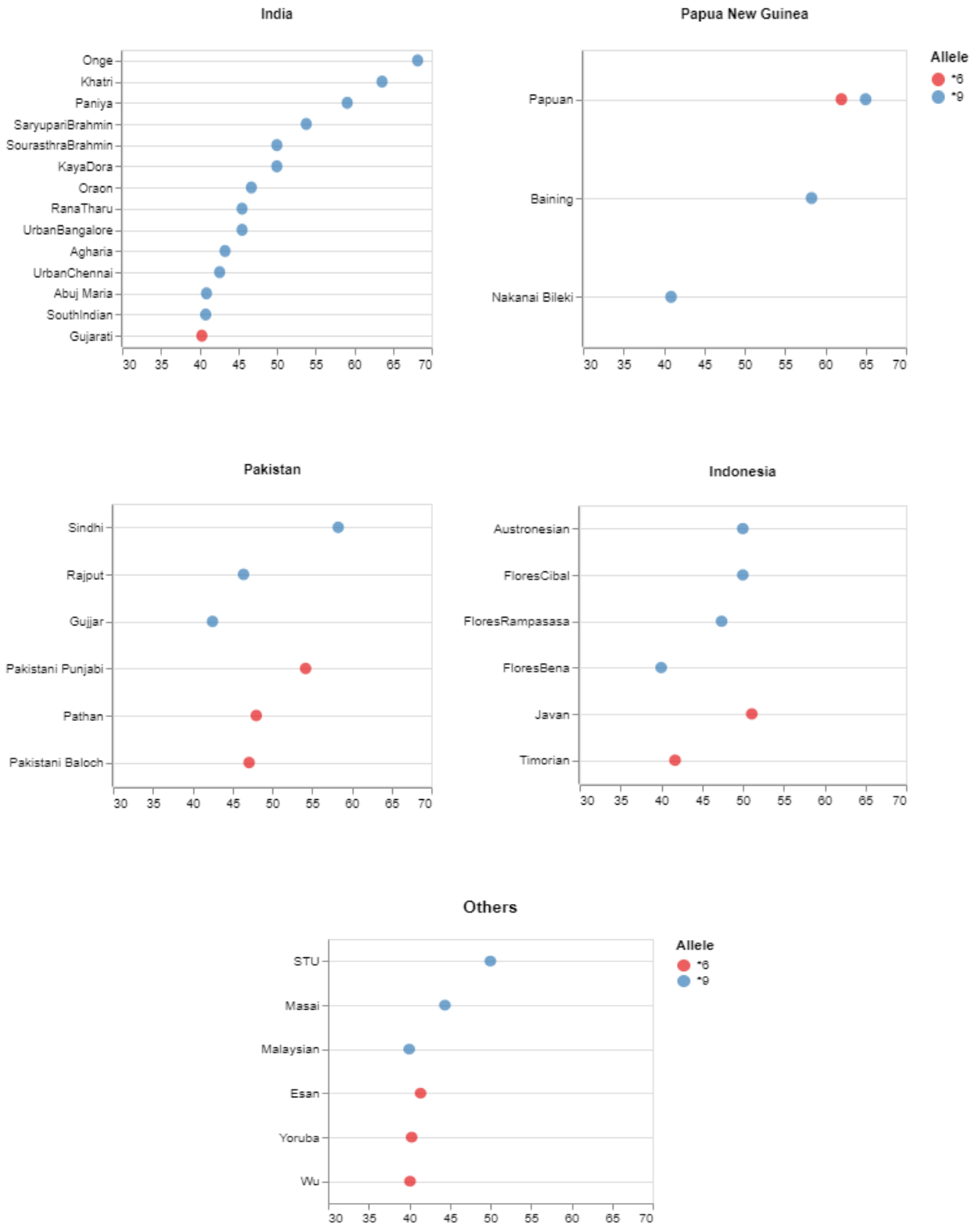

Figure 4. Ethnic groups across various geographical regions of Asia and surrounding sub-regions with allele frequencies of CYP2B6*6 (red) and CYP2B6*9 (blue) greater than or equal to 40% (0.4).

of 156 HIV-positive patients receiving 600 mg (regular, high dose) of efavirenz per day, suggesting a large prevalence of individuals with weak metabolizers. Blood EFV concentrations were found to be above therapeutic levels only in patients with the TT genotype. However, contrary to previous findings, those with the GG genotype had lower-than therapeutic levels of EFV, while those with the heterozygous genotype GT maintained therapeutic concentrations in blood. These unexpected observations could possibly be due to polymorphisms in other enzymes such as CYP3A5, CYP1A2, and CYP2A6 and/or interactions with other drugs consumed by the patients (di Iulio et al., 2009). Another contradiction was that patients with above-therapeutive EFV concentrations (and TT genotype) did not report any side effects, while those within the therapeutic range (and GT genotype) reported significantly higher incidences of neuropsychiatric symptoms. The CNS side effects reported were tiredness, dizziness, drowsiness, insomnia, impaired concentration, agitation, depression, and aggression. The authors believe that the lack of association between high plasma EFV concentrations and neuropsychiatric side effects was observed because this assessment was conducted in patients who had taken EFV for at least 3 months and majority of CNS side effects tend to subside within the first few weeks to months of treatment as patients develop tolerance. However, this lack of expected association also adds to the disagreement of previous findings and may suggest that external factors may play a bigger role in determining the development of neuropsychiatric side effects.

Though the DTG regimen replaced EFV in 2019 as the recommended first-line antiretroviral therapy, EFV continues to be offered as an alternative first-line treatment for children, adolescents, and adults (NDoH, 2019). But a report released by the Joint United Nations Programme on HIV and AIDS (UNAIDS) for the year 2020-2021 indicated that 90% of eligible patients had successfully transitioned from EFV to DTG (UNAIDS, 2021a). A recent

Table 1. Summary of people living with HIV (PLWH) estimates, neuropsychiatric side effects, correlation with implicated polymorphisms, and DTG cost-effectiveness and transition for the four countries with the highest prevalence of CYP2B6*6 and CYP2B6*9

Country	**PLWH (% total population)****	**Efavirenz-related CNS adverse effects**	**SNP and genotype correlation**	**DTG cost-effec-tiveness***	**DTG transition***
Papua New Guinea	51,000 (0.53)	Tiredness, dizziness, drowsiness, insomnia, impaired concentration, agitation, depression, aggression	*9, inverse relationship (CNS effects in those with GT, not TT; lowest blood EFV levels in GG)	Affordable	90% complete
Pakistan	213,310 (0.09)	Unknown	Unknown	Possibly affordable	In progress, slow
Indonesia	540,000 (0.20)	Depression, lifetime suicide ideation	Unknown	Possibly affordable	In progress
India	2,401,000 (0.17)	Giddiness, numbness, tremors, dizziness, insomnia, headache, somnolence, abnormal dreams, depressive symptoms, anxiety, suicide ideation	*9, predicted relationship (CNS effects in those with GT and TT; highest blood EFV levels in TT)	Possibly affordable	In progress

*As of 2021
** % population living with HIV calculated from total population estimates for the year the number of PLWH was reported for (World Bank Population estimates and projections, 2022).

study by Gare et al. (2022) urged for infrastructural changes to enhance nationwide availability and accessibility of DTG-based regimens to improve patient outcomes and treatment adherence, which may suggest that EFV phase-out is still under process.

The current relative cost benefits of EFV and DTG appear to favor the latter. In 2017, an agreement between the United Nations and several other AIDS organizations announced an average cost reduction of DTG by at least 10-15% to be supplied royalty-free to many low- and middle-income countries, including Papua New Guinea (UNAIDS, 2018). The agreement claimed that DTG prices are not expected to increase for several years, even after the expiration

of the agreement, and expected prices to decline in the future. In 2020, a progress report on HIV efforts in Papua New Guinea released by United Nations AIDS organization reported the average price per unit of DTG in 2019 as approximately $4.5 (USD), which was almost half the price of an efavirenz-containing formulation ($7) (UNAIDS, 2020a). Another drug containing a combination of DTG with other antiretroviral substances was slightly more affordable ($6.5) than the EFV-containing regimen. Further, according to a recent study by Gare et al. (2022), DTG offers a more affordable treatment to patients in Papua New Guinea than efavirenz, though the source of this claim has not been cited. These may suggest that the affordability of DTG in Papua New Guinea has significantly improved.

Pakistan

Compared to CYP2B6*9, CYP2B6*6 appears to be more prevalent in Pakistan, especially among the Punjabi demographic (54.2%). Among those with the *6 allele, 25.0% had the recessive TT genotype. Punjabis are also the largest ethnic group in Pakistan comprising of 44.7% of the country's population, followed by Pathan (15.4%), Sindhi (14.1%), Saraiki (8.4%), Muhajirs (7.6%), Balochi (3.6%), and other minorities (6.3%) (The World Factbook, 2023a). Many of these ethnicities also showed frequencies greater than 40% for both CYP2B6 alleles, such as Pathan, Baloch, Sindhi, Rajput, and Gujjar. The number of potentially affected ethnic groups along with the large demographic they cover makes Pakistan a vital country to study in terms of the use of efavirenz as an antiviral treatment for HIV patients.

In 2020, around 213,310 people in Pakistan were estimated to be living with HIV (UNAIDS, 2020b). The national HIV treatment guidelines were updated fairly recently in 2021 to favor DTG as the first-line regimen while EFV was suggested to be used as an alternative in lower doses (400 mg) or only in special circumstances (NACP, 2021). However, no evidence of

efavirenz-phase out could be found. At the time of the update in the treatment guidelines, a large number of patients were reported to be on an EFV-containing regimen (NACP, 2021). According to Batool et al. (2021), very few patients in the country were under a DTG-containing treatment. Batool et al. were also the first ones to determine the efficacy and safety of DTG as an antiretroviral treatment in Pakistan, which suggests that DTG testing and roll-out might still be underway.

According to the progress report published by UNAIDS (2020b), the current focus of the HIV program in Pakistan is to consolidate the existing infrastructure. Despite the update in the national guidelines, 38 different antiretroviral regimens were previously offered, and a large number of physicians were not properly trained to handle antiretroviral therapy. So, the country's priority is to systemize treatment plans, increase education, detection, and treatments, lower social stigma, and form community-level clinical interventions. The restrictions presented by the COVID-19 pandemic further slowed down these efforts. So, due to the need for consolidation of the HIV healthcare system along with the challenges presented by the pandemic, the roll-out of dolutegravir and the discontinuation of EFV have been slow. Though a reliable cost comparison between efavirenz and dolutegravir could not be found, as Pakistan is one of the countries promised to receive cheaper, royalty-free supply of DTG by the UNAIDS agreement (UNAIDS, 2018), the affordability of DTG can be assumed to improve.

No information on the presence of neuropsychological effects of EFV in Pakistani HIV patients could be found. The national guidelines acknowledged the neuropsychiatric side effects associated with efavirenz, it was most likely taken from the guidelines released by the World Health Organization and not a reflection of neuropsychiatric side effects reported by patients in Pakistan. The guidelines also reported that the EFV-containing regimen used by a large number

of patients were stable, though whether this stability was attributed to the efficacy of the treatment in viral suppression as well as lack of adverse CNS effects is unclear. The lack of evidence may suggest that these side effects are not prevalent in spite of widespread occurrence of implicated CYP2B6 polymorphisms in this population. Alternatively, neuropsychiatric symptoms may be underreported as patients may prefer to ignore, use over-the-counter drugs, or consult non-antiretroviral therapy physicians for such side effects. The lack of a fully-consolidated system along with deficits in medical training may have contributed to the underreporting of side effects as well. Therefore, this lack of reported symptoms could neither support nor reject the hypothesis of the correlation between CYP2B6 polymorphisms and neuropsychological adverse effects for the Pakistani population.

Indonesia

The CYP2B6*6 and CYP2B6*9 alleles had a prevalence of 40% or higher in many ethnic groups in Indonesia, such as Javan and Timorian (*6) and Austronesian, Cibal, Rampasasa, and Bena (*9). A large variation in the prevalence of genotypes of the *6 allele was observed. At 88.8%, the GT genotype appears to be the most prevalent among Javans, though they have significantly lower prevalence of GG and TT genotypes, while the Timorian sample had a relatively large occurrence of the latter homozygous genotype. However, all of these ethnic groups are of Austronesian origin, which forms the largest ancestral group in Indonesia, where the Javanese people emerge as the largest ethnic group comprising 40% of the country's population (The World Factbook, 2023b). So, the CYP2B6*6 and CYP2B6*9 polymorphisms appear to be fairly common in Indonesia.

Though ethnicity-specific effects of efavirenz could not be found, a study conducted in 86 HIV patients in 2020 reported that lifetime suicide ideation was prevalent among 23.3% of

the subjects, and suicide ideation was linked with factors such as EFV use, CD4 cell count, and and symptoms of depression (Ophinni et al., 2020). However, the prevalence of CYP2B6 polymorphisms was not discussed. It is possible that the prevalence of depression and suicide ideation observed by Ophinni et al. is linked with the high occurrence of *6 and *9 polymorphisms in several Indonesian ethnicities found in this study. However, neuropsychiatric side effects were not associated with efavirenz in a retrospective study conducted in 71 HIV patients in a Sumatran hospital during 2005 to 2020— no side effects were recorded for 55% of the patients (Wahidah et al., 2020). In the remaining 45%, skin rash was the only side effect reported, and was associated with antiviral drugs other than EFV, and about 72% of these patients were shifted to an EFV-containing regimen. Initially, only about 24% of patients were on an efavirenz-containing drug combination, and patient outcome after shifting to EFV are not known. Though it is possible that neuropsychiatric symptoms were not included in the records due to factors such as underreporting, these inconsistent findings make it difficult to estimate the occurrence of neuropsychiatric symptoms linked with efavirenz in this population.

The burden of HIV in Indonesia is among the highest in Asia (Wahidah et al., 2020), with about 540,000 people living with HIV in 2020 (UNAIDS, 2021b). The UNAIDS progress report states that the high price of antiretroviral drugs continues to be a challenge in Indonesia (UNAIDS, 2020c). Though Indonesia is a part of the UNAIDS agreement for reduced-price DTG, unlike Papua New Guinea and Pakistan, Indonesia has to pay 7.5% royalty (UNAIDS, 2018), which may drive up the cost of DTG. Efforts are being made to make HIV treatment more affordable through infrastructural and policy changes (UNAIDS, 2020c). Though it is unclear whether the national guidelines were updated to adopt dolutegravir as the first-line antiretroviral treatment, the support for the roll-out of DTG have been intensified and the transition is still far

from complete (UNAIDS, 2020c). Though reliable sources for a price estimate of DTG could not be found, the cost of efavirenz has dropped to $15 in 2020 from $28 in 2016 (Wardhana, 2020) and EFV-containing regimens seem to still be in widespread use (Wahidah et al., 2020). Like Pakistan, Indonesia's HIV control program is exerting more focus on improving access to healthcare in order to improve the management of the HIV epidemic.

India

Compared to CYP2B6*9, only the Gujarati ethnic group from India had a prevalence of at least 40% of the CYP2B6*6 polymorphism, perhaps due to lower representation of Indian ethnicities in the sample. In contrast, 13 groups were found to have a large allele frequency of CYP2B6*9, such as Onge, Khatri, Paniya, Saryupari Brahmin, Saurashtra Brahmin, Kaya Dora, Oraon, Rana Tharu, Agharia, Abuj Maria, and South Indian, and those from urban areas of Bangalore and Chennai. The Onge had the highest frequency of the *9 allele across samples from all countries.

Though ethnicity-based studies for the association between CYP2B6 polymorphisms and CNS adverse effects could not be found for populations in India, evidence for the link between CYP2B6*9 polymorphisms, EFV use, and mild neuropsychiatric symptoms have been demonstrated. Consistent with previous findings, a study conducted in Hyderabad, India on 276 HIV patients and 93 healthy controls reported that the GG, GT, and TT genotypes of the CYP2B6*9 polymorphism was found in 69%, 18%, and 13% of subjects in their sample and were extensive, intermediate, and poor metabolizers of EFV, respectively (Kurian et al., 2022). A similar association between genotypes and EFV blood concentration and exposure was found in another study in southern India (Ramachandran et al., 2009). Of those with the TT genotype, 2.6% reported hallucinations, 24% showed insomnia, and 12% had a decrease in CD4 cell

counts. About 8% of those with the GT genotype reported insomnia but incidences of hallucinations were not experienced, and 15% of these individuals also showed reduction in CD4 cell counts. Those with the GG genotype did not experience any CNS side effects or alterations in CD4 cell counts.

Neuropsychiatric symptoms have been reported in patients on a low-dose (400 mg) EFV-containing regimen, which is believed to have a lower toxicological profile though it may have lower efficacy in viral load suppression. In a study conducted in 502 subjects with HIV in Pune, India, 50% reported adverse effects after starting low-dose EFV (Dravid et al., 2020). Most common adverse effects were CNS-related, such as giddiness (23.7%), depressive symptoms (18.1%), insomnia (14.5%), anxiety (12.4%), headache (11.6%), somnolence (11.2%), and abnormal dreams (10.6%). Four subjects showed suicide ideation and discontinued the EFV-containing regimen. A total of 10 subjects discontinued EFV due to CNS-related adverse events. About 94% of all patients were previously on a high-dose (600 mg) efavirenz regimen, 45.97% of whom reported the switch to low-dose EFV reduced or cleared neuropsychiatric adverse effects from the previous dosage while 47.25% experienced similar adverse effects on both regimens and 6.78% preferred the high-dose treatment. The reason for these differences in the experience of neuropsychiatric symptoms was unclear. Another study in eastern India found that, among regimens containing antiretroviral drugs such as zidovudine, nevirapine, atazanavir, tenofovir, and stavudine, those on efavirenz-containing regimens reported the highest number of CNS-related side events (about 21% of 303 patients on EFV) including insomnia, headache, numbness, tremors, dizziness, and nightmares (Mukherjee et al., 2017). Based on these studies, neuropsychiatric adverse effects linked with EFV are quite common in at least southern and

eastern India, and the occurrence of these side effects are strongly correlated with the TT genotype (and GT to a lesser extent) of the G516T polymorphism.

As of 2021, around 2.4 million people were estimated to be living with HIV in India, though adult HIV prevalence has been declining since 2000 (NACO, 2021a). The country's national guidelines for the treatment of HIV were updated in 2018 to favor DTG as the preferred first-line regimen while EFV was designated as an alternative for women who do not wish to transition to DTG (NACO, 2021b). However, EFV continues to be widely used. In the revised version of the national guidelines published in 2021, EFV is still listed as one of the commonly used antiretroviral drugs in the country. The low-dose version of EFV was recommended by healthcare providers due its reduction in adverse effects than regular, high-dose EFV and its cost-effectiveness in comparison to DTG (Dravid et al., 2020). Safety and efficacy testing may still be underway (Dravid et al., 2022), further adding to the evidence that DTG transition is currently under process.

Like Indonesia, the United Nations price reduction agreement for dolutegravir levies a royalty fee of 5% on India, though it is slightly less than that on Indonesia (UNAIDS, 2018). However, a 2018 study used a simulation model and forecasted that, due to the higher efficacy and lower toxicological profile of DTG and increase in the roll-out of generic DTG by many pharmaceutical companies in India— including Aurobindo, one of the two DTG manufacturers under the UNAIDS price reduction agreement— the cost in the future is likely to drop and DTG would have a greater overall cost-effectiveness than EFV (Zheng et al., 2018).

Though the current status of transition to a DTG-based regimen could not be determined, based on these reports, EFV appears to still be in widespread use, the rollout of DTG is far from complete, and the affordability of DTG is expected to improve. The country's HIV program has

achieved many of its infrastructure development goals and current focus is to improve testing, screening, and treatment initiation and adherence as well as complete the transition to dolutegravir (UNAIDS, 2020d).

Chapter V

Discussion

The *6 and *9 polymorphisms were highly common among Pakistani, Indian, and (to a lesser extent) Sri Lankan groups, which is consistent with Zhou & Lauschke (2022) that these variations are more frequent among South Asians. Unlike studies that identified high prevalence of these single nucleotide polymorphisms in Africans and West Asians, these populations did not emerge as significant in this analysis, perhaps due to the inclusion of fewer samples from African nations. Two prominent ancestral groups in the Pacific— the Melanesians (Papuans) and the Austronesians (Indonesians)— also had a large occurrence of CYP2B6*6 and CYP2B6*9 as well as prevalence of CNS side effects, a key observation as Pacific and Oceanian populations have not been previously included in global population studies on CYP2B6 variations.

Only the relationship between allele and genotype frequencies, EFV plasma concentrations, and neuropsychiatric side effects in the samples from India were fully consistent with the hypotheses— those with GT and TT genotypes were intermediate and poor EFV metabolizers respectively, had higher plasma EFV levels than those with GG, and reported a wide range of neuropsychiatric symptoms including depression and suicide ideation. Papua New Guineans also had one of the highest frequencies of both alleles, and GT and TT genotypes were associated with intermediate and high levels of plasma EFV, indicating that these genotypes produce CYP2B6 metabolic activity consistent with previous studies. Contrary to the hypothesis, those with the GG genotype had lower-than therapeutic plasma EFV levels, and those with the TT genotype did not report any CNS adverse effects. To further add to the contradiction, heterozygous individuals with optimal plasma EFV levels experienced CNS side effects such as

tiredness, dizziness, insomnia, impaired concentration, depression, etc. Suicidality was not observed.

These findings suggest that prevalence of polymorphisms in other genes, such as CYP2A6, may be altering expected plasma EFV levels and the experience of neuropsychiatric side effects in these individuals (di Iulio et al., 2009; Kwara et al., 2009). These results in Papua New Guineans, along with the inconsistency in the reports of neuropsychiatric symptoms in Indonesian HIV patients despite the implicated SNPs being fairly common, suggest non-genetic factors such as age, income, poverty, social circumstances, history of psychiatric disorders etc. may also play a major role in the development of neuropsychiatric symptoms. The lack of literature on plasma EFV levels and CNS side effects in Pakistan may suggest the absence of these adverse reactions to EFV despite having very common occurrence of *6 and *9 among prominent ethnic groups. However, the lack of a fully-consolidated HIV healthcare system and inadequately trained medical professionals are more likely to cause any adverse drug reactions to be understudied. Due to the benefit of doubt, the hypothesis could neither be discarded nor supported for those living with HIV in Pakistan.

The relationship between the genotypes and the metabolic activity of their corresponding enzymes were largely consistent with the hypothesis and existing literature but mostly disagreed on the production of neuropsychiatric symptoms. Though these findings have been consistent with the commonly reported CNS adverse effects of efavirenz, such as, dizziness, insomnia, headaches, and depression, suicidality appears to be extremely infrequent, which is also in line with the implications of the literature review (Napoli et al., 2014; Chang et al., 2018; Nkhoma et al., 2016). Though suicidality may be a result of a rare adverse CNS reaction, it is more likely to be a product of factors other than EFV use. The results of this analysis are also in agreement with

Li et al. (2021) and Journot et al. (2006) as the disagreement in the experience of neuropsychiatric symptoms may be due to the larger role of external factors in the development of these adverse effects.

The current (2023) status for the discontinuation of efavirenz and the transition to less toxic and more efficient alternatives such as dolutegravir is unknown for all four countries, so present situation was deduced based on past evidence from years after 2017. As Papua New Guinea, Pakistan, Indonesia, and India are all part of the UNAIDS price reduction agreement for DTG along with the release of generic versions, the cost barrier has likely considerably diminished over the past decade or so. These countries are in different stages of DTG roll-out largely due to internal circumstances, despite which the future of this transition and improvement of HIV healthcare appears to be quite optimistic. Papua New Guinea shows the most evidence for DTG rollout and price reduction, while Pakistan and Indonesia appear to prioritize the strengthening of infrastructure over accelerating the transition to DTG, with the efforts of the former being the most affected by the pandemic, and India seems to consider the completion of DTG roll-out as the next goal in their HIV program.

Limitations

Only 43% of 51 countries in Asia were represented in the data collected, so the allele and genotype frequencies and prevalence of efavirenz-related CNS side effects of populations in 29 countries such as Afghanistan, Bangladesh, Iraq, Syria, Saudi Arabia, etc. could not be examined. The same can be said about the representation of regions in the vicinity of and overlapping with Asia, such as Armenia, Georgia, Greece etc. As Asia is ethnically diverse and many countries have hundreds to thousands of ethnic groups, the sample collected includes only a handful of Asian ethnicities. Therefore, the list of identified countries with highest CYP2B6

polymorphism prevalence is by no means complete. This dearth is accentuated the most in the samples from India— while only two population groups were included for the CYP2B6*6 polymorphism, over 33 ethnicities were represented in the CYP2B6*9 allele frequencies, many of which belonged to tribal groups that make up only 8.6% of the population (Office of Registrar General, 2011). These scarcities exist largely due to the lack of studies on CYP2B6 polymorphisms in these populations. Genotype frequencies for CYP2B6*9 were also not collected, so the relative occurrence of GG, GT, and TT and the approximation of fast, intermediate, and slow efavirenz metabolizers could not be explored.

This project was based on the assumption that individuals with the same ethnicity have similar ancestral and genetic profiles, which is not always the case. Populations with different ancestries can associate themselves with the same ethnicity through shared cultural and historical circumstances. In the same vein, geographical proximity does not always equate to genetic similarity as migration throughout history can bring distinct groups of people together. Nonetheless, ethnicity and geographical proximity are important factors to consider in terms of grouping populations for the study of inter-individual genetic variations.

The use of efavirenz, availability of alternatives, and reports of CNS adversities were not examined for all populations that have allele frequencies of 0.40 and above, so the pharmacological outcome of EFV in these countries is not taken into account. This is because the analysis was limited to populations with high prevalence of both *6 and *9 due to the limitations of the scale of the study. Further, while the allele and genotype frequencies were specific to ethnicities, the studies on plasma EFV concentrations and the experience of neuropsychiatric symptoms in their countries of origin were not ethnicity-specific. So, the support for the correlation in this project does not imply that high occurrence of the implicated CYP2B6

polymorphisms directly causes reduced metabolism and CNS adverse effects, if any, as the ethnicities of the subjects in these studies are not known. Lastly, allele and genotype frequencies for all included groups were determined based on samples that tended to be quite smaller than the actual size of the populations. So, the data collected comes with the typical statistical caveats of sampling in that these frequencies are estimates and may not reflect the actual frequencies in the population. The data was collected from existing literature with the assumption that these studies employed adequate sampling and statistical practices.

Future Directions

The debate on the relationship between efavirenz and neuropsychiatric side effects may benefit from studies that take a holistic approach to genetics, healthcare, and medicine, and incorporate ethnicity, ancestry, and social backgrounds and conditions along with relevant genetic polymorphisms to help resolve the relationships between genetic and/or environmental factors that result in neurotoxic patient outcomes. Additionally, CYP2B6 is involved in the metabolism of many other substrates such as methadone, ketamine, propofol, cyclophosphamide, bupropion, artemisinin, and nevirapine (Desta et al., 2016). So, it is crucial to determine the role of variations in this gene in the metabolism, pharmacological, and toxicological profiles of these drugs along with identification of populations most likely to experience negative outcomes. The interactions of polymorphisms in various cytochrome P450 genes that result in altered metabolism and pharmacological outcomes also need to be examined. These forms of population-based genetic profiling may help in understanding genetic diversity, providing informed healthcare, and improving individualized medicine in future.

Conclusions

Efavirenz use may lead to the development of neuropsychiatric side effects in some HIV-infected populations, such as those in Papua New Guinea, India, and Indonesia, due to high prevalence of the CYP2B6*6 (516 G>T and 785 A>G) and CYP2B6*9 (516 G>T) polymorphisms linked with less-efficient metabolizers and non-therapeutic plasma levels of EFV and related metabolites. Others may not experience these adverse effects despite exhibiting the implicated polymorphisms due to both internal (polymorphisms in other genes) and external factors (age, income, social circumstances, underreporting or undertreating symptoms, etc.). Those experiencing neurotoxicity can be transitioned to an alternative regimen such as dolutegravir or low-dose EFV if the former option proves to be difficult. Future pharmacological studies may incorporate genetically diverse samples to identify populations that may benefit from alternative treatments.

Chapter VI

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Supplementary Information

Table S1. Allele and genotype frequencies of CYP2B6*6 across Asian, African, and Oceanian ethnicities grouped by countries.

Country	Population	GG	GT	TT	Minor Allele Frequency
Azerbaijan	Azeri	0.550	0.350	0.100 (Ildirim, 2022)	0.275
Bangladesh	Bengali (Bangladesh)	0.407	0.453	0.140 (Cunningham et al., 2021)	0.366
China	Lahu	0.444	0.481	0.074 (Xu et al., 2007)	0.315
	Wa	0.356	0.485	0.158 (Xu et al., 2007)	0.401
	Bulang	0.505	0.404	0.091 (Xu et al., 2007)	0.293
	Hong Kong Chinese	0.513	0.256	0.231 (Xu et al., 2007)	0.359
	Han Chinese	0.709	0.262	0.029 (Cunningham et al., 2021)	0.160
	Southern Han Chinese	0.695	0.295	0.010 (Cunningham et al., 2021)	0.157
	Dai Chinese	0.484	0.376	0.140 (Cunningham et al., 2021)	0.328
	Uygur	--	--	--	0.287 (Qi et al., 2016)
	Tibetan	--	--	--	0.147 (Qi et al., 2016)
	Mongolian Chinese	--	--	--	0.179 (Qi et al., 2016)
Egypt	Egyptian	0.508	0.408	0.083 (Ellison et al., 2012)	0.288
Gambia	Gambian	0.425	0.451	0.124 (Cunningham et al., 2021)	0.350
India	Gujarati	0.388	0.417	0.194 (Cunningham et al., 2021)	0.403
	Telugu	0.412	0.461	0.127 (Cunningham et al., 2021)	0.358
Indonesia	Timorian	0.396	0.375	0.229 (Hananta et al., 2018)	0.417
	Javan	0.045	0.888	0.067 (Rahman et al., 2022)	0.511
Iran	Kurd	0.530	0.420	0.050 (Fattani et al., 2019)	0.260
	Lur	0.480	0.430	0.090 (Fattani et al., 2019)	0.305
	Azeri	0.530	0.400	0.070 (Fattani et al., 2019)	0.270
	Iranian Arab	0.520	0.410	0.070 (Fattani et al., 2019)	0.275
	Iranian Turkmen	0.546	0.392	0.062 (Fattani et al., 2019)	0.258
	Baloch	0.540	0.400	0.060 (Fattani et al., 2019)	0.260
	Persian	0.570	0.380	0.050 (Fattani et al., 2019)	0.240

Country	Population	GG	GT	TT	Minor Allele Frequency
Japan	Japanese	0.625	0.308	0.067 (Cunningham et al., 2021)	0.221
Kenya	Luhya	0.424	0.434	0.141 (Cunningham et al., 2021)	0.359
Malaysia	Malay	--	--	--	0.254 (Ismail et al., 2012)
	Malaysian Chinese	--	--	--	0.139 (Ismail et al., 2012)
	Malaysian Indian	--	--	--	0.185 (Ismail et al., 2012)
Mongolia	Mongolian	0.430	0.280	0.070 (Davaalkham et al., 2009)	0.210
Nigeria	Esan	0.313	0.545	0.141 (Cunningham et al., 2021)	0.414
	Yoruba	0.343	0.509	0.148 (Cunningham et al., 2021)	0.403
Pakistan	Pakistani Punjabi	0.458 (Ahmed et al., 2021a)	0.292	0.250	0.542 (Ahmed et al., 2021b)
	Pakistani Baloch	0.500 (Ahmed et al., 2021a)	0.222	0.278	0.471 (Ahmed et al., 2021b)
	Pathan	0.518 (Ahmed et al., 2021a)	0.401	0.081	0.480 (Ahmed et al., 2021b)
	Sindhi	0.697 (Ahmed et al., 2021a)	0.252	0.051	0.350 (Ahmed et al., 2021b)
Papua New Guinea	Papuan	--	--	--	0.620 (Mehlotra et al., 2006)
Sierra Leone	Mende	0.435	0.424	0.141 (Cunningham et al., 2021)	0.353
South Korea	Korean	--	--	--	0.156 (Lee et al., 2022)
Sri Lanka	Sri Lankan Tamil	0.353	0.500	0.147 (Cunningham et al., 2021)	0.397
Thailand	Thai	--	--	--	0.300 (Mauleekoonphairoj, 2020)
Turkey	Turkish	0.675	0.238	0.087 (Yuce-Artun et al., 2014)	0.253
Vietnam	Kinh Vietnamese	0.528	0.403	0.069 (Veiga et al., 2008)	0.271

Table S2. Allele frequencies of CYP2B6*9 across Asian, African, and Oceanian ethnicities grouped by countries.

Country Of Origin	Ethnicity Shortname	Ethnicity	Minor Allele Frequency
China	HAN	Han	0.1052631579
	DAI	Dai	0.34
India	ABM	Abuj Maria	0.4090909091
	AGH	Agharia	0.4333333333
	BIR	Birhor	0.1428571429
	BLR	UrbanBangalore	0.4545454545
	CHK	Chakma	0.2272727273
	DHR	Dhurwa	0.15
	DOR	Dorla	0.2083333333
	HKR	HillKorwa	0.15
	ITU	ITU	0.3076923077
	IYE	Iyer	0.3846153846
	JAM	Jamatia	0.2777777778
	JAR	Jarwa	0.35
	KAM	Kamar	0.1
	KHA	Khatri	0.6363636364
	KNR	KondaReddy	0.3
	KTA	Kota	0.25
	KYD	KavaDora	0.5
	LAM	Lambada	0.2916666667
	LOD	Lodha	0.2727272727
	MAA	UrbanChennai	0.4264705882
	MHR	Mahar	0.3684210526
	MOG	Mog	0.1388888889
	MUR	Muria	0.2
	ONG	Onge	0.6818181818
	ORN	Oraon	0.4666666667
	PNY	Paniya	0.5909090909
	RTH	RanaTharu	0.4545454545
	SOB	SourasthraBrahmin	0.5
	SRB	SaryupariBrahmin	0.5384615385
	SSI	SouthIndian	0.4078947368
	TOD	Toda	0.08333333333
	TTO	Toto	0.1875
	WBB	WestbengalBrahmin	0.2777777778
Indonesia	BEN	FloresBena	0.4
	CIB	FloresCibal	0.5
	MEN	Austronesian	0.5
	NIA	Austronesian	0.1666666667
	RAM	FloresRampasasa	0.4736842105
Japan	JPN	Japanese	0.3
Kenya	MAS	Masai	0.4444444444
Korea	KOR	Korean	0.1324503311
Malaysia	KEN	Kensiu	0.375
	KIN	Kintak	0.3125
	MLY	Malaysian	0.4
	SNS	SenoiSemai	0.1666666667
	TEM	Temuan	0.1923076923
Mongolia	BUR	Buryat	0.1666666667
	KHL	Xhalxh	0.125

Country Of Origin	Ethnicity Shortname	Ethnicity	Minor Allele Frequency
Nigeria	YRI	Yoruba	0.3666666667
Pakistan	BRA	Brahui	0.2272727273
	BRU	Burusho	0.3
	GUJ	Gujjar	0.425
	HAZ	Hazara	0.15625
	PAT	Pathan	0.2941176471
	RAJ	Rajput	0.4642857143
	SND	Sindhi	0.5833333333
Papua New Guinea	BAI	Bainin	0.5833333333
	NKB	Nakanai Bileki	0.4090909091
	PAP	Papuan	0.65
Philippines	AET	Aeta	0.3793103448
	ATI	Ati	0.2368421053
Sri Lanka	STU	STU	0.5
UK	GBR	GBR	0.2321428571
Vietnam	KHV	KHV	0.3035714286

Table S1 References

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