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Network-Based Analysis and Characterization of Adverse Drug−Drug Interactions

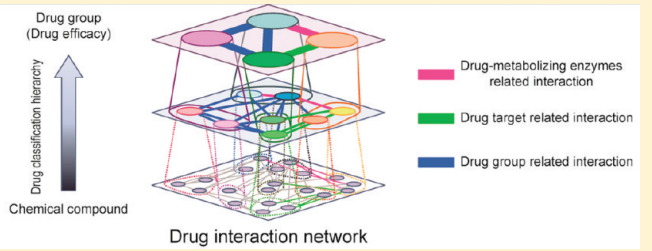
Masataka Takarabe,[†] Daichi Shigemizu,[†] Masaaki Kotera,[†] Susumu Goto,[†] and Minoru Kanehisa*[,†,‡]

[†]Bioinformatics Center, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

[‡]Human Genome Center, Institute of Medical Science, University of Tokyo, Minato-ku, Tokyo 108-8639, Japan

Supporting Information

ABSTRACT: Co-administration of multiple drugs may cause adverse effects, which are usually known but sometimes unknown. Package inserts of prescription drugs are supposed to contain contraindications and warnings on adverse interactions, but such information is not necessarily complete. Therefore, it is becoming more important to provide health professionals with a comprehensive view on drug−drug interactions among all the drugs in use as well as a computational method to identify potential interactions, which may also be of practical value in society. Here we extracted 1,306,565 known drug−drug interactions from all the package inserts of prescription drugs marketed in Japan. They were reduced to 45,180 interactions involving 1352 drugs (active ingredients) identified by the D numbers in the KEGG DRUG database, of which 14,441 interactions involving 735 drugs were linked to the same drug-metabolizing enzymes and/or overlapping drug targets. The interactions with overlapping targets were further classified into three types: acting on the same target, acting on different but similar targets in the same protein family, and acting on different targets belonging to the same pathway. For the rest of the extracted interaction data, we attempted to characterize interaction patterns in terms of the drug groups defined by the Anatomical Therapeutic Chemical (ATC) classification system, where the high-resolution network at the D number level is progressively reduced to a low-resolution global network. Based on this study we have developed a drug−drug interaction retrieval system in the KEGG DRUG database, which may be used for both searching against known drug−drug interactions and predicting potential interactions.



INTRODUCTION

The large-scale molecular data sets generated by genome sequencing and other high-throughput experimental technologies are the basis for understanding life as a molecular system and for developing practical applications in medical and pharmaceutical sciences. The key to linking such large-scale data sets to practical values lies in bioinformatics technologies, not only in terms of computational methods but also in terms of knowledge bases. We have been developing KEGG (http://www.genome.jp/kegg/), a reference knowledge base for biological interpretation of genomic and molecular data sets. Major efforts have been undertaken to manually create a knowledge base of systemic functions at the cellular and organism levels by capturing and summarizing experimental knowledge in computable forms, especially in the form of molecular network diagrams called KEGG pathway maps. This approach has been extended to drug information where drugs are considered as pertubants to the molecular system. The KEGG DRUG database,[1] which is a comprehensive collection of marketed drugs based on chemical structures and/or chemical components, contains manually curated molecular network information, in particular, about targets and metabolizing enzymes in the context of KEGG pathways. Here we report our efforts to collect and analyze another type of molecular network information, namely, adverse drug−drug interactions.

Co-administration of multiple drugs is known to sometimes cause serious adverse effects. Previous studies attempted to understand or predict adverse drug events focusing on specific aspects of drug interactions; for example, particular drugs,[2,3] diseases,[4] patients,[5] and molecular mechanisms including the alteration of drug metabolism or the antagonism of drug targets.[6−9] Systematic analyses were also made for adverse events by computational methods.[10,11] The goal of this study is to gain knowledge about general patterns of adverse interactions among all the drugs currently in use, which would enable predictions that are useful in practice and in society. Together with this study we develop a drug−drug interaction retrieval system integrated in the KEGG DRUG database, which identifies reported and potential drug interactions for a given drug according to the interaction patterns obtained here.

Adverse events are described in the medication package inserts, as contraindications, warnings and precautions, adverse reactions, drug interactions, etc. In this study we focus on drug

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pairs that are associated with adverse events and use the package inserts of all prescription drugs marketed in Japan to extract such pairs. The extracted data are then processed to characterize and classify different types of drug interactions based on the information on their chemical, pharmacological, and therapeutic properties. Roughly speaking, drug interactions are classified into two types: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions include the alterations of absorption, distribution, metabolism, or excretion of drugs, resulting in the changes of their blood concentrations. The best known pharmacokinetic drug interaction involves cytochrome P450 (CYP) enzymes.[6−8] Pharmacodynamic interactions arise from synergistic, additive, or antagonistic actions of drugs having the same or opposing pharmacologic effects.[9] In order to characterize various types of adverse events, the interaction data for individual drugs extracted from package inserts are merged in a hierarchical manner, first into the KEGG DRUG entries representing unique chemical structures, and then the lower chemical level to the higher therapeutic level of the Anatomical Therapeutic Chemical (ATC) classification system. Thus, the drug interaction networks are analyzed at different levels of granularity to find characteristic interaction patterns among drug groups.

MATERIALS AND METHODS

Databases. The package inserts of all marketed drugs in Japan are computerized as XML files by the Japan Pharmaceutical Information Center (JAPIC; http://www.japic.or.jp/). The Japanese-language JAPIC database is integrated with KEGG DRUG and made available at GenomeNet (http://www.genome.jp/kusuri/). As of November 2010, the JAPIC database contained 12,305 prescription drug entries, each of which is identified by the accession number (JAPIC ID), and almost all entries linked to the corresponding KEGG DRUG entry. The drug interaction information is described in the natural Japanese language and in the table with three columns indicating drug or drug class names, interaction mechanisms, and interaction symptoms.

The KEGG DRUG database (http://www.genome.jp/kegg/drug/) is a comprehensive drug information resource for approved drugs in Japan, USA, and Europe. The KEGG DRUG entry identifier, called the D number, distinguishes the chemical structure of pharmaceutical compounds or the chemical component of mixtures. It is also associated with the following molecular network information: target molecules in the context of KEGG pathway maps, drug metabolizing enzymes and transporters, and other interacting molecules including genomic biomarkers, CYP inducers/inhibitors, etc. As of November 2010, the database contained 9314 entries. Excluding crude drugs and Traditional Chinese Medicine (TCM) formulas, 8460 entries were used in this study.

For interpretation of drug interaction data, we use the KEGG PATHWAY and KEGG BRITE databases. KEGG PATHWAY is a collection of manually drawn KEGG pathway maps representing the molecular interaction and reaction networks for metabolism, various other cellular processes, organismal systems, and human diseases. We specifically used 306 pathway maps in order to search target pairs that are connected on the same interaction/reaction pathways. KEGG BRITE is a collection of hierarchical classifications for genes and proteins, small molecules, drugs, diseases, organisms, and other biological entities. Here we used BRITE hierarchies for protein families in order to characterize similar target pairs.

ATC Drug Classification. The Anatomical Therapeutic Chemical (ATC) classification is developed and maintained by the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/). It is a hierarchical classification of drugs with five levels representing progressively finer classifications. For example, the letter "D" represents the top level of the classification meaning "dermatologicals". The D class is further divided into, for example, D10 (antiacne preparations) in the second level, D10A (antiacne preparations for topical use) in the third level, D10AF (anti-infectives for treatment of acne) in the fourth level, and D10AF02 (erythromycin) in the fifth level. In this study, we use the third, fourth, and fifth levels in order to extract features of drug interaction networks. The third level classifies drugs based on mixed criteria of therapeutic or pharmacological properties, and the fourth level depends on therapeutic, pharmacological, and chemical properties. At the fifth level, drugs are grouped simply by the chemical property-based definition such as erythromycin, which actually includes minor variations of salts and hydrates. Each KEGG DRUG entry is manually linked to the seven-letter ATC code at this level. This enables the grouping of the same active ingredient, such as erythromycin (D00140) and erythromycin ethylsuccinate (D01361), and the linking from chemical categories to therapeutic categories.

It should be noted that some drugs have more than one ATC code because of different usages. For instance, there are three ATC codes, D10AF02, J01FA01, and S01AA17, for erythromycin at the fifth level. However, the third or fourth level codes have different definitions according to the purpose of use such as D10AF (antiinfectives for treatment of acne), J01FA (antibacterials for systemic use), and S01AA (antibiotic ophthalmic preparations). In other words, the same chemicals may be classified into multiple therapeutic categories in the classification tree, which makes the interpretation of drug interaction networks somewhat complicated.

Definition of Drug Groups and Their Interaction Patterns. Hence, we have designed a procedure to classify drugs in a simple tree structure, so that a drug belongs to a single group. This procedure is applied to the drugs with reported drug interactions. At a particular ATC level, each drug is represented by a profile (binary vector) $\mathbf{x} = (x_1, x_2, ..., x_i, ..., x_{ATC})$ in which 1 or 0 is given based on whether the drug belongs to the ATC category i (1 is given if yes, and 0 otherwise). The similarity score between the profiles is defined as the binary Jaccard coefficient $J(\mathbf{x}, \mathbf{x}') = |\mathbf{x} \cap \mathbf{x}'|/|\mathbf{x} \cup \mathbf{x}'|$. The dissimilarity score is defined by subtracting the similarity score from 1. The hierarchical clustering with UPGMA (Unweighted Pair Group Method with Arithmetic mean) is applied with the dissimilarity scores calculated for all pairs of the profiles, and the threshold dissimilarity score of 0.9 is used to define drug groups. This clustering procedure is performed at the fifth, fourth, and third levels of the ATC hierarchy to obtain drug groups viewed at the three different resolutions.

Interaction patterns between drug groups are also characterized by the ATC hierarchy. To quantify the significance of group interactions, we define the reported rate as follows. Given two drug groups A and B interacting with each other, let N_a and N_b denote the numbers of drugs (D numbers) included in A and B, respectively, and let N_i denote the number of reported drug interactions between A and B. The reported rate of the interactions between A and B is defined as $R_{ab} = N_i/N_aN_b$.

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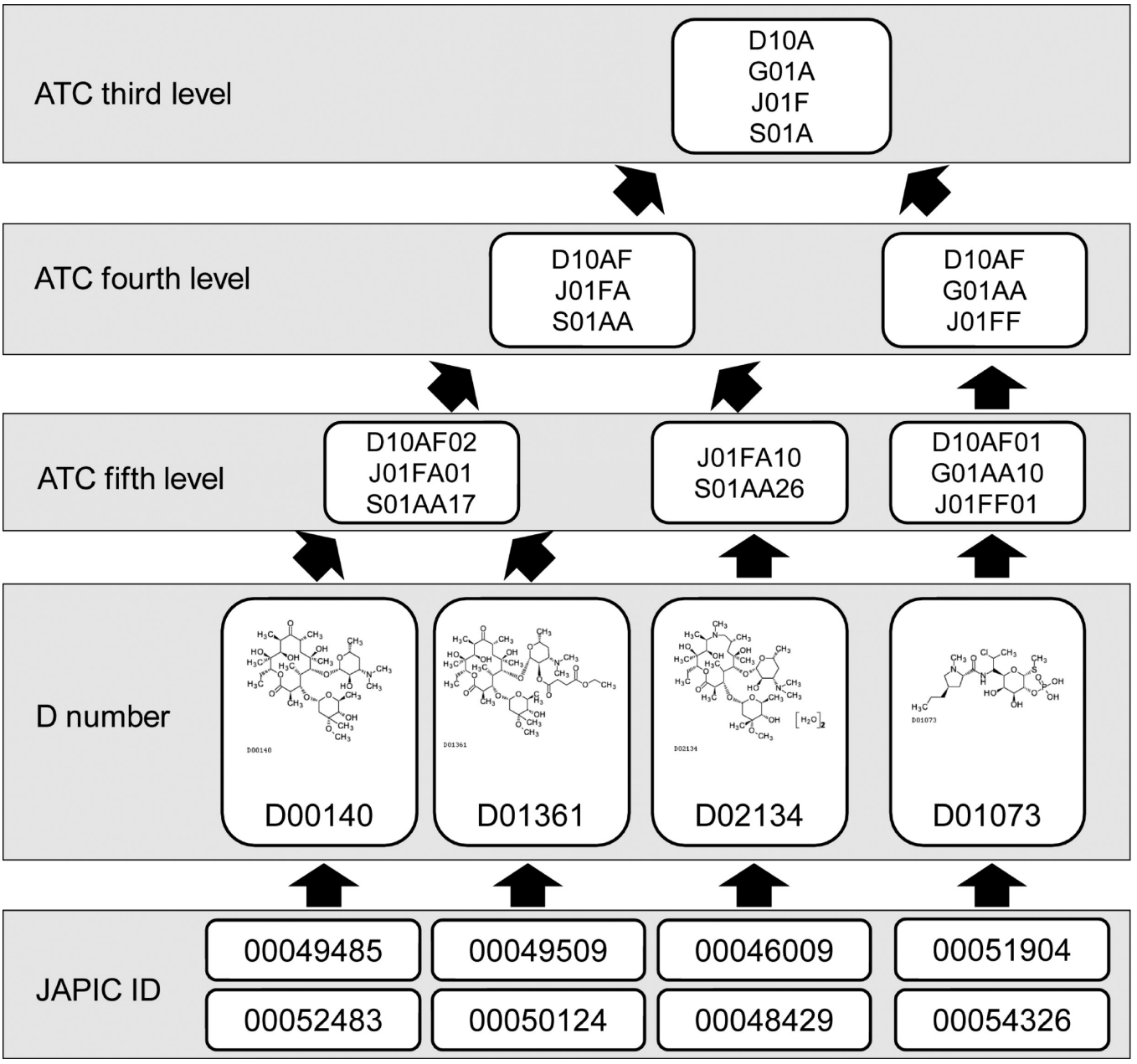

Figure 1. The drug hierarchy in this analysis. The JAPIC ID corresponds to a package insert of a pharmaceutical product. The D number corresponds to a chemical substance in KEGG DRUG, which may be linked to multiple pharmaceutical products (JAPIC IDs). The D numbers are then grouped into chemical and therapeutic categories by merging into the drug groups at the fifth to the third levels of the ATC hierarchy.

Natural Language Processing. The JAPIC package inserts written in the natural Japanese language are morphologically analyzed using the MeCab program (http://mecab.sourceforge.net/) to extract drug names from the tables of interaction information. Standardized generic names are given to the JAPIC entries, but the description of drug interactions may contain other names and drug class names. Thus, synonyms and drug class names are collected from KEGG DRUG, the Life Science Dictionary (LSD) Project (http://lsd.pharm.kyoto-u.ac.jp/en/index.html), and the ATC classification in order to enrich the MeCab dictionary data. Drug names extracted by the MeCab program are associated with the JAPIC IDs and D numbers. Extracted drug class names are first converted to individual drug names. For example, Orap (pimozide, JAPIC ID: 00052995) is an antipsychotic drug, which is described to interact with clarithromycin, erythromycin, and HIV protease inhibitors. Clarithromycin and erythromycin are individual drug names that directly correspond to JAPIC IDs, but the term "HIV protease inhibitors" is a drug class name that needs to be converted to individual names, such as atazanavir, indinavir, and saquinavir. The extracted pairs of drug names are manually verified to create a data set of drug interactions.

RESULTS

ID Conversion in the Drug Hierarchy. In order to interpret the extracted drug interaction data in the framework of chemical

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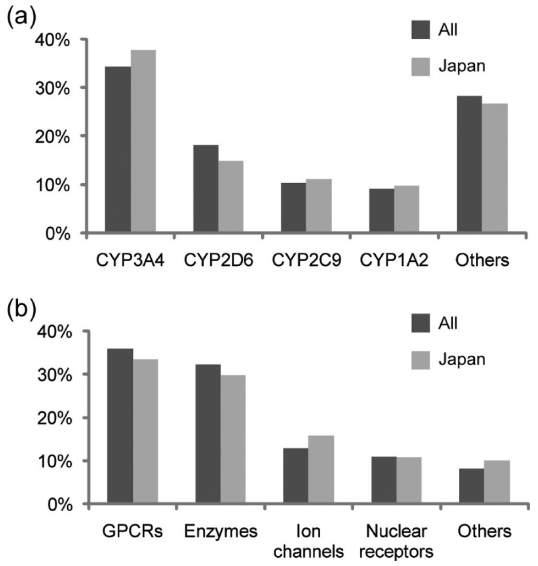

Figure 2. The distributions of (a) drug-metabolizing enzymes and (b) drug targets were compared between the entire set of drugs in KEGG DRUG and the subset of drugs associated with JAPIC entries. The number of drugs (vertical axis) is normalized by the total number of drugs with known drug-metabolizing enzymes or with known targets in each set. The number of drugs with known drug-metabolizing enzymes was 538 in the entire set and 313 in the JAPIC subset. The numbers of drugs with known targets was 2810 in the entire set and 892 in the JAPIC ID subset. The drug targets were grouped according to KEGG BRITE. Note that the sum exceeds 100% because some drugs have more than one known drug-metabolizing enzyme or drug target.

structures and the ATC category, the JAPIC IDs were first converted to the D number identifiers of KEGG DRUG. As a result, 9957 pharmaceutical products (JAPIC IDs) were grouped into 1642 chemical structures (D numbers). Since each D number is already associated with the seven-letter ATC code in the KEGG DRUG database, it is straightforward to do the grouping of D number entries at different levels of the ATC hierarchy, as illustrated in Figure 1.

Information about Metabolizing Enzymes and Targets. Among 8460 D number entries of KEGG DRUG, 538 and 2810 entries contained information about drug-metabolizing enzymes and drug targets, respectively. There were 30 different enzymes and 345 different targets. We first examined if the D number subset of 2137 entries that corresponded to JAPIC IDs was in any way biased, for it was possible that the drugs marketed in Japan were biased in comparison to those in other countries. The check was made using the distributions of the drug-metabolizing enzymes (Figure 2a) and drug targets (Figure 2b) and was assessed using the test for the difference between two proportions.[12] All *P*-values were corrected for multiple companions by the Bonferroni method[13] and were greater than 0.1. Thus, the two sets of drugs did not show any significant difference. This indicates that the drugs associated with JAPIC IDs can be regarded as a good sample for studying drug−drug interactions in general, and also that this study is applicable not only to the drugs in Japan but also to those in other countries.

Drug Interaction Data in the Drug Hierarchy. By automated extraction followed by manual curation, we obtained 1,306,565 drug interaction pairs from the JAPIC package inserts database. As shown in Table 1, when JAPIC IDs were converted to D numbers, the number of drug pairs was 45,180 containing 1352 drug entries, of which 1116 were assigned the ATC codes. Furthermore, when the ATC hierarchy was used to define drug groups (see Figure 1), the number of interaction pairs was reduced to 28,516, 6354, and 2756 at the fifth, fourth, and third levels, respectively. The reduced number of interaction pairs helps to grasp the overall picture of interaction networks and to understand the interactions in pharmacological and therapeutic points of view (see below). Full data sets of this drug hierarchy are given in the Supporting Information.

Table 1. Number of Extracted Drug Interactions at Different Levels of the Drug Hierarchy

node	# of nodes	# of interactions	# of D numbers
third level ATC code	162	2756	1116
fourth level ATC code	362	6354	1116
fifth level ATC code	1021	28,516	1116
D number	1352	45,180	1352
JAPIC ID	8289	1,306,565	1352

Classification of Drug Interactions. Next the drug interaction data were classified according to the metabolizing enzyme and target information given in the drug (D number) entry of KEGG DRUG. Thus, the extracted drug interaction pairs were tagged with overlapping drug-metabolizing enzymes and drug targets, which indicate pharmacokinetic and pharmacodynamic interactions, respectively. Among 45,180 interactions at the D number level, 14,441 interactions involving 735 drugs were linked to the same drug-metabolizing enzymes and/or overlapping drug targets. The interactions with overlapping targets were classified into three types: acting on the same target, acting on different but similar targets in the same protein family, and acting on different targets belonging to the same pathway. Thus, we define four types of drug interactions: "same enzyme", "same target", "same protein family", and "same pathway", where the latter two are defined according to the KEGG BRITE and KEGG PATHWAY databases, respectively.

Figure 3 shows further details of the four types of drug interactions. Among 14,441 interactions, the total of 3775 interactions were caused by drugs metabolized by the same enzyme, 2826 of which were related to the well-known drug-metabolizing enzyme CYP3A4 (Figure 3a). The total of 2209 interactions were identified as drugs acting on the same target protein, most of which were associated with G protein-coupled receptors (GPCRs) for biogenic amines (Figure 3b). GPCRs are the major class of drug targets,[14,15] and the drugs including GPCR agonists and antagonists are prescribed for the diseases of central nervous, cardiovascular, respiratory, metabolic, and urogenital systems.[16] GPCRs are highly divergent but closely related proteins, implying that the drugs targeting different proteins in the same GPCR family can have similar pharmacological properties, and combined use of such drugs may cause increased or decreased drug effects. In fact, among the total of 3617 interactions related to the same protein families, 3013 interactions were associated with drugs acting on biogenic amine GPCR families (Figure 3c).

Two interacting drugs with different targets are regarded to be on the "same pathway" when the targets appear in the same KEGG pathway map. The total of 5996 interactions were found to be in this category (Figure 3d). However, this number is misleading because the co-occurrence of two targets in the same pathway map

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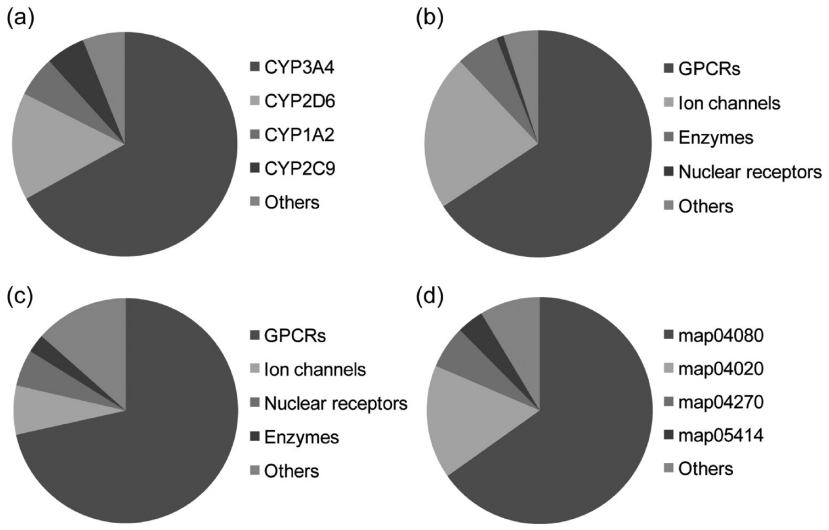

Figure 3. Subcategorization of drug interaction types: (a) same enzyme, (b) same target, (c) same protein family, and (d) same pathway. Pathway map IDs are the following: map04080, neuroactive ligand−receptor interaction; map04020, calcium signaling pathway; map04270, vascular smooth muscle contraction; and map05414, dilated cardiomyopathy. The number of occurrences were counted in terms of enzymes or targets rather than drug entries (D numbers); for example, multiple enzymes (e.g., CYP3A4 and CYP11A1) were counted when they were associated with a single drug entry.

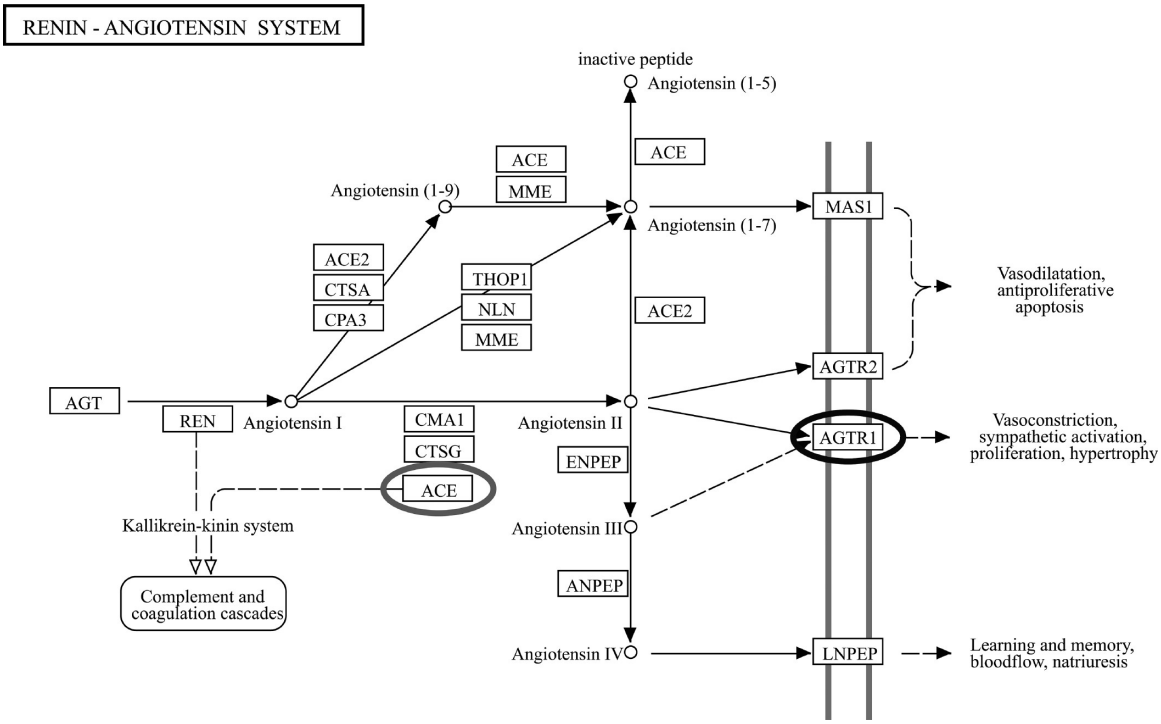

Figure 4. A drug interaction apparently caused by two different targets on the same pathway. Boxes and circles represent proteins and chemical substances, respectively, and arrows show regulation steps. Two drugs, angiotensin-converting enzyme (ACE) inhibitor and angiotensin II receptor type 1 (AGTR1) antagonist, act on two proteins indicated by ovals, causing increased antihypertensive effects.

does not necessarily mean that they are actually connected on the same pathway. In fact the most abundant map, "neuroactive ligand-receptor interactions", is simply a collection of ligand−receptor pairs mostly for GPCRs, and the co-occurrence in this map simply represents "same protein family" rather than "same pathway". By visual inspection, we have identified a clear-cut example of the "same pathway", which is shown in Figure 4. Two drugs, angiotensin-converting enzyme (ACE) inhibitor and angiotensin II receptor antagonist, have a similar beneficial effect on cardiac function,[17] and the combined use may cause increased antihypertensive effects. These two drugs act on different targets, ACE and angiotensin II receptor, in the renin−angiotensin system. ACE inhibitor may affect angiotensin II receptor since the two targets are on the same pathway as clearly seen in the KEGG map.

Global Views of Drug Interaction Networks. The interaction data shown in Table 1 can be viewed as a network of nodes

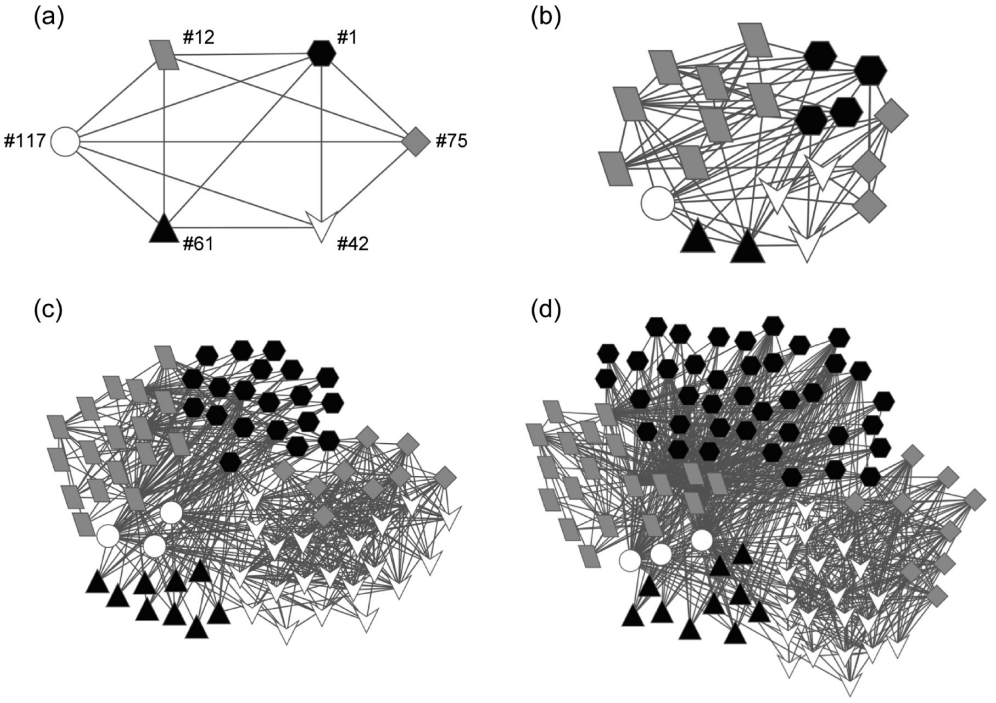

Figure 5. Drug interaction networks at four levels of the drug hierarchy: (a) the ATC third level, (b) the ATC fourth level, (c) the ATC fifth level, and (d) the D number level. The shapes of the nodes correspond to the six groups (clusters) at the third level of the ATC hierarchy. Group numbers are the following: 1, corticosteroids; 12, antiepileptics; 42, beta-blocking agents; 61, macrolides, lincosamides and streptogramins; 75, anesthetics; and 117, cardiac glycosides.

(drugs) and edges (interactions). Figure 5 graphically illustrates a subnetwork of the entire drug interaction network at four different levels of the drug hierarchy: the fifth, fourth, and third levels of the ATC hierarchy and the D number level (see Figure 1). Here edges are drawn when two nodes (groups) are linked by at least one pair of interacting members at a lower level of the drug hierarchy. The network consists of six nodes at the top level (Figure 5a); namely, six drug groups at the third ATC level: group #1 (corticosteroids: A01A, A07E, C05A, D07A, D07X, D10A, H02A, R01A, R03B, S01B, S01C, S02B, and S03B), group #12 (antiepileptics: N03A), group #42 (beta-blocking agents: C07A and S01E), group #61 (macrolides, lincosamides and streptogramins: J01F), group #75 (anesthetics: N01A and V09E), and group #117 (cardiac glycosides: C01A). At the lowest D number level (Figure 5d), the network consists of 100 nodes and 752 edges.

In this global view of drug interaction networks, the edges in the lower-level (higher-resolution) network are bundled together to the edges in the upper-level (lower-resolution) network. Thus, the lower-level edges tend to share common characteristics reflecting the properties of defined drug groups, which may reflect known drug interaction mechanisms or symptoms described in the package insert. For instance, in the highest-level network (Figure 5a), the interaction between corticosteroids (group #1) and macrolides and streptogramins (group #61) is reported to cause increased concentrations of corticosteroids by the inhibition of CYP3A4.[18−20] Cardiac glycosides (group #117) including digoxin may interact with corticosteroids[21] and macrolides,[22,23] resulting in enhancing the action of drugs included in cardiac glycosides. Furthermore, combined use of beta-blocking agents (group #42) and anesthetics (group #75) can result in cardiac dysrhythmias.[24]

Table 2. Reported Rate of Drug Interactions in Each Hierarchy

hierarchy	reported rate	extracted pairs	all possible pairs
ATC third level	0.13	36,200	274,388
ATC fourth level	0.31	36,200	117,760
ATC fifth level	0.96	36,200	37,865
D number	0.75	1,306,565	1,747,773

Reported Rates of Drug Interactions. The hierarchical drug interaction networks may reveal previously hidden interaction patterns among drugs and drug groups. This may be used to identify or predict possible drug interactions. At the third level of the ATC hierarchy (Figure 5a), corticosteroids (group #1) contain 39 drugs (D numbers) and cardiac glycosides (group #117) contain 3 drugs. The number of all possible drug pairs (D number pairs) between these two drug groups is 117, of which 80 are reported as drug interactions in the package inserts. Similarly, beta-blocking agents (group #42) and anesthetics (group #75) contain 20 and 9 drugs, respectively, and over 70% of the pairs (128/180) are reported drug interactions. These were the cases of strong associations between drug grouping and drug interactions.

In order to assess the significance of drug groups in terms of drug interactions, we computed the reported rate as described in the Methods section. The result is shown in Table 2. In the third and fourth levels of ATC, most reported rates were low (less than 0.5). In contrast, the ATC fifth level grouping has a reported rate of 0.96, meaning that interactions between chemical structure groups are well characterized.

In Table 2 the reported rate for the D number level was calculated in terms of the JAPIC ID pairs. The reported rate of

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Table 3. Drug Metabolizing Enzymes and Drug Targets Shared by the Drug Groups

drug group	category	name	# of D_r[a]	# of D_i[b]
corticosteroids/anti-inflammatory agents	target	GR	36	39
beta-lactam antibacterials	target	dac	31	34
antipsychotics	target	DRD2	30	32
antipsychotics	enzyme	CYP2D6	15	32
antineoplastic agents	enzyme	CYP3A4	12	32
antivirals	target	DNA polymerase	12	31
antivirals	enzyme	CYP3A4	11	31
hypnotics and sedatives	target	GABRA	16	21
antihistamines	target	HRH1	20	20
beta-blocking agents	target	ADRB1	19	20
beta-blocking agents	target	ADRB2	11	20
beta-blocking agents	target	ADRB3	11	20
anxiolytics	target	GABRA	15	17
antidepressants	enzyme	CYP2D6	13	17
antidepressants	target	HTT	12	17
NSAIDs	target	COX1	11	15
NSAIDs	target	COX2	11	15
adrenergics	target	ADRB2	12	12
selective calcium channel blockers	target	CACNA1C	11	11
selective calcium channel blockers	target	CACNA1D	11	11
selective calcium channel blockers	enzyme	CYP3A4	10	11

[a] Number of drugs (D numbers) related to the enzyme or target. [b] Number of all drugs (D numbers) in the drug group.

0.75 implies that in 25% of cases drug interactions may not be described in the package inserts. It would thus be important to present this missing information for use in practice based on the drug (D number) interaction data in the drug hierarchy.

DISCUSSION

We extracted adverse drug−drug interactions from the Japanese package inserts of prescription drugs stored in the JAPIC database. Molecular mechanisms were well-characterized for about one-third of the interactions (14,441 out of 45,180), which involved metabolizing enzymes and/or drug targets. For the rest we attempted to identify drug groups and their interaction patterns, using the Anatomical Therapeutic Chemical (ATC) classification. Prescription drugs stored in the JAPIC database cover 206 out of 218 third-level ATC codes and all 90 second-level ATC codes, reflecting the fact that prescription drugs marketed in Japan can be considered a representative data set for analyzing drug−drug interactions in general.

For the analysis of drug groups we mainly used the third level of the ATC hierarchy, which is the top level of the drug hierarchy defined in Figure 1. Table 3 shows drug metabolizing enzymes and drug targets that may be associated with the drug groups at this level. Here drug group names were taken and modified from the description of the ATC codes. As shown in the table, members of these drug groups share drug metabolizing enzymes or drug targets. For example, 36 out of 39 drugs in "corticosteroids" act on glucocorticoid receptor (GR), and 30 out of 32 drugs classified as "antipsychotics" act on the dopamine D2 receptor (DRD2). Thus, certain drug groups are relatively uniform allowing the analysis of drug group interactions.

In the analysis of Table 2 there was no significant difference of reported rates when the drug group pairs involving drug metabolizing enzymes or drug targets were removed. Therefore, there must be other characteristic interaction patterns that may be used for predictive purposes. We manually examined correspondences between drug group pairs at the top drug hierarchy level (ATC third level) and interaction mechanisms (or symptoms) described in the package inserts and the literature. Figure 6 shows some examples of such drug group interaction patterns, which are divided into three types: causing side effects of both drugs, causing a side effect of one drug, and causing modified efficacies of both drugs. Corticosteroids have a wide range of biological effects and thus can cause interactions with diverse drugs such as insulins, viral vaccines, nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, and cardiac glycosides. Side effects of corticosteroids include enhancement or reduction of drug efficacies such as for insulins,[25] viral vaccines,[26,27] and cardiac glycosides.[21] Corticosteroids exert similar side effects of NSAIDs[28] and diuretics,[29,30] which may increase the risk of peptic ulcer disease and hypokalemia, respectively. Adrenergics[31,32] and antipsychotics[33,34] can induce hyperglycemia, reducing the effect of blood glucose lowering drugs. The side effects of beta-blocking agents and NSAIDs can also alter the effects of insulins[35] and ACE inhibitors,[36] respectively. Immunosuppressants can enhance replication of viral vaccines.[37] Diuretics and beta-lactam antibacterials[38−40] may increase the risk of renal damage as a common side effect. Aminoglycoside antibacterials can depress the central nervous system and may enhance the effect of anesthetics, which results in severe respiratory depression.[41] The side effects of beta-blocking agents and anesthetics may cause excessive hypotension and bradycardia.[42]

We have noticed that the adverse drug−drug interaction information provided in package inserts is not necessarily complete. First, as we mentioned, the reported rate of 0.75 for the D number level (Table 2) means incompleteness of package inserts among the drugs with the same active ingredient. Second,

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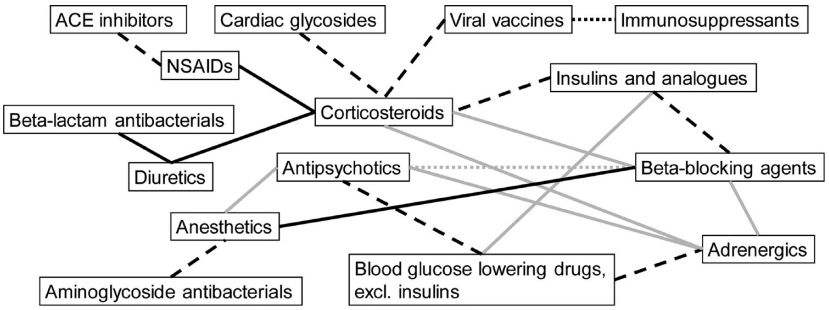

Figure 6. Example of interaction patterns among drug groups. Nodes represent the ATC third level drug groups, and their definitions are based on KEGG BRITE. Black edges indicate interaction patterns caused by side effects of both drug groups (solid line), a side effect of one drug group (dashed line), and efficacies of both drug groups (dotted line). Gray edges show interaction patterns characterized by the drug-metabolizing enzymes (dotted line) and targets (solid line). The ATC codes of the drug groups are the following: corticosteroids (A01A, A07E, C05A, D07A, D07X, D10A, H02A, R01A, R03B, S01B, S01C, S02B, and S03B), antipsychotics (N01A and N05A), NSAIDs (C01E, C04A, D11A, G02C, M01A, M02A, R02A, and S01B), immunosuppressants (D11A and L04A), beta-lactam antibacterials (J01D), beta-blocking agent (C07A and S01E), ACE inhibitors (C09A), anesthetics (N01A and V09E), blood glucose lowering drugs, excl. insulins (A10B and V04C), insulins and analogues (A10A), adrenergics (C01C, D06A, R01A, R01B, R03C, S01F, and S01G), cardiac glycosides (C01A), viral vaccines (J07B), aminoglycoside antibacterials (A07A, D06A, J01G, and S01A), and diuretics (C03B).

the interaction between two drugs may be written in both drugs or only in either drug. Among the drug interactions identified in this study, 291,152 interactions were the former cases, and 1,406,052 interactions were the latter. Possibly, commonly used drugs may not contain warnings for rarely used drugs. Third, when viewing the hierarchical drug network (Figure 5) at the D number level or the ATC fifth level, there were much less edges observed between the drugs that belong to the same drug group at a higher level than the drugs that belong to two different groups. In other words, there are few descriptions on the drugs that belong to the same group, although applying two similar drugs simultaneously would cause interactions similar to overdose. It is unnecessary to describe this type of information for medical experts, but the information should be made available somewhere for nonexperts.

The problem is related to the interactions with OTC drugs. Compared to professionally written package inserts for prescription drugs, package inserts of OTC drugs are usually prepared for nonexperts and do not necessarily describe the details of drug interactions. We briefly examined the package inserts of Japanese OTC drugs that were also provided by the JAPIC database. Chemical ingredients of OTC drugs are linked to chemical structures (D numbers) in KEGG, and we used the drug interaction data obtained here to estimate if a pair of OTC drugs may cause an adverse drug−drug interaction. As a result, 3,471,219 interactions were suggested among 5913 out of the 11,988 OTC drugs (in terms of JAPIC IDs), corresponding to 558 interactions among 150 ingredients (in terms of D numbers). There were also 5,821,789 interactions between 7269 OTC drugs and 7269 prescription drugs (in terms of JAPIC IDs), corresponding to 9256 interactions among 1132 drugs (in terms of D numbers).

In order to disseminate knowledge gained in this study we have developed a drug−drug interaction retrieval system in the KEGG DRUG database. In each KEGG DRUG entry, there is an option (DDI button) to search against known drug−drug interactions annotated with the information about mechanisms such as metabolizing enzymes, targets, etc. The search result can be displayed on top of the ATC classification, enabling predictions for missing data in the same hierarchy. Thus, the knowledge based approach presented here is comprehensive (covering all package inserts) and predictive (allowing complementation of missing data) for existing drugs. We believe that the data set of drug−drug interactions is already a valuable resource for research purposes. However, for use in clinical practice the data set as well as the retrieval system will have to be further refined. The general rules of interaction patterns presented here may be too general to be usable. For example, a typical DDI search will result in too many potential interactions, most of which are associated with precautions in multiple package inserts. There has to be a ranking mechanism for the severity of risks considering the level of warning and incorporating expert knowledge. We will continue to update the drug−drug interaction data set as part of the KEGG DRUG database and develop the retrieval systems that are useful in clinical practice and in wider society.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Drug clusters based on ATC codes. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +81-774-38-3270. Fax: +81-774-38-3269. E-mail: kanehisa@kuicr.kyoto-u.ac.jp.

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