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TOOLS

Systematic review on genetic polymorphisms associated with idiosyncratic drug-induced liver injury (iDILI): iDILInet as an interactive visualization tool

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Abstract Idiosyncratic drug-induced liver injury (iDILI) is a rare, dose-independent and unpredictable adverse reaction occurring at therapeutic drug exposure, and it presents a significant challenge for drug development and patient safety. Despite extensive research, genetic susceptibility to iDILI remains poorly understood. We conducted a comprehensive systematic study of 139 human genetic studies to identify

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and characterize genetic polymorphisms associated with increased risk or protection against iDILI. Our study included candidate gene studies and genome-wide association studies (GWAS), encompassing 83 risk and 25 protective genes, with NAT2, HLA-B, and SLCO1B1 among the most frequently reported. We performed functional enrichment analyses using KEGG and Gene Ontology, revealing key biological pathways related to immune response, xenobiotic metabolism, and bile secretion. To enhance data accessibility and interpretation, we developed iDILInet, a publicly available web application that enables interactive exploration and network-based visualization of iDILI-associated gene-variant-drug relationships, enriched with liver-specific expression data from the Human Protein Atlas (HPA). Our work provides a novel integrative resource that supports ongoing efforts in precision medicine and pharmacogenomics and represents a significant advancement in implementing living systematic reviews in toxicogenomics.

1. Introduction

Idiosyncratic drug-induced liver injury (iDILI) is an unpredictable, host-dependent adverse reaction to drugs and herbal and dietary supplements (HDS) that occurs at therapeutic doses and differs from intrinsic, dose-dependent hepatotoxicity. Although relatively rare (14−19 cases per 100,000 inhabitants[1]), it is a leading cause of acute liver failure in the USA and Europe[2] and represents a major reason for drug withdrawal and treatment discontinuation in clinical trials[3], posing a substantial challenge to public health and drug safety.

iDILI is a complex and multilayer condition that arises from the interplay between drug-specific properties and host and environmental factors[4]. Current evidence supports a multifactorial, multistep pathogenic process in which drug metabolism and bioactivation, immune tolerance and immune-mediated responses, and clinical factors such as comorbidities, concomitant medications, microbiota, age, sex, and physiological or environmental influences jointly shape individual susceptibility, clinical presentation, and disease outcome. Importantly, no single factor is sufficient to explain iDILI development, underscoring the heterogeneity and unpredictability of this adverse reaction.

Among host-related determinants, genetic susceptibility has been one of the most widely investigated areas. Numerous studies, including candidate gene analyses and genome-wide association studies (GWAS), have associated iDILI risk with specific variants, genotypes, and haplotypes, particularly within the human leukocyte antigen (HLA) region[3]. Notably, international collaborative efforts have enabled the assembly of large, well-characterized iDILI cohorts.

These consortia have been instrumental in validating drug-specific HLA associations, such as the significant association between *HLA-A**33:01, an HLA class I allele, and cholestatic and mixed iDILI for terbinafine, but not for hepatocellular iDILI, indicating that host genetic factors influence the pattern of iDILI[5], as well as in characterizing non-HLA genetic associations, which typically require larger sample sizes to be reliably detected.

Beyond HLA, variants in genes involved in immune regulation (*e.g.*, *PTPN22*[6]) and drug metabolism or transport pathways have been implicated. For example, the *NAT2* slow acetylator phenotype has been consistently linked to anti-tuberculosis (anti-TB) iDILI in Asian populations[7-10]. Although the implementation of pre-emptive genotyping is limited by the rarity of iDILI and the low positive predictive value of most associations[11], genetic testing can help clarify causality in ambiguous clinical scenarios when more than one drug is suspected[12].

Despite growing evidence, our understanding of the mechanisms underlying genetic susceptibility to iDILI remains incomplete[13]. Both frequently and infrequently reported genes may play key roles and deserve systematic functional exploration. A major challenge in this field is the integration and interpretation of heterogeneous data derived from candidate gene studies, GWAS, and high-throughput sequencing platforms. To address this, there is a growing need for comprehensive bioinformatic frameworks that can systematically link genetic variants to molecular pathways, cellular processes, and clinical phenotypes in a biologically meaningful way.

Network-based approaches have proven useful in representing large and small sets of genetic variants, enabling visualization of gene-phenotype relationships and supporting the identification of risk or protective associations[14-16]. Such methods have also been applied to drug-target prioritization and bibliometric mapping[17-20], but to our knowledge, network visualization of iDILI genetic associations, including variants and statistical measures, has not been previously reported.

In this study, we conducted a comprehensive systematic review of genetic associations with iDILI, followed by enrichment analysis to investigate the biological processes implicated. In addition, we developed an interactive web-based database (iDILInet) to facilitate access to genes, variants, and drugs extracted from the literature, including supporting data such as the number of studies, odds ratios (OR), and *P*-values. This integrative tool aims to complement and extend the concept of a living systematic review (LSR)[21], offering improved data accessibility, network-based visualization, and future updates.

2. Materials and methods

2.1. Study design and search strategy

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines[22]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), bearing registration number CRD42024594632.

Eligible literature published up to June 30th, 2023, was identified through a search in Web of Science, EMBASE, Scopus, and

PubMed, with no language restrictions. The search strategy comprised the following liver injury and genetic-related terms and Boolean operators: ('drug-induced liver' OR 'liver toxicity' OR 'hepatic toxicity' OR 'dili' OR 'hepatotox*' OR 'acute liver' OR 'herb*-induced liver') AND ('gen*' OR 'genome-wide' OR 'variant' OR 'typ*' OR 'allel*' OR 'snp' OR 'polymorphism' OR 'single nucleotid*' OR 'HLA' NOT 'general*' NOT 'generic*' NOT 'generat*' NOT 'gender*' NOT 'genera*' NOT 'type*' NOT 'typic*'). The complete search strategies for each database, including keywords, Boolean operators, and specific syntax, are provided in Supporting Information Table S1. Retrieved literature was managed using the Rayyan online tool[23].

2.2. Inclusion and exclusion criteria

To be included, studies had to meet the following criteria: I) be an original peer-reviewed article, including experimental and observational studies; II) perform a genetic study in patients with hepatotoxicity that fulfil iDILI criteria[24-27]. In this context, iDILI was considered as liver injury occurring at therapeutic drug exposure and distinct from intrinsic, dose-dependent hepatotoxicity; III) include at least one (exposed or non-exposed) control group, and IV) report at least one statistically significant genetic variant between groups.

Case reports, case series, and studies conducted with *in vitro* or animal models were excluded. Reviews, conference abstracts, editorials, and other reports with no relevant data were also excluded. Studies exclusively addressing intrinsic or overdose-related hepatotoxicity were also excluded.

2.3. Study selection and data extraction

Literature search, duplicate elimination, and screening for titles and abstracts were led by four researchers (GMC, ARD, ABG, and RLDSF). They also retrieved and reviewed the full text of the relevant studies identified. Pairs of authors independently revised each study included. Any disagreements regarding the identification of relevant studies for inclusion in the systematic review were resolved by two senior researchers (MVP and IAA), with the reasons for the final inclusion or exclusion of each study being specified and discussed.

Subsequently, the following data were extracted from the included articles by five researchers (GMC, ARD, ABG, RLDSF, and MVP): the surname of the first author, year of publication, Digital Object Identifier (DOI), type of genetic study and technology, gene ID and name, genetic variant name/ID, OR and *P*-value, iDILI criteria and culprit drug(s), drug dosage and exposure duration, concomitant drugs in iDILI cases, the number of iDILI and control cases, rule out of underlying/competing liver diseases, ethnicity/country of origin, sex, and age of each study group.

Based on the reported effect estimates, included articles were assigned to a DILI Risk and/or DILI Protective set according to the direction of the associations observed for the genes they evaluated. Specifically, an article was included in the DILI Risk set when it reported genetic variants with an OR > 1 and an adjusted *P*-value ≤ 0.05, and in the DILI Protective set when it reported variants associated with an OR < 1 and an adjusted *P*-value ≤ 0.05. Articles reporting both risk- and protection-associated variants meeting these significance criteria were included in both sets. Note that this classification refers to variant-level associations and does not imply that the gene's overall physiological function is intrinsically harmful or protective.

2.4. Quality assessment

The quality assessment of the included articles was conducted using the validated *Q-Genie* tool version 1.1, developed by Sohani et al.[28] In brief, the studies were evaluated based on 11 items scored on a 7-point Likert scale (ranging from 'poor' to 'excellent'), which covered the following topics: I) rationale for the study; II) selection and definition of the outcome of interest; III) selection and comparability of comparison groups; IV and V) technical and non-technical classification of the exposure; VI) other sources of bias; VII) sample size and power; VIII) *a priori* planned analyses; IX) statistical methods and control for confounding; X) testing assumptions and interferences for genetic analyses; and XI) the appropriateness of interferences drawn from the results. The studies were evaluated by pairs of researchers (GMC, ARD, ABG, RDF, MVP), and final scores were obtained by averaging the individual evaluations. The articles were then classified as 'poor', 'moderate', or 'good' quality studies.

2.5. Bioinformatic and statistical analysis of human data

Data extraction, management, and bioinformatics analysis were conducted using R v4.4.1, RStudio v2025.05.0, and Bioconductor v3.19 packages (including BiocManager v1.30.23, clusterProfiler v4.12.0, org.Hs.eg.db v3.19.1, KEGGREST v1.44.1, AnnotationDbi v1.66.0 and biomaRt v2.60.1), along with CRAN data handling and representation packages. Descriptive analysis and overall frequency calculations were performed for study type, iDILI criteria, genes, variants, and information about the culprit agent. Functional enrichment analyses of Risk and Protective Sets were carried out to explore the biological processes and signaling pathways in which the retrieved genes were involved. The collected gene pools (containing single values) were utilized to conduct enrichment analysis in the KEGG[29] and Gene Ontology (GO)[30] databases. For enrichment calculation, a hypergeometric distribution with multiple testing correction, using the Benjamini-Hochberg method (BH), was applied, with adjusted *P* and *Q* values of <0.05 to minimize the false discovery rate (FDR). Hierarchical clustering was performed using Jaccard's similarity index (JC) and Ward's minimum variance method from the KEGG Enrichment analysis results. Pathway proximity was obtained based on gene panel matches. For representation, statistically significant categories from KEGG and GO were selected by establishing an adjusted *P*-value cut, indicated in the text and figure caption.

2.6. Development of iDILInet web application

An in-house developed bioinformatics pipeline was used first to process and merge data obtained from the DILI Risk and Protective datasets of this systematic review (Supporting Information Fig. S1). Next, to access and facilitate visualization of the contents of the sets, iDILInet, a Shiny application in R[31] was developed.

iDILInet has been designed to allow the interactive exploration of systematically reviewed human genetic polymorphisms associated with higher or lower risk of developing iDILI (DILI Risk and Protective sets), using multi-partite networks *via* the visNetwork package in R[32]. The DILI Risk and Protective sets can also be visualized in table format in iDILInet, allowing users to browse, filter, and sort the information based on the R package DT[33]. Human Protein Atlas (HPA)[34] was used to further annotate human genes and their expression levels in the liver. Hepatocyte

and cholangiocyte-relevant gene expression data were integrated into iDILInet using the hpar R package[35].

The DILI Risk and Protective sets were manually curated and independently cross-checked by multiple co-authors to ensure accuracy and consistency. Standard operating procedures (SOPs), including automation using R scripts, were established to guide the conversion of curated Excel tables into the structured database format used by iDILInet and to cross-check input and output tables for validation, thereby ensuring reproducible updates.

Additionally, structured external usability testing was conducted by independent non-experts as well as domain experts in bioinformatics, hepatotoxicity or pharmacogenomics who were not involved in data curation. Evaluators assessed interface clarity, navigation, generation and interpretability of tabular and network outputs, and consistency between visualizations and source tables.

iDILInet is maintained by Bilkent University. The current release described in this manuscript corresponds to version 1.0. Future updates will be performed annually following systematic updates of the manually curated DILI Risk and Protective sets. Each update will receive a consecutive version number, and previous versions will be archived to ensure traceability and reproducibility.

3. Results

3.1. Literature search

The total number of articles to be assessed, derived from the search performed on all four databases, was 25,874. Of these, 10,943 duplicate records were removed, and the remaining 14,931 were screened. After screening for title and abstract, 14,461 records failed to meet the inclusion criteria and were excluded, mainly because they were irrelevant to the study ($\sim$97%). Thus, a total of 470 articles were reviewed.

After reviewing these records, 329 articles did not meet the eligibility criteria and were excluded. Hence, 139 studies were finally included[5,36-173] and assigned to the Risk and/or Protective sets based on the direction and statistical significance of the associations reported for the genes under investigation, with some studies contributing to both sets when reporting significant variants with opposite directions. Therefore, 124 articles were added to the DILI Risk set, 36 to the DILI Protective set, and 21 to both sets, to finally perform an in-depth analysis (Fig. 1).

3.2. Quality assessment analysis

The quality and reliability of the articles included were evaluated. Most articles (87.8%) received good quality scores, while 12.2% were rated as moderate quality. Notably, none of the articles were classified as poor-quality studies. A detailed item-by-item quality assessment is shown in Supporting Information Fig. S2.

3.3. Data analysis

Detailed data extracted from the 139 included articles, separated by Risk and Protective sets, are presented in Supporting Information Table S2a and S2b, respectively.

3.3.1. Study type

Among the 124 studies in the DILI Risk Set, 110 performed a candidate gene study (marked as targeted genotyping), 5 performed GWAS, and 9 combined both strategies. In the DILI Protective Set (36 studies), 33 conducted a candidate gene study, two performed GWAS, and one performed both.

3.3.2. iDILI criteria

Different biochemical iDILI criteria were used in the Risk Set. 37 studies followed Bénichou et al.[25], Aithal et al.[24] was used in 12 studies, and the Common Terminology Criteria for Adverse Events (CTCAE) v4.0[27], the Drug Induced Liver Injury Network (DILIN)[26], and CTCAE v5.0[27] were each used in 13, 8, and 6 studies, respectively. The remaining 48 articles applied their own criteria; at least alanine aminotransferase (ALT) levels $\geq$2 times the upper limit of normal (ULN), as indicated in Bénichou et al.[25]. In the Protective Set, 10 studies followed the criteria of Bénichou et al.[25], 5 adopted CTCAE v3.0[27], while the remaining 21 applied their own criteria (at least ALT levels $\geq 2 \times$ ULN, as indicated in Bénichou et al.[25]).

3.3.3. Gene panel

One count per gene per article was considered to calculate the total number of genes and their overall frequency in the Risk and Protective Sets. Gene combinations were discarded to avoid confounding factors.

In the Risk Set, a total of 89 results were obtained from the studies, with 6 of them located in unidentified or intergenic regions. Consequently, 83 genes were identified as having genetic profiles (*i.e.*, variants, alleles, genotypes, or haplotypes) associated with an increased risk of iDILI (Supporting Information Table S3). Genes identified in more than two studies included: *NAT2* (25 articles), *HLA-B* (14), *HLA-DRB1* (14), *HLA-A* (11), *HLA-DQB1* (7), *CYP2E1* (6), *HLA-C* (6), *SLCO1B1* (6), *SOD2* (5), *MTHFR* (4), *ABCC2* (3), *CYP2B6* (3), and *NOS2* (3).

In the Protective Set, 25 genes were identified with genetic profiles linked to a lower risk of developing iDILI (Table S3). The genes that appeared in more than two studies included: *NAT2* (8 articles), *ABCB1* (3), *MTHFR* (3), *NR1I2* (3), and *SLCO1B1* (3). While most genes are consistent between the sets, some are exclusive to the Protective Set: *MIR1208*, *MAFF*, *XRCC3*, *LTA*, *MTHFD1*, *UGT1A4*, and *SLC22A2*.

A structured overview of heterogeneity across the most frequently reported genes is provided in Supporting Information Table S4.

3.3.4. Genetic variant panel

Each genetic profile was counted once per article to calculate the total panel of genetic profiles and their overall frequency in the Risk and Protective sets. Combinations of genetic profiles were treated as a single genetic profile.

We identified the most frequent genetic profiles of the most common genes in the Risk Set (Supporting Information Table S5). For instance, in *NAT2*, among 15 different genetic profiles, *6 allele and *6/*7 genotype (five occurrences each), *13 allele (four occurrences), and *5/*7 genotype, *7 allele, and rs1495741 (three occurrences each) were the most common. The "slow acetylator" genetic profile was predominant but not included here due to its heterogeneity and inaccuracy. For *HLA-B*, among 13 different genetic profiles, *35:01 allele appeared three times, while *53:01, *57:01, and *58:01 alleles appeared two times each. In *HLA-DRB1*, out of 12 genetic profiles, *15:01 allele was reported in five studies. Lastly, for *HLA-A*, among eight genetic profiles, *02:01 allele was found four times, and *34:02 allele was reported two

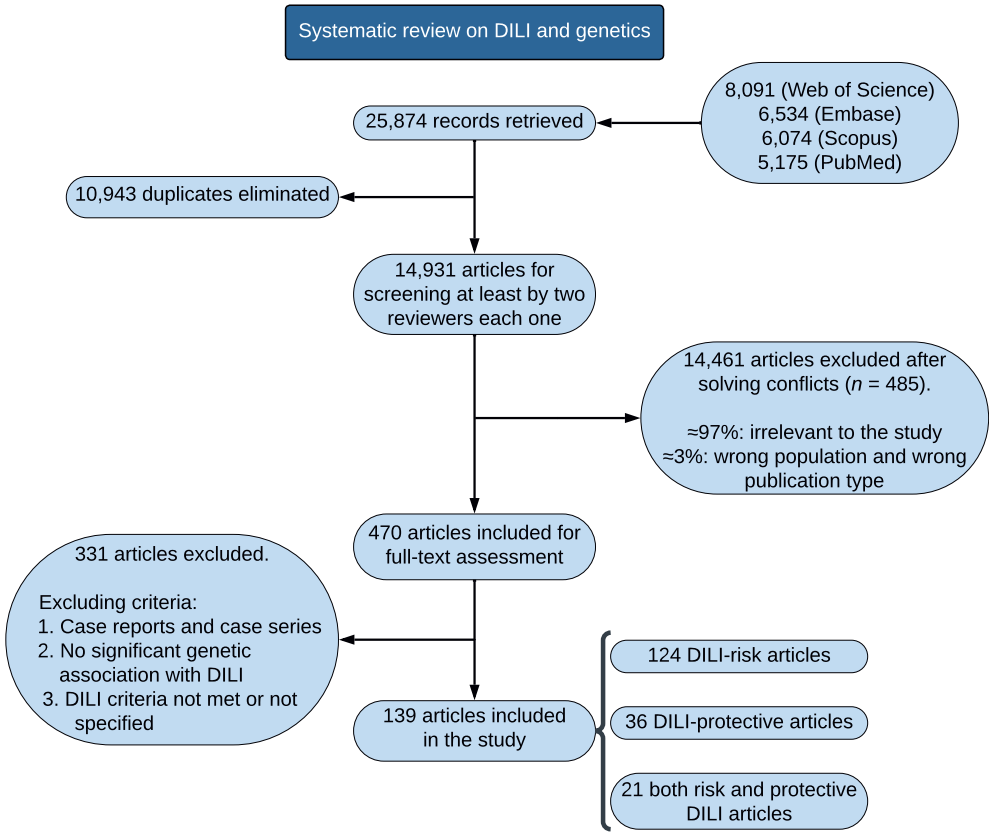


Figure 1 Flowchart of the literature review strategy. A total of 25,874 records were retrieved from four databases (Web of Science, Embase, Scopus, and PubMed). After removal of duplicates (n = 10,943), 14,931 articles were screened by at least two independent reviewers. Of these, 14,461 were excluded after resolving conflicts, mostly due to irrelevance (the article is not related to the research question or the inclusion criteria defined for the review, *i.e*., the article focuses on a disease other than iDILI) or incorrect population/publication type (articles that do not meet the inclusion criteria due to the population studied or the type of publication). A total of 470 articles underwent full-text assessment, with 331 subsequently excluded based on predefined criteria. Finally, 139 articles were included in the review: 124 focused on iDILI-risk variants, 36 on protective variants, and 21 on both.

times; for *HLA-DQB1* (comprising five genetic profiles), *06:02 allele was the most common, appearing three times.

The most frequent genetic profiles included in the Protective Set were also identified (Supporting Information Table S6). For *NAT2*, out of six different genetic profiles, *4 allele was the most common (two times). However, *SLCO1B1* and *NR1I2* showed unique genetic profiles (six and five, respectively). For *ABCB1*, rs1045642 was the only genetic profile found, while for *MTHFR* (two genetic profiles), rs1801131 (two times) was the most frequent allele.

3.3.5. *Drug analysis*

A frequency analysis of the most common culprit drugs was conducted using the Anatomical Therapeutic Chemical (ATC) classification system[174] (Table 1). In the Risk Set, the culprit drugs included Antiinfectives for systemic use (59.6%), being distributed as Antimycobacterials (46.8%), Antibacterials for systemic use (8.8%), and Direct-acting antivirals (4.0%), as well as Antineoplastic and Immunomodulating agents (23.4%). Herbal products and dietary supplements accounted for 1.6% of the studies.

For the Protective Set, the most common culprit drugs were Antiinfectives for systemic use (61.1%), comprising Antimycobacterials (44.4%), Direct-acting antivirals (11.1%), and Antibacterials for systemic use (5.6%), as well as Antineoplastic and immunomodulating agents (27.8%).

3.4. *Enrichment analysis*

GO and KEGG enrichment analyses were performed using previously obtained gene panels to explore biological processes and signaling pathways.

An initial GO analysis was conducted to obtain categories for *Biological Process*, *Cellular Component*, and *Molecular Function* in the Risk and Protective Sets (Supporting Information Table S7). The Risk Set had 872, 39, and 85 statistically significant results, respectively, while the Protective Set had 126, 32, and 27. The categories with lower *P*-values are detailed in Table 2.

In GO *Biological Process* enrichment analysis of Risk Set (Fig. 2A), categories with most significant adjusted *P*-values were mainly related to *xenobiotic detoxification*. When considering gene ratios, the first biological pathway had a gene ratio significantly higher than the average, with 40.74% of the total panel's genes involved. The next six most statistically significant categories had gene ratios equal to or higher than 19.75% (16/81) and correlated with xenobiotic metabolism and immune system pathways. Additionally, other noteworthy classes with lower gene ratios were associated with oxidative stress response (Fig. 2A and Table S7).

In GO *Biological Process* enrichment analysis of Protective Set (Fig. 2B), categories with most significant adjusted *P*-values

Table 1 Frequency analysis of the most common culprit drugs reported in the included studies, categorized according to the ATC classification system[a].

ATC classification			Main pharmacological categories	Frequency (% of 124 Risk studies)	Frequency (% of 36 Protective studies)
J			Antiinfectives for systemic use	59.6%	61.1%
	J01		Antibacterials for systemic use	8.8%	5.6%
		J01A	Tetracyclines	0.8%	–
		J01C	Beta-lactam antibacterials, penicillins	1.6%	–
		J01CR02	Amoxicillin-clavulanate	4.0%	2.8%
		J01E	Sulphonamides and trimethoprim	0.8%	–
	J04		Antimycobacterials	46.8%	44.4%
		J05A	Direct acting antivirals	4.0%	11.1%
L			Antineoplastic and immunomodulating agents	23.4%	30.6%
	L01		Antineoplastic agents	21.0%	30.6%
		L03A	Immunostimulants	1.6%	–
		L04A	Immunosuppressants	0.8%	–
M			Musculo-skeletal system	4.0%	–
		M01A	Nonsteroidal anti-inflammatory drugs	3.2%	–
		M04A	Antigout preparations	0.8%	–
C			Cardiovascular system	1.6%	–
		C01B	Antiarrhythmics, class I and III	0.8%	–
		C10AA	Statins	0.8%	–
H		H03	Thyroid therapy	1.6%	2.8%
N		N03A	Antiepileptics	1.6%	–
B		B01A	Antithrombotic agents	0.8%	–
–			Various	11.3%	6.0%
–			Herbal products and dietary supplements	1.6%	–

[a]Percentages were calculated based on the total number of studies included in the review (note that some studies reported more than one implicated drug).

and higher gene counts also correlated to xenobiotic metabolism (Table 2). Consistent with the Risk Set, the first metabolic pathway had a gene ratio significantly higher than the average, with 44.0% of the genes from the initial panel. The subsequent four categories have gene ratio values exceeding 16.0%. In contrast, all the remaining categories showed scores around 12%−15%, which is equivalent to having only four or three genes, primarily associated with major histocompatibility complex (MHC)-related immune system pathways.

GO *Cellular Component* analysis in Risk and Protective Sets yielded 39 and 32 statistically significant results, respectively (Table S7). For the Risk Set, the six most significant categories (adjusted *P*-value $<1 \times 10^{-8}$) were related to *MHC protein complex*, *endoplasmic reticulum (ER) membrane*, and *Golgi Apparatus* (Table 2). In the Protective Set, the five most significant categories were similar to those in the Risk Set; however, these classes achieved a higher gene ratio (20%) compared to the Risk Set.

For GO *Molecular Function*, the analysis yielded 85 significant results for the Risk Set and 27 for the Protective Set (Table S7). In the Risk Set panel, the six most statistically significant categories corresponded to *amide*, *peptide*, *heme*, *tetrapyrrole*, and *MHC class II protein complex binding*. The category with the highest gene ratio was the first one, with a value of 18.29%. In the Protective Set, the most statistically significant classes (adjusted *P*-value <0.001) differed slightly from those obtained in the Risk Set. However, along with the Risk Set results, the highest gene ratio corresponded to the *Amide binding* category (gene ratio = 6/24, 25.0%).

The KEGG Enrichment Analysis retrieved 104 statistically significant routes for the Risk-Set and 43 for the Protective-Set (Supporting Information Table S8). The *Human Diseases* category was excluded due to its overrepresentation in the KEGG database which could obscure study-relevant pathways. Therefore, the filtered analysis yielded 48 routes for the Risk Set and 21 for the Protective Set (adjusted *P*-value <0.05). The most significant pathways are shown in Table 3. Bar plots of Risk and Protective Set represented 27 and 21 routes, respectively (Fig. 3).

In the Risk Set, those corresponding to *Th cell differentiation, P450 cytochrome metabolism, intestinal immune network*, *antigen processing and presentation* and *bile secretion* categories were enriched (Fig. 3A). The gene count exceeded five in 36 routes and was equal to or greater than ten in the first eight categories, resulting in gene ratios above 14.7%. Highest gene ratio (gene ratio = 14/68, 20.59%), corresponded to *Th17 cell differentiation* category. Certain categories with higher adjusted *P*-values had also elevated gene ratios, such as *hematopoietic cell lineage*, *T cell receptor signaling pathway* and *steroid hormone biosynthesis* (gene ratios = 9/68, 13.24%).

In the Protective Set, the most significant pathways were related to *folate transport and metabolism*, *antigen processing and presentation*, *bile secretion*, c*ell adhesion molecules*, *phagosome*, and *the one-carbon pool by folate* (Fig. 3B). The overall gene count was lower than the Risk Set results, due to the size of the initial gene panel, with only five pathways including more than five genes (gene ratio = 5/20, 25.0%).

After conducting KEGG enrichment analysis, pathway clustering was performed based on the similarities of the genes involved. The heatmap for the Risk Set (Fig. 4) illustrates the hierarchical clustering of 58 genes associated with 48 different pathways. Notably, the genes represented in more than 8 KEGG pathways include *NFKB1* (24 pathways), *RELA* (24), *NFKBIA*

Table 2 Top Gene Ontology (GO) enrichment analysis results.

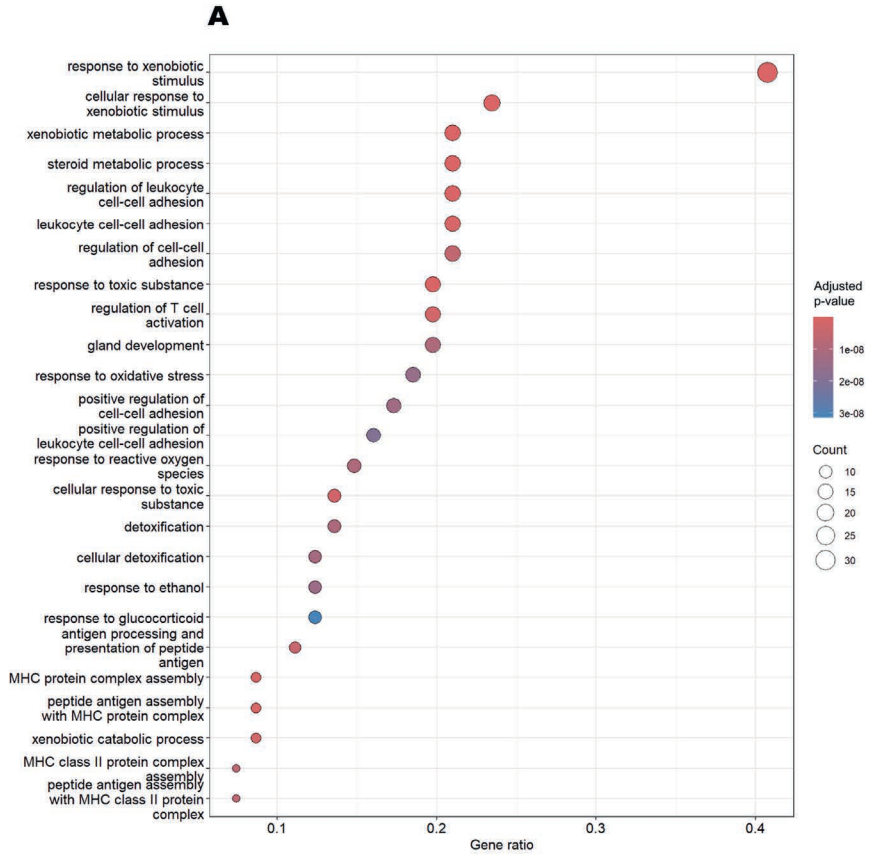
GO category ID	Category description	Gene ratio	Background ratio (BgRatio)	Adjusted *P*-value	*Q* value
Biological process (BP)					
Risk set					
GO:0009410	Response to xenobiotic stimulus	33/81	444/18888	2.89255E-29	1.7674E-29
GO:0006805	Xenobiotic metabolic process	17/81	126/18888	4.2049E-18	2.5692E-18
GO:0071466	Cellular response to xenobiotic stimulus	19/81	194/18888	5.47417E-18	3.3448E-18
GO:0009636	Response to toxic substance	16/81	260/18888	1.10153E-11	6.7305E-12
GO:0008202	Steroid metabolic process	17/81	329/18888	2.16119E-11	1.3205E-11
Protective set					
GO:0009410	Response to xenobiotic stimulus	11/25	444/18888	2.67987E-09	1.6851E-09
GO:0006805	Xenobiotic metabolic process	7/25	126/18888	8.16002E-08	5.1309E-08
GO:0006787	Porphyrin-containing compound catabolic process	4/25	13/18888	3.19455E-07	2.0087E-07
GO:0033015	Tetrapyrrole catabolic process	4/25	13/18888	3.19455E-07	2.0087E-07
GO:0071466	Cellular response to xenobiotic stimulus	7/25	194/18888	6.71602E-07	4.223E-07
Cellular component (CC)					
Risk set					
GO:0042611	MHC protein complex	9/82	25/19894	6.89361E-14	4.8525E-14
GO:0098553	Lumenal side of endoplasmic reticulum membrane	9/82	29/19894	1.66746E-13	1.1737E-13
GO:0098576	Lumenal side of membrane	9/82	39/19894	2.27561E-12	1.6018E-12
GO:0012507	ER to Golgi transport vesicle membrane	9/82	64/19894	2.04183E-10	1.4373E-10
GO:0042613	MHC class II protein complex	6/82	17/19894	1.58388E-09	1.1149E-09
Protective set					
GO:0042611	MHC protein complex	5/25	25/19894	8.02134E-09	4.0529E-09
GO:0098553	Lumenal side of endoplasmic reticulum membrane	5/25	29/19894	8.93454E-09	4.5143E-09
GO:0098576	Lumenal side of membrane	5/25	39/19894	2.86369E-08	1.4469E-08
GO:0012507	ER to Golgi transport vesicle membrane	5/25	64/19894	2.78515E-07	1.4072E-07
GO:0030134	COPII-coated ER to Golgi transport vesicle	5/25	94/19894	1.56419E-06	7.9033E-07
Molecular function (MF)					
Risk set					
GO:0042605	Peptide antigen binding	9/82	47/18522	1.5128E-10	9.9396E-11
GO:0033218	Amide binding	15/82	409/18522	4.44073E-08	2.9177E-08
GO:0020037	Heme binding	10/82	142/18522	5.56454E-08	3.6561E-08
GO:0016712	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen	7/82	43/18522	5.56454E-08	3.6561E-08
GO:0046906	Tetrapyrrole binding	10/82	152/18522	8.12007E-08	5.3352E-08
Protective set					
GO:0042605	Peptide antigen binding	5/24	47/18522	5.09238E-07	2.4067E-07
GO:0003823	Antigen binding	5/24	177/18522	0.000203055	9.5966E-05
GO:0023026	MHC class II protein complex binding	3/24	27/18522	0.000268425	0.00012686
GO:0033218	Amide binding	6/24	409/18522	0.000353504	0.00016707
GO:0023023	MHC protein complex binding	3/24	37/18522	0.000353504	0.00016707

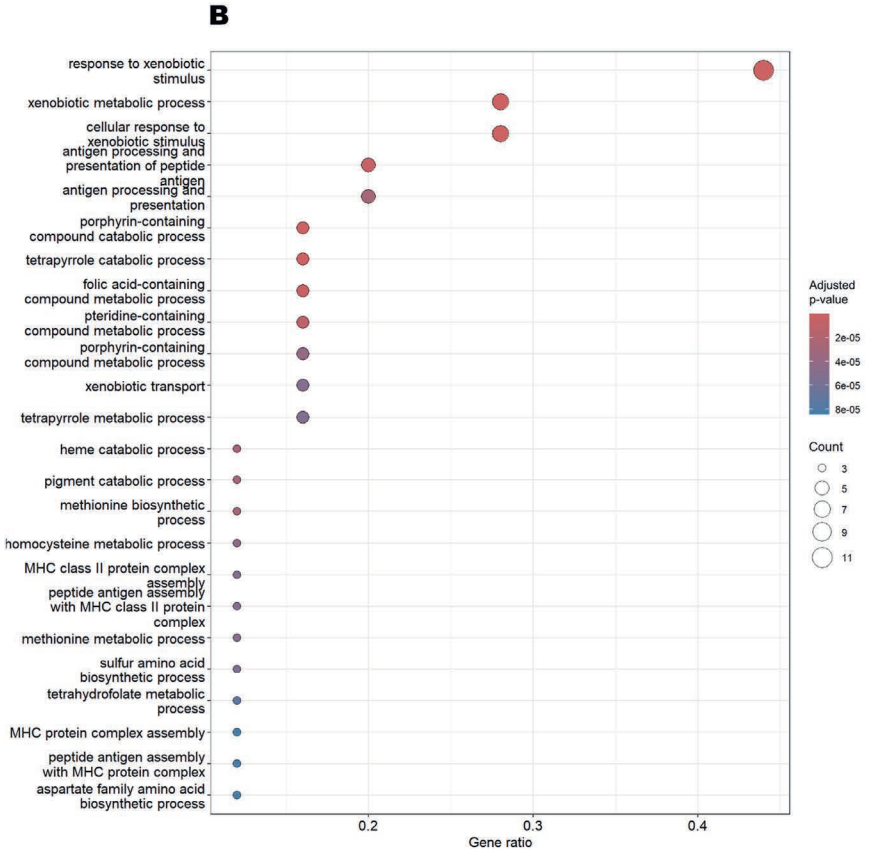
Gene Ratio: Proportion of genes in the input list annotated with the GO term (k/n); BgRatio: Proportion of genes in the background set annotated with the GO term (K/N); p.adjust: Adjusted *P*-value from the hypergeometric test, corrected with the Benjamini-Hochberg method (FDR); *Q*-value: Estimated minimum FDR at which the GO term would be considered significant, calculated by default Storey's method. A significance threshold of adjusted P and $Q < 0.05$ was applied.

(18), *TNF* (15), *IL6* (14), *NFKBIB* (10), *FOXO3* (9), *STAT1* (9), *UGT1A1* (9), *UGT1A9* (9), *UGT2B7* (9), *BCL2* (8), and *IL4* (8).

In terms of clustering, as observed in Figs. 4 and 5, several clusters of correlated genes were identified. For instance, *NFKBIA*, *NFKB1*, and *RELA* grouped within immune response and inflammatory signaling pathways (like the NF-κB pathway, the cytokine signaling pathway, and the overall inflammatory response); *UGT2B7*, *UGT1A1*, and *UGT1A9* in porphyrin, ascorbate, and aldarate metabolism, as well as in drug metabolism pathways mediated by cytochrome P450, where *CYP2E1*, *CYP3A4*, *GSTT1*, *GSTM1*, *GSTP1*, *CYP3A5*, *CYP2B6*, and *CYP2D6* genes were also involved. Additionally, various genes from the HLA family (*HLA-DRA*, *HLA-DRB5*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DRB1*, *HLA-DQB1*, *HLA-C*, *HLA-B*, and *HLA-A*) grouped within the same cluster, which was related to the adaptive immune response and cytotoxicity pathways mediated by T and NK cells. Another significant cluster was formed by the *ABCG2, ABCB11*, *ABCC2*, *ABCB1*, and *SLCO1B1* genes, related to biliary secretion.

For Protective-Set, 16 genes were associated with 21 pathways, among which *UGT1A1* (10), *UGT1A4* (10), *HLA-DPB1* (7), *HLA-DQA1* (7), and *HLA-DRB1* (7) were the most prevalent, each involved in more than six pathways (Fig. 5). In terms of clustering, there were genes that grouped within the same cluster, such as *UGT1A1* and *UGT1A4* for metabolism, biosynthesis, and chemical interconversions pathways; *HLA-DRB1*, *HLA-DQA1*, and


A
response to xenobiotic stimulus
cellular response to xenobiotic stimulus
xenobiotic metabolic process
steroid metabolic process
regulation of leukocyte cell-cell adhesion
leukocyte cell-cell adhesion
regulation of cell-cell adhesion
response to toxic substance
regulation of T cell activation
gland development
response to oxidative stress
positive regulation of cell-cell adhesion
positive regulation of leukocyte cell-cell adhesion
response to reactive oxygen species
cellular response to toxic substance
detoxification
cellular detoxification
response to ethanol
response to glucocorticoid
antigen processing and presentation of peptide antigen
MHC protein complex assembly
peptide antigen assembly with MHC protein complex
xenobiotic catabolic process
MHC class II protein complex assembly
peptide antigen assembly with MHC class II protein complex
0.1
0.2
0.3
0.4
Gene ratio
Adjusted p-value
1e-08
2e-08
3e-08
Count
10
15
20
25
30


B
response to xenobiotic stimulus
xenobiotic metabolic process
cellular response to xenobiotic stimulus
antigen processing and presentation of peptide antigen
antigen processing and presentation
porphyrin-containing compound catabolic process
tetrapyrrole catabolic process
folic acid-containing compound metabolic process
pteridine-containing compound metabolic process
porphyrin-containing compound metabolic process
xenobiotic transport
tetrapyrrole metabolic process
heme catabolic process
pigment catabolic process
methionine biosynthetic process
homocysteine metabolic process
MHC class II protein complex assembly
peptide antigen assembly with MHC class II protein complex
methionine metabolic process
sulfur amino acid biosynthetic process
tetrahydrofolate metabolic process
MHC protein complex assembly
peptide antigen assembly with MHC protein complex
aspartate family amino acid biosynthetic process
0.2
0.3
0.4
Gene ratio
Adjusted p-value
2e-05
4e-05
6e-05
8e-05
Count
3
5
7
9
11

HLA-DPB1 for cell differentiation and antigen presentation in immune system response; and *ABCB1*, *ABCC2*, and *SLCO1B1* for bile secretion and cellular transport.

Table 4 shows the complete set of genes associated with iDILI risk or protection retrieved from the selected literature, grouped by biological function.

3.5. iDILInet application

iDILInet is a web application, developed specifically for iDILI studies systematically reviewed and published up to June 2023 and presented in this work. The current version of iDILInet (v1.0) incorporates structured quality control procedures (Supporting Document S1) and external usability testing (Supporting Document S2), as detailed in Materials & Methods. iDILInet allows users to visualize gene-polymorphism-drug triplets as networks for a gene of interest from the integrated and ranked lists of genes associated with iDILI. In addition, iDILInet provide users with the ability to restrict their investigation to: a) "Risk" or "Protective" or "Both" alleles; b) the top-ranking genes based on the number studies in which the genes are reported; c) a specific set of drug categories for selected gene(s); and d) the presence of expression in liver (Fig. 6A).

In a user-defined iDILInet network, genes, variants, and drugs associated with iDILI are represented by different colors and shapes while DILI Risk and Protective tables could also be visualized in table format, allowing users to browse, filter, and sort the information. In iDILInet, genes, represented as circles, are color-coded based on their expression levels in the liver hepatocytes, while cholangiocyte expression is indicated as a node label.

Moreover, iDILInet's pull-down menus enable users to select iDILI association type (*i.e.*, Risk or Protective) and gene names, ranked in a descending order by the total number of studies citing each gene in the selected set. The drug categories are also organized according to the user's selection and reflect the overall number of studies for the chosen drug-associated polymorphisms. Furthermore, users can restrict genes expressed in the liver based on data from the HPA database. After completing the usability test, both experts and non-experts found iDILInet to be a fast, readable, easy-to-use, intuitive, and useful tool (Supporting Document S2). iDILInet can be accessed *via* the application web page (http://konulabapps.bilkent.edu.tr:3838/iDILInet/). A detailed use tutorial is presented in Supporting Document S3.

In a first use case of iDILInet, "Both" iDILI association types, shown with red and green edges in the network, respectively, were selected on the left side panel. In the *gene* pull-down menu, genes from CYP450, ABC transporters and UGT families were selected along with "All" drug categories. The resulting network was visualized on the main panel for selected genes across all drug categories, of which Antimycobacterials and Antineoplastic agents had the most connections with variants, with thirteen and seven edges, respectively (Fig. 6A). In the same network, rs1045624 of *ABCB1* gene represented a variant hub with two edges connected to different drugs. Moreover, when the "Show only genes expressed in liver" filter was applied, the updated network contained only genes expressed in hepatocytes, and hovering over a weighted edge displayed the association statistics for the selected triplet (*i.e.*, *CYP2E1;c1/c1;Antimycobacterials*) (Fig. 6B). For any given network, a specific table can be accessed from the *Data Table* tab on top of the network panel, enabling users to visualize further specific details of the studies (Supporting Information Fig. S3).

Another example of iDILInet use is the generation of color-coded visualizations in a network or table format to determine whether a gene has only "Risk" or "Protective" polymorphisms, as in the case of *HLA-A*[175] (Supporting Information Fig. S4). Other genes could also be added using the gene selection box to identify variants associated with selected drugs (Fig. 6A). For example, when *HLA-C* and *HLA-DQB1* were added to *HLA-A*, the three genes were observed to have only risk alleles associated with any drug (Supporting Information Fig. S5). In addition, use of iDILInet helps identify unique gene-variant-drug associations, as exemplified by the *HLA-A-rs111686806-Herbal products-dietary supplements* gene-variant-drug triplet. Thus, iDILInet has proven an accurate extraction and synthesis of information from the systematic review.

4. Discussion

This systematic review provides the most comprehensive synthesis to date of genetic variants associated with iDILI, integrating data from 139 studies and highlighting both well-established and emerging gene-variant associations. By mapping these findings to their biological mechanisms, this work facilitates the identification of key pathways involved in susceptibility and protection. Through the integration of these results into an interactive web platform (iDILInet), we enable the transition from static evidence to dynamic exploration, supporting translational applications in pharmacogenomics.

The most frequently reported genes in the Risk Set were *NAT2*, *HLA-B*, *HLA-DRB1*, *HLA-A*, *HLA-DQB1*, *CYP2E1*, *HLA-C*, *SLCO1B1*, *SOD2*, *MTHFR*, *ABCC2*, *CYP2B6*, and *NOS2*; in the Protective Set, *NAT2*, *ABCB1*, *MTHFR*, *NR1I2*, and *SLCO1B1* predominated. These frequently reported genes are not only prevalent in the literature but also mechanistically relevant, as they participate in key pathways known to be involved in iDILI pathogenesis; namely, drug metabolism, detoxification of reactive intermediates, oxidative stress, immune response, and hepatic transport[3,176-179].

4.1. Drug metabolism

The xenobiotic detoxification system comprises drug-metabolizing enzymes (DMEs) and transporters that together regulate hepatic drug exposure and the formation or clearance of potentially toxic metabolites. Phase I metabolism mainly involves cytochrome P450 enzymes (CYPs) and flavin-containing monooxygenases (FMOs), which may generate reactive intermediates.

Figure 2 Gene Ontology (GO) Biological Process (BP) enrichment analysis for genes associated with iDILI risk (A) and iDILI protection (B). Dot size represents the number of genes involved in each pathway (Count), while the gene ratio corresponds to the proportion of genes involved in the pathway relative to the total number of input genes. Color scale indicates the adjusted *P*-value, from higher significance (red) to lower significance (blue). All pathways shown have an adjusted *P*-value <0.05. For visualization purposes, adjusted *P*-value thresholds were applied to highlight the most enriched terms: $P < 3 \times 10^{-8}$ for the risk-associated set (A), and $P < 1 \times 10^{-4}$ for the protective set (B). Only the most representative categories, based on gene ratio and statistical significance, are displayed.

Table 3 Top enriched KEGG pathways associated with iDILI genetic variants in the Risk and Protective Sets.

Class	Subcategory	ID	Description	Gene ratio	BgRatio	Adjusted *P*-value	*Q* value
Risk set							
OS	Immune system	hsa04659	Th17 cell differentiation	14/68	109/8866	1.38155E-12	6.5908E-13
OS	Immune system	hsa04658	Th1 and Th2 cell differentiation	12/68	93/8866	6.02267E-11	2.8731E-11
M	Xenobiotics biodegradation and metabolism	hsa00982	Drug metabolism—cytochrome P450	11/68	73/8866	8.2677E-11	3.9441E-11
M	Xenobiotics biodegradation and metabolism	hsa00980	Metabolism of xenobiotics by cytochrome P450	11/68	79/8866	1.77283E-10	8.4574E-11
OS	Immune system	hsa04672	Intestinal immune network for IgA production	9/68	50/8866	1.05399E-09	5.0281E-10
M	Xenobiotics biodegradation and metabolism	hsa00983	Drug metabolism—other enzymes	10/68	81/8866	3.83085E-09	1.8275E-09
OS	Immune system	hsa04612	Antigen processing and presentation	10/68	81/8866	3.83085E-09	1.8275E-09
OS	Digestive system	hsa04976	Bile secretion	10/68	90/8866	1.05935E-08	5.0537E-09
M	Lipid metabolism	hsa00140	Steroid hormone biosynthesis	8/68	63/8866	1.76636E-07	8.4265E-08
OS	Immune system	hsa04640	Hematopoietic cell lineage	9/68	100/8866	4.385E-07	2.0919E-07
OS	Digestive system	hsa04981	Folate transport and metabolism	6/68	31/8866	7.46474E-07	3.5611E-07
EIP	Signaling molecules and interaction	hsa04514	Cell adhesion molecules	10/68	160/8866	2.14423E-06	1.0229E-06
OS	Immune system	hsa04660	T Cell receptor signaling pathway	9/68	122/8866	2.14423E-06	1.0229E-06
M	Metabolism of cofactors and vitamins	hsa00830	Retinol metabolism	7/68	68/8866	4.69127E-06	2,238E-06
OS	Endocrine system	hsa04920	Adipocytokine signaling pathway	7/68	70/8866	5.56278E-06	2.6537E-06
Protective set							
OS	Digestive system	hsa04981	Folate transport and metabolism	5/20	31/8866	2.25991E-07	1.2137E-07
OS	Immune system	hsa04612	Antigen processing and presentation	5/20	81/8866	9.58355E-06	5.1469E-06
OS	Digestive system	hsa04976	Bile secretion	5/20	90/8866	1.4427E-05	7.7481E-06
CP	Transport and catabolism	hsa04145	Phagosome	5/20	159/8866	0.000168788	9.0649E-05
EIP	Signaling molecules and interaction	hsa04514	Cell adhesion molecules	5/20	160/8866	0.000168788	9.0649E-05
M	Metabolism of cofactors and vitamins	hsa00670	One carbon pool by folate	3/20	39/8866	0.000521819	0.00028025
OS	Immune system	hsa04672	Intestinal immune network for IgA production	3/20	50/8866	0.001036747	0,00055679
M	Metabolism of cofactors and vitamins	hsa00830	Retinol metabolism	3/20	68/8866	0.002311209	0.00124125
M	Xenobiotics biodegradation and metabolism	hsa00982	Drug metabolism - cytochrome P450	3/20	73/8866	0.00257653	0.00138374
M	Xenobiotics biodegradation and metabolism	hsa00980	Metabolism of xenobiotics by cytochrome P450	3/20	79/8866	0.002965352	0.00159256
M	Xenobiotics biodegradation and metabolism	hsa00983	Drug metabolism—other enzymes	3/20	81/8866	0.003057263	0.00164192
OS	Immune system	hsa04658	Th1 and Th2 cell differentiation	3/20	93/8866	0.004357279	0.00234011
OS	Immune system	hsa04640	Hematopoietic cell lineage	3/20	100/8866	0.004832533	0.00259535
OS	Immune system	hsa04659	Th17 cell differentiation	3/20	109/8866	0.00578046	0.00310444
M	Carbohydrate metabolism	hsa00053	Ascorbate and aldarate metabolism	2/20	30/8866	0.006201375	0.00333049

Gene Ratio: Proportion of genes in the input list annotated with the KEGG term (k/n); BgRatio: Proportion of genes in the background set annotated with the KEGG term (K/N); p.adjust: Adjusted *P*-value from the hypergeometric test, corrected with the Benjamini-Hochberg method (FDR); *Q*-value: Estimated minimum FDR at which the KEGG term would be considered significant, calculated by default Storey's method. A significance threshold of adjusted *P* and $Q < 0.05$ was applied. OS: Organismal systems; M: Metabolism; EIP: Environmental Information Processing; CP: Cellular Processes.

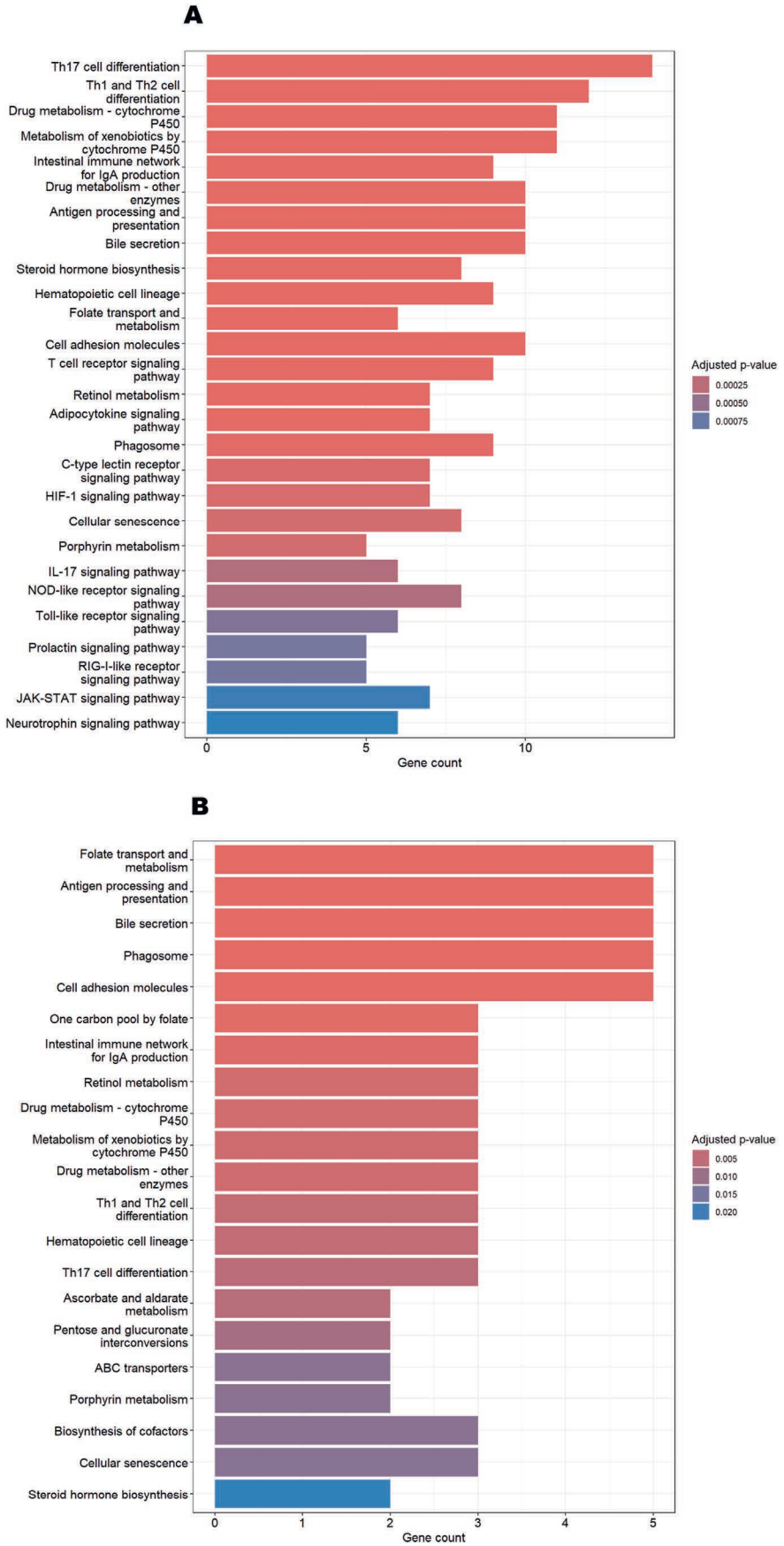


Figure 3 KEGG pathway enrichment analysis for genes associated with iDILI risk (A) and iDILI protection (B). Bar length represents the number of genes involved in each pathway (Gene count), and bar color indicates the adjusted *P*-value, with red colors denoting higher

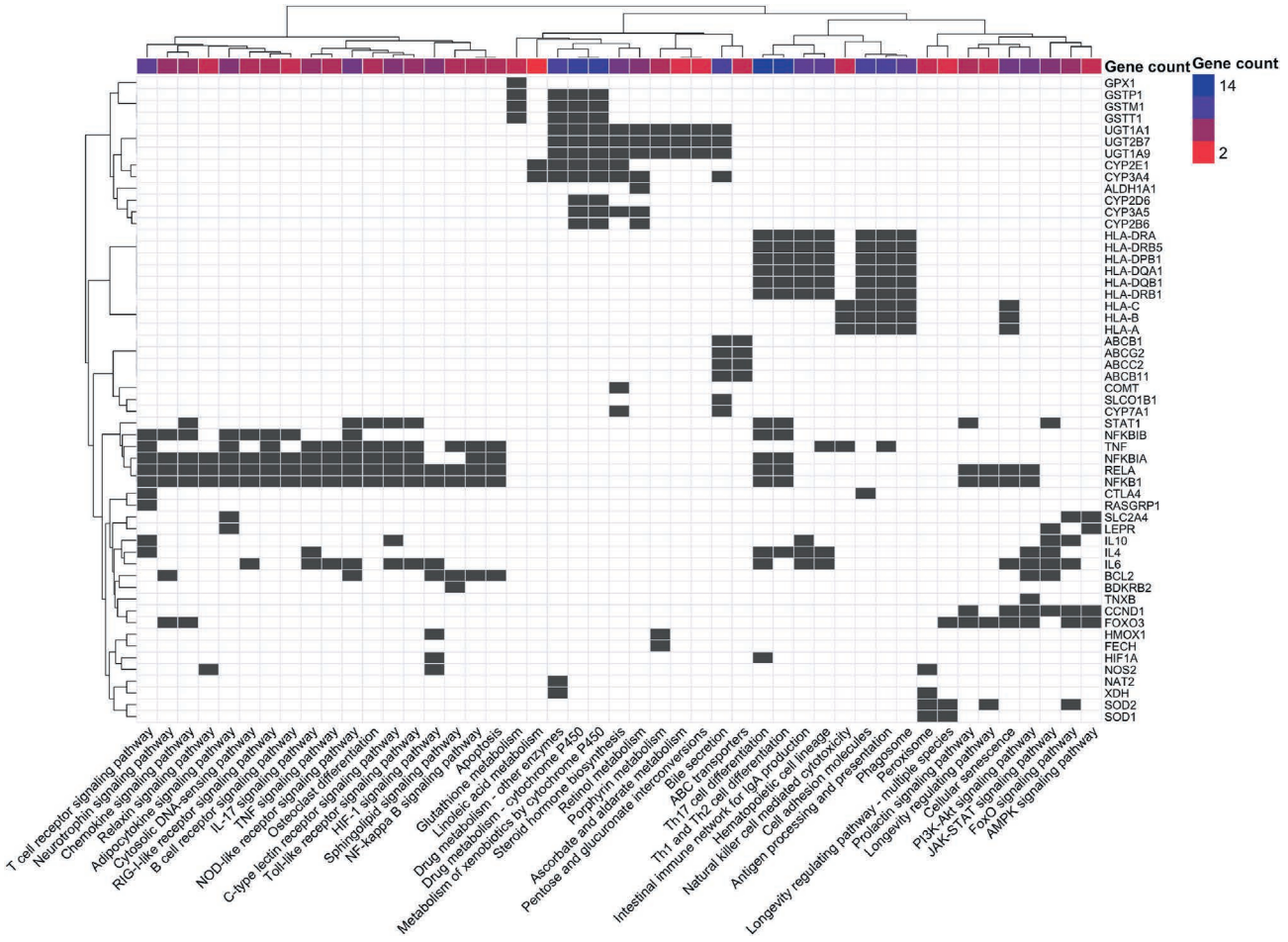


Figure 4 Hierarchical clustering heatmap of genes and enriched KEGG pathways associated with iDILI risk. Rows represent individual genes and columns correspond to significantly enriched pathways (adjusted $P < 0.05$). Black squares indicate the presence of a gene within a given pathway. Top annotations reflect the number of genes involved in each pathway. Clustering was performed to identify shared patterns of gene involvement across pathways.

Phase II enzymes, including glutathione *S*-transferases (GSTs), UDP-glycosyltransferases (UGTs), sulfotransferases (SULTs), and *N*-acetyltransferases (NATs), generally promote detoxification through conjugation reactions. Phase III processes are mediated primarily by ATP-binding cassette (ABC) and solute carrier (SLC) transporters, such as SLCO1B1, which regulate hepatocellular drug uptake and biliary efflux, thereby modulating intracellular drug exposure. Genetic variability across these pathways can shift the balance between bioactivation, detoxification, hepatic accumulation, and immune activation, ultimately modulating susceptibility to iDILI.

Polymorphisms in *CYP450* genes can alter metabolic capacity and the formation of reactive metabolites that contribute to iDILI[180].

An example of a highly polymorphic gene is *CYP2E1*, which is involved in the biotransformation of acetaminophen and isoniazid[181] and generates reactive oxygen species (ROS) in the process. Several promoter-region variants identified in this review, such as *5A/B (rs2031920), and haplotype A4, have been associated with increased *CYP2E1* transcriptional activity due to an amino acid substitution[182,183] or tandem repetitions respectively[184]. Genetic polymorphisms in the 5′ flanking region affect HNF-1 binding and other transcription factors with similar DNA-binding motifs, influencing the transcriptional activity and potentially enhancing ROS-mediated liver damage in the context of anti-TB drug use. In parallel, the intronic variant rs6413432, which also causes an aminoacidic change, might influence protein product by also altering binding affinity of regulatory elements, but available studies have not demonstrated a clear effect.

Similarly, *CYP2B6* rs3745274 (*6), a missense variant which causes aberrant gene splicing, lowering mRNA levels and reducing enzyme activity[185,186], has been associated with increased iDILI risk in patients receiving antiviral drugs[67,104,117]. This effect likely results from higher drug concentrations, impaired metabolism and prolonged exposure to hepatotoxic drug intermediates. Variants in the *POR* gene, such as rs3898649, may further modulate the activity of CYP enzymes in a substrate-specific manner, altering susceptibility to hepatotoxicity,

significance. A significance threshold was applied to enhance visualization: adjusted $P < 0.001$ for the risk-associated set (A), and adjusted $P < 0.05$ for the protective set (B). Only the top enriched pathways are shown in each panel.

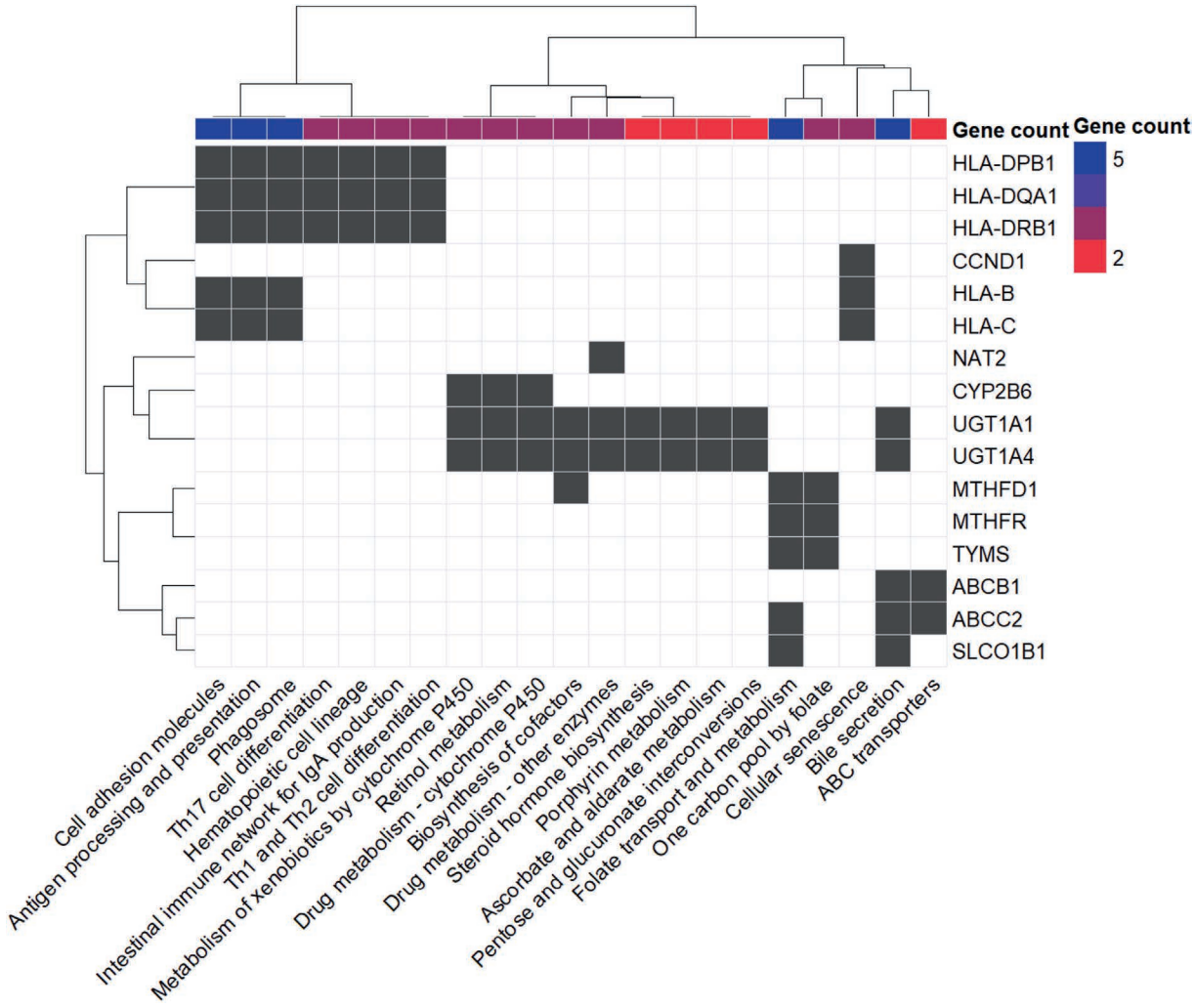


Figure 5 Hierarchical clustering heatmap of genes and enriched KEGG pathways associated with iDILI protection. Rows represent individual genes and columns correspond to significantly enriched pathways (adjusted $P < 0.05$). Black squares indicate the presence of a gene within a given pathway. The top color scale reflects the number of genes involved in each pathway. Clustering was performed to identify shared patterns of gene involvement across pathways.

particularly in anti-TB therapies[73]. Other *POR* variants have been identified to modulate CYP metabolic activity in patients[187,188] and in *in vitro* studies[189,190], although their effects remain inconsistently characterized.

Regarding Phase II metabolism, *NAT2* gene has been extensively studied, while the UGT and GST families have also been explored, though to a lesser extent, in the context of hepatic toxicity[191,192]. Reduced or null activity of these detoxifying enzymes may lead to the accumulation of reactive metabolites and a subsequent increase in oxidative stress and cellular damage.

In the present research, NAT2 was the phase II enzyme most frequently reported in the literature to be associated with iDILI, mainly due to anti-TB drugs. Functional polymorphisms in *NAT2* gene determine drug-metabolizing phenotypes, due to different acetylation status, with important consequences in drug and xenobiotic toxicity. Phenotypes are classified as fast, slow, or intermediate acetylators, originating from single variants or combinations. Slow acetylator phenotypes have been evaluated in human hepatic tissue[193] as well as in models, where the majority of polymorphisms have demonstrated to lower enzyme activity by reducing protein stability (translated to lower high life), maintaining equal mRNA levels. Others, alter substrate coenzyme A affinity, resulting in lower catalytic activity with some substrates[194,195].

NAT2 is the principal enzyme involved in isoniazid metabolism; however, there is controversy regarding the relationship between acetylator status and hepatotoxicity[196], probably due to interethnic variability[197]. *NAT2* acetylator status determines the formation and further detoxification of acetylhydrazine derived from isoniazid, while hydrazine may also be generated through *NAT2*-independent pathways. Both metabolites can undergo bioactivation by CYPs, particularly *CYP2E1*, to reactive species, thereby linking *NAT2*-and CYP-dependent pathways in the pathogenesis of isoniazid-induced liver injury[198]. Therefore, combined slow *NAT2* acetylation with changes in CYP-mediated bioactivation, can also favor specific hepatotoxic scenarios. In any case, this systematic review supports a consistent association between the slow acetylator status and increased iDILI risk, likely due to reduced metabolic clearance and increased hepatic accumulation of reactive derivatives. In fact, some studies report up to

Table 4 Catalog of genes associated with iDILI risk or protection, grouped by biological function.

Gene	NCBI ID	Description	Ref.
Drug metabolizing enzymes (DMEs)			
Phase I (CYP family and associated enzymes)			
POR[a]	5447	Cytochrome p450 oxidoreductase	73
CYP2E1[a]	1571	Cytochrome P450 family 2 subfamily E member 1	66,102,114,133,135,145,150
CYP3A5[a]	1577	Cytochrome P450 family 3 subfamily A member 5	95
CYP3A4[a]	1576	Cytochrome P450 family 3 subfamily A member 4	153
CYP2B6[c]	1555	Cytochrome P450 family 2 subfamily B member 6	39,67,69,104,117
CYP2D6[a]	1565	Cytochrome P450 family 2 subfamily D member 6	139,156
CYP7A1[a]	1581	Cytochrome P450 family 7 subfamily A member 1	146
Phase II (conjugation)			
UGT1A1[c]	54658	UDP glucuronosyltransferase family 1 member A1	52,100,144
UGT1A4[b]	54657	UDP glucuronosyltransferase family 1 member A4	59
UGT1A9[a]	54600	UDP glucuronosyltransferase family 1 member A9	99
UGT2B7[a]	7364	UDP glucuronosyltransferase family 2 member B7	74
GSTM1[a]	2944	Glutathione *S*-transferase mu 1	46,75,76,102
GSTT1[a]	2952	Glutathione *S*-transferase theta 1	46,75,102,135
GSTP1[a]	2950	Glutathione *S*-transferase pi 1	163
NAT2[c]	10	*N*-Aetyltransferase 2	42,51,63,66,67,70,71,77,81,90,94,97,98, 102,107,111,121,133,138,145,149,154, 159,161,164,165,172
Transporters			
ABCC2[c]	1244	ATP binding cassette subfamily C member 2	36,38,45,55,74
ABCB11[a]	8647	ATP binding cassette subfamily B member 11	121
ABCB1[c]	5243	ATP binding cassette subfamily B member 1	47,56,60,67
ABCG2[a]	9429	ATP binding cassette subfamily G member 2	152
SLCO1B1[c]	10599	Solute carrier organic anion transporter family member 1B1	36,44,52,78,83,88,128
SLC2A4[a]	6517	Solute carrier family 2 member 4	78
SLC19A1[a]	6573	Solute carrier family 19 member 1	54,85
SLC13A1[a]	6561	Solute carrier family 13 member 1	101
SLC22A2[b]	6582	Solute carrier family 22 member 2	68
Antioxidant enzymes and related to oxidative stress			
SOD1[a]	6647	Superoxide dismutase 1	141
SOD2[a]	6648	Superoxide dismutase 2	72,76,106,130,152
GPX1[a]	2876	Glutathione peroxidase 1	106
HMOX1[a]	3162	Heme oxygenase 1	105
TXNRD1[a]	7296	Thioredoxin reductase 1	109
NOS2[a]	4843	Nitric oxide synthase 2p	57,123,147
Transcription factors, nuclear receptors and transport, genomic preservation and regulation			
NR3C1[a]	2908	Nuclear receptor subfamily 3 group C member 1	84
NFE2L2[a]	4780	NFE2 like bZIP transcription factor 2	40
NR1I2	8856	Nuclear receptor subfamily 1 group I member 2	43,50,53,108
BACH1[a]	571	BTB domain and CNC homolog 1	123
MAFK[c]	7975	MAF bZIP transcription factor K	57,123
MAFF[b]	23764	MAF bZIP transcription factor F	40
HIF1A[a]	3091	Hypoxia inducible factor 1 subunit alpha	124
RELA[a]	5970	RELA proto-oncogene, NF-κB subunit	140

NFKB1[a]	4790	Nuclear factor kappa B subunit 1	53
NFKBIA[a]	4792	NFKB inhibitor alpha	140
NFKBIB[a]	4793	NFKB inhibitor beta	140
FOXO3[a]	2309	Forkhead box O3	118
XPO1[a]	7514	Exportin 1	148
ERCC1[a]	2067	ERCC excision repair 1, endonuclease non-catalytic subunit	113
XRCC3[b]	7517	X-ray repair cross complementing 3	41
POLG[a]	5428	DNA polymerase gamma, catalytic subunit	136
MIR1208[b]	100302281	microRNA 1208	37
Cytokines, HLA antigens, and immune regulators			
Cytokines			
IL10[a]	3586	Interleukin 10	79,169
IL4[a]	3565	Interleukin 4	79
IL6[a]	3569	Interleukin 6	147
LTA[b]	4049	Lymphotoxin alpha	42
TNF[a]	7124	Tumor necrosis factor	110
Major histocompatibility complex (HLA)			
HLA-A[a]	3105	Major histocompatibility complex, class I, A	5,87,91,119,125-127,129,132,134,151
HLA-B[c]	3106	Major histocompatibility complex, class I, B	49,51,82,91,96,125-127,129,132,137,151,155,173
HLA-C[c]	3107	Major histocompatibility complex, class I, C	49,51,58,119,126,132,155,173
HLA-DQA1[c]	3117	Major histocompatibility complex, class II, DQ alpha 1	42,58,93,131,158
HLA-DQB1[a]	3119	Major histocompatibility complex, class II, DQ beta 1	87,93,125,131,132,155,173
HLA-DPB1[c]	3115	Major histocompatibility complex, class II, DP beta 1	65,126,155
HLA-DRA[a]	3122	Major histocompatibility complex, class II, DR alpha	173
HLA-DRB1[c]	3123	Major histocompatibility complex, class II, DR beta 1	49,51,58,61,65,87,91,93,125,131,132,151,155,158,162,173
HLA-DRB5[a]	3127	Major histocompatibility complex, class II, DR beta 5	131
Immune signaling and regulation			
CTLA4[a]	1493	Cytotoxic T-lymphocyte associated protein 4	170
PTPN22[a]	26191	Protein tyrosine phosphatase non-receptor type 22	173
LRBA[a]	987	LPS responsive beige-like anchor protein	5
RASGRP1[a]	10125	RAS guanyl releasing protein 1	101
STAT1[a]	6772	Signal transducer and activator of transcription 1	166
Cell cycle regulators, proliferation and apoptosis			
CCND1[c]	595	Cyclin D1	48,80
BCL2[a]	596	BCL2 apoptosis regulator	122
TGFBRAP1[a]	9392	Transforming growth factor beta receptor associated protein 1	143
CYTOR[a]	112597	Cytoskeleton regulator RNA	112
Other genes related to cellular signaling and diverse functions			
Cell dynamics, morphology and polarity			
ARHGAP24[a]	83478	Rho GTPase activating protein 24	101
PARD3B[a]	117583	Par-3 family cell polarity regulator beta	101
RIPOR2[a]	9750	RHO family interacting cell polarization regulator 2	103
TNXB[a]	7148	Tenascin XB	93
KCNIP4[a]	80333	Potassium voltage-gated channel interacting protein 4	101
TENM2[c]	57451	Teneurin transmembrane protein 2	62
ASTN2[a]	23245	Astrotactin 2	51
SYT14[a]	255928	Synaptotagmin 14	116
BDKRB2[a]	624	Bradykinin receptor B2	62

(*continued on next page*)

Table 4 (*continued*)

Gene	NCBI ID	Description	Ref.
Metabolism-associated enzymes and others			
MTHFR[c]	4524	Methylenetetrahydrofolate reductase	54,55,64,86,115,157
MTRR[c]	4552	5-Methyltetrahydrofolate-homocysteine methyltransferase reductase	45,171
MTHFD1[b]	4522	Methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1	55
FECH[a]	2235	Ferrochelatase	92
XDH[a]	7498	Xanthine dehydrogenase	147,168
TYMS[c]	7298	Thymidylate synthetase	55,142
PNPLA3[a]	80339	Patatin like phospholipase domain containing 3	160
ALDH1A1[a]	216	Aldehyde dehydrogenase 1 family member A1	120
COMT[a]	1312	Catechol-*O*-methyltransferase	167
ST6GALI[a]	6480	ST6 beta-galactoside alpha-2,6-sialyltransferase 1	96
LEPR[a]	3953	Leptin receptor	89

Genes were considered associated with increased iDILI risk or protection when variants showed OR $>$ 1 or OR $<$ 1, respectively, with an adjusted *P*-value $\leq$0.05.
[a]Genes with variants associated with increased iDILI risk.
[b]Genes with protective variants.
[c]Genes with both risk and protective associations.

88% of isoniazid clearance variability and recommend genotyping-based drug dosage[199].

4.2. *Transporter proteins*

Hepatic transporters regulate the uptake and efflux of drugs and their metabolites, and genetic variants affecting their function can modulate intracellular concentrations, impacting iDILI susceptibility. As an example, *ABCC2* (encoding the MRP2 efflux transporter) is a canalicular efflux transporter expressed in hepatocytes that mediates biliary excretion of bilirubin conjugates and multiple drug derivatives. Reduced transporter function can impair the excretion of conjugated bilirubin, glucuronides and glutathione conjugates, leading to intrahepatic accumulation, promoting cholestasis and hyperbilirubinemia[200].

ABCC2 variants rs717620[74] and rs3740065[55] have been suggested to impair transport activity and increase iDILI risk[201]. Rs717620 has been hypothesized to modulate transporter expression *in vitro* by disrupting the binding of two transcription factors at the promoter level, ETS1 and SOX9[202], although other studies indicate haplotype-dependent effects[203]. Conversely, rs3740066 appears to confer a protective effect[38], while rs2273697 shows population-dependent effects[36,45]. These polymorphisms have been extensively studied in the context of drug resistance in epilepsy and cancer, often with inconsistent results, highlighting the complexity of interpreting transporter-related genetic variations.

Interestingly, *ABCB1* (MDR1) variant rs1045642, frequently associated with altered mRNA stability and protein expression[204], has shown a protective effect in multiple iDILI studies. Although MDR1 represents a secondary hepatic drug efflux transporter, primarily related to non-conjugated and lipophilic drug elimination, this variant might favor drug efflux and reduce intracellular drug accumulation. In addition, MDR1 is endogenously expressed in cytotoxic lymphocytes and is required for normal $CD8^+$ T cell activation, survival, and mitochondrial function by limiting oxidative stress during early activation, indicating a direct role in cell-mediated immunity beyond xenobiotic efflux[205].

SLCO1B1, encoding the OATP1B1 uptake transporter, has been linked to both increased susceptibility and protection to iDILI. This transporter mediates organic anion uptake from the portal circulation into hepatocytes, thereby regulating intracellular drug concentrations and hepatic clearance. Missense variants rs4149056 and rs2306283 have been associated with reduced transport activity[206] and a higher risk of iDILI in the context of several drugs, including anti-TB drugs[52,83], rifampicin[128], methimazole[44], and methotrexate[88]. Reduced transporter function may influence intrahepatic drug accumulation and systemic exposure. On the other hand, the *1b allele (rs2306283), functioning as a gain-of-function variant, appears protective in statin-related toxicity, reducing plasma concentrations and hepatic exposure[207]. Notably, rs11045879, another *SLCO1B1* variant, has been associated with reduced risk of pemetrexed- and cisplatin-induced liver injury. Still, conflicting evidence exists for its role in methotrexate-related hepatotoxicity[208], likely due to a reduced capability of the transporter to decrease the level of this drug.

The influence of transporter genetic variants on iDILI susceptibility is likely determined not only by single associations but also by the interplay between hepatic uptake and efflux transporters that govern intracellular drug accumulation and biliary elimination.

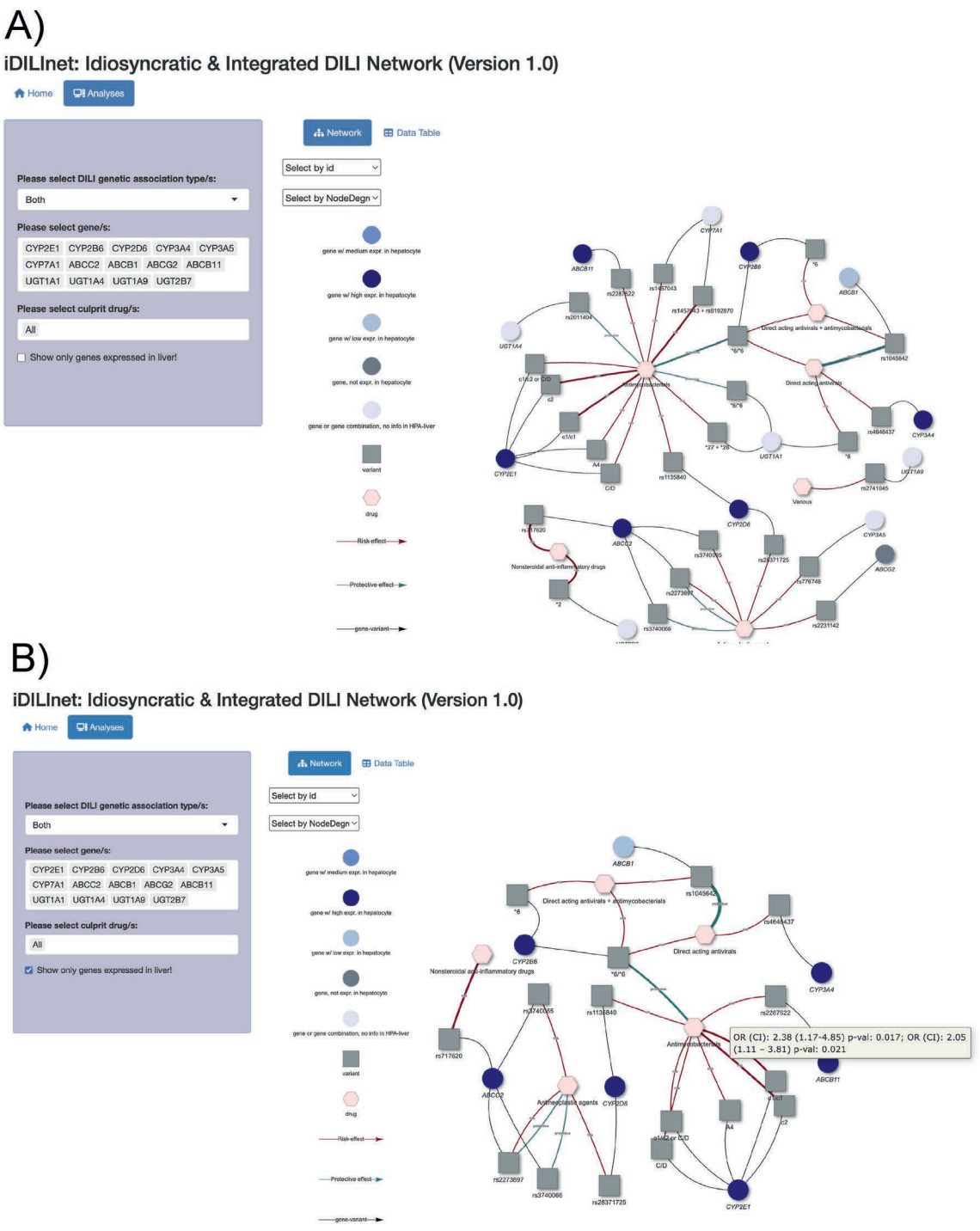


Figure 6 (A) Overview of the iDILInet interface, showing the gene−drug interaction network. The left side panel allows users to filter genes based on their association type (risk, protective, or both), select specific genes or culprit drugs, and restrict the display to genes expressed in the liver. The right panel displays the interactive network, where nodes and edges are styled according to their biological roles and associations. (B) iDILInet interface view focused on a liver-expressed subnetwork. Circular nodes represent genes expressed in hepatocytes, with dark blue indicating high expression levels based on The Human Protein Atlas. Pink hexagons represent drugs. Red and green edges denote statistically significant risk and protective associations, respectively, between specific gene variants and drugs. The network highlights interconnected modules relevant to iDILI susceptibility.

4.3. Immune system and HLA associations

The adaptive immune system plays a central role in the pathogenesis of iDILI, with HLA alleles functioning as key modulators of antigen presentation and T-cell activation. In contrast to the often drug-specific nature of metabolic gene variants, HLA associations tend to be stronger[12] and may span structurally unrelated compounds, suggesting a broader immunogenetic susceptibility. In this study, the most frequently reported HLA genes associated with iDILI were *HLA-B*, *HLA-DRB1*, *HLA-A*, *HLA-DQB1*, and *HLA-C*.

4.3.1. HLA class I genes

HLA class I genes (*HLA-A*, *HLA-B*, *HLA-C*) are widely expressed and present intracellular antigens to $CD8^+$ T cells. Among these, *HLA-A**02:01 emerged as the most commonly reported allele, particularly in association with amoxicillin-clavulanate (AC)-induced liver injury. Functional studies have confirmed its immunogenic role through T-cell activation and IFN-γ release upon drug exposure *in vitro*. This allele has also been linked to iDILI induced by methimazole and other drugs in Asian populations[119,134]. Its ability to bind a wider range of peptide lengths (up to 15 residues) may enhance the likelihood of presenting neoantigens formed by drug-protein adducts[209], potentially influencing iDILI development.

The *HLA-B* gene is the most polymorphic HLA class I gene, and different alleles have been associated with increased iDILI risk. *HLA-B**57:01 is one of the most studied alleles due to its strong association with flucloxacillin-induced iDILI and abacavir hypersensitivity. Although its positive predictive value is limited[96], *in vitro* studies support its mechanistic involvement through T-cell activation[210] and cross-reactivity with structurally similar antibiotics such as piperacillin and AC. Other *HLA-B* alleles have also been linked to iDILI. *HLA-B**35:01 allele has been associated to herb-induced liver injury (HILI) due to *Polygonum multiflorum*, *Garcinia cambogia*, and green tea, especially in Chinese populations, making it a promising biomarker despite unclear mechanisms[211]. The *35:01 allele has also been associated with TMP-SMX iDILI, but only in African American carriers[126]. Interestingly, *HLA-B**53:01, similar to *35:01, is linked to iDILI from antiepileptics in African Americans, suggesting shared immune mechanisms among similar *HLA-B* alleles[127] and highlighting the role of ethnicity and genetics in iDILI.

The *HLA-C* gene, although less frequently studied, interacts with KIR receptors on NK cells[212] and may contribute to immune regulation. *HLA-C**03:02 is associated with methimazole-induced liver injury. Although molecular docking suggests this drug does not directly bind HLA protein, its metabolites may form adducts with host proteins[119]. Limited knowledge of these metabolites hampers understanding of binding interactions with HLA, leaving a gap in methimazole iDILI mechanisms. *HLA-C**08:02 has also been associated with TMP-SMX iDILI, dependent on linkage with *HLA-B**14:01. In addition, despite *HLA-C**12:03 being linked to infliximab-induced liver injury, it may represent a haplotypic marker rather than a causative allele[155].

4.3.2. HLA class II genes

HLA class II genes (*HLA-DRB1*, *HLA-DQB1*) are expressed on antigen-presenting cells (APC) and present extracellular antigens to $CD4^+$ T cells. As with HLA class I genes, the biological basis underlying the associations between alleles of HLA class II genes and the risk of developing iDILI may rely on alterations of the peptide-binding groove of each allele. *HLA-DRB1**15:01 and *HLA-DQB1**06:02 have been repeatedly associated with iDILI caused by AC and lumiracoxib. Interestingly, both alleles are in strong linkage disequilibrium and form a haplotype commonly associated with cholestatic or mixed liver injury patterns. Moreover, this haplotype has also been associated with lower mortality in iDILI patients[125], suggesting a complex role in modulating disease severity. For *HLA-DRB1**15:01, it has been suggested that this allele could serve as a genetic marker to guide clinical decisions aimed at preventing AC-induced liver injury[11], and it may also confer protection against autoimmune hepatitis[213].

While many of the functional consequences of HLA polymorphisms remain to be elucidated, their consistent association with specific drug reactions points to an essential role in immune recognition and liver injury. Future studies combining HLA genotyping with T-cell functional assays and structural modelling will be critical to understand their contribution to iDILI susceptibility.

4.4. Oxidative stress

Polymorphisms in genes regulating oxidative stress and redox balance have also been implicated in iDILI susceptibility. Inadequate detoxification of ROS can result in cellular damage and trigger inflammatory or apoptotic pathways[176], playing a key role in the disease.

Genetic polymorphisms of key enzymes like *SOD1*, *SOD2*, *CAT*, *GPX*, and *TXNRD1* have already been associated with increased iDILI risk. These enzymes constitute an integrated antioxidant network that sequentially detoxifies ROS and maintains cellular redox homeostasis. SOD1 and SOD2 catalyze the conversion of superoxide to hydrogen peroxide in the cytosol and mitochondrial matrix, respectively, after which catalase and glutathione peroxidases detoxify hydrogen peroxide, while TXNRD1 sustains thioredoxin in its reduced state to preserve cellular redox homeostasis[214-217]. Among these, *SOD2* stands out as a key mitochondrial antioxidant. The rs4880 variant causes an aminoacidic substitution at the mitochondrial targeting sequence of SOD2, altering import efficiency and resulting in a 30%−40% reduction in effective mitochondrial enzymatic activity[218]. This variant has been associated with increased iDILI risk in patients treated with drugs known to generate ROS during metabolism, such as doxorubicin[219], isoniazid[220], and paracetamol[221]. This review has also gathered the association of this variant with iDILI due to other drugs such as asparaginase[72], and amiodarone[130].

NOS2, encoding inducible nitric oxide synthase (iNOS), is frequently implicated in this context, as excess NO and its derivatives can trigger mitochondrial damage and apoptosis[222] and, by modulating CYP activity, react with superoxide from SOD2 deficiency to form toxic compounds[223]. Several intronic variants (*e.g.*, rs11080344, rs944725, rs3794764, rs3730013, rs9906835) have been associated with increased risk of iDILI, particularly from anti-TB drugs. While their functional effects are not fully characterized, these polymorphisms may enhance *NOS2* expression, increasing the production of nitric oxide and reactive nitrogen species, which can interact with mitochondrial ROS to exacerbate cellular injury. Nitric oxide also plays an important immunomodulatory role in regulating inflammatory responses. Genetic variants associated with marked reduced nitric oxide production may favor sustained inflammatory activation, thereby indirectly increasing susceptibility to iDILI[224].

MTHFR, a gene involved in folate and methionine metabolism[225,226], has also been linked to iDILI. Many variants reduce its activity[227,228], increasing plasma homocysteine and

susceptibility to drugs like methotrexate that rely on folate metabolism, due to decreased tetrahydrofolate regeneration. Notably, the missense variant rs1801133 results in an amino acid substitution within the enzyme's catalytic domain, increasing thermolability and reducing its affinity for the cofactor FAD, leading to a 35% decrease in enzymatic activity per mutated allele[227]. This reduction in MTHFR activity alters methylation homeostasis, and may increase susceptibility to hepatotoxicity, particularly in response to antifolate drugs such as methotrexate[64,86,115,157]. Interestingly, a second variant, rs1801131, appears to confer a protective effect in some studies[54,64]. This protective association may reflect the relatively mild functional impact of rs1801131 when present alone, whereas compound heterozygosity with the risk variant rs1801133 has been associated with a more pronounced reduction in MTHFR enzymatic activity, to approximately 50%−60%, thereby increasing susceptibility to iDILI[229]. These contrasting effects highlight the importance of allele-specific functional consequences and their mechanistic interpretation.

4.5. Nuclear receptors

Nuclear receptors are key regulators of drug metabolism, functioning as xenobiotic-sensing transcription factors that coordinate hepatic detoxification pathways[230]. In particular, the pregnane X receptor (*NR1I2*/PXR) and the constitutive androstane receptor (CAR) regulate the expression of major drug-metabolizing enzymes, including cytochrome P450 isoforms (*e.g.*, CYP3A4/3A5, CYP2B6, CYP2C9), as well as phase II enzymes and transporters involved in hepatic drug clearance[231]. Consequently, interindividual variability in PXR and CAR activity may substantially modulate hepatic drug exposure and susceptibility to iDILI.

PXR is a highly promiscuous nuclear receptor that can be activated by a wide range of structurally diverse xenobiotics and endogenous compounds, including bile acids. Depending on the gene-drug context, activation of this regulatory network may exert either protective or risk-modifying effects. On one hand, induction of detoxification and efflux pathways may enhance clearance of potentially harmful compounds. On the other hand, increased expression of specific CYP enzymes may enhance the formation of reactive intermediates. For example, rifampicin, a potent PXR activator, induces CYP2E1 and other metabolizing enzymes and has been associated with increased risk of liver injury during isoniazid co-therapy, likely due to enhanced bioactivation and accumulation of reactive metabolites[232,233].

Beyond xenobiotic metabolism, PXR activation has also been shown to promote lipogenic remodeling and steatosis in human hepatic models, a phenotype that may increase hepatic vulnerability to drug-induced toxicity[234]. Nuclear receptors also modulate immune and inflammatory pathways[235]. Crosstalk between PXR/CAR signaling and NF-κB has been shown to influence cytokine expression and hepatic inflammatory responses[236].

In this context, genetic variants in *NR1I2* (PXR), such as rs3814055, have been associated with increased susceptibility to iDILI, whereas other variants (*e.g.*, rs3732361, rs3814058, rs6785049) have shown protective associations in specific drug settings[43,108]. These findings suggest that genetic variation in nuclear receptors may indirectly shape hepatic resilience to xenobiotic stress by modulating transcriptional control of detoxification and inflammatory pathways.

4.6. Protective-only genetic variants in iDILI

Although most genetic studies on iDILI focus on risk alleles, variants with a purely protective association are rare. In the present study, genes such as *MIR1208*, *MAFF*, *XRCC3*, *LTA*, *MTHFD1*, *UGT1A4*, and *SLC22A2* appeared exclusively linked to protection against iDILI.

For instance, rs2648841 in the premature sequence of hsa-miR-1208 changes G to T, potentially destabilizing the miRNA hairpin, reducing mature miRNA levels, and thereby increasing expression of targets involved in methotrexate metabolism (*DHFR*, *MTR*, *MTHFR*) and transport (*SLCO1A2*, *SLC46A1*), offering a protective effect[37]. However, other studies suggest this substitution may not alter miRNA structure[237].

XRCC3 encodes a DNA repair protein essential for homologous recombination[238]. The TT genotype of rs861539, a missense variant, has been associated with lower risk of antineoplastic-related iDILI in acute myeloid leukemia (AML) patients[41], possibly because impaired DNA repair in immune cells[239] could reduce immune-mediated liver injury.

LTA, encoding lymphotoxin alpha, plays roles in inflammation, adaptive immunity, lymphoid tissue development, and T-cell and dendritic cell regulation[240-243]. The variant rs1041981 affects both *LTA* and a nearby non-coding RNA (LOC100287329), potentially destabilizing the protein and altering gene expression[244], though the function of the non-coding RNA remains unclear.

Together, these findings highlight protective variants, though less studied, can offer mechanistic insights and potential avenues for therapeutic strategies.

4.7. Genes underrepresented in literature but overrepresented in enrichment analyses

Despite receiving limited attention in most iDILI genetic studies, certain genes may still play an important role in the development of the disease, since they stood out in our enrichment analyses as significantly overrepresented. Members of the UGT family and components of the NF-κB signaling pathway have central roles in hepatic detoxification, inflammation, and immune regulation. Their pivotal functions, together with a high degree of genetic variability, make them plausible candidates for influencing individual susceptibility or resistance to iDILI.

UGT enzymes catalyze substrate glucuronidation, accounting for approximately 35% of Phase II xenobiotic clearance in the liver[245]. At the mRNA level, multiple isoforms, particularly *UGT1A1*, *UGT1A4*, *UGT1A9*, and *UGT2B4*, *UGT2B7*, *UGT2B15*, are highly expressed in human liver tissue[246]. Functional interplay among UGT isoforms can modulate overall enzymatic capacity, making activity dependent on both isoform composition and substrate specificity[247]. For instance, *UGT1A1*, the principal enzyme for bilirubin clearance, harbors 113 variants influencing drug metabolism. The *UGT1A1**28 allele (a single TA insertion in the TATA box) significantly reduces enzymatic activity and is strongly associated with Gilbert syndrome and irinotecan-induced toxicity[248]. As a result, several clinical guidelines now recommend *UGT1A1* genotyping to guide dosing.

Other specific UGT superfamily variants have been associated with iDILI, including *UGT2B7**2 and diclofenac[74,249], *UGT1A9* rs2741045 variant with various drugs[99], *UGT1A1**6 with daclatasvir and asunaprevir-related iDILI[100], or *UGT1A1**27 and *28 variants with anti-TB drugs[144]. These associations suggest that

reduced glucuronidation capacity can impair drug clearance, prolonging hepatic exposure to reactive metabolites and increasing the risk of injury.

In parallel, the NF-κB signaling pathway, comprising *NFKB1*, *NFKBIA*, *NFKBIB*, and *RELA*, along with downstream effectors such as *TNF*, *IL6*, *STAT1*, and *BCL2*, was also overrepresented in enrichment analyses. NF-κB is a family of inducible transcription factors that regulate genes related to inflammation, immunity, and cell processes like proliferation, apoptosis, and differentiation[250,251]. In response to cellular stress, activation of NF-κB in hepatocytes and hepatic immune cells, including Kupffer and stellate cells, induces the transcription of pro-inflammatory cytokines and chemokines, thereby promoting immune cell recruitment and amplification of local inflammatory responses. At the same time, NF-κB signaling modulates hepatocellular survival and death pathways, influencing susceptibility to immune-mediated injury. In the context of drug exposure, maintained or dysregulated NF-κB activation may contribute to a sustained pro-inflammatory hepatic microenvironment that facilitates the propagation and persistence of immune-mediated liver damage[252]. Consistently, *in vitro* studies support the involvement of the NF-κB-mediated signaling in drug induced liver injury. Inhibition of NF-κB, signaling, along with an enhanced NRF2-driven stress response, predisposes hepatocytes to cytokine-induced apoptotic cascades, emphasizing the importance of NF-κB in preserving hepatocellular tolerance to toxic derivatives[253].

For NF-κB, T alleles of rs78872571 and rs4647992 in *NFKB1*[53] have been associated with a higher risk of iDILI due to anti-TB drugs, supporting a role for this signaling pathway in modulating immune-mediated liver damage. However, in contrast to other well-characterized variants such as rs28362491[254], which has been shown to increase promoter activity and transcription, there is currently no direct functional evidence demonstrating the impact of rs78872571 or rs4647992 on NF-κB signaling, and particularly in the context of drug-induced toxicity.

By contrast, *TNF* 308G/A polymorphism[110] has been functionally characterized and shown to increase promoter transcriptional activity, resulting in enhanced TNF-α production following immune stimulation[255,256], which has been associated with iDILI.

Lastly, there is functional evidence for promoter variants in *IL6* such as rs1800796[147], although their effects appear to be context and cell-lineage dependent[257]. This variant, located at promoter level, has been associated with increased IL-6 expression at both mRNA and protein levels in human hepatic parenchymal cells[258]. This is particularly relevant in iDILI, as IL-6 activates STAT3 signaling in hepatocytes, which can exert hepatoprotective effects during acute injury but may contribute to sustained inflammatory amplification when persistently activated.

4.8. Mechanistically relevant but underreported genes

Although their association with iDILI has been reported only sporadically in the literature, several genes merit attention due to the critical biological mechanisms they regulate. Many of these genes encode transcription factors and regulatory proteins that govern antioxidant defenses, xenobiotic metabolism, and immune responses, pathways directly implicated in liver injury and protection.

ROS and reactive nitrogen species (RNS) are normally detoxified by enzymes such as GSTs, *NQO1*, and *HMOX1*[259], whose promoters contain antioxidant-responsive elements (AREs). The expression of these enzymes is tightly regulated by transcription factors such as NRF2, BACH1[260], and small Maf proteins[261], which act as molecular switches to activate or repress antioxidant pathways. Disruption of these regulatory systems can impair redox homeostasis, destabilize proteostasis, and facilitate the onset of hepatotoxicity.

NRF2, encoded by the *NFE2L2* gene, is a particularly relevant example. Beyond orchestrating the hepatic response to oxidative and xenobiotic stress, NRF2 regulates inflammation, autophagy, and mitochondrial maintenance, suggesting a possible role in iDILI[262]. Upon activation, it induces a broad transcriptional program encompassing Phase I (*NQO1*, reductases, CYPs), Phase II (GST, UGT, *HMOX1*), and Phase III (MDR, BCRP, ABC transporters) metabolism, thereby strengthening the liver's detoxification capacity[263]. It also modulates glucose metabolism *via GLUT1* induction[264], promotes autophagy-related gene expression[265], and preserves mitochondrial DNA integrity, an essential factor in controlling cell death and inflammatory activation. Both genetic and pharmacological NRF2 activation have been shown to reduce inflammatory lesions in the liver[266], supporting its candidacy as a mechanistic contributor to iDILI susceptibility or protection. In this systematic review, several *NFE2L2* polymorphisms have been found, including rs4243387, rs2001350, and rs6726395. However, these intronic variants lack direct functional validation, and their mechanistic interpretation therefore remains limited. These associations may reflect linkage disequilibrium with regulatory elements that influence inflammatory or stress-response pathways, rather than direct causal effects. Further functional studies will be required to clarify their biological relevance in iDILI susceptibility.

Finally, genes encoding glutathione *S*-transferases, such as *GSTM1*, *GSTT1*, and *GSTP1*, have been studied for their association with iDILI. Null variants in *GSTT1* and *GSTM1*, alone or combined, have been linked to a higher risk of hepatotoxicity in patients receiving anti-TB treatments[46,75,76,102,135]. At the same time, *GSTP1* rs1695 has been associated with increased risk in similar settings[163]. Interestingly, the role of GSTs has been studied not only as detoxifying enzymes, but also as regulators of the cell cycle and death signalling[267,268]. GST enzymes encoded by *GSTP1* and *GSTM1* have a regulatory role in the mitogen-activated protein (MAP) kinase pathway[269], and the STAT3[270] and mTOR[271] signaling pathways, participating in cell proliferation, inflammation, and death mechanisms in the hepatocyte.

Collectively, these genes demonstrate how variants in detoxification enzymes and immune signaling pathways, even when underrepresented in the literature, may significantly influence iDILI risk through fundamental regulatory functions. Their mechanistic plausibility justifies their prioritization as candidates for targeted, large-scale genomic studies, ideally in the context of international patient cohorts, to clarify their contribution to iDILI pathogenesis.

Importantly, the classification of genes as "risk" or "protective" in this study should not be interpreted as implying uniform effects across all iDILI cases. Genetic associations were reported in specific drug and cohort contexts, and their direction reflects the available evidence for particular pharmacological exposures. Given that absorption, distribution, metabolism, and excretion (ADME) characteristics, primary molecular targets, and off-target interactions differ substantially across drugs, genetic susceptibility must be understood as drug-specific and context-dependent rather than universally applicable. This conceptual framework is essential for avoiding overgeneralization and for guiding future gene-drug-specific investigations.

4.9. Limitations and strengths

The limitations of this research include the wide heterogeneity among the collected studies, particularly in terms of methodology, which limits the feasibility of more powerful quantitative analyses. In addition, several studies reported country of origin rather than clearly defined ethnicity, complicating the interpretation of population-specific associations.

To provide a more structured assessment of this variability, we generated Table S4, which summarizes multidimensional heterogeneity across the most frequently reported iDILI-associated genes. As shown in this overview, variability was evident at multiple levels, including implicated drug classes, ethnic background of study populations, study design (candidate gene studies *vs.* GWAS), and direction of association. Immune-related loci within the HLA region predominantly exhibited drug-specific effects, whereas genes involved in drug metabolism, transport, oxidative stress, and detoxification pathways demonstrated context-dependent or bidirectional associations depending on pharmacological exposure and population background.

Collectively, these patterns underscore that genetic susceptibility to iDILI cannot be interpreted as universally applicable across drugs or populations. Rather, it reflects a complex interaction between host genetics, drug-specific properties, and environmental or clinical modifiers.

A similar degree of variability was observed in demographic reporting. Although age and sex information was available for most studies, reporting formats differed substantially. Overall, iDILI cases predominantly affected adults in mid-life, with reported mean or median ages typically ranging between approximately 35 and 55 years. However, inconsistent age metrics limited direct inter-study comparisons. Sex distribution was likewise variable: while several cohorts reported a slight male predominance, others showed balanced sex proportions or drug-specific female predominance. These differences likely reflect variations in drug exposure patterns, study design, and underlying population characteristics. The lack of standardized demographic reporting precluded structured pooled analyses and represents an additional limitation of the available literature.

However, the primary strength of this research lies in its pioneering, large-scale compilation of all available information on genes, drugs, and genetic polymorphisms associated with iDILI, as well as its exploration of biological pathway interactions in liver damage mechanisms. This will facilitate the development of polygenic risk scores in the future and highlight the importance of further mechanistic studies of genes linked to specific pathways of liver damage, which are currently underexplored in the published literature, establishing new avenues for preclinical research.

Moreover, integrating the results of this review into the iDILInet web server enhances the accessibility and prioritization of genetic variants associated with iDILI by enabling interactive exploration of gene-variant-drug relationships through dynamic network visualization. In line with previous network-based approaches that have incorporated expression datasets such as the HPA for annotation[272], iDILInet integrates hepatocyte-specific expression data to allow filtering and contextual interpretation of genetic associations. In addition, the platform supports the incorporation of new genetic and functional annotations as evidence emerges, ensuring its long-term adaptability and relevance. The multi-partite network framework complements the systematic review by facilitating the identification of complex relationships among genes, variants, and drugs that may not be readily apparent in tabular formats. This approach is broadly applicable to other diseases and pharmacogenomic contexts and may also support future integration of cross-species annotations. Overall, iDILInet advances the recently proposed LSR concept[273] by providing a scalable, sustainable, and functionally enriched resource for the study of genetic susceptibility to iDILI.

4.10. Future perspectives

These findings will contribute to a deeper understanding of iDILI pathophysiology through an integrative approach that emphasizes the role of complex metabolic pathways over the isolated analysis of individual genes. Moreover, these results will support the identification of new functional-orthologous genes, paving the way for the development of novel animal models, such as zebrafish, which have gained prominence in recent years. Finally, the compilation of data into an interactive network and online database offers the scientific community an updated and accessible resource to explore poorly characterized genes and to investigate iDILI mechanisms from a systems biology perspective focused on pathway-level interactions. Building upon this integrative framework, the present study also enables the prioritization of candidate genes for targeted functional validation. Based on enrichment analysis findings and their role in inflammatory and stress-response pathways, we propose a list of candidate genes for future functional investigation, including *RELA*, *NFKB1*, *NFKBIA*, *NFKBIB*, *TNF*, *BCL2*, *FOXO3*, *NFE2L2*, and *STAT1*. These genes are key regulators of pleiotropic pathways that integrate inflammation, oxidative stress responses, and cell survival mechanisms, which collectively underlie major processes involved in iDILI onset and progression. Dysregulation of these pathways may contribute to sustained inflammatory responses and exacerbate susceptibility to drug-induced liver toxicity. Although individual variants within these genes may exert modest effects, their central regulatory roles make them strong candidates for mechanistic studies. Future investigations integrating human genetics with functional assays, transcriptomic profiling, and experimental models will be essential to clarify their contribution to iDILI susceptibility and progression.

5. Conclusions

This systematic review provides a comprehensive and integrative synthesis of gene-variant associations related to iDILI, offering a consolidated reference framework for future research. However, the predominance of a limited set of genes in the literature reflects an ongoing bias driven by historical candidate gene studies and reporting frequency. This bias may obscure the relevance of other genes that, despite being underrepresented in iDILI studies, appear consistently in functional enrichment analyses and are likely to play key roles in underlying pathophysiological mechanisms.

To overcome these limitations, future studies should broaden their focus and systematically investigate biologically enriched genes across different drugs, populations, and clinical contexts. These efforts are essential for uncovering novel mechanisms and developing reliable biomarkers of susceptibility. Achieving this will require well-powered studies based on large, well-characterized patient cohorts, which are only possible through international collaboration. Coordinated global efforts will increase statistical power, enable the identification of population-specific effects, and enhance the clinical relevance of genetic findings.

In parallel, the integration of this research's output into the iDILInet platform provides a dynamic and biologically contextualized resource for navigating gene-variant-drug associations. By allowing users to explore the data beyond literature frequency, incorporate hepatic expression filters, and support future annotation, iDILInet helps mitigate current research biases and guides hypothesis generation. Together, these approaches contribute to a more systematic, pathway-driven, and translationally oriented understanding of genetic susceptibility to iDILI.

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2026.03.030.

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