

HLA Associations with Aromatic Antiepileptic Drug and Allopurinol-Induced Stevens- Johnson Syndrome/Toxic Epidermal Necrolysis in a European-Ancestry Cohort

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Abstract

Background. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening severe cutaneous adverse reactions associated with specific human leukocyte antigen (HLA) alleles. However, most available pharmacogenetic evidence has been derived from Asian populations, whereas patients of Eastern European ancestry remain underrepresented.

Objective. This study aimed to investigate HLA-associated susceptibility to allopurinol- and aromatic antiepileptic drug-induced SJS/TEN in a Russian cohort and to assess the relevance of established and potential population-specific pharmacogenetic markers.

Methods. This single-center observational case-control study included patients enrolled between 2023 and 2025 with clinically confirmed SJS/TEN associated with allopurinol, carbamazepine, or lamotrigine. Drug causality was assessed using the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN). When several potentially causative drugs had been administered, the drug with the highest ALDEN score was selected as the index drug; patients with identical highest scores for multiple drugs were excluded. Drug-tolerant individuals exposed to the corresponding medications served as controls. High-resolution HLA genotyping was performed using next-generation sequencing. Differences in HLA carrier frequencies were evaluated using the two-sided Fisher's exact test, with Benjamini-Hochberg correction for multiple comparisons. A bibliometric analysis of HLA-associated SJS/TEN literature indexed in PubMed between 1986, and April 2025 was also conducted using VOSviewer.

Results. Among patients with aromatic antiepileptic drug-induced SJS/TEN, HLA-A*32:01 was detected in 47.1% of cases and in none of the drug-tolerant controls and remained significantly associated with case status after correction for multiple comparisons. Significant associations were also observed for HLA-A*32:01 in both the carbamazepine and lamotrigine subgroups. HLA-B*38:01 remained significantly associated with antiepileptic drug-induced SJS/TEN overall and with lamotrigine-induced reactions. HLA-C*04:01 and HLA-C*12:03 demonstrated nominal associations that did not remain significant after Benjamini-Hochberg correction. In the allopurinol subgroup, HLA-B*58:01 was detected in all SJS/TEN cases and in none of the tolerant controls, and the association remained statistically significant after correction. The bibliometric analysis indicated that most established HLA risk associations have been identified predominantly in Asian populations.

Conclusion. This study replicated the established association between HLA-B*58:01 and allopurinol-induced SJS/TEN and identified HLA-A*32:01 and HLA-B*38:01 as candidate susceptibility markers for aromatic antiepileptic drug-induced SJS/TEN in Russian patients of predominantly European ancestry. These exploratory findings require validation in larger independent cohorts before their clinical utility or suitability for routine pharmacogenetic screening can be established.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are among the most severe forms of cutaneous adverse drug reactions. Both conditions constitute medical emergencies associated with substantial morbidity and mortality. They are characterized by extensive epidermal detachment, mucosal involvement, and systemic complications and are now widely recognized as immune-mediated disorders rather than the result of direct toxic effects of medications [1–4]. Reported mortality rates vary according to patient characteristics and disease severity. Overall mortality is estimated at approximately 15%-20%, whereas it may reach 50% among elderly and immunocompromised patients, reflecting the particular vulnerability of these groups [5–6].

The drugs most frequently implicated in the development of SJS/TEN include aromatic anticonvulsants, allopurinol, and several other pharmacological agents [7–11]. To assess the causal relationship between exposure to a specific medication and the development of epidermal necrolysis, clinicians commonly use the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN). Within this scoring system, a score of 4 or higher indicates that the suspected drug has a probable or very probable causal relationship with the reaction [12].

Over the past two decades, advances in immunology and pharmacogenomics have demonstrated that drug-induced SJS/TEN is not a nonspecific hypersensitivity reaction but a predominantly T-cell-mediated disease. In particular, HLA class I-restricted CD8 + cytotoxic T lymphocytes play a central role in initiating keratinocyte apoptosis and widespread epidermal necrosis. This understanding has provided important insights into the genetic contribution to individual susceptibility [13–17]. Nevertheless, for many drugs associated with SJS/TEN, no clearly defined HLA allele or other genetic biomarker has yet been identified.

Even when specific HLA risk alleles have been established, such as HLA-B*15:02 for carbamazepine-induced SJS/TEN and HLA-B*58:01 for allopurinol-induced severe cutaneous adverse reactions, their clinical relevance is not uniform across populations. An allele that has strong predictive value in one population may have limited utility in another because of differences in allele frequency, genetic background, environmental exposures, and other clinical factors. These population-related differences illustrate the complexity of interactions among the host immune system, genetic susceptibility, and drug exposure [18–20].

Although the prevalence and predictive value of particular risk alleles may vary across populations, the biological mechanisms underlying HLA-associated drug hypersensitivity are not determined by socially defined racial or ethnic categories. Therefore, race or ethnicity should not be used as a substitute for direct genetic assessment. Race-based pharmacogenetic testing strategies may result in stereotyping, incorrect classification of individual risk, and inappropriate clinical decision-making. A more accurate approach is to base preventive screening strategies on individual genetic characteristics and population-specific evidence rather than on broad racial or ethnic classifications [21–22].

Despite the growing body of evidence regarding HLA-associated susceptibility to SJS/TEN, data from patients of Russian and other Eastern European backgrounds remain limited. It is therefore unclear

whether HLA associations identified in Asian and other populations are also relevant to patients in Russia or whether alternative genetic markers may contribute more substantially to disease susceptibility in this population.

Accordingly, the objective of the present study was to investigate genetic predisposition to SJS/TEN in a cohort of patients of Russian descent who developed the reaction following exposure to allopurinol or aromatic antiepileptic drugs. Specifically, we aimed to assess the relevance of known HLA risk alleles in this population and to identify potential alternative genetic associations. We hypothesized that the distribution and clinical relevance of previously established HLA risk alleles may differ in patients of Russian descent because of population-specific genetic characteristics.

By examining an underrepresented European population, this study is intended to expand current knowledge of the immunogenetic factors underlying drug-induced SJS/TEN and to provide evidence for the development of more accurate pharmacogenomic screening strategies. Research involving diverse populations is essential for identifying novel genetic markers, evaluating their predictive value, and improving the prevention of these life-threatening adverse drug reactions. Such evidence may support the transition toward personalized prescribing practices based on an individual patient's genetic risk rather than on population-level assumptions.

Materials and methods

Ethical statement

The Ethics Committee of the Affiliated Moscow City Clinical Hospital 52 (Protocol № 12/1223, 27.12.2023, Chairperson Andreev S.S.) approved the sample collection and design. The study was conducted in accordance with the regulatory legal acts of Russia and the Helsinki Declaration of the World Medical Association. Confidentiality of patient data was maintained at all stages of data collection and processing and preparation of the manuscript text. All patients provided written informed consent to be included in the study.

Patient population

This was a single-center observational case-control study conducted at a specialized referral medical center. Patients were enrolled between 2023 and 2025. The study was designed to investigate associations between HLA alleles and susceptibility to Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) induced by allopurinol or aromatic antiepileptic drugs.

The case group included patients with clinically confirmed SJS, SJS-TEN overlap, or TEN associated with lamotrigine, carbamazepine, or allopurinol. The causal relationship between each suspected medication and the reaction was assessed using the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) [12]. In patients exposed to more than one potentially causative medication, the drug with the highest ALDEN score was selected as the index drug for subsequent analysis. Patients who had received

multiple potentially causative medications with identical highest ALDEN scores were excluded because the causative drug could not be reliably determined.

Clinical phenotypes were classified according to the extent of epidermal detachment. SJS was defined as epidermal detachment involving less than 10% of the body surface area (BSA), TEN as detachment involving more than 30% of the BSA, and SJS-TEN overlap as detachment involving 10%-30% of the BSA [1-2].

The control group consisted of drug-tolerant individuals who had received carbamazepine, lamotrigine, or allopurinol for at least three months without developing any documented adverse drug reactions. Controls were selected according to exposure to the same medication as the corresponding cases. The groups were comparable with respect to age and sex. The demographic and clinical characteristics of the study groups are presented in Table 1.

Bibliometric analysis

Bibliographic data for this study was collected from the PubMed® (<https://pubmed.ncbi.nlm.nih.gov>), which is a widely recognized and comprehensive bibliographic database. To gather relevant articles, an advanced [Title/Abstract] search formula based on subject terms in title was employed. The formula consisted of three main components (Table 2). The final dataset was obtained by combining the results of component 1, 2 and 3 using the logical operator “AND”. The total number of articles published between 1986, and April 2025 is 421. To analyze the bibliographic data VOSviewer 1.62.0 (<https://www.vosviewer.com/>) software was employed. Counting method for co-occurrence analysis was “Full counting”. Normalization method was LinLog/modularity. Minimum number of terms in cluster was 10. Random seed for reproducing was 42.

HLA Genotyping by Next-Generation Sequencing (NGS)

High-resolution HLA genotyping of the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci was performed using a next-generation sequencing-based approach. Peripheral blood samples were collected from all participants, and genomic DNA was extracted before library preparation. DNA concentration and purity were assessed spectrophotometrically.

Targeted amplification and library preparation were performed using NGSgo reagents (GenDx, Utrecht, the Netherlands) in accordance with the manufacturer’s instructions. Sequencing was conducted on a MiSeq platform (Illumina, San Diego, CA, USA).

Sequencing data were processed, and HLA alleles were assigned using NGSengine software (GenDx, Utrecht, the Netherlands). The software aligns sequencing reads with reference HLA allele sequences and enables high-resolution allele assignment at two-field resolution. This approach allows discrimination between HLA variants that may not be reliably resolved using conventional sequence-specific oligonucleotide probing or sequence-specific primer polymerase chain reaction methods.

Statistical analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test. As the data were not normally distributed, continuous variables were summarized as medians with interquartile ranges (Q1-Q3), and between-group comparisons were performed using the Mann-Whitney U test.

Categorical variables were presented as absolute numbers and percentages. Differences in HLA allele carrier frequencies between patients with SJS/TEN and drug-tolerant controls were assessed using the two-sided Fisher's exact test because of the small sample sizes and the presence of expected cell counts below five. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of the associations. When one or more cells contained a zero value, the Haldane-Anscombe correction was applied by adding 0.5 to each cell of the corresponding contingency table.

To account for multiple comparisons across the HLA alleles analyzed, p-values were adjusted using the Benjamini-Hochberg false discovery rate procedure. Both unadjusted and adjusted p-values were reported. A two-sided unadjusted p-value < 0.05 was considered nominally significant, whereas an adjusted p-value < 0.05 was considered statistically significant after correction for multiple testing. For the exploratory association analysis, 11 drug-allele comparisons corresponding to the most frequently observed HLA alleles in the study cohort were selected for detailed evaluation. Selection was based on carrier frequency in the pooled study population, irrespective of case-control status. To account for multiple comparisons within this selected subset, p-values were adjusted using the Benjamini-Hochberg false discovery rate procedure. Both unadjusted and adjusted p-values were reported. An unadjusted p-value < 0.05 was considered nominally significant, whereas an adjusted p-value < 0.05 was considered statistically significant within the 11-comparison exploratory analysis. Because the correction was restricted to the selected comparisons, the adjusted p-values do not control the false discovery rate across all HLA alleles identified by genotyping.

Results

Bibliographic analysis of HLA, SJS and TEN terms

As a preliminary step to evaluate the significance of genetic risk factors, we performed a bibliographic analysis of terms related to HLA, SJS, and TEN. Co-occurrence analysis of titles and abstracts identified a total of 7,805 terms, with a minimum occurrence threshold of 10. After applying this threshold, 257 terms remained, from which 89 terms most relevant to SJS, TEN, and HLA were selected for further analysis. Among these, the top 10 terms with the highest relevance scores were: acute inflammatory vesiculobullous reaction; HLA A02:06; cold medicine; HLA B44; severe ocular complication; HLA B13:01; mucosa; acetaminophen; dapsone; and oxypurinol. Analysis of HLA-related terms highlighted the 16 alleles with the highest relevance: HLA-A*02:06; HLA-B44; HLA-B*13:01; HLA-B*59:01; HLA-C*06; HLA-B13; HLA-B*40:01; HLA-B*15:02; HLA-B*57:01; HLA-A*31:01; HLA-A*11:01; HLA-A*33:03; HLA-B15; HLA-B*58:01; HLA-B*51:01; and HLA-A*24:02. These terms were subsequently grouped into three distinct clusters (Figure 1). These terms were divided into 3 distinct clusters (Figure 1). The first cluster

aggregates studies examining cutaneous adverse reactions across a broad pharmacologic spectrum—from antimicrobial and antigout agents to antivirals and antiepileptics. Prominent HLA associations include HLA-B*58:01 (strongest with allopurinol/oxypurinol), HLA-B*13:01 (dapsone), HLA-B*57:01 (abacavir hypersensitivity), and HLA-A*31:01 or HLA-B*15:02 (phenytoin). The convergence of multiple drug classes underscores a shared immunogenetic pathway in severe cutaneous adverse reaction pathogenesis and highlights the value of broad HLA genotyping in diverse patient populations. Focused on non-antibiotic, non-antigout medications, the second cluster emphasizes HLA-linked cutaneous reactions to pain relievers, diuretics, antiretrovirals, and barbiturates. Notable allelic risk factors include HLA-B*38:01 and HLA-C*04:01 (acetaminophen), HLA-B*59:01 (methazolamide), and HLA-DRB1 or HLA-B35 subtypes (nevirapine). The inclusion of phenobarbital further extends the pharmacogenomic relevance of HLA screening beyond the classic carbamazepine/abacavir paradigms (Table 3).

This tightly focused cluster captures the well-established HLA-B*15:02-mediated risk for antiepileptic-induced SJS/TEN, particularly in Southeast Asian cohorts. In addition to HLA-B*15:02, alleles such as HLA-A*31:01 and HLA-B*15:01 contribute to lamotrigine and oxcarbazepine hypersensitivity. The prominence of these agents underscores the success of population-based HLA screening programs which have demonstrably reduced SJS/TEN incidence.

Importantly, this bibliographic mapping underscores that most established HLA associations are population-specific and derived predominantly from Asian cohorts. Therefore, systematic evaluation in underrepresented populations, such as patients from Moscow with predominantly European ancestry, is essential to identify region-specific genetic risk factors and to assess the transferability of existing pharmacogenetic markers.

Overall drug-exposure cohort

Building on the bibliographic analysis and aiming to evaluate whether previously reported HLA associations were applicable to our population, we analyzed the distribution of HLA alleles in a Moscow-based cohort of patients with drug-induced SJS/TEN and drug-tolerant controls. HLA-A*32:01 was observed in 41.0% of SJS/TEN cases and was absent in controls (OR: 42.8; 95% CI: 2.4-751.2; unadjusted $p < 0.001$). HLA-B*38:01 was also enriched among cases (25.6% vs. 3.3%; OR: 10.0; 95% CI: 1.2-83.2; unadjusted $p = 0.018$), as was HLA-C*04:01 (15.4% vs. 0%; OR: 11.8; 95% CI: 0.6-219.0; unadjusted $p = 0.032$). These findings represent unadjusted associations in the overall drug-exposure cohort. Several additional alleles showed non-significant trends toward over- or under-representation in the SJS/TEN group: HLA-B*15:01 (20.5% vs. 3.3%; $p = 0.067$), HLA-B*58:01 (12.8% vs. 0%; $p = 0.064$), HLA-C*12:03 (20.5% vs. 3.3%; $p = 0.067$), HLA-B*56:01 (0% vs. 10.0%; $p = 0.077$), and HLA-C*01:02 (0% vs. 10.0%; $p = 0.077$).

Antiepileptic-induced SJS/TEN

In the subgroup of patients exposed to aromatic antiepileptic drugs, HLA-A*32:01 demonstrated the strongest association with SJS/TEN (47.1% vs. 0%; OR: 45.5; 95% CI: 2.6-807.5; unadjusted $p < 0.001$;

Benjamini-Hochberg-adjusted $p = 0.00023$). HLA-B*38:01 was also enriched among cases (29.4% vs. 4.0%; OR: 10.0; 95% CI: 1.2-84.3; unadjusted $p = 0.017$; adjusted $p = 0.032$). Both associations remained statistically significant after Benjamini–Hochberg correction within the 11-comparison exploratory analysis.

HLA-C*04:01 was detected exclusively among affected patients (17.6% vs. 0%; OR: 11.6; 95% CI: 0.6-216.9; unadjusted $p = 0.034$); however, this association did not remain statistically significant after Benjamini-Hochberg correction (adjusted $p = 0.053$). HLA-B*15:01 showed a non-significant trend toward enrichment among cases (23.5% vs. 4.0%; unadjusted $p = 0.065$; adjusted $p = 0.071$).

Carbamazepine-induced SJS/TEN

In the carbamazepine subgroup, HLA-A*32:01 was present in 41.2% of cases and in none of the drug-tolerant controls (OR: 19.3; 95% CI: 1.0-377.5; unadjusted $p = 0.010$; adjusted $p = 0.023$). This association remained statistically significant after correction for multiple comparisons.

HLA-B*15:02 was detected in 29.4% of cases and was absent in controls; however, the difference did not reach statistical significance (unadjusted $p = 0.052$; adjusted $p = 0.064$).

Lamotrigine-induced SJS/TEN

In the lamotrigine subgroup, HLA-A*32:01 was observed in 52.9% of cases and in none of the controls (OR: 27.9; 95% CI: 1.4-547.0; unadjusted $p = 0.003$; adjusted $p = 0.018$). HLA-B*38:01 was detected in 47.1% of cases and was absent in controls (OR: 22.4; 95% CI: 1.1-437.9; unadjusted $p = 0.009$; adjusted $p = 0.023$). Both associations remained statistically significant after Benjamini-Hochberg correction.

HLA-C*12:03 was more frequent among cases than among controls (47.1% vs. 8.3%; OR: 9.8; 95% CI: 1.0-93.5; unadjusted $p = 0.043$), but the association did not remain statistically significant after correction for multiple comparisons (adjusted $p = 0.059$).

Allopurinol-induced SJS/TEN

In the small allopurinol subgroup, HLA-B*58:01 was detected in all patients with SJS/TEN and in none of the drug-tolerant controls (100% vs. 0%; OR: 121.0; 95% CI: 2.0-7259.2; unadjusted $p = 0.008$; adjusted $p = 0.023$). The association remained statistically significant after Benjamini-Hochberg correction. The results are presented in Table 4 and Figure 2.

Discussion

In this study, we identified several HLA class I alleles associated with Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) induced by allopurinol and aromatic antiepileptic drugs in a Russian cohort of predominantly European ancestry. The strongest associations that remained statistically significant after correction for multiple comparisons were observed for HLA-A*32:01, HLA-

B*38:01, and HLA-B*58:01. HLA-C*04:01 demonstrated a nominal association and should be considered exploratory.

*HLA-B*15:02 is one of the most extensively studied pharmacogenetic markers for carbamazepine-induced SJS/TEN, particularly in Han Chinese, Thai, and other Asian populations. This association has led to the implementation of pre-treatment HLA-B*15:02 screening in several Asian countries before carbamazepine initiation. However, the predictive value of HLA-B*15:02 appears to vary substantially across populations, partly due to differences in allele frequency and genetic background. In European populations, this allele is relatively uncommon, and its association with carbamazepine-induced SJS/TEN has been less consistently reproduced. In our carbamazepine subgroup, HLA-B*15:02 was more frequent among cases than controls, although the difference did not reach statistical significance (29.4% vs. 0%; $p = 0.052$). This borderline finding should therefore be interpreted with caution and requires validation in larger independent cohorts.*

*By contrast, HLA-B*58:01 has been consistently associated with allopurinol-induced SJS/TEN across multiple populations. In our study, HLA-B*58:01 was detected in all patients with allopurinol-induced SJS/TEN and was absent in allopurinol-tolerant controls. Although the allopurinol subgroup was small, this result is consistent with previous evidence supporting HLA-B*58:01 as a clinically relevant pharmacogenetic marker for severe allopurinol hypersensitivity. Given the widespread use of allopurinol for gout and hyperuricemia, HLA-B*58:01 screening may have important clinical value for reducing the risk of life-threatening severe cutaneous adverse reactions.*

*In addition to confirming the relevance of known HLA markers, our study identified HLA-A*32:01 and HLA-B*38:01 as potential susceptibility alleles for antiepileptic drug-induced SJS/TEN. HLA-A*32:01 showed the strongest overall association in the full drug-exposure cohort and remained strongly associated in the antiepileptic subgroup, including both carbamazepine- and lamotrigine-induced reactions. HLA-B*38:01 was also enriched among affected patients, particularly in the lamotrigine subgroup. These findings suggest that alternative HLA risk alleles may contribute to SJS/TEN susceptibility in patients of Eastern European ancestry, where classical risk markers such as HLA-B*15:02 may have limited predictive utility.*

*We also observed enrichment of HLA-C*04:01 and HLA-B*15:01 among patients with SJS/TEN, particularly in those exposed to antiepileptic drugs. Although the available literature on these alleles in SJS/TEN is limited, their presence in affected patients suggests that they may act as additional susceptibility markers or be linked to broader high-risk haplotypes. However, given the small sample size and the number of alleles analyzed, these associations should be regarded as exploratory. Further studies with larger cohorts, independent replication, and appropriate correction for multiple testing are required to determine whether these alleles represent true independent risk factors.*

Our findings underscore the importance of population-specific pharmacogenetic research. Most established HLA associations with SJS/TEN have been identified in Asian populations, whereas data from Eastern European populations remain limited. The present study suggests that the distribution and

relevance of HLA susceptibility alleles in Russian patients of predominantly European ancestry may differ from those reported in Asian cohorts. However, given the limited sample size and exploratory nature of the analysis, these differences should be interpreted with caution. Pharmacogenetic screening strategies developed in one population may not be directly transferable to another without independent validation. Future approaches should therefore distinguish between well-established markers, such as HLA-B*58:01 for allopurinol-induced SJS/TEN, and candidate population-specific alleles, including HLA-A*32:01 and HLA-B*38:01, whose clinical relevance remains to be confirmed.

Overall, our results support further investigation of HLA genotyping as a potential component of precision medicine strategies for the prevention of severe cutaneous adverse reactions. Established pharmacogenetic screening, particularly for HLA-B*58:01 before allopurinol treatment in appropriate clinical settings, may contribute to improved drug safety. By contrast, the current findings are insufficient to support routine screening for HLA-A*32:01 or HLA-B*38:01 before carbamazepine or lamotrigine initiation. Large-scale, multicenter, and multiethnic studies are required to replicate these associations, evaluate their predictive performance in representative clinical populations, clarify their functional significance, and determine whether they may eventually be incorporated into clinically useful pharmacogenetic screening panels.

Conclusions

In conclusion, this study expands the current understanding of the immunogenetic architecture underlying Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) by providing data from a previously underrepresented Eastern European population. Using high-resolution next-generation sequencing-based HLA genotyping, we replicated the established association between HLA-B*58:01 and allopurinol-induced SJS/TEN. HLA-B*58:01 was detected in all affected patients and in none of the allopurinol-tolerant controls, and the association remained statistically significant after Benjamini-Hochberg correction.

Although the allopurinol subgroup was small, this finding is consistent with previous evidence supporting HLA-B*58:01 as a clinically relevant pharmacogenetic marker of severe cutaneous adverse reactions associated with allopurinol [13, 26-27]. Among patients with aromatic antiepileptic drug-induced SJS/TEN, HLA-A*32:01 and HLA-B*38:01 remained significantly associated with case status after correction for multiple comparisons. HLA-A*32:01 was associated with antiepileptic drug-induced SJS/TEN overall and remained significant in both the carbamazepine and lamotrigine subgroups. HLA-B*38:01 remained significantly associated with antiepileptic drug-induced SJS/TEN overall and with lamotrigine-induced reactions. These findings identify HLA-A*32:01 and HLA-B*38:01 as candidate susceptibility markers in patients of predominantly European ancestry; however, their predictive value and clinical utility require confirmation in larger independent cohorts. HLA-C*04:01 and HLA-C*12:03 demonstrated nominal associations with SJS/TEN but did not remain statistically significant after correction for multiple testing. They should therefore be regarded as exploratory findings rather than established susceptibility markers. Similarly, HLA-B*15:02 showed a higher frequency among patients

with carbamazepine-induced SJS/TEN than among tolerant controls, but the association did not reach statistical significance. Although HLA-B*15:02 remains the best-established genetic predictor of carbamazepine-induced SJS/TEN in several Asian populations, its low frequency and variable predictive performance in European populations emphasize the importance of population-specific pharmacogenetic research [7, 23-25]. The bibliometric analysis further indicated that much of the existing evidence on HLA-associated SJS/TEN has been generated in Asian populations. This imbalance highlights an important gap in pharmacogenomic research and supports the inclusion of underrepresented populations in future multicenter studies and international pharmacogenetic consortia [18-20].

Collectively, our findings support further investigation of population-specific HLA susceptibility patterns in drug-induced SJS/TEN. While the association between HLA-B*58:01 and allopurinol-induced SJS/TEN is consistent with established evidence, the associations involving HLA-A*32:01 and HLA-B*38:01 should be considered preliminary until independently replicated. The current results are therefore insufficient to support routine clinical screening for these candidate alleles before carbamazepine or lamotrigine treatment.

Large-scale, multicenter studies with appropriate correction for multiple comparisons are required to validate these associations, estimate their predictive performance in representative clinical populations, and investigate their functional role in T-cell-mediated epidermal injury. Expanding pharmacogenetic research across diverse populations will be essential for developing evidence-based, equitable, and clinically applicable strategies for the prevention of SJS/TEN.

Study Limitations

Several limitations of this study should be acknowledged. First, the sample size was relatively small, particularly in the subgroup of patients with allopurinol-induced SJS/TEN. This limited the statistical power of some associations and may have contributed to the borderline significance observed for specific alleles. Second, the single-center and case-control design and potential selection bias could restrict the generalizability of our findings to broader populations. Third, only patients of European ancestry residing in Russia were included, which may not fully reflect the genetic diversity present in other European populations. Finally, while next-generation sequencing (NGS)-based HLA typing provides high resolution and accuracy, functional studies exploring the mechanistic basis of the observed allele-drug interactions were beyond the scope of this work.

Despite these limitations, our results provide important new insights into the genetic risk architecture of SJS/TEN in European populations and highlight the need for larger, multicenter, and multiethnic studies to validate and expand upon our findings.

Declarations

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Author contributions

Conceptualization: E.N., A.D., D.F., A.Karaulov, P.L., M.Ly. Methodology: A.D., A.Karaulov., T.M., D.F., M.Ly. Formal analysis and investigation: E.N., A.D., Y.S., S.A., T.K., U.M., A.F., T.M., M.Le., K.G., A.Kalinkin. Writing – Original Draft preparation: E.N., A.D. Writing – Revision and Editing: E.N., A.D., Y.S., S.A., T.K., A.F., U.M., T.M., M.Le., A.Kalinkin., K.G., A.Karaulov, D.F., P.L., M.Ly. Funding acquisition: D.F., A.Karaulov, M.Ly. Supervision: D.F., A.Karaulov, P.L., M.Ly.

Ethics declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The Ethics Committee of the Affiliated Moscow City Clinical Hospital 52 (Protocol № 12/1223, 27.12.2023, Chairperson Andreev S.S.) approved the sample collection and design. The study was conducted in accordance with the regulatory legal acts of Russia and the Helsinki Declaration of the World Medical Association. Confidentiality of patient data was maintained at all stages of data collection and processing and preparation of the manuscript text. All patients provided written informed consent to be included in the study.

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Data Availability Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Tables

Table 1. Baseline characteristics of the study groups

	Group [†]	
	Main (n=39)	Control (n=30)*
Age, Mediana [IQR]		
Lamotrigine	26 [19,00-31,00]	25; [19,00-37,00]
Carbamazepine	29; [26,00-61,50]	27; [24,00-57,50]
Allopurinol	42; [39,00-69,00]	46; [37,00-67,50]
Sex		
Female	27 (69.2%)	18 (60.0%)
Male	12 (30.8%)	12; (40.0%)
Phenotype		
SJS	13; (33.3%)	-
TEN	26; (66.7%)	-
Drug		
Lamotrigine	17	12
Carbamazepine	17	13
Allopurinol	5	5
Duration of drug exposure (days), Mediana [IQR]		
Lamotrigine		
Carbamazepine	13 [9,00-19,00]	156 [91,00-243,00]
Allopurinol	14 [7,00-15,00]	110 [81,00-154,00]
	14 [13,00-15,00]	246, [154,00-367,00]

[†]All of Caucasian ancestry; * No adverse drug reactions were registered during this treatment period.

Table 2. Keywords used for the literature search

Components	Subject terms
1	"HLA" OR "human leukocyte antigen" OR "human leucocyte antigen"
2	"SJS" OR "stevens johnson syndrome"
3	"TEN" OR "toxic epidermal necrolysis"

HLA: Human Leukocyte Antigen, TEN: Toxic epidermal necrolysis. SJS: Stevens-Johnson Syndrome

Table 3. The relevance score of HLA alleles spreading between clusters.

Cluster 1		Cluster 2		Cluster 3	
HLA-B*13:01	3.67	HLA-A*02:06	5.88	HLA-B*40:01	0.68
HLA-C06	1.35	HLA-B*44	4.87	HLA-B*15:02	0.45
HLA-B13	1.25	HLA-B*59:01	2.06	HLA-A*31:01	0.39
HLA-B*57:01	0.44	HLA-A*33:03	0.32	HLA-B15	0.30
HLA-A*11:01	0.38	-	-	HLA-A*24:02	0.18
HLA-B*58:01	0.29	-	-	-	-
HLA-B*51:01	0.21	-	-	-	-

HLA: Human Leukocyte Antigen

Table 4. HLA alleles identified in the study cohort

	Groups		P, unadjusted	P, adjusted	Se, (%)	Sp, (%)	PPV,%	NPV,%
	SJS/TEN (n=39)	Control (n=30)						
Antiepileptic drug								
	SJS/TEN (n=34)	Control (n=25)						
HLA-A*32:01	16 (47,1%)	0 (0,0%)	<0,001*					
		1 (4,0%)	0,065	0,00023*	47,1	100,0	100	58,1
HLA-B*15:01	8 (23,5%)	1 (4,0%)	0,017*	0,071	23,5	96,0	88,9	48,0
	10 (29,4%)	3 (12,0%)	0,071	0,032*	29,4	96,0	90,9	50,0
HLA-B*38:01	0 (0,0%)	0 (0,0%)	0,034*	0,071	0,0	88,0	0,0	39,3
HLA-C*01:02	6 (17,6%)			0,053	17,6	100,0	100,0	47,2
HLA-C*04:01								
Carbamazepine								
	SJS/TEN (n=17)	Control (n=13)						
HLA-A*32:01	7 (41,2%)	0 (0,0%)	0,010*	0,023*	41,2	100,0	100,0	56,5
	5 (29,4%)	0 (0,0%)	0,052	0,064	29,4	100,0	100,0	52,0
HLA-B*15:02								
	SJS/TEN (n=17)	Control (n=12)						
Lamotrigine								
HLA-A*32:01	9 (52,9%)	0 (0,0%)	0,003*	0,018*	52,9	100,0	100,0	60,0
	8 (47,1%)	0 (0,0%)	0,009*	0,023*	47,1	100,0	100,0	57,1
HLA-B*38:01	8 (47,1%)	1 (8,3%)	0,043*	0,059	47,1	91,7	88,9	55,0
HLA-C*12:03								
Allopurinol								
	SJS/TEN (n=5)	Control (n=5)						
HLA-B*58:01	5 (100,0%)	0 (0,0%)	0,008*	0,023*	100,0	100,0	100	100

HLA: human leukocyte antigen; SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis, PPV: positive predictive value, NPV: negative predictive value, *statistically significant; Se - Sensitivity; Sp - Specificity; P, unadjusted were calculated using the two-sided Fisher's exact test. Adjusted p-values were calculated using the Benjamini-Hochberg false discovery rate procedure across the 11 comparisons presented. An adjusted p-value < 0.05 was considered statistically significant.

Figures

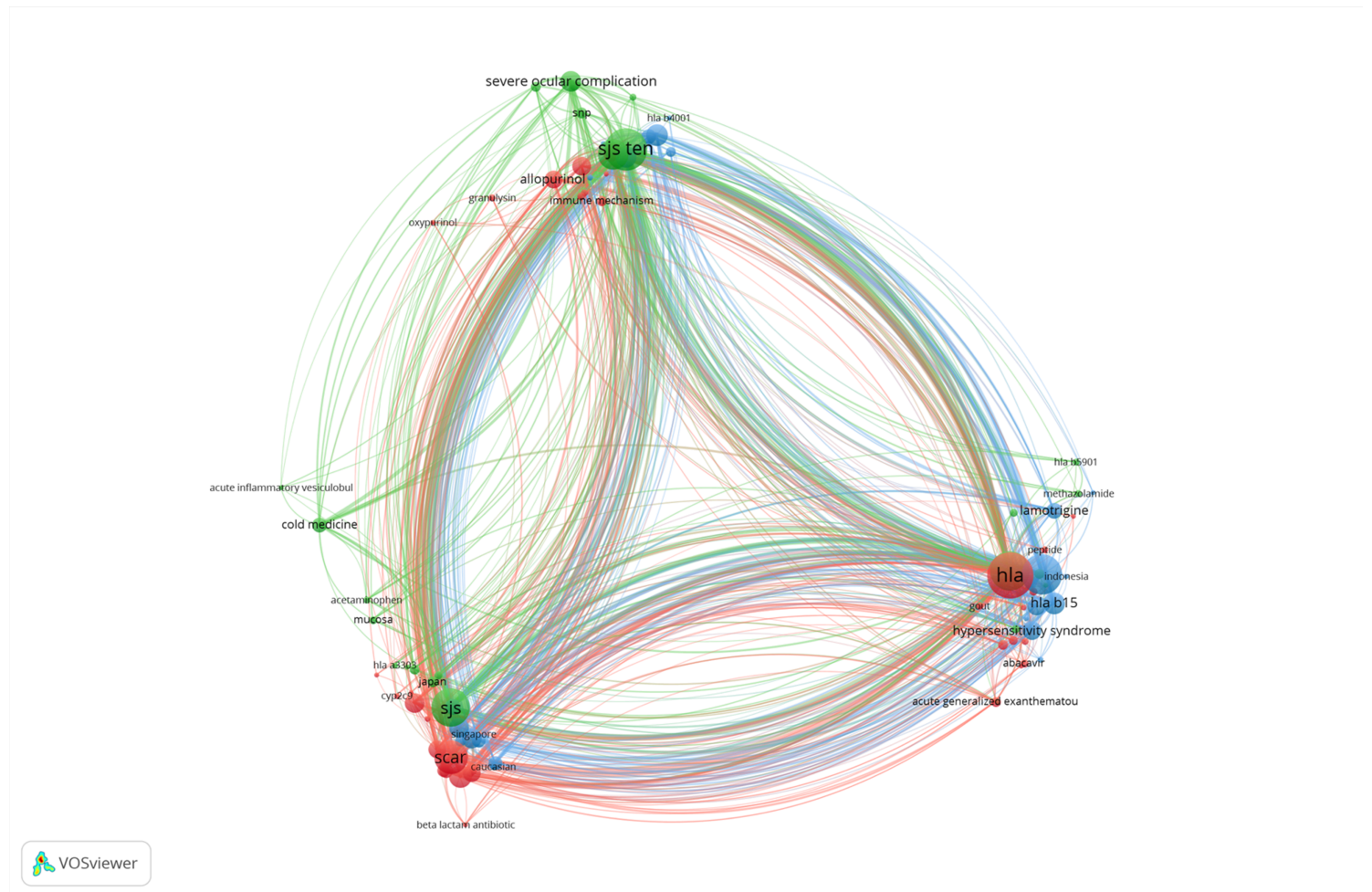


Figure 1

HLA, SJS and TEN co-occurrence network analysis. HLA - Human Leukocyte Antigens, SJS - Stevens-Johnson Syndrome, TEN - Toxic Epidermal Necrolysis

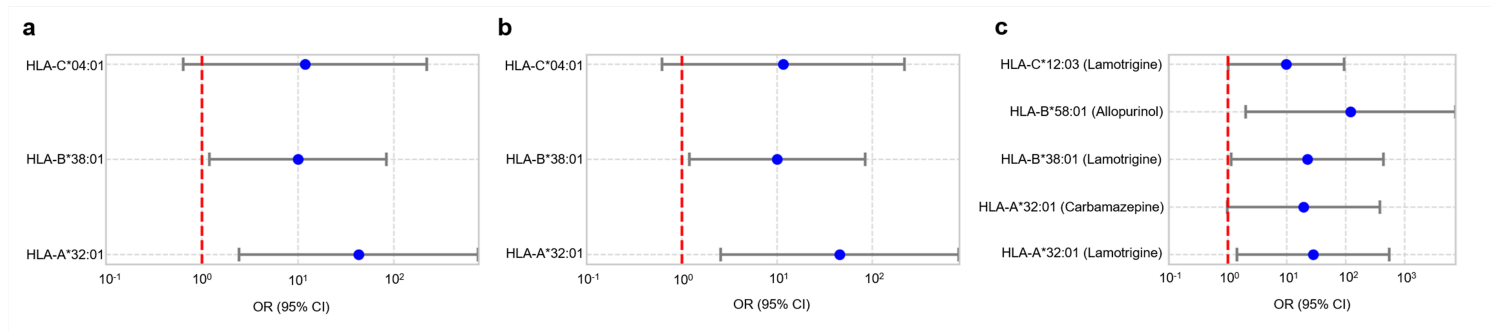


Figure 2

Odds ratio of HLA alleles associated with drugs hypersensitivity. (a) - odds ratio of HLA alleles associated with drugs hypersensitivity, (b) - odds ratio of HLA alleles associated with antiepileptic drugs hypersensitivity, (c) - odds ratio of HLA alleles associated with carbamazepine, lamotrigine and allopurinol hypersensitivity. HLA - Human Leukocyte Antigens, SJS - Stevens-Johnson Syndrome, TEN - Toxic Epidermal Necrolysis