HLA: phenytoin 6927

95% CI = 95% confidence interval, DRESS = drug reaction with eosinophilia and systemic symptoms, also known as hypersensitivity syndrome (HSS), HSS = hypersensitivity syndrome, including DRESS, NS = not significant, OR = odds ratio, OR_{adj} = adjusted odds ratio, S = significant, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Phenytoin can induce the life-threatening cutaneous adverse events SJS/TEN and DRESS. Incidences are estimated to be between 0.1% and 0.01% of users. Mockenhaupt 2005 estimated the incidences of phenytoin-induced SJS/TEN and DRESS to be 0.069% and 0.023-0.045% in European new users, respectively. and 0.24% and 0.21% in Asian new users, respectively (Mockenhaupt M et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology 2005;64:1134-8). Phenytoin can also induce mild maculopapular exanthema, but this was not investigated in the risk analysis. The hypersensitivity reactions generally develop between 2 weeks and 3 months after the start of phenytoin.
Because specific HLA proteins are involved in specific cellular immune reactions that cause specific hypersensitivity reactions, HLA proteins can affect the risk of hypersensitivity reactions.
HLA-B*1502
HLA-B*1502 is present at a frequency of more than 1% only in persons of Southeast Asian ancestry (Han Chinese, Thai, Malaysians, Indians).
Four meta-analyses (of respectively 10, 7, 4 and 2 case-control studies) showed that this allele increased the risk of phenytoin-induced SJS/TEN (OR = 3.48-4.26) (Phung 2022, Sukasem 2021, Bloch 2014 and Cheung 2013), but another meta-analysis of 2 case-control studies did not show an effect (Su 2019). Three meta-analyses (of respectively 5, 3 and 2 case-control studies) showed no effect of this allele on the risk of phenytoin-induced DRESS (Phung 2022, Sukasem 2021, and Su 2019). Ten case-control studies with at least 10 cases of phenytoin-induced severe cutaneous adverse events investigated the association between HLA-B*1502 and SJS/TEN and/or DRESS (9 in populations with a HLA-B*1502-carrier frequency of more than 10% (Han Chinese, Thai, Malay) and 1 in a population with a HLA-B*1502-carrier frequency of 6% (Su 2019, Taiwanese)). Of these 10 case-control studies, 4 found an increased risk for HLA-B*1502 carriers. A study with 65 Taiwanese SJS/TEN and 63 Taiwanese DRESS cases found an OR of 4.1 for severe cutaneous adverse events and an OR of 6.5 for SJS/TEN, both of which were also significant after correction for the 22 HLA-alleles with a carrier frequency >1% in the cohorts (Su 2019). A study with 13 Malay SJS/TEN cases found an OR of 5.7, which was also significant after correction for multiple comparisons (2 different HLA-B alleles were investigated) (Chang 2017). A study with 15 Han Chinese SJS/TEN cases found an OR of 3.5, which was not significant after correction for multiple comparisons (5 different drugs were investigated) (Cheung 2013). A study with 26 Han Chinese SJS/TEN cases found an OR of 5.1, which was not significant after correction for all comparisons, but was significant after correction for comparisons for the major HLA-alleles (12 alleles with carrier frequency > 20% in the cases) (Hung 2010). The other 6 case-control studies with respectively 22 paediatric Thai DRESS/SJS/TEN cases (17 DRESS, 5 SJS/TEN), 37 Thai DRESS and 25 Thai SJS cases, 39 Thai SJS/TEN and 21 Thai DRESS cases, 21 Thai DRESS/HSS and 15 Thai SJS cases, 13 Han Chinese SJS/TEN cases, and 17 paediatric Thai DRESS/SJS/ TEN cases (15 DRESS, 2 SJS/TEN), did not find an increased risk for HLA-B*1502 carriers (Manuyakorn 2020, Sukasem 2020, Tassaneeyakul 2016, Yampayon 2017, Shi 2017, and Manuyakorn 2013). The same was true for the association with DRESS in Su 2019 (63 Taiwanese DRESS cases).
Based on these data, the KNMP Pharmacogenetics Working Group considers the evidence to be sufficient to conclude that a gene-drug interaction is present. In addition, because life-threatening adverse events should be avoided if possible, even if both the incidence and the risk increase are low, the KNMP Pharmacogenetics Working Group decided that a warning is necessary (yes/yes-interaction).
A cost-effectiveness study calculated an incidence of phenytoin-induced SJS/TEN of 0.65% in HLA-B*1502 carriers (Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016; 86:1086-94. PubMed PMID: 26888992).
HLA-B*1301

A case-control study found an association of HLA-B*1302 with both all severe cutaneous adverse events and DRESS, but not with SJS/TEN after correction for the 22 HLA-alleles with a carrier frequency >1% in the cohorts (Su 2019; 65 Taiwanese SJS/TEN and 63 Taiwanese DRESS cases; HLA-B*1301-carrier frequency 10%). In addition, these results were confirmed in meta-analyses of the Taiwanese case-control study with a Thai and a Japanese case-control study. The Japanese case-control study was small and included only SJS/TEN cases. Of 4 other case-control studies investigating the association with HLA-B*1301, one also found an association with DRESS/HSS, but not with SJS (Yampayon 2017; 21 Thai DRESS/HSS and 15 Thai SJS cases; HLA-B*1301-carrier frequency 13.5%), one found an association with SJS/TEN (Hung 2010; 26 Han Chinese SJS/TEN cases; HLA-B*1301-carrier frequency 12.4%), and the other two found no association with DRESS and/or SJS/TEN (Sukasem 2020; 37 Thai DRESS and 25 Thai SJS cases; HLA-B*1301-carrier frequency 13.0%, and Tassaneeyakul 2016; 39 Thai SJS/TEN and 21 Thai DRESS cases; HLA-B*1301-carrier frequency 19.6%).
Because the results of the case-control studies are not consistent and there is only one small meta-analysis per outcome, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-B*5101

A case-control study found no association of HLA-B*5101 with either all severe cutaneous adverse events, DRESS, or SJS/TEN after correction for the 22 HLA-alleles with a carrier frequency >1% in the cohorts (Su 2019; 65 Taiwanese SJS/TEN and 63 Taiwanese DRESS cases; HLA-B*5101-carrier frequency 5%). However, significant associations with the three outcomes were found in meta-analyses of the Taiwanese case-control study with a Thai and a Japanese case-control study. The Japanese case-control study was small and included only SJS/TEN cases. Of 3 other case-control studies investigating the association of HLA-B*5101, one found an association with severe cutaneous adverse events (John 2021; 21 Indian cases (11 DRESS, 9 SJS/TEN, 1 exfoliative dermatitis); HLA-B*5101-carrier frequency 5%), one found an association with both severe cutaneous adverse events and DRESS (Manuyakorn 2020; 17 paediatric Thai DRESS/HSS and 5 paediatric Thai SJS cases; HLA-B*5101-carrier frequency 6.7%), and the third did not find an association with either SJS or DRESS (Tassaneeyakul 2016; 39 Thai SJS/TEN and 21 Thai DRESS cases; HLA-B*5101-carrier frequency 4.4%).
Because the results of the case-control studies are not consistent and there is only one small meta-analysis per outcome, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-B*5602/04

Of the four case-control studies investigating the association with HLA-B*5602/04, one found an association with SJS/TEN, but not with DRESS (Tassaneeyakul 2016; 39 Thai SJS/TEN and 21 Thai DRESS cases; HLA-B*5602-carrier frequency in tolerant controls 1.1%), two found the opposite (Yampayon 2017; 21 Thai DRESS/HSS and 15 Thai SJS cases; HLA-B*5602/04-carrier population frequency 0.5%, and Sukasem 2020; 37 Thai DRESS and 25 Thai SJS cases; HLA-B*5602/04-carrier frequency in tolerant controls 0%), and the fourth did not find an association with either severe cutaneous adverse events or DRESS (Manuyakorn 2020; 17 Thai paediatric DRESS and 5 Thai paediatric SJS/TEN cases; HLA-B*5602-carrier frequency in tolerant controls 0%).
Because the case-control studies contradict each other, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-B*1513

Of the three case-control studies investigating the association with HLA-B*1513, one found an association with both SJS/TEN and DRESS (Chang 2017; 13 Malay SJS/TEN and 3 Malay DRESS cases; HLA-B*1513-carrier population frequency 12%), one found no association with severe cutaneous adverse events and a borderline significant association with DRESS (significant according to the p-value, but not according to the 95% confidence interval) (Manuyakorn 2020; 17 Thai paediatric DRESS and 5 Thai paediatric SJS/TEN cases; HLA-B*1513-carrier frequency in tolerant controls 0%), and the third found no association with either SJS/TEN or DRESS (Tassaneeyakul 2016; 39 Thai SJS/TEN and 21 Thai DRESS cases; HLA-B*1513-carrier frequency in tolerant controls 0%).
Because the results of the case-control studies are not consistent, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-C*1402 (HLA-Cw*1402)

Of the four case-control studies investigating the association of HLA-C*1402, one found an association with both all severe cutaneous adverse events and DRESS (Manuyakorn 2020; 17 Thai paediatric DRESS and 5 Thai paediatric SJS/TEN cases; HLA-C*1402-carrier frequency 5.0%), one found an association after correction for multiple comparisons with severe cutaneous adverse events when compared to population but not to tolerant controls and no association with SJS/TEN (Tassaneeyakul 2016; 39 Thai SJS/TEN and 21 Thai DRESS cases; HLA-C*1402-carrier frequency 3.3%), one found no association with DRESS (Ramírez 2017; 5 Spanish Caucasian DRESS cases; HLA-Cw*1402-carrier frequency 2.8%), and the fourth found no association with SJS/TEN (Hung 2010; 26 Han Chinese SJS/TEN cases; HLA-Cw*1402-carrier frequency 4.4%).
The KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and thus not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-A*0201, HLA-A*2402, HLA-B*3802, HLA-Cw*0801, and HLA-DRB1*1602

For these alleles, one case-control study found an association, but this was not confirmed in other case-control studies investigating the allele (1 to 5 negative case-control studies per allele). For this reason, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for gene-drug interactions and not enough cause for inclusion of these gene-drug combinations in the electronic decision support systems and/or the KNMP Kennisbank.

Other alleles

None of the case-control studies showed an association for the other alleles. Therefore, the KNMP Pharmacogenetics Working Group decided that there was not enough cause for inclusion of these gene-drug combinations in KNMP Kennisbank.

For the included interaction between phenytoin and HLA-B*1502, you can find an overview of the effects in the background information text of this gene-drug interaction in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The justification for the therapeutic recommendation for this genotype group is provided below.

*Therapeutic recommendation for HLA-B*1502*

If an alternative is possible, choosing an alternative is recommended. If an alternative is not possible, it is recommended to advise the patient to report any rash immediately.

Carbamazepine is excluded as a possible alternative, because it increases the risk of severe cutaneous adverse events in these patients to a much higher extent than phenytoin (positive predictive values for SJS/TEN of 6.7% and 0.65% respectively according to Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94. PubMed PMID: 26888992). For lamotrigine, a similar increase in risk as for phenytoin has been reported (OR = 3.6) (see the lamotrigine risk analysis). For oxcarbazepine, a similar positive predictive value for SJS/TEN in HLA-B*1502-positive patients has been reported (0.73% for oxcarbazepine and 0.65% for phenytoin) (Chen CB et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology 2017;88:78-86 and Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94), but the most severe forms (SJS/TEN-overlap and TEN) have not been observed for oxcarbazepine.

Recommendation concerning pre-emptive genotyping, including justification of choices:

HLA-B*1502 has not been detected in a sample of 1350 Dutch persons (Allele Frequency Net Database: http://www.allelefrequencies.net). For this reason, the KNMP Pharmacogenetics Working Group does not consider genotyping of Dutch patients in general before starting phenytoin to be useful.

However, the HLA-B*1502 frequency is high in Asians, except for Japanese and Koreans. In Japanese the HLA-B*1502 frequency is very low (< 0.1%). In Korea, it is less than 1% in some populations and more than 1% in other populations, with a mean of approximately 2% according to the SmPC of carbamazepine. The KNMP Pharmacogenetics Working Group considers genotyping of patients of Asian descent other than Japanese descent before starting phenytoin to be beneficial for drug safety. It is advised to consider genotyping these patients before (or directly after) drug therapy has been initiated to guide drug and dose selection.

The clinical implication of the gene-drug interaction scores 5 out of the maximum of 10 points (with pre-emptive genotyping considered to be beneficial for scores ranging from 3 to 5 points) (see also the clinical implication score tables at the end of this risk analysis):

HLA-B*1502 has been shown to increase the risk of the severe and possibly life-threatening cutaneous adverse event SJS/TEN (code E corresponding to CTCAE grade 4). This results in 1 out of the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for code D or E (CTCAE grade 3 or 4)).

Four meta-analyses (of respectively 10, 7, 4 and 2 case-control studies) and 4 case-control studies showed that HLA-B*1502 increased the risk of phenytoin-induced SJS/TEN. This results in the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for at least three publications with level of evidence score ≥ 3).

Incidences of phenytoin-induced SJS/TEN are estimated to be between 0.1% and 0.01% of users, although an SJS/TEN risk of 0.24% has been reported in Asian new users. This indicates that if HLA-B*1502 would have been the only cause of phenytoin-induced SJS/TEN, a minimum of 417 patients would have to be genotyped to prevent one case of phenytoin-induced SJS/TEN. However, apart from the study of Cheung 2013, all studies showed less than a third of phenytoin-induced SJS/TEN being caused by HLA-B*1502. So, a minimum of 1250 patients would have to be genotyped to prevent one case of phenytoin-induced SJS/TEN. Because the number needed to genotype to prevent 1 adverse event code ≥ D (grade ≥ 3) is larger than 1000, this results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).

The Summary of Product Characteristics (SmPC) contains a warning that HLA-B*1502 increases the risk of SJS/TEN, but neither mentions HLA-B*1502 as a contra-indication for phenytoin nor recommends pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

Whereas genotyping of patients of Asian descent other than Japanese descent before starting phenytoin is beneficial for drug safety, there are conflicting results on the cost-effectiveness of genotyping these patients. In Hong Kong patients (HLA-B*1502 carrier frequency 18%), Chen 2016 found HLA-B*1502-guided carbamazepine therapy to be cost-effective (costs US $11,090 per QALY gained), but extension of HLA-B*1502-guided therapy to phenytoin to be

not cost-effective (costs US $197,158 per QALY gained). The genotype-guided therapy for carbamazepine and phenytoin would become cost-effective if the HLA-B*1502 genotyping costs were below US $33. Dong 2012 found HLA-B*1502-guided therapy for carbamazepine and phenytoin to be cost-effective for adult Singaporean patients (costs US $29,750 per QALY gained) (HLA-B*1502 carrier frequency 14.9%). However, with a positive predictive value lower than 3.8% (as is the case for phenytoin), genotype-guided therapy would not be cost-effective.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Phung TH et al.
The association between HLA-B*15:02 and phenytoin-induced severe cutaneous adverse reactions: a meta-analysis.
Pharmacogenomics 2022;23:49-59.
PMID: 34816768.</td>
<td>4

B*1502: E</td>
<td>Meta-analysis of 11 case-control studies in Asians with phenytoin-tolerant patients as controls. The studies included a total of 387 severe cutaneous adverse event cases and 1002 controls. For SJS/TEN, 10 studies with a total of 225 cases and 985 controls were included, and for DRESS, 5 studies with a total of 145 cases and 670 controls.
Quality of the included studies was assessed using Thakkinstian’s checklist for risk of bias assessment in genetic association studies. The assessment considered five domains: information bias, confounding bias, selective reporting, population stratification and Hardy-Weinberg equilibrium assessment. Each item was scored as ‘low’, ‘high’ or ‘unclear’. All of the included studies had a low bias in the ascertainment of control, population stratification, and selective reporting. Nine provided the criteria of severe cutaneous adverse events. Nine studies did not ascertain the genotyping examination, for example, did not report genotyping error rate. The risk of confounding bias was low in three studies. The Hardy-Weinberg equilibrium was assessed in only two studies.
Of the 11 studies in this meta-analysis, 8 were included in this risk analysis separately (Sukasem 2020, Su 2019, Chang 2017, Yampayon 2017, Tassaneeyakul 2016, Cheung 2013, Manuyakorn 2013 and Hung 2010). Of a ninth study (Locharernkul 2008), the association data were not included in this risk analysis, because the number of phenytoin-induced SJS cases in this study was lower than 10 (4 cases, all HLA-B*1502-positive).
Of the 11 studies in this meta-analysis, 6 were included in the meta-analysis of Sukasem 2021 (6 for SJS/TEN and 3 for DRESS), 4 in the meta-analysis of Bloch 2014, and 2 in the meta-analysis of Cheung 2013.
The protocol of the meta-analysis was registered prospectively. However, a random-effects model was used for the meta-analysis in case of significant heterogeneity between the studies and a fixed-effects model in the absence of heterogeneity, indicating that the statistical method was chosen afterwards. The search and selection strategy was transparent and data extraction was standardized.
Publication bias analysis was assessed using Egger’s test and funnel plot for all comparisons except the ones stratified by ethnicity.

Results:
<table>
<tr><td colspan="2">Association between HLA-B*1502 and severe cutaneous adverse reactions (SCAR):</td></tr>
<tr><td rowspan="2">all SCAR</td><td>OR = 2.29 (95% CI: 1.25-4.19) (S)</td></tr>
<tr><td>22% of the cases and 14% of the controls had B*1502.</td></tr>
<tr><td rowspan="2">SJS/TEN</td><td>OR = 3.63 (95% CI: 2.15-6.13) (S)</td></tr>
<tr><td>32% of the cases and 14% of the controls had B*1502.</td></tr>
<tr><td>DRESS</td><td>NS</td></tr>
<tr><td colspan="2">Heterogeneity between the studies was moderate for all SCAR. Adding ethnicity in the meta-regression analysis reduced the heterogeneity to mild, indicating that ethnicity may be the cause of heterogeneity. A subgroup</td></tr>
</table>
</td>
<td>Author’s conclusion:
”The results supported the recommendations of HLA-B*15:02 screening before treatment with phenytoin.”</td>
</tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td>analysis showed a significant association in Han Chinese patients (OR = 4.62 (95% CI: 2.94-7.25) (S)) (4 studies of which 3 only investigated SJS/TEN). However, this association was not found in the Thai population (NS) (5 studies of which 1 only investigated SJS/TEN).
Heterogeneity between the studies was also moderate for SJS/TEN and DRESS.
The OR was not significantly affected by the omission of any individual study for all SCAR, for SJS/TEN, and for DRESS.
No evidence of publication bias was found by either Egger’s test or funnel plot for all SCAR, for SJS/TEN, and for DRESS.</td><td></td></tr>
<tr><td>ref. 2
Sukasem C et al.
Spectrum of cutaneous adverse reactions to aromatic antiepileptic drugs and human leukocyte antigen genotypes in Thai patients and meta-analysis.
Pharmacogenomics J 2021;21:682-90.
PMID: 34175889.</td><td>3

B*1502: E</td><td>Meta-analysis of 7 case-control studies in Asians with phenytoin-tolerant patients as controls. For SJS/TEN, all 7 studies, including a total of 152 cases and 730 controls, were included in the meta-analysis. For DRESS, the meta-analysis included 3 studies with a total of 99 cases and 568 controls.
Of the 7 studies in this meta-analysis, 5 were included in this risk analysis separately (Su 2019, Chang 2017, Yampayon 2017, Tassaneeyakul 2016, and Cheung 2013). Of the sixth study (Locharernkul 2008), the association data were not included in this risk analysis, because the number of phenytoin-induced SJS cases in this study was lower than 10 (4 cases, all HLA-B*1502-positive).
Of the 7 studies in this meta-analysis, 2 were included in the meta-analysis of Bloch 2014, and 1 in the meta-analysis of Cheung 2013.
A random effects model was used for the meta-analysis, but prospective registration of the protocol was not mentioned. The search and selection strategy and the method of data extraction were not mentioned.
Quality of the included studies was not assessed.
Publication bias analysis was not performed.

Results:
Association between HLA-B*1502 and severe cutaneous adverse events:
SJS/TEN: OR = 4.12 (95% CI: 1.77-9.59) (S)
20% of the cases and 11% of the controls had B*1502.
DRESS: NS
Heterogeneity between the studies was significant and moderate for both SJS/TEN and DRESS.</td><td>Author’s conclusion:
”In meta-analysis, HLA-B*15:02 was associated with SJS/TEN induced by phenytoin (OR 4.12, 95%CI 1.77–9.59, p = 0.001).”</td></tr>
<tr><td>ref. 3
John S et al.
Association of HLA-B*51:01, HLA-B*55:01, CYP2C9*3, and phenytoin-induced cutaneous adverse drug reactions in the South Indian Tamil population.
J Pers Med 2021;11:737.
PMID: 34442381.</td><td>3</td><td>6 South Indian Tamil cases with phenytoin-induced severe cutaneous adverse events were pooled with 15 published North Indian cases and HLA-B*5101 carrier frequency was compared between cases and 130 phenytoin tolerant controls (30 South Indian Tamil and 100 North Indian). Of the 6 South Indian Tamil cases, 3 had DRESS, 2 SJS/TEN and 1 exfoliative dermatitis (ED). Of the 15 North Indian cases, 8 had DRESS and 7 SJS/TEN. Patients on phenytoin for more than 3 months without signs or symptoms of cutaneous adverse reactions were considered tolerant controls.
No HLA-B*1502 was detected in the South Indian Tamil cases and controls, whereas HLA-B*1502 is present in the North Indian population.
Relevant comedication, like CYP2C9 inhibitors, was not excluded, but only cases with adverse drug reactions being definitely (score of 9 on Naranjo’s scale), very probably (score > 6 on the ALDEN scale) or probably (Naranjo score 5-8 or ALDEN score 4-5) caused by phenytoin were included.</td><td>Author’s conclusion:
”Pooled data analysis has confirmed the association between HLA B*51:01/phenytoin-severe cutaneous adverse reactions (OR = 6.273, 95% CI 2.24–16.69, p = <0.001) and HLA-B*51:01/phenytoin-overall cutaneous adverse reactions (OR = 2.323, 95% CI 1.22–5.899, p = 0.037).”</td></tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td>B*5101: E</td><td>Results:<table><tr><td>Association between HLA-B*5101 and severe cutaneous adverse events:</td></tr><tr><td>OR = 6.27 (95% CI: 2.24-16.69) (S)</td></tr><tr><td>52% of the cases and 12% of the controls had B*1502.</td></tr></table></td><td></td></tr>
<tr><td>ref. 4
Manuyakorn W et al. Association of HLA genotypes with phenytoin induced severe cutaneous adverse drug reactions in Thai children. Epilepsy Res 2020;162:106321. PMID: 32272329.</td><td>3

B*5101: E

C*1402: E

B*5602: AA
B*1502: AA
B*3802: AA
C*0701: AA</td><td>22 Thai paediatric cases with phenytoin-induced severe cutaneous adverse events (17 DRESS and 5 SJS/TEN) were compared to 60 phenytoin tolerant controls and 649 population controls. Tolerant controls were defined as patients who had taken phenytoin for at least 12 weeks without any hypersensitivity reaction.
Bodyweight-corrected phenytoin dose was 1.6-fold higher in DRESS cases than in tolerant controls (S). The authors postulate that this is due to the short duration of phenytoin therapy in the cases. During treatment, phenytoin is adjusted to the lowest dose that can control the symptoms. Relevant comedication, like CYP2C9 inhibitors, was not excluded, but rashes from other causes were excluded.

Results:<table><tr><td colspan="4">Association between HLA alleles and severe cutaneous adverse events (comparison to tolerant controls):</td></tr><tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the tolerant controls</td></tr><tr><td>B*5101</td><td>5.25 (S)
27.3% of cases was B*5101 carrier.</td><td>1.32-20.91</td><td>6.7%</td></tr><tr><td>C*1402</td><td>5.59 (S)
22.7% of cases was C*1402 carrier.</td><td>1.21-25.82</td><td>5.0%</td></tr><tr><td>B*1513</td><td colspan="2">trend for an increased risk (p = 0.070) (NS)</td><td>0.0%</td></tr><tr><td>B*5602</td><td colspan="2">trend for an increased risk (p = 0.070) (NS)</td><td>0.0%</td></tr><tr><td>B*1502</td><td>NS</td><td></td><td>16.7%</td></tr><tr><td>B*3802</td><td>NS</td><td></td><td>5.0%</td></tr><tr><td>C*0701</td><td>NS</td><td></td><td>33.3%</td></tr><tr><td colspan="4">Results were similar in the comparison with population controls, except for the association being significant for B*1513 and B*5602 in this comparison.</td></tr><tr><td colspan="4">Compared to tolerant controls, there was also an association with the HLA-B*1501-C*1402 and HLA-A*1101-B*1501-C*1402 haplotypes and a trend for an association with the HLA-A*1101-C*1402 haplotype, whereas an association with the HLA-B*3802-C*0701 haplotype was lacking.
Compared to population controls, all four haplotype associations were significant.</td></tr></table><table><tr><td colspan="4">Association between HLA alleles and DRESS (comparison to tolerant controls):</td></tr><tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the tolerant controls</td></tr><tr><td>B*5101</td><td>5.83 (S)
29.4% of cases was B*5101 carrier.</td><td>1.36-25.00</td><td>6.7%</td></tr><tr><td>C*1402</td><td>5.85 (S)
23.5% of cases was C*1402 carrier.</td><td>1.16-29.35</td><td>5.0%</td></tr></table></td><td>Author’s conclusion:
”An association between HLA-B*51:01 and HLA-C*14:02 and phenytoin induced DRESS and HLA-B*38:02 and phenytoin induced SJS-TEN has been demonstrated in Thai children.”</td></tr>
</table>

<table>
<tr>
<td>ref. 4, continuation</td>
<td>B*1513: E</td>
<td>
<table>
<tr><td>B*1513</td><td>19.52 (S)</td><td>0.89-427.74</td><td>0.0%</td></tr>
<tr><td colspan="2">NS according to the 95% confidence interval, but S according to the p-value (0.046).</td><td></td></tr>
<tr><td>B*5602</td><td>NS</td><td></td><td>0.0%</td></tr>
<tr><td>C*0701</td><td>NS</td><td></td><td>33.3%</td></tr>
<tr><td colspan="4">Results were similar in the comparison with population controls, except for the association for B*1513 also being significant according to the 95% confidence interval in this comparison.</td></tr>
<tr><td colspan="4">Compared to tolerant controls, there was also an association with the HLA-B*1501-C*1402 and HLA-A*1101-B*1501-C*1402 haplotypes, whereas an association with the HLA-A*1101-C*1402 and HLA-B*3802-C*0701 haplotypes was lacking.
Compared to population controls, only the association with the HLA-B*3802-C*0701 haplotype was lacking.</td></tr>
</table>

Note: Because of the low number of SJS/TEN cases, association data with SJS/TEN separately were not included in this summary.
</td>
<td></td>
</tr>
<tr>
<td>ref. 5
Sukasem C et al. Genetic and clinical risk factors associated with phenytoin-induced cutaneous adverse drug reactions in Thai population. Pharmacoepidemiol Drug Saf 2020;29:565-74. PMID: 32134161.</td>
<td>3

B*5602/ 04: E

B*4601: AA

B*1301:</td>
<td>
62 Thai cases with phenytoin-induced severe cutaneous adverse events (37 DRESS and 25 SJS/TEN) were compared to 70 phenytoin tolerant controls. Tolerant controls were defined as patients who had taken phenytoin for at least 3 months without cutaneous adverse events.
The median time to onset was 21 days (range 13-34 days) for SJS/TEN and 22 days (range 14-36 days) for DRESS. Phenytoin plasma concentration corrected for albumin level was supratherapeutic at the time of DRESS (25.3 µg/ml; n = 4) and SJS/TEN (26.9 µg/ml; n = 3). Two weeks before the adverse event, it was also supratherapeutic for DRESS cases (28.3 µg/ml; n = 8), but within therapeutic range for SJS/TEN cases (10.3 µg/ml; n = 3). 5.6% of SJS/TEN cases had TEN and 94.4% had SJS.
Relevant comedication was not excluded. Patients were included if the cutaneous adverse event was possibly, probably, or very probably caused by phenytoin according to Naranjo's or ALDEN score. 28.6% of DRESS cases and 16.7% of SJS/TEN cases used the CYP2C9 and CYP2C19 inhibitor omeprazole. Adjustment for omeprazole use in multivariate analysis was only performed for DRESS, not for SJS/TEN. Omeprazole was previously found to increase the risk of phenytoin-induced cutaneous adverse events, but was not found to increase the risk in this study.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and DRESS:</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the tolerant controls</td></tr>
<tr><td rowspan="3">B*5602/ 5604</td><td>12.9 (S)</td><td>1.5-111.6</td><td rowspan="3">0.0%</td></tr>
<tr><td colspan="2">13.5% of cases was B*5602/ 5604 carrier.</td></tr>
<tr><td colspan="2">An association was also found in multivariate analysis for the subgroup with Naranjo score ≥ 5 (probable and definite) (OR = 29.3; 95% CI: 1.2-708.0) (S).</td></tr>
<tr><td rowspan="2">B*4601</td><td colspan="2">trend for an increased risk (p = 0,057) (NS).</td><td rowspan="2">18.6%</td></tr>
<tr><td colspan="2">No association was found in multivariate analysis either.</td></tr>
</table>
</td>
<td>Author's conclusion: "HLA-B*56:02/04 was found to have a significant association with phenytoin-induced DRESS/drug-induced hypersensitivity syndrome (OR 29.312; 95% CI, 1.213-707.994; P = .038)."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>AA B*3802: AA B*4001: AA

B*1502: AA</td>
<td>
<table>
<tr><td>B*1301</td><td>NS</td><td></td><td>13.0%</td></tr>
<tr><td>B*1502</td><td>NS</td><td></td><td>15.7%</td></tr>
<tr><td>B*3802</td><td>NS</td><td></td><td>7.1%</td></tr>
<tr><td>B*4001</td><td>NS</td><td></td><td>11.4%</td></tr>
</table>
<table>
<tr><td colspan="4">Association between HLA alleles and SJS/TEN:</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the tolerant controls</td></tr>
<tr><td>B*1502</td><td colspan="2">trend for an increased risk (p = 0,081) (NS).
No association was found in multivariate analysis either.</td><td>15.7%</td></tr>
<tr><td>B*1301</td><td>NS</td><td></td><td>13.0%</td></tr>
<tr><td>B*3802</td><td>NS</td><td></td><td>7.1%</td></tr>
<tr><td>B*4001</td><td>NS</td><td></td><td>11.4%</td></tr>
<tr><td>B*4601</td><td>NS</td><td></td><td>18.6%</td></tr>
<tr><td>B*5602/ 5604</td><td>NS</td><td></td><td>0.0%</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Su SC et al.
HLA alleles and CYP-2C9*3 as predictors of phenytoin hypersensitivity in East Asians.
Clin Pharmacol Ther 2019;105:476-85.
PMID: 30270535.</td>
<td>3

B*1502: E</td>
<td>
128 Taiwanese cases with phenytoin-induced severe cutaneous adverse events (65 SJS/TEN and 63 DRESS) were compared to 376 phenytoin tolerant controls. Tolerant controls were defined as patients who had taken phenytoin for more than 3 months without evidence for adverse events. For HLA-B*1502, a meta-analysis was performed of these Taiwanese data and data on 129 Thai cases (67 SJS/TEN and 62 DRESS) and 195 tolerant controls. For HLA-B*1301 and HLA-B*5101, a meta-analysis was performed of these Taiwanese and Thai data and data on 9 Japanese SJS/TEN cases and 94 tolerant controls.
The mean daily phenytoin dose was similar among cases and controls.
Relevant comedication, like CYP2C9 inhibitors, was not excluded. Patients were included if the ALDEN score for phenytoin causality was ≥4 (SJS/TEN) or the Naranjo score was ≥5 (DRESS).
P values were adjusted by using Bonferroni correction for multiple tests (n = 22 for HLA-B alleles (i.e. the number of HLA-B alleles with an allele frequency >1% in the cohorts)).
A random effects model was used for the meta-analysis, but prospective registration of the protocol was not mentioned. The selection strategy was not mentioned, but the method of data assessment was transparent.
Quality of the included case-control studies was not assessed.
Selection bias analysis was not performed.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and severe cutaneous adverse events:</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the tolerant controls</td></tr>
<tr><td>B*1502</td><td>4.11 (S)
22% of cases was B*1502 carrier.
No association was found in the meta-analysis of the Taiwanese and Thai case-control study (NS).
Heterogeneity between the</td><td>2.28-7.39</td><td>6%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”In addition to cytochrome P450 (CYP)2C9*3, we found that HLA-B*13:01, HLA-B*15:02, and HLA-B*51:01 were significantly associated with phenytoin hypersensitivity with distinct phenotypic specificities.”</td>
</tr>
</table>

ref. 6, continuation				case-control studies was significant and high.		
	B*1301: E	B*1301	2.76 (S)	1.64-4.66	10%	
			24% of cases was B*1301 carrier.			
			An association was also found in the meta-analysis of the Taiwanese, Thai and Japanese case-control study (OR = 1.95; 95% CI: 1.09-3.48) (S). 21% of cases and 11% of controls was B*1301 carrier. Heterogeneity between the case-control studies was not significant and mild.			
	B*5101: E	B*5101	NS after correction for multiple comparisons (S for an increased risk before)		5%	
			An association was found in the meta-analysis of the Taiwanese, Thai and Japanese case-control study (OR = 4.43; 95% CI: 2.83-6.95) (S). 22% of cases and 7% of controls was B*5101 carrier. Heterogeneity between the case-control studies was not significant and absent.			
	B*4001: AA	B*4001	NS after correction for multiple comparisons (S for a decreased risk before)		43%	
	B*4601: AA	B*4601	NS after correction for multiple comparisons (S for a decreased risk before)		28%	
	B*5801: AA	B*5801	NS before and after correction for multiple comparisons		19%	
		Association between HLA alleles and SJS/TEN:				
		HLA allele	OR	95% CI	allele carrier frequency in the tolerant controls	
		B*1502	6.52 (S)	3.34-12.73	6%	
			31% of cases was B*1502 carrier.			
			No association was found in the meta-analysis of the Taiwanese and Thai case-control study (NS). Heterogeneity between the case-control studies was significant and high.			
		B*1301	NS after correction for multiple comparisons (S for an increased risk before)		10%	
			No association was found in the meta-analysis of the Taiwanese, Thai and Japanese case-control study (NS). Heterogeneity between the case-control studies was not significant and mild.			
		B*5101	NS after correction for multiple comparisons (S for an increased risk before)		5%	
			An association was found in the meta-analysis of the Taiwanese, Thai and Japanese case-control study (OR =			

ref. 6, continuation

	4.37; 95% CI: 2.59-7.36) (S). 23% of cases and 7% of controls was B*5101 carrier. Heterogeneity between the case-control studies was not significant and absent.	
B*4001	NS before and after correction for multiple comparisons	43%
B*4601	NS before and after correction for multiple comparisons	28%
B*5801	NS before and after correction for multiple comparisons	19%

Association between HLA alleles and DRESS:			
HLA allele	OR	95% CI	allele carrier frequency in the tolerant controls
B*1301	3.46 (S)	1.82-6.55	10%
	29% of cases was B*1301 carrier.		
	An association was also found in the meta-analysis of the Taiwanese and Thai case-control study (OR = 2.76; 95% CI: 1.74-4.39) (S). 29% of cases and 12% of controls was B*1301 carrier. Heterogeneity between the case-control studies was not significant and absent.		
B*1502	NS before and after correction for multiple comparisons		6%
	No association was found in the meta-analysis of the Taiwanese and Thai case-control study (NS). Heterogeneity between the case-control studies was significant and moderate.		
B*5101	NS before and after correction for multiple comparisons		5%
	An association was found in the meta-analysis of the Taiwanese and Thai case-control study (OR = 4.55; 95% CI: 2.58-8.01) (S). 21% of cases and 5% of controls was B*5101 carrier. Heterogeneity between the case-control studies was not significant and absent.		
B*4001	NS before and after correction for multiple comparisons		43%
B*4601	NS before and after correction for multiple comparisons		28%
B*5801	NS before and after correction for multiple comparisons		19%

Note: No association of HLA-B*1502 and HLA-B*1301 with MPE (107 cases) was found.

Note: CYP2C9*3 resulted in a higher risk increase than each of the HLA-B alleles (OR = 17-21). 30% of the severe cutaneous adverse event cases, 34% of the SJS/TEN cases, 27% of the DRESS cases, and 2% of the controls was carrier of CYP2C9*3. 72% of the severe cutaneous

<table>
<tr><td>ref. 6, continuation</td><td></td><td>adverse event cases, 74% of the SJS/TEN cases, 70% of the DRESS cases, and 22% of the controls was carrier of CYP2C9*3, HLA-B*1502, HLA-B*1301, and/or HLA-B*5101. Based on an incidence of severe cutaneous adverse events of 0.45%, the positive predictive value of the presence of one of these 4 alleles for development of a severe cutaneous event was calculated to be 1.4%, the negative predictive value 99.8%, and the number needed to genotype to prevent one severe cutaneous adverse event 310.</td><td></td></tr>
<tr><td>ref. 7
Yampayon K et al. Influence of genetic and non-genetic factors on phenytoin-induced severe cutaneous adverse drug reactions.
Eur J Clin Pharmacol 2017;73:855-865.
PubMed PMID: 28391407.</td><td>3

B*1301: E

B*5602/04: E

B*1502, B*3502, B*3802, B*4001, B*4403, B*4601, B*5101, B*5102, B*5201, B*5801: AA</td><td>36 Thai cases with phenytoin-induced severe cutaneous adverse events (15 with Stevens-Johnson syndrome and 21 with DRESS or HSS) were compared to 100 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without cutaneous adverse events after using phenytoin for at least 3 months. In addition, a population control of 758 Thai persons was used.
HSS was defined as DRESS except for the absolute eosinophil count being < 1500/µl.
Cases and controls were not matched and co-medication and co-morbidities were not excluded.
Possible associations were analysed by comparing cases to phenytoin-tolerant controls by multiple logistic regression.

Results:
<table>
<tr><td colspan="4">Association between HLA-B alleles and DRESS/HSS:</td></tr>
<tr><td>HLA-B allele</td><td>OR_{adj}</td><td>95% CI</td><td>allele carrier frequency in the population control</td></tr>
<tr><td>B*1301</td><td>13.3 (S)
The sensitivity of B*1301 to predict DRESS/HSS was 52.4%, the specificity 86.0%.</td><td>3.8-56.9</td><td>13.5%</td></tr>
<tr><td>B*5602/04</td><td>56.2 (S)
The sensitivity of B*5602/04 to predict DRESS/HSS was 14.3%, the specificity 100%.</td><td>7.2-∞</td><td>0.5%</td></tr>
<tr><td>B*1502</td><td>NS</td><td></td><td>14.2%</td></tr>
<tr><td>B*3502</td><td>NS</td><td></td><td>0.4%</td></tr>
<tr><td>B*3802</td><td>NS</td><td></td><td>4.9%</td></tr>
<tr><td>B*4001</td><td>NS</td><td></td><td>17.5%</td></tr>
<tr><td>B*4403</td><td>NS</td><td></td><td>2.6%</td></tr>
<tr><td>B*4601</td><td>NS</td><td></td><td>17.5%</td></tr>
<tr><td>B*5101</td><td>NS</td><td></td><td>6.9%</td></tr>
<tr><td>B*5102</td><td>NS</td><td></td><td>2.2%</td></tr>
<tr><td>B*5201</td><td>NS</td><td></td><td>4.5%</td></tr>
<tr><td>B*5801</td><td>NS</td><td></td><td>18.7%</td></tr>
<tr><td colspan="4">The sensitivity of B*1301 and B*5602/04 combined to predict DRESS/HSS was 66.7%, the specificity 86.0%.</td></tr>
<tr><td colspan="4">HLA-B*1301, HLA-B*5602/04, CYP2C19*3, and omeprazole co-medication together explained about 50% of the variability in the occurrence of DRESS/HSS.</td></tr>
<tr><td colspan="4">A history of anti-epileptic drug allergy was not associated with phenytoin-induced DRESS/HSS (NS).</td></tr>
</table>
<table>
<tr><td colspan="4">Association between HLA-B alleles and SJS:</td></tr>
<tr><td>HLA-B allele</td><td>OR_{adj}</td><td>95% CI</td><td>allele carrier frequency in the population control</td></tr>
</table></td><td>Author’s conclusion:
”Multiple logistic regression models showed that genetic and non-genetic factors associated with phenytoin-induced severe cutaneous adverse reactions were specified to its phenotype. HLA-B*13:01, HLA-B *56:02/04, CYP2C19*3, and omeprazole co-medication were strong risk factors of DRESS/HSS. While CYP2C9*3 and having Chinese ancestry were significant risk factors of SJS.”</td></tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td></td>
<td>
<table>
<tr><td>B*1301</td><td>NS</td><td></td><td>13.5%</td></tr>
<tr><td>B*5602/04</td><td>NS</td><td></td><td>0.5%</td></tr>
<tr><td>B*1502</td><td>NS</td><td></td><td>14.2%</td></tr>
<tr><td>B*3502</td><td>NS</td><td></td><td>0.4%</td></tr>
<tr><td>B*3802</td><td>NS</td><td></td><td>4.9%</td></tr>
<tr><td>B*4001</td><td>NS</td><td></td><td>17.5%</td></tr>
<tr><td>B*4403</td><td>NS</td><td></td><td>2.6%</td></tr>
<tr><td>B*4601</td><td>NS</td><td></td><td>17.5%</td></tr>
<tr><td>B*5101</td><td>NS</td><td></td><td>6.9%</td></tr>
<tr><td>B*5102</td><td>NS</td><td></td><td>2.2%</td></tr>
<tr><td>B*5201</td><td>NS</td><td></td><td>4.5%</td></tr>
<tr><td>B*5801</td><td>NS</td><td></td><td>18.7%</td></tr>
<tr><td colspan="4">Only CYP2C9*3 and Chinese ancestry were associated with SJS. Together they explained about 20% of the variability in the occurrence of SJS.
Addition of HLA-B*1502 to Chinese ancestry improved the specificity to predict SJS from 75.0% to 96.0% (with a decrease in sensitivity from 53.3% to 26.7%).</td></tr>
<tr><td colspan="4">A history of anti-epileptic drug allergy was not associated with phenytoin-induced SJS (NS).</td></tr>
</table>

Note: 53 HLA-B-variants were characterized. 23 variants were present in the cases, of which 6 with an allele frequency of more than 5%. For 12 variants (including the 6 most prevalent variants in the cases) the association with SJS and DRESS/HSS was investigated.
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
Shi YW et al.
HLA-A*24:02 as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions.
Neurology 2017;88:2183-2191.
PubMed PMID: 28476759.</td>
<td>3

A*2402: E

A*0201: E

B*1502, A*0203, A*0206, A*0207, A*1101, A*2901, B*0705, B*1301, B*1325, B*1501, B*3501, B*3802, B*4001, B*4002, B*4601, B*5102,</td>
<td>In a case-control study, 13 southern Han Chinese cases with phenytoin-induced SJS/TEN were compared to 40 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without cutaneous adverse reactions after using phenytoin for at least 3 months.
Co-medication associated with SJS/TEN was excluded.
Co-medication with influence on phenytoin metabolism was not excluded.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and SJS/TEN:</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the controls</td></tr>
<tr><td>A*2402</td><td>6.00 (S)</td><td>1.42-25.37</td><td>12.5%</td></tr>
<tr><td></td><td colspan="2">The sensitivity of A*2402 to predict SJS was 46.2%, the specificity 87.5%.</td><td></td></tr>
<tr><td></td><td colspan="2">4 of the 6 cases with A*2402 also had B*1502.</td><td></td></tr>
<tr><td>A*0201</td><td>11.7 (S)</td><td>1.10-124.84</td><td>2.5%</td></tr>
<tr><td>B*1502</td><td>NS</td><td></td><td>22.5%</td></tr>
<tr><td>A*0203</td><td>NS</td><td></td><td>22.5%</td></tr>
<tr><td>A*0206</td><td>NS</td><td></td><td>10.0%</td></tr>
<tr><td>A*0207</td><td>NS</td><td></td><td>20.0%</td></tr>
<tr><td>A*1101</td><td>NS</td><td></td><td>60.0%</td></tr>
<tr><td>A*2901</td><td>NS</td><td></td><td>5.0%</td></tr>
<tr><td>B*0705</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>B*1301</td><td>NS</td><td></td><td>22.5%</td></tr>
<tr><td>B*1325</td><td>NS</td><td></td><td>0.0%</td></tr>
<tr><td>B*1501</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>B*3501</td><td>NS</td><td></td><td>0.0%</td></tr>
<tr><td>B*3802</td><td>NS</td><td></td><td>10.0%</td></tr>
<tr><td>B*4001</td><td>NS</td><td></td><td>25.0%</td></tr>
<tr><td>B*4002</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>B*4601</td><td>NS</td><td></td><td>22.5%</td></tr>
<tr><td>B*5102</td><td>NS</td><td></td><td>0.0%</td></tr>
<tr><td>B*5401</td><td>NS</td><td></td><td>7.5%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”HLA-A*24:02 was associated significantly with Stevens-Johnson syndrome induced by the aromatic antiepileptic drugs as a group and by individual drugs (carbamazepine, lamotrigine, phenytoin).”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>B*5401, B*5502, B*5601, C*0102, C*0303, C*0304, C*0401, C*0702, C*0801, C*1502, C*1505, DRB1 *0802, *0803, *0901, *1101, *1201, *1202, *1454, *1501, *1502, *1602: AA</td>
<td>
<table>
<tr><td>B*5502</td><td>NS</td><td></td><td>5.0%</td></tr>
<tr><td>B*5601</td><td>NS</td><td></td><td>0.0%</td></tr>
<tr><td>C*0102</td><td>NS</td><td></td><td>37.5%</td></tr>
<tr><td>C*0303</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>C*0304</td><td>NS</td><td></td><td>27.5%</td></tr>
<tr><td>C*0401</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>C*0702</td><td>NS</td><td></td><td>32.5%</td></tr>
<tr><td>C*0801</td><td>NS</td><td></td><td>27.5%</td></tr>
<tr><td>C*1502</td><td>NS</td><td></td><td>5.0%</td></tr>
<tr><td>C*1505</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>DRB1*0802</td><td>NS</td><td></td><td>5.0%</td></tr>
<tr><td>DRB1*0803</td><td>NS</td><td></td><td>12.5%</td></tr>
<tr><td>DRB1*0901</td><td>NS</td><td></td><td>32.5%</td></tr>
<tr><td>DRB1*1101</td><td>NS</td><td></td><td>5.0%</td></tr>
<tr><td>DRB1*1201</td><td>NS</td><td></td><td>2.5%</td></tr>
<tr><td>DRB1*1202</td><td>NS</td><td></td><td>32.5%</td></tr>
<tr><td>DRB1*1454</td><td>NS</td><td></td><td>7.5%</td></tr>
<tr><td>DRB1*1501</td><td>NS</td><td></td><td>20.0%</td></tr>
<tr><td>DRB1*1502</td><td>NS</td><td></td><td>7.5%</td></tr>
<tr><td>DRB1*1602</td><td>NS</td><td></td><td>7.5%</td></tr>
<tr><td colspan="4">HLA-C*0801 is located on the same haplotype as HLA-B*1502.</td></tr>
</table>

Note: HLA-A-, HLA-B-, HLA-C- and HLA-DRB1-variants were characterized. For all detected variants the association with SJS/TEN was investigated.
</td>
<td></td>
</tr>
<tr>
<td>ref. 9
Chang CC et al. Association of HLA-B*15:13 and HLA-B*15:02 with phenytoin-induced severe cutaneous adverse reactions in a Malay population. Pharmacogenomics J 2017;17:170-173. PubMed PMID: 26927288.</td>
<td>3

B*1502: E

B*1513: E</td>
<td>
In a case-control study, 16 Malay cases with phenytoin-induced severe cutaneous adverse events (13 SJS/TEN and 3 DRESS) were compared to 32 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without cutaneous adverse events after using phenytoin for at least 3 months. In addition, a population control of 300 Malay persons was used.
Relevant co-medication was not excluded.
A p-value < 0.025 was considered statistically significant (Bonferroni correction for 2 comparisons).

Results:
<table>
<tr><td colspan="4">Association between HLA-B alleles and SJS/TEN (cases compared to phenytoin-tolerant controls):</td></tr>
<tr><td>HLA-B allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the population controls</td></tr>
<tr><td>B*1502</td><td>5.71 (S)</td><td>1.41-23.10</td><td>15.7%</td></tr>
<tr><td></td><td colspan="2">Results were similar for cases compared to population controls (OR = 8.61, 95% CI: 2.70-27.47) (S).</td><td></td></tr>
<tr><td>B*1513</td><td>11.28 (S)</td><td>2.25-56.60</td><td>12.0%</td></tr>
<tr><td></td><td colspan="2">The sensitivity of B*1513 to predict SJS/TEN was 53.8%, the specificity 90.6%.</td><td></td></tr>
<tr><td></td><td colspan="2">Results were similar for cases compared to population controls (OR = 8.56, 95% CI: 2.72-26.88) (S).</td><td></td></tr>
<tr><td>one copy of either B*1502 or B*1513</td><td>8.62 (S)</td><td>1.44-51.72</td><td>21.3%</td></tr>
<tr><td></td><td colspan="2">Results were similar for cases compared to population controls (OR = 10.45, 95% CI: 2.06-53.05) (S).</td><td></td></tr>
<tr><td>two copies of B*1502 or B*1513,</td><td>57.5 (S)</td><td>4.32-764.93</td><td>4.3%</td></tr>
<tr><td></td><td colspan="2">Results were similar for cases compared to population</td><td></td></tr>
</table>
</td>
<td>Author’s conclusion:
”HLA-B*15:13, showed significant association with phenytoin (PHT)-SJS/TEN and PHT-DRESS when compared with PHT-tolerant controls. We also confirmed HLA-B*15:02 association with PHT-SJS/TEN when compared with PHT-tolerant controls. These alleles may serve as markers to predict PHT-severe cutaneous adverse events in Malays.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 9, continuation</td>
<td></td>
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<table>
<tr><td>or one copy of each</td><td>controls (OR = 42.88, 95% CI: 9.45-280.36) (S).</td><td></td></tr>
</table>
<table>
<tr><td colspan="4">Association between HLA-B alleles and DRESS (cases compared to phenytoin-tolerant controls):</td></tr>
<tr><td>HLA-B allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the population controls</td></tr>
<tr><td>B*1502</td><td>NS</td><td></td><td>15.7%</td></tr>
<tr><td></td><td colspan="2">Results were also NS for cases compared to population controls.</td><td></td></tr>
<tr><td>B*1513</td><td>59.00 (S)</td><td>2.49-1395.74</td><td>12.0%</td></tr>
<tr><td></td><td colspan="2">Results were similar for cases compared to population controls (OR = 50.73, 95% CI: 2.57-1002.07) (S).</td><td></td></tr>
</table>
Note: All HLA-B-variants were characterized. For the two variants with an allele frequency > 0.1 in either the severe cutaneous adverse event group or the phenytoin-tolerant control group (HLA-B*1502 and HLA-B*1513), the association with severe cutaneous adverse event was investigated.
</td>
<td></td>
</tr>
<tr>
<td>ref. 10
Ramírez E et al. Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population.
Pharmacol Res 2017;115:168-178.
PubMed PMID: 27888155.</td>
<td>3

A*0201, A*1101, A*2501, A*2601, A*2902, A*3002, A*3201, A*6601, A*8001, B*0702, B*0801, B*1401, B*1402, B*1501, B*1801,</td>
<td>In a case-control study, 14 Spanish Caucasian cases with phenytoin-induced severe cutaneous adverse events (9 SJS/TEN and 5 DRESS) were compared to 28 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without adverse events after using phenytoin for at least 3 months. In addition, a Spanish population control of 253 persons was used. In one of the 5 cases with DRESS, allopurinol instead of phenytoin might be the causative agent.
Relevant co-medication was not excluded.
For the total group of antiepileptic drug induced cases with severe cutaneous adverse events (14 SJS/TEN and 12 DRESS), the sample size was calculated to detect a specified OR > 5, with a given power of 80%.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and SJS/TEN (cases compared to phenytoin-tolerant controls):</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the population controls</td></tr>
<tr><td>A*0201</td><td>NS</td><td></td><td>52.6%</td></tr>
<tr><td>A*1101</td><td>NS</td><td></td><td>15.0%</td></tr>
<tr><td>A*2501</td><td>NS</td><td></td><td>5.1%</td></tr>
<tr><td>A*2601</td><td>NS</td><td></td><td>1.6%</td></tr>
<tr><td>A*2902</td><td>NS</td><td></td><td>19.4%</td></tr>
<tr><td>A*3002</td><td>NS</td><td></td><td>6.7%</td></tr>
<tr><td>A*3201</td><td>NS</td><td></td><td>9.5%</td></tr>
<tr><td>A*6601</td><td>NS</td><td></td><td>0.4%</td></tr>
<tr><td>A*8001</td><td>NS</td><td></td><td>0.0%</td></tr>
<tr><td>B*0702</td><td>NS</td><td></td><td>16.6%</td></tr>
<tr><td>B*0801</td><td>NS</td><td></td><td>13.4%</td></tr>
<tr><td>B*1401</td><td>NS</td><td></td><td>3.6%</td></tr>
<tr><td>B*1402</td><td>NS</td><td></td><td>7.1%</td></tr>
<tr><td>B*1501</td><td>NS</td><td></td><td>5.1%</td></tr>
<tr><td>B*1801</td><td>NS</td><td></td><td>18.2%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”We identified several significant genetic risk factors for the first time in the Spanish Caucasian population: HLA*02:01/Cw*15:02 combination as a risk factor for phenytoin-induced SJS/TEN, HLA-B*38:01 for lamotrigine- and phenytoin-induced SJS/TEN, HLA-A*11:01 for carbamazepine-induced SJS/TEN, and HLA-A*24:02 for lamotrigine- and phenytoin- induced DRESS.”</td>
</tr>
</table>

ref. 10, continuation

B*3501, B*3801, B*4402, B*4403, B*4901, B*5101, B*5301, Cw*0303, Cw*0401, Cw*0501, Cw*0701, Cw*0802, Cw*1203, Cw*1502, Cw*1505, Cw*1601, A*0201/ Cw*1502 : AA

B*3501	NS		13.8%
B*3801	NS		5.1%
B*4402	NS		8.7%
B*4403	NS		26.5%
B*4901	NS		5.1%
B*5101	NS		16.2%
B*5301	NS		3.6%
Cw*0303	NS		5.5%
Cw*0401	NS		27.7%
Cw*0501	NS		17.8%
Cw*0701	NS		28.5%
Cw*0802	NS		10.3%
Cw*1203	NS		13.4%
Cw*1502	NS		4.7%
Cw*1505	NS		2.8%
Cw*1601	NS		22.1%
A*0201/ Cw*1502	trend for an association (p = 0.06) (NS)		1.8%
	Compared to the population control, the association was significant (OR = 27.50, 95% CI: 4.04-187.07) (S).		
Results for all severe cutaneous adverse events combined (SJS/TEN + DRESS) were similar, except for the lack of a trend for an association for A*0201/Cw*1502 for cases compared to phenytoin-tolerant controls.			

A*0301, A*2301, A*2402, A*6802: AA

B*3503, B*3906, B*4101, B*5001: AA

Association between HLA alleles and DRESS (cases compared to phenytoin-tolerant controls):

HLA allele	OR	95% CI	allele carrier frequency in the population controls
A*0201	NS		52.6%
A*0301	NS		18.6%
A*2301	NS		7.5%
A*2402	NS		17.4%
A*6802	NS		1.6%
B*1402	NS		7.1%
B*1501	NS		5.1%
B*3503	trend for an association (p = 0.069) (NS)		2.0%
	Compared to the population control, there was no trend for an association (NS).		
B*3906	NS		0.4%
B*4101	NS		1.2%
B*4403	NS		26.5%
B*4901	NS		5.1%
B*5001	NS		1.6%
B*5101	NS		16.2%
B*5301	trend for an association (p = 0.069) (NS)		3.6%
	Compared to the population control, there was no trend for an association (NS).		
Cw*0303	trend for an association (p = 0.069) (NS)		5.5%
	Compared to the population control, there was no trend for an association (NS).		
Cw*0304	NS		5.1%
Cw*0401	NS		27.7%

<table>
<tr>
<td>ref. 10, continuation</td>
<td>Cw*0602
,
Cw*0702
,
Cw*1402
,
Cw*1701
: AA</td>
<td>
<table>
<tr><td>Cw*0602</td><td>NS</td><td></td><td>9.9%</td></tr>
<tr><td>Cw*0701</td><td>NS</td><td></td><td>28.5%</td></tr>
<tr><td>Cw*0702</td><td>NS</td><td></td><td>19.4%</td></tr>
<tr><td>Cw*0802</td><td>NS</td><td></td><td>10.3%</td></tr>
<tr><td>Cw*1402</td><td>NS</td><td></td><td>2.8%</td></tr>
<tr><td>Cw*1601</td><td>NS</td><td></td><td>22.1%</td></tr>
<tr><td>Cw*1701</td><td>NS</td><td></td><td>0.4%</td></tr>
</table>
Note: All HLA class I variants (HLA-A-, HLA-B- and HLA-C-variants) were characterized. For all variants in the cases, the association with severe cutaneous adverse event was investigated.
</td>
<td></td>
</tr>
<tr>
<td>ref. 11
Tassaneeyakul W et al.
Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population.
Pharmacogenet Genomics 2016;26:225-34.
PubMed PMID: 26928377.</td>
<td>3

B*5602: E

B*3802: E</td>
<td>
In a case-control study, 60 Thai cases with phenytoin-induced severe cutaneous adverse events (39 SJS/TEN and 21 DRESS) were compared to 92 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without cutaneous adverse events after using phenytoin for more than 6 months. Controls were significantly younger than both the patients with DRESS and the total group with severe cutaneous adverse events. A population control of either 986 or 400 Thai persons was derived from literature.
Cases were treated in hospital for a median duration of 28 days (4-74 days). None of the cases died as a result of the severe cutaneous adverse event.
Relevant co-medication was not excluded, but CYP2C9 substrates/inhibitors were not likely to be related to the severe cutaneous adverse events according to the Naranjo and ALDEN algorithms. The concomitant use of CYP2C9 substrates/inhibitors as a group did not differ between the case and control groups.
Bonferroni correction resulted in statistical significance at a p-value < 0.0028 for HLA-A (18 comparisons), a p-value < 0.0019 for HLA-B (26 comparisons), and a p-value < 0.0033 for HLA-C (15 comparisons).

Results:
<table>
<tr><td colspan="3">Association between HLA alleles and SJS/TEN (cases compared to phenytoin-tolerant controls):</td></tr>
<tr><td>HLA allele</td><td>OR (95% CI)</td><td>allele carrier frequency in the tolerant controls</td></tr>
<tr><td rowspan="2">B*5602</td><td>10.40 (1.12-96.31) (S, but NS after Bonferroni correction)</td><td rowspan="2">1.1%</td></tr>
<tr><td>Compared to the population control, the association was also significant after Bonferroni correction (OR = 112.6, 95% CI: 12.3-1033.5) (S). The same was true after comparison with B*5602/04 in the population control (OR = 15.98, 95% CI: 4.4-57.14) (S). The genotyping method employed in the case-control study does not always distinguish between B*5602 and B*5604.</td></tr>
<tr><td rowspan="2">B*3802</td><td>3.70 (1.19-11.51) (S, but NS after Bonferroni correction)</td><td rowspan="2">6.5%</td></tr>
<tr><td>Compared to the population control, the association was</td></tr>
</table>
</td>
<td>Author’s conclusion:
”Neither SJS/TEN nor DRESS caused by phenytoin was significantly associated with the HLA-B*15:02. Certain alleles of HLA, particularly HLA-B*56:02, were significantly associated with phenytoin-related severe cutaneous adverse reactions in the study population.”</td>
</tr>
</table>

ref. 11, continuation			also significant after Bonferroni correction (OR = 4.90, 95% CI: 2.00-12.04) (S).		
		C*1402	6.49 (1.59-26.62) (S, but NS after Bonferroni correction)	3.3%	
			Results were similar for cases compared to the population control: OR = 4.64, 95% CI: 1.81-11.94) (S, but NS after Bonferroni correction).		
		B*5101	4.81 (1.32-17.54) (S, but NS after Bonferroni correction)	4.4%	
	B*5101: AA		Results were similar for cases compared to the population control: OR = 3.02, 95% CI: 1.22-7.48) (S, but NS after Bonferroni correction).		
		B*5801	3.15 (1.11-8.91) (S, but NS after Bonferroni correction)	8.7%	
	B*5801: AA		Compared to the population control, there was no association (NS).		
	A*3303: AA	A*3303	2.70 (1.10-6.63) (S, but NS after Bonferroni correction)	14.1%	
			No population control was performed.		
	B*4601: AA	B*4601	0.40 (0.17-0.97) (S, but NS after Bonferroni correction)	39.1%	
			No population control was performed.		
	B*1301: AA	B*1301	0.22 (0.05-1.01) (S, but NS after Bonferroni correction)	19.6%	
			No population control was performed.		
	B*1502: AA	B*1502	NS	14.1%	
			Compared to the population control, there was also no association (NS).		
	A*0101,	A*0101	NS	1.1%	
	A*0201,	A*0201	NS	4.4%	
	A*0203,	A*0203	NS	28.3%	
	A*0207,	A*0207	NS	25.0%	
	A*0297,	A*0297	NS	3.3%	
	A*1101,	A*1101	NS	16.3%	
	A*1102,	A*1102	NS	0.0%	
	A*2314,	A*2314	NS	0.0%	
	A*2402,	A*2402	NS	19.6%	
	A*2403,	A*2403	NS	0.0%	
	A*2407,	A*2407	NS	5.4%	
	A*2410,	A*2410	NS	2.2%	
	A*3001,	A*3001	NS	3.3%	
	A*3101,	A*3101	NS	2.2%	
	A*3401,	A*3401	NS	4.4%	
	A*6801,	A*6801	NS	2.2%	
	A*7401,	A*7401	NS	0.0%	
	B*0705,	B*0705	NS	5.4%	
	B*0801,	B*0801	NS	1.1%	
	B*1302,	B*1302	NS	3.3%	
	B*1501,	B*1501	NS	2.2%	
	B*1513,	B*1513	NS	0.0%	
	B*1525,	B*1525	NS	2.2%	
	B*1801,	B*1801	NS	8.7%	
	B*1802,	B*1802	NS	1.1%	

ref. 11, continuation

B*3501, B*3915, B*4001, B*4402, B*4403, B*5102, B*5201, B*5401, B*5502, B*5614, B*5701, C*0102, C*0122, C*0302, C*0303, C*0304, C*0403, C*0602, C*0701, C*0702, C*0704, C*0801, C*1202, C*1203, C*1502: AA

C*1402: E

B*3501	NS	1.1%
B*3915	NS	1.1%
B*4001	NS	13.0%
B*4402	NS	1.1%
B*4403	NS	5.4%
B*5102	NS	1.1%
B*5201	NS	1.1%
B*5401	NS	0.0%
B*5502	NS	4.4%
B*5614	NS	1.1%
B*5701	NS	3.3%
C*0102	NS	40.2%
C*0122	NS	0.0%
C*0302	NS	9.8%
C*0303	NS	3.3%
C*0304	NS	25.0%
C*0403	NS	8.7%
C*0602	NS	5.4%
C*0701	NS	10.9%
C*0702	NS	21.7%
C*0704	NS	6.5%
C*0801	NS	23.2%
C*1202	NS	6.5%
C*1203	NS	3.3%
C*1502	NS	6.5%

Results for all severe cutaneous adverse events combined (SJS/TEN + DRESS) were similar, except for:
- the association for C*1402 being significant for cases compared to population controls also after Bonferroni correction (OR = 4.24; 95% CI: 1.86-9.71 compared to population controls (S) and OR = 5.93; 95% CI: 1.56-22.57 compared to phenytoin-tolerant controls (S, but NS after Bonferroni correction))
- the association for A*0201 being significant for cases compared to phenytoin-tolerant controls before Bonferroni correction
- the association for A*3303, B*1301 and B*5801 being also not-significant for cases compared to phenytoin-tolerant controls before Bonferroni correction

Association between HLA alleles and DRESS (cases compared to phenytoin-tolerant controls):

HLA allele	OR (95% CI)	allele carrier frequency in the tolerant controls
B*5101	5.18 (1.18-22.74) (S, but NS after Bonferroni correction) Compared to the population control, the association was not significant (NS).	4.4%
B*5602	NS	1.1%
B*3802	NS	6.5%
C*1402	NS	3.3%
B*5101	NS	4.4%
B*5801	NS	8.7%
A*3303	NS	14.1%
B*4601	NS	39.1%
B*1301	NS	19.6%
B*1502	NS	14.1%
A*0101	NS	1.1%
A*0201	NS	4.4%

ref. 11, continuation		A*0203	NS	28.3%
		A*0207	NS	25.0%
		A*0297	NS	3.3%
		A*1101	NS	16.3%
		A*1102	NS	0.0%
		A*2314	NS	0.0%
		A*2402	NS	19.6%
		A*2403	NS	0.0%
		A*2407	NS	5.4%
		A*2410	NS	2.2%
		A*3001	NS	3.3%
		A*3101	NS	2.2%
		A*3401	NS	4.4%
		A*6801	NS	2.2%
		A*7401	NS	0.0%
		B*0705	NS	5.4%
		B*0801	NS	1.1%
		B*1302	NS	3.3%
		B*1501	NS	2.2%
		B*1513	NS	0.0%
		B*1525	NS	2.2%
		B*1801	NS	8.7%
		B*1802	NS	1.1%
		B*3501	NS	1.1%
		B*3915	NS	1.1%
		B*4001	NS	13.0%
		B*4402	NS	1.1%
		B*4403	NS	5.4%
		B*5102	NS	1.1%
		B*5201	NS	1.1%
		B*5401	NS	0.0%
		B*5502	NS	4.4%
		B*5614	NS	1.1%
		B*5701	NS	3.3%
		C*0102	NS	40.2%
		C*0122	NS	0.0%
		C*0302	NS	9.8%
		C*0303	NS	3.3%
		C*0304	NS	25.0%
		C*0403	NS	8.7%
		C*0602	NS	5.4%
		C*0701	NS	10.9%
		C*0702	NS	21.7%
		C*0704	NS	6.5%
		C*0801	NS	23.2%
		C*1202	NS	6.5%
		C*1203	NS	3.3%
		C*1502	NS	6.5%
		Note: All HLA class I variants (HLA-A-, HLA-B- and HLA-C-variants) were characterized. For all variants with an allele frequency of more than 1% in either the cases or the phenytoin-tolerant controls, the association with severe cutaneous adverse event was investigated.		
ref. 12 Bloch KM et al. Pharmacogenetics of antiepileptic drug-induced hypersensitivity. Pharmacogenomics 2014;15:857-68. PubMed PMID: 24897291.	3	Meta-analysis of 4 case-control studies with phenytoin-tolerant controls. The 4 studies included in total 62 SJS/ TEN cases and 212 controls. All four studies were Asian (two Han Chinese, two Thai). Of the 4 studies in this meta-analysis, 3 were included in this risk analysis separately (Cheung 2013, Manuyakorn 2013 and Hung 2010). Of the fourth study (Locharernkul 2008), the association data were not included in this risk analysis, because the number of phenytoin-induced SJS cases in this study was lower than 10 (4 cases, all HLA-		Author's conclusion: "HLA-B*15:02 was associated with carbamazepine, lamotrigine and phenytoin-induced Stevens–Johnson syndrome in Asian populations indica-

<table>
<tr>
<td>ref. 12, continuation</td>
<td>B*1502: E</td>
<td>B*1502-positive).
Of the 4 studies in this meta-analysis, 2 were included in the meta-analysis of Cheung 2013 (Cheung 2013 and Hung 2010).
A fixed-effect model was used for the analysis, while a random-effect model should have been used, because heterogeneity between the studies turned out to be high.
The search strategy was transparent, but the selection strategy and the method of data extraction were not mentioned.
Quality of the included studies was not assessed.
Publication bias analysis was not performed.

Results:
Association between HLA-B*1502 and SJS/TEN (cases compared to phenytoin-tolerant controls (carrier frequency 12.7%)):
OR = 3.48; 95% CI: 1.75-6.91 (S)
32% of the cases was carrier of HLA-B*1502.
The heterogeneity between the studies was high.</td>
<td>ting that pre-treatment testing may prevent cross-reactivity.”</td>
</tr>
<tr>
<td>ref. 13
Cheung YK et al. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. Epilepsia 2013;54:1307-14. PubMed PMID: 23692434.</td>
<td>3

B*1502: E</td>
<td>A case-control study and a meta-analysis were performed.
In the case-control study, 15 Han Chinese cases with phenytoin-induced SJS/TEN were compared to 75 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without cutaneous adverse events after using phenytoin for at least 3 months.
Next to phenytoin, the case-control study also analysed carbamazepine, lamotrigine, valproic acid and phenobarbital.
Relevant co-medication was not excluded.
Meta-analysis of 2 case-control studies with Han Chinese patients, SJS/TEN cases and phenytoin-tolerant controls, including the case-control study in this article. The 2 studies included in total 41 cases and 188 controls.
Both studies in this meta-analysis, were included in this risk analysis separately (Cheung 2013 (see above) and Hung 2010).
A fixed-effect model was used for the analysis, indicating that the statistical method was chosen afterwards. The search and selection strategy was transparent, but the method of data extraction was not mentioned.
Quality of the included studies was not assessed.
Publication bias analysis was not performed.

Results:
Association between HLA-B*1502 and SJS/TEN (cases compared to phenytoin-tolerant controls (carrier frequency 20.0%)):
<table>
<tr><th></th><th>OR (95% CI)</th><th>B*1502 carrier frequency in the tolerant controls</th></tr>
<tr><td>case-control study</td><td>3.50 (1.10-11.18) (S, but NS after Bonferroni correction for multiple comparisons of five individual drugs)</td><td>20.0%</td></tr>
<tr><td></td><td>The sensitivity of B*1502 to predict SJS/TEN was 46.7%, the specificity 80.0%.</td><td></td></tr>
<tr><td>meta-analysis</td><td>4.26 (1.93-9.39) (S)</td><td>12.8%</td></tr>
<tr><td></td><td>There was no heterogeneity between the studies.</td><td></td></tr>
</table>
</td>
<td>Author’s conclusion:
”SJS/TEN induced by carbamazepine and phenytoin is strongly and moderately associated with HLA-B*15:02 in Han Chinese, respectively.”</td>
</tr>
</table>

<table>
<tr><td>ref. 13, continuation</td><td></td><td></td><td>The sensitivity of B*1502 to predict SJS/TEN was 36.6%, the specificity 87.2%.</td><td></td><td></td></tr>
<tr><td>ref. 14
Manuyakorn W et al.
Phenobarbital-induced severe cutaneous adverse drug reactions are associated with CYP2C19*2 in Thai children.
Pediatr Allergy Immunol 2013;24:299-303.
PubMed PMID: 23551241.</td><td>3

B*1502: AA</td><td colspan="3">In a case-control study, 17 paediatric Thai cases with phenytoin-induced severe cutaneous adverse events (2 SJS/TEN and 15 DRESS) were compared to 17 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without adverse events after using phenytoin for at least 2 months.
Cases were treated in hospital for a median duration of 8 days (3-31 days). None of the cases died as a result of the severe cutaneous adverse event.
Relevant co-medication was not excluded.
Conditional logistic regression analyses was used to calculate the OR.

Results:
Association between HLA-B*1502 and severe cutaneous adverse events (cases compared to phenytoin-tolerant controls (carrier frequency 17.6%)):
NS</td><td>Author’s conclusion:
”There was no association between the HLA-B*1502 and aromatic anticonvulsant-induced severe cutaneous adverse reactions.”</td></tr>
<tr><td>ref. 15
Hung SI et al.
Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese.
Pharmacogenomics 2010;11:349-56.
PubMed PMID: 20235791.</td><td>3

B*1502: E

B*1301: E

Cw*0801 : E</td><td colspan="3">In a case-control study, 26 Han Chinese cases with phenytoin-induced SJS/TEN (22 SJS, 1 SJS/TEN, 3 TEN) were compared to 113 phenytoin-tolerant controls. Phenytoin-tolerant controls were defined as patients without adverse events after using phenytoin for more than 3 months.
Relevant co-medication was not excluded.
Given that 8% of controls carry the risk allele as reported in previous studies, a sample of 26 cases (phenytoin study) and 6 cases (lamotrigine study), 60 controls each will reach 90% power if 80% of the cases carry the risk allele.

Results:
Association between HLA alleles and SJS/TEN (cases compared to phenytoin-tolerant controls):
HLA allele | OR | 95% CI | allele carrier frequency in the tolerant controls
B*1502 | 5.1 (S) | 1.8-15.1 | 8.0%
Results were NS after correction for all comparisons, but were S after correction for comparisons with the major alleles (frequencies > 20% in the cases) (12 HLA-alleles, significance for p < 0.0042 (0.05/12)).
None of the 3 patients with TEN was carrier of B*1502.
B*1301 | 3.7 (S) | 1.4-10.0 | 12.4%
Results were NS after correction for all comparisons and after correction for comparisons with the major alleles (frequencies > 20% in the cases) (12 HLA-alleles, significance for p < 0.0042 (0.05/12)). The association needs to be confirmed in a larger study.
Cw*0801 | 3.0 (S) | 1.1-7.8 | 15.0%
Cw*0801 is in linkage dis-</td><td>Author’s conclusion:
”We suggest that aromatic antiepileptic drugs, including carbamazepine, oxcarbazepine and phenytoin, should be avoided in the B*1502 carrier and caution should also be exercised for lamotrigine.”</td></tr>
</table>

ref. 15, continuation			equilibrium with B*1502. The B*1502 haplotype contains Cw*0801.		
	DRB1 *1602: E	DRB1*1602	4.3 (S)	1.4-12.8	8.0%
			Results were NS after correction for all comparisons and after correction for comparisons with the major alleles (frequencies > 20% in the cases) (12 HLA-alleles, significance for p < 0.0042 (0.05/12)). The association needs to be confirmed in a larger study.		
	A*0201, A*0203, A*0206, A*0207, A*1101, A*2402, A*2601, A*3303, B*1525, B*3501, B*3802, B*4001, B*4006, B*4601, B*4602, B*5101, B*5102, B*5201, B*5401, B*5601, B*5801, B*6701, Cw*0102, Cw*0302, Cw*0303, Cw*0304, Cw*0401, Cw*0403, Cw*0702, Cw*1202, Cw*1402, DRB1 *0301, *0317, *0403, *0405, *0406, *0803, *0901, *1101, *1201, *1202, *1302, *1312, *1401, *1443, *1501, *1502:	A*0201	NS		15.0%
		A*0203	NS		11.5%
		A*0206	NS		7.0%
		A*0207	NS		22.1%
		A*1101	NS		43.3%
		A*2402	NS		32.7%
		A*2601	NS		8.8%
		A*3303	NS		15.0%
		B*1525	NS		1.8%
		B*3501	NS		6.2%
		B*3802	NS		10.6%
		B*4001	NS		46.0%
		B*4006	NS		0.9%
		B*4601	NS		21.2%
		B*4602	NS		0.0%
		B*5101	NS		4.4%
		B*5102	NS		3.5%
		B*5201	NS		1.8%
		B*5401	NS		8.0%
		B*5601	NS		2.7%
		B*5801	NS		14.2%
		B*6701	NS		0.0%
		Cw*0102	NS		36.3%
		Cw*0302	NS		14.2%
		Cw*0303	NS		14.2%
		Cw*0304	NS		19.5%
		Cw*0401	NS		15.0%
		Cw*0403	NS		0.9%
		Cw*0702	NS		42.5%
		Cw*1202	NS		5.3%
		Cw*1402	NS		4.4%
		DRB1*0301	NS		10.6%
		DRB1*0317	NS		0.0%
		DRB1*0403	NS		9.7%
		DRB1*0405	NS		13.3%
		DRB1*0406	NS		3.5%
		DRB1*0803	NS		11.5%
		DRB1*0901	NS		29.2%
		DRB1*1101	NS		19.5%
		DRB1*1201	NS		5.3%
		DRB1*1202	NS		22.1%
		DRB1*1302	NS		3.5%
		DRB1*1312	NS		1.8%
		DRB1*1401	NS		8.0%
		DRB1*1443	NS		0.9%
		DRB1*1501	NS		21.2%
		DRB1*1502	NS		2.7%
		Note: The association with SJS/TEN was investigated for all HLA-A-, HLA-B-, HLA-Cw-, and HLA-DRB1-variants			

<table>
<tr><td>ref. 15, continuation</td><td>AA</td><td>present in cases and/or controls.</td><td></td></tr>
<tr><td>ref. 16
Locharernkul C et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia 2008;49:2087-91. PubMed PMID: 18637831.</td><td>4</td><td>This study investigated whether 3 HLA-B*1502-positive patients with phenytoin-induced SJS/TEN developed SJS/TEN induced by other antiepileptic drugs given at different times. In addition, the study investigated whether 3 HLA-B*1502-positive patients with carbamazepine-induced SJS/TEN developed SJS/TEN induced by phenytoin given at a different time. Patients were considered to be tolerant to a drug if they did not develop any allergic reactions when treated for more than 3 months.
Patients who developed SJS/TEN after simultaneous use of more than one drug were excluded.

Results:
<table>
<tr><td>HLA-B*1502-positive patients with phenytoin-induced SJS/TEN</td><td>All patients were tolerant to all other antiepileptic drugs given:
- carbamazepine (n = 1)
- lamotrigine (n = 1)
- phenobarbital (n = 1)
- valproic acid (n = 3)
- levetiracetam (n = 2)
- topiramate (n = 1)
- clobazam (n = 1)</td></tr>
<tr><td>HLA-B*1502-positive patients with carbamazepine-induced SJS/TEN</td><td>All 3 patients were tolerant to phenytoin.</td></tr>
</table></td><td>Author’s conclusion:
”Some patients, who were HLA-B*1502 and suffered from carbamazepine-induced SJS, could be tolerant to phenytoin and vice versa. This suggests that HLA-B*1502 may be a common attribute required for a Thai patient to develop SJS from these two antiepileptic drugs; other different elements, however, are also needed for each antiepileptic drug.”</td></tr>
<tr><td>ref. 17
SmPC Diphantoïne-Z (phenytoin) 01-11-21.</td><td>0

HLA-B*1502: E</td><td><u>Warning</u>:
Anticonvulsant Hypersensitivity Syndrome
Life-threatening skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients using phenytoin.
HLA-B*1502 can be associated with an increased risk of developing Stevens-Johnson syndrome (SJS) in patients of Han Chinese or Thai ancestry using phenytoin. In patients testing positive for HLA-B*1502, phenytoin should only be used when the benefits of use are higher than the risk.
In the Caucasian and Japanese population, the frequency of the HLA-B*1502 allele is extremely low. At this moment, it is therefore not possible to draw a conclusion about the risk. Adequate information on the risk in other races is currently not available.</td><td></td></tr>
<tr><td>ref. 18
SmPC Dilantin (phenytoin), USA, 03-03-22.</td><td>0

HLA-B*1502: E</td><td><u>Warning</u>:
Serious dermatologic reactions
Dilantin can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine.
Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin.
Consider avoiding Dilantin as an alternative to carbamazepine in patients who are positive for HLA-B*1502.
The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management.</td><td></td></tr>
</table>

Risk group	CYP2C9 IM and PM

Comments:

- We only included studies with at least 10 cases with severe cutaneous adverse events and studies and case reports investigating possible alternatives in the risk analysis. Other articles did not contribute enough to the evidence to be included. There were no studies on genotype-guided therapy.
- Cost-effectiveness:
  QALY = quality-adjusted life-year
  - Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94. PubMed PMID: 26888992.
    For Hong Kong patients and assuming full policy adherence and preferable testing practices, HLA-B*1502-guided carbamazepine therapy is cost-effective (costs US $11,090 per QALY gained), but extension of HLA-B*1502-guided therapy to phenytoin is not (costs US $197,158 per QALY gained). A cost-effectiveness threshold of US $50,000/QALY was used.
    Genotype guided therapy consisted of carbamazepine or phenytoin for patients without HLA-B*1502 and another antiepileptic drug for patients with HLA-B*1502. Genotyping was only performed for patients planned to receive carbamazepine or phenytoin.
    The genotype-guided therapy for carbamazepine and phenytoin would become cost-effective if the HLA-B*1502 genotyping costs were below US $33 or the actual incidence of phenytoin-SJS in HLA-B*15:02 carriers exceeded 4.1%.
    Costs were calculated for a period of 1 year. Efficacy of seizure control was assumed to be comparable among the different antiepileptic drugs. For therapy without HLA-B*1502 screening, the calculated costs were US $164 and the calculated QALYs 0.8273. For the genotype-guided therapy for carbamazepine, the calculated costs were US $171 and the calculated QALYs 0.8279. For the genotype-guided therapy for carbamazepine and phenytoin, the calculated costs were US $320 and the calculated QALYs 0.8281. The calculation was based on a price of treatment with carbamazepine of US $278/year, a price of treatment with non-carbamazepine antiepileptic drugs of US $105/year, a weighted average price of treatment of SJS/TEN of US $ 10,110, and genotyping costs of US $192.20. The HLA-B*1502 carrier frequency in the Hong Kong population was 18%. In 13,231 Hong Kong people with newly diagnosed and treated epilepsy, incidences of carbamazepine-SJS for HLA-B*1502 carriers and non-carriers were 6.69% and 0.07%, respectively. Based on a reported odds ratio for phenytoin-SJS of 3.50 (Cheung 2013), the incidences for phenytoin-SJS were estimated to be 0.65% for HLA-B*1502 carriers and 0.19% for non-carriers. In this population, 11.8% of epilepsy patients were planned for carbamazepine treatment and 59.1% for phenytoin treatment.
    By varying the input parameters, the probability of genotype-guided therapy for carbamazepine and phenytoin being cost-effective, was calculated to be 0.05%. Sensitivity analysis showed that the genotype-guided therapy for carbamazepine and phenytoin would become cost-effective if the HLA-B*1502 genotyping costs were below US $33 or the actual incidence of phenytoin-SJS in HLA-B*1502 carriers exceeded 4.1%, while maintaining other variables constant.
  - Dong D et al. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology 2012;79:1259-67. PubMed PMID: 22955130.
    Compared with carbamazepine or phenytoin for all, HLA-B*1502-guided therapy is cost-effective at a willingness to pay threshold of U$ 50,000/QALY for adult Singaporean Chinese and Malaysian epilepsy patients (costs US$ 37,030/quality-adjusted life year (QALY) gained and US$ 7,930/QALY, respectively), but not for adult Singaporean Indian epilepsy patients (costs US$ 136,630/QALY). For the total Singaporean population, it is cost-effective (costs US$ 29,750/QALY). Population frequency of HLA-B*1502 (mean 14.9% in Singapore; approximately 14% in Chinese, 29% in Malaysians and 4% in Indians), positive predictive value, duration of treatment relative to life expectancy, and costs of alternative drugs were the key drivers influencing cost-effectiveness. Cost-effectiveness is lost if treatment with antiepileptic drugs is lifelong.
    Genotype guided therapy consisted of carbamazepine or phenytoin for patients without HLA-B*1502 and valproic acid for patients with HLA-B*1502.
    Valproic acid treatment for all patients was more expensive and did not provide more QALYs than genotype guided treatment.
    Lifelong direct medical costs were calculated for a period of 30 years. The treatment period was 7 years. For carbamazepine/phenytoin for all patients, the calculated costs were US$ 4,110 and the calculated QALYs 18.846. For the genotype-guided therapy, the calculated costs were US$ 4,680 and the calculated QALYs 18.865. For valproic acid for all patients, the calculated costs were US$ 6,780 and the calculated QALYs 18.865. The calculation was based on a price of treatment with carbamazepine or phenytoin of US$ 170/ year, a price of treatment with valproic acid of US$ 470/year, a price of treatment of SJS, SJS/TEN or TEN of respectively US$ 3,480, US$ 10,250 and US$ 17,030, and genotyping costs of US$ 270. The incidence rate of carbamazepine/phenytoin-induced SJS/TEN in Singapore Chinese was assumed to be the same as the reported incidence rate of carbamazepine-induced SJS/TEN in Taiwan Chinese (0.23%) (Chen P et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126 - 33). The relative incidences in different Singaporean ethnicities were estimated based on a voluntary reporting registry of adverse drug reactions of the Singapore Health Sciences Authority. Based on these relative incidences, an incidence of 0.61% and 0.14% was calculated for carbamazepine/phenytoin-induced SJS/

TEN in Singaporean Malaysians and Indians respectively. With the sensitivity and specificity values of Chen 2011, positive predictive values for SJS/TEN development in HLA-B*1502 carriers were calculated to be 5.1% for Singaporean Chinese, 12.5% for Singaporean Malays, and 3.2% for Singaporean Indians. The mean incidence rate and positive predictive value in Singapore were 0.27% and 5.96% respectively.
By varying the input parameters, the probability of genotype guided therapy being cost-effective, was calculated to be 75%. With a willingness to pay threshold of US$ 31,000/QALY, the probability of genotype-guided therapy being cost-effective, would be more than 50%. However, if treatment is lifelong, genotype-guided therapy would not be cost-effective, regardless of the remaining life expectancy. With a positive predictive value lower than 3.8% or an HLA-B*1502 frequency less than 6.1%, genotype-guided therapy would not be cost-effective. However, lower genotyping cost could compensate for a lower positive predictive value.

- Existing guideline:

Caudle KE et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther 2014;96:542-8. PubMed PMID: 25099164 and Karnes JH et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther 2021;109:302-9. PMID: 32779747.
CPIC indicates that there is substantial evidence linking HLA-B*1502 with the risk of SJS/TEN. As references they originally mentioned the meta-analysis of Cheung 2013 and the two case-control studies included in this meta-analysis (Cheung 2013 and Hung 2010), which are also included in our risk analysis. In addition, they mentioned the case-control study of Locharernkul 2008, of which the association data were not included in this risk analysis, because the number of phenytoin-induced SJS cases in this study was lower than 10 (4 cases). Finally, they mentioned two case-control studies (Man CB et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007;48:1015-8 (1 case with a severe cutaneous adverse event) and Neuman MG et al. Genetic and immune predictors for hypersensitivity syndrome to antiepileptic drugs. Transl Res 2012;159:397-406 (4 cases of serious adverse events (drug-induced liver injury)) and a case report (Min FL et al. HLA-B*1502 genotyping in two Chinese patients with phenytoin-induced Stevens-Johnson syndrome. Epilepsy Behav 2011;20:390-1), which were not included in our risk analysis for the same reason. In the update, they indicate that the level of evidence for the association is generally high. They indicate that the studies show that the absence of HLA-B*1502 does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN. In addition, they originally indicated that the strength of the association between phenytoin use and SJS/TEN was weaker than that of the association between carbamazepine use and SJS/TEN due to the limited number of studies and observations with phenytoin or fosphenytoin in the literature. They consider the association to support the US Food and Drug Administration recommendations to avoid phenytoin as substitute for carbamazepine in individuals who test positive for HLA-B*1502.
The Food and Drug Administration warning for phenytoin states, “Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502” due to the increased risk of SJS/TEN in patients of Asian ancestry. CPIC indicates that the evidence linking HLA-B*1502 to phenytoin-induced SJS/TEN was generated in individuals of Asian ancestry because the frequency of HLA-B*1502 is very low in other populations that have been studied. However, HLA-B*1502 may also occur in other populations throughout the world yet to be studied, and patients may be unaware of or fail to disclose more distant Asian ancestry in their families. Furthermore, much of the evidence linking HLA-B*1502 to phenytoin-induced SJS/TEN was generated in both children and adults. Therefore, regardless of the CYP2C9 genotype and the individual’s ancestry or age, if the HLA-B*1502 test result is positive, CPIC recommends to avoid carbamazepine, oxcarbazepine and phenytoin. CPIC classifies this recommendation as strong, meaning that the evidence is high quality and the desirable effects clearly outweigh the undesirable effects. In addition, CPIC indicates that weaker evidence exists linking SJS/TEN with the HLA-B*1502 allele in association with the use of alternative medications such as eslicarbazepine, lamotrigine, and phenobarbital, and thus caution should be used in choosing alternatives to phenytoin. They do not classify this recommendation.
Phenytoin-induced SJS/TEN usually develops within the first 3 months of therapy; therefore, patients who have been taking phenytoin for longer than 3 months without developing cutaneous reactions are at low risk (but not zero) of phenytoin-induced adverse events in the future, regardless of HLA-B*1502 status. CPIC recommends to cautiously consider use of phenytoin if a HLA-B*1502-positive patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions. CPIC classifies this recommendation as optional, meaning that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations; there is room for differences in opinion as to the need for the recommended course of action.
CPIC mentions potential benefits and risks for patients with existing HLA-B*1502 genotype information. A potential benefit is in avoiding adverse effects by selecting alternative agents for those who are HLA-B*1502 carriers. For HLA-B*1502 carriers, a potential risk is that phenytoin therapy may have been needlessly avoided in patients who may not have developed SJS/TEN; however, this risk is mitigated because alternatives to phenytoin with comparable effectiveness exist. Another potential risk would be an error in genotyping. Due to the fact that the absence of HLA-B*1502 does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN, a high-risk patient could be prescribed phenytoin. Moreover, because not all phenytoin-induced adverse events are attributable to HLA-B*1502, clinicians should carefully monitor all patients according to standard practices.
In the update, CPIC indicates that HLA-B*1502 is linked to SJS and TEN but not to a predisposition for other phenytoin-induced cutaneous adverse events such as MPE or DRESS/HSS (Yip VL et al. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. Clin Pharmacol Ther 2012;92: 757-65. PubMed: 23132554). In addition, CPIC indicates that other HLA-B alleles have also been associated with

phenytoin-induced drug reactions with eosinophilia and systemic symptoms (DRESS) (Tassaneeyakul 2016 and Ihtisham K et al. Association of cutaneous adverse drug reactions due to antiepileptic drugs with HLA alleles in a North Indian population. Seizure 2019;66:99-103. PubMed: 30826555). Finally, CPIC indicates that no association between HLA-A*3101 and phenytoin-induced SJS and TEN has been presently found.
CPIC provides the following recommendations for HLA-B*1502-positive patients:

Therapeutic recommendation	Classification of recommendation	Considerations
If patient is phenytoin-naive, do not use phenytoin/fosphenytoin. Avoid carbamazepine and oxcarbazepine.	Strong[a]	Other aromatic anticonvulsants including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the HLA-B*1502 allele; however, caution should still be used in choosing an alternative agent.
If the patient has previously used phenytoin continuously for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4-28 days), and cases usually occur within three months of dosing.	Optional[b]	Previous tolerance of phenytoin is not indicative of tolerance to other aromatic anticonvulsants.

[a]: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
[b]: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

On 3-5-2022, there was not a more recent version of the recommendations present on the CPIC-site.

Date of the literature search: 8 April 2022.

	Genotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working group decision	HLA-B*1502	4 F	yes	yes	23 May 2022

Signaal bij eerste en tweede uitgifte.

Mechanism:
Although the mechanism of hypersensitivity for phenytoin is not exactly known, analogy with other drug-hypersensitivity reactions suggests the mechanism described below.
A cellular immune reaction against tissue cells is induced if peptides derived from proteins within these tissue cells bind to specific HLA proteins, are transported to the cell surface and are ”recognised” as foreign by specific immune cell proteins (T-cell receptors). (A metabolite of) phenytoin binds to either the cellular proteins or derived peptides, to specific HLA proteins or to specific T-cell receptors, thus inducing an interaction between an HLA peptide complex and a T-cell receptor, resulting in a cellular immune reaction against tissue cells.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	

• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	5+
Corresponding Clinical Implication Score:		Beneficial