ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 12 | December - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# PREVALENCE AND ASSOCIATION OF HLA B* 15:02 WITH CARBAMAZEPINE INDUCED STEVENS JOHNSON SYNDROME IN SOUTH INDIAN POPULATION-PHARMACOGENETIC STUDY

**Pharma**

| | |
|---|---|
| **Ahil. M.S** | MD. Associate Professor of Pharmacology, KAPV Government Medical College, Trichirappalli |
| **Sarojini.R*** | MD. Professor of Pharmacology, Madurai Medical College, Madurai.*Corresponding Author |
| **Geetharani.G** | MD. Professor and Head of the Department of Dermatology, Government Rajaji Hospital, Madurai, |
| **Balakrishnan.K** | M.SC.,M.Phil.,PhD Former Professor and Head of the Department of Immunology, Madurai Kamarajar University , Madurai |
| **Shakthi.C** | MD.,D.M Consultant Neurologist, Vadamalayan Hospitals, Madurai, |


## ABSTRACT

**Background :** This is an era of new drug development and the newer drugs have made revolution in the treatment of many diseases. But the adverse effects reduce the patient compliance and made few valuable drugs to be withdrawn from the market. Majority of the drug withdrawals are due to idiosyncratic adverse reactions which are due to genetic variation in a subset of population. If the genetic basis of such reactions is well studied it can help us to prevent such adverse effects. Carbamazepine a commonly prescribed antiepileptic, produces severe skin reaction, Stevens Johnson syndrome. Presence of HLA B* 15:02 has been implicated as a risk factor for this reaction. So this genetic correlation was evaluated in this study. **Aim:** To determine the prevalence and the association of HLA B* 15:02 with the Stevens Johnson syndrome due to carbamazepine. **Method:** Eleven patients who developed SJS due to carbamazepine were selected and their blood tested for the presence of HLA B*15:02. Twenty two persons on carbamazepine for 6 months and more for various conditions and tolerating the drug were selected as controls and their blood was tested for the presence of HLA B * 15:02.**Result:** One among the patients and one among the controls were positive for HLA B*15:02.**Conclusion:** The prevalence of HLA B*15:02 is negligible and the association between HLA B*15:02 and SJS due to carbamazepine was not ascertained in the study population.

## KEYWORDS

Stevens Johnson syndrome, HLA B*15:02, pharmacogenetics

**Introduction:**
Carbamazepine is an antiepileptic used for grandmal epilepsy and myoclonic seizures. It is the drug of choice for trigeminal neuralgia and an alternative drug for mania. As all the above mentioned conditions are chronic in nature the patient has to take carbamazepine for a longer duration. Majority of the patients tolerate the drug and thousands of prescriptions are written on carbamazepine daily. But a severe skin reaction namely Stevens Johnson syndrome occurs in 1 in 10000 patients.[1] It is characterized by maculopapular rashes all over the body with peeling of the skin and lesions in the mucous membranes. It may be accompanied by systemic manifestations like fever, liver and kidney disorders. If it is severe it may even result in the death of the patient. If less than 10% of body surface is involved it is termed as SJS and if more than 30% of body surface is involved it is diagnosed as Toxic epidermal necrolysis (TEN). It was found that the presence of HLA B* 15:02 increases the risk for the development of SJS. It is more prevalent in Chinese population. It was recommended by FDA to check for HLA B* 15: 02 before prescribing carbamazepine in Asian ancestry.[2] In India, several reports have implicated carbamazepine as among the most common cause for SJS/TEN. There are few studies done in Gujarat, Chandigarh and Kerala about this genetic correlation. So in this study it is intended to evaluate this association between HLA B *15:02 and the risk for SJS induced by carbamazepine in the population in and around Madurai.

**Method:**
**Study Setting :** It is done in Dermatology Department and Neurology Department of Government Rajaji Hospital, Madurai.

**Duration :** 2 years
**Study design**: Case control study
**Selection of Cases and Controls**
**Cases**: Patients diagnosed as Stevens Johnson syndrome due to carbamazepine. They were selected from the dermatology department

**Controls**: Patients who are on carbamazepine for 6 months or more and not developed SJS. The controls were selected from patients attending neurology outpatient department

**Exclusion Criteria**
Patients who are on other drugs which tend to produce SJS
Patients with a history of allergy to any other drug
Patients unwilling to undergo the study

**Sample size** : The prevalence of HLA B* 15:02 is 2-4% in Indian population and taking Odds Ratio for the fore mentioned association from a study done by Timr.Y.Mehta et.al sample size was calculated. The result obtained was 9 pairs .

After obtaining institutional ethical clearance patients diagnosed as Stevens Johnson syndrome due to carbamazepine were selected. All the patients were clearly explained about the nature of the study and written informed consent was obtained. The age, sex, duration of drug intake and address of the individuals were recorded .After proper aseptic precautions, 5ml blood was collected in ethylene diamine tetra acetic acid (EDTA) coated sterile vials for HLA testing It was sent to the laboratory to test for the presence of HLA B*15:02

**HLA Testing :** It was done in the Immunology Department of Madurai Kamarajar University, Madurai. The salting out method (Miller et al., 1988) was used to extract DNA from 3-5 ml of peripheral blood collected in an EDTA vacutainer. HLA B typing was performed by Sequence Specific Primer.[3,4,5].The PCR products were detected by electrophoresing in a 1.5% agarose gel. After electrophoresis, the gel was visualized under ultra-violet illumination and documented in a gel documentation unit. The alleles were assigned according to the pattern of band formation

**Statistical Analysis:** All variables were analyzed descriptively. All categorical data were analyzed by Chi square test; and Fishers exact test

**Results :** There were 11 patients of SJS due to carbamazepine with a definite history satisfying the criteria of the study protocol. From neurology OPD, 22 matched controls were selected. HLA typing was done for both controls and cases. The results are as follows.

**Table 1: Prevalence of HLA B*15:02 in cases and controls**

| | SJS patients | Controls |
|---|---|---|
| HLA B* 15:02 present | 1 | 1 |
| HLA B* 15:02 absent | 10 | 21 |

On applying the Fisher exact test statistic value is 1. The result is not significant at p<0.05. The association of HLA B*15:02 with the SJS induced by CBZ is not proved in the study population.

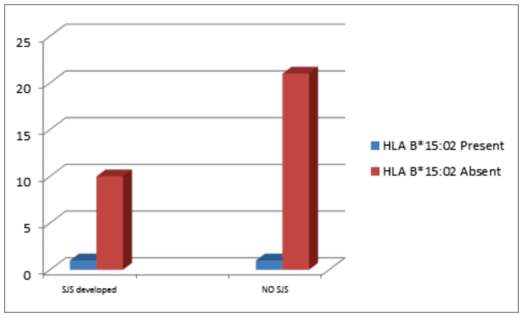


**Figure 1: Prevalence of HLA B*15:02 in cases and controls**

The age range of SJS patients is between 9-54 years. The average age is 23. The maximum no of patients were in the age group between 10-20 (5).

The time gap between the ingestion of CBZ and the development of SJS is from 2 days to 5 months. The average time gap is 31 days. But it appeared within 10 days in 6 patients (54%); between 11-20 days in 2 patients; between 21-60 days in 2 patient and more than 60 days in 1 patient. Majority of the patients developed SJS . Only one patient had the severe reaction TEN.

Among the SJS patients 9 were prescribed carbamazepine for epilepsy and 2 had the drug for neuralgia.

**Discussion:** Only one case and matched control had HLA B*15:02. By statistical analysis the p value is not significant at 0.05 level. So HLA B*15:02 cannot be ascertained as a risk factor for SJS induced by CBZ in and around Madurai.

In a study done in Modassa, Gujarat 71% association is observed between the presence of HLA B *15:02 and the incidence of SJS in carbamazepine treated patients.[6]

The presence of the allele in HLA B* 15:02 is found in North Indian population by a study done in PGI Chandigarh. In that study 22% association is seen between the presence of HLA B *15:02 and the incidence of SJS in carbamazepine treated patients.[7]

But in a study done by Devi.K et al in Kottayam, Kerala they found only one patient had HLA B*15:02 in 12 cases and 11 controls.[8]

So it appears the prevalence of HLA B* 15:02 is negligible in South Indian population.

**Conclusion:** HLA B*15:02 cannot be considered as a risk factor for carbamazepine induced Sevens Johnson syndrome in South Indian population. Studies should be extended to find associations of other genetic markers and SJS induced by carbamazepine.

## REFERENCES:

1. Bae, H. M., Park, Y. J., Kim, Y. H., & Moon, D. E. (2013). Stevens-johnson syndrome induced by carbamazepine treatment in a patient who previously had carbamazepine induced pruritus - a case report -. The Korean journal of pain, 26(1), 80–83. https://doi.org/10.3344/kjp.2013.26.1.80
2. Ferrell, P. B., Jr, & McLeod, H. L. (2008). Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics, 9(10), 1543–1546. https://doi.org/10.2217/14622416.9.10.1543
3. Olerup, O., & Zetterquist, H. (1992). HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue antigens, 39(5), 225–235. https://doi.org/10.1111/j.1399-0039.1992.tb01940.x
4. Bunce, M., Fanning, G. C., & Welsh, K. I. (1995). Comprehensive, serologically equivalent DNA typing for HLA-B by PCR using sequence-specific primers (PCR-SSP). Tissue antigens, 45(2), 81–90. https://doi.org/10.1111/j.1399-0039.1995.tb02422.x
5. Tonks, S., Marsh, S. G., Bunce, M., & Bodmer, J. G. (1999). Molecular typing for HLA class I using ARMS-PCR: further developments following the 12th International Histocompatibility Workshop. Tissue antigens, 53(2), 175–183. https://doi.org/10.1034/j.1399-0039.1999.530208.x
6. Mehta, T. Y., Prajapati, L. M., Mittal, B., Joshi, C. G., Sheth, J. J., Patel, D. B., Dave, D. M., & Goyal, R. K. (2009). Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian journal of dermatology, venereology and leprology, 75(6), 579–582. https://doi.org/10.4103/0378-6323.57718
7. Aggarwal, R., Sharma, M., Modi, M., Garg, V. K., & Salaria, M. (2014). HLA-B 1502 is associated with carbamazepine induced Stevens-Johnson syndrome in North Indian population. Human immunology, 75(11), 1120–1122. https://doi.org/10.1016/j.humimm.2014.09.022
8. Devi K. (2018). The association of HLA B*15:02 allele and Stevens-Johnson syndrome/toxic epidermal necrolysis induced by aromatic anticonvulsant drugs in a South Indian population. International journal of dermatology, 57(1), 70–73. https://doi.org/10.1111/ijd.13812