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# HLA-B*15:02与芳香族类抗癫痫药物诱发SJS/TEN关联性的Meta分析

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## 摘　要

**目的：通过meta分析来评估HLA-B*15:02等位基因与芳香族类抗癫痫药物(AEDs)诱发史蒂文斯－约翰逊综合征/中毒性表皮坏死松解症(SJS/TEN)的关联。方法：全面检索PubMed、Embase、The Cochrane Library、知网、万方、维普数据库，检索时间截止2024年7月1日，采用Revman5.3软件进行meta分析。结果：共纳入26篇文献，均为病例对照研究，共计芳香族类AEDs诱发SJS/TEN患者794例，对照2851例，分析结果合并为OR (95% CI)为26.32 (15.67~44.21) (Z = 12.36, P < 0.00001)。结论：HLA-B*1502等位基因引香族类AEDs引起SJS/TEN存在明显关联。**

## 关键词

**芳香族抗癫痫药物，白细胞抗原，Meta分析**

# Meta-Analysis of the Association of HLA-B*15:02 with Aromatic Antiepileptic Drugs Inducing SJS/TEN

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## Abstract

**Objective: To assess the association of HLA-B*15:02 allele with aromatic antiepileptic drugs (AEDs)**

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**induced Stevens-Johnson syndrome/toxic epidermal necrolysis with laxity (SJS/TEN) by meta-analysis. Methods: A comprehensive search of PubMed, Embase, The Cochrane Library, Zhi.com, Wanfang, and Wipu databases was performed up to 1 July 2024, and meta-analysis was performed using Revman 5.3 software. Results: A total of 26 papers, all of which were case-control studies, were included, with a total of 794 patients with SJS/TEN induced by aromatic AEDs and 2851 controls, and the combined results of the analyses showed an OR (95% CI) of 26.32 (15.67~44.21) (Z = 12.36, P < 0.00001). Conclusion: There was a significant association of HLA-B*1502 allele eliciting AEDs of the Fragrant family class causing SJS/TEN.**

## Keywords

**Aromatic Antiepileptic Drugs, Leukocyte Antigens, Meta-Analysis**



## 1. 引言

一线抗癫痫药物包括卡马西平(CBZ)、奥卡西平(OXZ)和苯妥英钠(PHT)等均为芳香族 AEDs。然而，AEDs 常与皮肤药物不良反应(cADR)相关[1]，包括轻微斑丘疹(MPE)、药物超敏综合征(DHS)和严重皮肤不良反应(SCR)，如 SJS/TEN。SJS 和 TEN 的死亡率分别为 3%和 27%，其表现皮肤出现红色或暗红色斑块、非典型靶样病变、大疱、糜烂和皮肤脱落[2]等。近年来 HLA-B*15:02 等位基因与 AEDs 引起严重皮肤不良反应发生的相关性研究越来越多，但是各研究纳入标准不同，如地域、种族、样本量、等位基因的阳性率等不同，如中国云南不同民族[3]该等位基因携带率不尽相同，研究显示壮族频率最高；此外中国台湾汉族[4]、伊朗[2]、泰国[5]等针对不同人群研究结果也存在差异。本研究应用循证医学原理系统分析了近年国内外相关的研究，全面评估 HLA-B*15:02 与芳香族类 AEDs 引起的 SJS/TEN 关联性，为芳香族类 AEDs 的临床合理应用及严重皮肤不良反应预防提供参考。

## 2. 资料与方法

### 2.1. 文献纳入与排除标准

纳入标准：(1) 研究对象为癫痫患者；(2) 病例对照研究；(3) SJS/TEN 由芳香族类 AEDs (CBZ、OXZ、PHT、LTG 或 PB)诱发；(4) 研究对象能检测到 HLA-B*15:02 等位基因；(5) 研究中可获得病例和对照中 HLA-B*15:02 携带率；(6) SJS/TEN 的诊断定义[6]按照皮损面积百分比划分。

排除标准：(1) 非正规期刊发表文献；(2) 相关描述不清楚；(3) 文献数据不完整；(4) 研究对象年龄未满 3 岁。

### 2.2. 检索策略

检索电子文献数据库。其中，中文数据库包括：中国知网(CNKI)、万方、维普数据库；外文数据库包括：PubMed、Embase、The Cochrane Library。检索时限从建库至 2024 年 7 月 1 日。通过主题词与自由词结合方式检索，中文检索词为(芳香族类抗癫痫药物 OR 卡马西平 OR 奥卡西平 OR 拉莫三嗪 OR 苯妥因 OR 苯巴比妥) AND (药疹 OR 皮疹 OR 斯蒂文斯－约翰逊综合征 OR 中毒性表皮坏死松解症) AND (人类白细胞抗原 OR 基因多态性 OR 等位基因)；英文检索式为(HLA-B*1502) AND (HLA-

B*1502) AND (Carbamazepine OR CBZ OR Oxcarbazepine OR OXZ OR Lamotrigine OR LTG OR Phenytoin OR PHT OR Phenobarbital OR PB OR Aromatic) AND (Stevens-Johnson Syndrome OR Toxic Epidermal Necrolysis OR severe cutaneous adverse reactions OR adverse drug reaction)。

### 2.3. 数据提取

根据检索公式检索中英文数据库，两位研究人员摘要阅读，符合纳入标准后进行全文阅读，提取每项研究中的所需的信息，其中包括：第一作者、种族、对照组和病例组例数等。在文献纳入与数据提取过程中，研究者对于相关研究有异议可以进行讨论并最终达成统一意见。

### 2.4. 文献质量评价

纳入文献质量评价采用纽卡斯尔－渥太华量表(NOS)评价纳入的病例对照研究确定文献质量。

### 2.5. 资料分析

采用 RevMan5.3 软件进行 Meta 分析，检查每项研究数据是否存在异质性，如 $P > 0.1$，$I^2 < 50\%$认为同质性良好，如 $P < 0.01$，$I^2 > 50\%$认为存在异质，并选择随机效应模型，行亚组和敏感性分析。

## 3. 结果

### 3.1. 文献筛选结果

按照文献纳排标准最终纳入 26 篇文献，均为英文文献，检索过程、筛查过程及最终结果见图 1。

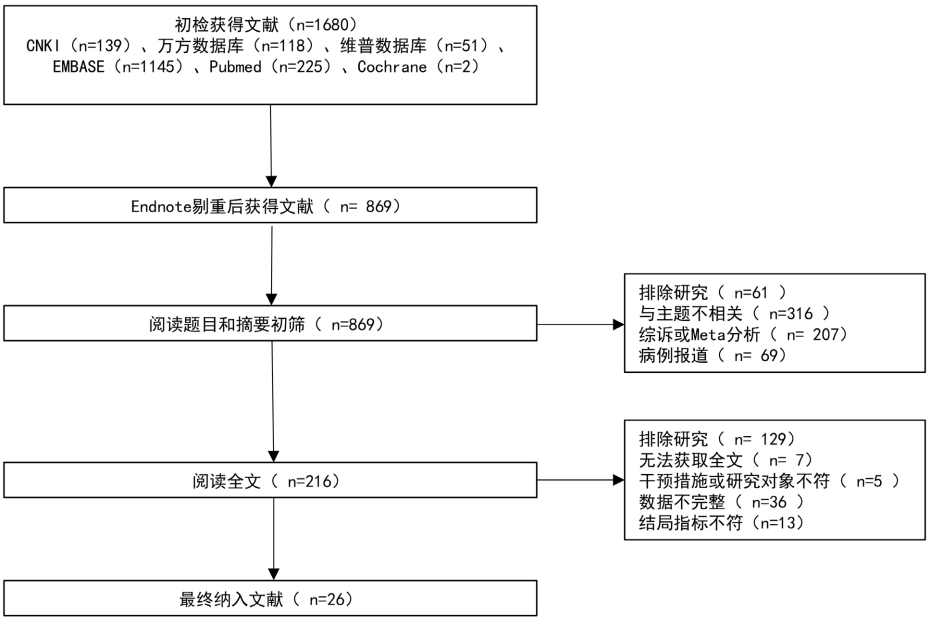


**Figure 1.** Literature screening process and results
**图 1.** 文献筛选流程及结果

### 3.2. 文献纳入特征

文献纳入 26 项研究中，13 项来自中国，3 项来自马来西亚，8 项来自泰国，2 项来自印度。文献的质量采用 NOS 标度进行评估，总分为 9 分，≥6 分视为高质量文献。结果详见表 1。

**Table 1.** Including the basic characteristics of the study
**表 1.** 纳入研究基本特征

| 纳入研究及年份 | 种族 | 诱发 SJS/TEN 药物 | 病例组 | 对照组 | NOS 分值 |
|---|---|---|---|---|---|
| Aggarwal 2014 [7] | 印度 | CBZ, PHT | 17 | 50 | 6 |
| An 2010 [8] | 中国四川 | LTG | 3 | 21 | 7 |
| Chang 2017 [9] | 马来西亚 | PHT | 13 | 32 | 6 |
| Chang 2011 [10] | 马来西亚 | CBZ | 21 | 300 | 6 |
| Cheung 2013 [11] | 中国香港 | CBZ, LTG, PHT | 47 | 240 | 6 |
| Chung 2004 [12] | 中国台湾 | CBZ | 44 | 101 | 8 |
| He 2013 [13] | 中国东北 | CBZ | 35 | 125 | 7 |
| Hsiao 2014 [14] | 中国台湾 | CBZ | 112 | 152 | 7 |
| Hung 2006 [15] | 中国台湾 | CBZ | 60 | 144 | 7 |
| Hung 2010 [16] | 中国台湾 | OXZ, LTG, PHT | 32 | 113 | 6 |
| Khor 2017 [17] | 马来西亚 | CBZ | 28 | 227 | 7 |
| Koomdee 2017 [18] | 泰国 | LTG | 4 | 50 | 7 |
| Kulkantrakorn 2012 [19] | 泰国 | CBZ | 34 | 40 | 7 |
| Kwan 2014 [20] | 中国香港 | CBZ, LTG, PHT | 47 | 239 | 6 |
| Locharernkul 2008 [21] | 泰国 | CBZ, PHT | 10 | 50 | 6 |
| Mehta 2009 [22] | 印度 | CBZ | 8 | 10 | 7 |
| Nakkam 2022 [23] | 泰国 | CBZ | 88 | 144 | 7 |
| Shi 2012 [24] | 中国南方 | CBZ | 18 | 93 | 7 |
| Sukasem 2018 [25] | 泰国 | CBZ | 16 | 271 | 7 |
| Tassaneeyakul 2016 [26] | 泰国 | PHT | 39 | 92 | 7 |
| Tassaneeyakul 2010 [27] | 泰国 | CBZ | 42 | 42 | 7 |
| Wang 2011 [28] | 中国南方 | CBZ | 9 | 80 | 6 |
| Wang 2014 [29] | 中国四川 | CBZ, PHT, PB | 27 | 64 | 6 |
| Wu 2010 [30] | 中国华中 | CBZ | 8 | 50 | 8 |
| Yampayon 2017 [31] | 泰国 | PHT | 15 | 100 | 7 |
| Zhang 2011 [32] | 中国苏州 | CBZ | 17 | 21 | 6 |

## 3.3. Meta 分析结果

### 3.3.1. 芳香族类 AEDs 诱发 SJS/TEN 与 HLA-B*15:02 等位基因关联性

26 项研究涉及了 794 例病患和 2851 例耐受对照，通过 Meta 分析发现 HLA-B*15:02 等位基因与芳香族类 AEDs 诱发 SJS/TEN 存在一定相关性(OR = 26.32, 95% CI = 15.67~44.21, P < 0.00001)，但异质性较高($I^2$ = 73% > 50%)，见图 2。通过敏感性分析逐一剔除文献后 $I^2$ 波动于 69%~73%，P 值不变，表明结果较为稳定。

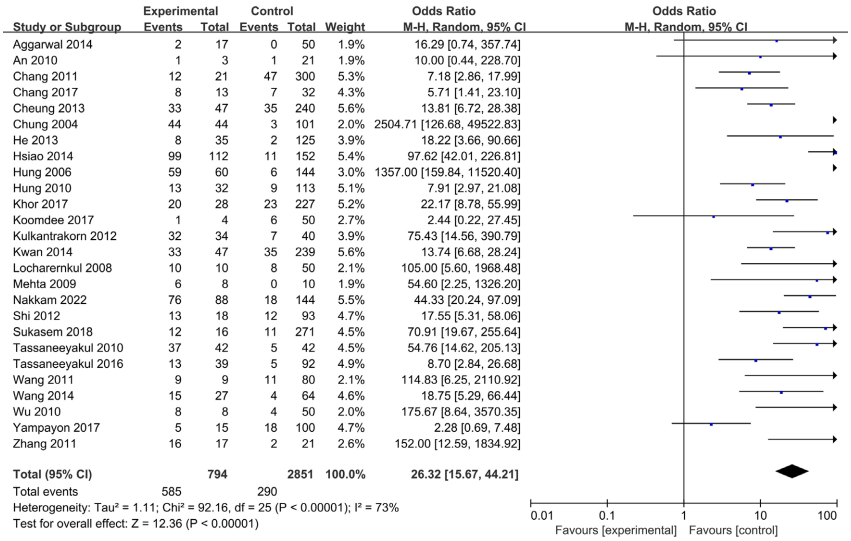


**Figure 2.** A forest plot of HLA-B*15:02 alleles in AEDs-induced SJS/TEN cases and tolerant controls
**图 2.** 芳香族类 AEDs 诱发 SJS/TEN 病例组和耐受对照组 HLA-B*15:02 等位基因的森林图

### 3.3.2. 亚组分析

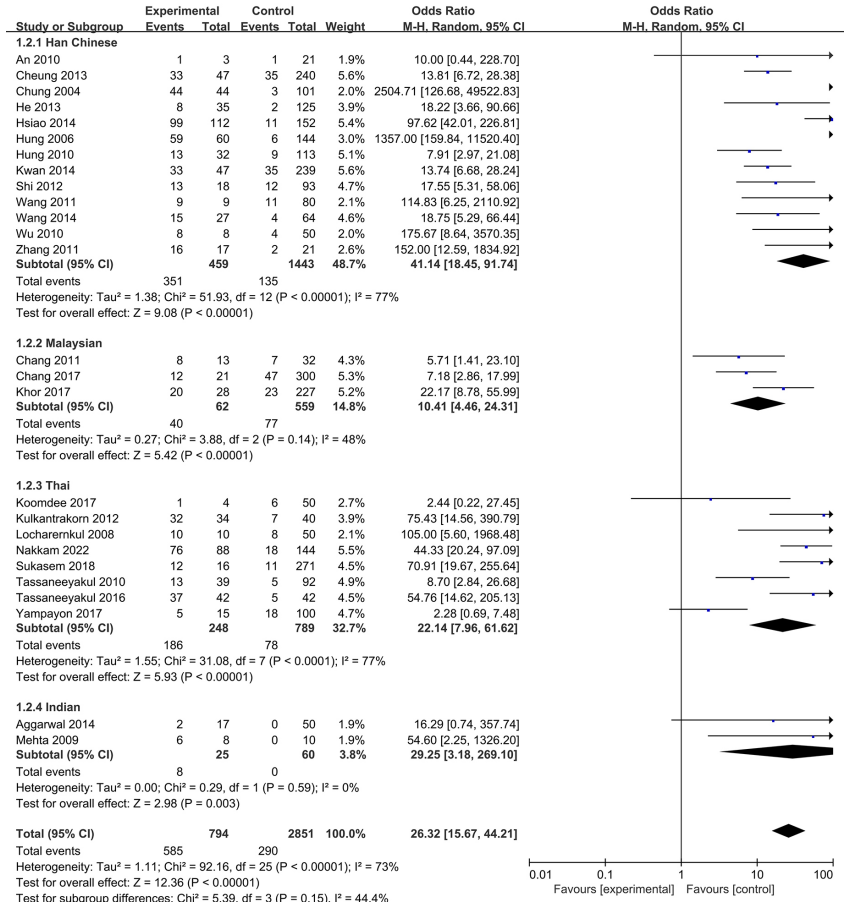


**Figure 3.** Forest plot of HLA-B*15:02 allele positivity in different races
**图 3.** 不同种族 HLA-B*15:02 等位基因阳性率森林图

由于研究间存在较大异质性，为明确异质性来源行亚组分析，因等位基因会受地域和种族的影响，针对种族进行亚组分析。亚组中马来西亚($I^2$ = 48%, P < 0.00001)，印度($I^2$ = 0%, P = 0.003 < 0.05)，异质性均<50%，具有统计学差异。而中国汉族($I^2$ = 77% > 50%, P < 0.00001)，泰国($I^2$ = 77% > 50%, P < 0.00001)，异质性偏高，见图 3。进行敏感性分析，将纳入文献逐一剔除，结果显示中国汉族组在剔除“Chung2004”、“Hsiao2014”和“Hung2006”3 篇文献后，异质性检验(P = 0.35, $I^2$ = 10%)，合并效应量后 P < 0.00001，结果指标未发生改变，考虑这三篇为异质性来源；泰国组在剔除“Koomdee2017”和“Yampayon2017”后，异质性检验(P = 0.10, $I^2$ = 45%)，合并效应量后 P < 0.00001，结果指标同样未发生改变，考虑这两篇文献为异质性来源，见图 4。

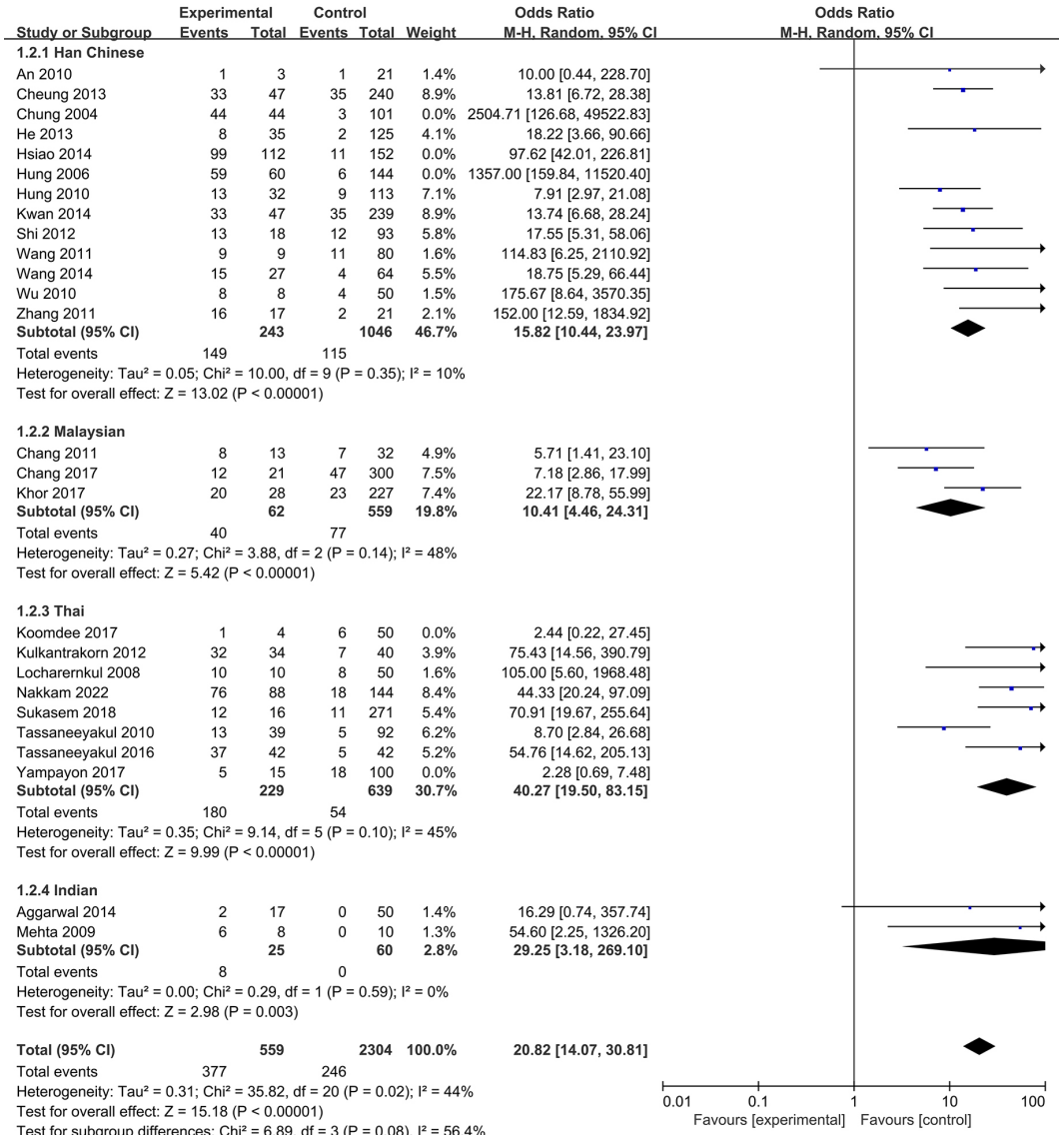


**Figure 4.** The sensitivity of positive rate of HLA-B*15:02 allele in different races was analyzed by forest plot
**图 4.** 不同种族 HLA-B*15:02 等位基因阳性率敏感性分析森林图

### 3.3.3. 发表偏倚

对以上纳入文献进行发表偏倚评估，发现散点对称性较好，相关研究发表偏倚较小，具体见图 5。

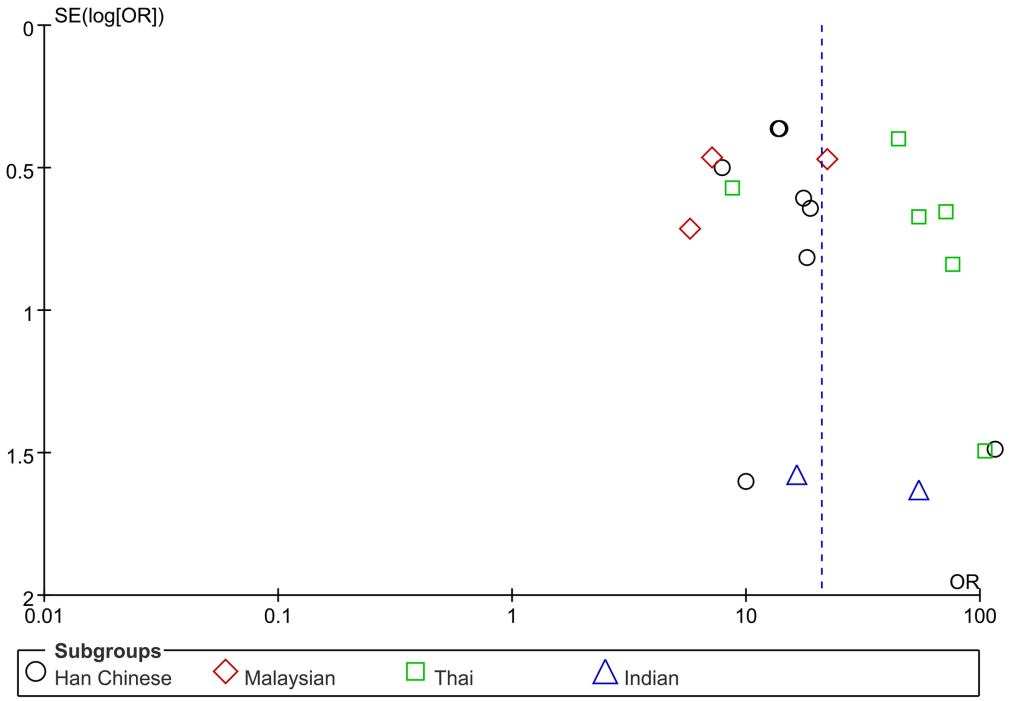


**Figure 5.** Publication bias funnel plot
**图 5.** 发表偏倚漏斗图

## 4. 讨论

随着药物基因组学的发展和推广，越来越多研究表明药物不良反应与人类白细胞抗原息息相关。近年来，有关 HLA-B*15:02 等位基因与严重皮肤不良反应相关的研究得以证实，特别在东亚，中亚，拉丁裔等人群，在 pharmGKB 数据库(https://www.pharmgkb.org/)东亚和中亚人群 HLA-B*15:02 等位基因频率高达 4.56%和 2.59%，如中国[33] [34]、马来西亚[35]、泰国[36]、印度[37]、爪哇[38]、伊朗[39]等研究都证实了 HLA-B*15:02 与 SJS/TEN 的关联性，但日本[40]和韩国[41]相比之下 HLA-B*15:02 等位基因频率较低；欧洲、美国等地区 HLA-B*15:02 等位基因频率较低仅为 0.01%和 0.17%，说明该等位基因携带率有很强的地域人种的差异。芳香族类 AEDs 诱发的 SJS/TEN 与 HLA-B*15:02 等位基因关联研究也较多，但大部分都集中在 CBZ 和 OXZ，PHT 次之，LTG 和 PB 相关研究较少，本篇 Meta 分析系统纳入了这五种药物来评价芳香族类 AEDs 诱发 SJS/TEN 与 HLA-B*15:02 的关联。

Meta 分析研究结果表明芳香族类 AEDs 诱发的 SJS/TEN 与 HLA-B*15:02 等位基因具有强关联性，但结果异质性较高，行敏感性分析后结果稳定，为寻求异质性来源讲纳入文献按种族分类进行亚组分析，发现印度组和马来西亚组异质性明显降低，考虑其种族的差异是异质性主要来源，另中国汉族组和泰国组逐一剔除文献进行敏感性分析后找到异质性来源的几篇文献，经详细研读后发现在中国汉族组中异质性来源文献是来自中国香港和中国台湾的研究，而泰国组主要是集中在对 PHT 和 LTG 的研究。根据等位基因数据库(http://www.allelefrequencies.net)中国香港人群 HLA-B*15:02 等位基因频率 0.10%，中国台湾人群 0.05%，且中国香港 25%药物皮肤不良反应来自卡马西平[12]，中国台湾 SJS/TEN 关于 HLA-B*15:02 等位基因携带率为 8.38% [4]，而中国北方汉族为 0.02%，南方汉族为 0.07%，相比之下，中国香港和中国台湾汉族人群该等位基因频率偏高，与 SJS/TEN 关联性也会更强[11]，说明同种族人群有地域差异。泰国组中关于 PHT 研究[31]发现 HLA-B*15:02 等位基因与 SJS/TEN 并无显著相关，这与

Tassaneeyakul 等人[26]研究结果一致；而泰国组关于 LTG 的研究[18]仅有一篇，样本量较小，需要更多关于泰国人群的研究证明其关联性。此外，关于 CBZ 和 OXZ 研究证据较为充分[42]，PHT [43]次之，而其他芳香族类 AEDs 如 LTG 和 PB 等将 SJS/TEN 与 HLA-B*15:02 等位基因联系起来的证据较弱，要得出更有意义的结论，需在不同种族人群中开展更多的多中心或更大规模的随机对照试验，像 Nakkam 等[23]对泰国人群、Yuliwulandari 等[38]对爪哇人和桑丹人群等研究。综上，芳香族类 AEDs 诱发的 SJS/TEN 与 HLA-B*15:02 等位基因有显著关联性，因此应用临床中在开始使用该类药物治疗前，患者应接受 HLA-B*1502 基因检测，以预测是否会出现严重的皮肤不良反应，然后调整治疗方案或联合用药，以控制此类不良反应的发生。

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