\textit{NAT2} genetic variants and toxicity related to anti-tubercular agents: a systematic review and meta-analysis

Running head: NAT2 and anti-TB drug-related toxicity

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SUMMARY

Tuberculosis patients receiving anti-tuberculosis treatment may experience serious adverse drug reactions, such as hepatotoxicity. Genetic variants of the NAT2 gene may increase the risk of experiencing such toxicity events. This systematic review and meta-analysis provides a comprehensive evaluation of the evidence base for associations between NAT2 genetic variants and anti-tuberculosis drug-related toxicity.

We searched for studies in Medline, EMBASE, BIOSIS and Web of Science. We included data from 41 articles (39 distinct cohorts of patients). We pooled effect estimates for each genotype on each outcome using meta-analyses stratified by country. We performed a qualitative assessment of the quality of the included studies.

The quality of included studies was variable, with many areas of concern. NAT2 slow/intermediate acetylators were statistically significantly more likely to experience hepatotoxicity than rapid acetylators (OR=1.59, 95% CI 1.26–2.01). No heterogeneity was detected in the overall pooled analysis ($I^2=0\%$).

NAT2 acetylator status is significantly associated with the likelihood of experiencing anti-tuberculosis drug-related hepatotoxicity. We encountered many challenges in performing robust syntheses of data from pharmacogenetics studies, and we outline recommendations for the future reporting of pharmacogenetics studies to enable high-quality systematic reviews and meta-analyses to be performed.
INTRODUCTION

Tuberculosis (TB) is one of the most important challenges in global health. There were an estimated 1.3 million TB deaths in 2016 among HIV-negative people and 374,000 deaths among HIV-positive people. The World Health Organisation (WHO) currently recommends a combination of four first-line drugs for individuals with drug-susceptible TB: isoniazid, rifampicin, ethambutol and pyrazinamide.

TB patients receiving a combination of these drugs may experience adverse drug reactions, the most serious of which is anti-TB drug-induced hepatotoxicity (ATDH). Reported incidence rates of ATDH among patients treated with standard multidrug treatment vary from 2% to 28%, depending on the regimen given, definition of ATDH, and patient characteristics such as age, race and sex. ATDH can be fatal, with reported mortality rates of 6–12% if drugs are not promptly stopped. ATDH and other anti-TB drug-related adverse effects also contribute to non-adherence, eventually leading to treatment failure, relapse and the emergence of drug-resistance.

The proposed genetic risk factors for ATDH include polymorphisms of the N-acetyltransferase 2 (NAT2) gene, which codes for the drug-metabolising enzyme, NAT2. NAT2 gene polymorphisms may affect the activity of the NAT2 enzyme, altering the chemical modification of anti-TB drugs and their metabolites in the liver, leading to hepatic adverse reactions. Toxic metabolites may also cause other toxicity events, such as peripheral neuropathy and maculopapular eruption, although the majority of evidence on the pharmacogenetics of anti-TB drugs focuses on hepatotoxicity.

Isoniazid is the anti-TB drug for which the genetic contribution to ATDH is most widely studied and best understood. Specifically, it is thought that NAT2 acetylator status may be associated with isoniazid-related hepatotoxicity, as NAT2 is one of the main enzymes involved in the metabolism of isoniazid in the liver. There are three phenotypes of acetylator status. Individuals who are slow NAT2
acetylators have higher plasma drug concentrations. This may be beneficial for treatment efficacy, but may also cause an accumulation of toxic metabolites as part of the metabolic activation of acetylhydrazine to harmless diacetylhydrazine. Isoniazid suppresses the acetylation of acetylhydrazine, hence producing more toxic metabolites, which contributes to the increased risk of hepatitis.[7] Fast acetylators have lower plasma drug concentrations, and so treatment may be less effective, but also less toxic. Intermediate acetylators fall between these two extremes.

Rifampicin and pyrazinamide have also been reported to be hepatotoxic;[8] however, the mechanisms for rifampicin- and pyrazinamide-induced hepatotoxicity are unknown.[9] The OATP1B1 *15 haplotype has been reported to be a predictor of rifampicin-induced liver injury;[10] no research into genetic predictors of pyrazinamide-induced hepatotoxicity has been reported.[11] No hepatotoxicity has been described for ethambutol.[8]

The objective of this systematic review and meta-analysis is to evaluate evidence on the effect of NAT2 on anti-TB drug-related toxicity in TB patients receiving anti-TB treatment. Meta-analyses investigating the effect of NAT2 on toxicity outcomes have been published previously.[6, 12-15] However, conclusions from these meta-analyses are conflicting. Our review and meta-analysis updates and adds to the existing evidence base on associations between NAT2 and anti-TB drug-related toxicity.

**METHODS**

This review has been conducted in line with methods outlined in our protocol (PROSPERO registration number: CRD42017068448).[16] The search strategy and study selection process were used to identify studies that investigated the association between any genetic variant and anti-TB drug-related toxicity. However, in this article we
focus only on the subset of studies that considered NAT2 variants. Studies investigating association between other genetic variants and anti-TB drug-related toxicity will be reported separately.

Selection criteria

Types of studies
We included cohort studies, case–control studies and RCTs. We did not include case series studies as this type of study design would be inappropriate to investigate the effect of genetic variants on anti-TB drug-related toxicity. We did not require a minimum number of enrolled patients for a study to be included in our review.

Types of participants
We included studies that recruited TB patients who were either already established on anti-TB treatment or commencing treatment (at least one of isoniazid, rifampicin, pyrazinamide, or ethambutol), and who were genotyped to investigate the effect of genetic variants on anti-TB drug-related toxicity. We only included studies where over 50% of included patients were TB patients receiving anti-TB treatment.

Types of outcomes
We included studies that measured any drug-related toxicity outcomes.

Search strategy
An information specialist (EK) designed the search strategy (Supplementary File 1), and searched for relevant studies in Medline, PUBMED, EMBASE, BIOSIS, and Web of Science (date of search: 3rd March 2016). We hand searched reference lists from relevant studies, and contacted experts in the
field to identify eligible studies. We included studies published in English only. We did not restrict by year of publication, or publication status.

Study selection

The search results were imported to Covidence.[17] We removed duplicates, and one author (MR) scanned the study abstracts to remove irrelevant studies. A second author (AJ, JK, or KD) independently screened a sample of 10% of studies.

We obtained the full text for each potentially relevant study. One reviewer (MR) assessed eligibility based on the selection criteria. A second author (AJ, JK, or KD) independently assessed a sample of 10% of studies for eligibility. Disagreements between the two reviewers at the abstract and full-text screening stages were resolved through discussion, and by consulting a third author if necessary.

Outcomes

The primary outcome of this review was hepatotoxicity by any definition used by the original investigators. The secondary outcomes were all other toxicity outcomes.

Data collection

We designed and piloted a data extraction form. We collected data on study design, participant characteristics, treatment regimen, and outcomes. One author (MR) extracted data in accordance with the methods outlined in the Cochrane Handbook[18] and The HuGENet HuGE Review Handbook.[19] A second author (AJ, JK, or KD) independently extracted all outcome data. Disagreements between the two reviewers were resolved through discussion, and by consulting a third author if necessary. We contacted study authors if outcome data necessary for inclusion in a meta-analysis were not published in the paper.
We contacted individuals who were listed as authors of multiple included articles to enquire whether there was overlap between articles in terms of the patient cohorts. We examined locations, dates of recruitment and other study characteristics to identify articles that reported outcomes for the same patient cohort. If an author confirmed that multiple articles reported outcomes for the same patient cohort, or if we suspected this based on reported study characteristics, we assigned a group identifier (GI) to these articles, and ensured that no data for the same patient cohort were included more than once in any meta-analysis.

**Quality assessment**

One author applied criteria for the quality assessment of pharmacogenetic studies[20] to each study. A second author (AJ) independently assessed the quality of a sample of 10% of studies. Disagreements between the two reviewers were resolved through discussion. We obtained the number of studies meeting each criterion and summarised this information in the text.

**Data synthesis**

We performed meta-analyses for associations between NAT2 and any anti-TB drug-related toxicity outcome that were investigated by at least two studies. The effects of both NAT2 acetylator status (as predicted by genotyping methods) and individual NAT2 single nucleotide polymorphisms (SNPs) were investigated.

**Primary analysis**

The primary analysis compared risk of hepatotoxicity for slow/intermediate acetylators in comparison to rapid acetylators. Data were pooled from studies that reported data for each acetylator group separately together with data from studies that combined slow and intermediate acetylator groups.
Two sensitivity analyses were conducted:

i. Pairwise comparisons of slow versus rapid acetylator status, and intermediate versus rapid acetylator status. Here, it was only possible to include data from studies that reported on each acetylator group separately.

ii. Comparison of slow versus rapid/intermediate acetylator status. Here, data were pooled from studies that combined data for intermediate and rapid acetylator groups, and from studies that reported data for each acetylator group separately.

Secondary analysis

The secondary analysis compared risk of hepatotoxicity between genotype groups for NAT2 SNPs.

For each SNP, two pairwise comparisons were undertaken: heterozygous genotype versus homozygous wild-type, and homozygous mutant-type versus homozygous wild-type. For SNPs investigated by one study only, ORs comparing genotype groups were calculated and summarised in a table, together with the pooled estimates from the meta-analyses. There were insufficient data to perform meta-analyses for association between NAT2 (acetylator status and individual SNPs) and other toxicity outcomes; ORs and 95% CIs for each pairwise comparison were calculated and reported in a table.

Meta-analyses were performed using Stata 14 (metan package);[21] ORs with 95% CIs were the chosen measure of effect. We used the random-effects model, as we anticipated heterogeneity between studies due to differences in study design, methodological quality, ethnicity of participants, and outcome definitions. The random-effects model used the method of DerSimonian and Laird,[22] with the estimate of heterogeneity being taken from the Mantel–Haenszel model.[23] If zero events were observed in one of the genotype groups, a continuity correction of 0.5 was used. Data were excluded from the analysis if there were no patients in one of the genotype groups in a comparison.
The HuGENet HuGE Review Handbook recommends that meta-analyses of genetic association studies are stratified by ethnicity, and that meta-analyses should only be performed if effect estimates for different ethnic groups appear sufficiently similar. However, information on participants’ ethnicity was sparsely reported in the studies included in this review. Therefore, we performed analyses stratified by the countries in which studies were conducted, as a proxy for ethnicity.

Investigation of heterogeneity

We assessed heterogeneity by visually examining the forest plots, and by referring to the $I^2$ statistic. If substantial heterogeneity had been observed (>50%), we planned to undertake subgroup analyses according to study design, outcome definitions, treatment regimens, and date of study publication.

Selective reporting

We assessed the possibility of selective reporting as part of the quality assessment. Potential sources of selective reporting considered were genetic variants, outcomes, and modes of inheritance.

Publication bias

We produced a funnel plot for the primary analysis to assess the risk of publication bias.
RESULTS

Included and excluded studies

A PRISMA flowchart, showing selection of studies during the literature search, is provided in Figure 1. The initial search identified 77 articles investigating the association between any genetic variant and anti-TB drug-related toxicity, from which 52 distinct cohorts of patients were identified.

[FIGURE 1]

Forty-six articles reported data for the association between NAT2 variants and anti-TB drug-related toxicity, and from these articles, 40 distinct patient cohorts were identified. In this review, we include data from 40 articles (39 distinct patient cohorts).[24-63] We did not include data from the remaining six articles.[64-69] Of these six, five reported data for patient cohorts for whom data were also reported in other articles (or we suspected that this was the case); and for the sixth article,[69] the numbers of patients in each genotype group were not reported, and we were unable to obtain this information from the authors. The characteristics of studies included in this review are provided in Supplementary Table 1.

Quality assessment

Choosing which genes and SNPs to genotype

Twenty-seven articles reported reasons for choosing all genes and SNPs investigated. For the 13 articles[27, 30, 32, 36, 50, 51, 53, 56, 58, 59, 61-63] that did not report this information, no articles limited their reporting to only statistically significant associations. Consequently, there is no evidence to suggest that selective reporting of genes and SNPs occurred.
Sample size

The median sample size was 170 (interquartile range 108.5–285). Only two articles[25, 62] provided details of the a priori power to detect pre-specified effect sizes.

Study design

Eleven articles described case–control studies, 27 articles described prospective cohorts, one article described a retrospective cohort, and one article described an RCT. For one case–control study,[32] the case and control groups were not clearly defined. No articles describing case–control studies reported that the two groups were genotyped in mixed batches.

Reliability of genotypes

Only three articles[25, 31, 45] mentioned genotype quality control procedures, and only 12 articles[25, 32, 34, 36, 40, 44, 48-51, 54] compared genotype frequencies of all investigated SNPs to those previously published for the same population. Of the articles describing case–control studies and retrospective cohorts, only two[44, 45] mentioned that genotyping personnel were blinded to outcome status.

Missing genotype data

For most articles (29/41), on comparing the number of participants included in the analyses with the study sample size, it was apparent there were no missing genotype data. For the remaining 11 articles,[31, 32, 41-43, 51, 55, 57, 59, 62, 63] only five articles[31, 55, 57, 62, 63] summarised the extent of missing data for all genes and SNPs analysed. None of these articles described checking whether missing data were randomly distributed.
Population stratification

One article[51] mentioned undertaking tests for population stratification; no population stratification was identified. One article used a study design that ensured that the included patients were from a non-diverse ethnic group.[53] All other studies were at potential risk from confounding due to population stratification.

Hardy–Weinberg equilibrium (HWE)

Twenty-three articles[29, 31, 33-38, 40-42, 45-48, 51, 56, 57, 59-63] reported testing for HWE for all investigated SNPs, and a further three[24, 50, 55] tested for HWE for a subset of SNPs. The remaining 14 articles reported no testing for HWE.

Mode of inheritance

Nineteen articles made a specific assumption regarding the underlying mode of inheritance.[24, 28, 30, 33, 34, 39, 42, 43, 47, 49, 51, 54-56, 58-60, 62, 63, 69] Of these, only two provided justification;[28, 59, 69] for the remaining 17 articles, there is a risk of selective reporting under different modes of inheritance. Two articles[41, 57] applied models assuming different modes of inheritance to the genotype data, although only one of these articles[41] adjusted these analyses for multiplicity of testing.

Choice and definition of outcomes

There was large variation in definition of hepatotoxicity (Supplementary Table 2). Of the 37 articles reporting hepatotoxicity data, one did not provide a definition,[61] two provided vague definitions,[29, 69] and the remaining 35 articles provided 31 different definitions. Definitions of other toxicity outcomes were generally not sufficiently detailed (Supplementary Table 3).
Nine articles did not provide justification for the choice of outcomes, but outcomes were in line with the main study aim as conveyed in the article’s introduction.[26, 31, 37, 47-49, 55, 56, 62] The remaining articles all provided justification for the choice of outcomes. Consequently, there is no evidence to suggest that selective reporting of outcomes occurred.

Treatment adherence

Six articles[30, 31, 42, 44, 49, 56] mentioned assessing treatment adherence. One article[53] reported that treatment was administered by directly observed therapy, short-course (DOTS), so it was unnecessary to measure adherence. Of the six articles that reported assessing adherence, one[49] did not report adjusting the analyses for adherence. It was not necessary to adjust for adherence in the analyses of two articles, as patients were reported to have good treatment adherence.[30, 31]

Association between NAT2 genetic variants and anti-TB drug-related toxicity

NAT2 acetylator status and hepatotoxicity

A forest plot displaying the results of the primary analysis is provided in Figure 2.

Slow/intermediate acetylators were significantly more likely to experience hepatotoxicity than rapid acetylators (OR=1.59, 95% CI 1.26–2.01). No heterogeneity was detected in this analysis ($I^2=0\%$).

Results of the sensitivity analyses are provided in Supplementary File 2. Results from the pairwise comparisons suggested that slow acetylators are significantly more likely to experience hepatotoxicity than rapid acetylators (OR=3.68, 95% CI 2.23–6.09, $I^2=60.0\%$), but there were no significant differences between intermediate and rapid acetylators (OR=1.12, 95% CI 0.87–1.45,
The sensitivity analysis that compared slow acetylators with rapid/intermediate acetylators suggested that slow acetylator status significantly increases the risk of hepatotoxicity (OR=3.12, 95% CI 2.45–3.97, \(I^2=59.0\%\)).

Moderate heterogeneity was observed in the sensitivity analyses of slow versus rapid acetylator status, and slow versus rapid/intermediate acetylator status. This moderate heterogeneity may be due to the variable distribution of genotypes in different geographic areas.

The funnel plot for the primary analysis (Supplementary File 3) provided no evidence of publication bias.

NAT2 SNPs and hepatotoxicity

The included studies reported data for 12 NAT2 SNPs. A summary of all data for the association between NAT2 SNPs and hepatotoxicity is provided in Table 1. There were sufficient data to perform meta-analyses for six SNPs. Forest plots showing the results of these meta-analyses are provided in Supplementary File 4. The main findings from these meta-analyses are:

- For 590G-A and 857G-A, both heterozygous genotype and homozygous mutant-type significantly increase hepatotoxicity risk compared with homozygous wild-type (590G-A: GA versus GG, OR=1.30, 95% CI 1.06–1.59, \(I^2=0\%\); AA versus GG, OR=2.05, 95% CI 1.24–3.40, \(I^2=47.7\%\); 857G-A: GA versus GG, OR=1.30, 95% CI 1.03–1.64, \(I^2=0.9\%\); AA versus GG, OR=1.99, 95% CI 1.02–3.91, \(I^2=11.3\%\)).

- For 282C-T, homozygous mutant-type significantly increases hepatotoxicity risk compared with homozygous wild-type (OR=3.95, 95% CI 2.21–7.05, \(I^2=5.5\%\)), but no significant difference was observed for heterozygous genotype compared with homozygous wild-type (OR=1.27, 95% CI 0.80–2.02, \(I^2=0\%\)).
For 481C-T, heterozygous genotype significantly increases hepatotoxicity risk compared with homozygous wild-type (OR=1.48, 95% CI 1.12–1.97, $I^2=0$%), but no significant difference was observed for the homozygous mutant-type compared with homozygous wild-type (OR=1.91, 95% CI 0.93–3.92, $I^2=34.1$%). The lack of statistical significance for the latter comparison may be caused by the relatively small number of homozygous mutant-type patients (n=162) among the patients contributing data to this analysis (n=3604).

For 341T-C and 803A-G, no significant differences were observed for either pairwise comparison (341T-C: TC versus TT, OR=1.15, 95% CI 0.72–1.82, $I^2=0$%; CC versus TT, OR=1.54, 95% CI 0.58–4.04, $I^2=0$%; 803A-G: AG versus AA, OR=1.14, 95% CI 0.67–1.96, $I^2=0$%; GG versus AA, OR=1.90, 95% CI 0.66–5.52, $I^2=0$%).

Results were relatively homogeneous between studies for most comparisons, except for the comparison between homozygous mutant-type and homozygous wild-type for the 590G-A SNP ($I^2=47.7$%). This moderate heterogeneity may be due to the variable distribution of genotypes in different geographic areas.

**[TABLE 1]**

NAT2 variants and other toxicity outcomes

A summary of all data for the association between NAT2 variants and toxicity outcomes (other than hepatotoxicity) is provided in Table 2. Each reported result is based on data from a single study, as there were no comparisons where more than one study provided data.

**[TABLE 2]**
1. WHO. Global Tuberculosis Report 2017 2017. Available from:


3. Dash LA, Comstock GW, Flynn JP. Isoniazid Preventive Therapy: Retrospect and Prospect 1–


For peripheral neuropathy, no significant associations were reported for either of the pairwise comparisons conducted for acetylator status, 191G-A, or 341T-C. Similarly, for skin rash and eosinophilia, the pairwise comparisons for acetylator status demonstrated no significant effects.

None of the SNPs investigated by Kim et al. (2011) (GI: KIM) had a significant effect on anti-TB drug-induced maculopapular eruption. Slow acetylators were significantly more likely to experience adverse drug-induced hepatotoxicity outcomes (definition unclear; OR=3.31, 95% CI 1.03–10.62), and adverse drug reactions (defined as at least one of the following: gastric, joint, neuromuscular, or skin reactions, hepatotoxicity; OR=3.20, 95% CI 1.31–7.80) compared with rapid or intermediate acetylators. However, slow acetylator status was not found to increase the risk of gastrointestinal adverse drug reactions.
DISCUSSION

There is a substantial evidence base for the association between \textit{NAT2} genetic variants and anti-TB drug-related toxicity outcomes, as previously identified and as our systematic review confirmed. However, we established that performing robust synthesis of this evidence is challenging, due to several factors, including variability between studies in terms of how participants are classified according to genotype, choice and definition of outcomes and variants to investigate, ethnicity of participants and methodological quality. In conducting our review, we carefully considered these challenges, stratifying meta-analyses by genetic variants, genotype contrasts and outcomes. We also stratified further by the country where the study was conducted as a proxy for ethnicity, which was not widely reported. We supplemented our data synthesis with a rigorous assessment of the methodological quality of included studies.

Meta-analyses

Where possible, meta-analyses were undertaken to improve power to estimate genetic effects. We found that slow/intermediate acetylators were significantly more likely to experience hepatotoxicity than rapid acetylators. This result is consistent with the findings of several previously conducted meta-analyses.\cite{12-15} The result is not consistent with the meta-analysis reported by Sun et al.,\cite{6} who did not identify a significant association between slow acetylator status and hepatotoxicity. However the search date for Sun et al.\cite{6} (May 2007) is several years earlier than the search dates for the other meta-analyses, and many relevant studies have been published in recent years. As more studies are published, the power to detect a statistically significant association increases.

To the best of our knowledge, no meta-analyses on individual SNPs of the \textit{NAT2} gene have been published, so our results add to the existing knowledge of the association between \textit{NAT2} genetic variants and hepatotoxicity.
Isoniazid remains an essential drug in the treatment of active TB and is the mainstay of chemoprophylaxis in latent TB infection (LTBI), an intervention that is being rapidly expanded in recent strategies to eliminate TB as a public health problem. Hence, global use of the drug will greatly increase worldwide in the coming decade. While transaminase testing is a readily available biomarker of possible ATDH, baseline values have modest predictive value and routine monitoring is not generally recommended. Where slow acetylator status is common, pharmacogenetic testing could make a clinically useful contribution to risk stratification for ATDH. However, the need for testing of a relatively large panel of SNPs and the current lack of a clear substitute to isoniazid for LTBI chemoprophylaxis mean that such a strategy may not be cost-effective or feasible. Studies investigating the cost-effectiveness and/or feasibility of such a strategy would be beneficial. Nevertheless, based on the nearly three-fold increased risk of ATDH in slow acetylators observed in this review, pharmacogenetic epidemiology should certainly be a factor in national policymaking on the need for transaminases monitoring during treatment of active TB and LTBI locally.

Quality assessment

The quality of included studies was variable, with some areas of concern. Most studies were significantly smaller than typically required to provide sufficient power,[20] and the reader was left unaware of the likelihood of false-negatives in all studies due to the lack of reported a priori power calculations. The fact that no studies described checking that missing data were missing at random is also a concern; missing genotype data are unlikely to be missing at random, as heterozygotes are notoriously more difficult to call than homozygotes.[20] Few studies reported testing of HWE, which can highlight genotyping errors, population stratification and other problems.[20] Furthermore, in studies that did not adjust for treatment adherence, the proportion of variability explained by genetic variants in these studies may be underestimated.[20]
The quality assessment was qualitative rather than quantitative, so it was not possible to exclude studies from meta-analyses based on a single summary score. Although we identified issues of concern relating to some of the quality criteria, we did not identify any studies that were thought to be of particularly poor quality overall, so we did not deem it necessary to exclude any single study in sensitivity analyses.

Limitations

Most included studies did not report the ethnic background of participants. We therefore performed analyses stratified by the country in which the study was conducted, as a proxy variable for ethnicity. Clearly, this approach is not ideal, as the population of any given country is often ethnically diverse. However, stratifying by country was deemed the most suitable approach in the absence of definitive information on ethnicity.

An additional challenge was identifying distinct patient cohorts from the included articles. If multiple articles report data for the same patient cohort, data for this patient cohort must only be included in meta-analysis once, otherwise a unit-of-analysis error occurs.[18] We found that it was often not possible to determine from the articles alone whether the patient cohorts were the same or not. We contacted several study authors for clarification. For two articles,[50, 67] we did not receive a response, and consequently, data from the older article[67] were excluded from a meta-analysis to which both articles contributed data. If the two articles reported data for two distinct cohorts, then information has been lost by excluding one article. Furthermore, there is a possibility that there were cases of multiple articles reporting outcomes for the same cohorts that we did not identify; if this is the case, some patients may be double-counted in the meta-analyses.

There was considerable variability in the definitions of hepatotoxicity in the included studies, introducing heterogeneity into the meta-analyses. Jorgensen et al.[70] and Contopoulos-ioannidis et
al.\[71\] made similar observations about the variability of definitions of outcomes across pharmacogenetics studies. If outcome definitions were more consistent between pharmacogenetic studies, the amount of heterogeneity observed in meta-analyses would be reduced.

Finally, an important limitation of the systematic review is a lack of evidence from studies conducted in Africa. There is a great deal of NAT2 diversity across Africa,\[72\] where TB is endemic, but there is little mapping of pharmacogenomic polymorphisms in African populations. Only four studies included in this review were conducted in Africa. Therefore, the vast majority of evidence included in this review is not representative of the global population most affected by TB.

**Recommendations for authors of pharmacogenetic studies**

We make several recommendations regarding the reporting of future pharmacogenetic studies in order to facilitate the conduct of high-quality systematic reviews and meta-analyses, and thus improve the power to detect genetic associations.

i. Report the number of patients in each genotype group.

ii. Report outcomes for each genotype group separately (i.e. number of events for dichotomous outcomes, and means and standard deviations for continuous outcomes).

iii. Report the rs number of each genotyped SNP.

iv. Report the ethnicity of included patients.

v. If a study includes more than one ethnic group, provide the summary data specified in i) and ii) per ethnic group.

vi. Provide the reference to the published protocol.

vii. Provide information on patient cohort overlap.

viii. Report full details of all variants and outcomes investigated, and of all analyses undertaken.
ix. Consensus should be reached between experts in specific areas of research, on the definitions of outcomes that are commonly reported in pharmacogenetic studies of a particular treatment.

We also recommend that papers adhere to the criteria of the quality assessment tool,[20] as improvement in methodological quality of studies included in meta-analyses would in turn improve the strength of the evidence synthesised in meta-analyses. Furthermore, we recommend that the “STREGA” reporting guidelines are referred to, which provide guidance on the reporting of genetic association studies in general.[73]

**Conclusion**

This review shows that slow/intermediate acetylators are significantly more likely to experience hepatotoxicity than rapid acetylators; therefore, pharmacogenetic testing may be useful in clinical practice in terms of risk stratification for ATDH during treatment of TB. However, more studies are needed to overcome the reported methodological limitations and to assess if this strategy might be feasible and cost-effective.

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AUTHOR CONTRIBUTIONS

MR is the guarantor, and drafted the manuscript. All authors contributed to development of the objectives for the review, the search strategy and selection criteria. JK and KD provided statistical expertise on meta-analysis methodology. DS and GD provided expertise on the pharmacogenetics of anti-tuberculosis drugs, and the disease area in general. AJ provided statistical expertise on pharmacogenetics studies, and contributed to the development of meta-analysis methodology tailored for pharmacogenetics studies, i.e. the quality assessment checklist. All authors read, provided feedback and approved the final manuscript.

TRANSPARENCY DECLARATIONS

MR, JK, KD, DS, GD, and ALJ have no conflicts of interest to declare.
### TABLES

**Table 1** Summary of all reported data for the association between NAT2 SNPs and hepatotoxicity

<table>
<thead>
<tr>
<th>NAT2 SNP</th>
<th>Comparison</th>
<th>Country (no. of studies)</th>
<th>Ethnicity</th>
<th>OR (95% CI) parc</th>
<th># cases</th>
<th># controls</th>
<th>$I^2$ value</th>
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<tbody>
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<td>190C-T</td>
<td>Het (CT) vs Hom WT (CC)</td>
<td>China (1 study)</td>
<td>NR</td>
<td>0.21 (0.01, 4.38)</td>
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<td>107</td>
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<td></td>
<td>Hom MT (TT) vs Hom WT (CC)</td>
<td>China (1 study)</td>
<td>NR</td>
<td>Data excluded*</td>
<td></td>
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<td></td>
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<tr>
<td>191G-A</td>
<td>Het (GA) vs Hom WT (GG)</td>
<td>Taiwan (1 study)</td>
<td>NR</td>
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<td>Hom MT (AA) vs Hom WT (GG)</td>
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<td>South Korea (1 study)</td>
<td>NR</td>
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CI: confidence interval; Het: heterozygous genotype; Hom MT: homozygous mutant-type; Hom WT: homozygous wild-type; N/A: not applicable; NR: not reported; OR: odds ratio; SNP: single nucleotide polymorphism.
* Data excluded due to zero patients in one of the genotype groups
1 Data from two of the three Chinese studies were excluded due to zero counts
Table 2 Summary of results for all other toxicity outcomes

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<th>Variant</th>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Comparison</th>
<th>OR (95% CI)</th>
<th># cases</th>
<th># controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Acetylator status</td>
<td>Azuma (2013)</td>
<td>Japan</td>
<td>NR</td>
<td>Intermediate vs rapid</td>
<td>1.36 (0.32, 5.75)</td>
<td>8</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slow vs rapid</td>
<td>4.29 (0.66, 27.8)</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>191G-A (rs1801279)</td>
<td>Dhoro (2013)</td>
<td>Zimbabwe</td>
<td>NR</td>
<td>Het (GA) vs hom WT (GG)</td>
<td>0.69 (0.33, 1.41)</td>
<td>102</td>
<td>56</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Hom MT (AA) vs hom WT (GG)</td>
<td>2.48 (0.12, 53.02)</td>
<td>79</td>
<td>38</td>
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</tr>
<tr>
<td></td>
<td>341T-C (rs1801280)</td>
<td>Dhoro (2013)</td>
<td>Zimbabwe</td>
<td>NR</td>
<td>Het (TC) vs hom WT (TT)</td>
<td>1.01 (0.50, 2.07)</td>
<td>84</td>
<td>48</td>
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<td></td>
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<td></td>
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<td>Hom MT (CC) vs hom WT (TT)</td>
<td>1.34 (0.32, 5.62)</td>
<td>54</td>
<td>30</td>
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<tr>
<td>Adverse DIH outcome</td>
<td>Acetylator status</td>
<td>Bose (2011)</td>
<td>India</td>
<td>NR</td>
<td>Slow vs rapid/intermediate</td>
<td>3.31 (1.03, 10.62)</td>
<td>16</td>
<td>202</td>
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<tr>
<td>ADRs</td>
<td>Acetylator status</td>
<td>Costa (2012)</td>
<td>Brazil</td>
<td>84% Black/mixed race, 16% other</td>
<td>Slow vs rapid/intermediate</td>
<td>3.20 (1.31, 7.80)</td>
<td>40</td>
<td>47</td>
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<tr>
<td>Skin rash</td>
<td>Acetylator status</td>
<td>Higuchi (2007)</td>
<td>Japan</td>
<td>NR</td>
<td>Intermediate vs rapid</td>
<td>0.83 (0.32, 2.19)</td>
<td>22</td>
<td>68</td>
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<td>Slow vs rapid</td>
<td>1.21 (0.27, 5.46)</td>
<td>15</td>
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<td>Eosinophilia</td>
<td>Acetylator status</td>
<td>Higuchi (2007)</td>
<td>Japan</td>
<td>NR</td>
<td>Intermediate vs rapid</td>
<td>1.44 (0.60, 3.45)</td>
<td>31</td>
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<td></td>
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<td></td>
<td>Slow vs rapid</td>
<td>0.98 (0.22, 4.35)</td>
<td>17</td>
<td>39</td>
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</tr>
<tr>
<td>ATD-induced MPE</td>
<td>R197Q (590G-A, rs1799930)</td>
<td>Kim (2011) (Gi: KIM)</td>
<td>South Korea</td>
<td>NR</td>
<td>Hom MT (AA) or het (GA) vs hom WT (GG)</td>
<td>0.96 (0.50, 1.84)</td>
<td>58</td>
<td>150</td>
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<td>G286E (857G-A, rs1799931)</td>
<td>Kim (2011) (Gi: KIM)</td>
<td>South Korea</td>
<td>NR</td>
<td>Hom MT (AA) or het (GA) vs hom WT (GG)</td>
<td>1.65 (0.86, 3.18)</td>
<td>59</td>
<td>152</td>
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<td>-9796 T-A (rs4646244)</td>
<td>Kim (2011) (Gi: KIM)</td>
<td>South Korea</td>
<td>NR</td>
<td>Hom MT (AA) or het (TA) vs hom WT (TT)</td>
<td>1.08 (0.59, 2.00)</td>
<td>62</td>
<td>159</td>
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<td>-9601A-G (rs4646267)</td>
<td>Kim (2011) (Gi: KIM)</td>
<td>South Korea</td>
<td>NR</td>
<td>Hom MT (GG) or het (AG) vs hom WT (AA)</td>
<td>0.65 (0.33, 1.27)</td>
<td>61</td>
<td>159</td>
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<tr>
<td>Gastrointestinal ADRs</td>
<td>Acetylator status</td>
<td>Possuelo (2008) (Gi: POSSUELO)</td>
<td>Brazil</td>
<td>57% White</td>
<td>Slow vs rapid/intermediate</td>
<td>1.18 (0.51, 2.70)</td>
<td>33</td>
<td>207</td>
</tr>
</tbody>
</table>

ATD: anti-tuberculosis drug; ADR: adverse drug reaction; CI: confidence interval; DIH: drug-induced hepatotoxicity; Gi: group identifier; Het: heterozygous genotype; Hom MT: homozygous mutant-type; Hom WT: homozygous wild-type; MPE: maculopapular eruption; NR: not reported; OR: odds ratio
FIGURE LEGENDS

[FIGURE 1 Flowchart of study according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).]

[FIGURE 2 Slow/intermediate versus rapid acetylator status for the outcome of hepatotoxicity.]

*Vuilleumier 2006[56] and Yamada 2009[60] were both conducted in the latent TB population

**Caucasian: 38 (43%), Hispanic: 22 (25%), South American: 15 (17%), Asian: 5 (6%), Middle Eastern: 1 (1%)

*** Asian: 72 (42%), Caucasian: 49 (29%), South Asian: 22 (13%), Hispanic: 7 (4%), Middle Eastern: 8 (5%), First nations: 5 (3%), Other/mixed/unknown: 7 (4%)

CI: confidence interval; GI: group identifier; OR: odds ratio.


