CYP2D6 Overview: Allele and Phenotype Frequencies

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Introduction

Genetic variation has a significant impact on an individual's metabolism and response to a wide range of medications. The cytochrome P450 family of enzymes are key determinants in the metabolism of multiple pharmacologic compounds. One such member, CYP2D6 is involved in the metabolism of a wide range of medications including drugs for pain management, cancer, mental health disorders, some cardiovascular symptoms, chorea, and Gaucher disease (1, 2). This enzyme is encoded by the *CYP2D6* gene, which is highly polymorphic. The *CYP2D6* alleles can be classified as having no function, decreased function, normal function or increased function. The combination of alleles present in an individual (also referred to as genotype or diplotype) allows for prediction of metabolizer phenotype ranging from poor metabolizer (PMs, no enzymatic activity) through ultrarapid metabolizer (UMs, increased enzyme activity). Poor metabolizers exhibit no enzyme activity, intermediate metabolizers (IMs) have decreased enzyme activity, and UM's have increased enzyme activity relative to the normal metabolizer (NM) phenotype. Increased enzyme activity is most often due to gene copy number variation, namely, the presence of one or more functional gene copies.

As is commonly observed with genomic variation, the frequency of *CYP2D6* alleles differs from one population to another. Knowing the frequency of specific alleles and metabolizer phenotypes among sub-populations of different ethnic, or geographical groups, or both, will enable clinicians to identify individuals who can most benefit from preemptive genetic testing for actionable pharmacogenetic variation. As the *CYP2D6* locus has such a high degree of variation, there is an extensive field of literature regarding allele and phenotype frequencies for various populations. The purpose of this document is to provide a centralized resource for key information on the *CYP2D6* gene, allele function, and phenotype prediction, as well as an overview of the recent literature reporting the allele and phenotype frequencies.

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP* genes involved in drug metabolism and disposition are highly polymorphic and contribute to the wide range of activity observed among individuals (no function to increased function).

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The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. Many of these medications have their own chapters within the Medical Genetics Summaries.

The *CYP2D6* gene on chromosome 22q13.2 is one of the most variable among all *CYP* genes. Over 135 distinct star (*) alleles have been described and catalogued by the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, absent, or unknown enzyme function, as defined by the Clinical Pharmacogenomics Implementation Consortium (CPIC) (Table 1). (1, 3)

The combination of *CYP2D6* alleles a person harbors determines their diplotype (often also referred to as genotype). Examples are *CYP2D6*1/*2* or *CYP2D6*4/*5*. Based on function, each allele can be assigned a value to calculate the activity score of the diplotype, which in turn is often used to assign phenotype. Briefly, a value of 1 is assigned to each allele of a *CYP2D6*1/*2* diplotype giving rise to an activity score of 2 (NM), while both alleles of the *CYP2D6*4/*5* diplotype receive a value of 0, which results in an activity score of 0 (PM). If an individual has a gene duplication at the *CYP2D6* locus, then the additional copy is also counted toward the total activity score. An individual who has no detected variants and is determined to have triplication of the *CYP2D6* gene would thus be genotyped as *CYP2D6*1x3* and have an activity score of 3. This CPIC-recommended genotype to phenotype translation method was developed to facilitate standardization (4), it is however, not consistently utilized across clinical laboratories for reporting *CYP2D6* pharmacogenetic test results.

- Ultrarapid metabolizers (UM) have a diplotype with an activity score greater than 2.25
- Normal metabolizers (NM) have an activity score of 1.25 to 2.25
- Intermediate metabolizers (IM) have an activity score of 0.25 to 1
- Poor metabolizers (PM) have an activity score of 0

Table 1. Clinical Allele Function Assignment from CPIC of Selected *CYP2D6* Alleles

Allele type	CYP2D6 alleles	Value for activity score calculation
Normal function	*1, *2, *35	1
Decreased function	*9, *17, *29, *41	0.5
"Severely" decreased function[#]	*10	0.25
No function	*3, *4, *5, *6, *40	0
Increased function	*1x2, *2x2	2

For a comprehensive list of *CYP2D6* alleles, please See PharmVar. Table updated on 13 October 2021, see the allele functionality table from CPIC for the most recent function assignments.
[#] CPIC does not use the term "severely decreased function" to describe the *CYP2D6*10* allele, this designation has been provided for clarity in this document.

The *CYP2D6*1* allele is considered the reference allele and is often inferred when no variants interrogated by a genotyping test are detected. The *CYP2D6*1* allele confers normal enzyme activity and can be found in many individuals with a NM phenotype. Some groups refer to this phenotype as an "extensive" metabolizer. Other alleles including *CYP2D6*2* and *35* (to name a few) have activities that are similar to that of *1* and are thus also classified by CPIC as having normal function.

Other *CYP2D6* alleles have one or more single nucleotide polymorphisms (SNPs, indels) that obliterate function (for example, *CYP2D6*3, *4*, and *6*) (5, 6, 7, 8) or cause decreased function (for example, *10, *17, *29*, and *41*) (9, 10, 11) (see Table 1) (3). Duplication of a no-function *CYP2D6* allele has the same effect on the metabolizer phenotype as a single copy, however duplicated decreased-function alleles will contribute additively to the final activity score. Clinical testing does not always specify which allele is duplicated; thus, interpretation of these testing results may be ambiguous regarding the metabolizer phenotype.

The role of CYP2D6 in drug metabolism is well established. Whether a particular medication should be administered at lower doses or be avoided entirely by individuals with altered CYP2D6 metabolism will often be discussed on the regulatory agency-approved drug prescribing Information or label (namely, the Food and Drug Administration in the United States) and in published guidelines from professional societies (for example, the Clinical Pharmacogenetics Implementation Consortium, the Canadian Pharmacogenomics Network for Drug Safety, or the Dutch Pharmacogenetic Working Group). In addition to the information presented here, additional published reviews are available that discuss *CYP2D6* gene variations and its role in personalized medicine (1, 2, 12).

Allele and Phenotype Frequencies

There are substantial differences for *CYP2D6* allele frequencies not only among ethnic groups, but also among populations within the major ethnic groups. These differences are illustrated by *CYP2D6*3, *4, *5, *6,* and **41,* which are more common in people of European descent, while *CYP2D6*17* is more prevalent in Africans and their descendants, and *CYP2D6*10* is more common in Asians (13, 14, 15). While the frequency of specific alleles is useful knowledge for the implementation of pharmacogenetics and genetic testing, clinical recommendations are typically based on an individual's phenotype.

Globally, normal and IM phenotypes are the most common. Normal metabolizers comprise 43–67% of populations and IMs comprise an additional 10–44% (3). Poor and UMs are less common, but these individuals are at a higher risk for adverse reactions or treatment failure when treated with a drug that is metabolized or bioactivated by CYP2D6.

If there is any concern regarding an individual's CYP2D6 metabolism, genetic testing provides valuable information to inform drug choice or dosage for the individual. We refer to the NIH Genetic Testing Registry (GTR) and Bousman et al (16) for more information regarding whether testing should be performed and available clinical testing options. The available *CYP2D6* tests include targeted single-gene tests, as well as multi-gene panels and genome-wide sequencing tests (see comment below regarding genotyping methodology). In addition, variant *CYP2D6* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (AMP) (17). These alleles, their defining 'core' variants and reported frequencies in the major ethnic groups are summarized in Table 2.

Table 2: The AMP Tier 1 and Tier 2 *CYP2D6* Star Alleles and Reported Population-Specific Frequencies.

	Star allele	Core SNPs	AS	African (%)	European (%)	Asian (%)	Latino (%)	Other [#] (%)
Tier 1	*2	rs16947, rs1135840	1	16–20	28	12–29		
	*3	rs35742686	0	<1	1.60	<1		
	*4	rs3892097	0	3–5	18.50	0.5–9.1		
	*5	Gene Deletion	0	3–5	3–5	3–5		
	*6	rs5030655	0	0.50	1	0.50		
	*9	rs5030656	0.5	<0.5	2.80	<0.5	1.60	
	*10	rs1065852, rs1135840	0.25	4–6	<2	9–44		
	*17	rs28371706, rs16947, rs1135840	0.5	17–19	<0.5	<0.5	2.30	

Table 2 continued from previous page.

	Star allele	Core SNPs	AS	African (%)	European (%)	Asian (%)	Latino (%)	Other [#] (%)
	*29	rs59421388, rs61736512 + rs1058164, rs16947, rs1135840	0.5	9–12	<0.5	<0.5	1.50	
	*41	rs28371725, rs16947, rs1135840	0.5	4–11.5	9	2–12		
	(any)xN	Gene duplication	ASxN	Freq. and AS varies based on the specific allele that is duplicated				
Tier 2	*7	rs5030867	0	<0.05	<0.05	0.01–0.6		
	*8	rs5030865, rs16947, rs1135840	0		0.02			American: 0.1
	*12	rs5030862, rs16947, rs1135840	0	0.08–0.3	0.02			Indigenous American: 1.7
	*14	rs5030865, rs16947, rs1135840	0.5			0.30		
	*15	rs774671100	0	0.60	<0.05	<0.05		
	*21	rs72549352, rs16947, rs1135840	0			0.40		
	*31	rs267608319, rs16947, rs1135840	0	<0.1	<1	<0.1	<1	
	*40	rs72549356, rs28371706, rs16947, rs1135840	0	0.5–1.3	<0.1			
	*42	rs72549346, rs16947, rs1135840	0	<0.5		<0.5 (Central/South Asian)		
	*49	rs1135822, rs1065852, rs1135840	0.5			1 (East Asians)		
	*56	rs72549347, rs1135840	0	<0.2	<0.2			
	*59	rs79292917, rs16947, rs1135840	0.5		0.70			
	Hybrid Genes	Variable	0	<1	<1	1 (East Asians)		

AMP: Association for Molecular Pathology. SNP: Single Nucleotide Polymorphism; the underlined SNP (rs) identifiers are the variant(s) associated with altered function. AS: Activity score. (any)xN: any star allele duplicated N-many times. Frequency of the specific allele for the indicated population is given in percentage. [#] The specific population is stated before the allele frequency. Table is adapted from (17).

Literature Summaries

Many studies have sought to determine allele frequencies of interest in specific ethnic populations or study cohorts across the globe with new data being published regularly. The sections below describe the summarized findings of many of these studies, organized by geographic region of the population studied. Upon review of many of these studies, Zhang and Finklestein noted that broad race classifications are not adequate to accurately

capture the ethnicity-specific allele frequencies, and many of these classifications are applied differently by different author groups (18). Thus, we have grouped the literature references based on geographic location, rather than race or ethnicity, which is often self-reported by the study participants. When provided by the authors, racial and ethnic composition of the study population is noted. The geographic groupings used herein follow the Biogeographical Groups from PharmGKB (19, 20) where possible. Further regional or country-specific divisions have been provided for clarity. Some of the larger studies that include multi-ethnic populations provide ethnicity-specific allele frequencies. These data are presented herein as reported by the authors, and readers are encouraged to verify the population definitions from the original publication.

Readers are encouraged to review any articles of interest in more detail and search out additional literature if the information regarding a specific population is not adequately described below. The following literature summaries are not exhaustive for all *CYP2D6* allele frequency reports. Rather, the most recent literature covering any specific region or people group has been included, along with landmark studies that are commonly cited by newer publications.

There are various genotyping methods utilized in the cited literature below and used in clinical testing, each with their own caveats for accuracy of final genotype and phenotype assignment. Targeted allele testing (by TaqMan or other probe-based technologies) for the core, defining SNPs (recommended by AMP or provided by PharmVar) will provide the highest specificity in identifying known alleles. However, these targeted tests alone may not detect copy number variants (CNVs), which may change the assigned phenotype. For example, an individual whose genotype is homozygous for the *CYP2D6*2 variant SNPs may in fact have a gene duplication on one chromosome, thus they would be given a phenotype of UM rather than NM (AS of 3 for *CYP2D6*2x3*). Gene duplication testing may not include identification of which allele is duplicated in a heterozygous genotype. If the duplication is a decreased or no-function allele versus a normal-function allele, the resulting phenotype may be different. Additionally, some variants are shared among star alleles and not all author groups interrogate the frequency of the distinguishing variants. Thus, reporting the specific variant frequency overestimates the frequency of the most common allele, which is defined (partially) by that SNP. This is particularly common for the *CYP2D6*10* allele and tests of SNP rs1065852. Genotyping for gene hybrids may be beyond the scope of some of the literature herein. As such, some star allele frequencies may be overestimated due to the combined counting of the core allele without regard to the potential for hybrid alleles (for example, *CYP2D6*10+*36* hybrids may be only identified as *CYP2D6*10*). While the advances in next-generation sequencing (NGS), including whole exome (WES) and whole genome sequencing (WGS), have made this technology available to a broader range of laboratories and researchers, WES/WGS has its own limitations in accurate diplotype identification. Phasing of identified variants is difficult with short sequencing reads, thus obscuring which variants occur in *cis* or in *trans*. Other technical limitations of NGS approaches include potential interference of pseudogenes, limited information regarding structural variants, and difficulty with interpreting novel or rare haplotypes.

Global Population studies

I Gaedigk, et al. (2017) (14) PubMedCentral: PMC5292679. This publication is frequently cited as a point of reference for specific subpopulation studies. Gaedigk and colleagues performed a literature review and summarized the predicted allele and activity score based 'phenotype' frequencies for global major ethnic groups: African American, African, American, East Asian, European, Middle Eastern/Oceanian, S. Central Asian, Jewish.

Among these groups, PM's were present in 5.9–5.4% of the Jewish and European populations, 2.3% of African Americans and 2.8% of Africans, and ~1% or less of the other ethnicities. Intermediate metabolizer^ were most prevalent in the Jewish population at 37.7%, followed by 38–34% of African, African American, East Asian and European populations, South Central Asians were predicted to have an IM phenotype prevalence of 28.6% and

Middle Eastern and American populations had the lowest frequency of IM phenotype at 24–22%. Normal metabolizer phenotype^ was most common in South Central Asian, Middle Eastern and East Asian populations (64–68%), but least common in the Jewish population at 44.8%. Ultrarapid metabolizer phenotype was predicted to be highest in Jewish and Middle Eastern populations (~11%) and least common in East Asian (~1%). (^Note: The intermediate and NM frequencies are adjusted to the CPIC activity score definitions provided above, an update from the original publication.) Figure 1 shows the predicted phenotype based on genotype; frequencies are shown in percentage (%) based on the ethnicity. A corrigendum for this table is available from PubMedCentral.

II. Koopmans, et al. (2021) (15) PubMedCentral: PMC7904867. This review summarizes the phenotype frequencies among global populations from over 300 published articles and provides the non-NM (either poor, intermediate, or ultrarapid) phenotype frequencies for CYP2D6 and CYP2C19 to facilitate optimized dosing for psychiatric medications. The authors used allele frequency data and activity scores as described above to translate genotype to phenotype. The population with the highest prevalence of non-NMs was Algeria, and the lowest prevalence was in Gambia. The frequency of UM phenotype was nearly 40% in the Mozabite people, a Berber ethnic group in North Africa. Non-Austronesian Melanesians and Druze (from the Middle East) groups also were noted to have high frequencies of UM. The PM frequencies were highest in British (12.1%), Danish (10.6%) and Basque French (9.7%) populations. The global average for non-NM phenotypes was reported as 36.41%. It is important to note that some of the populations included in this study had small sample sizes (less than 50 individuals) and as such, the phenotype frequencies made be over- or underestimated.

III. Taliun, et al. (2021) (21) reported on the sequencing data from 53,831 diverse genomes in the National Heart Lung and Blood Institute's (NHLBI) Trans-Omics for Precision Medicine (TOPMed) program. The TOPMed program aims to combine more than 80 "omics" studies from a broad range of populations of varying race and ethnicity. The entire current set of ~155,000 selected participants consists of approximately 41% European ancestry (European, European American), 31% African ancestry (African, African American, African Caribbean), 15% Hispanic/Latino (including Mexican, Mexican American, Central American, South American, Cuban, Dominican, Puerto Rican), 9% Asian ancestry (Chinese, Taiwanese, Asian American, Pakistani) and 4% 'Other' (Samoan, Native American, multiple groups, or unknown). Among the data in the TOPMed analysis, the authors described the frequency of *CYP2D6* star alleles as identified by WGS in the supplemental data from this report. The frequencies of 99 alleles (including known star alleles, duplications, deletions, hybrid alleles and novel alleles) are reported for individuals of European, African, Hispanic/Latino, Asian, Samoan, and Amish ancestry. In all populations, the *CYP2D6*1* allele was most common, but this ranged from 29% in African ancestry up to 47% in Hispanic/Latino ancestry. The TOPMed data are available here. Detailed Tier 1 allele frequencies for AMP recommended alleles are shown in Table 3. As stated above, the identification of hybrid alleles and phasing of variants for accurate haplotype calls is difficult with NGS data. The authors cite methods using the program Stargazer to perform haplotype analysis.

Table 3: Allele Frequencies of Common *CYP2D6* Alleles from TOPMed Studies

Country/ancestry	*2	*3	*4	*5	*6	*9	*10	*17	*29	*41	Ref
European	14.81	1.57	13.80	3.08	1.06	2.54	1.58	0.16	0.07	9.83	(21)
African	16.11	0.35	3.63	5.67	0.26	0.53	3.83	15.71	8.40	2.40	(21)
Hispanic/Latino	16.48	0.86	9.55	2.96	0.55	1.46	1.65	1.72	1.24	5.72	(21)
Asian	9.53		0.51	6.24			12.88	0.036		4.02	(21)
Samoan	17.20	0.05	0.16	1.30		0.10	1.51	0.31		5.41	(21)

Table 3 continued from previous page.

Amish	9.33		8.44	5.11			4.89			7.33	(21)

The alleles shown are commonly observed across populations and correspond to those designated by AMP as Tier 1 in their clinical allele testing recommendations (17).
Allele frequencies are given as percentages (%).
Blank values indicate that no frequency was given for that allele from the cited study.

American Allele Studies

Table 4: Allele Frequencies of Common *CYP2D6* Alleles from North American Studies

Country/ancestry	*2	*3	*4	*5	*6	*9	*10	*17	*29	*41	(any)xN	Ref
American	17.30	1.40	16.75	3.40	1	2.40	1.80	2.72	1.40	8.20	2.70	(22)
American/AFR		0.20	6.10	6.10	0.10	0.10	4.10	21.80	6.50	8.70	4.50	(23)
American/EUR		1.90	18.60	2.80	2.00	2.60	2.80	2.00	0.10	8.70	3.40	(23)
American	14.30	1.10	13.50	3.80	1	3.50	2.40	0.60	0.20	11.10	1.20	(24)
African American	21.30	0.00	6.90	5.60	0.00	0.00	4.40	12.50	10.60	2.50	9.40	(25)
Asian	14.20	0.60	5.10	4.60	0.00	0.60	13.60	0.00	0.60	7.40	1.10	(25)
Caucasian	16.90	1.80	16.90	1.80	0.60	1.20	3.00	0.00	0.00	12.70	1.80	(25)
Hispanic	22.60	0.60	9.10	3.00	0.00	2.40	0.00	0.60	0.60	7.30	2.40	(25)
Ashkenazi	9.90	0.50	20.30	0.50	0.50	0.50	7.80	1.00	0.00	14.10	10.40	(25)
non-EUR	15.00	0.52	9.20	3.40	0.49	1.10	7.70	3.10	1.60	5.80	3.18	(26)
AFR	13.00	0.16	3.90	5.90	0.22	0.32	3.20	17.00	7.50	1.80	6.21	(26)
AMR	17.00	0.53	11.00	2.20	0.53	1.40	1.20	0.81	0.64	4.40	2.73	(26)
EAS	15.00	0.02	0.26	3.70	0.02	0.10	34.00	0.00	0.00	3.00	2.84	(26)
EUR		1.50	18.00	3.00	1.00	2.50	1.30	0.19	0.04	9.30	1.75	(26)
SAS	21.00	0.41	9.90	2.80	0.08	0.08	5.30	0.00	0.00	15.00	2.10	(26)
Other	16.00	0.71	12.00	3.30	0.67	1.40	4.20	2.60	1.40	7.00	3.02	(26)
American	23	1.40	20	3.90	1	2.50	1.70	<1		9	3.80	(27)
Caucasian Canadian		3	19				21			12		(28)
Inuit Canadian		0	6.7–8.3				2.20					(29)
Native Indian Canadian		0	3				3					(30)
Mexican Native and Mestizo	77.8–79.6 §						10.2–12.4	0.5–0.7		0–2.8		(31)
Mexican Amerindian	12–28	0	0.6–5.3	0.50	0		0			1	1.50	(32)

Table 1 Phenotype predictions from genotypes

Major ethnicities	AS = 0 p^2 gPM	AS = 0.5 $2pq$ gIM	AS = 1 q^2 gNM-S	AS = 1 $2pr$ gNM-S	AS = 1 (sum) $q^2 + 2pr$ gNM-S	AS = 1.5 $2qr$ gNM-F	AS = 2 r^2 gNM-F	AS = 2 $2ps$ gNM-F	AS = 2 (sum) $r^2 + 2ps$ gNM-F	AS = 1+1.5+2 $q^2 + 2pr + 2qr + r^2 + 2ps$ gNM-S+F	AS = 2.5 $2qs$ gUM	AS = 3 $2rs$ gM	AS = 4 s^2 gUM	AS >2 $2qs + 2rs + s^2$ gUM
African American	2.38	10.99	13.60	14.40	28.00	32.92	22.11	0.66	22.77	83.69	1.69	1.93	0.05	3.67
African	2.78	10.63	13.92	13.97	27.89	32.60	22.95	0.92	23.88	84.36	1.56	2.17	0.07	3.80
From the Americas	1.92	2.77	1.98	18.10	20.08	12.44	59.08	0.72	59.80	92.32	0.88	3.62	0.12	4.61
East Asian	0.41	5.48	23.92	5.14	29.06	43.16	21.46	0.11	21.57	93.79	0.69	0.67	0.01	1.37
European	5.44	5.37	1.47	28.47	29.93	14.78	43.77	0.83	44.59	89.31	0.42	2.65	0.06	3.13
Middle Eastern or Oceanian	0.91	5.19	8.99	10.68	19.67	32.91	32.93	1.38	34.31	86.89	3.46	7.32	0.43	11.20
South Central Asian	1.05	3.82	12.55	12.22	24.77	30.46	37.79	0.40	38.20	93.42	0.55	2.19	0.03	2.77
Jewish	5.95	10.64	4.75	22.35	27.10	19.97	20.98	3.90	24.88	71.95	3.49	7.33	0.64	11.46

Phenotype frequencies are averages (in %) and were calculated from average allele-frequency data. A summary table including ranges (minimum and maximum) is provided in **Supplementary Table S2** online (Summary tab).
AS, activity score; PM, IM, NM-S, NM-F, and UM, poor, intermediate, normal-slow, normal-fast, and ultrarapid metabolizer, respectively; the prefix "g" indicates genotype-predicted phenotype. p, q, r, and s, variables of the Hardy Weinberg equilibrium. (See **Supplementary Table S3** online).

Figure 1: Global ethnicity-specific predicted phenotype frequencies based on genotype. AS : activity score. gPM: genetic poor metabolizer, gIM: genetic intermediate metabolizer, gNM: genetic normal metabolizer, gUM: genetic ultrarapid metabolizer. This article predates the adjustment of the AS to phenotype translations described above. This figure is reproduced under Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License. © A Gaedigk et al. (2016)

Table 4 continued from previous page.

Country/ ancestry	*2	*3	*4	*5	*6	*9	*10	*17	*29	*41	(any)xN	Ref
Mexican Mestizo	10.7–19.3	0.9–1.4	11.2–13.1	1.3–2.7	0		2.3–12.4			2.20	4.1–12.8	(32)

The alleles shown are commonly observed across populations and correspond to those designated by AMP as Tier 1 in their clinical allele testing recommendations (17).
AFR: Africa; EUR: Europe; AMR: Americas; EAS: East Asia; SAS: South Asia.
Allele frequencies are given as percentages (%).
Blank values indicate that no frequency was given for that allele from the cited study.
§ This frequency is for the rs16947 SNP, which is found in multiple *CYP2D6* haplotypes.

US-Based Allele Studies

I. Del Tredici, et al. (2018) (22) reported on a study of a multi-ethnic population selected from across the United States, though ethnicity was self-reported and optional. The study covered 104,509 individuals. Based on those who chose to self-report their ethnicity (44.6%), Caucasians were most prevalent across all regions of the US and both Asian and Hispanic-descent individuals were underrepresented (based on comparison to US census data). A total of 37 different alleles were detected in the assay panel data (counting CNV haplotypes as distinct from single-copy haplotypes of the same star allele). Normal-function alleles were most prevalent in the study, comprising roughly 60% of the alleles, with 2% having duplications of normal-function alleles. No-function alleles were present at a frequency of 23% and decreased-function alleles were observed at a frequency of nearly 17%. Frequencies determined by this study for the AMP recommended Tier 1 alleles are shown in Table 4. Overall, 2.2% of the study participants were predicted to be UM, 81.4% NMs, 10.7% IMs, and 5.7% PMs.

II. Chanfreau-Coffinier, et al. (2019) (23) examined the prevalence of actionable *CYP2D6* genotypes among veterans who utilized the U.S. Veterans Health Affairs (VHA) pharmacy services between 2011–2017. Out of the 7,769,359 individuals studied, roughly 90% of the subjects enrolled were men. A comparison between individuals of European (EUR) or African (AFR) descent was made to determine if any heritage-specific allele frequencies could be identified. The alleles studied were *CYP2D6*3, *4, *5, *6, *7, *9, *10, *17, *29, *41* and *CYP2D6* duplications; the absence of these specific alleles was assumed

to be the *CYP2D6*1* reference allele. Overall, 7.6% of the individuals studied had an "actionable" *CYP2D6* genotype, suggesting they were at risk for an undesirable outcome for a CYP2D6 substrate medication. Within the AFR sub population, 10.5% of individuals had actionable genotypes and 7.1% of the EUR subpopulation had actionable genotypes. The results projected that UMs are more frequent at 4.5% among the AFR group compared with 3.3% of the EUR group, with an overall projected frequency within the VHA of 3.4%. The AFR subpopulation was predicted to have a frequency of 12.6% IMs, with EUR predictions of IMs were at 7.2% and overall frequency of 8% in the VHA. The authors report PMs were more prevalent in the EUR group at 6.1% while only 1.9% of the AFR group were predicted to have this phenotype. Detailed allele frequencies for AMP recommended Tier 1 alleles are shown in Table 4.

III. Dalton, et al. (2020) (24) studied human liver tissue samples from 2 biobanks to examine the relationship between *CYP2D6* genotype and actual metabolic activity. Over 300 samples were examined (predominantly of European descent) and allele frequencies determined. Next-generation sequencing-based testing detected 23 alleles; if no variants or structural variation were found, the *CYP2D6*1* reference allele was assigned. Overall, the *CYP2D6*1* allele was observed with a frequency of 32%, followed by *CYP2D6*2* at 14.3%, both of these alleles are categorized as normal function. The no-function *CYP2D6*4* allele was observed at a frequency of 13.5% and the *CYP2D6*41* decreased-function allele was observed at 11.1%. The authors found novel *CYP2D6* alleles and suggested that structural variation should be considered alongside SNP genotyping for improved phenotype prediction from genotype. The authors reported the prevalence of UMs was 1.3%, NM frequency was 51.6%, IM frequency was 39.5%, and PM frequency was 7.6% (scored based on the revised CPIC definitions). Detailed allele frequencies for AMP recommended Tier 1 alleles are shown in Table 4.

IV. Qiao, et al. (2018) (25) studied 854 blood donors with self-reported ethnic and racial backgrounds. Blood donors were from the New York Blood Center and unrelated healthy Ashkenazi Jewish donors were from the greater New York City, NY area. Ethnicities represented in the study were African American (AA), Asian (A), Caucasian (C), Hispanic (H) and Ashkenazi Jewish (AJ). Sixteen variant alleles and gene duplications were analyzed using a Luminex *CYP2D6* genotyping kit, and the absence of detected variation led to *CYP2D6*1* allele assignment; CNVs were also detected by a multiplex ligation-dependent probe amplification (MLPA) kit. They report that UMs were most common among the AJ (10–20%), followed by AA (~5%) with H, A, and C least likely to have UM phenotype. The authors provide frequencies for the different phenotypes under 2 different scoring scenarios: in the first an AS of one results in an NM phenotype, and in the second an AS of one results in an IM phenotype. Under the latter scoring rubric (more in alignment with the latest CPIC scoring described above), the NMs were most common (~70%) in H, with C, A and AA groups demonstrating 50–60% frequency; NMs were found to be the least frequent (40–50%) in AJ. A phenotype of IM was most common in AA (~40%), next most common in C and AJ (<40%) and least in H (~25%). The PM frequency was 3–4% in C, AJ, and AA, 1% in H and none were detected in the Asian group. Detailed Tier 1 allele frequencies for AMP recommended alleles are shown in Table 4. The authors noted that among individuals of Asian descent, the *CYP2D6*36+*10* tandem had a frequency of 15% (many studies do not discriminate between *CYP2D6*10* and *CYP2D6*36+*10* in which case the reported frequency captures both [and depending on the platform used, other alleles as well]).

V. Luo, et al. (2021) (33) published an additional resource of multi-ethnic US *CYP* allele frequencies and phenotypes, termed the Helix DNA project. This study reported all 86,490 study participants were residing in the USA at the time of sample collection but did not rely on self-reported ethnicity. Relevant variants of interest were extracted from exome sequencing data and used to impute genetic heritage from one of these 5 reference populations: AFR (Africa), AMR (America), EAS (East Asia), EUR (Europe), SAS (South Asia). Individuals who were admixed but had >80% markers for a specific population were called as member of that group. Any sample with <80% markers for any of the genetic groups was classified as "other." The authors noted their study population was less diverse than the

broader US population. Authors observed that for a subset of very rare alleles in the EUR cohort, these alleles were present at a higher frequency in other ethnic groups. A total of 1,288 unique genotypes were observed at the *CYP2D6* locus in the study cohort. Notably, the decreased-function allele *CYP2D6*29* was present in 7.5% of individuals with AFR genetic markers; this allele was present in only <0.05% in EUR ancestry individuals. This study also reports the non-functional *CYP2D6*36* gene being present at a frequency of 22% in the EAS genetic group, much higher than the frequency provided by the PharmGKB reported 1.2% for the same group. The Helix DNA project also reports a prevalence of 5.2% for the *CYP2D6*68* loss-of-function allele in their EUR individuals. It is likely that due to the limitations of NGS genotyping, these allele frequencies reflect the combined frequencies of the single and hybrid alleles, thus are over estimations. Access to the full resource is available via GitHub where users can download tables of either specific allele frequencies or genotype-phenotype frequencies (26). Detailed Tier 1 allele frequencies for AMP recommended alleles are shown in Table 4.

VI.   Zhu, et al. (2021) (34) performed genotype to phenotype predictions for 2,877 individuals who were enrolled in the Right Drug, Right Rose, Right Time-Using Genomic Data to Individuals Treatment (RIGHT) study who were also prescribed a CYP2D6-substrate opioid medication. The frequency of UMs in this study was 2%, NMs comprised 50% of the cohort, 41% were IMs and 7% were PMs. Among this cohort, 94% of the individuals identified as "white," 11 individuals (<1%) were African American, 22 (1%) individuals identified as Asian/Native and the remaining 5% of the study cohort identified as "Other", which included unknown and mixed heritage. Only 1% of the cohort separately identified as "Hispanic" for their ethnicity. Preliminary sequencing data for the RIGHT protocol (1,013 individuals) was reported in 2014 by Bielinski and colleagues (27). Detailed Tier 1 allele frequencies for AMP recommended alleles are shown in Table 4.

VII. Salyakina, et al. (2019) (35) studied a diverse population of 413 individuals. These individuals self-reported their ethnicity; 75% of the study population identified as Hispanic and 62% of the population identifying as "White-Hispanic." Overall, the most common phenotype was NM (90%), followed by IM (4%), with UM and PM both seen in 3% of the study participants. White non-Hispanic participants had a low frequency of decreased-function alleles (2.8%) but mixed non-Hispanics had a higher rate (50%). The low frequency of decreased-function alleles in White, non-Hispanic study participants may be an underestimate due to the low number of these individuals in the study cohort (18 out of 413). The study authors concluded there are differences in *CYP2D6* allele frequencies among the various distinct racial and ethnic populations of south Florida but acknowledged this study had limited power to detect differences between smaller ethnic groups. The specific allele studied were *CYP2D6*2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14A, *15, *17, *19, *20, *29, *35, *36*, and *41*; however only 14 were detected in the study population by the targeted testing panel. The specific allele frequencies with 95% confidence intervals are displayed in the publication.

VIII. Oshikoya, et al. (2019) and Rossow, et al. (2021) (36, 37) studied a pediatric population from the Vanderbilt University Medical Center. The 257 individuals were predominantly white (84%), with the next most prevalent ethnicity being African American (11%) and most participants identifying as "non-Hispanic" (96%). Next-generation sequencing data was used to detect variants; deletions or duplications were detected by long-range polymerase chain reaction (PCR). At total of 23 distinct *CYP2D6* star alleles were interrogated in this study. The authors reported ~13% of the study cohort genotyped as PM or IM and the remaining 87% were NM, UM or "rapid" metabolizers.

IX.   Davis, et al. (2021) (38) reported on the prevalence of actional pharmacogenetic genotypes in a population of 4,230 individuals enrolled in the Alabama Genomic Health Initiative (AGHI). The genotyping data available to the authors from the AGHI study only interrogated 5 *CYP2D6* alleles (*6, *7, *9, *17,* and *41*), yielding only 7.6% of the study population as carriers of actionable *CYP2D6* alleles. The frequency of actionable *CYP2D6* alleles was 5.9% in individuals of African ancestry and 8.3% in individuals of European ancestry. The authors note that this is likely an underestimate based on the limited alleles covered by the genotyping array.

Canadian Allele Studies

Canadians of European descent likely have a similar frequency of the *CYP2D6*10* allele compared with indigenous populations (2% versus 2–3%). The *CYP2D6*4* allele is also more common in European Canadians (19%) as compared with native populations (3–8%). Most of the native Canadians were predicted to be NMs, though there are limited studies for these populations in the recent literature.

X. Gulilat, et al. (2019) (28) reported on the utility of a targeted exome NGS sequencing panel for pharmacogenetic testing, using a study cohort of 246 'Caucasian' individuals. Targeted genotyping was performed to validate variants found in the *CYP2D6* alleles. The validated variants were found in the no-function alleles *CYP2D6*3A* and *4*, as well as the decreased-function *CYP2D6*10* and *CYP2D6*41* alleles. The concordance rate was high for individual allele calls (98–100%), but the *CYP2D6*4* and *10* alleles share the SNP rs106585.2 The *CYP2D6*10* allele was most common, observed in 21% of the alleles sequenced, however this does not account for the overlap with *CYP2D6*4*. The second variant in *CYP2D6*4* was present in 19% of the samples. (Thus, the unique frequency of the *10* allele is likely only 2%.) The *CYP2D6*3A* allele was least common at 2% (the rationale for reporting the *CYP2D6*3A* sub-allele over the *3* allele is unclear). These variant frequencies all agreed with the published EUR group frequencies from 1000 Genomes Project and Exome Aggregation Consortium (ExAC). The *CYP2D6*41* allele was observed at a rate of 12%, higher than the published rate of 9% from ExAC. Most individuals with these decreased or no-function alleles were heterozygous, indicating a probable IM phenotype. Detailed allele frequencies for AMP recommended alleles are shown in Table 4.

XI. Jurima-Romet, et al. (1997) (29) studied the CYP2D6 phenotype and genotyped for 152 individuals from a Canadian Inuit population. Three individuals phenotyped as PM based on dextromethorphan metabolism, the other 149 individuals were classified as NM. Genotyping did not detect any *CYP2D6*3* alleles. However, the frequency of the *4* allele was estimated to be between 6.7% and 8.3% in this population. The frequency of the *10* allele was estimated to be 2.2%. Detailed allele frequencies for AMP recommended alleles are shown in Table 4.

XII. Nowak, et al. (1997) (30) reported on the CYP2D6 phenotypes in 115 Canadian Native Indian (also called First Nation) individuals. One individual in the study demonstrated a PM phenotype based on dextromethorphan metabolism (1.1% frequency). Genotyping did not detect any individuals with the *CYP2D6*3* allele, while the *4* and *10* alleles were both seen with a frequency of 3%. Detailed allele frequencies for AMP recommended alleles are shown in Table 4.

Mexico and Amerindian Allele Studies

XIII. Leitao, et al. (2020) (39) reviewed 13 distinct studies that reported on Amerindian populations from multiple countries. Seven of the reviewed studies focused on Mexican populations, but others studied populations from Argentina, Chile, Costa Rica, Paraguay, Peru, and the United States. Phenotype frequencies varied among the Amerindian populations in these countries. The highest frequency of PMs was observed in Costa Rica (30%), with Argentina and Paraguay next at 13%, and Venezuelan and US cohorts at 6%. The frequency of IMs ranged from 1% in Argentina/Paraguay up to 22% in Mexico. The NMs were most commonly seen in the US (90%), with rates between 80–87% in most other studies. Notably Mexico and Costa Rica reported much lower NM frequencies: 69% in Mexico and 45% in Costa Rica. Diplotypes resulting in UM phenotype were seen at higher rates in Mexico (9%) and Costa Rica (7%) but less often in the US (1%).

XIV. Henderson, et al. (2018) (40) performed a literature review of 27 studies focused on Amerindian (also called Indigenous North American) populations residing in Canada, the United States of America, and Mexico, 13 of those studies included some analysis of *CYP2D6* variation. Indigenous populations in the USA had a reported frequency of 14.6–20.9% for *CYP2D6*4*, 1.3–2.8% for *CYP2D6*5*, 1.3–2.0% for *10*, 1.1% or less for

CYP2D6*25, and 6.9–11.2% for *CYP2D6*41*. A large number of studies of Mexican Amerindian groups were also reviewed, with a notably low frequency of *CYP2D6*3, *6,* and **10* alleles. The authors note that the low frequencies of no-function *CYP2D6* alleles in these populations appear to correlate well with the phenotype studies of dextromethorphan metabolism in a subset of the Mexican indigenous studies. The American Indian populations in the northwest USA were notably different from populations in Mexico with regard to higher frequencies of *CYP2D6*4* and **41* alleles. Overall, allele frequencies in these indigenous populations vary as compared with European descent populations. The authors note that not all studies reviewed were comprehensive in their genotyping approaches and alleles of altered function may be present in these populations that were not detected.

XV. Gonzales-Covarrubias, et al. (2019) (31) studied pharmacogenetic markers among natives (94 individuals) and Mestizos (1284 individuals) in Mexico. By performing WES, they studied genetic variation in 17 different pharmacogenes. They observed 76 variants in the *CYP2D6* gene among their study participants. A handful of variants were notably different in population frequency among the native and Mestizo study cohort compared with global minor-allele frequencies. The variant associated with the *CYP2D6*10* allele was more common in the Native population than Mestizo. However, this variant is shared among other haplotypes, so it likely represents an over-estimate of this allele frequency. In contrast, the variant associated with the **41* allele was more common the Mestizo population. Detailed allele frequencies for AMP recommended alleles are shown in Table 3.

XVI. Sosa-Macias, et al. (2013) (32) reviewed published allele and phenotype frequencies among the indigenous populations of Mexico, focusing primarily on 4 studies from Mexico while comparing to data from 8 other studies from different populations from the Americas. Among the studies of Mexican indigenous populations, 993 individuals were genotyped for the *CYP2D6*4* allele, though some studies reported on the frequency of as many as 8 star alleles and the frequency of gene duplications. Most notably, there was a near total absence of PM-predicting genotypes for Mexican Amerindian populations. This corresponded with the absence of PMs based on dextromethorphan metabolism. Overall, the genetic and phenotypic diversity at the *CYP2D6* locus among the indigenous groups reported is notably lower than the Mestizo population. Detailed allele frequencies for AMP recommended alleles are shown in Table 3.

Latin American Allele Studies

Similar to reports of Mestizo and Native populations in Mexico, these populations in Latin America as a whole show differences from one another in allele frequencies for *CYP2D6*. The frequencies of NM and UM were high in native populations from the south (NM) and northern regions (UM). Owing to their ancestry, most reported "mestizo" populations had allele frequencies similar to reported European frequencies. The mestizo population of Columbia stands out as noteworthy for a higher incidence of UMs (18%) compared with other Hispanic mestizo populations. The *CYP2D6*10* allele frequencies reported in Brazilian populations may be overestimated (10.2–94%), though the possibility remains that this allele is more common in Brazil as compared with global "Caucasian" frequencies. However, the *CYP2D6*41* allele had a lower population frequency in Brazil. Some native people groups were found to have a higher frequency of the *CYP2D6*4/*4* diplotype (25% in the Bari group from Venezuela), leading to a higher proportion of PMs.

XVII. Naranjo, et al. (2018) (41) reported a large cohort (6,060 individuals) study spanning multiple countries in Latin America. The groups studied were Native Americans (1395 individuals either from Mexico [North], Costa Rica [Central] or Peru [South]), Afro-Latin Americans (96 individuals, self-reported as being of African descent and living in Costa Rica or determined to have 4 black grandparents and living in Cuba), White Latin Americans (287 individuals from Cuba with 4 white or Caucasian grandparents), Admixed Latin Americans (2571 individuals who may be described as "Mestizo" in other studies), Iberians (1537 individuals from Spain or Portugal), and Argentinian Ashkenazi Jews (174 individuals). The study interrogated the presence of distinct star alleles *(*2, *3, *4, *6, *10, *17, *29, *35,* and **41*) via real-time PCR with TaqMan allelic discrimination assays, the **5* allele and gene duplications were detected by long-range PCR, and overall gene copy number was assessed

by TaqMan copy-number assay. A *CYP2D6*1* allele was assigned in the absence of any variants. The PM phenotype was observed at rates between 0–10.2%, being most prevalent in Central native Americans. The prevalence of IMs (an AS of either 0.5 or 1) was between 0–8.67% (AS=0.5) or 12.62–31.12% (AS=1). The combined frequencies of these 2 IM AS were highest in Central native Americans (~33%) and Argentinean Ashkenazi Jews (~34%). Normal metabolizers were observed at rates ranging from 29–86%, based on an AS of either 1.5 or 2. Overall, 64% of all individuals studied were NM, but the highest frequency was observed highest in South Native American (~87%), ~64–65% in Afro-Latin Americans and Admixed Latin Americans, ~51% in Central Native Americans. The frequency of UM ranged from 0.47–11.56%, with Argentinian Ashkenazi Jews having the highest frequency, followed closely by North Native Americans (~9.5%) and an overall average frequency of 6.15%. The authors noted that the *CYP2D6*10* and **41* alleles did not fit Hardy-Weinberg equilibrium in the admixed population, but all other specific alleles were within the expected equilibrium range. Notably, the admixed populations and Native American populations showed the widest difference in population frequencies across the alleles studied, supporting the main hypothesis that Native Americans are notably different from other populations in Ibero-America.

BRAZIL

XVIII. Ameida Melo, et al. (2016) (42) studied the *CYP2D6*4, *10,* and **17* alleles in Brazilian individuals undergoing tamoxifen treatment. Though the cohort was small (80 females), they noted a higher frequency of the decreased-function *CYP2D6*10* allele in their population relative to Caucasians, an allele often associated with the IM phenotype. However, they used only a single variant to define each of the 3 star alleles, which likely means the authors overestimated the *CYP2D6*10* frequency.

XIX. Suarez-Kurtz (2004) (43) reported the development of a database specifically for Brazilian pharmacogenetic variation. The Brazilian populations is highly heterogeneous and the author states that racial classifications used in a county like the United States may not be similarly applied in Brazil, thus determination of regional allele frequencies within Brazil is more useful than comparing to global classifications. The author introduces an online database from the Brazilian National Pharmacogenetics/pharmacogenomics Network (REFARAGEN) that provides allele frequencies for multiple pharmacogenes (including *CYP2D6*) broken out by 4 regional populations as well as overall county-wide frequencies. http://www.refargen.org.br/

XX. Suarez-Kurtz (2018) (44) discussed the role of pharmacogenetics in oncology treatment in Brazil. Several drug-gene interactions are discussed but notably the author summarizes studies relating to *CYP2D6* variation and tamoxifen response and notes that the NM phenotype was most common (83.5%), with PM (2.5%) and UM (3.7%) phenotypes being less prevalent in one study, and similar phenotype frequencies were projected from the data of other studies. At the time of this publication, the Refargen database held data from 2 studies: one with 1,034 healthy individuals from 4 different regions of Brazil and a second with 270 healthy individuals from the Southeast region of Brazil.

XXI. Salles, et al. (2021) (45) studied the frequency of 4 star alleles in specific regions of the Amazon: Novo Repartimento, Goianésia do Pará, Macapá, Porto Velho, and Plácido de Castro in a total of 180 individuals. The authors interrogated a single variant for each of the 4 alleles via targeted Sanger sequencing methods, which may have resulted in an over estimation of the allele frequencies. They reported that the frequency of the *CYP2D6*2* (normal-function) allele within all 5 Amazonian regions was less than other published studies (5.6–16.7%). The reported *CYP2D6*10* (decreased-function) allele frequency varied within the 5 regions studied, similar to other Brazilian reports (ranging between 10.2–94.4%). The *CYP2D6*41* (decreased-function) allele was seen only in a single study participant, in the heterozygous state. They did, however, note that the no-function *CYP2D6*4* allele was more frequent in their study than in other reports (31–35% in the current study). However, the authors discussed that these alleles were primarily observed in the heterozygous state and were unlikely to affect primaquine therapy. It is likely, given the genotyping methods utilized in this study, that the reported *CYP2D6*4* allele frequency is overestimated and includes hybrid alleles, given the lack of homozygotes for this genotype.

XXII. Silvino, et al. (2020) (46) reported CYP2D6 phenotype and genotype results from a 10-year retrospective study of 261 individuals who were treated for malaria in Rio Pardo in the Amazon region. The authors performed real-time PCR genotyping with TaqMan assays for 8 variants and one small deletion, then inferred haplotypes using PHASE software and assigned alleles using the PharmVar allele definitions. However, their phenotype assignment did not follow CPIC scoring outlined above. The frequency of PMs (AS=0) was 1.2%, IMs (AS=0.5) were observed in 2.4%, and "normal-slow" metabolizers (AS=1, which is IM per CPIC scoring) were observed at a frequency of 21.8%. The frequency of UMs (AS>2) was reported to be 4.4%. The remaining 70.2% were classified as "normal-fast" metabolizer (AS=1.5–2) phenotype.

VENEZUELA

XXIII. Cirillo, et al. (2014) (47) reviewed several reports of pharmacogene variation in Venezuela. The authors reported on a previous study where most altered-function alleles were present in the admixed Venezuelan population at similar frequencies to Western Eurasian and other Central or South American populations. The predicted PM phenotype was present at a rate of 2% in the analyzed Venezuelan population. Among the Amerindian populations in Venezuela, the Bari population had a notably high frequency of individuals with the CYP2D6*4/*4 diplotype (25%) predicting PM status.

CHILE

XXIV. Munoz, et al. (1998) (48) reported on polymorphisms in multiple CYP genes in the South-Amerindian population of Chile. The specific population studied was the Mapuche Indian population living in the national reservation of the Haupi Island, Lake Ranco. A total of 84 individuals enrolled in the study. The authors reported the CYP2D6*1 and CYP2D6*2 normal-function alleles were present in roughly 84% of the population, with the CYP2D6*10 decreased-function allele present in less than 2% and no-function alleles present in roughly 8% of the population. The authors noted technical difficulties in full genotyping of some individuals and suggested unknown variation may have interfered with their analyses. However, the genotyping methods and limitations of known alleles at the time of publication likely contributed to difficulties in genotyping and an overestimation of the CYP2D6*1 allele.

XXV. Varela, et al. (2015) (49) genotyped 4 selected alleles as well as gene duplications, and analyzed in vivo metabolism of debrisoquine, a known CYP2D6 substrate, to confirm genotype predictions in a smaller sample of the cohort. The 321 genotyped study participants were described as Chilean mestizo. The frequencies of the tested alleles (40.6% for CYP2D6*2 [normal-function], 1.09% for CYP2D6*3 [no-function], and 11.8% for CYP2D6*4 [no-function]) were similar to reported frequencies in the Spanish population. The CYP2D6*17 allele was not observed. Some discordance between predicted and actual metabolizer phenotype (5 out of the 23 subjects tested) was observed, but most of the genetic predictions were validated with the in vivo metabolic study. The authors noted that a non-coding genetic variation at the promoter that is associated with UM phenotype was not assessed in the genetic analysis, potentially contributing to genotype-phenotype mismatch. It is also possible that incorrect haplotype assignments were made based on limited variant genotyping data, further contributing to the discordance of phenotype.

COLUMBIA

XXVI. Sarmiento, et al. (2020) (50) reported on the genotype and phenotype frequency among 212 healthy mestizo individuals from Columbia. The authors report that this study improves upon previously published worked by Isaza, et al. (51) by more closely characterizing gene duplications before automatically assigning a UM phenotype. The authors performed genotyping for 8 known star alleles and tested for gene duplications and deletions (the CYP2D6*5 allele). Based upon verification that duplicated alleles were indeed functional, Sarmiento and colleagues reported 18.4% of their study cohort were classified as UMs. However, only 4.7% were classified as PMs. The prevalence of the IM phenotype was reported to be 22.6%. The authors noted that the

prevalence of UMs in this study is significantly higher than in other Hispanic mestizo populations, while the PM prevalence is similar across this and other cited studies.

European Allele Studies

Gene duplication events are more common in south-eastern Europe, while loss-of-function alleles are more common in north-western Europe. The frequency of UM phenotype in Denmark and the Netherlands are between 0–5% and PM frequency is between 4.2–11%. Lithuanian populations may have a lower frequency of the *5 allele as compared with the European average. Studies from the Czech Republic and Bosnia reported a higher frequency of the *10 allele among these populations and the Romani people living in the Czech Republic as compared with other Caucasian European groups.

I　Petrovic, et al. (2019) (52) published a systematic review of *CYP2C19* and *CYP2D6* allele frequencies from multiple European countries and compared the relative frequencies of alleles. The article provides detailed summaries of the literature but further notes a trend of frequencies of *CYP2D6* gene duplications formed a clear South-East to North-West gradient ranging from <1% in Sweden and Denmark to 6% in Greece and Turkey. The inverse trend was observed for the no-function *CYP2D6*4* and *CYP2D6*5* alleles (higher in the Nordic, north-west countries, lower in the south-east).

DENMARK

II. Lunenberg, et al. (2021) (53) studied 77,684 individuals from Denmark to determine pharmacogenetic genotype and phenotype frequencies in this population. A genotyping array was used to detect variants in pharmacogenes, this included 8 variants in *CYP2D6* as well as deletions (*CYP2D6*5* allele) and duplications at this locus. The frequency of NM was 62.4%, IM was 33.4%, and PM was 4.2%. The authors noted there was an absence of *CYP2D6* gene deletions or duplications in their cohort, thus no UM predicted phenotypes were detected.

NETHERLANDS

III. Poulussen, et al. (2019) (54) reported on the allele and phenotype frequencies of 7 different *CYP2D6* variants and gene duplications among 105 hospitalized individuals from the Netherlands who were being treated with metoprolol. The authors reported the frequency of PM was 11%, IM frequency was 45%, NM frequency was 39% and UM frequency was 5%. These frequencies were based on the Royal Dutch Pharmacist Association genotype-phenotype translation guidelines as of January 2019, before the publication of the above AS and phenotype harmonization report.

LITHUANIA

IV. Dlugauskas, et al. (2019) (55) studied 179 individuals from Lithuania for *CYP2D6* polymorphisms. Variants were identified by Sanger sequencing of *CYP2D6* exons 1, 2, 3–4, 5–6, 6–7, and 9; CNVs were detected by MLPA. The authors noted similar allele frequencies to other European populations, with the exception that the *CYP2D6*5* allele was less common in Lithuania. A total of 9 star alleles were detected by sequencing as well as one individual with a duplication of the *CYP2D6*2* allele. The predicted phenotype frequencies among the Lithuanian population are 1.15% for PM, 0.56% for UM, 4.47% for IM and the remainder were predicted NM. (Note: the phenotypes were predicted based on these activity score values: PM 0, IM 0.5, NM 1–2 and UM >2.)

SPAIN

V. Lopez de Frutos, et al. (2020) (56) reported on the frequency of genetic and phenotypic variation at the *CYP2D6* locus in individuals from Spain who were diagnosed with type I Gaucher disease. Out of the 109 individuals enrolled in the study, 87 were predicted to be NM (80%), 14 were predicted to be IM (13%), 6 were predicted to be PM (5%), and only 2 individuals were predicted to be UM (1.8%). These frequencies were

compared with previous reports from other Iberian populations, noting a higher incidence of IM phenotype in their report versus previous publications. The study utilized an xTAG assay on the Luminex platform that detects 19 different variants, most of which were previously associated with known star alleles, as well as duplications and deletions to characterize the metabolizer phenotypes.

VI. Barreda-Sanchez, et al. (2019) (57) studied a cohort of 50 individuals in southern Spain with acute intermittent porphyria. They performed targeted genotyping via TaqMan SNP or CNV assays at multiple CYP loci; at the *CYP2D6* locus, they tested for the presence of the *CYP2D6*4* and *CYP2D6*5* alleles. The frequency of the *CYP2D6*4* allele in this small cohort was 12% and the *CYP2D6*5* allele was observed with a frequency of 1% of the cohort. Phenotype predictions were not given for metabolizer status.

ITALY

VII. Dagostino, et al. (2018) (58) reported on the utility of *CYP2D6* genotyping for opioid safety in the treatment of chronic back pain among a cohort of 196 Italians in the PainOMICS study. They observed 79.6% of their study participants were predicted to be NM, 16.8% were predicted as either IM or PM, and 3.6% were predicted UM. They examined 10 different star alleles and also tested for duplication of the *CYP2D6*1* and *CYP2D6*2* alleles on the Luminex platform.

SERBIA

VIII. Skadric and Stojkovic (2020) (59) published a description of multiple cytochrome P450 gene variants among more than 7,000 DNA samples from Serbia. The authors divided the samples into 5 distinct groups based on geography, historic precedent, and ethnically distinguishable populations. These regions are north Serbia, west Serbia, east and south Serbia, central Serbia, and Belgrade. Based on the sample size and number of genes interrogated in this study, only 4 variants were tested at the *CYP2D6* locus. In general, the data from the Serbian population closely followed other European allele frequencies, including 3 out of the 4 variants associated with altered CYP2D6 function. The authors noted that rs28371706 in *CYP2D6* was very rare and thus may not be an informative variant in the Serbian population. This variant is associated with several no-function alleles. Because limited variants were genotyped at the *CYP2D6* locus, accurate star allele calls are not feasible from this dataset.

BOSNIA

IX. Nefic (2018) (60) reported on the frequency of gene duplication and the frequency of the c.100C>T variant (commonly associated with the *CYP2D6*10* decreased-function allele, among other known haplotypes) in 151 unrelated, healthy individuals from Bosnia. Gene duplications were observed at a frequency of 2.73%, similar to other Caucasian populations. The variant associated with the decreased-function allele was observed at a higher frequency of 15.56%, more commonly than was reported in other Caucasian groups, but less common than in Asian populations.

CZECH REPUBLIC

X. Dlouhá, et al. (2020) (61) compared the frequencies of variants in multiple CYP enzymes between the Roma (302 individuals) and non-Roma (298 individuals) populations residing in the Czech Republic. Study participants were genotyped for 2 variants in *CYP2D6* and one variant each in *CYP1A2*, *CYP2A6*, and *CYP2B6*. The authors reported a higher frequency of the variant that defines the no-function *CYP2D6*4* allele in the Roma populations as compared with the Czech population (39.2% versus 38.2%). The variant commonly associated with the *CYP2D6*10* allele was observed at a similar frequency in the 2 populations (24%). However, the frequency of the predicted *CYP2D6*10/*10* IM genotype, was higher in the Czech population (9.1%) than the Roma population (6.5%). This study does not account for potential hybrid gene structures or other alleles incorporating the c.100C>T variant that may contribute to an overestimate of homozygosity for this variant.

RUSSIA

The prevalence of the no-function *CYP2D6*4* allele ranges from 17.4–27.1% in the Russian population but is notably lower in the Nanai people group (1.4%), Tatar group (11.5%), and Mari group (8.98%). The predominant predicted phenotype is NM, with IM's present at a frequency of 21.5–33%.

XI. Sychev, et al. (2017) (62) compared allele frequencies at several pharmacogenes between Russian and Nanai populations. The study enrolled 70 individuals of the Nanai people group and 642 individuals from the broader Russian population. At the *CYP2D6* locus, they interrogated a variant associated with the no-function *CYP2D6*4* allele. The *CYP2D6*4* allele was more common the Russian population (17.4%) than the Nanai (1.4%), and consequently the authors predicted a higher frequency of NM phenotypes in the Nanai population. (Note: The Nanai population in Russia live in the eastern region of the country, an area that is technically part of the "East Asian" region defined by PharmVar. Because this study compares this ethnic group to the broader Russian population, it is grouped here with other Russian population studies.)

XII. Muradian, et al. (2021) (63) studied the effects of *CYP2D6* and *CYP2C9* variants on pain management with tramadol and ketorolac. A total of 107 individuals were genotyped for the *CYP2D6*4* allele. The authors reported 21.5% of the individuals in the study were heterozygous or homozygous for the no-function *CYP2D6*4* allele, resulting in either an IM or PM phenotype, depending upon the functional status of the other allele in heterozygotes.

XIII. Zastrozhin, et al. (2021) (64) analyzed the effect of the no-function *CYP2D6*4* allele on the efficacy and safety of fluvoxamine in 96 males treated for major depressive disorder. They performed targeted variant genotyping for a defining SNP variant (rs3892097, G>A) and determined that 72.9% of the cohort were homozygous WT and 27.1% were heterozygous (*CYP2D6*4* present for one allele, leading to a possible IM phenotype). No individuals in the study were determined to be homozygotes for the *CYP2D6*4* allele.

XIV. Ivashchenko, et al. (2021) (65) studied the pharmacogenetics of *CYP2D6*, *CYP3A4/5* and *ABCB1* variants and the efficacy and safety of antipsychotics in adolescents with acute psychotic episodes. A total of 101 individuals were enrolled, aged 10–18, and targeted variant genotyping was performed to detect the *CYP2D6*4, *9,* and **10* alleles. Individuals with at least one decreased or no-function allele were assumed to be IMs, and those with 2 no-function alleles were phenotyped as PMs. Individuals with no variation detected were assumed to be NMs. The authors reported 68/101 individuals were NMs, 33/101 were IMs, and there were no PMs detected in the study cohort.

XV. Abdullaev, et al. (2020) (66) examined clinically relevant pharmacogenetics markers in Tatars and Balkars, 2 ethnic groups living in in the Volga and Caucasus regions of Russia. A total of 341 individuals were enrolled in the study. Targeted genotyping at 10 variants was performed, but only the *CYP2D6*4* allele was tested at the *CYP2D6* locus. The authors observed that 77% of the 141 Tatar subjects did not have the *CYP2D6*4* allele and the remaining 23% of individuals were heterozygous or homozygous for the *CYP2D6*4* variant. The *CYP2D6*4* allele frequency in Europeans is similar to the Balkar group, but the Tatar group had a slightly lower allele frequency. The PM phenotype in Europeans is often associated with the *CYP2D6*4* allele.

XVI. Mirazev, et al. (2020) (67) studied polymorphisms in several pharmacogenes in 845 healthy individuals from the Volga and northern Caucasus regions of Russia. These individuals were from multiple ethnic groups: 238 from the Chuvash ethnic group, 206 Mari, 157 Kabardins and 244 Ossetians. The only allele studied at the *CYP2D6* locus was *CYP2D6*4*. The frequency of heterozygotes for the defining *CYP2D6*4* variant was 22.69% in the Chuvash group, 17.96% in the Mari group, 30.74 in the Ossetians and 32.48% in the Kabardins. The Ossetians and Kabardins' *CYP2D6*4* allele frequencies were most similar to the overall Russian population (15–16% versus 18%), the frequency in the Chuvash and Mari groups was statistically significantly lower. These frequencies suggest the rates of PM and IM due to the presence of the *CYP2D6*4* allele will be lower in the Chuvash and Mari as compared with the Ossetians, Kabardins, and Russian population at large.

Near Eastern Allele Studies

The prevalence of the decreased-function *CYP2D6*41* allele may be higher in the United Arab Emirates, Saudi Arabia, and Turkey than other populations. The frequency of NM phenotype ranges between 54–82%.

I   Khalaj, et al. (2019) (68) reported on the distribution of various *CYP2D6* alleles across the Middle East. A total of 32 studies were reviewed, with the total number of individuals in each study ranging from 43–552. Overall, the most common allele was the *CYP2D6*1*, normal-function allele at 68% average frequency, though this may be overestimated due to default assignment when no variants are detected. The *CYP2D6*3*, *4*, and *5* no-function alleles combined for an average frequency of 37.5%. As one might expect, the NM phenotype was most common in every country reported, ranging from a peak of ~82% in Saudi Arabia to 54% in Egypt. The UM phenotype was most commonly seen in Saudi Arabia (20%), Syria (15%), Jordan (14%), and Emirates (13%). Individuals with PM phenotype were most frequently observed in Egypt (19%) and Iran (9%) with other countries having PM frequencies fewer than 5%.

SAUDIA ARABIA

II. Almeman (2020) (69) reviewed CYP450 gene polymorphism in Saudi individuals from 10 different studies in this population. The number of individuals in each study ranged between 90 and 200, though not all reviewed studies examined *CYP2D6* function or genotype. Overall, the author summarizes the findings of these studies and notes there are rare PM individuals and associated no-function allele frequencies were also low (with some alleles notably absent). Gene duplication at the *CYP2D6* locus was noted to be frequent in the Saudi population. The author reported the frequency of the *CYP2D6*41* decreased-function allele within the Saudi population was higher than in other populations, such as Chinese, Mexican, Caucasian and Ghanaians. Overall, the Saudi population demonstrates similar allele frequencies for the reported loci as other Middle Eastern populations.

TURKEY

III. Arici & Ozhan (2016) (70) reported on multiple CYP gene profiles and susceptibility to drug response in a Turkish population of 160 individuals. This study examined the frequency of variation leading to the decreased-function *CYP2D6*9* and *41* alleles within the *CYP2D6* locus. They observed a minor-allele frequency of 4% for the *CYP2D6*9* allele (a 3-nucleotide deletion) and 15% for the *CYP2D6*41* allele. Thus, the *9* decreased-function allele was more prevalent in Turkish individuals than in European or Asian populations. Similarly, the prevalence of the *41* allele was higher in the Turkish study cohort as compared with Caucasian or Chinese populations.

EGYPT

IV. Mutawi, et al. (2021) (71) reported on a genotyping study of 145 healthy Egyptian individuals with the goal of elucidating the frequency or major allelic variants at the *CYP2D6* locus. From the variant genotyping data of 5 *CYP2D6* alleles and CNVs (detected with CNV TaqMan assay), the authors concluded the NM phenotype was the most common among their cohort, with a frequency of 67.6%. They did not identify any study participants with 2 no-function alleles suggesting that PM phenotype in Egypt is rare. Gene duplications, however, were observed and the authors predict a frequency of UMs of 4.8% in this Egyptian cohort.

Sub-Saharan Africa Allele Studies

The IM phenotype has been reported as the most common phenotype in Kenya and Madagascar. The *CYP2D6*17* and *CYP2D6*29* decreased-function alleles both have frequency greater than 10) in multiple regions of Africa (Zimbabwe, Kenya, Ethiopia, and Madagascar for *CYP2D6*17*; Tanzania, Kenya for *CYP2D6*29*). Multiple studies report a very low frequency (<2%) of PMs.

I Rajman, et al. (2017) (72) performed a literature-based review (80 articles total) of cytochrome P450 variants across the continent of Africa. While results from multiple genes are presented, the *CYP2D6* alleles discussed specifically are *3, *4, *9, *10, *17,* and *29. The no-function *CYP2D6*3* and *CYP2D6*4* alleles were most common the San population from Zimbabwe (9% allele frequency). The decreased-function *CYP2D6*17* and *CYP2D6*29* alleles were notably higher in certain populations; *CYP2D6*17* was seen at a frequency of 34% in Zimbabwe (Shona), and *CYP2D6*29* was observed in 20% of the alleles in Tanzania. The *CYP2D6*9* decreased-function allele was not present in any population reviewed, while the *CYP2D6*10* decreased-function allele was most common in the South African Venda population (19%), but not present in multiple other populations. The other decreased-function allele, *CYP2D6*29*, was present in nearly 30% of the Igbo (Nigeria) population, but only 2% of the San population.

ETHIOPIA

II. Ahmed, et al. (2019) (73) studied the genotype and predicted phenotype of female individuals being treated for breast cancer with tamoxifen in Ethiopia. The authors reported the frequency of 5 specific star alleles detected via variant genotyping and the duplication of the *CYP2D6*1* and *CYP2D6*2* alleles, detected via TaqMan CNV assays. Among the 181 participants, 22.2% were predicted to be UM, roughly 60% were NM, approximately 16% had activity scores resulting in a current predicted phenotype of IM, and 1.2% were PM. The authors reported differences in tamoxifen metabolites among individuals with the same metabolizer phenotype but distinct diplotypes (for example, *CYP2D6*1/*1* individuals had different endoxifen levels as compared with *CYP2D6*2/*2* genotyped individuals).

KENYA

III. Rico, et al. (2020) (74) reported on the *CYP2D6* genotype frequencies and functional characterization of novel variants found in the Ni-Vanuatu (Melanesia/Polynesia) and localized Kenyan populations. The 278 Ni-Vanuatu study participants were residents of 6 different islands from Melanesia or Polynesia. Within Kenya, the authors enrolled 195 individuals residing on islands or the shore of Lake Victoria in western Kenya. All study participants were healthy and unrelated. Eight variant star alleles were identified by PCR-based sequencing, allele fusions and duplications were also detected along with 6 novel variants. Detailed allele frequencies are presented in tables 1 and 2 within the publication. Among the Kenyan population, 34.4% of the individuals were predicted to be IM, 1% UM, and 0.5% PM.

MADAGASCAR

IV. Mehlotra, et al. (2021) (75) conducted a study of 211 individuals from 2 health regions in Madagascar to determine the frequency of CYP2D6 metabolizer phenotypes associated with primaquine therapy failure for *Plasmodium vivax* (*P. vivax*)-caused malaria. A total of 29 variants were tested, allowing for identification of 27 distinct star alleles. Duplications, deletions, and complex gene arrangements (hybrids or tandem genes) were detected by previously published multiplex methods. The authors predicted 51.2% of individuals in the study population were IM. The frequency of UM phenotype in the study population was 4.88% and NM phenotype comprised 43.9% of the study population. No PM genotypes were identified in the study population, but the predicted population-wide PM phenotype rate was 0.32%.

East Asian Allele Studies

The most common altered-function allele in this region of the world is the *CYP2D6*10* allele, with frequencies near 40–60% in most countries. Notably, Japan has a slightly lower frequency of the *CYP2D6*10* allele (36%). The IM phenotype is significantly enriched in populations from to this region. The no-function *CYP2D6*5* allele (gene deletion) is rare, observed at a rate of 9% or less.

I   Dorji, et al. (2019) (76) performed a systematic literature review of 86 studies of CYP gene allele frequencies in South-East and East Asian (SEEA) populations. Multiple tables in the original publication delineate allele frequencies for the specific CYP loci by specific population. In total, 8 variant *CYP2D6* star alleles were commonly reported in the reviewed articles. Overall, the authors report that no-function alleles (namely *CYP2D6*3*, **4*, and **6*) are exceedingly rare (or absent) in Asian populations, whereas the *CYP2D6*5* no-function allele is present at rates similar to other populations. The decreased-function *CYP2D6*10* allele is present at a rate of up 50% in many SEEA populations, making that allele the major contributor to the IM phenotype in Asians. Specifically, the *CYP2D6*5/*10* diplotype may be of clinical significance to individuals of Asian descent, given the prevalence of these alleles. The normal-function alleles that were most commonly seen were *CYP2D6*1* and *CYP2D6*2*. Duplication of the *CYP2D6*1* and *CYP2D6*2* (or even **10* alleles) are rarely seen among SEEA populations, leading to a very low frequency of the UM phenotype.

SINGAPORE

II. Goh, et al. (2017) (77) reported on an analysis of CYP450 genes and allele frequencies among residents of Singapore. At the *CYP2D6* locus, 12 different variants were examined for a total of 10 star alleles. A total of 506 individuals were enrolled: 126 Malays, 179 Indians, and 201 Chinese. Overall, the authors report that NM phenotype was most common, followed by IM. The frequency of PMs ranged from 0.7–3.4% but was not observed in any of the Chinese subjects. In fact, the highest frequency of UM phenotype was observed in Chinese study participants (11%), followed by Indian (5%), and Malay (4.8%).

III. Bakar (2021) (38) reviewed pharmacogenetic variation of common alleles, making a comparison between Singaporean/Malaysian populations and European populations. Special emphasis was given to the decreased-function alleles *CYP2D6*4* and **10*, as described in 3 of the reviewed studies. As in Chinese populations, the *CYP2D6*10* allele is more common in Singapore and Malaysia than in European populations. The author reports that individuals from Asia who are homozygous for the *CYP2D6*10* allele are more likely to have altered tamoxifen pharmacogenetics and have higher odds of developing metastatic cancer.

KOREA

IV. Byeon, et al. (2018) (78) studied the frequency of 4 *CYP2D6* alleles and gene duplications in 3,417 individuals from Korea and compared their results to published frequencies from east Asian, Caucasian, and African populations. The authors report the *CYP2D6*10* decreased-function allele was most prevalent at 46.2%, more common than the wild-type *CYP2D6*1* allele (34.6% allele frequency). Among studies of east Asian populations, the *CYP2D6*10* allele was observed with a frequency between 38–53%, notably higher than the 1.4% reported for Caucasians. The no-function *CYP2D6*4* allele was also noted to be far less frequent in east Asians than Caucasians or Africans. Overall, the Korean population showed an NM phenotype in roughly 22% and only 7 out of the 3,417 (0.2%) individuals had a predicted PM phenotype.

V. Ryu, et al. (2017) (79) reported on the effects of *CYP2C19* and *CYP2D6* on individual responses to amitriptyline in healthy Koreans. A total of 53 volunteers enrolled in the study and were genotyped for the *CYP2D6*10* and **5* alleles. The authors reported 12 individuals (22.6%) had 2 normal-function alleles, indicative of NM phenotype. There were 17 individuals with genotype combinations including one function allele, leading to IM phenotype (32%). The authors reported 24 additional individuals with decreased function diplotype associated with IM phenotype (45%). Thus, most study participants would be predicted to be IM.

VI. Han, et al. (2021) (80) reported on variation of multiple pharmacogenes among the Korean Genome and Epidemiology Study (KoGES) cohort, a total of 69,027 individuals were genotyped via SNP array and copy number variation (CNV) data was available from 947 individuals (614 individuals were both genotyped and tested for CNVs). Three variants at the *CYP2D6* locus were reported. Variation at the *CYP2D6* locus was notable for the SNP rs1065852, also called c.100C>T, which is associated with the decreased-function allele *CYP2D6*10*

(among other alleles). The frequency of the variant was 48.23% of all alleles genotyped. Variation at rs16947 (G>A) was observed in 25% of the alleles; this variant is associated with multiple *CYP2D6* star alleles. Variation at rs1135840 (G>C) was observed in 46.3% of the tested alleles; this variation is associated with decreased and no-function star alleles. Based on the nature of the study and how the genomic data was obtained, there was no data regarding CNVs for the *CYP2D6* locus, nor could specific star allele haplotypes be assigned to this cohort.

HONG KONG

VII. Chan, et al. (2018) (81) reported on the allele and phenotype frequencies from 800 individuals residing in Hong Kong who self-reported their ethnicity. The authors tested for 12 different star alleles via targeted variant genotyping. The vast majority identified as Asian descent, with the other members of the cohort either identifying as Caucasian or "mixed race." Among the individuals of Asian descent, the UM phenotype was seen at a rate of 3.3%, NM at 49.9%, IM at 46.4%, and PM at only 0.4%. The frequencies of the specific alleles within the Asian study participants showed a frequency of 32% for the *CYP2D6*36-*10* fusion allele (characterized by a tandem arrangement of the no-function *CYP2D6*36* allele and the decreased-function *CYP2D6*10* allele, see PharmVar's page on structural variants for additional information).

CHINA

VIII. Liu, et al. (2020) (82) reported on the genetic variation in a cohort of 105 individuals from the Zhuang people group of southern China. Overall, among several "very important pharmacogenes" (VIPs), the genetic variation of the Zhuang population was notably similar to Han Chinese in Beijing, southern Han Chinese, and the Japanese population in Tokyo, Japan. Two variants in *CYP2D6* were interrogated. The SNP rs1065852 in the *CYP2D6* locus was a notable deviation between the Zhuang and other global people groups, including some Asian populations. The data suggests this variant may be present at a higher frequency in this subpopulation. This variant has been associated with the decreased-function *CYP2D6*10* allele and the authors mention that variation at this position has been previously associated with altered responses to multiple drugs.

IX. Qi, et al. (2019) (83) reported on the frequency of specific *CYP2D6* alleles in the Chinese Millinome WGS database. The database comprises data from 141,431 individuals from 31 different provinces in China. Note: the genotyping data is obtained from WGS, and as such there may be inaccuracies in calling of the specific haplotype frequencies. The frequency of the *CYP2D6*2, normal-function allele was reported as 27% and the *CYP2D6*10* decreased-function allele was present at 68%. Because the genotype calls were determined by WGS, the study examined known variants associated with star alleles as well as identified novel genomic variants with potential functional impact. The identified variants in *CYP2D6* were not listed in full, but no novel variants were reported.

X. Huang, et al. (2021) (84) studied *CYP2D6* genotype in 120 individuals living in the Yunnan province, China to identify correlation between genotype and malarial *P. vivax* infection relapse following chloroquine and primaquine therapy. The authors interrogated 12 variants at the *CYP2D6* locus and 5 known star alleles. They observed the most common allele was the decreased-function *CYP2D6*10* allele, present in 45.4% of all alleles tested. Additionally, 60 individuals carried at least one copy of the *CYP2D6*10* allele, suggesting the IM phenotype was present in 50% of the study population.

XI. Lu, et al. (2021) (85) reported on *CYP2D6* genotype in 76 individuals prescribed risperidone who were seen at a hospital in the Jiangsu province, China. Five common variants were tested, translating into 3 variant star alleles. The authors observed the *CYP2D6*10*, decreased-function allele was present in 81.6% of the individuals in the study. The authors reported that the *CYP2D6*65* allele was present in 17.1% of the individuals in the study and the *CYP2D6*2* allele was present in just 9.2% of the individuals. The functional classification of the *CYP2D6*65* allele is uncertain (as reported by the authors and per CPIC (3)).

JAPAN

XII. Kisoi, et al. (2020) (86) reported on a method for genotyping variants and CNVs (CNVs) in a cohort of 216 healthy females from Japan. The specific star alleles studied were *CYP2D6*2, *5, *10, *14*, and *41*. Similar to other studies from Asia, the most commonly observed variant allele in this cohort was the *CYP2D6*10* decreased-function allele (36.3%). Diplotype combinations including the *CYP2D6*10* allele, likely leading to an IM phenotype, were observed in over 60% of the study cohort. The NM-associated diplotype of 2 WT (*CYP2D6*1*) alleles was observed in 16.2% of the cohort.

VIETNAM

XIII. Nguyen, et al. (2019) (87) studied the frequency of single nucleotide variants and structural variations in a cohort of 136 Kinh Vietnamese unrelated individuals by Sanger sequencing the coding region and targeted copy number analysis of *CYP2D6*. The authors reported 7 novel variants in the sequencing data as well as 23 known variants. The normal-function alleles (*CYP2D6*1* and *2*) comprised less than 30% of the alleles identified in this study. The decreased-function *CYP2D6*10* allele had a frequency of approximately 44%, the most common allele in the study. Consequently, the 3 most common diplotypes all involved the *CYP2D6*10* allele, resulting in at least 50% of the cohort having allele combinations that would predict an IM phenotype. No individuals with increased copy number were detected in this cohort, suggesting an extreme rarity for the UM phenotype in this population.

THAILAND

XIV. Puaprasert, et al. (2018) (88) reported on targeted allele genotyping of 6 star alleles the *CYP2D6* locus among members of the Karen population living in Tak, a western province of Thailand. The authors reported a high frequency of the decreased-function *CYP2D6*10* allele (40%), with the next most common variant allele being the normal-function *CYP2D6*2* allele (33%). However, only one variant (c.100C>T) was used to define the *CYP2D6*10* allele, as this frequency may be indicative of multiple haplotypes. Duplication (1%) and deletion (*CYP2D6*5* allele, 3%) alleles were relatively rare in this study cohort. Based on the high prevalence of the decreased-function allele, the authors advise the efficacy of the malaria medication primaquine may be affected in this population.

XV. Mauleekoonphairoj, et al. (2020) (89) performed WGS on 291 individuals of self-reported Thai ethnic origin. While several pharmacogenes were studied, the *CYP2D6* sequencing revealed 20 distinct star alleles in the study cohort. There were 5 duplications (1.9% of the identified alleles), 1 deletion (*CYP2D6*5* allele, 4.5% of the alleles), and 6 rearrangements (34.7% of the alleles). The most common decreased-function alleles in the cohort were the *CYP2D6*36+*10* fusion and the *CYP2D6*10* allele. Overall, 25% of the Thai cohort was found to have a "high risk" diplotype for at least one of the studied pharmacogenes. This study utilized WGS and Stargazer analysis to impute haplotypes and diplotypes.

CAMBODIA

XVI. Spring, et al. (2020) (90) reported the prevalence of 18 different *CYP2D6* star alleles as well as gene duplications and reported the predicted phenotypes among 96 Cambodians at high risk for Malaria. Genotyping was performed using the Luminex xTAG kit, which detects specific variants and identifies copy number variants. The overall phenotype frequencies were 46% for NM, 52% for IM, and 1% for PM. The authors also provide a table comparing the specific allele frequencies in their study and other publications focused on the greater Mekong subregion.

Central/South Asian Allele Studies

The phenotype frequencies in India range from 1–3% for PMs, IMs were observed in 7.3%, and NMs were most common at 91.7%.

INDIA

XVII. Manoharan, et al. (2019) (91) published a study on the allele frequency of *CYP2D6* variants in South India. The study cohort was comprised of 105 individuals with mild to moderate depression but no other noted medical conditions. Targeted sequencing of the *CYP2D6* locus led to the identification of 18 distinct star alleles, and the *CYP2D6*1* allele was assigned in the absence of variants of interest. Based on the predicted activity scores, the NM phenotype was most common at 91.7%, with IM frequency of 7.3%, and the PM phenotype was present in 1% of their cohort. The authors noted that the *CYP2D6 *41* allele was the most common decreased-function allele in their cohort and reported on 4 novel missense variants that have been integrated into the star allele nomenclature. The *CYP2D6*1* and *2* normal-function alleles were most common, with a combined frequency of approximately 70%.

XVIII. Dhuya, et al. (2020) (92) tested 97 individuals to assess their metabolism of dextromethorphan as a measure of CYP2D6 metabolizer status. In contrast to other recent publications, genotyping was not performed. Their data suggests 3/97 (~3%) individuals to be PM's and the rest (94/97, ~97%) were NMs. The authors conclude the prevalence of *CYP2D6* polymorphisms is similar in the region of east India to other regions in the country, with overall a low frequency of PMs.

PAKISTAN

XIX. Ahmed, et al. (2018) (93) reported on the frequency of variation in multiple pharmacogenes among 244 healthy individuals in an indigenous Pakistani population. Fifteen variants were genotyped via targeted sequencing and the frequencies were compared with published frequencies of these variants in other populations. The SNP rs16947, which defines the *CYP2D6*41* allele but has been found in haplotypes for normal, decreased and no-function *CYP2D6* alleles was observed in nearly 40% of the individuals in the study, but was slightly higher in the Azad Kashmir region. This specific variant genotype distribution varies notably from east Asians, admixed Americans, most Africans and Europeans, but was similar to other south Asians. Another SNP, rs1135840, was present at a lower rate (35.2%) in the Pakistani population compared with all other populations. This variant has also been associated with haplotypes of varying functional activity, though the authors conclude in this study that both this and the rs16947 SNP are responsible for a UM phenotype. The combination of these 2 variants defines the *CYP2D6*2* normal-function allele. The authors did not interrogate CNVs, thus the presumption of a UM phenotype is dubious.

XX. Ullah, et al. (2020) (94) reported the frequency of the no-function *CYP2D6*4* allele in 16 different ethnic groups from Pakistan. Over 900 individuals were enrolled in the study. The frequency of the *CYP2D6*4* allele in these groups was highest at 13.64% in the Meo population, and lowest in the Kalash population at 3.73%. The frequency of homozygotes for the *CYP2D6*4* allele, with a predicted PM phenotype, was highest in the Sindhi group (4.49%) and lowest in the Pathan group (0.83%).

BHUTAN

XXI. Dorji, et al. (2019) (95) reported a study of CYP allele frequencies in a Bhutanese population cohort. Specifically, the authors studied the *CYP2D6*10* and presumed *CYP2D6*1* allele frequencies via targeted analysis in 443 individuals. The *CYP2D6*10* allele was observed at frequency of 21%, lower than other Asian populations (see Dorji et al., 2019 (64)) but more commonly than Caucasians and Africans. The genotyping method (PCR with restriction fragment polymorphism) may not accurately differentiate between the *CYP2D6*10* allele and alleles with similar variants. The frequency of the *CYP2D6*1* allele is overestimated here, due to limited testing for *CYP2D6* variants.

Oceanian Allele Studies

Australian studies reported a frequency for UMs in this population to be around 2%, NMs were predicted in slightly more than 50% of the population, IM frequencies were more discordant and ranged between 11–30%.

The frequency of PMs ranged between 5.7–19.7%. The no-function *4 allele was seen, on average, at a frequency of 20%.

AUSTRALIA

I. Chen, et al. (2019) (96) studied *CYP2D6* allele frequency among members of the Australian Defense Forces personnel who were deployed to regions with endemic malaria and were subsequently treated for *P. vivax* infection with primaquine. While the primary purpose was to examine whether *CYP2D6* genotype correlated with malarial relapse, the authors reported the prevalence of 14 star alleles and duplication of the *CYP2D6*1* allele within the 157 individuals enrolled in the study. The most common allele was the normal-function *CYP2D6*1* allele (~32%), but the *CYP2D6*4* no-function allele was also relatively common (24.5%). The authors found roughly 1.3% of the study participants were predicted to have a UM phenotype, 50.9% had an NM-associated diplotype, approximately 29% had an IM-associated diplotype, 19.7% had a PM-predicting diplotype and one individual had 2 novel, unknown function alleles.

II. Mostafa, et al. (2019) (97) analyzed genotype and phenotype frequencies in 5,408 Australian individuals at several pharmacogene loci. Fifteen variant star alleles were studied via Sanger sequencing and CNV analysis was based on published methods (14). The *CYP2D6*1* allele was assigned in the absence of detected variants. This large cohort was ethnically diverse and subsequent analysis of study participants with medication histories enabled further analysis of the frequency of phenoconversion in a subset of the cohort. The most common altered-function allele was *CYP2D6*4*, at 17.8%. Genotyping results led to the predicted prevalence of UMs at 2.8%, NMs at 53.2%, IM at 11.4% (with an additional 26.2% of "low normal metabolizer" diplotypes that would be reclassified as IM based on the current CPIC definition), PMs were observed at 5.7% and one individual could not be genotyped. When considering medications that may alter the predicted metabolizer phenotype, the frequency of CYP2D6 PMs increased from 5.4% in the sub-cohort to 24.7%, all the result of other metabolizer phenotype groups being decreased in predicted enzyme activity levels.

MELANESIA/POLYNESIA

III. Rico, et al. (2020) (74) reported on the *CYP2D6* genotype frequencies and functional characterization of novel variants found in the Ni-Vanuatu (Melanesia/Polynesia) and localized Kenyan populations. The 278 Ni-Vanuatu study participants were residents of 6 different islands from Melanesia or Polynesia. Within Kenya, the authors enrolled 195 individuals residing on islands or the shore of Lake Victoria in western Kenya. All study participants were healthy and unrelated. Eight variant star alleles were identified by PCR-based sequencing, allele fusions and duplications were also detected along with 6 novel variants. Detailed allele frequencies are presented in tables 1 and 2 within the publication. Overall, the phenotype frequencies in the Ni-Vanuatu population were predominantly NM, with only 5.8% as predicted IM, 5% UM, and 0% PM.

Genetic Variation Frequency Resources

At the National Library of Medicine at the National Institutes of Health, the National Center for Biotechnology Information (NCBI) has several resources for learning more about genetic variation. These resources do not focus on established star allele haplotypes but are typically limited to the data available for single SNPs or other short variants. The dbSNP database is a repository of known "short" genetic variants, ranging from single base changes to small deletions or insertions and microsatellite repeats. In the nomenclature table below, the dbSNP-assigned identifiers are provided as a link to the entry for that specific variant. Within dbSNP, users can access allele frequency data from the Allele Frequency Aggregator (ALFA) project, explore the clinical significance data stored in ClinVar and access literature citations from PubMed for the variant of interest. Specific dbSNP identifiers, star alleles, and gene names can also be searched in the LitVar database. When available, dbSNP pages also display frequency data from other studies including the 1000Genomes project, the Exome

Aggregation Consortium (ExAC), the genome Aggregation Database (gnomAD), and country-specific studies that have been submitted to the BioProject database at NCBI. Additionally, the data from TOPMed are available at the NHLBI website. These individual variant frequencies do not inherently translate to star allele frequencies.

Genetic variation data from the *CYP2D6* locus is also available in databases such as Ensembl and gnomAD, though these data do not specifically address pharmacogenetics.

Other resources specific to pharmacogenomics data include PharmVar, PharmGKB, and CPIC. The Allele Frequency Table maintained by CPIC and available from PharmGKB, is an excellent resource for star allele frequency data. These tables are periodically updated by these pharmacogenomic expert communities based on peer-reviewed scientific publications. Furthermore, the PharmVar Consortium provides data on the known star alleles for multiple pharmacogenes. Data on *CYP2D6* includes the key variants that define each star allele, the assigned CPIC clinical function category, citations for the initial reports of the specific alleles, and a detailed description of the more complex structural variants at the *CYP2D6* locus. The PharmGKB database provides a wide range of data and resources, including specific variant annotations, clinical annotations, and drug label annotations for the *CYP2D6* gene, as well as multiple pharmacogenes. It should be noted that PharmGKB is a resource for drug-specific data, as well. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an authoritative source for clinical recommendations based on drug-gene interactions. The CPIC page for *CYP2D6* guidelines links to their specific guidelines and each guideline further provides information on allele definitions, functionality, frequency data and diplotype-phenotype translation tables. It should be noted that PharmVar, PharmGKB, and CPIC coordinate much of their data and cooperatively update their shared resources.

Resources from additional publications described in detail above include:

REFARGEN (Brazil)

Helix DNA project (USA)

TOPMed (USA; NHLBI, NIH)

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*2*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*3*	2550delA (Arg259fs)	NM_000106.6:c.775del	NP_000097.3:p.Arg259fs	rs35742686
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Gene deletion			
*CYP2D6*6*	1707 del T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2D6*27	3854G>A (Glu410Lys)	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
CYP2D6*31	2851C>T (Arg296Cys)	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A (Arg440His)	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*36 [3]	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G (Pro469Ala)	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G (Thr470Ala)	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C (His478Ser)	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C (Gly479Arg)	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G (Phe481Val)	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G (Ala482Ser)	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*41	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*49	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A (Phe120Ile)	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

Allele definitions are maintained by the Pharmacogene Variation (PharmVar) Consortium. If there is a discrepancy between this table and information from PharmVar, the authors defer to PharmVar's authority.

[1] In the literature, 1023C>T is also referred to as 1111C>T

[2] In the literature, 2851C>T is also referred to as 2938C>T

[3] *CYP2D6*36* is a gene conversion with *CYP2D7;* variants provided here are from PharmVar.

Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (98).

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

Acknowledgments

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