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Pharmacogenomics of Drug Transporters

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ABSTRACT

Pharmacogenomics deals with the notion that suggests that an individual's genes which encode for various drug transporters, drug targets, and drug metabolizing enzymes affect the drug's disposition and effects in the body.Pharmacogenomics deals with individualized drug therapy where it detects the variations (SNPs, slicing in genes, etc.) in genes which give rise to suitable medicine dosage to individuals without them causing adverse drug reactions which requires the constant observation of the pharmacokinetics, pharmacodynamics and the effects of drugs in the patients.Polymorphisms have been detected and characterized in many genes encoding for drug transporters. Drug transporters help in mediating the drug through the cell membrane of various tissues like intestine, kidney, liver, brain. Transporters are of two types depending upon their function: uptake (OAT and OCT) and efflux (P-gp, MATE, BCRP etc.) These polymorphisms affect the drug's response and disposition in the body which can lead to adverse drug reactions for example; gefinitib toxicity is caused by the polymorphisms in gene ABCG2. This report entails the several polymorphisms present in the genes for encoding drug transporters and their impact on drug response. The clinical applications of pharmacogenomics are limited because to prove that these clinical results which are based on genetics and individualizing drug therapy have favourable outcome through pharmacogenomics studies is difficult. Recently, proteomics and other molecular genotyping methods have been incorporated with pharmacogenomics as a means of individualized drug therapy.

I. INTRODUCTION

Pharmacogenomics deals with the notion that suggests that an individual's genes which encode for various drug transporters, drug targets, and drug metabolizing enzymes affect the drug's disposition and effects in the body. Pharmacogenomics as a science has modified over the past 50 years having the first idea of it generate in the 1950s where an association between the hereditary information of an individual and the erratic responses of a drug was established. It wasn't until the 1980s where the notion of genetic polymorphisms affecting the drug response was fully developed. Usually the dosage of a particular drugthat is prescribed by physicians is dependent on clinical research, where, the drug that elicits the most optimal results in mitigating the symptoms in a small population is chosen. This method is applicable for most individuals whose drug response is effective in treating the disease. But in some patients, the drug showed lack of therapeutic response and instead resulted in adverse drug reactions (ADRs)which could be capable of death of that individual. Pharmacogenomics deals with individualized drug therapy where it detects the variations (SNPs, slicing in genes, etc.) in genes which give rise to suitable medicine dosage to individuals without them causing ADRs which requires the constant observation of the pharmacokinetics, pharmacodynamics and the effects of drugs in the patients. But there are still obstacles in the arena of identifying polymorphisms and relating them to an individual's drug response which in turn has created barriers for the clinical applications of pharmacogenomics. In the recent years, pharmacogenomics has shifted from its "one drug-one gene" notion and focused more on the polygenic determinants of drug effects and take into account the variables of ethnic origins in the responses to pharmacotherapy.

Polymorphisms have been detected and characterized in many genes encoding for drug transporters. Drug transporters help in mediating the drug through the cell membrane of various tissues like intestine, kidney, liver, brain and they have an important function in the ADME which represents the absorption, distribution, metabolism, excretion of a particular drug. They are involved in the efflux and influx of drugs and the transporters are divided based on these functions. Uptake transporters transport the substances inside the cell (influx) and efflux transporters transport the substances outside the cell (efflux). The transport of drugs takes place through various ways across the membrane. Processes like simple diffusion, facilitated diffusion, active transport, and endocytosis help in the moving

of drugs through the membrane. Uptake transporters comprises of organic anion transporter which transport anionic drugs and metabolites and organic cation transporters which transport cationic drugs and metabolites. These two transporters belong to thesolute carrier family. Efflux transporters include MDR/TAP family MRP2 protein, BCRP protein and MATE (multidrug and toxin extrusion) protein along with P-glycoprotein (p-gp). All these are associated with the ATP binding cassette family with the exception of MATE. Polymorphisms in these transporters can cause the toxicity of drugs and can result in ADR which takes place through a probable pathway which starts with the decrease in activity of the efflux transporter mediated excretion of drugs through liver or kidney which gives rise to the increase in oral bioavailability and decreased activity of cell membrane and which ultimately leads to the increased levels of drugs in the cell and drug toxicity. For example, polymorphisms in the gene MDR1, also known as ABCB1 which codes for p-glycoprotein results in neurotoxicity after the administration of the drug tacrolimus and cyclosporine toxicity, polymorphisms in ABCB2 cause atorvastatin toxicity, polymorphisms in SLCO1B1 cause irregularities in the response of flusvastatin, gefinitib and erlonitib toxicity by the polymorphisms present in ABCG2. The frequencies of these polymorphisms occurring in the genes depends on ethnicities and races which has given rise to them being used as a factor in genetic association studies.

II. REVIEW OF LITERATURE

1. **Toshihisa Ishikawa et al, 2013**deals with the excretion of excess uric acid by kidney by ABC transporter ABCG2. Excess uric acid can cause complications in the body like gout and diabetes. Two SNPs in ABCG2 namely 421C>A and 376>T give rise to disturbance in the transport activity because of two reasons, proteosomal degradation moderated by ubiquitination and ABCG2 reduction. The distribution of these SNPs varies in races with a higher percentage among Asian populations. A new and fast method has been made for the detection of the 421C<A SNP which requires just a drop of blood. For the refinement of prevention for high risk patients in the field of personalized medicine, in which pharmacogenomics play a huge role, the successful formulation of new genotyping methods might help immensely.
2. **Li J et al, 2007**studied the importance of the polymorphisms in the transporter ABCG2 in the pharmacokinetics of getifinib and erlotinib. The SNP in question is the ABCG2 421C>A. This SNP was discovered through direct sequencing. It was observed that there was a fall in the level of gefinitib and erlonitib aggregation in cells comprising of the wild type ABCG2 compared to ones without ABCG2. There was no observed cellular accumulation of gefinitiband erlonitibin variant cell lines. There was also observed that the accumulation of gefinitib and erlonitibwas elevated inheterozygous patients at the ABCG2 421C>A locus after 30 days of cancer therapy. It was concluded that gefinitib and erlonitib are the substrates of ABCG2 and they restrict their activity at increased concentrations.
3. **Sadhasivam Set al, 2015** deals with the consequence of the polymorphisms present in ABCB1 with respect to morphine movement through the blood-brain barrier. It might cause analgesic and adverse side effects in patients. This study was focussed on the study of the development of the relations between ABCB1 variants and the clinical results together with respiratory depression (RD) caused by opioids. It also aimed at studying the effect of RD on 263 tonsillectomy patients with respect to their increased stay at the hospital. It was observed that there was an increased risk of RD which in turn gave rise to increased hospital stay in patients having the GG and GA genotypes of SNP rs 92822584.
4. **King Leung Funget al, 2013**studies the effect of polymorphisms in the efflux of drug action by P-gp encoded by ABCB1. Epithelial cell lines with DNA similar to ABCB1 were formed and named LLC-MDR1-WT as it expressed wild type P-gp, LLC-MDR1-3H as it expressed a typical haplotype along witha mutant strain LLC-MDR1-3HA which comprised of a valine codon in 3435 position. In each of these cell lines, P-gp was expressed adequately in the apical surfaces but the mutant and the haplotype cells expressing P-gp was observed to fold differently compared to the wild type. It was also observed through drug transport assays that the effect of the inhibition of drug efflux action of mitoxantrone was expressed differently in wild type and haplotype P-gps. It was also seen that after being subjected to inhibitors, the haplotype P-gpsshowed more resistance than mutant ones to the mitoxantrone. In these cell lines, with different degrees of expression of P-gps it was observed that it does not influence the ATP reactions or the cell's growth rate or the structure of the cell. This study helps to conclude that the P-gp action of the cell is greatly affected by silent polymorphisms (polymorphisms not having a phenotype) which can directly affect the drug nature and response of a patient.

5. **Ziyu Li et al, 2016**studied the significance of the polymorphic changes in various genes such asMTHFR, DPYD, UMPS, ABCB1, ABCC2, GSTP1, ERCC1, and XRCC1 and their functionality as biomarkers. This was studied with a group of 100 gastric cancer individuals having preoperative chemotherapy. After the extraction of DNA, it was observed that the genotype *ABCC2*-24C > T (rs717620) was directly affecting the clinical response to neoadjuvant chemotherapy. Additionally,it was seen that there was a greater feedback to neoadjuvant chemotherapy in individuals having TC and TT compared to patients with CC genotype, thus confirming the effect of polymorphism in the response prediction of preoperative chemotherapy to individuals with gastric cancer.

6. **Hoenig MR et al, 2011** deals with the relation between the polymorphism C3435T occuring in the transporter ABCB1 and the decrease in the response of low density lipoprotein cholesterol (LDL-C) to atorvastin. The study aimed at testing the association between the genotype and efficacy of Atorvastin while being independent of the variation in the metabolism of cholesterol and the occurrence of myalgia. About 117 Patients with high risk were dosed 60mg of atorvastin for 6 weeks and the decrease in LDL-C due to Atorvastin was observed with respect to the C3435T polymorphism in patients. Irrespective of them having myalgia, the genotypes of the patients were assessed. It was observed that 10 patients contracted myalgia while 98 patients showed accurate Atorvastin adherence with majority of myalgia patients having the T allele than the C allele (0.80 vs 0.20). There was also a 58% reduction of LDL-C with the CC genotype having a less decrease than the TT/TC genotype. These findings were independent of the metabolism of cholesterol. Thus it was inferred that the C3435T polymorphism in ABCB1 of the CC genotype is directly associated with the efficacy of Atorvastin with the TT allele having a higher frequency in patients suffering from myalgia.

7. **Ferarri M et al, 2014** deals with the relation between the polymorphisms in the transporters responsible for statins in the body with the increase in the levels of creatine kinase (CK). By the observation of the CK levels, myopathy which is an adverse drug side effect of statin can be prevented. Genotyping of patients having or not having increased levels of CK due to statin were done to detect the polymorphic changes in genes SLCO1B1, i.e. SLCO1B1 A388G and SLCO1B1 T521C), ABCB1 i.e. ABCB1 C1236T and ABCB1 C3435T and ABCG2 i.e. ABCG2 C421A. It was observed that the patients having SNP ABCB1 C1236T had a odd ratio od 4.67 and the patients having the SNP SLCO1B1 A388G had an odd ratio of 0.24. Thus it was concluded that the genotyping of SLCO1B1, ABCB1 along with ABCG2 was essential for the efficacy of statin and reducing the cost of the various tests required for the level of CK.

8. **George C. et al, 2006** researched the link between the transporter ABCB1 and the polymorphisms in ABCG2 with the adverse side effects of the intake of gefibitib. Commonly, diarrhoea and skin toxicity occur as adverse drug reactions which restrict the function of gefinitib. 124 patients were dosed 250 mg of diarrhea once every day. Out of them, 7 in 16 patients with SNP ABCG2 421C>A heterozygous had diarrhea compared to 14 in the rest 108 patients with wild type homozygous. But the aforementioned SNP was nowhere related to the adverse side effects. Thus the study showed that the SNP due to which the activity of ABCG2 is inhibited there is a higher risk of substrate drug–induced diarrhea which calls for the increase in the development of treatment with these.

9. **Hon-Kit Lee et al, 2013**studied the relation of the polymorphisms in ABCG2 and other genes which regulate the pharmacokinetics of rosuvastatin with their effect on the rosuvastatin plasma concentration on hypercholesterolemia patients of Chinese descent. The patients were given a rosuvastatindosage of 10mg for 4 weeks and the concentration rosuvastatin and N-desmethylrosuvastatin plasma were determined. It was observed that in patients having the genotype ABCG2 421AA, the concentration of plasma of rosuvastatin was 41% higher than those patients with the 421CA genotype and as much as 99% higher than the patients with 421CC genotype. It was also seen that the polymorphismABCG2 421C>A affected the relation between the concentration of plasma of rosuvastatin with the decrease in LDL-C and the polymorphism SLCO1B1 521T>C inhibited N-demethylation of rosuvastatin but increased the concentration of plasma of rosuvastatin and it alsoshowed no effect on the lipid lowering. Other genes like CYP2C9, CYP2C19 and SLC10A1 did not have any effect.

10. **Amanda Hays et al, 2013**studies the expression of OATs in mainly epithelial tissues like in this case in human pancreatic ductal adenocarcinomas and their prospective usage in the treatment of cancer by using them for the transportation of anticancer drugs. All the 11 anion transporters are expressed at the level of mRNA and the highest expression is identified at the protein level. In all the pancreatic tissues, SLCO1B3,

SLCO2A1, SLCO3A1 and SLCO4A1 along with expression of protein in OATP1B3, OATP2A1, OATP3A1 and OATP4A1 were observed. It was seen that the transporter expressionin the pancreatic tissues with adenocarcinoma was elevated as juxtaposed to typicalpancreatic tissues. Among these, in the pancreatic hyperplasia and stage one adenocarcinomas, the expression of OATP1B3 was the greatest as compared to adenocarcinomas of stage 2 or 3. In conclusion, in pancreatic adenocarcinoma, the response of the transporters OATP1B3, OATP2A1, OATP3A1 and OATP4A1 are increased and they could be possibly used as drug targets to treat pancreatic cancer. Also OATP1B3 being the highest expressed transporter in pancreatitis and pancreatic cancer, it can be used as a marker for the diagnostic purposes in the likely future.

11. **R G Tirona et al, 2001**studies the important polymorphisms present in OATP-C. OATP-C is a significant transporter which helps in the uptake of drugs specifically through the liver. Frequencies of polymorphisms are highly dependent on race and ethnicity. This was deduced by the study of 14 non-synonymous polymorphisms. It was observed that there was a decrease in the uptake of estronesulfate and estradiol 17-beta-d-glucuronide which are substrates of OATP-C after the testing of 16 variant alleles. This indicated that the SNPs hindered the transport of these substrates by changing the amino acid sequences in the trans-membrane-bridging domains. Another reason for the decrease in uptake of these substrates was found to be the reduction of the function of plasma membrane by biotinylation experiments based on cell surface. This study was done in a population of European-and African-Americans. A higher frequency of T521C transient changes was observed in European-Americans whereas G1463C transformations in African-Americans. Thus, polymorphisms in OATP-C are an unidentifiable factor which affects the drug behaviour and function.

12. **YoheiNishizato BS et al, 2003** deals with the assessment of the importance of polymorphisms in the anion transporters, OATP-C and OAT 3 in the pharmacokinetics of pravastatin. 120 subjects were taken and the polymorphisms in these transporters were detected and analysed by PCR and DNA sequencing. To determine the ability of these genes to modify the path of the drug pravastatin, 23 subjects were taken and clinical evaluation was done by taken pravastatin as a selective probe drug. It was observed that within the 120 subjects, 5 variants of OATP-C and 1 variant of OAT3 were found, both non-synonymous. The polymorphisms in OATP-C related to the dissimilarity in the character of the pravastatin pharmacokinetics whereas in OAT3 they did not appear to have any effect on the real or tubular clearance of pravastatin. SNPs like T521C (Val174Ala) are expected to be related to the change in the pharmacokinetics of pravastatin which can only be confirmed by large scale clinical evaluations.

13. **Chew SCet al, 2011** study the irregularity of the docetaxel pharmacokinetics and pharmacodynamics in between 54 individuals with Asian descent having nasopharyngeal carcinoma. A dosage of 30mg of docetaxel was administered to the patients over a course of 28 days and their DNA was isolated and genesCYP3A4, CYP3A5, ABCB1, ABCC2, ABCG2 and SLCO1B3 were genotyped for polymorphisms. It was observed that there was a greater area below the plasma concentration-time curve of docetaxel and lower clearance for patients homozygous withGG of SLCO1B3 rs11045585 as juxtaposed in AA or AA patients. It was also observed that the patients heterozygous for genotypeGA, GT and TA for ABCB1 rs2032582 had the greatest measure of reduction of nadir haemoglobin as compared to CC or TT patients. Thus this confirms the effect SLCO1B3 and ABCB1 polymorphisms in the disposition of docetaxel in patients withnasopharyngeal cancer.

14. **VibhaBhatnagar et al, 2006** studies the OATs associated with the movement of drugs and other metabolites through the kidney. The transporter OAT1 and OAT3 are presumably directly associated with the movement of drugs from the blood to the proximal tubules of the kidney. Polymorphic changes in the genes encoding for these drugs have a principle function in drug disposition specifically in the 5' regulatory region. So having screened for polymorphisms in the 5' regulatory region of genes SLC22A6 and SLC22A8 which encode for OAT1 and OAT3 in 96 subjects, only one SNP was found in SLC22A6 whereas seven were detected in SLC22A8. Having these polymorphisms so close to transcriptional elements, it might be possible that these SNPs affect the transcription of these genes which in turn affects their drug behaviour and excretion. Also the high degree of accumulation of the OAT genes in the genome suggests the fact that the polymorphisms of SLC22A6 and SLC22A8 can affect the functionality of each other.

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III. OBJECTIVES

1. To understand pharmacogenomics with the treatment of lymphoblastic leukaemia and breast cancer.
2. To understand the mechanism and different types of drug transporters
3. To understand the polymorphisms in drug transporters
4. To understand the significance of pharmacogenomics
5. To understand scope of clinical applications of pharmacogenomics

IV. DISCUSSION

PHARMACOGENOMICS

Pharmacogenomics is generally related to the concept of scanning across the entire genome to try and find genes, generally, genes that relate to pharmacodynamics, the mechanism of drug response, which helps in the identification of new drug targets. Pharmacogenomics is a critical component of individualized or personalized medicine. There are many purposes of pharmacogenomics. Drugs can have unfavourable side effects along with their use in treating the disease. Pharmacogenomics helps to avoid these side effects, like adverse drug reactions and it helps in maximizing drug efficacy. It also helps in potentially selecting responsive patients in the front end which may mean that the era of the "blockbluster drug" (it is usually referred to as the most popular drug sold by a company which can generate revenue upto $1 billion) might be fading away. One of pharmacology's main goals is to link genomics or metabolomics or proteomics to variation in the drug response phenotype and to understand the underlying mechanism and to translate that link at the end into increased understanding, enhanced diagnosis, treatment and ultimately prevention of disease. One of the main examples of this is the cure of cancer by drugs. The evolution of pharmacogenomics starts with the concept of pharmacogenetics which deals with one gene at a time,whether it is cytochrome p450 or drug transporter gene or genes that code for drug metabolizingenzymes. Research on this was significant in the 20th century, and now in the 21st century, research continues, including the entire genome and it begins integrating all these -omics techniques to know more about drug response. To understand this even further, here are the examples of two totally different diseases. First we have acute lymphoblastic leukemia, the most common cancer in kids. Second we have breast cancer, the most invasive cancer in women. Here are some drug gene pairs that the FDA has labelled: Thiopurines-TPMT, Irinotecan-UGT1A1, Warfarin-CYP2C9-CYP4F2-VKOR1, Tamoxifen-CYP2D6, Codeine-CYP2D6, Clopidogrel-CYP2C19.

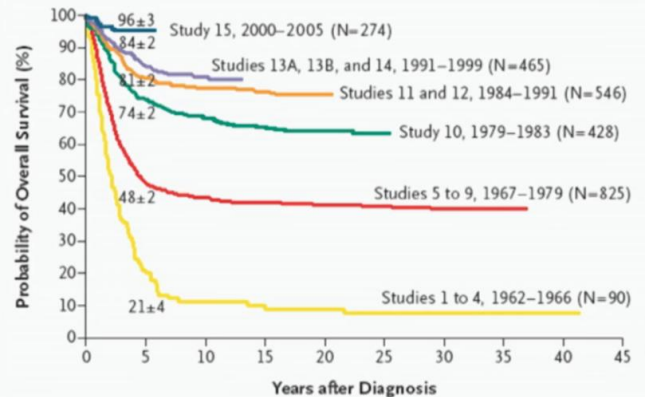

Fig 1: Kaplan-Meier curve of St. Jude experience of childhood leukemia.

The above figure are the Kaplan-Meier curves (it shows the probability of survival at a certain time interval) of the St. Jude experience where childhood acute leukemia was studied through various years starting from 1960s to 2000s. In the early days, when a child was diagnosed with this leukemia, they would have been dead within a year or two. With the advancement of drug therapy, the survival rate has been increased which is a triumph of modern medicine. This was possible with involvement of 6-mercaptopurine in those drugs which was used for the treatment. In the structure of 6-mercaptopurine, there is sulphur which kills the rapidly dividing cells by damaging the DNA in those cells. It was known that the way the body metabolizes these drugs is by xanthine oxidase or s-methylation which was discovered by Remy in rats and mice.

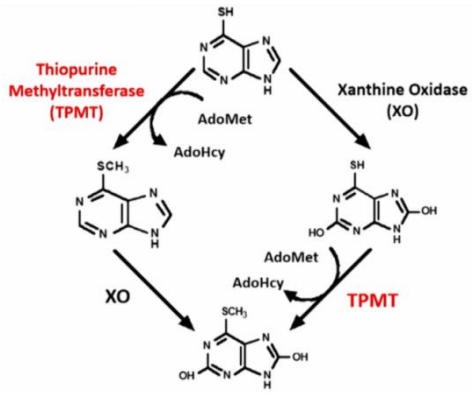

Fig 2: 2,8-Dihydroxy-6-Methylmercaptopurine

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There might be possibility of genetic variation in some of the kids which prevents them to metabolize the drug properly because according to the PDR from 1980, one in 300 kids, when treated with these drugs, showed profound mild suppression which can be fatal. Below is a trimodal frequency distribution histogram of 300 randomly selected blood samples and this study was done at Fudan Medical School, Shanghai and the variant has never been seen before in East Asia.

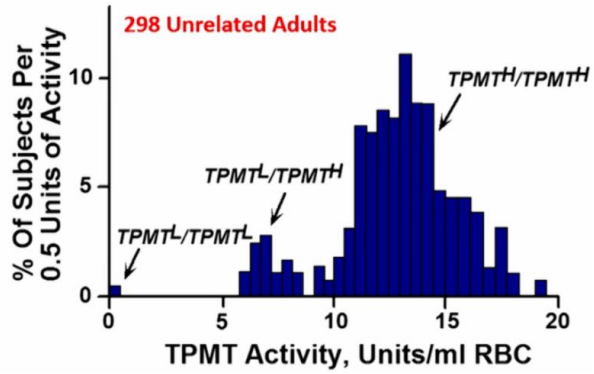

Fig 3: TPMT activity in 300 unrelated individuals.

This distribution is exactly what is predicted by the Hardy-Weinberg theorem for a single genetic locus, for high and low enzyme activity, with a minor allele frequency of 5% (this is proved to be accurate, because this is the result, when the genes are cloned). When there is low TPMT, there is increased thiopurine activity and greater risk of secondary neoplasm. With high TPMT, there is reduced therapeutic activity. This example personifies what pharmacogenomics is. Recently this information is put into the electronic medical records and there are drug gene alerts put into place like thiopurine, tamoxifen, warfarin etc.

To further understand pharmacogenomics, we use breast cancer as an example which is the greatest invasive cancer in women. The major advancement in the treatment of breast cancer in the past 60 years was endocrine therapy and the understanding was that 70-80% of the tumours express the estrogenreceptor, which was driving the tumour growth even further. So, in order to block this effect, the drug tamoxifenis used which is an antagonist,by which, the recurrence of estrogen receptors can decrease by 50%. Also aromatase inhibitors are used to block estrogen synthesis which gives the same effect. These drugs can prevent the possibility of breast cancer. FDA has approved tamoxifen to prevent breast cancer in high risk women. To prove this, a study was done with NSABP (The National Surgical Adjuvant Breast and Bowel Project) with two clinical trials P1 and P2 which involved 33,000 women and which went on for over a decade in Riken centre for Genomic Medicine. Here are the results, P1: It went on for 5 years and was placebo controlled. It was started in 1992 and samples were taken from 13,388 high risk women and it was seen that it reduced the occurrence of breast cancer by 50%. P2: It started in 1999 and samples were taken from 19,747 women and it was 5 years of raloxifene versus 5 years of tamoxifen. The results were the same as P1. There was no difference in breast cancer rates. Both tamoxifen and raloxifene are FDA approved drugs for breast cancer. It was found out that in about 600 women, despite the treatment of these drugs, they developed symptoms of cancer (invasive carcinoma and ductal carcinoma in situ). Two controls were developed for each of those women. A GWAS (genome wide association study) was done genotyping across the genome. Below is the Manhattan plot (a type of scatter plot used in GWAS) for that particular study:

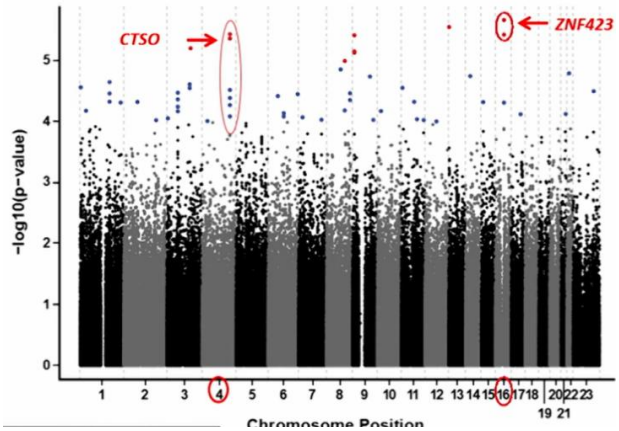

Fig 4: GWAS of 600 women with breast cancer after treatment of tamoifen and raloxifene

From the above plot, we can notice two gene circled high up, ZNF423 on chromosome 16 and CTSO on chromosome 4. These were relatively unknown genes unlike TPMT which metabolized thiopurine. These were not genome wide significant. The p value was not 5 times 10^{-8}, but it was about 10^{-6}. This was because 60% of all the samples in the world were not looked at with regard to breast cancer and it was pursued functionally. So about 300 lymphoblastoid cell lines were gathered, 100 from African-American subjects, 100 from Han Chinese-American and a 100 from Caucasian American so that all the common genotypes were established and tested. The results are below:

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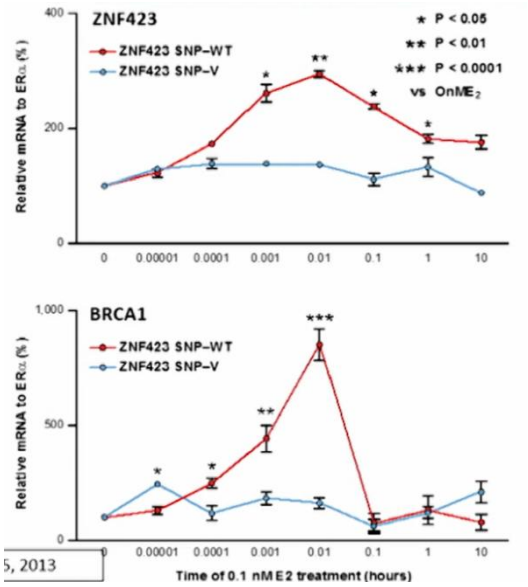

Fig 5: ZNF423 and BRCA 1 expression in ERα stably transfected LCLs

The red line shows the ZNF423 for the wild type genotype. These subjects could induce it with estrogen while the drug is blocking the estrogen receptor whereas the variant subjects could not do that (blue line). In the bottom graph, it can be seen that BRCA1 which is a gene which codes for tumour suppression can also be induced. In women, BRCA1 is turned on in favourable conditions. The snips present in ZNF423 turned out be zinc finger transcription factor that grabs on to the promoter for BRCA1 and turns it on but only in some women taking tamoxifen.

With CTSO, it is exactly the same thing. Two proteins were found to be involved in the induction of the expression of BRCA1. It is known that BRCA1 is induced by estrogen but it wasn't known what was doing that. It was known that it wasn't the estrogen receptor directly bound to the ligand estradiol. Now a novel mechanism is found to turn on BRCA 1.

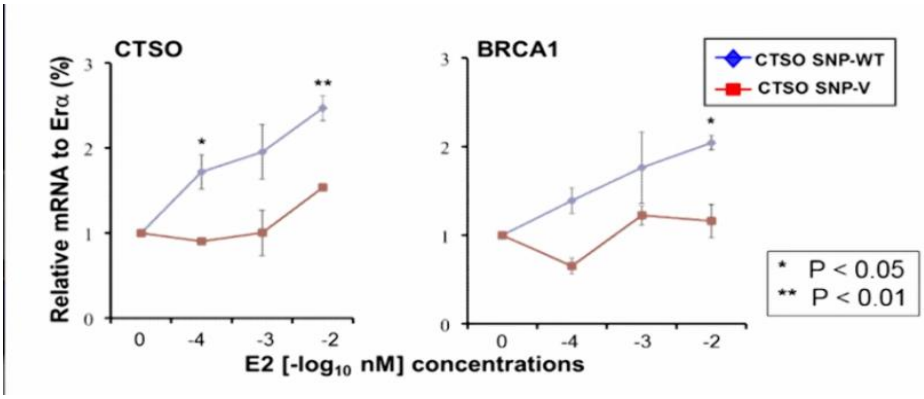

Fig 6: CTSO and BRCA 1 expression in ERα stably transfected LCLs

If individuals homozygous for the two protective alleles are taken and they are compared to individuals homozygous for both of the risk alleles, it is seen that there is a six fold increase in the chances of breast cancer while the tamoxifen is taken compared with someone who has the protective alleles as shown in the table below. (M=major allele, risk allele for ZNF423 with an OR of 0.7 alone; m=minor allele, risk allele for CTSO with an OR of 1.4 alone)

	CTSO (rs10030044)		
ZNF423 (rs8060157)	MM (OR) (95% Cl)	Mm (OR) (95% Cl)	Mm (OR) (95% Cl)
mm(OR) (95% Cl)	1.00	2.49	4.71
Mm(OR) (95% Cl)	1.86	3.16	3.55
MM(OR) (95% Cl)	3.94	3.88	5.71

Table 1: ZNF243 and CTSO SNP joint effect on the danger of breast cancer during SERM therapy.

In today's world of medicine, tamoxifen is not used as a drug to prevent breast cancer because inorder to prevent one case of breast cancer, 50 women need to be treated. If this therapy is individualized, knowing that these drugs have side effects, the patient can be directly told about her risk and protected. In April 2013, the USPSTF (United States HHS Preventive Services Task Force) advised tamoxifen and raloxifene for the prevention of invasive breast cancer.

DRUG TRANSPORTERS

Drug transporters are drug mediators that carry drugs in and out of cells (uptake and efflux). Organs like liver, kidney and intestine have localized systems for efflux and uptake of drugs. Drug transporters can be differentiated into two groups based on their functionality: SLC (solute carrier family) and ABC (ATP binding cassette). Mainly uptake drug transporters are SLC based and efflux drugs are ABC based. Drug transporters have immense pharmacological importance as they have a very important function in ADME which is the absorption, distribution, metabolism and excretion of a drug.

Apart from drug-transporters interactions, there are drug-drug interactions where drugs essentially compete with each other to bind to a specific transporter which may cause toxic and adverse side effects. Among the transporters, two of ABC transporters: ABCB1 (also called MDR1 and P-glycoprotein) and ABCG2 (also called BCRP) and five of SLC transporters: SLC22A6 (also called OAT1), SLC22A8 (also called OAT3), SLC22A2 (also called OCT2), SLCO1B1 (also called OATP1B1) and SLCO1B3 (also called OATP1B3) have received the most attention and research. So to study ADME, these 7 transporters are extensively used. SLC transporters are mainly uptake transporters and they mediate substances like drug and drug metabolites outside the cell. Its members are OAT and OCT (organic cation and anion transporter). They do not utilize ATP hydrolysis unlike ABC transporters. They are mainly efflux transporters meaning they transport substances out of the cell. Its members are MDR family and MATE proteins (these proteins are an exception because they belong to SLC family) which are multipurpose drug proteins, BCRP protein, MRP2 protein and P-glycoprotein.

The drug transporter ABCB1 is one of the earliest transporters to be discovered and it is one of the few well researched and examined mammalian transporters. It has its relevance and importance in cancer treatment and chemotherapy. Research on this has been mainly concentrated on a few tissues like epithelial, kidney and intestine but in the recent years with the detection of drug transporters in blood-brain barrier, choroid plexus, and retina etc. research has been expanding. It is very challenging to fully map out the pathway for a specific drug when it enters the body. Multiple transporters can attach to a particular drug. For example: the drug methotrexate when it enters the body can have multiple possible transporters which can attach to it. Transporters like SLC22A6 of the SLC family and ABCC transporters of the ABC family can transfer the drug. Gene knockout studies have proven the significance of drug transporters even further. In the proximal tubule cells of the kidney, the diuretic transporters which function on the baso-lateral side of the kidney (one in contact with blood) are SLC22A6 and SLC22A8. Also in the proximal tubule, the transporters required for the secretion of the anti-diabetic drug metformin is SLC22A2 and MATE (on both the baso-lateral surface and the apical surface). To discern the pharmacological and toxicological functions of transporters in detail, below are two well examined transporters from the SLC family: SLC22A6 and SLC22A8.

SLC22A6: it is associated with the OAT family and SLCC subfamily. Various years of research on oocytes of *Xenopus*prove that SLC22A6 transports anionic drugs, drug metabolites and toxins. Drugs like antibiotics, non-inflammatory drugs, statins, diuretics, non-steroidal and chemotherapy drugs etc. can be transported via SLC22A6. Although latest gene knockout studies of SLC22A6 on mice have revealed that it carries out damaged handling of these substances along with natural environmental toxins. For example: in the human body, kidney, as well as nervous toxicity, can be caused by mercury, which is a considerable environmental concern, if ingested. Recent studies have proposed that mercury binds with cysteine *in vivo* and it is transported adequately by SLC22A6 like it does with other anions. This way, mercury is prohibited to enter the kidney hence the mouse is saved from mercury poisoning. SLC22A8: identical results have been found when *in vivo* and *in vitro* studies regarding SLC22A8 were done. SLC22A8 has been found to remove the toxin aristolochic acid which causes kidney failure. Similar to SLC22A6 it binds with the toxin and prohibits its entry into the proximal tubules of kidney. In the recent years, the human applicability of these transporters has been gaining new insight. The drug probenecid which shows aggressive inhibition of these transporters has been effective in increasing the half-life of certain drugs like penicillin and other antiviral drugs. The

drug methotrexate, which is used in chemotherapy, has been observed to show toxicity in rare cases when non-steroidal drugs were administered because of the interactions between various drugs caused by the competition of drugs to bind with SLC22A6 and SLC22A8.

Mutations in transporter genes: Mutations in genes which code for transporters can cause serious diseases. Transportation of drugs like methotrexate, anti-viral drugs etc. and metabolites like uric acids, bile acids etc. are carried out by SLC and ABCtransporters. Mutation in these transporters causes the dysfunctional secretion of these drugs and metabolites, for example: a) the gene SLC22A12 which typically used for controlling the uric acid levels in the body can cause gout and the formation of kidney stones with some specific mutations; b) the gene SLC22A5 which is typically used for coding a transporter of zwitterionic nature of OAT and OCT, causes systemic carnitine deficiency which causes cardiomyopathy; c) ABCC2 is a drug transporter which is typically used for binding with and transporting bilirubin glucuronide, causes the Dubin-Johnson syndrome which is essentially a condition where bilirubin is concentrated in the serum leading up to hyperbilirubinaemia by certain mutations. Below are some other transporters which have been observed to show probable mutation related medical associations:

Transporter genes	Association
SLC22A2	Metformin and platinum based drug toxicity
SLC22A4	Inflammatory disease
SLC22A5	Systemic carnitine deficiency, inflammatory disease, cardiomyopathy
SLC22A6	Mercuric toxicity, diuretic response
SLC22A8	Mercuric toxicity and antibody handling, diuretic response
SLC22A12	Hypouricaemia, hyperuricaemia
SLC47A1	Metformin toxicity handling
SLCO1B1	Hyperbilirubinaemia, statin-induced myopathy
ABCB1	Resistance to chemotherapy, inflammatory bowel disease
ABCC2	Dublin-Johnson syndrome
ABCG2	Resistance to chemotherapy, hyperuricaemia

Table 3: Effects caused by mutation in transporters.

POLYMORPHISMS ANDTHEIR SIGNIFICANCE IN PHARMACOGENOMICS

There have been found an increasing amount of polymorphisms in drug transporters which affect the ADME and the maximum efficacy of the drug in the body. These drug effects are generally monogenic (controlled by a single gene) and exceedingly penetrant i.e. causes characteristic changes in the phenotype of the individual. This serves as an example of pharmacogenetics. But this is not the case with most drugs in which multiple genes play a part in the consequence of the effects and the treatment. This has given rise to pharmacogenomics where an entire genome is scanned and studied for genetic polymorphisms and the genetic determining factors of a drug's response. This is done by taking advantage of the information from the Human Genome Project and various technologies like DNA and protein micro assays, high throughout sequencing, bioinformatics etc. The assimilation of these refined methods with comprehensive characterization of phenotypes of patients can define the inherited nature of these drug effects. These polymorphisms in genes which affect a particular drug response can be identified by candidate gene approach which is established on pharmacological studies of proteins and pathways which are involved in a drug's pharmacokinetic and pharmacodynamics response. This approach may not give accurate results due to many causes, like post translational modifications of proteins. It is scientifically challenging to determine the functionally significant polymorphisms like promoter and enhancer polymorphisms, gene duplications, SNPs that change the stability of transcripts, intronic SNPs which helps in the formation of stop codons, SNPs that causes changes in amino acid subtitutions, etc. This approach can also fail due to the false targeting of genes. Methods like expression arrays, genome scans and proteomic assays help in determining the as of yet indistinguishable candidate genes. This is possible by determining the genes whose expression separates drug responders from non-responders by

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analysing the heterozygosity of genomic regions and the existing proteins. Below is an example of these methods used for identifying possible candidate genes that affect drug response.

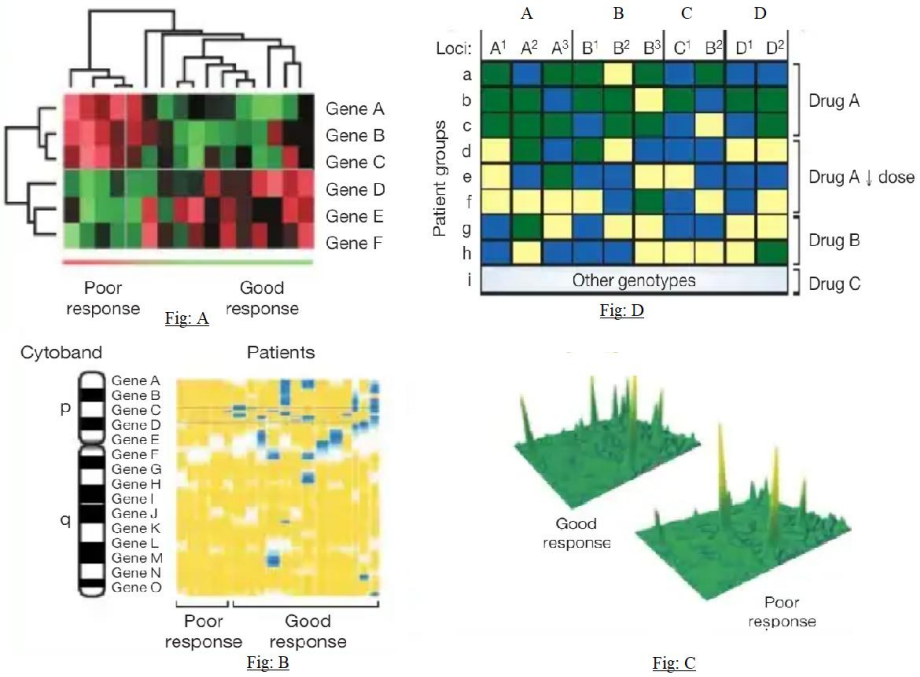

Fig 7:Three genome wide approaches for identifying possible candidate genes which affect drug response.

Fig A: Gene expression, it shows DNA microarray analysis of 6 genes in 16 patients. 4 patients appear to have low response whereas 12 patients appear to have good response; Fig B: Genome scans, it shows haplotype map with 16 gene loci on one chromosome for 5 patients appearing to have low response and 13 patients with a good response; Fig C: Proteomic assays, it shows LC-MS examination of plasma for differentiating between good and bad responders on the basis of protein differences; Fig D: Multi-locus genotypes, it shows a body of multiple genes and loci which differentiates patients on the basis of their response to the drugs.

Gene expression and proteomic assays have an edge over other methods in a way that, in them, the level of signal will precisely affect the functional variation but their limitation lies in their choice of tissue which can directly affect the toxicity response and may give rise to the likelihood of faulty negatives and positive cases. For accurate determination of drug effects with genetic variability extensive molecular epidemiological studies, biochemical functional studies and animal models of gene polymorphisms can be done.

Pharmacogenomics can be used to increase the effectiveness and quality of drug discovery and development. It can be done in 2 ways: a) drug target identification b) drug development for specific populations like in cancer treatment, to determine new targets by discovering genes which are over-or under expressed in cancerous cells and susceptible to anti-cancer agents, genomics is utilized. Gene expression can be also be used in an alternative function where it can be used to detect cancer tissues to confirm the effects of chemotherapy and drugs. Pharmacogenomics can also be used to determine genetic polymorphisms in patients which can cause negative side effects which ultimately hinders the further development of the drug. One of the main methods to do so is by collecting DNA from patients in the phase 3 of clinical trials of a new drug and identifying the polymorphisms which gives rise to toxicity. The goal is to not have toxicity appear for latest developing drugs. However in the case of the occurrence ofdrug toxicity in a small number of patients, they can be identified through their genotype and then an effective new drug can be retained from disposal. For example: abacavir hypersensitivity can be determined in patients by their HLA-B genotypes. Testing withcontemporary medicines with pharmacological characteristics can be justified by such deathly toxicities.

Frequencies of genotype subgroups (heterozygous, homozygous dominant and

homozygous recessive) of pharmacogenetic polymorphisms conflict significantly between different races. There are frequencies of some specific genetic polymorphisms which differ so broadly between races that they affect drug toxicity and effectiveness. Such data has given rise to arguments on the examination of races in genetic association studies. Complete studies of genotype-phenotype associations might give rise to the use of markers and counter the adoption of racesin such studies. However, the inclusion of race dependent studies brings the argument to a crossroad which is compelling enough to consider not only genetic anomalies but also take into account non-genetic factors like food habits. In this case, considering race or ethnicity may be significant in a way which can surpass genetic combinations. This might give rise to racially exclusive development of drugs due to genetic differences deliberately.

POLYMORPHISMS IN DRUG TRANSPORTERS AND THEIR PHARMACOGENOMIC APPLICATION

ABC transporters

ABCB1: The drug transporter ABCB1 is one of the earliest transporters to be discovered and it is one of the few well researched and examined mammalian transporters. It comprises of 50 SNPs and three polymorphisms. Prevalent SNPs include the c.C1236T in exon 12, the c.G2677A/T polymorphism occurring at exon 21 which gives rise to a difference in amino acid sequence p.A893S (G2677T) SNP and the c.C3435T at exon 26. Racial and ethnical alterations in allelic variant arrangements are present. These three SNPs and their haplotypes are very essential for the functionality and expressiveness of ABCB1 with the SNP C3435T first studied and analysed for the clinical applications of ABCB1. For that digoxin was taken as a substrate and a relation was established between the lower expression of ABCB1 and the increment of the bioavailability of digoxin and concentration of plasma. Administration was oral in TT homozygotes with decreased activity of ABCB1. Investigatory studies presented that the CC genotype of C3435T SNP is correlated with decreased potency and an increased danger of myalgia subsequently following the treatment with atorvastin and an increase in serum creatine kinase which is associated with statin apparently because of the low concentration in the cell and increased concentration of statin in the plasma. The concentration and clinical effects of protease inhibitors are affected by these polymorphisms. A study where patients with TT genotype were kept in a six month therapy with nelfinavir or efavirenz was conducted. It was seen that there was an increase in CD4 (cluster of differentiation) cells compared with patients with genotype CC. Thus, it was concluded that ABCB1 might have a function in estimating feedback to protease inhibitors. Also, the *ABCB1* haplotype TTT was observed to increase exposure of morphine and demonstrating sensitivity to morphine in a patient. There was another study done by Sadhasivam et al., where a relation between ABCB1 variant and elevated danger of respiratory disease caused by morphine was seen in individuals with genotype GG and GA. Clashing inferences have been observed with respect to the functional and clinical importance of polymorphisms of various substances like psychotropics, immune-suppressants, anticancer medicine and antiretroviral protease inhibitors. Reasons for this might be in the usage of various assays and methods to determine ABCB1 polymorphic substrates,the interference and coinciding specificity of substrate between ABCB1 and other transporters and the presence of linkage disequilibrium requiring a haplotype approach in preference to SNPs in association studies. Further interpretation studies on ABCB1 will show the impact of mutations on the function and the specificity of substrate.

ABCC1 and ABCC2: They help in the movement and elimination of drugs like tamoxifen, glucoronides (conjugated drugs), methotrexate, pravastatin (non-conjugated drugs) as well as organic anions. Polymorphisms in ABCC1 are occasional but polymorphisms in ABCC2 are more frequent. The c.1249G>A SNP occurring at exon 10 in ABCC2 results in exchange of p.V4171 and decrease in the expression of proteins. Additionally, another polymorphism in ABCC2 occurring at exon 12 is the c.3972C>T SNP with exchange of amino acid p.I324I. A study where individuals having 1249G>A were given tenofovir resulted in them having greater risk of renal proximal tubulopathy induced by drug. This was estimated to be a consequence of decreased renal excretion of drug. In another study of a relation between haplotypes with disposition of irinotecan and polymorphisms abcc2 with 167 patients having tumor were done. From 6 variants of abcc2 genes 15 abcc2 haplotypes were formed. Decreased clearance of irinotecan of 28.3L/h was observed in ABCC2*2 haplotype contrast to patients without the haplotype with clearance at 31.6L/h. However, patients with ABCC2∗2 haplotype and no UGT1A1∗28 allele had decreased chances of contracting severe diarrhoea in comparison to patients with the allele, thus indicating a defensive effect of ABCC2∗2 haplotype

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countering the occurrence of diarrhoea. The reason behind this is that ABCC2 helps in the SN-38 glucuronide secretion into the bile thus having the intestinal epithelial cells having a low exposure of SN-38 after β-glucuronidase helps in the formation of cleavage in SN-38 glucuronide.

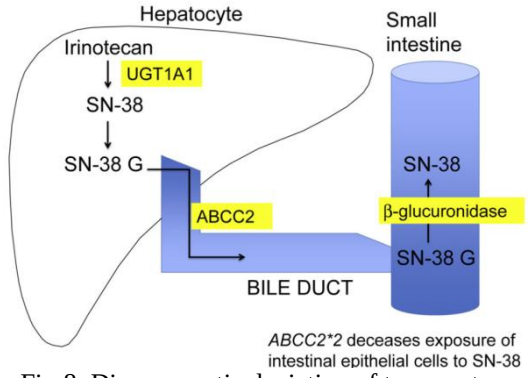

Fig 8: Diagrammatic depiction of transporter ABCC2 possessing shielding effect which counters irinotecan-induced diarrhoea.

ABCG2: This gene codes for MXR (mitoxantrone resistant protein), additionally recognized as placenta specific ABC transporter. In ABCG2, more than 80 polymorphic changes in genes have been observed. Among these the c.421C>A SNP occurring at exon 5 is most extensively studied and researched. It substitutes p.Q141K and results in its decreased expression. The occurrence of this polymorphism differs between different races. Among other ethnicities, sub-Saharan Africans have reported the lowest occurrence of c.421C>A SNP. People with c.421C>A SNP were observed to have higher accumulations of gefitinib and topotecan, thus ensuing in the increased chances of diarrhoea caused by gefinitib. This increased chance of diarrhoea was also seen in cancer patients with ABCG2 polymorphism undergoing rituximab plus cyclophos-phamide (R-CHOP) therapy. Variant of c.421C>A was also seen to reduce the excretion of apixaban, doluteg and rosuvastin through the liver. A study was conducted with 300 hypercholesterolemiapatients where they were given a 10mg dose of rosuvastatin per day. It was observed that there was a reduction in the levels of LDL-C in patients having the c.421C>A. In the JUPITER trial where more than 4000 patients were studied for the therapy of rosuvastatin in cardio-vascular diseases resulted in the inference that there is a strong relation between c.421C>A variant and altered stain efficacy at an entire genome level significance.

SLC transporters

Organic Anion Transports:

OAT1B1: It is encoded by SLCO1B1 and it is additionally recognized as OATP-C. Over the years, many SNPs and 17 distinguishable alleles have been observed in SLCO1B1 gene. The first one to be discovered and studied was the c.521T>C SNP. The 521T>C SNP with substitution of p.V174A gives rise to lowered OATP1B1 protein expression and decrease in its movement. Its occurrence in African ethnicity is limited as compared to other racial groups. The c.388A>G SNP is a mutation present in humans irrespective of ethnicity. The hepatic uptake of pravastatin, rosuvastatin and simvastatin acid which are (3-hydroxy-3-methylglutaryl-Coenzyme) reductase inhibitors are regulated by OATP1B1. The 521T>C variant is related to the alteration of pharmacokinetics of simvastatin acid with greater degree of alteration (more than 2/3rd fold increase in systemic exposure) in CC homozygotes compared to other genotypes. This gives rise to the increasing of the toxicity and the reduction of the intracellular concentration of simvastatin acid due to the inhibition of HMG-CoA reductase, thus resulting in a decreased effectiveness in the depletion of cholesterol. A genome wide association study (GWAS) was conducted with 96 patients with myopathy were medicated with a dosage of 80mg of simvastatin per day with 96 control subjects. Around 316,184 SNPs were analysed and compared. The results was that a non-coding rs4363657 SNP in intron 11 of SLCO1B1 was found out and it was observed that it was in almost absolute linkage disequilibrium with 521T>C SNP with variant V174A (rs4149056). The rs4363657 SNP was found out to be the only strong SNP marker correlated with myopathy which is simvastatin induced. Recent studies have shown that genes carrying T521C SNP have greater degree of OR (8.86) compared to genes carrying A388G SNP (0.24) for serum creatine kinase elevation by statin. The clinical importance from these studies has great immensity because it potentially proposes the theory that the genotyping value to distinguish patients with atypical OATP1B1 action can improve the therapeutic action of simvastatin and maybe for pravastatin. It has also been observed that statin linked adverse drug reactions like rhabdomyolysis can be caused by the alteration of statin transport and metabolism.

OATP2B1: It is additionally recognized as OATP-B and it is encoded by SLCO2B1. It has selectivity of substrate alike to that of OATP1B1. OATP2B1 has been observed to express in the small intestine enterocytes particularly in the luminal membrane

and thus has a role in the absorption of drug. Many different mutations have been discovered in OATP-B like the c.1457C>T SNP, c.601G>A SNP, c.935G>A SNP and the c.43C>T SNP. The concentrations of these SNPs vary with ethnicities. For example: Asian ethnicities have higher occurrence of c.1457C>T SNP than Caucasian subjects. A study was conducted on Japanese subjects with regards to fexofenadine pharmacokinetics to estimate the consequence of the 1457C>T SNP. The results showed parallel pharmacokinetic parameters among the three genotype groups. However, 1457C>T SNP did not influence motelukast, the leukotriene receptor. It was seen that patients with the 935A allele of the c.935G>A SNP exhibited decreased levels of the concentration of plasma and reduced pharmacological response. But a different study observed the absence of a relation between the c.935G>A SNP and motelukast which impliesthat SLCO2B1 SNP effect on the absorption of drug can be substrate based, however further studies need to be done on SLCO2B1 with other substrates with respect to drug disposition for clarification purposes.

OATP1B3: It was formerly recognized as OATP8. The gene SLCO1B3 encodes for OATP1B3. Many different polymorphisms occur for OATP1B3 and it varies according to race and ethnicity for example: the c.334T>G SNP and the c.699G>A SNP is present in high occurrence in Caucasian subjects. The OATP1B3 helps in the uptake of drugs like taxanes by the liver but a study done with 90 cancer patients expanding through 6 different ethnicities showed that there was no relation between both the paclitaxel clearance and the docetaxel pharmacokinetics and the two OATP1B3 SNPs. Future studies will further elucidate the function of the polymorphisms of OATP1B3. Recent studies show an important function of the particular SNPs of the OATP1B3 gene. It involves adverse drug side effects and efficacy of statin. The value of genotyping SLCO1B3 and its variants in individualizing drug therapy would be evidential in further clinical studies of the substrates of OATP1B3. The functional importance of the polymorphisms in SLCO1B3 are not that well known and studied which is why research is being done for the clarification of the significance of these SNPs so that the response to these substrates can be studied as well as the pharmacokinetic profile can be determined.

Organic Cation Transporting Polypeptides.

The three cationic transporters that have been found in humans are: OCT1, OCT2 and OCT3. All of these transporters are the members of the SLC22A family and SLC22A1, SLC22A2, SLC22A3 genes encode them respectively. SLC22A1: it is found on chromosome 6 and it has a high degree of polymorphism. The four polymorphisms: c.181C>T, c.1393G>A, c.1201G>A and OCT1 deletion of Met420 which is three bases ATG at codon 420 of exon 7decreases the functionality of the transportation activity. The frequency of the omission of Met420 variant depends on race and ethnicities with greater frequency in Caucasians compared to other groups. Genotypes of OCT1 have been observed to provide for variability in individuals for the disposition of many drugs like ondansteron, metformin, morphine and tramadol. SLC22A2: this is also a highly polymorphic gene and among the several different SNPs that been found out for SLC22A2 gene, the most important one is the c.808G>T SNP which gives rise to the substitution of p.A270S. Metformin, which is an anti-diabetic drug, is essentially eliminated through the kidney by tubular secretion by OCT2. There have been observed low excretion of metformin in people homozygous with low activity 270S variant. They also have increased concentration of metformin in their blood plasma in comparison to people homozygous with wild type 270A. A study conducted by Tzetkov et al. proved that the expression of OCT 1 is also present in the distal convoluted tubule and it might have significant importance in the reabsorption of metformin. The results showed that the people with homozygous and heterozygous expression of low activity alleles of SLC22A1 SNPs of OCT1 were related to the increase in metformin clearance levels by about 20%-30%. These same alleles have been observed to reduce the uptake of metformin by liver with low blood glucose response outcome. Recent studies have also shown the same for fenoterol giving rise to higher levels of systemic exposure and toxicities.

CLINICAL APPLICATIONS OF PHARMACOGENOMICS

Pharmacogenomics is hardly used in clinical practice, despite being included in more than a decade of research in molecular genetics. When we go to the depth of the matter, we find that it is quite a pertinent question, as there are many well proven instances of genetic polymorphisms in drug transporters, as mentioned above as well as in drug metabolising enzymes. These have a manifold effect on a drug's response compared to parameters used in the laboratory for the adjustment of drug therapy. Additionally, molecular genotyping methods for these polymorphisms have been conclusive, so there still remains a question as to

why the applications of pharmacogenomics have not been popular in clinical practices today.

The first step to undergo is to inform doctors and clinicians about the prescription and treatment with a default average dose. Over the years, the medical community has not entirely welcomed the concept of individualized medicine even when it is based on effortlessly obtained characteristics of patients like age, sex, renal function etc. There has been defiance against the dependency of medical tests for every conclusive remark on a patient. Instead of that a trial and error method of drug dosing has been conceptualized and it is being used by majority. For the integration of pharmacogenomics, medical workers need to be familiar with molecular genetics and a compulsory laboratory test is required. Furthermore, to prove that these clinical results which are based on genetics and individualizing drug therapy have favourable outcome through pharmacogenomics studies is difficult. This is due to the incapacity to control non-genetic factors like diet and smoking and drug-drug interactions and the shortage of capital funding for the large scale pharmacogenomics research coupled with accurate results. Genetic technology has had tremendous strides in developing the mechanisms to such an extent that some of those have been attested to and can be easily used in laboratories. The wide variety of mechanisms that are involved in the polymorphisms of these transporters and other substances make it increasingly difficult for presenting accurate outcomes even for a single gene. This has been seen in the case of genes BRCA1 and BRCA2 which are involved in breast cancer and cystic fibrosis. Essentially, the obstacles in the path for the testing of pharmacogenomics polymorphisms should be overpowered like those which come in the way of other molecular diagnostics.

V. CONCLUSION

The concept of individualized medicine is an ambitious yet a challenging method of drug therapy amongst the current state of medicinal technology and pharmacology. The clinical applications of pharmacogenomics are far and wide considering the impact of it in the field of medicine but it's rather a tedious task to educate medical professionals with the intricate genotyping methods and techniques to determine the polymorphisms in the genes coding for transporter proteins. In the future though, the probability of success in the technical field with respect to the minimization of the cost of genotyping is rather high thus determining polygenic models for the successful establishment of drug therapy without the side effects is easier. But such models can only be established through large scale research and trials of drugs in carefully evaluated patients because of the indefinite possibilities of polymorphisms in the human genome. The way these clinical trials should be conducted is by integrating the careful study of pharmacogenomics with pre-symptomatic models that can strengthen the genotype-phenotype associations. Having to integrate these models into the clinical trials is not necessarily contemporary but it is very useful for the advancement of the trials.

In the event that drug therapy shifts from a trial and error method to a more individualized approach, there are two particular facets of medical management that needs modification. One being the chance of exploitation of genetic information of a particular individual and its protection and ramifications and second being the economic cost of involving the mechanisms of genotyping, sequencing, and incorporating the genetic information in drug therapy. Ultimately, pharmacogenomics will be reducing the recurrence of ADRs, thus making the prospect of successful therapy much higher, which might eventually reduce the cost of health care.

Not long ago, the aim of pharmacogenomics had always been the generation of prediction models to predict and undermine the ADRs associated with drugs in individuals and populations across ages, sexes, ethnicities and races and comparing them to the percentage of the population who show contrasting results. But now recently, pharmacogenomics techniques are integrating with proteomics and other progressive molecular genotyping methods and they are becoming the foundation to individualized drug therapy mainly when the deliberation of differential genetic responses to xenobiotics are done covering distinct ethnicities.

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