Review Article

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Distribution of genetic polymorphisms of genes encoding drug metabolizing enzymes & drug transporters - a review with Indian perspective

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Phase I and II drug metabolizing enzymes (DME) and drug transporters are involved in the absorption, distribution, metabolism as well as elimination of many therapeutic agents, toxins and various pollutants. Presence of genetic polymorphisms in genes encoding these proteins has been associated with marked inter-individual variability in their activity that could result in variation in drug response, toxicity as well as in disease predisposition. The emergent field pharmacogenetics and pharmacogenomics (PGx) is a promising discipline, as it predicts disease risk, selection of proper medication with regard to response and toxicity, and appropriate drug dosage guidance based on an individual's genetic make-up. Consequently, genetic variations are essential to understand the ethnic differences in disease occurrence, development, prognosis, therapeutic response and toxicity. For that reason, it is necessary to establish the normative frequency of these genes in a particular population before unraveling the genotype-phenotype associations. Although a fair amount of allele frequency data are available in Indian populations, the existing pharmacogenetic data have not been compiled into a database. This review was intended to compile the normative frequency distribution of the variants of genes encoding DMEs (CYP450s, TPMT, GSTs, COMT, SULT1A1, NAT2 and UGTs) and transporter proteins (MDR1, OCT1 and SLCO1B1) with Indian perspective.

Key words Cytochrome P450 - drug metabolizing enzymes - Indians - pharmacogenetics - pharmacogenomics - polymorphism - SNP - transporters

Introduction

Patients or individuals may not respond in similar ways when administered with the same drug in a standard dose. Both genetic and non-genetic factors including age, gender, nutrition, concomitant medications, organ function, co-morbidness and drug interactions can modulate the efficacy of pharmacotherapy[1]. However, to a great extent the inter-individual variability in drug response is attributable to the presence of single nucleotide polymorphisms (SNPs) in the sequence of the genes encoding proteins that are involved in the absorption, distribution, metabolism and excretion (ADME) of many therapeutic agents, toxins and

various pollutants[2,3]. The pharmacogenetics and pharmacogenomics (PGx) predicts disease risk, selection of proper medication with regard to response and toxicity, and appropriate drug dosage guidance based on an individual's genetic make-up[4]. Genetic variations in genes encoding ADME proteins have been associated with marked inter-individual variability in drug response, toxicity as well as disease susceptibility. The variation can occur at various levels of ADME as well as in drug action. Presence of SNPs in genes encoding drug metabolizing enzymes (DME) can cause the alteration of the enzyme leading to normal, reduced, increased or absence of activity. Based on this level of enzyme activity, patients can be divided into four phenotypes: *(i)* Poor metabolizer (PM) - no activity; *(ii)* Intermediate metabolizer (IM) - reduced activity; *(iii)* Extensive metabolizer (EM) - normal activity; and *(iv)* Ultra-extensive or Ultrarapid metabolizer (UM) – increased activity[2,4]. Polymorphisms exhibited by these DMEs and transporters are well known and their prevalence varies among different ethnic populations[4]. Therefore, the knowledge of genetic variations is essential to understand the ethnic differences in disease occurrence, development, prognosis, therapeutic response and toxicity. Before unraveling the genotype-phenotype associations in a particular population, it is of paramount importance to establish the normative frequency of these genes. In recent years we have performed pharmacogenetic studies on clinically important genes and established their normative frequencies in south Indian populations[5-14]. Since the Indian populations are highly heterogeneous in nature, our results could not be extrapolated to the entire Indian population.

India is the world's second most populous country and inhabited by more than 1.21 billion humans comprising 4,693 communities, 325 languages and 25 scripts[15,16]. There is extreme diversity in terms of culture, biological, social characteristics, language and religion in Indians and genetically they are unique from other races. Based on their ethnic origin, Indian populations are morphologically classified into four groups *viz.*, Caucasoid, Mangoloid, Protoaustraloid and Negrito. The Caucasoid and Protoaustraloid are the most predominant populations, mostly confined to northern and southern India. The Mangoloids live along the Himalayan fringe of Jammu and Kashmir and north-eastern region of the country, whereas the Negritos limited to Andaman Islands alone. In the same way, on the basis of their linguistic lineages the languages spoken in India belong to four major families: Austro-Asiatic (Central & East India), Dravidian (South India), Indo-European (North India) and Tibeto-Burman (North-East India)[16,17]. The Indian populations have been characterized as ancestral North Indians (ANI) and ancestral South Indians (ASI) on the basis of their ancestry components[17]. The authors have also shown that unlike the ANI, the ASI are not genetically close to any of the contemporary population outside India[17]. A recent Indian genome variation consortium (IGVC) study of genetic markers in 55 diverse Indian populations revealed high heterogeneity among the Dravidian populations and showed dissimilarity with HapMap populations[16]. The Indian population comprised multiple ethnic groups but there have been no published data available on the allele frequencies of these genes for Indians. Hence, we compiled the frequency distribution of the variants of genes encoding drug metabolizing enzymes and drug transporters, with Indian perspective. We compiled the normative frequency data of DME and transporters in various geographical regions of India reported from different studies and pooled them as North Indians (NI), South Indians (SI) and North East Indians (NEI) based on their ancestral ethnicity. Furthermore, we also compared the pooled mean allele frequency of Indian populations with the data from previous reports in Africans, Asians and Caucasians.

Literature search and data collection

A keyword literature search of the articles published (up to June 2012) on genes encoding drug metabolizing enzymes and drug transporters in Indian populations was done from databases such as PubMed, Medline and Google Scholar. The following search terms were used: "CYP450", "*CYP1A1", "CYP1A2", "CYP2A6", "CYP2C8", "CYP2C9", "CYP2C19", "CYP2D6", "CYP2E1",* "CYP3A", *"CYP3A4", "CYP3A5",* "GSTs", *"GSTM1", "GSTT1", "GSTP1",* "UGTs", *"UGT1A1", "UGT1A7", "TPMT", "SULT1A1", "SULT1A2", "COMT", "NAT1", "NAT2", "MDR1* or *ABCB1", "OCT1* or *SLC22A1", "SLCO1B1* or *OATP1B1"* "transporters", DME and ADME in combinations with words "polymorphism" or "variation", "pharmacogenetics", pharmacogenomics", "India", "South Indian", "North Indian" and "Population" using the limit Human. Studies with the following inclusion criteria were included *(i)* original papers carried out in native Indians, *(ii)* studies containing data on unrelated healthy individuals, *(iii)* with information on normative genotype or allele frequency distribution, and *(iv)* well defined ethnicity.

Accordingly, the related reference articles were also searched to identify other relevant publications. The reasons for exclusion of studies, were *(i)* overlapping data, *(ii)* family-based studies, *(iii)* meta-analysis, *(iv)* studies on non-residential Indians, and *(v)* studies that did not report genotype or allele frequency. Ethnicities were categorized as NI, SI, and NEI based on their geographical origin. When more than one publication was available for a gene SNP frequency for the same population from the same group, only the study with highest total number of subjects was included to avoid bias and overlapping data.

Drug metabolizing enzymes

Phase I enzymes

Enzymes involved in phase I drug metabolism largely belong to the cytochrome P450 (CYP) super family of drug metabolizing enzymes which catalyze the reactions such as hydrolysis, oxidation and reduction in which the functional groups of a substrate are added or deleted. This CYP450 system is divided into 18 families and 44 subfamilies consisting of 57 genes and 58 pseudo genes. Among them, the oxidative metabolism of 90 per cent drugs has been controlled by CYP1, CYP2 and CYP3 subfamilies[18]. The allele frequency distribution of phase I enzymes in various Indian populations is described in Table I[7-9,11,13,19-63].

CYP1A (CYP1A1 & CYP1A2): Human CYP1A belongs to the group of phase I DME CYP450 isoforms. It consists of two members, CYP1A1 and CYP1A2. These are the key enzymes in the biotransformation of estrogens, polycyclic aromatic hydrocarbons and aromatic amines. In addition, CYP1A2 is also involved in the metabolism of a number of therapeutic drugs including caffeine, clozapine, olanzapine, amitriptyline, R-warfarin, veramapil, theophylline, propranolol, clomipramine, imipramine, haloperidol and acetaminophen. The gene encoding CYP1A1 is located at 15q22-q24, spanning 5,810 bp with seven exons and six introns. While the gene encoding CYP1A2 is located at 15q22, extending 7.8 kb with six exons and so far, more than 150 variant alleles have been described worldwide[64-66]. Polymorphisms in these genes lead to variability in the enzyme activity and is shown to be associated with various cancers such as colon, ovarian, breast, lung, oral and acute lymphoblastic leukaemia (ALL). The most common being *CYP1A1*2A* or *m1* (3798T>C), also known as *Msp1*, *CYP1A1*2C* or *m2* (2455A>G), *CYP1A1*3* or *m3* (3204T>C) and *CYP1A1*4* or *m4* (2452C>A) polymorphisms for *CYP1A1*. For *CYP1A2*, *CYP1A2*1F* (163C>A) is the most common variant. The frequency of the mutant alleles *CYP1A1*2A* and *CYP1A1*2C* were significantly (P<0.05) different among the Indian populations as well as in comparison with other populations (P<0.0001)[9,19-38,67-71]. *CYP1A1**3 was absent in Indians, while *CYP1A1*2B* (9.5%) was determined only in NEI[35], which was significantly different from other populations (P<0.0001). The *CYP1A1*4* frequency in NEI[35] was different from NI, Caucasians and Africans but absent in Asians (P<0.0001). Similarly, *CYP1A1*4* frequency in NI was in agreement with Caucasians but different from Africans (P<0.0001). Conversely, the frequency of *CYP1A2* polymorphisms is available only in NI population. The distribution of *CYP1A2* alleles were 8, 24.5, 9.5, 50.7 and 0 for **1C, *1D, *1E, *1F & *2*, respectively. Significant interethnic differences were observed between NI and other major populations, P<0.001 (Table II)[67-74].

CYP2A6: Human CYP2A6 is the major hepatic CYP2A enzyme and its role in the metabolism of drugs is small (3%) but it is important in the oxidative metabolism of nicotine. In addition, it is involved in the catalytic metabolism of valproic acid, fadrozole, methoxyflurane, artesunate, coumarin, disulfiram, halothane, losigamone, tegafur and letrozole. It also metabolizes environmental toxins, procarcinogens, retinoic acids and steroids[75]. The gene encoding *CYP2A6* spans about 6kb with 9 exons and is mapped on chromosome 19q13.2 with other CYP2A sub-family (CYP2A7 and CYP2A13) members. Importance of CYP2A6 had risen considerably after the finding of a relationship between defective *CYP2A6* alleles, smoking behaviour and cigarette consumption, drug clearance as well as tobacco related cancer risk. The *CYP2A6* gene is extremely polymorphic and up to now, more than 81 variant alleles have been known[75,66]. Besides the normal type allele designated as *CYP2A6*1*, three non-functional alleles which result in absence of CYP2A6 activity **2* (1799T>A, Leu160His), **4A* (gene deletion), and **5* (1436G>T and 6582G>T, Gly479Val) have been well known. The frequency data of *CYP2A6*1B* polymorphisms are available only for NI[43] and similarly *CYP2A6*2* and **5* are available only in SI populations[13]. Among the *CYP2A6* variants, **1B* is the most prevalent allele followed by **4*, whereas **2* and **5* were found to be rare (Table I). The comparison of *CYP2A6*1B* between NI (32.7%) and other populations indicates similarity with Caucasians (27.6%) and significant difference with Africans 11.2 per cent and Asians 42.8 per cent (P<0.001). The

Table I. Allele frequencies (%) of genes encoding phase I drug metabolizing enzymes (DME) in various Indian populations

Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
CYP1A1	**2A*	NI	Total*	2495	30.3 (28.9-31.4)	
			Chandigarh	76	25.7 (18.7-32.6)	19
			Chandigarh	201	19.4 (15.5-23.2)	20
			Delhi	136	25.0 (20.2-30.5)	21
			Delhi	309	40.3 (36.4-44.2)	22
			Delhi	250	34.0 (29.8-38.2)	23
			Lucknow, Uttar Pradesh	162	25.6 (20.9-30.4)	24
			Lucknow, Uttar Pradesh	116	30.6 (24.7-36.5)	25
			Lucknow, Uttar Pradesh	160	26.3 (21.4-31.1)	26
			Mumbai, Maharashtra	727	31.0 (28.6-33.4)	27
			Srinagar, Kashmir	163	30.1 (25.1-35.0)	28
			Srinagar, Kashmir	195	28.7 (24.2-33.2)	29
		SI	Total*	1195	21.6 (20.0-23.3)	
			Hyderabad, Andhra Pradesh	63	25.4 (17.8-33.0)	30
			Andhra Pradesh	230	20.0 (16.3-23.7)	31
			Thiruvananthapuram, Kerala	165	10.0 (6.9-13.8)	32
			Kerala	367	19.3 (16.5-22.2)	33
			Puducherry and Tamil Nadu	220	27.0 (22.9-31.2)	9
			Chennai, Tamil Nadu	150	33.0 (27.7-38.3)	34
		NEI	Total*	416	33.8 (30.6-37.0)	
			Kolkata, West Bengal	126	27.4 (21.9-32.9)	35
			Gangtok, Sikkim	290	36.6 (32.6-40.5)	36
	**2B*	NEI	Total*	126	9.5 (6.2-13.8)	
			Kolkata, West Bengal	126	9.5 (6.2-13.8)	35
	**2C*	NI	Total*	1463	22.0 (20.5-23.5)	
			Chandigarh	76	54.6 (46.7-62.5)	19
			Chandigarh	201	14.0 (10.5-17.3)	20
			Delhi	309	31.0 (27.4-34.7)	22
			Delhi	136	11.0 (7.3-14.8)	21
			Srinagar, Kashmir	163	26.6 (21.9-31.5)	28
			Eastern Uttar Pradesh	300	16.6 (13.7-19.6)	37
			Lucknow, Uttar Pradesh	162	13.9 (10.1-17.7)	24
			Lucknow, Uttar Pradesh	116	22.0 (16.7-27.3)	25
		SI	Total*	634	16.0 (14.0-18.0)	

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Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Hyderabad, Andhra Pradesh	249	25.5 (21.7-29.3)	38
			Thiruvananthapuram, Kerala	165	9.7 (6.7-13.4)	32
			Puducherry and Tamil Nadu	220	10.0 (7.3-13.2)	9
		NEI	Total*	416	11.5 (9.4-13.7)	
			Kolkata, West Bengal	126	2.0 (0.6-4.6)	35
			Gangtok, Sikkim	290	15.7 (12.7-18.6)	36
	**3*	NI	Total*	479	0	
			Chandigarh	201	0	20
			Lucknow, Uttar Pradesh	162	0	24
			Lucknow, Uttar Pradesh	116	0	25
	**4*	NI	Total*	951	3.0 (2.3-4.0)	
			Chandigarh	201	1.2 (0.4-2.8)	20
			Delhi	309	0	22
			Srinagar, Kashmir	163	0	28
			Lucknow, Uttar Pradesh	162	5.9 (3.5-9.0)	24
			Lucknow, Uttar Pradesh	116	15.0 (10.1-19.2)	25
		NEI	Total*	116	40.5 (34.2-46.8)	
			Kolkata, West Bengal	116	40.5 (34.2-46.8)	35
CYP1A2	**1C*	NI	Total*	586	8.0 (6.5-9.8)	
			Delhi	250	6.1 (4.1-8.5)	39
			Delhi	136	13.0 (8.9-16.8)	21
			Lucknow, Uttar Pradesh	200	7.2 (4.9-10.2)	40
	**1D*	NI	Total*	200	24.5 (20.3-28.7)	
			Lucknow, Uttar Pradesh	200	24.5 (20.3-28.7)	40
	**1E*	NI	Total*	200	9.5 (6.8-12.8)	
			Lucknow, Uttar Pradesh	200	9.5 (6.8-12.8)	40
	**1F*	NI	Total*	450	50.7 (47.4-53.9)	
			Delhi	250	48.8 (44.4-53.2)	41
			Lucknow, Uttar Pradesh	200	53.0 (48.1-57.9)	40
	**2*	NI	Total*	200	0	
			Lucknow, Uttar Pradesh	200	0	42
CYP2A6	**1B*	NI	Total*	350	32.7 (29.2-36.2)	
			Lucknow, Uttar Pradesh	350	32.7 (29.2-36.2)	43
	**2*	SI	Total*	479	1.0 (0.5-1.9)	
			Gulbarga, Karnataka	115	0.9 (0.1-3.1)	13

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Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Kakinada, Andhra Pradesh	119	1.7 (0.4-4.2)	13
			Puducherry and Tamil Nadu	116	1.3 (0.3-3.7)	13
			Thiruvananthapuram, Kerala	129	0.4 (0.006-2.1)	13
	**4*	NI	Total*	350	11.3 (8.9-13.6)	
			Lucknow, Uttar Pradesh	350	11.3 (8.9-13.6)	43
		SI	Total*	479	8.9 (7.1-10.9)	
			Gulbarga, Karnataka	115	7.4 (4.4-11.6)	13
			Kakinada, Andhra Pradesh	119	10.9 (6.9-14.9)	13
			Puducherry and Tamil Nadu	116	8.6 (5.3-13.0)	13
			Thiruvananthapuram, Kerala	129	8.5 (5.4-12.6)	13
	**5*	SI	Total*	479	0.7 (0.3-1.5)	
			Gulbarga, Karnataka	115	0.9 (0.1-3.1)	13
			Kakinada, Andhra Pradesh	119	0.4 (0.01-2.3)	13
			Puducherry and Tamil Nadu	116	0.4 (0.01-2.4)	13
			Thiruvananthapuram, Kerala	129	1.2 (0.2-3.4)	13
CYP2C8	**2*	SI	Total*	245	0.8 (0.2-2.1)	
			Puducherry and Tamil Nadu	245	0.8 (0.2-2.1)	11
	**3*	SI	Total*	245	2.9 (1.6-4.7)	
			Puducherry and Tamil Nadu	245	2.9 (1.6-4.7)	11
CYP2C9	**2*	NI	Total*	803	9.0 (7.6-10.5)	
			Ahmadabad, Gujarat	192	4.4 (2.6-7.0)	44
			Delhi	134	6.0 (3.5-9.5)	45
			Lucknow, Uttar Pradesh	375	13.5 (11.0-15.9)	46
			Lucknow, Uttar Pradesh	102	4.9 (2.4-8.8)	47
		SI	Total*	481	3.6 (2.5-5.0)	
			Andhra Pradesh	116	4.0 (1.8-7.2)	7
			Karnataka	110	6.0 (3.2-9.9)	7
			Kerala	120	2.0 (0.6-4.8)	7
			Puducherry and Tamil Nadu	135	3.0 (1.3-5.8)	7
	**3*	NI	Total*	538	9.7 (8.0-11.7)	
			Ahmedabad, Gujarat	192	9.6 (6.9-13.0)	44
			Delhi	134	14.2 (10.0-18.4)	45
			Lucknow, Uttar Pradesh	102	3.9 (1.7-7.6)	47
			Lucknow, Uttar Pradesh	110	9.9 (6.4-14.8)	48
		SI	Total*	481	8.0 (6.4-9.9)	

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Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Andhra Pradesh	116	9.0 (5.7-13.5)	7
			Karnataka	110	8.0 (4.9-12.6)	7
			Kerala	120	8.0 (4.8-12.1)	7
			Puducherry and Tamil Nadu	135	7.0 (4.3-10.8)	7
	*5	NI	Total*	192	0	
			Ahmedabad, Gujarat	192	0	44
CYP2C19	*2	NI	Total*	785	33.1 (30.8-35.4)	
			Ahmedabad, Gujarat	150	41.3 (35.8-46.9)	44
			Chandigarh	121	30.0 (24.0-35.5)	49
			Lucknow, Uttar Pradesh	375	27.7 (24.5-30.9)	46
			Pune, Maharashtra	139	41.7 (35.9-47.5)	50
		SI	Total*	673	36.8 (34.3-39.4)	
			Andhra Pradesh	115	33.0 (27.0-39.1)	7
			Hyderabad, Andhra Pradesh	220	40.5 (35.9-45.0)	51
			Karnataka	108	39.0 (32.4-45.4)	7
			Kerala	118	31.0 (25.0-36.8)	7
			Puducherry and Tamil Nadu	112	38.0 (31.6-44.3)	7
	*3	NI	Total*	710	1.9 (1.2-2.7)	
			Ahmedabad, Gujarat	150	0	44
			Chandigarh	121	0	49
			Lucknow, Uttar Pradesh	300	4.0 (2.6-5.9)	52
			Pune, Maharashtra	139	1.1 (0.2-3.1)	50
		SI	Total*	673	1.1 (0.6-1.8)	
			Andhra Pradesh	115	0	7
			Hyderabad, Andhra Pradesh	220	1.1 (0.4-2.6)	51
			Karnataka	108	1.0 (0.1-3.3)	7
			Kerala	118	1.0 (0.2-3.7)	7
			Puducherry and Tamil Nadu	112	2.0 (0.7-5.1)	7
	*17	SI	Total*	206	19.2 (15.4-23.0)	
			Puducherry and Tamil Nadu	206	19.2 (15.4-23.0)	14
CYP2D6	*2	NI	Total*	285	29.3 (25.6-33.0)	
			Ahmedabad, Gujarat	160	23.1 (18.5-27.7)	44
			Lucknow, Uttar Pradesh	125	37.2 (31.2-43.2)	53
		SI	Total*	447	34.8 (31.7-37.9)	
			Andhra Pradesh	106	36.3 (29.8-42.8)	8

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Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Karnataka	94	38.3 (31.3-45.2)	8
			Kerala	107	36.9 (30.5-43.4)	8
			Puducherry and Tamil Nadu	140	29.6 (24.3-35.0)	8
	**3*	NI	Total*	294	9.2 (6.9-11.8)	
			Ahmedabad, Gujarat	160	0.3 (0.006-1.7)	44
			Delhi	134	19.8 (15.0-24.5)	45
		SI	Total*	447	0	
			Andhra Pradesh	106	0	8
			Karnataka	94	0	8
			Kerala	107	0	8
			Puducherry and Tamil Nadu	140	0	8
	**4*	NI	Total*	2050	11.5 (10.5-12.5)	
			Ahmadabad, Gujarat	160	10.3 (6.9-13.6)	44
			Chandigarh	100	9.0 (5.4-13.8)	44
			Delhi	134	10.0 (6.5-13.7)	45
			Eastern Uttar Pradesh	300	15.8 (12.9-18.8)	37
			Lucknow, Uttar Pradesh	375	13.5 (11.0-15.9)	46
			Mumbai, Maharashtra	100	17.0 (11.8-22.2)	54
			Western Central India	881	9.3 (7.9-10.8)	44
		SI	Total*	510	7.3 (5.8-9.1)	
			Andhra Pradesh	106	10.8 (6.7-15.0)	8
			Hyderabad, Andhra Pradesh	63	8.0 (3.9-14.1)	30
			Karnataka	94	4.8 (2.2-8.9)	8
			Kerala	107	7.5 (4.3-11.9)	8
			Puducherry and Tamil Nadu	140	6.1 (3.5-9.5)	8
		NEI	Total*	143	8.7 (5.7-12.6)	
			Kolkata, West Bengal	143	8.7 (5.7-12.6)	35
	**5*	NI	Total*	160	1.9 (0.6-4.0)	
			Ahmedabad, Gujarat	160	1.9 (0.6-4.0)	44
		SI	Total*	447	1.8 (1.0-2.9)	
			Andhra Pradesh	106	1.4 (0.3-4.1)	8
			Karnataka	94	1.1 (0.1 -3.8)	8
			Kerala	107	3.7 (1.6-7.2)	8
			Puducherry and Tamil Nadu	140	1.1 (0.2-3.0)	8
	**6 & *9*	NI	Total*	160	0	

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Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Ahmedabad, Gujarat	160	0	44
	**10*	NI	Total*	1025	27.2 (25.3-29.1)	
			Ahmedabad, Gujarat	160	5.9 (3.6-9.1)	44
			Delhi	140	22.5 (17.6-27.4)	55
			Delhi	250	57.8 (53.5-62.1)	23
			Lucknow, Uttar Pradesh	375	19.5 (16.6-22.3)	46
			Mumbai, Maharashtra	100	20.5 (14.9-26.1)	54
		SI	Total*	447	10.2 (8.2-12.2)	
			Andhra Pradesh	106	9.0 (5.5-13.6)	8
			Karnataka	94	11.2 (6.7-15.7)	8
			Kerala	107	7.0 (3.9-11.3)	8
			Puducherry and Tamil Nadu	140	12.9 (8.9-16.8)	8
	**14*	SI	Total*	447	0	
			Andhra Pradesh	106	0	8
			Karnataka	94	0	8
			Kerala	107	0	8
			Puducherry and Tamil Nadu	140	0	8
	**17*	NI	Total*	160	0	
			Ahmedabad, Gujarat	160	0	44
		SI	Total*	447	0	
			Andhra Pradesh	106	0	8
			Karnataka	94	0	8
			Kerala	107	0	8
			Puducherry and Tamil Nadu	140	0	8
	**29*	NI	Total*	160	0	
			Ahmedabad, Gujarat	160	0	44
	**41*	NI	Total*	160	12.5 (8.9-16.1)	
			Ahmedabad, Gujarat	160	12.5 (8.9-16.1)	44
	1xN	NI	Total*	160	0.6 (0.08-2.2)	
			Ahmedabad, Gujarat	160	0.6 (0.08-2.2)	44
	2xN	NI	Total*	160	1.6 (0.5-3.6)	
			Ahmedabad, Gujarat	160	1.6 (0.5-3.6)	44
	4xN	NI	Total*	160	0.3 (0.006-1.7)	
			Ahmedabad, Gujarat	160	0.3 (0.006-1.7)	44
	10xN	NI	Total*	160	0	

Contd...

Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Ahmedabad, Gujarat	160	0	44
	41xN	NI	Total*	160	0	
			Ahmedabad, Gujarat	160	0	44
CYP2E1	**1B*	NI	Total*	147	13.0 (9.0-16.8)	
			Delhi	147	13.0 (9.0-16.8)	56
		SI	Total*	637	14.2 (12.3-16.1)	
			Gulbarga, Karnataka	153	15.7 (11.6-19.8)	13
			Kakinada, Andhra Pradesh	154	14.3 (10.0-17.6)	13
			Puducherry and Tamil Nadu	149	17.5 (13.1-21.8)	13
			Thiruvananthapuram, Kerala	181	10.5 (7.3-13.7)	13
	**4*	SI	Total*	132	0	
			Chennai, Tamil Nadu	132	0	57
	**5B*	NI	Total*	578	8.4 (6.8-10.1)	
			Chandigarh	76	0	19
			Delhi	147	0.7 (0.07-2.4)	56
			Srinagar, Kashmir	160	23.7 (19.1-28.4)	58
			Srinagar, Kashmir	195	4.9 (2.9-7.5)	29
		SI	Total*	637	1.3 (0.8-2.1)	
			Gulbarga, Karnataka	153	0.7 (0.07-2.3)	13
			Kakinada, Andhra Pradesh	154	0.6 (0.07-2.3)	13
			Puducherry and Tamil Nadu	149	1.7 (0.5-3.8)	13
			Thiruvananthapuram, Kerala	181	2.2 (0.9-4.3)	13
		NEI	Total*	124	0.8 (0.1-2.9)	
			Guwahati, Assam	124	0.8 (0.1-2.9)	59
	**6*	NI	Total*	147	17.7 (13.3-22.0)	
			Delhi	147	17.7 (13.3-22.0)	56
		SI	Total*	636	22.2 (20.0-24.5)	
			Gulbarga, Karnataka	153	20.3 (15.8-24.8)	13
			Kakinada, Andhra Pradesh	154	23.0 (17.7-26.9)	13
			Puducherry and Tamil Nadu	149	20.1 (15.6-24.7)	13
			Thiruvananthapuram, Kerala	180	25.6 (21.0-30.1)	13
		NEI	Total*	124	0.8 (0.1-2.9)	
			Assam	124	0.8 (0.1-2.9)	59
CYP3A4	**1B*	NI	Total*	509	1.2 (0.6-2.0)	

Contd...

Gene	SNP	Population	Geographical origin	n	Frequency (95% CI)	References
			Chandigarh	100	1.0 (0.1-3.6)	60
			Delhi	309	0	22
			Mumbai, Maharashtra	100	5.0 (2.4-9.0)	61
	**2, *4, *5, *6, *10*	NI	Total*	100	0	
			Chandigarh	100	0	60
CYP3A5	**3*	NI	Total*	308	68.2 (64.5-71.9)	
			Lucknow, Uttar Pradesh	208	67.0 (62.6-71.6)	62
			Mumbai, Maharashtra	100	70.5 (64.2-76.8)	61
		SI	Total*	785	56.0 (53.5-58.5)	
			Andhra Pradesh	241	33.8 (29.6-38.0)	63
			Gulbarga, Karnataka	115	65.2 (59.1-71.4)	13
			Kakinada, Andhra Pradesh	146	64.0 (58.5-69.5)	13
			Puducherry and Tamil Nadu	110	63.2 (56.8-69.6)	13
			Thiruvananthapuram, Kerala	173	62.1 (57.0-67.2)	13
	**2 &*4*	SI	Total*	544	0	
			Gulbarga, Karnataka	115	0	13
			Kakinada, Andhra Pradesh	146	0	13
			Puducherry and Tamil Nadu	110	0	13
			Thiruvananthapuram, Kerala	173	0	13
	**6*	NI	Total*	208	0	
			Lucknow, Uttar Pradesh	208	0	62
		SI	Total*	544	0	
			Gulbarga, Karnataka	115	0	13
			Kakinada, Andhra Pradesh	146	0	13
			Puducherry and Tamil Nadu	110	0	13
			Thiruvananthapuram, Kerala	173	0	13
	-44A>G	NI	Total*	134	34.7 (29.0-40.4)	
			Delhi	134	34.7 (29.0-40.4)	45

DME, drug metabolizing enzymes; n, total number of subjects; NI, North Indians; SI, South Indians; NEI, North East Indians; CI, Confidence Interval; *Total number of subjects analyzed and the mean allele frequency values for every geographical region. The mean value may not sum 1 because the number of subjects analyzed for each SNP in a region may vary

Table II. Summary of normative allele frequency distribution of genes encoding major human Phase I and II drug metabolizing enzymes (DME) and drug transporters in different ethnics

Gene and SNP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
CYP1A1																
m1 or *2A (3798T>C)	3' UTR	-	rs4646903	445	21.8[a,c] (19.1-24.5)	350	18.9[a,c] (16.0-21.8)	265	8.5[a,b,c] (6.3-11.2)	2495	30.3[b,c] (28.9-31.4)	1195	21.6[a,c] (20.0-23.3)	416	33.8[a,b] (30.6-37.0)	Increased
*2B (3798T>C) (2455A>G)	3'UTR, Exon 7	Ile462Val	-	445	1.8[c] (1.0-2.9)	626	21.2[c] (19.0-23.5)	265	1.3[c] (0.5-2.7)		na		na	126	9.5 (6.2-13.8)	
m2 or *2C (2455A>G)	Exon 7	Ile462Val	rs1048943	445	0.7[a,b,c] (0.2-1.5)	350	32.8[a,b,c] (29.4-36.3)	265	0.2[a,b,c] (0.006-1.0)	1463	22.0[b,c] (20.5-23.5)	634	16.0[a,c] (14.0-18.0)	416	11.5[a,c] (9.4-13.7)	
m3 or *3 (3204T>C)	3'UTR	-	rs4986884	464	9.3 (7.5-11.3)	100	0	265	0.4 (0.04-1.4)	479	0		na		na	
m4 or *4 (2452C>A)	Exon 7	Thr461Asn	rs1799814	285	1.2[a,c] (0.5-2.5)	284	0	265	4.3[c] (2.8-6.4)	951	3.0[c] (2.3-4.0)		na	116	40.5[a] (34.2-46.8)	
CYP1A2																
*1C (-3860G>A)	5'UTR	-	rs2060514	120	0.8[a,+] (0.1-3.0)	159	21.1[a] (16.6-25.6)	120	51.7[a,+] (45.3-58.0)	586	8.0 (6.5-9.8)		na		na	Decreased
*1D (2467Tdel)	5'UTR	-	rs35694136		na	159	42.0[a] (36.7-47.6)	329	30.2 (26.7-33.8)	200	24.5 (20.3-28.7)		na		na	
*1E (-729T>G)	Intron 1	-	rs2069526	226	12.8[+] (9.7-15.9)	159	8.2 (5.4-11.7)	226	0.4[a,+] (0.05-1.6)	200	9.5 (6.8-12.8)		na		na	
*1F (-163C>A)	Intron 1	-	rs762551	173	49.6 (44.2-54.7)	159	61.3[a] (56.0-66.7)	333	30.5[a] (27.0-34.0)	450	50.7 (47.4-53.9)		na		na	Higher inducibility
*2 (63C>G)	Exon 2	Phe21leu	rs56160784		na		na		na	200	0		na		na	
CYP2A6																
*1B	3'UTR	-		94	11.2[a] (6.7-15.7)	209	42.8[a] (38.1-47.6)	165	27.6 (22.8-32.4)	350	32.7 (29.2-36.2)		na		na	Increased
*2 (479T>A), (1799T>A)	Exon 3	Leu160His	rs1801272	305	0.3 (0.04-1.2)	209	0	320	2.3 (1.3-3.8)		na	479	1.0 (0.5-1.9)		na	None
*4A	-	Gene deletion	-	94	0.5[a,b] (0.01-2.9)	209	11 (8.0-14.0)	165	3.0[a,b] (1.5-5.5)	350	11.3 (8.9-13.6)	479	8.9 (7.1-10.9)		na	None

Contd...

Gene and SNP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
*5 (1436G>T), (6582G>T)	3'UTR, Exon 9	Gly479Val	rs5031017	94	0	209	0.5 (0.05-1.7)	165	0		na	479	0.7 (0.3-1.5)		na	None
CYP2C8																
*2 (805A>T)	Exon 5	Ile269Phe	rs11572103	203	17[b] (13.3-20.6)	360	0	161	0.3 (0.006-1.7)		na	245	0.8 (0.2-2.1)		na	Decreased
*3 (416G>A), (1196A>G)	Exon 8	Arg139Lys Lys399Arg	rs10509681	203	0	360	0	161	10.9[b] (7.5-14.3)		na	245	2.9 (1.6-4.7)		na	Decreased
CYP2C9																
*2 (430C>T)	Exon 3	Arg144Cys	rs1799853	600	2.8[a] (1.9-3.9)	574	0	430	10.7[b] (8.6-12.8)	803	9.0[b] (7.6-10.5)	481	3.6[a] (2.5-5.0)		na	Decreased
*3 (1075A>C)	Exon 7	Ile359Leu	rs1057910	600	2.0[a,b] (1.3-3.0)	574	1.1[a,b] (0.6-1.9)	430	7.4 (5.8-9.4)	538	9.7 (8.0-11.7)	481	8.0 (6.4-9.9)		na	Decreased
*5 (1080C>G)	Exon 7	Asp360Glu	rs28371686	135	2.2 (0.8-4.8)	180	0	200	0	192	0		na		na	Decreased
CYP2C19																
*2 (681G>A)	Exon 5	Splicing defect	rs4244285	985	16.0[a,b] (14.4-17.6)	271	28.4[b] (24.6-32.2)	765	13.3[a,b] (11.6-15.0)	785	33.1 (30.8-35.4)	673	36.8 (34.3-39.4)		na	None
*3 (636G>A)	Exon 4	Premature stop codon	rs4986893	982	0	271	10.1[a,b] (7.6-12.7)	765	0.2[a,b] (0.04-5.7)	710	1.9[b] (1.2-2.7)	673	1.1 (0.6-1.8)		na	None
*17 (-806C>T), (-340C>T)	5'FR	Increased transcription	rs12248560	99	26.3 (20.1-32.4)	271	1.5[b] (0.6-2.9)	896	19.1 (17.3-21.0)		na	206	19.2 (15.4-23)		na	Increased
CYP2D6																
*2 (2850C>T), (4180G>C)	Exon 2 & 6	Arg296Cys, Ser486Thr	rs16947, rs1135840	405	23.0[b] (20.1-25.9)	100	14.0[a,b] (9.2-18.8)	200	4.0[a,b] (2.3-6.4)	285	29.3 (25.6-33.0)	447	34.8 (31.7-37.9)		na	Normal
*3 (2549delA)	Exon 5	Frameshift	rs35742686	651	0.4[a] (0.1-0.9)	384	1.0[a] (0.5-2.0)	200	2.8[a] (1.4-4.9)	294	9.2 (6.9-11.8)	447	0		na	None

Contd...

Gene and SNP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
**4* (1846G>A)	Intron3-Exon 4 junction	Splicing defect	rs3892027	651	6.8[a] (5.4-8.3)	384	4.0[a,b,c] (2.8-5.7)	200	14.0[c,b] (10.6-17.4)	2050	11.5[b] (10.5-12.5)	510	7.3 (5.8-9.1)	143	8.7 (5.7-12.6)	None
**5*	-	Gene deletion		651	6.6[a,b] (5.3-8.1)	100	7.0[a,b] (3.9-11.5)	672	6.9[a,b] (5.6-8.4)	160	1.9 (0.6-4.0)	447	1.8 (1.0-2.9)		na	None
**6* (1707delT)		Frameshift	rs5030655	193	0	400	0	200	1.5 (0.5-3.2)	160	0		na		na	None
**9* (2615-2617 delAAG)		Lys281del	rs5030656	193	0	400	0	195	2.0 (0.9-4.0)	160	0		na		na	Decreased
**10* (100C>T)	Exon 1	Pro34Ser	rs1065852	405	5.6[a,b] (4.1-7.4)	672	39.4[a,b] (36.7-42.0)	672	1.5[a,b] (0.9-2.3)	1025	27.2[b] (25.3-29.1)	447	10.2[a] (8.2-12.2)		na	Decreased
**14* (1758G>A)	Exon 3	Gly169Arg	rs5030865		na	100	1.5 (0.3-4.3)		na		na	447	0		na	None
**17* (1023C>T), (2850C>T)	Exon 2	Thr107Ile, Arg296Cys	rs28371706, rs16947	191	20.9 (16.9-25.0)	802	0	672	0.1 (0.006-0.5)	160	0	447	0		na	Decreased
**29* (1659G>A), (1661G > C), (3183G > A)		Val136Ieu, Val338Met	rs61736512, rs59421388	251	7.2 (5.0-9.8)	400	0	142	0	160	0		na		na	Decreased
**41* (2988G> A)		Aberrant splicing	rs28371725		nd	400	1.9[a] (1.0-3.0)	142	8.5 (5.5-12.3)	160	12.5 (8.9-16.1)		na		na	Decreased
1xN		Gene Duplication	-	251	1.2 (0.4-2.5)	400	0.1 (0.006-0.7)	195	0	160	0.6 (0.08-2.2)		na		na	Increased
2xN (+ 2850C >T, 4180G> C)		Gene Duplication	-	193	1.6 (0.5-3.3)	400	0.5 (0.1-1.3)	195	1.5 (0.5-3.3)	160	1.6 (0.5-3.6)		na		na	Increased
4xN (+1846G> A)		Gene Duplication	-	251	0.3 (0.04-1.4)	400	0	195	0	160	0.3 (0.006-1.7)		na		na	None

Contd...

Gene and SNP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
10xN (+ 100C > T)		Gene Duplication	-		na	400	0.5 (0.1-1.3)	195	0	160	0		na		na	Decreased
41xN (+2988G> A)		Gene Duplication	-		na		na	142	0	160	0		na		na	Decreased
CYP2E1																
**1B* (9896C>G)	Intron 7	-	rs2070676	449	65.9[a,b] (62.8-69.0)	481	18.1[a,b] (15.7-20.5)	375	13.5 (11.0-15.9)	147	13.0 (9.1-16.8)	637	14.2 (12.3-16.1)		na	
**4* (4768G>A)	Exon 4	Val179Ile	rs6413419	449	17.5 (15.0-20.0)	481	0.1 (0.006-0.6)	389	2.8 (1.8-4.2)		na	132	0		na	Normal
**5B* (-1293G>C) (-1053C>T)	Promoter	-	rs2031920 rs3813867	449	4.3[a,b,c] (3.1-5.9)	359	14.0[a,b,c] (11.4-16.5)	1454	3.8[a,b,c] (3.2-4.6)	578	8.4[b,c] (6.8-10.1)	637	1.3[a] (0.8-2.1)	124	0.8[a] (0.1-2.9)	
**6* (7632T>A)	Intron 6	-	rs6413432	449	10.1[a,b,c] (8.2-12.1)	359	19.6[c] (16.7-22.5)	1360	7.7[a,b,c] (6.7-8.8)	147	17.7[c] (13.3-22.0)	636	22.2[c] (20.0-24.5)	124	0.8[a,b] (0.1-2.9)	
CYP3A4																
**1B* (-392A>G)	5'UTR	-	rs2740574	987	26.0[a] (24.1-27.9)	1382	0.1[a] (0.02-0.3)	135	7.0[a] (4.3-10.8)	509	1.2 (0.6-2.0)		na		na	
**2* (15713T>C)	Exon 7	Ser222Pro	rs55785340		0		na	95	0	100	0		na		na	
**4* (13871A>G)	Exon 5	Ile118Val	rs55951658		na	451	2.4 (1.5-3.7)		na	100	0		na		na	Decreased
**5* (15702C>G)	Exon 7	Pro218Arg	rs55901263		na	451	0.7 (0.2-1.4)		na	100	0		na		na	Decreased
**6* 17661insA)	Exon 9	Frameshift	rs4646438		na	387	0.5 (0.1-1.3)		na	100	0		na		na	Decreased
**10* (14304G>C)	Exon 6	Asp174His	rs4986908	21	2.4[+] (0.05-12.6)	86	0[+]	265	0.6[+] (0.2-1.6)	100	0		na		na	
CYP3A5																
**2* (27289C>A)	Exon 11	Thr398Asn	rs28365083	120	0[+]	265	0	500	1.0 (0.4-1.8)		na	544	0		na	Unknown

Contd...

Gene and SNP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
**3* (6986A>G)	Intron 3	Splicing defect	rs776746	203	15.0[a,b] (11.3-18.2)	434	80.6[a,b] (78.0-83.3)	500	91.6[a,b] (89.7-93.2)	308	68.2[b] (64.5-71.9)	762	56.0[a] (53.5-58.5)		na	None
**4* (14665A>G)	Exon 7	Gln200Arg	rs56411402	150	0[+]	265	0	500	0		na	544	0		na	
**6* (14690G>A)	Exon 7	Lys208Lys	rs10264272	194	14.2 (10.7-17.6)	194	0	500	0.1 (0.006-0.5)	208	0	544	0		na	None
-44A>G	Promoter	-			na	110	28.2 (22.2-34.1)	300	9.2[a] (7.0-11.8)	134	34.7 (29.0-40.4)		na		na	
GSTM1																
**0* (null)	-	Gene deletion	-	279	36.6[a,b] (30.9-42.2)	366	42.9[a,b,c] (37.8-48.0)	228	57.0[a,b,c] (50.6-63.4)	3463	30.6 (29.0-32.1)	1146	28.8[c] (26.2-31.4)	427	34.4[b] (29.9-38.9)	None
GSTT1																
**0* (null)	-	Gene deletion	-	279	41.6[c,b] (35.8-47.4)	366	49.2[c,b] (44.1-54.3)	228	19.7 (14.6-24.9)	3189	17.2 (15.9-18.6)	1296	14.8[c] (12.9-16.7)	427	19.7[b] (15.9-23.4)	None
GSTP1																
**B* (313A>G)	Exon 5	Ile105Val	rs1695	186	36.8[a,b,c] (31.9-41.7)	366	20.6[b] (17.7-23.6)	478	25.9[b] (23.2-28.7)	1525	23.8[b] (22.3-25.3)	451	14.6[a,c] (12.3-16.9)	290	21.7[b] (18.4-25.1)	Decreased
UGT1A1																
**28* (TA)6>7	Promoter	-	rs8175347	161	55.3 (49.8-60.7)	1083	13.1 (11.6-14.5)	314	29.6 (26.0-33.2)		na	450	39.7 (36.5-42.9)		na	Abolished activity
UGT1A7																
**2* (387T>G), (392G>A)	Exon 1	Asp129Lys; Arg131Lys	-	136	38.6 (32.8-44.4)	317	20.0[a] (16.9-23.1)	105	22.0[a] (16.3-27.5)	201	35.6 (30.9-40.3)		na		na	High
**3* (387T>G), (392G>A), (622T>C)	Exon 1	Asp129Lys; Arg131Lys; Arg208Trp	-	136	22.8[a] (17.8-27.8)	317	25.0[a] (21.6-28.3)	105	42.4 (35.7-49.1)	201	35.6 (30.9-40.3)		na		na	Decreased
**4* (622T>C)	Exon 1	Arg208Trp	rs1126802	136	0.7[a] (0.09-2.6)	317	0.5[a] (0.1-1.4)	105	0.5[a] (0.006-2.6)	201	3.2 (1.7-5.4)		na		na	Decreased
**12* (-57T>G)	Promoter	-	rs7586110		na			427	38.8 (35.5-42.0)	201	37.0 (32.6-42.0)		na		na	Decreased

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Gene and SNP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
TPMT																
**2* (238G>C)	Exon 5	Ala80Pro	rs1800462	250	0	327	0	1214	0.3 (0.09-0.5)	120	0	934	0.1 (0.02-0.4)		na	Decreased
**3A* (460G>A), (719A>G)	Exon 7 & 10	Ala154Thr; Tyr240Cys	rs1800460 rs1142345	250	0.2 (0.006-1.1)	327	0.3 (0.04-1.1)	1214	4.5[a] (3.7-5.5)	120	0.4 (0.006-2.3)	934	0		na	Abolished activity
**3B* (460G>A)	Exon 7	Ala154Thr	rs1800460	250	0	327	0	1214	0	120	0	934	0.1 (0.02-0.4)		na	Decreased
**3C* (719A>G)	Exon 10	Tyr240Cys	rs1142345	217	7.6[a,b] (5.3-10.5)	327	0.9 (0.3-2.0)	1214	0.4[a,b] (0.1-0.7)	120	2.1 (0.7-4.8)	934	1.1 (0.6-1.7)		na	Decreased
**8* (644G>A)	Exon 10	Arg215His	rs56161402	250	1.6 (0.7-3.1)	526	0	1214	0		na	608	0		na	Intermediate Activity
SULT1A1																
**2* (638G>A)	Exon 7	Arg213His	rs9282861	93	28.5 (22.0-35.0)	809	8.7[c,b] (7.3-10.1)	310	41.5[c,b] (37.6-45.3)		na	495	22.6 (20.0-25.2)	290	27.2 (23.6-30.9)	Decreased
COMT																
472G>A	Exon 4	Val158Met	rs4680	389	34.0[a,b] (30.6-37.3)	1191	27.5[a,b] (25.7-29.3)	445	48.5[b] (45.3-51.8)	421	49.0[b] (45.7-52.4)	606	41.6[a] (38.8-44.4)		na	Decreased
5289A>G	Intron 1	-	rs3788319		na		na		na		na	241	47.3 (42.8-51.8)		na	
4239T>C	Intron 1	-	rs737865	226	10.6[b,+] (7.8-13.5)	170	32.9[b+] (27.9-37.9)	224	32.6[b,+] (28.2-36.9)		na	236	24.8 (20.9-28.7)		na	
VS2 (98A>G)	Intron 2	-	rs6269		na		na	445	40.5 (37.2-43.7)		na	238	31.1 (26.9-35.3)		na	
186C>G	Exon 4	Leu136Leu	rs4818		na		na	224	39.8 (36.6-43.0)		na	236	32.0 (27.8-36.2)		na	
36C>T	Exon 3	His62His	rs4633	120	26.7[b,+] (21.1-32.3)	90	23.3[b+] (17.2-29.5)	445	51.5[b] (48.2-54.7)		na	240	44.0 (39.5-48.4)		na	
522G>A	3'UTR	-	rs165599		na		na	80	36.9 (29.4-44.4)		na	239	42.1 (37.6-46.5)		na	
NAT2																
**5* (341C>T)	Exon 2	Ile114Thr	rs56935242	127	47.2[b] (41.1-53.4)	441	6[b] (4.5-7.8)	729	43[b] (40.5-45.5)		na	166	30.0 (24.9-34.7)		na	Abolished activity
**6* (590G>A)	Exon 2	Arg197Gln	rs60190029	127	28.7[b] (23.2-34.3)	299	24.0[a,b] (20.5-27.3)	729	29.0[b] (26.7-31.3)	406	31.5 (28.3-34.7)	166	37.0 (31.9-42.2)	144	26.0[b] (21.0-31.1)	Decreased

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Gene and NP	Location	AA change	dbSNP ID	Allele frequency % (95% Confidence Interval)												Functional effect
				n	Africans[1]	n	Asians[1]	n	Caucasians[1]	n	NI*	n	SI*	n	NEI*	
**7* (857G>A)	Exon 2	Gly286Glu	rs1799931	127	3.1[a,b] (1.4-6.1)	237	15.2[b] (12.0-18.4)	729	3.0[a,b] (2.2-4.0)	406	13.3[b] (11.0-15.6)	166	25.0[a] (20.3-29.7)	144	11.1[b] (7.5-14.7)	Decreased
**11* (481C>T)	Exon 2	Leu161Leu	rs1799929	127	45.7[a,b] (39.5-51.8)	237	5.1[a,b] (3.3-7.5)	1312	46.0[a,b] (44.1-47.9)	406	29.2[b] (26.1-32.3)	166	22.0[a] (17.5-26.4)		na	Rapid acetylation
**12* (803A>G)	Exon 2	Arg268Lys	rs56599719rs 58999469	127	55.1[a,b] (49.0-61.2)	212	9.8[a,b] (7.0-12.9)	729	41.0[a,b] (38.5-43.5)	147	25.0 (19.6-29.4)	166	29.0 (24.0-33.8)		na	No Effect
**13* (282C>T)	Exon 2	Tyr94Tyr	rs1041983	127	33.4[b] (27.7-39.3)	441	30.5[b] (27.5-33.5)	729	32.0[b] (29.6-34.4)		na	166	44.0 (38.6-49.3)		na	Decreased
**14* (191G>A)	Exon 2	Arg64Gln	rs1801279	127	3.1 (1.4-6.1)	237	0	1312	1.3 (0.9-1.8)		na	166	0		na	Decreased
MDR1																
3435C>T	Exon 26	Ile1145Ile	rs1045642	206	16.5[a,b] (12.9-20.1)	288	38.4[a,b] (34.4-42.3)	488	49.0[a,b] (45.8-52.1)	977	53.6[b] (51.4-55.8)	821	59.5[a] (57.1-61.9)		na	Alters substrate specificity
2677G>T/A	Exon 21	Ala893Ser Ala893Thr Ala893Pro	rs2032582	111	0.9[a,b] (0.1-3.2)	207	58.5[a] (53.7-63.2)	461	43.5[a,b] (40.3-46.7)	739	42.4[b] (39.8-44.9)	714	60.0[a] (57.4-62.5)		na	Decreased Expression
1236C>T	Exon 12	Gly412Gly	rs1128503	111	15.0[a] (10.2-19.5)	207	65.2[a] (60.6-69.8)	461	41.0[a] (37.8-44.2)	734	51.9 (49.4-54.5)		na		na	Unknown
OCT1																
1022C>T	Exon 6	Pro341Leu	rs2282143	100	8.0 (4.6-12.7)	150	16.7[b] (12.4-20.9)	100	2.0[b] (0.5-5.0)		na	112	8.9 (5.5-13.5)		na	Decreased
1222A>G	Exon 7	Met408Val	rs628031	100	73.5 (67.4-79.6)	150	74.0 (69.0-79.0)	102	57.4[b] (50.6-64.1)		na	112	80.3 (75.2-85.6)		na	No alteration
1386C>A	Intron	-	rs622342	224	15.6[b,+] (12.3-19.0)	170	20.6[+] (16.3-24.9)	222	41.0[b,+] (36.4-45.6)		na	112	24.5 (18.9-30.2)		na	Unknown
SLCO1B1																
**1B* (388A>G)	Exon 4	Asn130Asp	rs2306283	366	87.0[a] (84.6-89.5)	267	64.0[a] (60.0-68.1)	423	37.0[a] (33.7-40.3)	270	45.0 (40.8-49.2)		nd		nd	Decreased
463C>A	Exon 4	Pro155Thr	rs11045819	226	6.2[a,+] (4.1-8.8)	90	1.1[+] (0.1-3.9)	120	15.0[a,+] (10.5-19.5)	173	2.6 (1.2-4.9)		nd		nd	No alteration
521T>C	Exon 6	Val174Ala	rs4149056	226	9.0[a,+] (6.6-12.1)	172	11.0[a,+] (7.7-14.4)	120	15.8[a,+] (11.2-20.5)	173	1.4 (0.5-3.3)		nd		nd	Decreased

DME, drug metabolizing enzymes; NI, North Indians; SI, South Indians; NEI, North East Indians; AA, aminoacid; na, not available; nd, not determined.

*;;Pooled mean allele frequency; n = total number of subjects; + HapMap data derived from NCBI dbSNP database; [a]$P<0.05$ compared with NI ; [b]$P<0.05$ compared with SI ; [c]$P<0.05$ compared with NEI ; [1]References: [67-74 for *CYP1A1* and *CYP1A2*, 13,76-78 for *CYP2A6*, 82-84 for *CYP2C8*, 87-89 for *CYP2C9*, 91-94 for *CYP2C19*,44, 97-100 for *CYP2D6*, 103, 104, 6 for *CYP2E1*, 13, 108-117 for *CYP3A4* and *CYP3A5*, 138-141, 124 for *GSTM1*, *GSTT1* and *GSTP1*, 12 for *UGT1A1* and *TPMT*, 145-148 for *UGT1A7*, 152, 153 for *SULT1A1*, 156-159 for *COMT*, 161 for *NAT2*, 172-174 for *MDR1*, 10 for *SLC22A1*, 181 for *SLCO1B1*]

prevalence of the defective allele *CYP2A6*4A* was higher in NI (11.3%), SI (8.9%) and Asians (11%) but significantly lower in Africans (0.5%) and Caucasians 3 per cent (P<0.0001). In contrast, the other variant *CYP2A6*2* was lower in SI (1%), Africans (0.3%), Caucasians (2.3%) and absent in Asians. Similarly, *CYP2A6*5* were lower in SI (0.7%), Asians (0.5%) and virtually absent in Africans and Caucasians (Table II)[13,76-78].

CYP2C8: The enzyme CYP2C8 comprises approximately 7 per cent of the total hepatic cytochrome system, which metabolizes around 5 per cent of drugs in phase I metabolism[64]. CYP2C8 plays significant role in metabolizing antidiabetics (troglitazone, pioglitazone, rosiglitazone & repaglinide), anticancer (paclitaxel), antihypertensive (veramapil), non-steroidal anti-inflammatory drugs (NSAID) (ibuprofen), 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor (cerivastatin), antimalarial (chloroquine, amodiaquine) and antiarrhythmic (amiodarone) drugs. Additionally, it is the principal enzyme responsible for the metabolism of retinoic and arachidonic acid in the kidneys[79]. The human *CYP2C8* gene which encodes CYP2C8 enzyme is localized in the long (q24.1) arm of the chromosome 10, consists of 9 exons and spans about 31 kilo base. *CYP2C8* gene exhibits several polymorphisms and so far, more than 20 polymorphisms have been reported in different populations[66]. Among them, the most commonly studied SNPs that lead to decreased enzyme activity are *CYP2C8*2* in exon 5 (805A>T, I269F), *CYP2C8*3* in exons 3 and 8 (416G>A/1196A>G, R139K/K399R), *CYP2C8*4* in exon 5 (792C>G, I264M) and *CYP2C8*5* (475delA). The enzymes encoded by these variant alleles impair the metabolism of several drug substrates of *CYP2C8*. Subjects who are homozygous (**2/*2* or **3/*3*) have lower intrinsic clearance of CYP2C8 substrates than those who are heterozygous (**1/*2* or **1/*3*). Further, the polymorphisms of *CYP2C8* have been associated with diseases such as myocardial infarction (MI) [80]. The only study which determined the frequency distribution of *CYP2C8* alleles in any of the Indian population was carried out in SI Tamilians[11] with a frequency of about 0.8 per cent (95% CI 0.2-2.1) and 2.9 per cent (95% CI 1.6-4.7) for *CYP2C8*2 and **3*, respectively (Table I). Population studies from around the world in different populations indicate that *CYP2C8*2* variant is rare in SI and Caucasians, whereas it is a common variant among Africans. Allele *CYP2C8*3* is a common variant in Caucasians while it occurs either at small frequency or not present in SI and Africans. With regard to Asians subjects, the *CYP2C8* polymorphism was monomorphic for *CYP2C8*1* allele (Table II)[81,83].

CYP2C9: Drugs undergoing oxidative metabolism such as S-warfarin, rosiglitazone, tolbutamide, phenytoin, glyburide, glibenclamide, glimepiride, glipizide, losartan, irbesartan, torsemide, tamoxifen, fluvastatin, fluoxetine, amitriptyline and other commonly used anti-inflammatory drugs (diclofenac, ibuprofen, naproxen, piroxicam, aceclofenac, celecoxib) have been described to be principally metabolized by CYP2C9[84-86]. It is encoded by the gene *CYP2C9*, which is located on chr10q24.2. Among the CYP2C isoforms, CYP2C9 is the most abundant one and constitutes about 20 per cent of total CYP450 hepatic content[85]. The gene *CYP2C9* is known to be polymorphic and inter-individual differences in the enzyme activity of CYP2C9 categorize subjects into EMs, IMs and PMs. Currently, 41 different variant alleles are known for *CYP2C9* gene[66]. Among the many variants, *CYP2C9*2* (430C>T, Arg144Cys) in exon 3 and *CYP2C9*3* (1075A>C, Ile359Leu) in exon 7 are the most characterized alleles and individuals with these variant alleles are reported to have decreased CYP2C9 activity. These variants are reported to be associated with acute MI, hypertension, colorectal cancer and major depressive disorders; also with certain adverse drug reactions including gingival hyperplasia, hypoglycaemia and gastrointestinal bleeding. In addition, a number of other alleles such as *CYP2C9*5* (1080C>G, D360E), **6* (818Adel), **9* (752A>G, H251R), **11* (1003C>T, R335W) and **12* (1465C>T, P489S) may cause impaired metabolism, which may give rise to life threatening drug toxicity and may have impact on drug metabolism and disease susceptibility[64,66,84]. The prevalence of *CYP2C9*2* was significantly different between NI and SI (9% *vs.* 3.6%, P<0.0001)[7,44-47], whereas *CYP2C9*3* (9.7% *vs.* 8%) allele was equally distributed among the Indian populations (Table I). With regard to *CYP2C9*2*, NI showed similarity with Caucasians but difference with Africans (P<0.0001)[44-47,87,88]. In contrast, the SI showed similarity with Africans but different from Caucasians (P<0.0001). Indians had higher frequency of *CYP2C9*3*, as compared to Africans and Asians (P<0.0001) but no difference was observed with Caucasians (Table II)[87-89].

CYP2C19: CYP2C19 is a polymorphically expressed CYP450 enzyme, constitutes about 16 per cent of the CYP2C family in liver and it is encoded by the gene *CYP2C19* located on chr10q24. It is involved

in the metabolism of a broad range of clinically important drugs including antimalarial (proguanil), oral anticoagulants R-warfarin, anti-epileptics (S-mephenytoin, diazepam, phenobarbitone), antivirals (nelfinavir), antiplatelets (clopidogrel), chemotherapeutic agents (cyclophosphamide), proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole) as well as several antidepressants (amitriptyline, clomipramine)[64,90]. Upto now, 35 polymorphisms have been identified. The frequencies of these alleles in different ethnic populations were extremely variable. Carriers of the non-functional alleles such as *CYP2C19*2* in exon 5 (681G>A) and *CYP2C19*3* in exon 4 (636G>A) have diminished ability to metabolize therapeutic agents that are substrates of CYP2C19[66,84]. The *CYP2C19*2* allele notably occurred at a higher frequency among the Indian populations (NI 33.1% and SI 36.8%) than Africans 16 per cent, Caucasians 13.3 per cent and slightly higher than Asians 28.4 per cent (P<0.001). The *CYP2C19*3* alleles in Indians were 1.9 and 1.1 per cent in NI and SI, respectively (Table I). Marked inter- and intra-ethnic variations were observed among the Indian populations (P<0.05) and as compared to other major ethnics such as Asians and Caucasians (P<0.001) individually with regard to the distribution of the polymorphic allele *CYP2C19*3*[7,44,49-52,91-93]. On the other hand, a novel variant allele in the regulatory region defined as *CYP2C19*17* (-806C>T, -340C>T) increases the activity of *CYP2C19* protein resulting in ultrarapid metabolism of *CYP2C19* substrates[66]. The ultrarapid metabolizer *CYP2C19*17* was studied only in SI Tamilians[14] with a frequency of about 19.2 per cent (Table I). The comparison of SI subjects with Asian individuals indicates significant difference in UM allele, P<0.0001 (Table II)[91-94].

CYP2D6: Cytochrome P450 2D6 (CYP2D6) is responsible for the metabolism of clinically important drugs, namely anticancer, antiarrhythmic, antihistamines, antipsychotics, β-blockers, opioids, antihypertensives and antidepressants. Of the total CYP450 content, CYP2D6 constitutes approximately 2-4 per cent and involved in the elimination of 25 per cent currently prescribed drugs[95,96]. The *CYP2D6* gene consists of 9 exons and 8 introns and is located on chromosome 22q13.2. The sequence of *CYP2D6* is highly polymorphic. Up till now, over 135 allelic variants have been reported and *CYP2D6*2* (2850C>T;4180G>C) in exon 2 and 6, **3* (2549delA) in exon 5, **4* (1846G>A in intron 3 - exon 4 junction), **5* (whole gene deletion), **10* in exon 1(188C>T, P34S), **14* (1758G>A), **17* (1023C>T; 2850C>T) in exon 2 and **41* (2988G>A) variants were the most characterized alleles of *CYP2D6*[66]. The frequencies of the defective alleles in different races vary widely. Apart from PMs, IMs individuals also had been classified as UMs of *CYP2D6* substrates depending upon the presence of *CYP2D6* allele combinations. PMs are those who carry two defective alleles (inactive enzyme), resulting in increased concentrations of the parent drug in plasma, whereas in the case of UMs, as a result of gene duplication individuals carry more than two copies of the functional gene leading to increased enzyme activity, resulting in decreased parent drug concentration in blood[96].

The dosage recommendation is based upon the *CYP2D6* genotype for drugs that are substrates of CYP2D6 in order to avoid both treatment failure and adverse drug reaction. Of the five variants which contribute to the loss of CYP2D6 activity (**3,*4, *5, *6* and **14*), only **14* was not detected in Indian populations. Similarly, the other variants (**9*, **17* and **29*) leading to diminished enzyme activity were also not found in Indians. The functional allele *CYP2D6*2* was most prevalent in Indians which was found at comparable frequencies between NI (29.3%) and SI (34.8%). Both the Indian populations showed significant difference compared with Asians and Caucasians (P<0.0001, Table II)[8,44,53]. Although the NI showed similarity with Asians, SI showed significant difference (P<0.0001). The *CYP2D6*3* allele was found only in NI 9.2 per cent (95% CI 6.9-11.8) and it was absent in SI. Its frequency in NI was significantly higher as compared to Africans 0.4 per cent, Asians 1 per cent and Caucasians 2.8 per cent (P<0.0001)[8,44,45,97-100]. Likewise, the polymorphism *CYP2D6*5* which leads to gene deletion was determined with a frequency of about 1.9 and 1.8 per cent in NI and SI, respectively. It was significantly lower than those observed in Africans 6.6 per cent, Asians 7 per cent and Caucasians 6.9 per cent (P<0.0001). On the other hand, *CYP2D6*4* was evenly distributed in SI (7.3%), NEI (8.7%) and Africans (6.8%), while it was higher in NI (11.5%) and Caucasians (14%) and lower in Asians (4%), (P<0.0001) (Table II)[8,30,35,37,44-46,54]. The occurrence of the *CYP2D6* allele **10* which confers partially decreased activity, was found at higher frequencies (27.2%) in NI than (10.2%) SI and the difference was significant (P<0.0001). With regard to *CYP2D6*10*, both the Indian populations showed significant difference when compared with other populations, P<0.001 (Table II)[8,23,44,46,54,55]. The frequency of allele **41* showed

high frequency in NI 12.5 per cent, Caucasians 8.5 per cent and lower in Asians 1.9 per cent (P<0.0001). The active gene duplication alleles of *CYP2D6* were studied only in NI Gujarati population[44]. Alleles associated with ultra-rapid metabolism (*1xN* and *2xN*) and loss of enzyme activity (*4xN*) were found at fewer frequencies in NI and major ethnics. On the contrary, abridged activity alleles (*10xN* and *41xN*) were absent in NI (Table II)[44,97-100].

CYP2E1: CYP2E1 is toxicologically important enzyme, which is present mostly in liver, and at lower levels in several extrahepatic tissues. Its levels are increased during fasting, diabetes, and exposure to alcohol. It catalyses the bioactivation of several procarcinogens and protoxins including N-nitrosodimethylamine, styrene, benzene and N-alkylformamides and also chlorzoxazone, acetaminophen, and the volatile anaesthetics (enflurane, sevoflurane, halothane, methoxyflurane and isoflurane) drugs[101]. The gene encoding CYP2E1 protein is located on chr10q26.3 and until now 12 different SNPs have been reported[66]. The polymorphisms of *CYP2E1* have been linked to many chemically induced cancers and to alcoholic liver disease, in particular liver cirrhosis. Any functional polymorphism of this enzyme might be an important factor in determining the relative risk of alcohol-mediated hepatotoxicity, cancer or susceptibility to drug toxicity[102]. Polymorphic alleles with mutation in intron 7 *CYP2E1*1B*, in the 5'flanking region *CYP2E1*5B* (C1/C2, Rsa I) and intron 6 *CYP2E1*6* (C/D, Dra I) are the common variants associated with altered gene function and expression. Their prevalence has been related to the occurrence of alcoholic liver disease and lung cancer. The frequency of *CYP2E1*1B* was equally distributed in NI, SI and Caucasians, while it was significantly higher in Asians, 18.1 per cent (P<0.05) and relatively highest in Africans, 65.9 per cent (P<0.001)[6,13,56,103,104]. With regard to *CYP2E1*5B*, similarity was observed between SI and NEI[59] (1.3% *vs.* 0.8%) but different in NI, 8.4 per cent (P<0.001). Likewise, similarity was observed between NI and SI (17.7% *vs.* 22.2%) but different in NEI[59], 0.8 per cent (P<0.001) with respect to *CYP2E1*6* (Table II). The frequency of *CYP2E1*5B* in NI was different from other ethnic populations whereas **6* was similar to Asians but different from Africans and Caucasians (P<0.0001). The SI were different from other major populations (P<0.0001) for *CYP2E1*5B* but similar to Asians and different when compared with Africans and Caucasians for *CYP2E1*6* (P<0.0001). The comparison of the frequency of *CYP2E1*5B* and **6* alleles in NEI with other ethnicities indicates significant dissimilarity (P<0.01)[6,103,104].

CYP3A (CYP3A4 & CYP3A5): The CYP3A isoenzymes metabolizes about 50-60 per cent of all currently prescribed drugs. Its subfamily consists of homologous proteins encoded by four different CYP3A genes namely *CYP3A4, CYP3A5, CYP3A7* and *CYP3A43*[105]. These are located adjacent to each other on chromosome 7q21. Among these, CYP3A4 is the largest portion of CYP3A protein present in the adult liver and its catalytic activity may show up to 90 fold variation. Till now, 41 *CYP3A4* alleles have been identified and characterized[66], Out of these **1B* (4713G>A) is the only defining variant of *CYP3A4* reported at present. Subjects carrying the defective alleles of *CYP3A4* have been implicated in disease predisposition to prostate cancer, estrogen receptor negative breast cancer and type 2 diabetes mellitus[106]. The frequency of *CYP3A4*1B* was available in NI (1.2%) only and the comparison between NI and other populations indicates significant variations (P<0.01)[60,61]. The other *CYP3A4* variants such as **2, *4, *5, *6* and **10* were not detected in NI[60] (Table I). On the contrary, CYP3A5 is polymorphically expressed in about 10-30 per cent adult livers and along with CYP3A4, metabolizes >50 per cent of currently used drugs. It shares about 85 per cent of amino acid sequence identity with CYP3A4 but it has different degrees of catalytic activity and regioselectivity towards substrates[105]. Kuehl *et al*[107] have demonstrated that at least one *CYP3A5*1* allele is needed for expressing CYP3A5 protein. They have identified *CYP3A5*3* (A to G at 6986) in intron 3 and *CYP3A5*6* (G to A at 14690) in exon 7, which led to the absence of CYP3A5 protein 6986A allele (*CYP3A5**1) was before correlated with high expression[107]. Further, two more variants in the coding regions *viz.*,**2* (27289C>A, Thr398Asn) in exon 12 and **4* (14665A>G, Gln200Arg) in exon 8 were identified. CYP3A5 may represent upto 50 per cent of the total hepatic CYP3A content in people expressing *CYP3A5*[105,106]. This gene may be an important contributor to individual and inter-racial variation in CYP3A mediated metabolism of drugs including antipsychotics (olanzapine), antiestrogen (tamoxifen), anticancer (irinotecan, docetaxel, vincristine), antimalarial (mefloquine, artemether, lumefantrine), immunomodulators (tacrolimus, cyclosporine), antihistamines (chlorpheniramine, terfenadine, astemizole), antiplatelets (clopidogrel), antihypertensives (nifedipine, amlodipine, felodipine,

verapamil), antivirals (indinavir, nelfinavir, ritonavir, saquinavir), HMG-CoA reductase inhibitors (atorvastatin, cerivastatin, lovastatin) antibiotics (clarithromycin) and steroids (testosterone, estradiol, progesterone and androstenedione).

The presence of non-functional polymorphic alleles of *CYP3A5* has been associated with blood pressure, MI, breast cancer and acute myeloid leukemia (AML) or ALL[106]. In Indians, *CYP3A5*3* is the only variant allele present in NI and SI. None of the other variants **2, *4* and **6* were identified in Indians (Table I). The frequency of *CYP3A5*3* in SI 56 per cent (95% CI 53.5-58.5) was significantly different (P<0.0001), as compared to NI 68.2 per cent (95% CI 64.5-71.9). Similarly, both the Indian populations were statistically different compared with Caucasians 91.6 per cent, Asians 80.6 per cent and Africans 15 per cent (P<0.0001)[13,61-63]. Further, a promoter polymorphism -44A>G was observed only in NI[45] 34.7 per cent which was higher than Caucasians 9.2 per cent (P<0.0001) and similar to Asians 28.2 per cent (Table II)[108-117].

Phase II enzymes

Phase II enzymes are involved in sulphation, acetylation, conjugation and glucuronidation reactions which may lead to the excretion of drugs by increasing the hydrophilicity of the substrate or deactivation of highly reactive substrates. Glutathione S-transferases (GSTs), N-acetayltransferases 1 and 2 (NAT1 and NAT2), thiopurine S-methyltranferase (TPMT), uridine disphosphate glucoronosyl transferases (UGTs), catechol methyl trasferase (COMT) and sulphotransferases (SULT) are the main phase II enzymes[118]. Table III illustrates the allele frequency distribution of phase II enzymes in various Indian populations[5,6,12,19,20,27,30,32-37,,53,56,119-135].

GST (GSTM1, GSTT1 & GSTP1): The polymorphic cytosolic glutathione S-transferase (GST) isoenzymes GSTM1, GSTT1 and GSTP1 are the predominant class of phase II drug metabolizing enzymes. The chromosome location of the genes encoding GSTM1 (mu), GSTT1 (theta) and GSTP1 (pi) are chr1p13.3, chr22q11.2 and chr11q13.2, respectively. They play a significant role in the biotransformation and detoxification of a wide range of xenobiotics and endogenous substances including carcinogens (halomethanes and methyl bromide). GSTs protect cells against reactive oxygen metabolites by the conjugation of glutathione with electrophilic compounds[136,137]. Both the genetic polymorphisms and expression pattern of GST genes may have a major impact on cancer susceptibility, inter-individual variability in the prognosis, drug effects and toxicity[137]. Of all the human GSTs, GSTM1 and GSTT1 isoenzymes are highly polymorphic. Those who carry the respective null genotypes termed as *GSTM1*0/*0* and *GSTT1*0/*0* due to homozygous gene deletions do not have these enzymes. On the other hand, single base pair substitution 313A>G of *GSTP1* (Ile105Val) in exon 5 marks reduced enzyme activity. In addition, individually or in combination the null genotypes of *GSTM1* and *GSTT1* genes increase the risk of gastric, colon, bladder and lung cancers[137].

The frequencies of *GSTM1* and *GSTT1* null alleles were found to be 30.6 and 16.7 per cent in NI; 28.8 and 14.8 per cent in SI and 34.4 and 19.7 per cent in NEI[5,19,20,27,29,30,32,34-37,119-125]. On the whole, a general uniformity was observed between NI *vs.* SI and NI *vs.* NEI with regard to *GSTM1* and *GSTT1* null polymorphisms. Conversely, it was significantly different between SI and NEI (P<0.04)[5,30,32,34-36,124,125]. The frequency distribution of *GSTM1* null variant in Indian populations was significantly different from Africans, Asians and Caucasians (P<0.03). Similarly, the frequency of *GSTT1* null polymorphism in SI was in line with NI and different from NEI (P<0.01)[5,19,27,29,30,32,34-37,119-121,123-125]. Further, its frequency in Indian populations was significantly less prevalent as compared to Africans and Asians (P<0.001), but showed similarity with Caucasians (Table II). The *GSTP1* 105Val allele was equally distributed at a frequency of 23.8 and 21.7 per cent in NI and NEI, respectively (Table III). However, it was significantly different in SI 14.6 per cent (P<0.001), as compared to NI, NEI, Africans (36.8%), Asians (20.6%) and Caucasians (25.9%)[6,29,30,36,37,121,124,126,127]. Likewise, a significant difference was observed in Africans (P<0.0001) as compared to NI and NEI. As the distribution of *GSTM1*0* (null), *GSTT1*0* (null) and *GSTP1* (105Val) alleles occurs at high frequencies in different populations, their genotyping becomes necessary (Table II)[124,138-141].

UGT1A1: The uridine diphosphate glucuronosyl transferase1A1 (UGT1A1) is a major phase II drug metabolizing enzyme belonging to UGT1A family. It is of major importance in the conjugation and subsequent elimination of potentially toxic xenobiotics, carcinogens and drugs. UGT1A1 catalyzes glucoronidation of a variety of compounds including estrogens, bilirubin and therapeutic drugs[142,143]. Genetic polymorphism has been described for six of the 16 functional human

Table III. Distribution of genes encoding phase II drug metabolizing enzymes (DME) allele frequencies in different Indian populations

Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	References
GSTM1	*Null*	NI	Total*	3463	30.6 (29.0-32.1)	
			Chandigarh	76	31.6 (21.4-43.4)	19
			Chandigarh	201	26.4 (20.3-32.5)	20
			Srinagar, Kashmir	195	40.5 (33.6-47.4)	29
			Mumbai, Maharashtra	727	37.0 (33.5-40.5)	27
			Delhi	309	21.0 (16.5-25.6)	119
			Eastern Uttar Pradesh	300	28.0 (22.9-33.1)	37
			Lucknow, Uttar Pradesh	200	36.5 (29.8-43.2)	120
			Lucknow, Uttar Pradesh	500	32.0 (27.9-36.1)	121
			Orissa	72	24.0 (14.4-35.1)	122
			Western Central India	883	26.6 (23.7-29.5)	123
		SI	Total*	1146	28.8 (26.2-31.4)	
			Andhra Pradesh	115	33.0 (24.4-41.6)	5
			Chennai, Tamil Nadu	255	22.4 (17.2-27.5)	124
			Hyderabad, Andhra Pradesh	63	36.5 (24.7-49.6)	30
			Karnataka	110	36.4 (27.4-45.4)	5
			Kerala	122	31.9 (23.7-40.2)	5
			Puducherry and Tamil Nadu	170	23.5 (17.2-29.9)	5
			Thiruvananthapuram, Kerala	146	26.7 (19.5-33.9)	125
			Thiruvananthapuram, Kerala	165	32.7 (25.6-39.9)	32
		NEI	Total*	427	34.4 (29.9-38.9)	
			Kolkata, West Bengal	137	24.8 (17.6-32.1)	35
			Gangtok, Sikkim	290	39.0 (33.4-44.6)	36
GSTT1	*Null*	NI	Total*	3189	17.2 (15.9-18.6)	
			Chandigarh	76	14.5 (7.4-24.4)	19
			Delhi	309	27.4 (22.5-32.5)	119
			Eastern Uttar Pradesh	300	15.0 (11.0-19.0)	37
			Srinagar, Kashmir	195	25.1 (19.0-31.2)	29
			Lucknow, Uttar Pradesh	200	14.0 (9.2-18.8)	120
			Lucknow, Uttar Pradesh	500	20.6 (17.1-24.1)	121
			Mumbai, Maharashtra	726	16.0 (13.1-18.3)	27
			Western Central India	883	13.0 (10.8-15.2)	123
		SI	Total*	1296	14.8 (12.9-16.7)	
			Andhra Pradesh	115	13.0 (6.8-19.2)	5

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Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	References
			Chennai, Tamil Nadu	255	17.6 (13.0-22.3)	124
			Chennai, Tamil Nadu	150	13.3 (7.8-18.8)	34
			Hyderabad, Andhra Pradesh	63	17.5 (9.0-29.1)	30
			Karnataka	110	19.1 (11.7-26.4)	5
			Kerala	122	15.6 (9.1-22.0)	5
			Puducherry and Tamil Nadu	170	18.8 (12.9-24.7)	5
			Thiruvananthapuram, Kerala	146	9.0 (4.8-14.7)	125
			Thiruvananthapuram, Kerala	165	9.7 (5.6-15.3)	32
		NEI	Total*	427	19.7 (15.9-23.4)	
			Kolkata, West Bengal	137	8.0 (4.0-13.9)	35
			Gangtok, Sikkim	290	25.2 (20.2-30.2)	36
GSTP1	**B*	NI	Total*	1525	23.8 (22.3-25.3)	
			Eastern Uttar Pradesh	300	20.1 (17.0-23.4)	37
			Srinagar, Kashmir	160	15.6 (11.6-19.6)	126
			Srinagar, Kashmir	195	23.8 (19.6-28.1)	29
			Lucknow, Uttar Pradesh	370	30.5 (27.2-33.9)	127
			Lucknow, Uttar Pradesh	500	23.5 (20.9-26.1)	121
		SI	Total*	451	14.6 (12.3-16.9)	
			Chennai, Tamil Nadu	255	22.0 (10.8-38.3)	124
			Hyderabad, Andhra Pradesh	63	27.0 (19.2-34.7)	30
			Puducherry and Tamil Nadu	133	32.7 (27.1-38.3)	6
		NEI	Total*	290	21.7 (18.4-25.1)	
			Gangtok, Sikkim	290	21.7 (18.4-25.1)	36
UGT1A1	**28*	SI	Total*	450	39.7 (36.6-43.0)	
			Gulbarga, Karnataka	124	29.0 (23.4-34.7)	12
			Kakinada, Andhra Pradesh	107	32.2 (26.0-38.5)	12
			Puducherry and Tamil Nadu	106	52.8 (46.1-59.6)	12
			Thiruvananthapuram, Kerala	113	46.5 (40.0-53.0)	12
UGT1A7	**2*	NI	Total*	201	35.6 (30.9-40.3)	
			Chandigarh	201	35.6 (30.9-40.3)	128
	**3*	NI	Total*	201	35.6 (30.9-40.3)	
			Chandigarh	201	35.6 (30.9-40.3)	128
	**4*	NI	Total*	201	3.2 (1.7-5.4)	
			Chandigarh	201	3.2 (1.7-5.4)	128

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Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	References
	-57T>G	NI	Total*	201	37.0 (32.6-42.0)	
			Chandigarh	201	37.0 (32.6-42.0)	128
TPMT	**2*	NI	Total*	120	0	
			Delhi	120	0	12
		SI	Total*	934	0.1 (0.02-0.4)	
			Gulbarga, Karnataka	161	0	12
			Kakinada, Andhra Pradesh	158	0	12
			Manipal, Karnataka	326	0.3 (0.04-1.1)	129
			Puducherry and Tamil Nadu	112	0	12
			Thiruvananthapuram, Kerala	177	0	12
	**3A*	NI	Total*	120	0.4 (0.006-2.3)	
			Delhi	120	0.4 (0.006-2.3)	12
		SI	Total*	934	0	
			Gulbarga, Karnataka	161	0	12
			Kakinada, Andhra Pradesh	158	0	12
			Manipal, Karnataka	326	0	129
			Puducherry and Tamil Nadu	112	0	12
			Thiruvananthapuram, Kerala	177	0	12
	**3B*	NI	Total*	120	0	
			North India	120	0	12
		SI	Total*	934	0.1 (0.02-0.4)	
			Gulbarga, Karnataka	161	0	12
			Kakinada, Andhra Pradesh	158	0	12
			Manipal, Karnataka	326	0.3 (0.04-1.1)	129
			Puducherry and Tamil Nadu	112	0	12
			Thiruvananthapuram, Kerala	177	0	12
	**3C*	NI	Total*	120	2.1 (0.7-4.8)	
			North India	120	2.1 (0.7-4.8)	12
		SI	Total*	934	1.1 (0.6-1.7)	
			Gulbarga, Karnataka	161	0.9 (0.2-2.7)	12
			Kakinada, Andhra Pradesh	158	1.9 (0.7-4.1)	12
			Manipal, Karnataka	326	0.8 (0.2-1.8)	129
			Puducherry and Tamil Nadu	112	1.3 (0.3-3.8)	12
			Thiruvananthapuram, Kerala	177	0.8 (0.2-2.4)	12

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Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	References
	**8*	SI	Total*	608	0	
			Gulbarga, Karnataka	161	0	12
			Kakinada, Andhra Pradesh	158	0	12
			Puducherry and Tamil Nadu	112	0	12
			Thiruvananthapuram, Kerala	177	0	12
SULT1A1	**2*	SI	Total*	495	22.6 (20.0-25.2)	
			Manipal, Karnataka	128	48.0 (41.5-53.8)	130
			Thiruvananthapuram, Kerala	367	13.9 (11.4-16.4)	33
		NEI	Total*	290	27.2 (23.6-30.9)	
			Gangtok, Sikkim	290	27.2 (23.6-30.9)	36
COMT	rs4680	NI	Total*	421	49.0 (45.7-52.4)	
			Delhi	255	53.0 (48.6-57.3)	131
			Lucknow, Uttar Pradesh	166	43.0 (37.7-48.4)	132
		SI	Total*	606	41.6 (38.8-44.4)	
			Bangalore, Karnataka	239	43.9 (39.5-48.4)	33
			Thiruvananthapuram, Kerala	367	40.0 (36.5-43.6)	33
	rs4818	SI	Total*	236	32.0 (27.8-36.2)	
			Bangalore, Karnataka	236	32.0 (27.8-36.2)	133
	rs4633	SI	Total*	240	44.0 (39.5-48.4)	
			Bangalore, Karnataka	240	44.0 (39.5-48.4)	133
	rs6269	SI	Total*	238	31.1 (26.9-35.3)	
			Bangalore, Karnataka	238	31.1 (26.9-35.3)	133
	rs737865	SI	Total*	236	24.8 (20.9-28.7)	
			Bangalore, Karnataka	236	24.8 (20.9-28.7)	133
	rs165599	SI	Total*	239	42.1 (37.6-46.5)	
			Bangalore, Karnataka	239	42.1 (37.6-46.5)	133
	rs3788319	SI	Total*	241	47.3 (42.8-51.8)	
			Bangalore, Karnataka	241	47.3 (42.8-51.8)	133
NAT2	**5*	SI	Total*	166	30.0 (24.9-34.7)	
			Thiruvananthapuram, Kerala	166	30.0 (24.9-34.7)	134
	**6*	NI	Total*	406	31.5 (28.3-34.7)	
			Delhi	147	37.0 (31.6-42.6)	56
			Delhi	134	25.4 (20.2-30.6)	135
			Lucknow, Uttar Pradesh	125	31.6 (25.8-37.4)	53

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Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	References
		SI	Total*	166	37.0 (31.9-42.2)	
			Thiruvananthapuram, Kerala	166	37.0 (31.9-42.2)	134
		NEI	Total*	144	26.0 (21.0-31.1)	
			Kolkata, West Bengal	144	26.0 (21.0-31.1)	35
	**7*	NI	Total*	406	13.3 (11.0-15.6)	
			Delhi	147	7.0 (4.4-10.7)	56
			Delhi	134	22.8 (17.7-27.8)	135
			Lucknow, Uttar Pradesh	125	10.4 (6.6-14.2)	53
		SI	Total*	166	25.0 (20.3-29.7)	
			Thiruvananthapuram, Kerala	166	25.0 (20.3-29.7)	135
		NEI	Total*	144	11.1 (7.5-14.7)	
			Kolkata, West Bengal	144	11.1 (7.5-14.7)	35
	**11*	NI	Total*	406	29.2 (26.1-32.3)	
			Delhi	147	31.3 (26.0-36.6)	56
			Delhi	134	31.3 (25.8-36.9)	135
			Lucknow, Uttar Pradesh	125	24.4 (19.1-29.7)	53
		SI	Total*	166	22.0 (17.5-26.4)	
			Thiruvananthapuram, Kerala	166	22.0 (17.5-26.4)	134
	**12*	NI	Total*	147	25.0 (19.6-29.4)	
			Delhi	147	25.0 (19.6-29.4)	56
		SI	Total*	166	29.0 (24.0-33.8)	
			Thiruvananthapuram, Kerala	166	29.0 (24.0-33.8)	134
	**13*	SI	Total*	166	44.0 (38.6-49.3)	
			Thiruvananthapuram, Kerala	166	44.0 (38.6-49.3)	134
	**14*	SI	Total*	166	0	
			Thiruvananthapuram, Kerala	166	0	134

DME, drug metabolizing enzymes; n, total number of subjects; NI, North Indians; SI, South Indians; NEI, North East Indians; CI, Confidence Interval; *Total number of subjects analyzed and the mean allele frequency values for every geographical region. The mean value may not sum 1 because the number of subjects analyzed for each SNP in a region may vary

UGT genes characterized to date, namely *UGT1A1*, *1A6*, *1A7*, *2B4*, *2B7* and *2B15*[142]. Polymorphisms of *UGT1A1* gene causes decrease in enzyme activity which ultimately results in interpatient differences in the pharmacokinetics of irinotecan, an anticancer drug[143]. Human UGT1A1 enzyme is encoded by *UGT1A1* gene, which is located on chromosome 2q37 and spans about 160 kb[143]. To date, more than 50 variants in the promoter and coding regions of *UGT1A1* gene are known to disrupt enzyme activity. The most common being *UGT1A1* (TA) 6>7 (*UGT1A1**28) polymorphism in the TATA element of the 5'promoter region. It is characterized by (TA) 7 repeats instead of more common (TA) 6 repeats, resulting in lower promoter activity. It

is the genetic basis for several clinical conditions such as, mild unconjugated hyperbilirubinemia associated with reduced hepatic bilirubin glucuronidation (Gilbert syndrome) and irinotecan mediated toxicity[142,143]. Irinotecan, an inhibitor of intracellular topoisomerase-I is metabolized to form active SN-38, which is further conjugated and detoxified by UGT1A1 enzyme[143]. The only study which determined the frequency of *UGT1A1**28 in native Indians was carried out in SI[12] namely, Andhra Pradesh 32.2 per cent, Karnataka 29 per cent, Kerala 46.5 per cent and Tamil Nadu 52.8 per cent (Table III). Significant differences in the frequencies of this variant were observed in SI 39.7 per cent, as compared to Africans 55.3 per cent, Asians 13.1 per cent and Caucasians 29.6 per cent, $P<0.0001$ (Table II)[12].

UGT1A7: The uridine 5'-diphosphate-glucuronosyltransferase 1A7 (UGT1A7) is an extrahepatic phase II DME expressed in pancreas, lung, stomach, oropharynx and oesophagus. It catalyzes the glucoronidation and detoxification of a wide variety of endogenous and exogenous compounds such as bilirubin, drugs, steroid hormones, phenols, coumarin and environmental carcinogens including nitrosamines and benzo[a]pyrene present in tobacco[142,144]. The gene *UGT1A7* is highly polymorphic and localized on chromosome 2q37 and 11 missense variants have been characterized till now. The common being *UGT1A7*1* (N129 R131 W208), *UGT1A7*2* (K129-K131-W208), *UGT1A7*3* (K129-K131-R208), and *UGT1A7*4* (N129-R131-R208)144,145. Population epidemiological studies have suggested that individuals carrying *UGT1A7* genetic variations which confer low detoxification activity are associated with the development of cancer of the liver, colon, oral, gastrointestinal, pancreas and chronic pancreatitis[144]. The frequencies of *UGT1A7* gene polymorphisms were available only in NI[128] which have not been studied in other Indian populations (Table III). Overall, the variant of *UGT1A7* seems to be more common in NI. The *UGT1A7* 2, *3* and *4* alleles shows significant interethnic variability as compared to Africans, Asians and Caucasians ($P<0.01$). In contrast, no interethnic differences were observed for *UGT1A7*12* polymorphism (Table II)[145-148].

TPMT: The gene thiopurine S-methyltransferse (*TPMT*) encodes the cytosolic enzyme TPMT which catalyzes S-methylation of thiopurine drugs such as 6-mercaptopurine (6-MP), azathioprine (AZA) and 6-thioguanine (6-TG). These drugs are commonly used for the treatment of ALL, autoimmune disorders, dermatological conditions and as an immunosuppressant in graft transplantations[149]. Polymorphism of *TPMT* alters the enzymatic activity of TPMT which is a major factor influencing interindividual differences in toxicity and therapeutic efficacy of thiopurine drugs. The TPMT enzyme activity in erythrocytes shows trimodal distribution in Caucasians[149]. Individuals with *TPMT*1/*1* wild type show high enzyme activity (89-94%), while carriers of heterozygotes and homozygotes of *TPMT* mutant alleles show intermediate (6-11%) and low enzyme activity (33%) respectively. In contrast, Southeast Asians have unimodal distribution, which is perhaps due to the absence or low frequency of *TPMT*3A*[149].

The gene *TPMT* has 10 exons spreading over 27kb of genomic DNA on chromosome 6p22.3[149]. Till date, more than 24 polymorphisms have been reported for *TPMT* gene. Amongst these, *TPMT*2* (238G>C), **3A* (460G>A and 719A>G), **3B* (460G>A) and **3C* (719A>G) are the four major variant alleles that cause 80-95 per cent intermediate and low enzyme activity. Carriers of theses alleles have been shown to have clinical implications with respect to metabolism, toxicity and therapeutic efficacy of thiopurine drugs. *TPMT*2*, **3A* and **3B* were rare, while *TPMT*3C* appears to be the most common variant in Indians. Another variant allele, the African specific *TPMT*8* (644G>A) in exon 9 which is responsible for intermediate activity, was absent in Indians[12]. The mutant allele *TPMT*3A* which causes the largest decrease in TPMT activity was detected only in NI (0.4%) but it was absent in SI, Similarly *TPMT*2* and *TPMT*3B* was present only in SI (0.1% and 0.1%) but not in NI (Table III). With regard to *TPMT*3A*, the NI were different from Caucasians ($P<0.004$) and similar to Asians and Africans[12]. With regard to *TPMT*3C*, the NI and SI were different from Caucasians, Africans ($P<0.01$) and similar to Asians[12]. On the whole, the Indians have relatively low frequency of *TPMT* variant and it shows that they have higher TPMT activity and are likely to be at a lower risk of developing toxicity when treated with thiopurine drugs compared to Africans, Asians and Caucasians[12] (Table II).

SULT1A1: Human sulphotransferase 1A1 (SULT1A1) is the most widely expressed of the SULTs isoform which catalyzes the sulphate conjugation of hormones, neurotransmitters, drugs (tamoxifen) and other xenobiotics. Differences in the ability of the SULT1A1 protein to catalyze the sulphonation reaction lead to

altered therapeutic efficacy, toxicity and disease process (carcinogenesis)[144,150]. The gene encoding SULT1A1 is mapped to the short arm of the chromosome 16p12.1-p11.2. The *SULT1A1*2* variant was the most common of the two common non-synonymous SNPs observed namely *SULT1A1*2* (638G>A, Arg213His) and *SULT1A1*3* (667A>G, Met223Val). Individuals carrying the variant allele *SULT1A1*2* will have diminished capacity to sulphate the substrates of SULT1A1 due to shorter protein life and more susceptible to cancer risk as well. Gene duplication and deletion was more common in *SULT1A1* gene and a correlation between the enzymatic activity and *SULT1A1* gene copy numbers has been observed by Hebbring *et al*[151] in an *in vitro* study. The frequency of *SULT1A1*2* in Indian populations was established in SI[130,33] (22.6%) and NEI[36] (27.2%) but not in NI (Table III). It was significantly higher than those reported in Asians 8.7 per cent and lower than Caucasians 41.5 per cent (P<0.0001), however, it was similar between SI, NEI and Africans 28.5 per cent (Table II)[152,153].

COMT: The enzyme catechol-O-methyltrasferase (COMT) is involved in the metabolism of catecholamines (adrenaline and noradrenaline), catecholestrogens, dopamine and their hydroxlated metabolites. The gene encoding COMT is located on chromosome 22q11.2 and produces two diverse proteins *i.e.* low affinity soluble COMT (S-COMT) and high affinity membrane bound (MB-COMT) by alternative transcription. Polymorphism in the human *COMT* is an important cause for the inter-individual variation in the enzyme activity of COMT. Further evidence has shown that the existence of COMT variants in individuals contributes to schizophrenia, breast cancer, endometrial cancer, Parkinson's disease, variation in pain sensitivity and therapeutic response (analgesics, levodopa)[154,155]. However, the results were not consistent and to date, approximately more than 30 SNPs have been described for *COMT* gene[154]. Among these, the most common being the *COMT* rs4680 (472G>A) in exon 4, where the nucleotide change A to G results in the replacement of valine with methionine at codon 158 in MB-COMT and 108 in S-COMT leading to 3-4 fold decrease in methylation activity. Except the SNP rs4680, the frequency of the other reported alleles such as rs3788319, rs737865, rs6269, rs4818, rs4633, rs165599 were available only in SI[133] (Table III). The frequency of rs4680 was significantly different between NI and SI (49 *vs.* 41.6%), P<0.001[131,133]. As compared to NI population, significant difference was obtained with Africans and Asians (P<0.0001). The difference in the frequencies of *COMT* rs4680, rs737865 and rs4633 in SI were significant, as compared to Africans, Asians and Caucasians, P<0.01(Table II)[156-159].

NAT2: Human genome consists of two acrylamine N-acetyltransferase enzymes 1 (NAT1) and 2 (NAT2), which catalyze the metabolism of N-acetylation of arylamines, arylhydroxylamines and arylhydrazines[160,161]. The genes encoding both the isoforms, *NAT1* and *NAT2* localized on chromosome 8p21.3-23.1 and exhibit numerous polymorphisms. Based on *NAT* genotype, individual phenotype (acetylation activity) can be divided into slow, intermediate and rapid acetylator[160,161]. Genetic variations of *NAT1* were not determined in native Indians. The common defective alleles of *NAT2* are 191G>A (Arg64Gln), 282C>T (Tyr94Tyr), 481C>T (Leu161Leu), 341T>C (Ile114Thr), 590G>A (Arg197Gln), 803A>G (Arg268Lys) and 857G>A (Gly286Glu)[161]. Among these, the most studied alleles were *NAT2*5*, *NAT2*6* and *NAT2*7* at positions 341, 590 and 857, respectively.

The variant *NAT2*6* corresponding to inactive enzyme was detected with a frequency of 37 per cent in SI[134] which was similar to 31.5 per cent in NI and different from NEI[35] 26 per cent, (P<0.003). Likewise, *NAT2*7* accounts to 13.3 per cent in NI and it was similar to NEI (11.1%) but different from SI, 25 per cent (P<0.0001). The other variants *NAT*5* and **13* were studied only in SI and occurred with a frequency of 30 and 44 per cent, respectively, while **14* was virtually absent[134]. The *NAT* gene polymorphic frequency of **11* was different between NI and SI (29.2 *vs.* 22%), whereas **12* was equally distributed among them (Table III). A comparison of *NAT2* allele frequencies of Indians with Africans, Asians and Caucasians reveals significant interethnic difference (Table II)[161]. Carriers of these alleles will have variation in the metabolism of isoniazid, hydralazine, ribavirin, retigabine, sulphamethoxazole and may influence susceptibility to some cancers[160,161].

Drug transporters

Drug transporters are those proteins that carry either endogenous compounds or xenobiotics across the biological membranes. These play an important role in the uptake, bioavailability, efficacy, toxicity and clearance of drugs[3]. Generally, transporters that influence ADME of drugs are classified into *(i)* adenosine triphosphate (ATP)-binding cassette (ABC)

family, and *(ii)* solute carrier (SLC) family[162,163]. The ABC transporters are efflux transporters, consisting of seven subfamilies and 49 genes, whereas the SLC are influx transporters with 360 genes and 46 subfamilies. The allele frequency of drug transporter genes in different Indian populations is shown in Table IV[10,12,63,164-170].

MDR1: The multidrug resistance 1 gene *MDR1,* also known as *ABCB1*, is localized at chromosome 7q21.1, consisting of 29 exons ranging in size from 49 to 209 bp, encoding an mRNA of 4.5 kb. P-glycoprotein (P-gp), the product of *MDR1* gene is a 170 kDa transmembrane protein, belongs to ABC super family of transporter proteins which is well recognized for its role in drug transport and chemoresistance. It protects the tissues from toxic xenobiotics and other endogenous substances by exporting the substrates from intracellular to extracellular space[162,171]. The amount of expression, regulation and activity of P-gp influenced by *MDR1* gene polymorphisms can directly affect the pharmacokinetics and pharmacodynamics of drugs that are substrates of P-gp, leading to inter-individual variation in drug response and toxicity[171].The substrate specificity of P-gp is broad including clinically relevant agents, *i.e.* anti-neoplasmics (doxorubicin, actinomycin D, paclitaxel), antibiotics (erythromycin, levofloxacin, sparfloxacin, rifampicin), antihypersentives (losartan), antivirals (nelfinavir, indinavir, efavirenz), analgesics (morphine), antiepileptics (phenytoin, phenobarbital), antidepressants (amitriptyline), immunosuppressants (cyclosporin A, tacrolimus, rapamycin), antiarrthythmics (digoxin, verapamil), antilipidemic (atorvastatin) and steroids (aldosterone, cortisol, dexamethasone)[162]. In addition, the polymorphism exhibited by *MDR1* gene is one of the factors responsible for individual susceptibility to various diseases such as breast cancer, colorectal cancer, Parkinson's disease and ulcerative colitis[171].

Human *MDR1* gene is highly polymorphic and over 50 SNPs have been identified. Among these, variants 2677G>T/A/C in exon 21, 3435C>T in exon 26 and 1236C>T in exon 12 are the most studied alleles of *MDR1* gene[171]. *MDR1* gene is extensively explored in Indian populations except NEI. In general, the Indians have at least one variant allele of *MDR1*. Among the Indian populations, the lowest 42.4 per cent and the highest 60 per cent frequency of 2677T/A allele were observed in NI and SI, respectively[12]. Similarly, the frequency distribution of the synonymous SNP 3435C>T was found to be 53.6 per cent in NI and 59.5 per cent in SI (Table IV). A significant inter- and intra-ethnic difference was observed when these two alleles were compared among Indians and with other major populations (Table II)[172-174]. On the other hand, the frequency of 1236C>T was available only in NI populations (51.9%) and it was different from other populations, $P<0.0001$ (Table IV).

SLC22A1: SLC22A1 belongs to the solute carrier, SLC22, super family of transporters, and these are also known as organic cation transporter 1 (OCT1). These translocate a wide variety of endogenous substances, environmental toxins and therapeutic drugs of cationic nature[163,175]. There are three important isoforms of OCTs namely - OCT1, OCT2 and OCT3 with similar membrane topology consisting of 12 transmembrane domains[175]. Of these, OCT1 is one of the most highly expressed transporters in the hepatocytes and plays a significant role in the hepatic uptake, elimination, distribution and renal transport of several xenobiotics including therapeutic agents (*e.g.* metformin, levodopa, amantadine, pramipexole and imatinib)[176-178]. Animal studies have shown that the concentration of metformin in liver was greatly decreased in *OCT1* gene knockout mice than in mice with normal OCT1 transporter activity[175,176]. The gene encoding human SLC22A1 is mapped onto chromosome 6q25.3, spanning 37kb with 11 exons. Numerous polymorphisms have been described for *SLC22A1* gene in various populations leading to differences in transporter function[175]. Studies across the globe have evaluated the association between genetic variations of *SLC22A1* gene and the pharmacokinetics and clinical consequences of metformin, levodopa, imatinib with inconsistent results[10,177,178].

In Indians, the frequency of the three variants rs2282143 in exon 6 (Pro341Leu, 1022C>T), rs628031 in exon 7 (Met408Val, 1222A>G) and rs622342 (1386C>A) located in an intron between exon 8 and exon 9 were described in Tamilian healthy subjects[10]. No data are available in any of the other Indian populations. Genetic variants of *OCT1* were common in SI Tamilians with a frequency of 8.9 per cent (95% CI 5.6-13.5), 80.3 per cent (95% CI 75.2-85.6) and 24.5 per cent (95% CI 18.9-30.2) for the alleles rs2282143 (T), rs628031 (G) and rs622342 (C), respectively[10]. It was different to the frequencies observed from those in Caucasians, $P<0.004$ (Tables II and IV). However, the frequency was similar to Africans and other Asian populations for rs628031. With regard to rs2282143, similarity was observed for Africans but not with

Table IV. Frequency distribution of drug transporter genes in diverse Indian populations

Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	Reference
MDR1	3435C>T	NI	Total*	977	53.6 (51.4-55.8)	
			Chandigarh	150	29.0 (23.9-34.1)	164
			Delhi	93	64.0 (57.1-70.9)	165
			Lucknow, Uttar Pradesh	216	50.0 (44.8-54.3)	166
			Ludhiana, Punjab	274	59.9 (55.7-64.0)	12
			Mumbai, Maharashtra	100	61.0 (54.2-67.8)	61
			Pune, Maharashtra	144	62.0 (56.2-67.4)	167
		SI	Total*	821	59.5 (57.1-61.9)	
			Andhra Pradesh	249	54.6 (50.2-59.0)	168
			Gulbarga, Karnataka	149	58.1 (52.5-63.7)	12
			Kakinada, Andhra Pradesh	152	66.8 (61.5-72.1)	12
			Puducherry and Tamil Nadu	112	61.6 (55.2-68.0)	12
			Thiruvananthapuram, Kerala	159	60.1 (54.7-65.4)	12
	2677G>T/A	NI	Total*	739	42.4 (39.8-44.9)	
			Chandigarh	150	18.0 (13.7-22.3)	164
			Delhi	99	67.7 (61.2-74.2)	165
			Lucknow, Uttar Pradesh	216	27.0 (23.1-31.5)	166
			Ludhiana, Punjab	274	58.4 (54.3-62.5)	12
		SI	Total*	714	60.0 (57.4-62.5)	
			Andhra Pradesh	252	52.7 (48.2-56.9)	63
			Gulbarga, Karnataka	126	62.7 (56.7-68.7)	12
			Kakinada, Andhra Pradesh	128	69.5 (63.9-75.2)	12
			Puducherry and Tamil Nadu	82	56.1 (48.5-63.7)	12
			Thiruvananthapuram, Kerala	126	64.7 (58.8-70.6)	12
	1236C>T	NI	Total*	734	51.9 (49.4-54.5)	
			Delhi	100	65.5 (58.9-72.1)	165
			Lucknow, Uttar Pradesh	216	33.0 (28.2-37.1)	166
			Ludhiana, Punjab	274	56.9 (52.8-61.1)	12
			Pune, Maharashtra	144	62.0 (56.2-67.4)	167
OCT1	1022C>T	SI	Total*	112	8.9 (5.5-13.5)	
			Puducherry and Tamil Nadu	112	8.9 (5.5-13.5)	10
	1222A>G	SI	Total*	112	80.3 (75.2-85.6)	
			Puducherry and Tamil Nadu	112	80.3 (75.2-85.6)	10
	1386C>A	SI	Total*	112	24.5 (18.9-30.2)	

Contd...

Gene	SNP	Population	Geographical origin	n	Frequency % (95% CI)	Reference
			Puducherry and Tamil Nadu	112	24.5 (18.9-30.2)	10
SLCO1B1	388A>G	NI	Total*	270	45.0 (40.8-49.2)	
			Lucknow, Uttar Pradesh	270	45.0 (40.8-49.2)	168
		NI	Total*	173	2.6 (1.2-4.9)	
			Lucknow, Uttar Pradesh	173	2.6 (1.2-4.9)	169
		NI	Total*	173	1.4 (0.5-3.3)	
			Lucknow, Uttar Pradeh	173	1.4 (0.5-3.3)	169

n, total number of subjects; NI, North Indians; SI, South Indians; NEI, North East Indians; CI, Confidence Interval; *Total number of subjects analyzed and the mean allele frequency values for every geographical region. The mean value may not sum 1 because the number of subjects analyzed for each SNP in a region may vary

Asians (P<0.05), and for rs622342, similarity was shown for Asians but not with Africans (P<0.05)[10]. The available data indicate significant delineation in the allele frequencies of the *OCT1* gene variants between different ethnic groups leading to dissimilarity in the pharmacokinetics and clinical consequences of the substrates of OCT1.

SLCO1B1: Organic anion transporting polypeptide 1B1 (OATP1B1) is a transmembrane protein with 12 domains, and plays important role in the hepatocellular uptake of various exogenous and endogenous substances of anionic nature including therapeutic drugs such as statins (simvastatin, rosuvastatin, pravastatin, and atorvastatin), methotrexate, repaglinide, irinotecan and rifampin[179]. It is encoded by the gene *OATP1B1*, also known as *SLCO1B1*, and consists of 14 coding and one non-coding exons and spans 108.59 kb, located on chromosome 12p12.2. Polymorphisms in the *SLCO1B1* gene decreases the transporter function and ultimately influencing the pharmacokinetics, toxicity and efficacy of OATP1B1 substrates. The variants of *SLCO1B1* increase the risk of statin-induced myopathy; methotrexate induced gastrointestinal toxicity and also susceptibility to gallstone disease[169,179,180]. The most common polymorphisms were *SLCO1B1*1B* in exon 5 (388A>G), *SLCO1B1*4* (463C>A) and *SLCO1B1*5* in exon 6 (521T>C). The prevalence of these variants were available only in NI[169] population and its frequency was reported to be 45, 2.6 and 1.4 per cent for *1B, *4 and *5, respectively (Table IV). The comparison of *1B allele frequency showed significant difference with being higher in Africans 87 and Asians 64 per cent but lower in Caucasians 37 per cent (P<0.001)[169,181]. Similarly, the other variants (*4 and *5) were higher in other populations but Asians showed similarity with NI with regard to *SLCO1B1*4* (Table II)[181].

Future directions

Currently, there are studies in India which established the normative frequency of clinically important genes, but most of these analyzed a limited number of individuals from south and north Indian populations. As Indian populations are highly heterogeneous in nature, these results may not be applied to the entire country population. Further, the frequency and impact of these gene polymorphisms on the enzyme activity are available for other major populations of the world (Celera, dbSNP, HapMap, HGVbase, JSNP and Refargen), but there are no such data for Indians. The Indian Genome Variation Consortium (IGVC) has generated a database IGVBrowser which harbours allele and genotype frequency for 4,229 SNPs from over 900 genes in distinct Indian populations, but it focused largely on disease predisposition biomarkers and lacks information on ADME genes[16]. Considering this along with the endogamous and polygenetic nature of Indian populations and being deficient in functional studies of these polymorphisms in Indians, there is a need for the systematic study to identify and functionally characterize clinically important ADME gene polymorphisms. In doing so, eventually we will have an opportunity to create an Indian database, perhaps an IndMap with the establishment of a nation-wide network among the Indian PGx researchers. This would provide information which would aid the researchers as well as the health care professionals for understanding the ethnic genetic diversity of the Indian population and its impact on drug pharmacokinetics and pharmacodynamics.

Additionally, the ultimate benefit of PGx studies is the usage of personalized medicine in clinical practice. One of the major problems in India is the non-availability of a cost-effective PGx testing method which is specific for Indian populations. Henceforth, it becomes imperative to develop a PGx chip in India and multicentre studies are required to validate the utility and clinical benefit of such chip. Finally, it can be concluded that understanding the role of genetics in influencing the pharmacodynamics and pharmacokinetics of clinically used drugs might help in tailoring pharmacotherapy. Therefore, information regarding the frequency distribution of the defective alleles of genes encoding enzymes concerned with ADME within particular populations is essential in adapting PGx.

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