Published Online on 21 February 2018

Proc Indian Natn Sci Acad **84** No. 1 March 2018 pp. 195-223

DOI: 10.16943/ptinsa/2017/49229

Review Article

Status of Pharmacogenomics Research in India During the Last Five Years

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(Received on 07 August 2017; Accepted on 12 November 2017)

Studies related to pharmacogenomics have considerably increased in recent years in India. The interests shown by our researchers are largely reflecting the global trend towards the multi-omics approach comprising transcriptomics, proteomics, metabolomics and microbiomics techniques which could help in accomplishing the most precise and personalized way of disease management. Pharmacogenetic trials related to bronchial asthma, breast cancer, acute lymphoblastic leukemia, chronic myeloid leukemia, colorectal cancer, head and neck cancer, rheumatoid arthritis, epilepsy, schizophrenia, major depressive disorder, bipolar disorder, diabetes mellitus, acquired immune deficiency syndrome (AIDS) and tuberculosis are included in this review; pharmacogenetic studies involving drug-groups like anticoagulants, antiplatelets, statins and others are also reviewed. Conditions like breast cancer and drugs such as warfarin, acenocoumarol and clopidogrel were found to be studied more extensively than others. On the other hand, a minimal number of pharmacogenetic studies were done in the field of diabetes, bronchial asthma, tuberculosis, and AIDS.

Keywords: Pharmacogenomics; Pharmacogenetics; Bronchial Asthma; Cancer; Cardiovascular Diseases; Neuropsychiatric Illnesses; Anticoagulants

Introduction

The current definition of 'precision medicine' — *"Understanding disease at a deeper level in order to develop more targeted therapy"* — clearly requires the armamentarium of pharmacogenomics to succeed optimally (Ashley, 2016). Though the science of precision or personalized medicine is gaining momentum in the recent years, its clinical application at point-of-care settings is still largely limited worldwide and in India (Chang *et al.*, 2015).

India is a country with extremely diverse cultures, religions, languages, social and biological characteristics. It is thus likely to have within it populations of varied genetic structures (Umamaheswaran and Shewade, 2014). Hence, the genetic knowledge base gathered from studies on Indian populations can be so enormous that if utilized judiciously can be the hub of rational pharmacotherapy.

In the last decade, the country has witnessed a rise in the number of studies related to pharmacogenetics. This review collates data for the past 5 years (from January 2012 to July 2017) on pharmacogenetic and pharmacogenomic trials done in the fields of bronchial asthma, breast cancer, acute lymphoblastic leukemia, chronic myeloid leukemia, colorectal cancer, head and neck cancer, rheumatoid arthritis, epilepsy, schizophrenia, major depressive disorder, bipolar disorder, diabetes mellitus, acquired immune deficiency syndrome (AIDS), tuberculosis, and also in drug-groups like anticoagulants, antiplatelets, statins among others.

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Respiratory Disorders

Bronchial Asthma

Salbutamol : Asthma is a chronic inflammatory disease affecting bronchial airways. Currently, there are around 25 to 30 million people diagnosed with bronchial asthma living in India as per the National Family Health Survey (NFHS)-3. Short-acting beta-2 agonists (SABAs) form the cornerstone of bronchodilator therapy in asthma though there are multiple treatment options for the management of asthma.

ADRB2 (adrenergic receptor beta-2) gene polymorphisms have been found to be associated with the variability in treatment response in asthmatic patients on salbutamol.

In South Indian patients with bronchial asthma (n = 112), the SNPs, rs1042713 (Arg16Gly, A285G) and rs1042714 (Gln27Glu, C318G) in *ADRB2* gene was not associated with salbutamol response (Shah *et al*., 2015). The increase in Forced Expiratory Volume in 1st second (FEV_1), Forced Vital Capacity (FVC) and Peak Expiratory Flow Rate (PEFR) were similar across various genotypes and haplotypes in both the polymorphisms.

On similar lines, a study concluded that the SNP rs1042713 (Arg16Gly) in *ADRB2* gene cannot be utilized as a predictive marker to bronchodilator response in South Indian population with bronchial asthma (n = 398) (Bandaru *et al*., 2015).

Around 6 to 13% of the Indian children are affected with asthma. Like in adults, SABAs do play a major role in the pharmacotherapy of bronchial asthma in children. A cross-sectional study revealed that there is no correlation between salbutamol responsiveness and *ADRB2* (rs1042713, c.46A>G, p.Arg16Gly) genotype in North Indian children (n = 120) with asthma with mild-to moderate exacerbation (p = 0.55). However, those children with AA genotype had a better bronchodilator response compared to those with GG genotype. Median change in percent predicted FEV_1 were 14.5% and 7.5% in AA and GG genotypes, respectively (Sahi *et al*., 2016).

Hence, the above studies revealed that the SNP rs1042713 in *ADRB2* gene does not determine the treatment response to salbutamol in the Indian population.

Corticosteroids

Systemic corticosteroids are given to patients who do not respond completely to initial doses of SABA therapy and patients who have moderate or severe exacerbations. Corticotrophin releasing hormone receptor1 (*CRHR1*) gene encoding for the CRHR1 receptor has been studied (Awasthi *et al*., 2015). They concluded that the SNP rs242941 (G>T) was associated with better therapeutic response in Indian asthmatic children during acute exacerbation (n = 68).

The SNPs in genes related to inhaled corticosteroid (ICS) response, viz., *CRHR1* [rs242941] has been reported (Revathy *et al*., 2016); Fc fragment of IgE receptor II (*FCER2*) [rs28364072] and glucocorticoid induced 1 (*GLCCI1*) [rs37972] were the other genes studied. After following up 111 healthy volunteers, the minor allele frequency of the SNPs was established (51% in rs242941, 33% in rs28364072 and 38% in rs37972). They also found no relation between the studied SNPs and asthma causation in 78 asthmatics on ICSs from Tamilian population.

Cancers

Breast Cancer

Neo-adjuvant Chemotherapy (NACT) : One out of 22 women in India is likely to have breast cancer and one out of every two newly diagnosed breast cancer patients in India eventually succumb to it (Malvia *et al*., 2017). Treatment failure or recurrence of the disease is one of the main reasons for breast cancer mortality. Chemotherapy plays a major role in management of breast cancer patients. In breast cancers, chemotherapy is initiated either following the primary surgery called as adjuvant chemotherapy or even before the surgery is undertaken when it is known as neo-adjuvant chemotherapy (NACT).

NACT is usually provided for patients with locally advanced breast cancers (LABC) or large operable breast cancers (LOBC). Cyclophosphamide, 5'-fluorouracil (5-FU), anthracyclines, and taxanes are the fundamental part of systemic treatment of breast cancer patients. There is a profound variability in both the treatment response and adverse effect profile with respect to the genetic make-up of an individual.

P-glycoprotein

P-glycoprotein (P-gp), an ATP-dependent drug efflux pump, transports various exogenous substrates including the chemotherapeutic agents used as part of NACT in the management of breast cancer. Multi-drug resistance-1 (*MDR1*) gene also known as *ABCB1* codes for the P-gp. After studying 48 breast cancer patients it has been reported that those patients with high P-gp expression had 3.6 times more chance of having poor response to NACT by WHO criteria (Vishnukumar *et al*., 2013). They also added that those patients with high P-gp expression had 14.4 times more chance of having poor response to NACT when compared with those having low expression levels, according to the Response Evaluation Criteria in Solid Tumors (RECIST). The genotype distribution of *MDR1* 2677T (60.3%), 2677A (3.7%) and 3435T (61.6%) in the South Indian population was reported previously (Umamaheswaran *et al.*, 2012).

It was reported that the patients with CT/TT genotypes of *ABCB1* gene (C1236T) showed better tumor response than those with CC genotype [Odds Ratio (OR): 2.94, 95% Confidence Interval (CI): 1.15 to 7.52, $p = 0.032$] (Priyadarshini *et al.*, 2016). Plasma levels of docetaxel were also in line with the tumor response i.e., the mean of the plasma concentration ratios (C_0/C_1) of docetaxel in CT/TT genotypes (13.49 ± 6.48 ng/mL) were significantly higher than those of the CC genotype (8.19 ± 3.10 ng/mL) ($p = 0.003$).The study population included 129 LABC patients of South India.

Glutathione-S-transferase

A multi-analytical approach was employed (Tulsyan *et al*., 2013) on the *GSTM1* and *GSTT1* deletion polymorphisms, and *GSTP1* $Ile^{105}Val$ (rs1695) polymorphisms in 207 North Indian cases of histology-proven invasive breast carcinoma who received anthracycline-based chemotherapy. *GSTM1, GSTT1* and *GSTP1* are members of the glutathione-*S*-transferase (GST) super family of the phase II metabolic enzymes. The results showed that the patients with*GSTM1* null-*GSTP1* Ile/Val had better response rates to NACT ($p = 0.032$) and patients with Ile/Val and Ile/Val + Val/Val genotypes of the *GSTP1* $Ile^{105}Val$ (rs1695) polymorphism were more commonly associated with grade 2-4anemia ($p = 0.019$, $p = 0.027$).

The allele and genotype frequencies of *GSTT1* (Null Allele) and *GSTP1* (Ile105Val) variants in South Indian populations (n = 212) have been established (Lakkakula *et al*., 2013). Previously, a similar study in 504 healthy unrelated volunteers of Gujarat origin was performed (Senthilkumar and Thirumurugan, 2012). They found that the frequencies of the homozygous null genotypes of *GSTM1* and *GSTT1* as 20% (95% CI: 16.7 to 23.9) and 35.5% (95% CI: 31.4 to 39.9), respectively. The frequency of homozygous null type of *GSTT1* of the studied population differed significantly from that of other Indian ethnicities in sharp contrast to that of *GSTM1* null frequency which was similar in all Indian ethnicities including the studied one.

Other Proteins

Combination of genetic variants, viz., *OCT4* (rs3130932), *NANOG* (rs11055786), and *SOX2* (rs11915160) were found to negatively influence the response to NACT in North Indian LOBC or LABC patients (n = 128). *OCT4* (octamer-binding transcription factor 4), *NANOG* and *SOX2* are genes encoding the factors necessary for the self-renewal capacity of embryonic cancer stem cells (Tulsyan *et al.*, 2014a).

Haplotype analysis found a significant association in $G_{rs10509681}$-$*1_{rs1799853}$-$*3_{rs1057910}$-$G_{rs4244285}$ of $CYP2C8*3_{rs10509681}$-$CYP2C9*2_{rs1799853}$-$CYP2C9*3_{rs1057910}$-$CYP2C19*2_{rs4244285}$ (chromosome 10) with overall toxicity ($p = 0.024$) and grade 2–4 leucopenia ($p = 0.03$)(Tulsyan *et al.*, 2014b). The study population included 111 breast cancer patients on cyclophosphamide-based NACT. *CYP2C8*3* (rs10509681), *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910) and *CYP2C19*2* (rs4244285) were the SNPs studied.

251 healthy unrelated North Indians were studied and the frequencies of *CYP2C8*2*, *CYP2C8*3*, and *CYP2C8*4* as 3, 4, and 4%, respectively were reported (Minhas *et al*., 2013). The genotype and allele frequencies differed from that of South Indian and other global population.

Genetic polymorphisms in methylene tetrahydrofolate reductase (*MTHFR*) and NADH-quinone oxidoreductase (*NQO1*) genes were analysed (Chaturvedi *et al*., 2015) in 115 breast cancer

patients receiving FEC/FAC/FMC (5-FU, epirubicin/ adriamycin/methotrexate, and cyclophosphamide) combination NACT. They concluded that patients with TT genotype of *NQO1* (609C>T variant) had more chances of getting chemotherapy-induced toxicity of grade 2-4 (OR: 0.33,95% CI: 0.13-0.88, $p = 0.027$) and anemia of grade 2-4 (OR: 0.34,95% CI: 0.12 to 0.95, $p = 0.041$). However, no association was seen with either response to NACT or drug-induced toxicity in patients with polymorphisms in MTHFR gene (677C>T).

It has been reported that clinical response to LABC patients (n = 170) on anthracycline-based NACT could be partially determined by the p53 tumor suppressor gene 72 codon polymorphism (P5379G>A) (RR: 0.2972, 95% CI: 0.078 to 1.122, $p = 0.03$) (Gopinath *et al*., 2017).

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator used as an adjuvant hormonal therapy to prevent recurrence in estrogen receptor positive (ER +ve) breast cancer and to prevent breast cancer in high-risk women. CYP2D6 enzyme, encoded by the gene *CYP2D6*, plays a key role in the biotransformation of tamoxifen to 4-hydroxytamoxifen and endoxifen which possess 30 to 100 times more potent anti-estrogenic activity than tamoxifen.

CYP2D6 alleles **1,*2,*4, *5* and **10* in breast cancer patients (n = 141) on adjuvant tamoxifen therapy have been studied (Damodaran *et al*., 2012). It was determined that patients with reduced CYP2D6 activity due to genetic polymorphisms were more commonly associated with increased risk of recurrence of breast cancer.

Aromatase Inhibitors

Aromatase (CYP19A1) is involved in the bioconversion of androgens to estrogens. Anastrazole, letrozole and exemestane are some of the aromatase inhibitors (AIs) which are the preferred anti-estrogen agents for treating postmenopausal women with breast cancer.

Haplotype structures and functional polymorphic variants of the drug target enzyme aromatase (*CYP19A1*) were determined in 163 healthy subjects of South Indian origin (Umamaheswaran *et al*., 2013). The observed frequencies of the *CYP19A1* minor alleles for the SNPs rs4646 (T), rs10046 (T), rs700519 (T), rs700518 (G), rs727479 (G), rs4775936 (T), rs10459592 (G), rs749292 (A), rs6493497 (T), and rs7176005 (A) were 41.1 (35.8-46.4), 20.0 (15.6-24.3), 33.7 (28.6-38.9), 17.8 (13.6-21.9), 25.8 (21.0-30.5), 19.9 (15.6-24.3), 33.7 (28.6-38.9), 24.9 (20.2-29.5), 35.9 (30.7 41.1), and 35.9 (30.7-41.1), respectively. The most common haplotype (H1) was GCTATCTGTG with a frequency of about 17.8%.

Similarly, T-cell leukemia 1A (*TCL1A*) gene, which was found to be associated with musculoskeletal toxicity risk while on AIs, wasalso evaluated (Umamaheswaran *et al*., 2014). By studying 247 unrelated healthy South Indians, the incidence of polymorphic variant allele (G) frequencies of rs7158782, rs7159713, rs2369049 and rs11849538 was determined as 22.1%, 23.5%, 18.2% and 22.9%, respectively.

Also reported the allele and genotype frequency distribution of *CYP19A1* and *TCL1A* genes in Tamil population was also reported (Umamaheswaran *et al.*, 2015a). The polymorphic variant allele frequencies of *CYP19A1* were 42.3% (rs4646, T), 18% (rs10046, T), 36% (rs700519, T), 16.7% (rs700518, G), 26.1% (rs727479, G), 18% (rs4775936, T), 32% (rs10459592, G), 15.3% (rs1062033, C), 33.8% (rs749292, A), 40.1% (rs6493497, T) and 40.1% (rs7176005, G). *TCL1A* gene allele frequencies were 26.1% (rs7158782, G), 27% (rs7159713, G), 21.2% (rs2369049, G) and 27.5% (rs11849538, G).

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukaemia (ALL) is one of the most common childhood cancers. In India, approximately 10,000 new ALL cases are being diagnosed every year. Though cure rates have improved drastically, the number of children relapsing after initial control has also increased.

Maintenance therapy of ALL encompasses 6-mercaptopurine (6-MP) as a major drug. The genetic polymorphisms in thiopurine *S*-methyltransferase (*TPMT*) gene and genes in relation to the folate metabolic pathway have been studied (Dorababu *et al.*, 2012). The following genetic variants, viz., *GCPII* C1561T (rs61886492), *RFC1* G80A (rs1051266), *cSHMT* C1420T (rs1979277),*TYMS* 5'-UTR 2R3R,

TYMS 3´-UTR ins6/del6, *MTHFR* C677T (rs1801133) and *MTR* A2756G (rs1805087) of the folate pathway and also the SNPs in *TPMT* were also studied. TPMT catalyzes the *S*-methylation of 6-MP which accounts for the efficacy and toxicity of 6-MP treatment. *GCPII* codes for GCPII which acts as folate hydrolase that converts folyl polyglutamate into folyl monoglutamates, thereby facilitating intestinal absorption of folate. RFC1 (reduced folate carrier-1, SLC29A1) determines the transport of folate, 6-MP and methotrexate (Mtx) across red blood cell membranes. Thymidylate synthase (TYMS) catalyzes the synthesis of thymidylate from uridylate in the presence of 5,10-methylene THF. Ninety six ALL children who were receiving maintenance therapy with 6-MP and Mtx were recruited. The results portrayed independent association of *GCPII* C1561T with 6-MP-mediated toxicity [Adjusted OR: 5.14 (1.28 to 20.67)]. With the aid of multifactor dimensionality reduction analysis it was found that the following interactions synergistically increased the toxicity of 6-MP, such as, *TPMT*12* × *RFC1* G80A; *TPMT* CTTAT haplotype × *RFC1* G80A; *TPMT* CTTAT haplotype × RFC1 G80A × *TYMS* 2R3R.

The genotype distribution of *TPMT* was reported after following 72 children with newly diagnosed ALL; three (4.2%) of them were heterozygous for *TPMT* (Linga *et al*., 2014). Among the heterozygous variants one each (33.3%) were heterozygous for 2A (G238C), 3B (G460A), 3C (A719G).

A novel genetic variant in nucleoside diphosphate-linked moiety X-type motif 15 (*NUDT15*) gene was found to be strongly associated with thiopurine intolerance (Shah *et al*., 2017). In the study, it was noted that 6 out of 9 patients who had *NUDT15* variant developed thiopurine-induced leukopenia whereas none of the other 60 patients without *NUDT15* variant developed leukopenia ($p < 0.0001$); total number of subjects were 69.

150 children with ALL were studied and it was reported that children with *MTHFR* 677C>T polymorphisms and1298A>C polymorphisms had a greater incidence of febrile neutropenia ($p < 0.0001$) and mucositis ($p < 0.007$), respectively (Roy Moulik *et al*., 2015). MTHFR catalyzes FAD-dependent reduction of 5,10-methylene THF to 5-methyl THF which is an important step in the folate metabolic pathway. The children were treated with a 4-week induction therapy with intravenous vincristine and daunomycin (on days 0, 7, 14 and 21), oral prednisolone (days 0-28) and L-asparaginase (days 2, 4, 6, 8, 10, 12, 14, 16 and 18) and intrathecal methotrexate (days 0, 7 and 28) following the uniform Children's Cancer Group (CCG)-1961 based chemotherapy protocol.

The anticancer activity of Mtx is due to its inhibitory potential of the enzyme dihydrofolate reductase (DHFR). South Indian ALL patients who were on Mtx-based therapy (n = 70) were recruited and it was found out that those patients with GG genotype of *DHFR*-317A>G variant were associated with increased risk of ALL relapse (RR: 2.25, 95% CI: 1.38 to 3.6, $p = 0.02$) and lower overall survival and also the patients with variants -317 AA and -680 CA of *DHFR* gene were associated with severe leucopenia ($p < 0.05$) (Kodidela *et al*., 2015).

The normative allele and genotype distribution of *DHFR* variants in unrelated healthy Indian population (n = 235) were also reported The frequency of *DHFR* -317G and -680 A alleles was found to be 33.3% and 59.8%, respectively (Kodidela and Pradhan, 2016).

A subset of high-risk ALL children receive higher doses of Mtx of more than 1000 mg/m^2 resulting in more pronounced toxicities of Mtx. Genetic mutations can predict the occurrence of Mtx toxicity. Children with ALL on high-dose Mtx therapy (n = 21) were studied and it was concluded that there were more requirement for packed red cell transfusions in patients with *MTHFR* 1298 polymorphisms (3.4 ± 3.6 units in 1298 mutations *vs.* 0.9 ± 1.6 units in 1298 wild genotype; $p = 0.03$) (Roy Moulik *et al*., 2016).

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a myeloproliferative disease in which there is neoplastic proliferation of pluripotent hematopoietic stem cell. It is characterized by the presence of Philadelphia chromosome (Ph) that occurs following a balanced reciprocal translocation between chromosomes 9 containing the Abelson murine leukemia (*ABL*) gene and 22 containing the breakpoint cluster region (*BCR*) gene [t (9; 22) (q34; q11)]. The consequent *BCR-ABL1* fusion gene codes for BCR-ABL1 fusion

protein (p210), which has intrinsic tyrosine kinase activity and plays a key role in the pathogenesis of CML.

Imatinib mesylate, a specific small molecule competitive tyrosine kinase inhibitor, is the current drug of choice for CML. The ATP-binding cassette (ABC) transmembrane efflux transporter, P-glycoprotein 1 (P-gp) functions as a substrate to imatinib. The gene for which is located on chromosome 7 (7q21.1), viz., the multidrug resistance-1 (*MDR1*) gene also known as *ABCB1* gene.

ABCB1 3435 C>T (rs1045642), *ABCB1* 2677 G>T/A (rs2032582); *ABCG2* 421 C>A (rs22311442) and *OCT1* 1022 C>T (rs2282143), *OCT1* 1222 A>G (rs628031), *OCT1* 1386 C>A (rs622342) were the SNPs studied (Francis *et al.*,2015a) in 111 CML patients (chronic phase) with a stable dose (400 mg) of imatinib. None of the SNPs in the efflux (*ABCB1* and *ABCG2*) and influx (*OCT1*) transporter genes was found to be associated with imatinib mesylate induced thrombocytopenia.

It has also been reported that only *ABCB1* C3435T ($p = 0.001$) was found to influence the overall survival in CML patients (n = 111) after studying the polymorphisms in *ABCB1*, *OCT1*, and *ABCG* genes; the patients with T allele had better overall survival (54.8 months) compared to those with C allele (43.9 months). However, the SNP*ABCG2* 421 C>A showed a significant association with complete cytogenetic response ($p = 0.035$) (Francis *et al*., 2015b).

CML patients (n = 86) were recruited and genotyped for C1236T, G2677T and C3435T SNPs of *ABCB1* gene. Imatinib resistance was found to be more frequent in patients with TT genotype of C1236T than in those with CT/CC genotypes (p=0.003) (Chhikara *et al.,* 2015).

Healthy unrelated Maharashtrian individuals (n = 222) residing in the Vidarbha region of central India were enrolled for assessing the allele and genotype frequency distribution of *ABCB1* gene polymorphisms (C3435T and C1236T) (Pramanik *et al.,* 2014). The results showed that the genotype distributions of Maharashtrians did not differ significantly from that of Gujarati Indians in Houston, Texas (as per the HapMap database).

A study on chronic phase CML patients (n = 160) revealed that patients with *SLCO1B3* 334TT genotype had a higher risk of failure of cytogenetic response (OR: 13.36, 95% CI: 0.622 to 287.2, $p = 0.04$), compared to those with *SLCO1B3* 334GT/GG genotype; rather patients with *SLCO1B3* 334GT/GG (OR: 0.127, 95% CI: 0.016 to 1.008, $p = 0.04$) genotype was found to be associated with a lower risk association to cytogenetic response (Nair *et al.*, 2017). The *SLCO1B3* gene codes for the organic anion-transporting polypeptide 1B3 (OATP1B3) which plays a pivotal role in the influx transport of imatinib.

It was concluded in a study that chronic-phase CML patients with CC genotype for *MDR1*-C1236T polymorphism were at significantly higher risk for cytogenetic relapse (OR: 4.382, 95% CI: 1.145 to 16.774, $p = 0.022$), while those with TT genotype for *MDR1*-C3435T polymorphism had significantly lower risk of relapse (OR: 0.309, 95% CI: 0.134 to 0.708, $p = 0.005$). The study patients were on imatinib therapy and had completed five years of follow-up, after starting with imatinib (Harivenkatesh *et al*., 2017a).

Another study by the above authors propounded that the plasma trough levels of imatinib was significantly higher in patients with GG genotype of *CYP3A5*-A6986G ($p = 0.016$) and TT genotype of *MDR1*-C3435T ($p = 0.013$) SNPs (Harivenkatesh *et al*., 2017b). Their results also showed that there was a higher risk for failure of imatinib therapy in patients with AA genotype of *CYP3A5*-A6986G (RR: 1.448, 95% CI:1.126 to 1.860, $p = 0.029$) and CC genotype of *MDR1*-C1236T (RR: 1.397, 95% CI: 1.066 to 1.831, $p = 0.06$) & *MDR1*-C3435T (RR: 1.508, 95% CI: 1.186 to 1.917, $p = 0.018$). CYP3A5 is involved in the bio-activation of imatinib to CGP74588.

A large study in 652 unrelated healthy volunteers of South Indian origin (Andhra Pradesh, Karnataka, Kerala and Tamil Nadu) was performed to assess the genetic polymorphisms of drug-metabolizing phase I enzymes CYP2E1, CYP2A6 and CYP3A5. *CYP2E1*1B*, *CYP2E1*5B* and *CYP2E1*6* alleles were noted to be in 14.3, 1.3 and 22.4% of the population, respectively; the frequencies of *CYP2A6*2*, *CYP2A6*4A* and *CYP2A6*5* alleles were found to be 1, 8.9 and 0.7%, respectively; *CYP3A5*3* allele was seen in 63.5% of the patients. The variant alleles of *CYP3A5*2*, *CYP3A5*4* and

*CYP3A5*6* were absent in South Indian population (Krishna Kumar *et al*., 2012).

Colorectal Cancer

Colorectal cancer is placed 4th among the deaths due to cancer worldwide. Capecitabine, an oral pro-drug of 5-FU, along with oxaliplatin (CAPOX) is a standard treatment option in advanced CRC and as an adjuvant therapy in colon cancer. Dihydropyrimidine dehydrogenase (DPD), encoded by *DPYD* gene, is the metabolizing enzyme involved in the breakdown of 5-FU.

The genotype and allelic frequencies of 22 intronic, synonymous and nonsynonymous SNPs in the DPYD gene has been documented by evaluating a healthy Indian cohort of 50 [66% Maharashtrians (South West Indians), 18% South Indians, 12% North Indians and 4% Gujarat is (West)] (Iyer *et al*., 2015).

An intriguing study was conducted to divulge the association of *MTHFR* genetic polymorphisms between normal and tumor tissues (Rai *et al.*, 2014). They reported that the allele and genotype frequencies of C677T and A1298C in *MTHFR* gene differed significantly between tumour tissues and matched normal tissues in 155 colon cancer patients. The study results emphasize the importance of tissue-specific genotyping.

The effect of SNPs has been studied in *TS*, *MTHFR*, *DPYD* and *GSTP1* genes on toxicity and efficacy in CRC patients on CAPOX therapy. They observed that patients with *TS* 2R/2R genotypes were not good responders to CAPOX therapy. However, there was no association between the studied SNPs and occurrence of CAPOX-induced toxicities. Sample size (n = 16) was a major limitation of this study (Ramalakshmi *et al*., 2016).

Head and Neck Cancer

Head and neck cancer stands 6th among the most common cancers worldwide. A study was conducted in 100 male cases of head and neck squamous cell carcinoma (HNSCC) on cisplatinum-based sequential chemo-radiotherapy and was concluded that the polymorphisms in the gene coding for CYP2D6 could influence the chemotherapeutic response. *CYP2D6*4* and *CYP2D6*10* were the variants which showed poor response in the study (Shukla *et al*., 2012).

500 male HNSCC patients of North Indian origin receiving chemotherapy (cisplatin and 5-FU) or combination of chemotherapy and radio therapy were recruited (Dhawan *et al*., 2017). The trial results showed that patients with variant genotypes of *TPMT*3B, TPMT*3C* or *DPD* IVS14+1G>A were responding poorly.

Miscellaneous Cancers

Gemcitabine, a pyrimidine antimetabolite, is widely used for treatment of solid breast, colon, lung and colorectal tumors in India. Gemcitabine after exerting its cytotoxic effects on cancer cells undergoes rapid degradation by virtue of the enzyme cytidine deaminase (CDA). CDA activity determines the occurrence of toxicity with gemcitabine; lower activity of CDA leads to disproportionate accumulation of active metabolites therefore leading to adverse effects. The genotype distribution of the SNP in *CDA* gene, i.e., the variants in 79A>C and c.325-209T>C were found to be 14% and 6% in the studied healthy volunteers (n = 50) (Iyer *et al*., 2013).

A study revealed that patients with non-synonymous coding variant 79A>C in *CDA* gene were associated with cytarabine (Ara-C) induced-cytotoxicity after studying 100 adult patients with *de novo* acute myeloid leukemia (AML) (Abraham *et al*., 2012). AML is commonly managed with Ara-C in combination with daunorubicin. Like discussed above, CDA causes the systemic deamination of Ara-C.

North Indian cancer patients (n = 33) who were on carboplatin-based chemotherapy for various cancers were genotyped for *GSTT1* null and *MPO* -463G>A polymorphisms (Bag *et al*.,2013). Carboplatin, like other platinum compounds, act through the genes involved in DNA detoxification. One such gene is the *MPO* gene which codes for the lysosomal enzyme myeloperoxidase (MPO). MPO has the propensity to generate reactive oxygen species (ROS) which can exert cytotoxic action on tissues. The results showed that patients with variant A allele of *MPO* -463G>A had a lesser incidence of hematological toxicity.

The genotype distribution of SNPs rs2740574 in *CYP3A4*1B* and rs776746 in *CYP3A5*3* after studying 126 South Indian lung cancer patients was established (Subhani *et al.*, 2015).

For the chemotherapy of high-risk neuroblastoma, 13-*cis* retinoic acid (13-cisRA) has become an essential component. CYP3A5, CYP2C8 and UDP glucuronyl transferase (UGT) are enzymes involved in the metabolism of 13-cisRA. The SNPs in *UGT2B7, CYP2C8*2/*3/*4* or *CYP3A5*3* genotype did not have any effect on 13-cisRA pharmacokinetics. The study population included 36 children less than 16 years of age on 160 mg/m^2/day of 13-cisRA (Gota *et al.*,2016).

Immunological Disorders

Rheumatoid Arthritis

The first choice of disease-modifying antirheumatic drug (DMARD) for the management of rheumatoid arthritis (RA) is Mtx owing to its high efficacy, low toxicity, and long-term affordability. But around 40% of the patients initiated with Mtx do not respond optimally. Hence, pharmacogenetic markers are need of the hour for predicting Mtx response to RA.

457 North Indian RA patients (297 good and 160 poor responders) on Mtx monotherapy were recruited for the first ever genome-wide analysis on Mtx treatment response in RA patients (Senapati *et al*., 2014). They reported 10 new risk loci on the genes related to Mtx response. The associations of candidate genes, viz., *DHFR* (OR: 1.44, 95% CI: 1.08 to 1.93, $p = 0.014$), *FPGS* (OR: 0.73, 95% CI: 0.54 to 0.98, $p = 0.035$), and *TYMS* (OR: 1.48, 95% CI: 1.12 to 1.94, $p = 0.005$) with poor response to Mtx were reaffirmed. FPGS codes for the enzyme folylpolyglut amyl synthase which aids in the conversion of Mtx to methotrexate polyglutamates (Mtx-PG).

The *RFC-1* 80G>A gene polymorphism (rs1051266) was evaluated in 649 South Indian Tamil population (327 patients with RA and 322 healthy controls) (Muralidharan *et al*., 2016a). As discussed earlier, RFC-1 is a bidirectional anion exchanger which transports Mtx and folinic acid. They found that people with heterozygous *RFC-1* 80 GA genotype less frequently develop RA (OR: 0.69, 95 % CI: 0.50 to 0.95, $p = 0.02$). However, none of the genotypes were associated with neither Mtx treatment response nor Mtx-induced adverse effects.

However, a positive relation was exposed between the *MDR1* 3435C>T gene polymorphism (rs1045642) and the clinical phenotype and adverse events to Mtx in the South Indian patients with RA (n = 336; 122 good responders and 107 each of partial & non-responders) (Muralidharan *et al*., 2015). The MDR1 3435T allele was found to be associated with high RA disease activity (OR: 1.50, 95%CI: 1.06 to 2.13, $p = 0.02$). The heterozygous *MDR1* 3435CT genotype was associated with deforming disease (OR: 1.79, 95% CI: 1.11 to 2.88, $p = 0.02$) and Mtx-induced adverse events (OR: 2.01, 95% CI: 1.15 to 3.52, $p = 0.01$); however, the RA patients with this genotype had lesser chance of developing infections (OR: 0.05, 95% CI: 0.006 to 0.460, $p = 0.002$).

Indian RA patients (n = 322) were studied for 12 SNPs in nine candidate genes of folate-Mtx pathway. The polymorphisms in *GGH* (rs3758149), *SHMT1* (rs1979277) and *TS* (rs34489327) were associated with Mtx-related adverse events (Ghodke-Puranik *et al.*, 2015). Patients with A allele in *MTHFR* rs1801131 (OR: 2.6, 95% CI: 1.1 to 5.8, $p = 0.02$) and *RFC1* rs1051266 (OR: 2.2, 95% CI: 1.1 to 4.4; $p = 0.03$) were found to respond better. Higher plasma levels of Mtx were observed in patients possessing TS'5' UTR and *SHMT1* polymorphisms. *GGH* coding for ϒ-glutamyl hydrolase is involved in the regeneration of Mtx from Mtx-PG and *SHMT1* coding for serine hydroxymethyltransferase-1 is involved in the tetrahydrofolate (THF) to 5'10'-methylene THF conversion reactions.

In another study, it was found that the *ATIC* 347C>G gene polymorphism (rs2372536) was associated with the development of Mtx-induced gastrointestinal adverse effects in South Indian Tamil patients with RA (n = 319) (Muralidharan *et al*., 2016b). Those patients with G allele (OR: 2.60, 95% CI: 1.27 to 5.35, $p = 0.01$) or GG genotype (OR: 4.46, 95% CI: 1.28 to 15.52, $p = 0.02$) were found to experience gastrointestinal adverse effects of Mtx more frequently. *ATIC* codes for the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase which is involved in the conversion of AICAR to 10-formyl-AICAR.

Recently, it was also reported that the 28-bp tandem repeat polymorphism (rs34743033) and 6-bp insertion/deletion polymorphism (rs34489327) in *TYMS* gene were not found to influence the treatment response to Mtx or the occurrence of Mtx-induced

adverse effects. Their study included 254 patients with RA of South Indian Tamil origin on Mtx (Muralidharan *et al.*, 2017).

Neurological Disorders

Epilepsy

Epilepsy affects six persons out of 1000 people in India. Numerous anti-epileptic drugs (AEDs) with different mechanisms of action are currently available. However, about 33% of the patients are found not to respond optimally to AEDs and others experience AEDs-associated adverse effects in excess. Pharmacogenetics could be responsible for these deficiencies.

Phenytoin

Indian patients with epilepsy on phenytoin (n = 259) were studied and a significant association (OR: 2.6, 95% CI: 1.19 to 5.7; p = 0.008) between toxic phenytoin levels and the polymorphic variant alleles *CYP2C9*2* and **3* was reported. It should be noted that phenytoin is predominantly metabolized by CYP2C9 enzymes (90%) and hence, variations in the *CYP2C9* gene influence the phenytoin plasma levels (Thakkar *et al.*, 2012).

A similar study revealed that epilepsy patients of ethnic Kashmiri population (n = 92) had a positive association between *CYP2C9* genotype (**2* and **3*) polymorphism and phenytoin AUC_{0-4}. The frequencies of *CYP2C9 *1*, **2*, and **3* alleles as 64%, 6.6% and 29.3% in healthy controls (n = 121) were also determined in that study (Kousar *et al.*, 2015).

The genotypic association with the phenytoin plasma levels was reaffirmed in another study (Thaker *et al.*, 2017). Toxic plasma concentrations of phenytoin were seen more commonly in patients with *CYP2C9*1/*3* genotype (Adjusted OR: 3.36; 95% CI: 1.61 to7.01).

Patients with tuberculous meningitis (TBM) or tuberculoma develop seizures as a primary complication in more than 50% of the cases. In these neurological tuberculosis patients, isoniazid (INH) and phenytoin are often co-prescribed. INH is catalyzed by *N*-acetyltransferase 2 (NAT2) which exhibits two distinct phenotype groups, viz., the slow and rapid acetylators based on the genotype of *NAT2* gene. Phenytoin metabolism can be inhibited by INH owing to its enzyme inhibiting property. A trial divulged that the patients with homozygous mutant alleles of the variants, rs1041983 (C282T), rs1799929 (C481T), rs1799931 (G857A), rs1799930 (G590A), rs1208 (A803G) and rs1801280 (T341C) in *NAT2* gene were more prone for phenytoin toxicity (Adole *et al.*, 2016).

Valproate

Sodium valproate being a broad-spectrum AED is effective against absence, myoclonic, and primarily generalized tonic-clonic seizures. Uridine 5'-diphospho glucuronosyl transferases (UGTs) play a major role in the biotransformation reactions of valproate; as glucuronidation is a key pathway in valproate metabolism. UGT1 and UGT2 are the two main sub-families of the Phase II UGT family. The polymorphism in *UGT 1A6* was studied and found that the North Indian epileptic patients (n = 100) with allelic mutants 541A>G ($p = 0.0006$) or 552A>C ($p = 0.0002$) in *UGT1A6* had a significant association with sodium valproate toxicity (Munisamy *et al.*, 2013). They also reported that elimination half-life of valproic acid was longer ($p< 0.01$) and the clearance rate was lower ($p< 0.01$) in the poor metabolizers group of *UGT1A6* (552A>C) polymorphism who showed comparatively more toxicity than in the intermediate metabolizers group or the extensive metabolizers group.

Recently, the genotype and allele distribution of *UGT1A6* SNPs in children (n = 80) aged 3 to 12 years diagnosed with epilepsy on valproate monotherapy for at least 1 month were studied (Jain *et al.*, 2015). They estimated the frequency of *UGT1A6* T19G,*UGT1A6* A541G and *UGT1A6* A552C as TT (45%), TG (38.8%), and GG (16.3%); AA (48.8%), AG (38.8%), and GG (12.5%); and AA (43.8%), AC (40%), and CC (16.3%), respectively.

Other Genes Affecting AEDs Response

A pilot study in 120 North Indian persons with epilepsy proposed that the genetic polymorphisms of the promoter regions of *IL-1*β-511C>T (rs16944), *TNF*-α-308G>A (rs1800629) and *IL-6*-174G>C (rs1800795) genes could influence the therapeutic response in patients with drug refractory epilepsy. The results portrayed that the patients with 308G>A

(rs1800629) SNP in *TNF-α* gene had a strong association with drug refractory epilepsy ($p < 0.05$) (Tiwari *et al*., 2012).

The genetic expression of the drug-efflux transporter P-glycoprotein (P-gp) can influence the response to AED therapy, as P-gp is involved in the transport of AEDs. P-gp is a product of ATP-Binding Cassette Subfamily B Member 1(*ABCB1*) also known as multi-drug resistance 1 (*MDR1*) gene. After studying 220 newly diagnosed epileptic patients it was revealed that the risk of drug resistance was significantly higher in patients possessing TT genotype when compared to carriers of the homozygous CC genotype of SNP C3435T in *ABCB1* gene (OR: 2.34, 95% CI: 1.942 to 11.32; $p = 0.001$) (Shaheen *et al*., 2014).

On the similar lines, a study corroborated that the *ABCB1* 34535CC genotype (OR: 4.5, 95% CI: 1.04 to 20.99) and *ABCB1* 3435C allele (OR: 1.73; 95% CI: 1.02 to 2.95) were significantly associated with the treatment response. The enrolled patients with epilepsy were on phenytoin and/or phenobarbital and/or carbamazepine (n = 115) (Taur *et al*., 2014).

Along with MDR1 transporter, another transporter by name Breast Cancer Related Protein (BCRP) is involved in the efflux of AEDs. BCRP is encoded by the gene *ABCG2*. A study included patients of Malayalam speaking South Indian ancestry comprising of mesial temporal lobe epilepsy with hippocampal sclerosis (n = 259) (prototype for AED-resistant epilepsy); juvenile myoclonic epilepsy (n = 201) (prototype for AED-responsive epilepsy); and healthy non-epileptic controls. None of the studied SNPs in neither *ABCB1* (rs3213619, rs2214102, rs1202168, rs1128503, rs1922242, rs2032582 and rs1045642) nor *ABCG2* (rs2231137 and rs2231142) genes were associated with AED-resistance (Balan *et al*., 2014).

The teratogenic potential of women taking AEDs is two to three times more than their normal counterparts. Hence, the polymorphisms in *ABCB1*, *CYP2C9*, *CYP2C19* and methylene tetrahydrofolate reductase (*MTHFR*) genes were studied in 266 women with epilepsy; recruited either in the pre-pregnant stage or first trimester of pregnancy. The results showed that the patients with CC genotype of *ABCB1* Ex07 + 139C/T (rs1202168) polymorphism had a significant association with occurrence of foetal malformations ($p = 0.0032$). Similarly, the incidence of malformations was more in patients with poor metabolizer allele **2* ($p = 0.007$) and **2*2* ($p = 0.005$) genotype of *CYP2C*19* (Jose *et al*., 2014).

Carbamazepine (18.2%) and phenytoin (13.4%) were the common causative drugs in the occurrence of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Indian population. A study concluded that *HLA-B*1502* is a strong determinant of occurrence of carbamazepine-induced SJS/TEN in North Indian population (Aggarwal *et al*., 2014). *HLA* gene codes for the human leukocyte antigen molecules which are crucial for antigen presentation to T cell receptor and responsible for subsequent triggering of immune response.

Likewise, by following up 192 patients with epilepsy who were on carbamazepine as monotherapy or in combination therapy it was ascertained that the *HLA-A*3101* can function as a marker for carbamazepine-induced adverse effects (Duraivel *et al*., 2015).

A major study was undertaken by recruiting 408 North Indian patients with epilepsy and genotyping 155 SNPs in 12 genes from the ion channels and related gene sets and seven genes from synaptic vesicle cycle (SVC). The subjects were on phenytoin, carbamazepine, valproate, phenobarbitone, or their combinations/multi-therapy (Baghel *et al*., 2016). The noteworthy findings were that patients with *GABRA1* and *SCN1A* genetic variants showed robust haplotypic and diplotypic associations with response to phenytoin. Diplotype analysis of *GABRA1* variants revealed association of rs12658835|rs7735530(AG/AG) (p-value$_{corrected} = 0.034$, OR: 3.75, 95% CI: 1.36 to 11.05) and rs12658835|rs7735530|rs7732641|rs2279020 (AGCA/AGCA) (p-value$_{corrected} = 0.035$, OR: 2.48, 95% CI: 0.96 to 6.41) with recurrent seizures. *SCN1A* haplotype rs6432860|rs3812718 (AC:p-value$_{corrected} = 0.022$, OR: 2.72, 95% CI: 1.39 to 5.35) and diplotype (AC/AC:p-value$_{corrected} = 0.034$, OR: 6.42, 95% CI: 1.10 to 65.76) were further observed to be associated with recurrent seizures. *GABRA1* codes for the GABA and glutamate receptors and *SCN1A* codes for the voltage-gated sodium channels (α subunit type 1). It should be noted that phenytoin exerts its antiepileptic effect by acting on the voltage-dependent

sodium channels and also by potentiation of GABAergic neurotransmission.

North Indian women (n = 351) possessing 'A' allele and 'AA' genotype of variant rs2606345 in *CYP1A1* gene with epilepsy were found to be poor responders to AEDs. CYP1A1 enzyme is involved in the biotransformation of estrogens, i.e., estrone (E1) and estradiol (E2) into hydroxylated derivatives, namely 2-OH-E1 and 2-OH-E2, respectively (Talwar *et al*., 2016). And, E2 has been found to increase the neuronal excitability in women with epilepsy and hence, accentuation in the occurrence of seizures. A loss-of-function mutation in *CYP1A1* could result in increased blood levels of E2 leading to drug refractory epilepsy.

Recently, it was propounded that there was no association with *HLA* genotyping and levetiracetam-induced cutaneous adverse drug reactions (cADRs) in North Indian epileptic patients (Bhargavi Ramanujam *et al.,* 2016). Out of 589 patients, there were five patients with maculopapular exanthema (MPE), two with SJS, and 1 with drug reaction eosinophilia and systemic symptoms (DRESS); so, in total therewere 8 cases of cADRs. It was also noted that patients with *HLA-A*33:01* were more prone to MPE though statistically insignificant.

Schizophrenia

The pharmacological management of schizophrenia follows a trial and error method, as almost 70% of the patients do not show even a minimal therapeutic response early on in treatment. Pharmacogenetics does play a role in these differential therapeutic responses.

Antipsychotics like risperidone, olanzapine, clozapine, haloperidol and quetiapine also act as substrates to the P-gp (MDR1). A study characterized the favourable influence of the homozygous genotypes of C3435T (rs1045642) (CC*vs* TT; $p = 0.0053$) and G2677T/A (rs2032582) (GG *vs* TT; $p = 0.0093$) in *ABCB1*. The study subjects were Malayalam-speaking genetically homogenous Dravidian populations, particularly from the state of Kerala (n = 192) (Vijayan *et al*., 2012).

Owing to less severe adverse reactions as compared to the previously prescribed typical antipsychotics, atypical antipsychotic (AAPs) drugs are the preferred choice for the treatment of schizophrenia. It has been demonstrated that the patients with the genotypic combination of four SNPs, rs265967 (*DRD1*)-rs10934254 (*DRD3*)-rs878567 (*HTR1A*)-rs1176744 (*HTR3B*) would not show favorable response to AAP therapy. The present study comprised of three hundred and seventy one schizophrenia patients of South Indian origin. *DRD* and *HTR* are dopaminergic and serotonergic receptors genes; dopamine receptor D_2 and serotonin receptor $5\text{-}HT_{2A}$ are the primary targets of most of the AAPs (M. Gupta *et al*., 2013).

The clinical significance of antipsychotic response to clozapine has been demonstrated (Rajkumar *et al*., 2012); the study population included 101 treatment-resistant schizophrenia (TRS) patients. The minor alleles of both the SNPs on the *HTR3A* gene, viz., T allele in rs1062613 and G allele in rs2276302, were significantly associated with good clinical responses to clozapine ($p = 0.02$).

It has been established that the 120 base-pairs (bp) tandem duplication in the *DRD4* gene greatly influenced the occurrence of clozapine-induced sialorrhea in patients of South Indian ethnicity (n = 95), who had been diagnosed with treatment-resistant schizophrenia (Rajagopal *et al*., 2014). The patients who were on stable doses of clozapine for at least 12 weeks were recruited.

The synergistic association of *PI4KA* (rs165854) and *GRM3* (rs1468412) genetic polymorphisms with poor antipsychotic response in South Indian schizophrenia patients with low severity of illness (OR: 12.4; 95% CI: 3.69 to 41.69) has been elucidated (Kaur *et al*., 2014). They genotyped 423 schizophrenia patients for 48 SNPs from 5 different genes to confirm this epistasis. The patients were on typical antipsychotics such as chlorpromazine, fluphenazine or flupenthixol and atypical antipsychotics such as clozapine, risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole, amisulpride, or levosulipride or combination of two or more typical/atypical antipsychotic drugs. The biosynthesis of phosphatidylinositol-4, 5-bisphosphate is regulated by *PI4KA* whose expression is necessary for exocytotic fusion of synaptic vesicles (glutamate, dopamine) with the plasma membrane thereby regulating the duration

of signal transduction of GPCRs. Whereas *GRM3* regulates glutamate and dopamine transmission.

However, no significant associations were found between the genotype, allele, or haplotype distributions of the SNPs in *GRIN1*, *ABCB1*, and *DRD4* genes with antipsychotic drug response.*GRIN1*codes for the glutamate receptor ionotropic *N*-methyl D-aspartate 1 (Pai *et al*., 2015). Majority of the study subjects were on either risperidone or olanzapine.

Schizophrenia patients were studied from Indian populations of Indo-European (North Indian) and Dravidian (South Indian) descent (n = 742). They identified that patients in the low severity group with SNPs in *CCL2* (rs4795893: OR = 1.79, 95% CI: 1.27 to 2.52, $p = 7.62 \times 10^{-4}$; rs4586: OR = 1.74, 95% CI: 1.24 to 2.43,$p = 1.13 \times 10^{-3}$) and *GRIA4*(rs2513265: OR = 0.53, 95% CI: 0.36 to 0.78, $p = 1.44 \times 10^{-3}$] experienced incomplete responses with antipsychotic therapy (Jajodia *et al*., 2016). Similarly, the patients in the high severity group were found to respond poorly if they possessed the SNPs in *ADCY2* (rs1544938: OR = 0.36, 95% CI: 0.19 to 0.65, $p = 7.68 \times 10^{-4}$) and *NRG1* (rs13250975: OR = 0.42, 95% CI: 0.23 to 0.79, $p = 6.81 \times 10^{-3}$; rs17716295: OR = 1.78, 95% CI: 1.15 to 2.75, $p = 8.71 \times 10^{-3}$).

The influence of genetic variants *DRD2* (–141 C Ins/Del; rs1799732) and 5HTR2C (–759 C>T; rs3813929) on the safety profile of risperidone was inquired. After investigating 289 schizophrenic patients on a risperidone-based therapy (4 to 8 mg/day; for a minimum period of 4 weeks), they opined that these mutants were strongly associated with the rise in serum prolactin levels (OR: 10.45, 95% CI: 1.29 to 84.89, $p = 0.004$) (Alladi *et al.*, 2017).

Major Depressive Disorder

Selective serotonin reuptake inhibitors (SSRIs) are the first-line drugs for the management of major depressive disorder (MDD) patients. However, almost 35% of the patients have been found not to respond optimally to SSRIs and also the time lag to significant therapeutic outcome was substantial (more than 3 weeks). Hence, the necessity for identification of pharmacogenetic markers for SSRI-based therapeutic response in MDD patients arose.

No significant association between the SNPs [*HTR1A* (rs6295), *HTR2A* (rs6311 and rs6313) and *SLC6A4* (44 base-pair insertion/deletion at *5-HTTLPR*)] evaluated and response to escitalopram in North Indian MDD patients (n = 55) was reported (Basu *et al*., 2015). However, they found a significant association between the side effect of memory loss and the variant rs6311 ($p = 0.03$). *SLC6A4* (*5-HTTLPR*) codes for the serotonin transporter.

South Indian major depression patients with LL genotype and L_AL_A haplotype of *SLC6A4* were associated with a favorable treatment response to fluoxetine. The promoter region of the serotonin transporter gene (*SLC6A4*) encompasses a common biallelic polymorphism, i.e., serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) (Manoharan *et al*., 2016). The biallelic variants are the short S allele and the long L allele consequent to the insertion/deletion. rs25531 (A > G) is a functional polymorphism within the L allele leading on to a triallelic variation (L_A, L_G, S).

Bipolar Disorder

One hundred and twenty two bipolar I disorder (BD) patients of Indian origin were included in a trial to explore the association of serotonin transporter triallelic *5-HTTLPR* and *STin2* VNTR polymorphisms with lithium prophylaxis. *STin2* VNTR stands for variable number tandem repeats in the second intron of the serotonin transporter gene. They elucidated that the *STin2* polymorphism strongly influenced the response to lithium ($p = 0.02$). Similarly, the haplotype consisting of the 10 repeat allele of *STin2* and the S allele of *5-HTTLPR* was associated with lithium response ($p = 0.01$) (Tharoor *et al*., 2013).

The SNPs (rs17026688 and rs17026651) in the gene *GADL1*, encoding the glutamate decarboxylase-like protein 1, were not found to be associated with response to lithium therapy in BD patients of Indian ancestry; the trial was conducted in 151 BD patients (Kotambail *et al*., 2015).

Endocrine Disorders

Diabetes Mellitus

Around 415 million diabetes mellitus patients are estimated to be present globally and India harbors around 69.2 million of them. Inter-individual genetic composition has been shown to influence the variability in the glycemic response. Polymorphismsin in genes

encoding various diabetic drug metabolizing enzymes, drug transporters and receptors have been found to be associated with the efficacy and toxicity of various antidiabetic drugs.

Metformin

The clinical significance of the organic cation transporter 1 (OCT1) also known as SLC22A1, encoded by the *SLC22A1* gene, has been illustrated (Umamaheswaran *et al.,* 2015b). They studied the SNP rs622342 (*SLC22A1*) in a cohort of 122 South Indian type 2 diabetes mellitus patients on metformin monotherapy. Patients with the variant C allele responded poorly compared to those with A allele, i.e., metformin responders (AC: 22.6%; CC: 4.3%) possessed lesser number of C alleles compared to non-responders (AC: 44.8%; CC: 13.8%). Metformin being a monovalent cation depends on these transporters (OCTs) for the hepatic uptake and renal transport.

Recently, the genotypic and allelic frequencies of the *SLC47A1*(rs2289669) and *SLC47A2* (rs12943590) gene polymorphisms in South Indian population (n = 102) were established. *SLC47A1* and *SLC47A2* are the genes coding for the transporters MATE1 (multidrug and toxin extrusion protein) and MATE2/2-K, respectively; involved in the efflux transport of metformin across the liver and kidney. The unique finding was that, in contrast to other populations, the minor allele in *SLC47A1* gene was found to be G with a frequency of 46.6% in South Indian population (Raj *et al*., 2017).

The allele and genotype frequency of the genetic variant rs11212617 in ataxia telangiectasia mutated (*ATM*) gene was determined (Vilvanathan *et al*., 2014). The *ATM* gene is involved in the functioning of 5'-adenosine monophosphate activated protein kinase (AMPK) the major target of metformin. In the studied healthy volunteers from South India (n = 112), the frequency of major A allele was 65% and the minor C allele was 35%.

Sulfonylureas and Others

It has been reported that there was no association between *ABCB1* C3435T genetic polymorphism and therapeutic response to glibenclamide, plasma glibenclamide levels and the occurrence of adverse events in South Indian patients with type 2 diabetes mellitus (n = 80). *ABCB1* gene codes for the P-glycoprotein for which the substrate is glibenclamide (Surendiran *et al*., 2015).

CYP enzymes, particularly CYP2C8 and CYP2C9 are involved in the metabolism of antidiabetic drugs. Drugs like pioglitazone and repaglinide are metabolized by CYP2C8; glimepiride and glipizide are metabolized by CYP2C9. *CYP2C8*3* (rs10509681) and *CYP2C9*2* (rs1799853) genotype frequencies were determined in North Indian type 2 diabetes mellitus patients (n = 360) (Mahdi *et al.,* 2016). The frequencies were found to be 0%, 92.8% and 7.2% for CC, TT and CT genotypes of *CYP2C8*3* and 3.1%, 12.5% and 84.4% for CC, AA and CA genotypes of *CYP2C9*2*.

Miscellaneous

Two SNPs, viz., T-786C and G894T were genotyped in the endothelial nitric oxide synthase (*eNOS*) gene and a variable number tandem repeat polymorphism (aa 27VNTR bb) in North Indian type 2 diabetic mellitus patients (Cheema *et al*., 2013). It was a case control study with cases (n = 320) having diabetic nephropathy (DN) and controls (n = 490) without DN. All the subjects were on angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) therapy. The results showed that those patients with *eNOS* -786 CC genotype and haplotypes C-b-G and C-b-T had a lesser renoprotective response to ACEI and the same genetic subset of patients on the contrary had a better renoprotective response to ACEI/ARB if they are macroalbuminuric.

Infectious Diseases

AIDS

The management of patients with HIV/AIDS infection relies heavily on the highly active antiretroviral (ARV) therapy (HAART). The ARV drugs are highly toxic and are associated with numerous adverse drug reactions owing to which many patients require withdrawal of the drug or even discontinue the treatment resulting in treatment failure. ARVs are commonly associated with hepatotoxicity due to intensified oxidative stress to the hepatocytes; genetic polymorphisms in the Phase 1 and Phase 2 drug

metabolizing enzymes could be one of the determinants of occurrence of hepatotoxicity.

As discussed previously, glutathione *S*-transferase (GST) family of enzymes are Phase II conjugating enzymes involved in the detoxification of ARVs by catalyzing the oxidation of glutathione. *GSTM1* null, *GSTT1* null and *GSTP1*-313A/G polymorphisms in 165 HIV-positive patients on ART were studied.These patients were on non-nucleoside reverse transcriptase inhibitor (NNRTI) based ARV therapy (ART) regimen (Effavirenz, n = 23; Nevirapine, n =142). Patients with *GSTM1* null and *GSTT1* null were significantly associated with the risk of hepatotoxicity ($p = 0.004$, OR = 2.67) owing to a synergistic gene-gene interaction (Singh *et al*., 2017a).

The influence of *CYP* gene (Phase I enzymes) polymorphisms on NNRTIs-associated hepatotoxicity has also been described in the same population. rs4646903 (3801T/C in *CYP1A1m1*), rs1799853 (c.430C/T in *CYP2C9*2*), and rs1057910 (c.1075A/C in *CYP2C9*3*) were the polymorphisms genotyped (Singh *et al*., 2017b). However, none of the variants were associated with the ARV-induced risk of development or severity of hepatotoxicity.

Tuberculosis

The current incidence and prevalence of tuberculosis (TB) in India is 171 and 211 per 1,00,000 population, respectively. Around 3 lakh patients succumb to TB in India every year. The standard of care is antituberculosis therapy (ATT) which comprises rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin as the first line drugs. The minimal duration of treatment is 6 months and during this period the patient can be initiated on other non-ATT drugs for the management of co-existing diseases leading on to drug-drug interactions. Rifampicin is a strong pleiotropic CYP enzyme inducer while isoniazid is a potent CYP enzyme inhibitor.

Newly diagnosed tuberculosis patients (n = 48) were recruited and phenytoin 300 mg was utilized as a probe drug for phenotyping CYP2C9 activity (George *et al*., 2012). The patients were on rifampicin 10 mg/kg, isoniazid 5 mg/kg, pyrazinamide 25 mg/kg and ethambutol 15 mg/kg per day. The point of importance in this study was that the CYP2C9 activity was induced irrespective of the genotype status, i.e., even in the combined hetero-mutant (*CYP2C9*1*2* and *CYP2C9*1*3*) and homo-mutant (*CYP2C 9*3*3*) patients the CYP2C9 enzyme was found to be induced ($p < 0.05$).

In the similar way, the influence of ATT on CYP2C19 enzyme activity in genetically polymorphic newly diagnosed tuberculosis South Indian Tamilian patients (n = 125) was described (Xavier *et al*., 2016). The patients were genotyped for *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893) and *CYP2C19*17* alleles (rs12248560). With omeprazole (20 mg) as the probe drug, the findings revealed that the percentage reduction in omeprazole hydroxylation index (OHI) was highest with poor metabolizers (84.1, IQR: 74.6 to 86.6), compared to that of ultra-rapid metabolizers (39.6, IQR: 12.7 to 54.7) in whom it was lowest. OHI tells about the phenotype of CYP2C19 enzyme. However, like in the above study, the authors conclude that the genetic polymorphisms in the *CYP2C19* could not account for the interindividual differences in induction.

The frequency distribution of *CYP2C19*17* (-806C>T) allele and genotypes was reported in South Indian Tamilian population (n = 206); the occurrence of this variant was high in the studied population (19.2%, 95% CI: 15.4 to 23.0%) (Anichavezhi *et al*., 2012a). In another study, the absence of copy number variations of *CYP2C19* in the South Indian population was also described (Anichavezhi *et al*., 2012b).

Currently, the prognosis of TB has improved a lot due to the development of effective ATT with shorter-duration treatment regimens. However, ATT-related adverse effects, especially the incidence of hepatotoxicity, have plagued the success of ATT. Genetic make-up of an individual can determine the development of these side effects which are prevalent in the range from 1 to 36%. In a study comprising 244 North Indian TB patients receiving ATT were studied for the genetic polymorphisms in *GSTM1*, *GSTT1* and *CYP2E1* genes and their effect on ATT-induced hepatotoxicity (Ambreen *et al*., 2014). They found out that patients with *GSTT1* null genotype are more prone to ATT-induced hepatotoxicity (Adjusted-OR: 2.39; 95% CI: 1.06 to 5.39; $p = 0.04$).

Previously, in a similar study in Western Indian population (n = 296) it was reported that the TB patients with either *GSTM1-null* genotype ($p < 0.02$)

or *GSTT1* genotype ($p < 0.007$) were associated with the occurrence of ATT-induced hepatotoxicity (V. H. Gupta *et al*., 2013).

N-acetyltransferase (NAT2) is the primary enzyme involved in the metabolism of isoniazid. It helps in the conversion of isoniazid into acetyl-isoniazid, which is further hydrolysed to produce acetylhydrazine. NAT2 is also involved in the subsequent conversion of acetylhydrazine to diacetylhydrazine, a non-toxic compound. A part of acetylhydrazine is also oxidized into hepatotoxic intermediaries by CYP2E1. 33 Indian patients were enrolled with antituberculosis drug hepatotoxicity (ATDH) in a case-control study to identify the influence of variants in *NAT2* gene (rs1799929, 14240C>T; rs1799930, 14349G>A and rs1799931, 14616G>A) and *CYP2E1* gene (rs2031920, 3979C>T) on ATDH. The patients who contained the mutant A allele for the SNP rs1799930 in *NAT2* gene were found to be positively associated with ATDH (OR: 2.24, 95% CI: 1.31 to 3.84, $p = 0.007$); whereas the other variants were not found to influence the occurrence of ATDH. However, it was also found that patients with two or more mutant alleles, a marker of slow acetylator status, had more incidence of ATDH (OR: 3.23, 95% CI: 1.45 to 7.19, $p = 0.004$) (Mishra *et al*., 2013).

As discussed above, the emphasis of evaluating the *NAT2* genetic status in the Indian population was realized. The NAT2 gene was sequenced in its entirety by assessing an adult Indian population (n = 181) originating in different regions [Maharashtrians (61), North Indians (26), South Indians (41), Gujaratis (42) and Parsees (11)] of the country. Six known SNPs in the *NAT2* gene, viz., 803A > G, 590G > A, 481C > T, 341T > C, 282C > T, and 191G > A were studied and the overall frequency of the slow acetylator haplotypes was 65%, followed by 26% and 9% of intermediate and rapid acetylators, respectively. Of all the haplotypes studied, the *NAT2*5B/*6A* haplotype, a slow acetylator allele, was of the highest frequency (25%) (Tilak *et al*., 2013).

A similar study in the same year was conducted wherein 250 Indians from six different geographic zones [including three tribes inhabiting Odisha (East India)] were genotyped for the SNPs 282C>T, 341T>C, 481C>T, 590G>A, 803A>G and 857G>A in *NAT2* gene.

North India, South India, East India, West India, Central India and Northeast India were the six different geographic zones. In total 35 *NAT2* alleles were identified and out of which 27 acetylator alleles were noted; however, the frequency distribution of slow (47±2.5%) and fast (53±2.3%) acetylators in this study was equal (Khan *et al*., 2013).

Cardiovascular Disorders

Warfarin and Acenocoumarol

For the prevention and treatment of thromboembolic events in patients with deep vein thrombosis, atrial fibrillation, pulmonary embolism or mechanical valve replacements anticoagulation therapy is necessary and warfarin is the most commonly used agent for this purpose. Warfarin has a narrow safety margin and exerts a broad inter individual variability in dose requirements; overestimation of dose causes bleeding events and underestimation of dose results in thromboembolic episodes.

Cytochrome P450 family 2, subfamily C, polypeptide 9 (CYP2C9) is the major enzyme involved in the metabolism of warfarin; almost 90% of warfarin's biotransformation into inactive derivatives is by CYP2C9. Vitamin K epoxide reductase complex 1 (VKORC1) is the pharmacodynamic target for warfarin. Variations in the warfarin dosage requirement for achieving the target therapeutic anticoagulation in different populations is generally due to the genetic polymorphisms in the *CYP2C9* and *VKORC1* genes. Warfarin is one of the few drugs for which genetic testing is recommended before initiating therapy as per the United States Food and Drug Administration (FDA), International Warfarin Pharmacogenetics Consortium (IWPC) and Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines. And in India numerous trials have been undertaken in this field of pharmacogenetics of warfarin in the last few years.

The frequency distribution of *CYP2C9*2* (C430T, rs1799853), *CYP2C9*3* (A1075C, rs1057910), *VKORC1* (-1639G>A, rs9923231) and *VKORC1* (1173C>T, rs9934438) in the Indian population (n = 100) was reported (Shalia *et al*., 2012). By following up 83 patients (aortic or mitral valve replacement) on warfarin anticoagulation therapy, they propounded that the warfarin dosage requirement was

decreasing proportionately from the wild type genotypes to heterozygous genotypes in all the four studied SNPs. The actual stable therapeutic dose reached and the calculated dose for each group was found to be correlated ($r = 0.51$, $p < 0.001$). Based on the international normalized ratio (INR) data available for 26 patients, it was noted that higher the incidence of variant alleles in individual patients more was the INR; hence, the implication is warfarin dose has to be reduced in these patients.

An Indian population-specific pharmacogenomic algorithm to optimize warfarin dosing was put forward (Pavani *et al.*, (2012a); a total of 240 patients on warfarin were included in the study. *CYP2C9*2* (Arg144Cys), *CYP2C9*3* (Ile359Leu), *VKORC1*3* (9041 G>A), *VKORC1*4* (6009 C>T), *VKORC1* p.D36Y (5417 G4T) and *VKORC1* (-1639 G>A) were the explored variants. The algorithm postulated by them is as follows,

Predicted warfarin dose (mg per week) = -(0.1850797953 x age) + (8.107223532 x male gender) + (0.1390121899 x body mass index) + (6.697769856 x *CYP2C9*2*) - (8.275810018 x *CYP2C9*3*) - (10.72676854 x *VKORC1*3*) + (8.873462677 x *VKORC1*4*) + (11.14958922 x *VKORC1* -1639 G>A) - (4.824633754 x vitamin K intake) + 34.9588747.

The dose predicted by them had a significantly positive correlation with other algorithms, such as the Wadelius algorithm ($r = 0.50$, $p < 0.0001$), the Gage algorithm ($r = 0.23$, $p = 0.004$) and the IWPC algorithm ($r = 0.31$, $p < 0.005$). And also the predicted dose of warfarin correlated well with the therapeutic dose ($r = 0.64$, $p < 0.0001$). The newly developed algorithm also possessed better characteristics compared to that of dosing based on the clinical data, like in overall accuracy in predicting warfarin dose (89% *vs* 51%), sensitivity (87% *vs* 52%) and specificity (93% *vs* 50%); similarly, the rate of overestimation (6% *vs* 50%) and underestimation (13% *vs* 48%) were considerably lower with the algorithm.

An expanded genetic algorithm for warfarin dosing has also been described by studying 243 South Indian patients on warfarin therapy for valve replacement, deep vein thrombosis or atrial fibrillation (Pavani *et al.*, 2012b). The algorithms given by them are,

In males, warfarin dose = -(0.1013885349 × age) + (1.449999606 × BMI) + (8.054730665 × *CYP2C9*2*) + (1.726919455 × *CYP2C9*3*) - (4.437335987 × *VKORC1*3*) - (2.771903482 × *VKORC1*4*) + (1.511628517 × *VKORC1* -1639) + (1.570215716 × *CYP4F2* V433M) +(2.409742997 × *GGCX*) + (11.05198035 × *CYP2C9*8*) + 7.970140851

In females, warfarin dose = - (0.05440552061 × age) - (0.2938201651 × BMI) - (1.576151039 × *CYP2C9*2*) - (5.950436495 × *CYP2C9*3*) + (2.983528309 × *VKORC1*3*) + (8.699010214 × *VKORC1*4*) - (11.00733747 × *VKORC1* -1639) - (2.282918521 × *CYP4F2* V433M) - (4.097105716 × *GGCX*) - (2.96671589 × *CYP2C9*8*) + 44.53497515

The current pharmacogenomic algorithms had the ability to account for 61% of the variability in warfarin dose requirements compared to their previous algorithm (44.9%). Like in the above study, the pharmacogenomic predicted dose showed greater accuracy, sensitivity, specificity and lower rate of overestimation and underestimation compared to that of standard empirical dosing. The model was also found to prolong time in therapeutic range and minimize out-of-range INRs. The gene *CYP4F2* is involved in the functioning of vitamin K mono-oxidase and *GGCX* gene is responsible for vitamin K-dependent carboxylation.

Later, it was found that the pharmacogenomic algorithm for warfarin dosing extrapolated by multiple polynomial regression (MPR) was superior to multiple linear regression (MLR) (Pavani *et al.*, 2014). The predicted dose computed by MPR model was better correlated to therapeutic dose ($r = 0.62$ *vs* 0.52); exhibited better diagnostic utility in differentiating the warfarin-sensitive and warfarin-resistant patients (area under the receiver operating characteristic curves: 0.89 *vs* 0.81) and lower rate of underestimation (13.9 *vs* 20%) compared with the MLR model.

Warfarin along with acenocoumarol and phenprocoumon come under the coumarin class of anticoagulants known as 'coumarinic oral-anticoagulants' (COAs). Acenocoumarol is more commonly used than warfarin as anticoagulant therapy in North India. Hence, a population (North Indians, n = 225) specific pharmacogenetic dosing algorithm for acenocoumarol was proposed (Rathore *et al.*, 2012).

By means of multiple regression analysis the daily warfarin dose can be predicted as,

Dose (mg/day) = 3.082-0.013 (smoking status, 1 for smoker and 0 for non-smoker) – 0.433 (sex, 1 for male and 0 for female) – 0.004 (age in years) + indication (0.327 for double valve replacement and – 0.092 for atrial valve replacement) + 0.026 (height in centimetres) + 0.151 (weight in kilograms) – 7.660 (body surface area in cm^2) – 0.862 (*VKORC1* GA) – 2.257 (*VKORC1* AA) – 0.049 (*CYP2C9*2* CT) – 0.456 (*CYP2C9*3* AC) + 0.449 (*CYP4F2* GA) + 0.230 (*CYP4F2* AA) + 0.245 (*GGCX* CG) + 1.055 (*GGCX* GG).

41.1% of the dosage variation with acenocoumarol could be explained by this dosing algorithm ($p < 0.001$). There was also an improvement in various performance measures like sensitivity (76% *vs* 51%), specificity (64% *vs* 49%), rate of overestimation (22% *vs* 27%), rate of underestimation (15% *vs* 23%), overall accuracy (63% *vs* 50%), accuracy in dug sensitive cases (60% *vs* 51%) and accuracy in drug resistant cases (72% *vs* 49%) with the new predictive model compared to the clinical data. Only the variant *VKORC1* -1639G>A was found to be strongly associated with acenocoumarol sensitivity according to recessive model (OR: 4.42, 95% CI: 2.44 to 7.99).

As *CYP4F2* 1347 G>A and *GGCX* 12970 C>G polymorphisms were part of the algorithm, it was proposed to identify these SNP frequency in North Indians and their effect on acenocoumarol dosing. 102 healthy volunteers and 225 patients receiving acenocoumarol after cardiac valve replacement surgery were included; the minor allele frequencies for the SNPs in *CYP4F2* and *GGCX* were 43.1% and 1.4%, respectively in the healthy population. However, the studied SNPs were not found to influence the acenocoumarol dosing (Rathore *et al*., 2014).

South Indian patients on stabilized warfarin therapy (n = 136) were recruited and genotyped for rs9923231 (*VKORC1*-1639G>A), rs9934438 (*VKORC1*1173C>T), rs1799853 (*CYP2C9*2*) and rs1057910 (*CYP2C9*3*) variants. They concluded that those patients who had a novel mutation in the promoter region of the *VKORC1* gene, viz., insertion of G at 3725 position (Ins-Ge1586 with respect to the start codon) along with *VKORC1* -1639G>A variation were on a higher dosage (> 7 mg/day) of warfarin (Shukla *et al*., 2013).

On similar lines, the polymorphism *VKORC1* – 1639 G>A was deduced to be a major determinant of acenocoumarol dose requirement in South Indian population (Krishna Kumar *et al*., 2013). Their trial included 170 patients on acenocoumarol therapy following heart valve replacement surgery. Subjects who contained at least one variant allele of CYP2C9 (**1*2* or **1*3*) required a lower daily maintenance dose of acenocoumarol (2.0 mg and 2.5 mg, respectively) than those with normal CYP2C9**1*1* genotype group (3.4 mg) ($p < 0.05$). In *VKORC1* gene, the patients with wild GG genotype required higher dose (3.3 mg) as compared to those with the mutant genotypes GA (2.3 mg) and AA (1.0 mg) ($p < 0.001$). In summary, patients with both *CYP2C9*1*2/ *1*3* and *VKORC1* GA genotype required a lower dose (2.46 mg) than those with *CYP2C9*1*1* and *VKORC1* GG genotype (3.52 mg) ($p < 0.0001$).

The ethno-geographically distinct North (n = 209) and South Indian (n = 82) populations were studied for predicting the genetic variations influencing warfarin response (Nahar *et al*., 2013). The minor allele frequency of South Indians (SI) and North Indians (NI) were 0.6% *vs* 5% ($p < 0.001$) in *CYP2C9*2*, 9% *vs.* 11% ($p > 0.05$) in *CYP2C9*3* and 14% *vs.* 19% ($p > 0.05$) in *VKORC1*- 1639A. Owing to the increased frequency of *CYP2C9*2* and **3* variants in NI (30.6%) compared to SI (15.9%) considerably larger proportion of NI were genetically predisposed to warfarin-induced bleeding episodes or over anticoagulation (INR > 3) as compared to SI (RR: 1.93; 95% CI: 1.13 to 3.31, $p = 0.012$).

Patients with wild type *VKORC1* genotype (4.72 mg) had more warfarin dose requirements compared to both heterozygous (3.74 mg) and homozygous (2.07 mg) mutants ($p = 0.02$). It was also deciphered that patients with *VKORC1* variants had 13.96 times more chance of developing a supra therapeutic INR than the patients with wild genotypes (OR: 13.96, 95% CI: 4.85 to 44.65) (Natarajan *et al*., 2013).

A major study on six genetic variants [rs1799853 (*CYP2C9*2*), rs1057910 (*CYP2C9*3*), rs2108622 (*CYP4F2*3*), rs7294, rs9923231 and rs99344380] in three important genes involving 2680 individuals across

24 ethnically diverse Indian sub-populations revealed that majority of Indian subpopulations (except, the Tibeto-Burmans) may require higher doses of warfarin for attaining therapeutic INR or stable anticoagulation. The *VKORC1* -1639G>A displayed a higher degree of variation across Indian subpopulations, with frequencies as low as 6.5% in an out-group subpopulation to >70% in Tibeto-Burmans. The frequency of *CYP4F2*3* (V433M) was higher in North Indians (30% to 44%) compared to other world populations; similarly, compared to most other Asian populations the frequency of *CYP2C9*3* (I359L) in North Indians was found to be greater (Giri *et al.*, 2014a).

A 49-year-old patient on low dose warfarin (2.5 mg/day) for the past 8 years presented with a lethal subdural hematoma. The patient was found to possess *CYP2C9* gene polymorphism (*1/*3) with a PT-INR of 9 (Karnik *et al*., 2014).

Another pharmacogenetic algorithm for explicating warfarin maintenance dose was synthesized (Krishna Kumar *et al*., 2014),

Log_{10} dose = 0.656 – 0.187(*VKORC1* rs9923231) + 0.003 (Weight) – 0.196 (*CYP2C9*3*) – 0.144 (*CYP2C9*2*) + 0.083(*VKORC1* rs7294) – 0.003 (Age) + 0.033 (*CYP4F2* rs 2108622) + 0.037 (Clinical condition) – 0.074(*VKORC1* rs 9934438) – 0.097 (*VKORC1* rs 2359612) – 0.130 (*GGCX* rs 11676382)

They studied 240 South Indian patients receiving stabilized warfarin therapy. The above algorithm could explain for 62.1% of the overall inter-individual variation in warfarin daily maintenance dose. Patients with wild-type *CYP2C9*1/*1* genotype (5.2 mg) required a higher daily maintenance dose compared to those with *CYP2C9*1/*2* (2.8 mg), **1/*3* (2.3 mg) and **2/*3* (2.2 mg) variant genotypes ($p <$ 0.0001).

An acenocoumarol-based pharmacogenetic dosing algorithm for South Indian (Dravidian) population (n = 230) was postulated by the same authors (Krishna Kumar *et al*., 2015).

Log_{10} dose = 0.436 – 0.004 (age) + 0.018 (BMI) –0.239 (*VKORC1* rs9923231) –0.163 (*CYP2C9*2*) –0.293 (*CYP2C9*3*) + 0.043 (*CYP4F2*) –0.142 (*GGCX*) + 0.057 (*VKORC1* rs7294).

About 62% of the variability in acenocoumarol dosing could be attributed to the factors in the above algorithm (adjusted $R^2 = 0.615$, $p < 0.0001$). Among the studied eight factors for acenocoumarol dosage prediction, the variants *VKORC1* (rs9923231) and *CYP2C9*3* were the major decisive factors as they accounted for 28.6% and 16.4%, respectively, of the dosage variation. Wild-type carriers of *CYP2C9* (i.e., *CYP2C9*1*1*) 4.1mg had a higher daily acenocoumarol maintenanace dosage requirement compared to *CYP2C9*1*2* (2.0 mg), *CYP2C9*1*3* (1.6 mg), and *CYP2C9*2*3* (1.5 mg) variant genotypes ($p < 0.0001$).

The genotype and allele frequencies of eight SNPs in *VKORC1*, viz., rs9923231 (G), rs7196161 (T), rs2884737 (T), rs17708472 (C), rs9934438 (C), rs8050894 (G), rs23596121 (C) and rs7294 (A) by studying 204 healthy volunteers of Tamilian descent was previously established. The frequency of the haplotype HAP1 (GTTCCGCA) was found to be considerably higher (80%) compared to other 17 haplotypes which had a frequency of less than 8% (Krishna Kumar *et al*., 2013a). In another study, it was ascertained that the variant allele rs7294 in *VKORC1* was (80.1%) more frequent and the variant allele *CYP4F2*3* was found to be 41.8% in South Indians. The study included 470 unrelated healthy volunteers of South India (Krishna Kumar *et al*., 2013b).

Acenocoumarol-treated cerebral venous thrombosis (CVT) patients (n = 476) were genotyped for *CYP2C9*2* and *CYP2C9*3* polymorphisms. Both during the initiation and maintenance phase of anticoagulation the acenocoumarol dose requirement was low in patients carrying *CYP2C9*2* or *CYP2C9*3* variant alleles. The adjusted ORs for the association of the *CYP2C9*2* variant with the likelihood of requiring a low acenocoumarol dose in the initiation and maintenance phase were 5.38 (95% CI: 1.65 to 17.49) and 19.67 (95% CI: 2.46 to 157.19), respectively; similarly, for the *CYP2C9*3* variant they were 12.79 (95% CI: 4.74 to 34.57) and 11.98 (95% CI: 2.61 to 55.08), respectively (De *et al*., 2014).

High prevalence of *VKORC1*3* (G9041A) genetic polymorphism in North Indians was ascertained (Sehgal *et al.*, 2015); the frequency was found to be 72%. The study population included 53

patients with cardiac valve replacement and on acenocoumarol with stable INR. Acenocoumarol dosing requirements were lesser in patients with *CYP2C9*3* (p = 0.03) or *VKORC1*2* (p = 0.02) gene polymorphisms.

Recently, another warfarin dosing prediction algorithm was put forward by studying 300 warfarin-treated Indian patients. The following equation was generated based on the multiple regression analysis,

Square root of dose (mg) = 2.61 – 0.41 (*VKORC1* -1639) – 0.21 (*1/*2) – 0.58 (*1/*3) – 0.86 (*2/*3) – 0.86 (*3/*3) – 0.002 (Age in years) – 0.08 (diet)

The above regression model was found to account for 67% of dose variability with warfarin (R^2 = 0.67, p = 0.001) (Gaikwad *et al*., 2017).

Very recently, the genetically diverse *CYP2C9* variants in the Indian-subcontinent were studied using 1278 subjects from 36 populations. The 36 populations comprised subjects from the States of Jharkhand, Chhattisgarh, Madhya Pradesh, Andhra Pradesh, Tamilnadu, Karnataka, Uttar Pradesh, Jammu Kashmir, Gujarat, Uttarakhand, Maharashtra, Haryana, Nagaland and Mizoram; the studied variants were compared with the populations of 1000 genome project (Nizamuddin *et al*., 2017). The frequency of *CYP2C9*3* (rs1057910, ATT>CTT, I359L) was observed to be higher (0 to 0.179) compared to other populations including the Europeans and the frequency of *CYP2C9*3/*3* was 0 to 0.05 in the Indian sub-continent. They observed a novel non-synonymous mutation of L362V (rs57814497) in *CYP2C9*3*; the allele, heterozygous (L/V) and homozygous (V/V) mutant genotype frequencies were 0 to 5.6%, 0 to 3.7% and 0 to 3.7%, respectively.

Clopidogrel

Patients with acute myocardial infarction and to patients undergoing percutaneous coronary intervention (PCI), clopidogrel, a platelet P_2Y_{12} receptor inhibitor is commonly administered to prevent the occurrence of adverse cardiovascular events. There is a great interindividual variability in clopidogrel response and more than 80% of which can be explained by genetic polymorphisms. The CYP enzyme system is involved in the bio-activation of clopidogrel into active metabolites; CYP2C19 (44.9%), CYP1A2 (35.8%) and CYP2B6 (19.4%) aid in the conversion of clopidogrel to 2-oxoclopidogrel. In the next step, conversion of 2-oxoclopidogrel to its active thiol metabolite takes place in the presence of enzymes viz., CYP3A4 and CYP3A5 (39.8%); CYP2B6 (32.9%); CYP2C19 (20.6%) and CYP2C9.

After analyzing 149 ischemic heart disease patients on clopidogrel maintenance therapy (75 mg daily dose) it was revealed that the patients with *CYP2C19*2* or *CYP2C19*3* gene polymorphisms had higher values of platelet impedance denoting higher residual platelet activities and hence, reduced anti-platelet response to clopidogrel (Subraja *et al*., 2013). They divided patients into two groups viz., Group 1 comprising poor metabolizers (PM) & Intermediate metabolizers (IM) and Group 2 comprising extensive metabolizers (EM) & Ultra-rapid metabolizers (URM). *CYP2C19*2/*2* and *CYP2C19*2/*3* constitute PM; *CYP2C19*1/*2* and *CYP2C19*2/*17* constitute IM; *CYP2C19*1/*1* constitutes EM and *CYP2C19*1/*17* and *CYP2C19*17/*17* constitute URM.

In a study on 102 healthy individuals and 26 clopidogrel naive acute myocardial infarction (AMI) patients it was propounded that the patients with 3435T of *MDR1* (52.4%), *CYP2C19*2* (681A, 35.2%), i-744C of P_2Y_{12} (8.8%) as well as wild type allele *CYP2C19*17* (C806, 89.7%) were associated with decreased response to clopidogrel (Shalia *et al*., 2013). And also the variant genotypes of *CYP2C19*2* and i-T744C of P_2Y_{12} were associated with impaired response of clopidogrel to inhibit platelet aggregation compared to wild genotypes. The subjects were Maharashtrian, Gujarati and Marwadi in decreasing number representing the Western region of India based out of Mumbai. P_2Y_{12} is receptor for ADP which plays a major role in platelet activation and aggregation.

One hundred and forty seven patients on 75 mg/day of clopidogrel as maintenance dose were recruited and genotyped for *CYP3A5*3* (6986 A>G). CYP3A5 accounts for the conversion of 2-oxoclopidogrel to its active thiol metabolite (Priyadharsini *et al*., 2014). Clopidogrel resistance was assessed by ADP-induced platelet aggregation inhibition response; impedance values of >5 ohms at the end of 6 min were considered as clopidogrel resistance. The risk of developing

clopidogrel resistance was more in homomutants (OR: 2.78, $p < 0.05$) and heteromutants (OR: 2.4, $p < 0.05$) of *CYP3A5*3* gene.

Very recently, a significant association ($p < 0.05$) between the risk of development of coronary artery disease and the presence of i744T>C polymorphism in P_2Y_{12} gene was ascertained (Priyadharsini *et al*., 2017). The study population included 221 healthy volunteers and 150 patients of Tamilian origin.

A largest population-scale genetic epidemiology study was undertaken in 2128 Indo-Europeans [Punjab (225), Haryana (108), Delhi (207), Uttar Pradesh (1098) and Bihar (267)] residing in North India for presence of mutants associated with pharmaco genetics of clopidogrel (Giri *et al*., 2014b). Genetic variants of *CYP2C9*2* (rs 1799853, C>T), *CYP2C9*3* (rs1057910, A>C) and *P2RY1* (rs 701265, A>G) were found to occur more commonly in North Indians than in the other world populations (1000 Genome population & HapMap population). Whereas, the variants *ABCB1* (rs 1045642, A>G), *CYP1A2* (rs762551, A>C), *CYP2C19*2C* (rs12571421, A>G), *CYP3A5* (rs 776746, C>T) and *PON1* (rs 662, T>C) were found to occur less frequently. The increased clopidogrel responsiveness seen in North Indian could be due to the presence of complex functional interactions in these variants resulting in improved clopidogrel absorption and active metabolite formation.

The genetic distribution of *CYP2C19* in North-East population of India with cardiovascular diseases (n = 60) was delineated (Prasanthi *et al.*, 2013). They found that the mutant allele frequency for *CYP2C19*2* (rs4244285) as 40% and none of the patients carried the variants of *CYP2C19*3* (rs4986893) and *CYP2C19*17* (rs12248560).

Recently, the genetic influence of *CYP2C19*, P_2Y_{12} and *ABCB1* polymorphisms on phenotypic response to clopidogrel in healthy Indian adults (n = 90) was evaluated. A single dose of 300 mg clopidogrel (4 tablets of 75 mg clopidogrel) was administered (Sridharan *et al.*, 2016). Platelet aggregation was assessed at baseline, 4 hours and 7 days after clopidogrel administration. From patients with wild genotype (*1/*1) to the ones with mutant genotypes (*1/*2, *1/*3, and *2/*2) a decreasing trend in platelet aggregation was noted. In P_2Y_{12} gene, the patients with H2 haplotype showed an increase in platelet aggregation; whereas, the *ABCB1* variant was not found to influence platelet aggregation.

Statins

Statins are the most commonly prescribed cardiovascular drug worldwide and are indicated for the primary and secondary prevention of atherosclerotic cardiovascular diseases. However, the therapeutic response to statins is not the same in all individuals; this inter individual variability can be accounted by the genes related to pharmacokinetics or pharmacodynamics of statins.

Indian patients (n = 177) treated with 10 mg of atorvastatin for 8 weeks were recruited and it was found that the patients possessing wild-type genotypes of *CYP7A1* (rs3808607), *CYP3A4* (rs2740574), *SLCO1B1* (rs2306283) and variant allele-carrying genotypes of *ABCB1* (rs2032582, rs1045642) showed significantly greater LDL-cholesterol reductions in response to atorvastatin therapy (Kadam *et al*., 2016). *CYP7A1* codes for the cholesterol-7-alpha-hydroxylase enzyme involved in the cholesterol synthesis pathway; *SLCO1B1* codes for the transporter solute carrier organic anion transporter family, member 1B1 (SLCO1B1).

The Influence of SNP in 'Sterol Regulatory Element-binding Factors Cleavage-activating Protein' (SCAP) gene

The Influence of SNP in 'Sterol Regulatory Element-binding Factors Cleavage-activating Protein' (SCAP) gene on lipid-lowering response to rosuvastatin in Indian patients with metabolic syndrome (n = 63) was studied (Rafeeq *et al*., 2016). Genotyping was done for *SCAP* 2386A>G gene polymorphism in these patients who were on rosuvastatin 5 mg for 3 months. The presence of G allele was positively associated with rosuvastatin response ($p = 0.043$), i.e., the carriers of GG/GA genotypes showed a greater reduction in total cholesterol levels compared to that of AA genotypes ($p = 0.0048$).

Of late, the allele and genotype frequency distributions for *HMGCR* (rs5908, 1912A>G; rs17238540, 74655498T>G; rs12916, 372C>T), *LDLR* (rs688, 1773C>T), *CYP7A1* (rs3808607, 58500365G>T), *ABCB1* (rs1128503, 87550285A>G), and *SLCO1B1* (rs4149056, 521T>C) genetic variants among healthy subjects of South Indian Tamil

population (n = 100) has been established (Indumathi *et al.,* 2017). The frequencies of SNPs *HMGCR* rs17238540 and *LDLR* rs688 differed significantly from that of other ethnicities worldwide. *HMGCR* codes for 3-hydroxy-3-methylglutaryl-CoA reductase which is the rate-limiting enzyme for cholesterol synthesis and *LDLR* codes for low-density lipoprotein receptor, which is involved in endocytosis of LDL cholesterol.

Miscellaneous

Corticosteroids are the main stay of management in children with Idiopathic Nephrotic Syndrome (INS). It was discovered that the SNP G2677T in *MDR1* gene was associated with both disease susceptibility and resistance to steroid therapy. The study group consisted of 100 healthy volunteers and 150 INS patients (Dhandapani *et al.,* 2015).

The success of IVF is determined by the ovarian response to exogenously administered FSH. In a study it was propounded that the patients with A/A–Asn/Asn genotype in g.-29G>A and p.Asn680Ser of *FSHR* gene portrayed poorer ovarian response (OR: 7.92, $p = 0.009$) (Desai *et al.*, 2013). A total of 150 normogonadotrophic ovulatory women (menstrual cycle length 25 to 35 days) with infertility due to male or tubal factor or with unexplained infertility were included in the study.

The renal transplant patients (n = 25) with mutant allele *CYP3A5*3* (A6986G) showed higher plasma tacrolimus levels compared to other patients. And the *CYP3A5*1/*1* homozygous patients showed significantly more frequent incidence of acute rejection episodes (40%) compared to patients with *CYP3A5*1/*3* (20%) or *CYP3A5*3/*3* (13%) genotypes (Nair *et al.,* 2015).

One hundred and seven healthy volunteers from North India were administered bupropion 75 mg and genotyped for *CYP2B6*. It was divulged that 20.56% individuals in the study population were poor metabolizers for the category of drugs metabolized by CYP2B6 (Varshney *et al.,* 2012).

Mtx is still the gold standard for the treatment of moderate to severe psoriasis despite development of several other novel agents. Very recently, it was proposed that the genetic variants *HLA-Cw6* and *FOXP3* (rs3761548, T-regulatory gene) could function as genetic predictors of clinical response to methotrexate in psoriasis ($p < 0.005$) (Indhumathi *et al.,* 2017). They recruited 189 South Indian Tamil patients with moderate to severe psoriasis out of which 132 were found to be responders.

It was reported that the carriers (19.7%) of the *CYP2C19*17* allele (rapid and ultra-rapid metabolizers) did not respond to the standard dose of proton pump inhibitors after evaluating healthy urban and tribal subjects (Koya and Naik tribes) from South India (Deshpande *et al.,* 2016).

Based on a study in 69 South Indian patients with symptoms of alcohol withdrawal administered with both loading (10 mg) and maintenance (20 mg q2h, based on the symptoms) dose of diazepam it was clarified that *CYP2C19* polymorphism did not have any significant effect on the diazepam dose requirement, time duration for reversal of acute symptoms or on the persistent symptoms after loading dose of diazepam (Jose *et al.,* 2016).

β-thalassemia patients require frequent blood transfusions resulting in chronic iron overload; deferiprone is used as a chelation agent. β-thalassemia major patients (n = 286) for three most common nonsynonymous *UGT1A6*2* polymorphisms, viz., Thr181Ala (541 A/G), Arg184Ser (552 A/C) and Ser7Ala (19 T/G) were studied. The occurrence of *UGT1A6*2* Thr181Ala polymorphisms differed significantly between responders and non-responders; likewise in *UGT1A6*2* Ser7Ala polymorphism there was a significant difference between responders with and without ADRs and non-responders with and without ADRs (Dadheech *et al.,* 2013).

A retrospective study was undertaken in Tamilian population comprising of three groups, viz., Group 1 consisting of 287 myocardial infarction (MI) patients, Group 2 consisting of 279 risk control patients (i.e., patients who had one of the conventional risk factor for coronary heart disease like hypertension) and Group 3 with 321 healthy individuals. The results showed that patients with *CYP2J2*7* polymorphism were significantly associated with the occurrence of MI (Arun Kumar *et al.,* 2015).

However, an association between *eNOS*3 gene polymorphisms (894G>T and -786T>C) and the risk of acute myocardial infarction in the same study population could not be identified (Arun Kumar *et*

al., 2013).

Similarly, it has been reported that the 894G>T and 786T>C of *eNOS* gene polymorphisms were not associated with salbutamol evoked endothelium dependent vasodilation in South Indian healthy subjects (n = 102); 400 micrograms of salbutamol was given through inhalational route (Kumar *et al.,* 2013).

Conclusion

The research in the field of pharmacogenetics and pharmacogenomics had flourished in the Indian arena in the last few years to such an extent that we could cite more than 130 odd research publications from MEDLINE (PubMed) and Google Scholar; we have not referred to other databases which could be a limitation. Only original research articles conducted in Indian populations and published between January 2012 and July 2017 are included in this review; we have not considered other article types. 'Pharmacogenetics AND India', 'pharmacogenomics AND India', 'genetic variations AND drugs AND India', 'genetic polymorphisms AND drugs AND India', 'personalized medicine AND India' and 'precision medicine AND India' are some of the search items used.

There are some disparities with respect to the various ethnic populations studied. More studies were from the North and South Indian ethnicities, geographically or the Indo-Europeans (Aryans) and Dravidians, linguistically compared to their counterparts; the ethnically distinct North-Eastern Tibeto-Burman populations were studied very sparsely. These racial differences play a major role in determining the diverse genetic make-up of populations.

Through this review, it is appreciable that there is a bias in the category of diseases or drugs studied for pharmacogenetic variations in efficacy and safety. Drugs such as warfarin, acenocoumarol, clopidogrel and diseases like breast cancer are studied more extensively than others; studies on diabetes and bronchial asthma pharmacogenetics were found to be very minimal, ironically. Similarly, no or meagre pharmacogenetic studies were done on drugs like abacavir, irinotecan and capecitabine for which the testing of pharmacogenetic markers are already made mandatory by the US (FDA) and European (European Medicines Agency, EMEA) drug regulatory agencies and recommended by the Indian drug regulatory agency Central Drugs Standard Control Organization (CDSCO).

However, more research in the areas involving anticancer drugs, anticoagulants and antiplatelets could be justified by the fact that India is in line with other worldwide regions wherein also the same trend is reflected. But having said so, in a nation like India equal emphasis should be on conditions like tuberculosis, AIDS and diabetes which are more rampant.

Currently, there is a call for a multi-omics approach, wherein application of pharmacogenomics along with transcriptomics, proteomics, metabolomics and microbiomics techniques ("integrative genomics") will support in delineating the interactions between gene and environment (including drugs) comprehensively; hence, making way for the most precise and personalized management of all disease conditions. And in India with its extreme heterogeneity in all forms attaining this state can be an unrelenting task – but not impossible!

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