# GENETIC INFLUENCE OF *CYP3A4* (rs2740574) GENE POLYMORPHISM ON CARBAMAZEPINE PHARMACOKINETICS IN EPILEPSY PATIENTS FROM KHYBER PAKHTUNKHWA: A PROSPECTIVE STUDY

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## ABSTRACT

**Objectives**: This study examines *CYP3A* genotypes regulating CYP enzymes, specifically *CYP3A4* rs2740574, in Pashtun epilepsy patients in Khyber Pakhtunkhwa, Pakistan. This study documents the pharmacogenomic effects of this single nucleotide polymorphism on carbamazepine serum levels and dose-adjusted levels. It aims to promote customized medicine by providing insights that could lead to more effective epilepsy treatments for this population.

**Methods**: *CYP3A4* (rs2740574) genotyping was performed on 223 patients using Sanger sequencing. DNA extraction was done by salting out method manually. In subsequent follow ups serum for separated for the detection of serum levels of Carbamazepine through HPLC. Finch TV identified gene polymorphisms, and HPLC examined their effects on plasma CBZ levels.
**Results:** Both TC (*CYP3A4* *1A/*1B) and TT (*CYP3A4**1B) genotypes had higher mean doses from the first to the second follow-up, with no statistically significant difference. Carbamazepine plasma levels increased by 0.70 ± 2.55 mg/L and CDR decreased by 0.41 mg/L per mg/kg/day among TT genotype carriers in the 2nd follow up. TT & CT were 96.4% & 3.6% whereas wild CC (*CYP3A4* *1A/*1A) genotype was not encountered in the study sample.
**Conclusion:** Genotypes of the selected gene revealed a statistically insignificant correlation with Carbamazepine pharmacokinetics.
**Key Words:** Genotypes, *CYP3A4* (rs2740574), *CYP3A4**1B, CDR, CBZ, HPLC, Sanger Sequencing.

## INTRODUCTION

Epilepsy is a widely prevalent neurological condition that has become a significant public health issue.[1] The prevalence of epilepsy in Pakistan is almost ten per 1000 individuals, with approximately 10 million people afflicted with epilepsy.[2] The identification of a vast number of genes in epilepsy offers an intriguing, but laborious, opening for the individualization of treatments. This falls in line with the reality that the brain relies on the most genes for its maturation and operation out of all other organs.[3] Several drugs are used for the management of epilepsy.

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Carbamazepine is among the top five most frequently prescribed anti-epileptic medications in developing countries used to manage epilepsy.[4,5] CBZ is mainly metabolized in the liver, with its primary oxidative pathway converting it into carbamazepine 10,11-epoxide, which is both pharmacologically and electrophilically active.[6] Research has shown that CYP enzymes are responsible for approximately 75% of metabolic reactions. CYP3A4 is abundantly present in the liver and small intestine, playing a crucial role in the oral bioavailability and clearance of various drugs including carbamazepine. The CYP3A family, known for its role in phase I metabolism, comprises of four genes: *CYP3A4, CYP3A5, CYP3A7*, and *CYP3A43*, all situated within a 231-kb segment of chromosome 7q21.1. It consists of 13 exons.[7] With advancements in pharmacogenomics, it has been demonstrated that the variability in individual responses to antiepileptic drugs is influenced not only by non-genetic factors such as age, environment, and concurrent medications but also by genetic factors.[8,9] Genetic polymorphisms influence drugs both at the pharmacokinetic level (including absorption, distribution, transport, metabolism, and clearance) and the pharmacodynamic level (at the sites of action).[10] Variations in the frequency of genetic

polymorphisms lead to diverse gene expressions, which in turn are associated with different drug responses and variable drug plasma levels.[8,11] The most prevalent single-nucleotide polymorphism in the promoter region of the *CYP3A4* gene is rs2740574, also referred to as *CYP3A4**1B. The wild type and heterozygous are referred to as *CYP3A4**1A & *CYP3A4**1A/*1B respectively. This polymorphism is known to modify the transcriptional efficiency of the gene, affecting the overall catalytic activity of CYP3A4 enzyme.[12] The *CYP3A4**1B polymorphism is linked to decreased expression or reduced catalytic activity of the CYP3A4 enzyme,[13] whereas some researchers reported this promoter region mutation leads to an increase in CYP450-3A4 enzymatic activity by enhancing its expression.[14] Genetic consortia like PharmGKB and CPIC guidelines assigned the SNP, third level of evidence warranting further research in more ethnic groups to come to a conclusive phenotype in response to genotypes of *CYP3A4* (rs2740574). The distribution of *CYP3A* genotypes among Pashtun epilepsy patients in the Khyber Pakhtunkhwa region of Pakistan has not been previously studied. This research examines the frequency of *CYP3A* genotypes and the potential pharmacogenomic effects of the *CYP3A4* rs2740574 SNP on carbamazepine serum levels and adjusted serum levels that is concentration to dose ratio (CDR) in Pashtun epilepsy patients in Khyber Pakhtunkhwa, Pakistan.

## MATERIALS AND METHODS

**Study Samples:** After acquiring confirmation from the Advanced Studies and Ethics Board of Khyber Medical University, Peshawar (letter number Dir./KMU-EB/PS/000807), patients with epilepsy for this cohort study were enrolled from the government Lady Reading Hospital. Subjects were informed regarding the study's goals and procedures. For minors, consent was obtained from their legal guardians. The sample size was determined to be 180 using the Web-based OpenEpi tool, with a 7.5% margin of error and a 95% confidence interval.[15] To account for potential follow-up withdrawals and to maintain the validity of the study results, the initial number of participants was set at 234. Eight subjects declined to participate. The research focused on anti-epileptic drug-naive patients with epilepsy. Both males and females aged 5 to 70 years, who were suitable for carbamazepine therapy, were enrolled. A standardized proforma, ratified by the physicians of Khyber Medical University and the Advanced Studies and Research Board, was used to document patient history, conduct a comprehensive general physical examination, and record laboratory test results.

**Pharmacotherapy:** Patients were prescribed Carbamazepine as monotherapy. The basic Pharmacopoeia criteria were reliably accomplished by the tablet dosage forms manufactured by a multinational pharmaceutical corporation. The steady-state concentration was adjusted according to the dose and body weight, as patient doses varied. Patients were prescribed doses ranging from 10 to 20 mg/kg based on disease severity, maintenance of appropriate plasma levels, and the CDR of Carbamazepine. At the first follow-up (3rd month), the Carbamazepine dose was adjusted according to the patient's disease status.

**Blood sampling For Drug Assay:** A minimum of 8 to 10 weeks (due to fluctuations) was required for drug levels to stabilize; thus, then the initial follow-up was conducted. The second follow-up was scheduled for the 6th month from the baseline visit. Research by Ullah et al. indicated changes in Carbamazepine levels until 10-12 weeks.[16] Samples were collected at three-month intervals for both follow-ups, considering the period of fluctuations. Carbamazepine requires 5.9 ± 1.8 hours(T-max) to reach its maximum drug concentration. Therapeutic drug monitoring was performed at T- max to ascertain the maximal plasma concentration (C- max). Specimens were collected and stored at 8°C in EDTA containers for DNA extraction during the baseline visit.

**DNA Extraction and PCR:** The salting-out method was utilized for manual DNA extraction.[17,18] Buffers tailored for nuclear and red blood cell lysis were employed. The mixture was vortexed (Heidolph, Schwabach, Germany) later centrifuged following the addition of NaCl and chloroform. DNA was stored at -20°C (Servizo Assistenza, Model KFDC 350, Italia) following the addition of elution buffer. Purity and concentration were evaluated through a nanodrop spectrophotometer.[19] Amplification of targeted SNP in *CYP3A* gene was performed using a gradient Thermo Cycler. Primers for the gene were designed utilizing the UCSC genome database https://genome.ucsc.edu/cgi-bin/hgPcr. The primers used were GTAGGTGTGGCTTGTTGGGA (forward) & AGGAGCCTGGACAGTTACTC (reverse). Prior to amplifying the target SNP, PCR assays were optimized using DNA from healthy controls. After optimization, the targeted DNA regions underwent multiple rounds of PCR

amplification. The PCR products were then analyzed on a 2% agarose gel.[15]

**Genotyping:** Sanger sequencing of the targeted gene was performed using the Seq Studio™ system, following the manufacturer's instructions.[20] The amplified products were sequenced and optimized using the BigDye X-terminator™ kit. After establishing a medium run for electrophoresis and adding the samples, the analysis was conducted. The Hardy-Weinberg equilibrium test was employed to assess the genotype distribution within the context of the global population. The sequences generated through Sanger sequencing were analyzed for the presence of polymorphisms using Finch TV,[21] as shown in Figure.1.

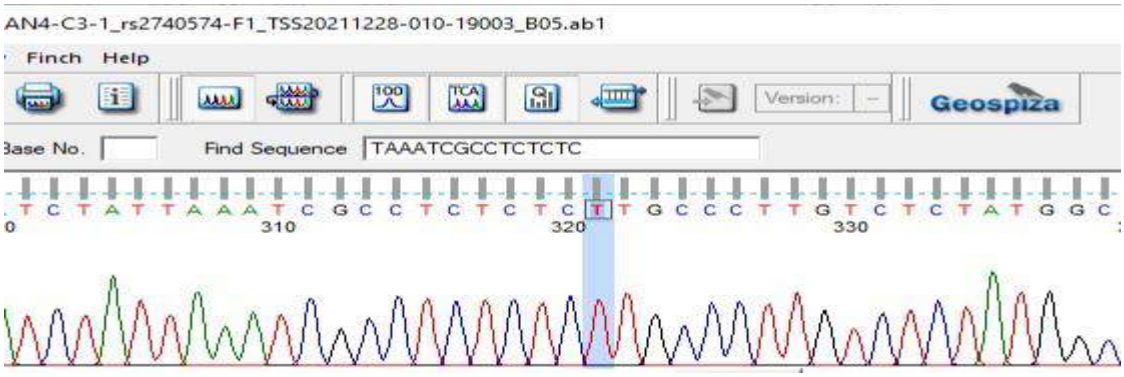


**Figure 1 (a): Homozygous Mutant variant (TT) of *CYP3A4* rs2740574**

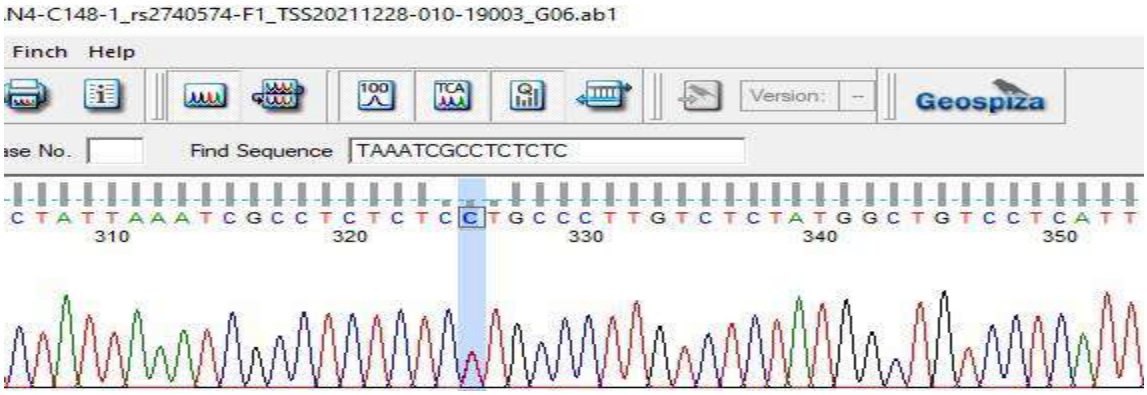


**Figure 1 (b): Heterozygous variant (TC) of *CYP3A4* rs2740574**

**Therapeutic Monitoring of Plasma CBZ Levels:** Modifications were made to the HPLC LC-20AT system, equipped with an SPD-20A/20AV UV detector (Shimadzu, Kyoto, Japan), following the protocols outlined by Ullah et al. Carbamazepine (CBZ) plasma concentrations were measured using reversed-phase high-performance liquid chromatography.[16] Plasma was deproteinized by mixing it with acetonitrile in a 3:1 ratio. Following centrifugation, the organic layer was removed. The formed dry extract was reconstituted with a mobile phase composed of demineralized water, methanol, and glacial acetic acid in a 65:34:1 (v/v/v) ratio, maintained at a pH of 5.6. The sample was injected into a C18 column at a flow rate of 0.8 ml/min, and CBZ was identified using UV detection at λmax 220 nm. Diclofenac sodium was employed as the Internal Benchmark. The procedure was validated by evaluating metrics like CV% and %recovery across intra-day and inter-day bases.[22]

**Statistical Analysis**: Means and standard deviations were used to organize numerical data. The correlation between genotypes and CBZ levels was assessed using one-way ANOVA, with significance set at $p < 0.05$. Categorical data were analyzed through frequencies and percentages. Graphs were created using Microsoft Excel, and data interpretation and analysis were performed using SPSS version 22.

## RESULTS

**Genotype Frequency of *CYP3A4* (rs2740574):** *CYP3A4*-rs2740574, the homozygous mutant (*CYP3A4**1B) was the frequently encountered genotype followed by

heterozygous variant (*CYP3A4**1A /*1B), comprising 96.4% & 3.6% of the population. None of the individuals carried the wild (*CYP3A4**1A) genotype.

**Association Between *CYP3A4* Gene Polymorphism and CBZ Dose Requirements Across 1st and 2nd follow ups:** Study revealed as shown in Tab. 1, the doses utilized across both the follow ups. There was an increase in the mean dosages from the first to the second follow-up for both TC and TT genotypes.

**Table 1**: **Mean doses of CBZ across the follow ups in perspective of *CYP3A4* rs2740574.**

| | Genotype | Mean ± SD [a] | *P- value | 95%[a] C.I |
|---|---|---|---|---|
| **1st follow up.** | | | | |
| ***CYP3A4* (rs2740574)** | CC | ----- | ----- | ------ |
| | TC | 350.0±141.4 | 0.854 | 231.77 to 468.23 |
| | TT | 339.5±158.1 | 0.854 | 318.27 to 360.80 |
| **2nd follow up.** | | | | |
| ***CYP3A4* (rs2740574)** | $CC_{ref}$ | ----- | ----- | ------ |
| | TC | 525±212.13 | > 0.05 | 347.6 to 702.3 |
| | TT | 502.7±205.7 | > 0.05 | 475.1 to 530.4 |

***** Chi Square test. Post hoc tests were not performed for *CYP3A4* (rs2740574) because there were fewer than three groups. [a] CBZ Dose in mg/day., .I: Confidence Interval.

The dosages of CBZ for TC and TT genotypes do not differ significantly in either follow-up, as indicated by the high p-values.

**Association of *CYP3A4* gene Polymorphisms with CBZ plasma levels and its CDR:** As documented in Tab.2, the analysis examined plasma levels and concentration dose ratios (CDR) of CBZ in relation to the *CYP3A4* (rs2740574) gene polymorphism. The highest plasma levels and CDR were observed in individuals with the *CYP3A4**1B variant, followed by those with the *CYP3A4**1A/*1B variant.

**Table 2: Mean Plasma Conc.& CDR across the follow-ups in perspective of *CYP3A4* (rs2740574).**

| Variable | Genotype | 1st Follow-Up | | | 2nd Follow-Up | | |
|---|---|---|---|---|---|---|---|
| | | Mean ± SD | 95% CI | *P-value | Mean ± SD | 95% CI | *P-value |
| **Plasma levels [a]** | $CC_{ref}$ | ------ | ------ | > 0.05 | ------ | ------- | > 0.05 |
| | TC | 4.61±2.13 | 2.83 to 6.40 | | 4.71±2.1 | 2.93 - 6.5 | |
| | TT | 5.13±1.80 | 4.89 to 5.37 | | 5.83±1.8 | 5.58 to 6.0 | |
| **CDR [b]** | $CC_{ref}$ | ------ | --------- | > 0.05 | --------- | --------- | > 0.05 |
| | TC | 1.59±1 | 0.504 -2.68 | | 1.25±1.4 | 0.06 to 2.4 | |
| | TT | 1.94±1.2 | 1.784 to 2.11 | | 1.53±1.1 | 1.37 to1.6 | |

***** Chi Square test, Post hoc tests were not performed for *CYP3A4* (rs2740574) because there are fewer than three groups. [a] mg/l, [b] mg/l per mg/kg/day.

The p-values generated by ANOVA indicate statistically insignificant association between the genotypes and plasma levels or CDR. Notably, carriers of the *CYP3A4**1B genotype exhibited the highest plasma concentrations and CDR across both follow-ups. In the second

follow-up, among the *CYP3A4**1B carriers there was an increase in plasma levels by 0.70 ± 2.55 mg/L and a decrease in CDR by 0.41 mg/L per mg/kg/day.

## DISCUSSION

This study focuses on Pakistan's high epilepsy prevalence, providing valuable region-specific pharmacogenetic insights into CBZ metabolism variability due to CYP3A4 gene variants. By comparing findings with other populations, it adds to the limited literature on CBZ pharmacokinetics and highlights the potential for personalized treatment in epilepsy. The average global prevalence of active epilepsy is approximately 0.8% (8 per 1,000) of the general population, emphasizing the huge global burden of this neurological disorder.[23,24] Pakistan has a 1.0% (10.0 per 1,000) epilepsy rate, higher than several other countries in the region. Vietnam has 0.44–1.4% prevalence, while India has 0.3%–1.19%, overlapping with Pakistan. Lower prevalence rates are found in Laos (0.77%),[23] Nepal (0.73%),[25] Bangladesh (8.4%), [26] Thailand (0.72%), and Cambodia (0.58%).[27] In China, prevalence ranges from 0.46% to 0.7%. This shows that Pakistan has a high epilepsy prevalence rate in the region, a major public health issue.[28,29]

The large number of different syndromes and seizure types together with an interindividual variable response to antiepileptic drugs (AEDs) make the treatment of epilepsy challenging.[30]

Utilizing pharmacogenetic research, we evaluated the association between metabolic enzyme regulating gene variation of *CYP3A4* (rs2740574) with CBZ steady-state, dose-normalized, and necessary doses to determine interindividual variability.

Puranik et al. discovered in their combined cohort study that patients genotyped with *CYP3A4**1A (wild type) exhibited significantly higher clearance (CL) values and decreased plasma levels compared to those with at least one (T) *CYP3A4**1B allele.[31] In a comparable manner, our investigation revealed that individuals with the *CYP3A4**1B variant exhibited elevated CBZ plasma levels and decreased clearance rates. R. Rachda et al. also reported comparable findings in the South Indian population. They observed that the wild genotype was associated with high clearance and low plasma levels, while the *CYP3A4**1B variant correlated with lower plasma levels.[32] M.A. López-García et al. also reported the same findings in Mexican population documenting *CYP3A4**1B linked with poor metabolism due to decreased enzyme activity.[33] The existing literature on the associations between CBZ pharmacokinetics and pharmacogenomics is scant and primarily based on studies conducted in small cohorts, underscoring the importance and necessity of the present study.

## CONCLUSION

Advances in pharmacogenomics indicate that genetic and non-genetic variables impact the antiepileptic drug's efficacy. Polymorphic genes like *CYP3A4* (rs2740574) modify treatment efficacy by changing the pharmacokinetics and pharmacodynamics of CBZ. Patients with at least one wild allele, 'C' (*1A), exhibit higher clearance rates and lower plasma levels of CBZ, suggesting that they are proficient metabolizers, as demonstrated by our research. Conversely, individuals who possess the *CYP3A4**1B variant exhibit elevated plasma levels and reduced clearance, which signifies them as poor metabolizers. Heterozygous variant carriers with a wider confidence interval indicate a greater degree of dose variability, whereas *CYP3A4**1B genotype carriers with a narrower confidence interval suggest far more consistent dosages. The current literature on CBZ pharmacokinetics and pharmacogenomics is not sufficient and hinges on small cohorts, which underscores the critical need for thorough investigation to develop a more comprehensive understanding of these relationships. Furthermore, the occurrence of failed trials in epilepsy treatment can be mitigated by prior knowledge of a patient's genome, which can assist in the selection of an ideal prescription of medicines and the most appropriate dosages.

## AUTHORS' CONTRIBUTIONS

AJ: Methodology, Execution, Data collection, Investigation, Formal analysis, writing the original draft. MSF: Investigation, Data curation, Formal analysis. NA: Supervision, Conceptualization, Formal analysis, MSK and GM: Validation, Review and Editing, SFF: Results and discussion.

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## COMPETING INTERESTS

The authors declare that they have no competing interests.

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