Get to know a gene: HLA-B*1502 and HLA-A*3101

Summary: The human leukocyte antigen (HLA) complex plays an important role in immune regulation. HLA-B*1502 has demonstrated the ability to predict an increased risk of severe skin reactions, such as Stevens-Johnsons syndrome (SJS), when taking certain mood stabilizers, specifically carbamazepine, oxcarbazepine, lamotrigine, and phenytoin. HLA-A*3101 is predictive of severe skin reactions with carbamazepine. Caution should be used with these medications for patients testing positive for the HLA-B*1502 or HLA-A*3101 alleles.

What are the HLA genes?

The human leukocyte antigen (HLA) complex, encoded by the HLA gene family, plays a critical role in immunity. The HLA proteins are present on the surface of most cells and help the immune system to recognize foreign substances, such as viral and bacterial peptides. HLA-B*1502 and HLA-A*3101 are two alleles that have been associated with severe cutaneous adverse drug reactions (cADRs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), when taking certain mood stabilizers. Carbamazepine, oxcarbazepine, lamotrigine, and phenytoin are some of the antiepileptic drugs most commonly associated with cADRs.

What do the data say about HLA polymorphisms and carbamazepine-induced SJS/TEN?

The association between the HLA-B*1502 allele and carbamazepine-induced SJS/TEN has been extensively studied. A meta-analysis by Grover et al. (n=205 cases, n=692 carbamazepine-tolerant controls) found a significant association between HLA-B*1502 and carbamazepine-induced SJS/TEN (Table 1, OR=80.70, $p=1.88x10^{-51}$).[1] The robustness of these data prompted the FDA to add a black box warning to the carbamazepine package insert, stating that carbamazepine should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks.[2]

A meta-analysis of six studies (n=105 cases, n=968 carbamazepine-tolerant controls) found that the HLA-A*3101 allele is significantly associated with carbamazepine-induced SJS/TEN (Table 1, OR=5.65, $p=4.03x10^{-6}$).[1] The package insert discourages the use of carbamazepine in HLA-A*3101 positive patients.[2]

What do the data say about HLA polymorphisms and oxcarbazepine-induced SJS/TEN?

The FDA-approved package insert for oxcarbazepine, a structural derivative of carbamazepine, also warns against the use of oxcarbazepine in patients positive for HLA-B*1502.[3] A meta-analysis by Tangamornsuksan et al. (n=19 cases, n=109 oxcarbazepine-tolerant controls) found a significant association between HLA-B*1502 and oxcarbazepine-induced SJS (Table 1, OR=26.4).[4]

The studies looking into the potential association between HLA-A*3101 and oxcarbazepine-induced SJS are scarce. A study by Chen et al. (n=17 cases, n=101 oxcarbazepine-tolerant controls) found no association between the allele and oxcarbazepine-induced SJS (Table 1).[5]

What do the data say about HLA polymorphisms and lamotrigine-induced SJS/TEN?

A meta-analysis by Deng et al. pooled results from 7 studies (n=54 cases, n=313 lamotrigine-tolerant controls) and found a significant association between HLA-B*1502 and lamotrigine-induced SJS/TEN (Table 1, OR=2.4, p=0.01).[6] The FDA label for lamotrigine contains a black-boxed warning addressing the risk of "serious skin rashes" (including SJS/TEN) associated with lamotrigine treatment but does not mention HLA-B*1502.[7]

The HLA-A*3101 allele does not appear to be a clinically relevant predictor of lamotrigine-induced adverse events as a genome-wide association study (GWAS) failed to find an association between the allele and lamotrigine-induced cADRs (OR=0.756, p=0.698).[8]

What do the data say about HLA polymorphisms and phenytoin-induced SJS/TEN?

The HLA-B*1502 allele has been implicated in phenytoin-induced SJS/TEN. A meta-analysis by Li et al. (n=46 cases, n=246 phenytoin-tolerant controls) found a significantly increased risk of phenytoin-induced SJS/TEN in HLA-B*1502 subjects (Table 1, OR=5.65, p< 0.00001).[9] The FDA-approved package insert warns against the use of phenytoin in HLA-B*1502 positive patients.[10]

A GWAS failed to find an association between HLA-A*3101 and phenytoin-induced cADRs (OR=0.791, p=0.746).[8]

Table 1: Association of HLA variations with SJS/TEN

HLA Allele	Carbamazepine	Oxcarbazepine	Lamotrigine	Phenytoin
HLA-B*1502	OR=80.70[1]	OR=26.4[4]	OR=2.40[6]	OR=5.65[9]
HLA-A*3101	OR=5.65[1]	Not significant[5]	Not significant[8]	Not significant[8]

Who should be tested?

The frequency of the HLA-B*1502 allele is highest in certain Asian populations. Malaysian, Thai, Vietnamese, and Chinese populations have allele frequencies of 7-16%.[11-14] Screening may be beneficial for these patients. HLA-B*1502 is much less frequent in Japanese and Caucasian populations, with allele frequencies of <1%.[15] In contrast, up to 10-15% of Japanese, Native American, Indian, Arabic, Han Chinese, Korean, and European patients are expected to carry the HLA-A*3101 allele, but it is less common in African-American, Thai, and Taiwanese populations.[2]

While the HLA-B*1502 and HLA-A*3101 alleles are more frequent in some populations than in others, the associations with adverse drug reactions may not necessarily be ancestry dependent. Additionally, while the FDA-approved package insert for carbamazepine recommends testing for HLA-B*1502 in patients of Asian descent prior to starting carbamazepine, the label also states that the difficulty in determining ethnic ancestry and the likelihood of mixed ancestry should also be considered. Furthermore, a large cohort study conducted in the United States identified more than twice as many HLA-B*1502 carriers to have non-Asian ethnicity. Therefore, testing only patients of Asian ancestry may not identify a large portion of HLA-B*1502 positive patients, especially in an ethnically diverse population such as that found in the United States.[16]

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