LITERATURE REVIEW:

As per the normal designation of the Pharmacogenomics explain as it is science to study knowledge of genomics and proteomics to recognize the new drug targets and mechanism of their action. Whereas the Pharmacogenetics explains as it is science of to study the inter-individual specific genetic variation correlated to drug response. When these two ways comes together then it help to pharmaceutical and health care related sectors by facilitated by drug development and personalized medicine for more drug safety and prevents its adverse effects. But current scenario, the very few applications have shown successful outputs in clinical drug practices.

CURRENT STATUS OF METHODS FOR SCREENING OF ACETYLATION PROCESS OR ACETYLATOR PHENOTYPE

Acetylation is a phase II conjugation reaction occurring in human body that metabolises sulfamethazine, hydralazine, dapsone, isoniazid, aminogluthimide, aminofide, and other drugs. The rate at which an individual acetylates these compounds has been found to be genetically determined, and the trait is inherited in an autosomal dominant fashion by a single gene. There are methods used for determine the action of Acetylator Phenotype by using various drugs in latest time period as follows:-

1)Du Souich P, et, al(1979) Investigated the computer simulations interpretations indicate that all the usual Phenotyping procedures were susceptible to changes in absorption and urinary elimination rate constants. While these predictions require experimental confirmation, results show that this method is least sensitive to changes and suggesting this method may minimize errors in Phenotyping screening. The potential influence of changes in non metabolic parameters on the markers of Acetylation capacity normally used in clinical screening procedures to determine phenotype. For example, seven normal subjects were classified as slow (SA) or fast acetylators (FA) according to their metabolic rate constant in blood and urine samples of human volunteers. [19]
2) Chapron C J, Khan A K, et al (1983) Studied the relationship between sulfamethazine disposition kinetics and acetylation phenotype in man. Sulfamethazine pharmacokinetic parameters were determined after the administration of the drug as an oral suspension. The failure to identify the assumed homozygous rapid acetylator using the commonly working indices of drug metabolism, i.e., half-life, metabolic rate constant, or per cent of the dose metabolized, was credited to a significant increase in the apparent volume of distribution of this genotype, as well as the low renal clearance of sulfamethazine found in all genotypes. The value of using metabolic clearance as an index of drug metabolizing capacity and suggests its application to further pharmacogenetic studies. [20][21]

3) Adam A M et al (1984) Investigated auto-induction of oxidative enzymes involved in aminoglutethimide metabolism. Aminoglutethimide (AG) 500 mg was administered orally to four normal volunteers and eight patients undergoing treatment for metastatic breast cancer. Acetyl-aminoglutethimide (acetylAG) rapidly appeared in the plasma and its disposition paralleled that of aminoglutethimide[22]

4) Iyer, Ratain M J et al (2001) evaluated that patients who are fast acetylators of aminofide (and other drugs) have increased toxicity at standard doses of aminofide. The recommended phase II dose of aminofide separately for slow and fast acetylators. Twenty-six patients with advanced cancer underwent acetylator phenotyping with caffeine and were assigned to a dose level. Two patients were not typeable, and two patients appear to have been mis-phenotyped, one in each phenotype category. Pharmacodynamic analysis yielded a model for nadir WBC including acetylators phenotype, 24-h N-acetyl-aminofide plasma concentration, gender, and pretreatment WBC. They recommend doses of 250 and 375 mg/m2 (for 5 days) for further phase II testing of aminofide in fast and slow acetylators, respectively. [23][24]

5) Ahmad, Carr, Clark, Weber, et al (1981) Studied Isoniazid is still a widely used substrate to determine acetylator status, although dapsone is becoming increasingly popular as an alternative. Isoniazid would be preferred in patients with glucose-6-phosphate dehydrogenase deficiency to avoid haemolysis or in those already receiving isoniazid (which interferes with dapsone elimination) [25] Also isoniazid may more clearly distinguish slow
from fast acetylators have found dapsone to be unable to accurately phenotype subjects in 2-6% of cases. [26][27] Although the half life method is generally used to phenotype the human subject yet it has the disadvantages of being dependent on volume of distribution (Vd) which may vary in different cases and is inversely related to clearance and therefore product of metabolities. Since in fast acetylators, isoniazid undergoes extensive presystemic elimination, half life method would be relatively insensitive towards measuring the acetylation rate) [28].

6) Phili P.A.et al(1984) Investigated A specific, rapid and sensitive h.p.l.c. method for the determination of DDS, MADDS suitable for rapid allocation of acetylator phenotype in population. The determination of monoacetyldapsone (MADDS) and dapsone (DDS) in plasma following a single dose of DDS and demonstrated that individual Acetylation characteristics for dapsone, isoniazid and sulphamethazine were the same.[29]

7) Zacest R, Gotlieb T B, Petinger W A et al(1972) Studied drug is major importance in the treatment of hypertension. When used in combination with a diuretic and beta blocker, it has been shown to be effective in patients resistant to prior therapy[30]. It would be clinically useful to have a systematic method by which patient responsiveness to hydralazine might be predicted and dosing regimens optimized for individual patients. However, examples of inadequate blood pressure (BP) responses to regimens that include hydralazine are not infrequent. [31][32]

8) Shepherd A.M.et al(1981) Investigated a relationship between plasma concentration of hydralazine are determined by a specific assay and the magnitude of hypotensive effect after oral administration of hydralazine. This correlation was significant following both single dose and the fifth dose of a series administered at 12-hour intervals. The experimental analysis implies that a major factor accounting for inter-individual differences in the response to oral hydralazine is the plasma concentration of the unmetabolized drug. Other factors, in particular the absolute level of pretreatment BP, may also be expected to influence the magnitude of response. [33]
9) Grant D.M. et al (1984) Developed a simple method for acetylator phenotype using caffeine. Each of 146 subjects provided a spot sample of urine between 2 and 6 h after coffee, tea, or cola soft drink consumption, and the molar ratio of 5-acetylamino-6-formylamino-3- methyluracil (AFMU) to 1-methylxanthine (1X) was determined by a simple h.p.l.c. assay. [34]

10) Irving W.W. (1995) US5830672 Invented that enzyme link immune sorbent assay (ELISA) kit for rapid determination of N-Acetyltransferase of (NAT-2) phenotype which can be routine basic of clinical laboratory. The ELISA kit allow physician to a individual therapy of drug such as procanamide, dapsone, isonizide etc, ELISA have been successfully applied in the determination of low amount of drug and other antigenic component in plasma and urine sample, involve no extraction step and are simply to carry our. [35]

11) Thomann et al (2002) Invented that polymorphism of the NAT-2 gene and the method of using them in diagnostic and therapeutics, also the polymorphism exist within the general population and within various racial group. [36]

12) Mayers A. (2004) Studied the genetic variation was responsible for the diversity in some drug responses were already being made five decades ago. [37]

13) David W. et al (2000) Studied the pharmacogenetics of the NAT-1 and NAT2 arylamine N-acetyltransferases, including developmental regulation, structure-function relationships, and their possible role in susceptibility to breast, colon, and pancreatic cancers. [38]

14) Jonna E, Charles F.B. (1988) Investigated the distribution of acetylation of sulphamethazine exhibit bimodality. The bimodal population frequency distribution for percentage acetylated sulphamethazine showed 42 of the tested population to be fast and 58 to be slow acetylators, that is, an estimation of q=0.72±0.03 as the frequency of the allele controlling slow acetylation. The study also revealed ample evidence that the assay of the drug in urine can be done in a significantly shorter time. [39][40]

15) Charuvind K. A. et al (2011) Investigated Acetylator Phenotype and researches components that strike the utility of medical and clinical practices to avoid problems occurring due to incorrect metabolism of the routinely prescribed drugs. The concept of
personalize medicine used by health care organizations now days. This happens because the vast knowledge of genomics and genetics available now days but still much work is going to persist. Hence the terminologies as Pharmacogenomics or Pharmacogenetics uses very frequently due to great potential in both life sciences as well as pharmaceutical sciences research. [41]

16) Hoirun Nisa et al (2010) Investigated the relation of cigarette smoking and related genetic polymorphisms to colorectal cancer risk, with special reference to the interaction between smoking and genetic polymorphism. a population-based case-control study, including 685 cases and 778 controls who gave informed consent to genetic analysis. Interview was conducted to assess lifestyle factors, and DNA was extracted from buffy coat. Cigarette smoking may be associated with increased risk of rectal cancer, but not of colon cancer. Umar Farooq et al (2009) PCR showed size polymorphism in all the target genes. Three alleles were observed in msp-2 and ama-1, while only two in csp. RFLP of ama-1 and csp with Dra-1 and Ssp-1 endonucleases respectively, failed to differentiate isolates in sub-allelic types, while Hinf-I digestion of msp-2amplicons differentiated three alleles into two distinct allelic families, i.e. FC-27 and 3D7.[42]

17) Umar Farooq et al (2009) Investigated extent of genetic polymorphism in potential vaccine candidate antigen genes, i.e. msp-2, ama-1 and csp of P. falciparum isolates prevalent in northern and north-western parts of India. Overall 88 parasite isolates of P. falciparum were collected during July 1998–March 2002 from different parts of northern and north-western India. DNA was extracted and analyzed for genetic polymorphism by PCR-RFLP method[43]

18) Gupta V.K et al (2009) Investigated genetic variability in the isolate are support the analysis of the similarity indices and UPGMA dendrogram. six representative isolate of Fusarium solani, collected from different places of India were subjected to analysis of genetic variability in terms of Carboxylesterases isozyme pattern and DNA polymorphism using RAPD-PCR.Pattern of Carboxylesterase revealed a similar isozyme cluster in the isolate namely, Allahabad (isolate-3), Faizabad,(isolate-4), Unnao (isolate-5) and Lucknow (isolate-6). [44]
19) Junji Saruwatari et al (2010) Investigated the effects of mutations of drug-metabolizing enzymes on the pharmacokinetics and pharmacodynamics of AED therapies. Future directions for the dose-adjustment of AED. The defective alleles of cytochrome P450 (CYP) 2C9 and/or CYP2C19 could affect not only the pharmacokinetics, but also the pharmacodynamics of phenytoin therapy. CYP2C19 deficient genotypes were associated with the higher serum concentration of an active metabolite of clobazam, N-desmethyloclobazam, and with the higher clinical efficacy of clobazam therapy than the other CYP2C19 genotypes. The defective alleles of CYP2C9 and/or CYP2C19 were also found to have clinically significant effects on the inter-individual variabilities in the population pharmacokinetics of phenobarbital, valproic acid and zonisamide. EPHX1 polymorphisms may be associated with the pharmacokinetics of carbamazepine and the risk of phenytoin-induced congenital malformations [45]