Chapter 1

Introduction and Aims of the Study
1.1. Introduction

Epilepsy is a highly prevalent chronic neurological disorder with seizures as the basic clinical representations/symptom of the disease. It affects 50 million people worldwide and 55,00,000 in India (Sridharan, 2002). Therapeutic interventions are the major mode of treatments available. Epilepsy treatment to date, are symptomatic in nature as all the medications are anti-seizure medications rather than cause specific (Ferraro, 2012). A revolution in the field of AED development is the need of present time, however it is only possible after the detailed understanding of epilepsy pathophysiology. This may lead to identification of new pathophysiology genes, which may act as novel therapeutic targets for future drug discovery (Casillas-Espinosa et al., 2012).

Epilepsy since decades has been considered as a monogenic disorder however, it has recently been established that only a small fraction of epilepsies belong to the monogenic class and of which majority are ion-channels (Ferraro, 2012).

Despite availability of many AEDs and after many decades of research in the field, response rate of patients has remains only 70% with the presence of risk of developing various adverse drug reactions (ADRs) (Schmidt, 2009). These points towards the limited and restricted approach employed for genetic as well as pharmacogenetic studies that further heads towards the resource limited drug discoveries. The failures in achieving efficacious and safe drug response instigate the updating of existing methodologies along with development of new as per the requirement.

It has been observed that majority first-line AEDs (phenytoin, carbamazepine and valproate) target sodium channels and are effective for wide range of epilepsy patients (Ferraro, 2012). Despite small section of epilepsy patients being associated with sodium channel mutations, the wide effect of first-line AEDs highlights that sodium channel mutations may however be final common pathway for seizure activity, but there may also exist some other nervous system molecules with weak links. Identification of these weak links present in the chain of events from development and function of nervous system may provide therapeutic entry points (novel targets) for more efficacious therapy management.
The poor and ADR associated response requires the development of personalized genetic tests by application of advanced pharmacogenetic approaches. Performing all the epilepsy related research whether genetic or pharmacogenetic by considering epilepsy as a complex multigenic disorder rather than monogenic. Detailed understanding of epilepsy pathophysiology by employing new gene set in order to identify novel therapeutic targets. Employing the same gene set in pharmacogenetic studies will lead to understanding the role of these genes in development of variable drug response as well as validation of their potential to act as novel therapeutic target.

Present study takes into consideration the concept of multigenic inheritance of epilepsy and the possible involvement of gene set other than ion channels for both epilepsy pathophysiology understanding and drug response prediction.

The ultimate goal behind a good patient care deals with developing a successful epilepsy control and epilepsy diagnostic model that can be employed in future for the betterment of a large pool of patients.
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1.2. Aim and the objectives of the study

The overall aim of the thesis is to understand the inter-individual variability towards AEDs response, prescribed doses and the drug levels patients achieve. We aim to identify pharmacogenetic variants for predicting this variable drug response, optimal doses required by the patients to achieve steady-state drug levels. This will help in achieving safe and efficacious treatment of patients towards first-line AEDs. In addition to this, we also aim to understand the epilepsy pathophysiology by means of the prioritized gene variants from epilepsy pathology related genes.

The specific objectives of the thesis are:

1. To study the role of epilepsy pathophysiology genes on drug response to first-line AEDs in North Indian population

We hypothesize that other than ion channels, their functionally related genes and additional epilepsy pathophysiology genes i.e., SVC genes may also influence variable patient’s response. Thus, genetic variants from these genes were prioritized for the present study. Genetic variants from the prioritized genes were than analyzed to understand their role in influencing seizure control and therapy optimization parameters i.e., dose and adjusted drug levels.

2. To study the role of drug metabolizing enzymes and transporters on drug response to first-line AEDs in North Indian population

Drug Metabolizing Enzymes (DME’s) and Transporters have been considered as the major modifiers behind the variable drug response patients experience, towards the prescribed AEDs. Therefore in the second objective we prioritize genetic variants from DME’s and Transporters and then analyze them to understand their role on seizure control and therapy optimization parameters i.e., dose and adjusted drug levels.

3. To study the role of epilepsy pathophysiology genes in manifestation of epilepsy in patients

For this the prioritized genetic variants from ion channels, their functionally related genes and SVC genes were employed in case-control analysis. They were analyzed in all epilepsy cases and their different subgroups in order to understand their role in epilepsy manifestation of patients.