NETWORK ANALYSIS OF ADVERSE DRUG INTERACTIONS

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Harmful effects associated with use of drugs are caused as a result of their side effects and combined use of different drugs. These drug interactions result in increased or decreased drug effects, or produce other new unwanted effects and are serious problems for medical institutions and pharmaceutical companies. In this study, we created a drug-drug interaction network from drug package inserts and characterized drug interactions. The known information about the potential risk of drug interactions is described in drug package inserts. Japanese drug package inserts are stored in the JAPIC (Japan Pharmaceutical Information Center) database and GenomeNet provides the GenomeNet pharmaceutical products database, which integrate the JAPIC and KEGG databases. We extracted drug interaction data from GenomeNet, where interactions are classified according to risks, contraindications or cautions for coadministration, and some entries include information about enzymes metabolizing the drugs. We defined drug target and drug-metabolizing enzymes as interaction factors using information on them in KEGG DRUG, and classified drugs into pharmacological/chemical subgroups. In the resulting drug-drug interaction network, the drugs that are associated with the same interaction factors are closely interconnected. Mechanisms of these interactions were then identified by each interaction factor. To characterize other interactions without interaction factors, we used the ATC classification system and found an association between interaction mechanisms and pharmacological/chemical subgroups.

Keywords: drug interaction; network; KEGG

1. Introduction

Adverse drug events caused by drug interactions are significant problems in medications and the development of new drugs. These drug interactions lead to increase or decrease of drug effects or other serious reactions. For example, cyclosporin, which is widely used as an immunosuppressant drug, is known to interact with many other drugs such as ketoconazole and erythromycin [1, 2]. Cyclosporin is metabolized by CYP3A4, which is a member of a cytochrome P450 family and catalyzes the oxidation of a number of substrates, whereas, ketoconazole and erythromycin inhibit CYP3A4 enzyme activity. Thus, the combined use of these drugs results in delayed clearance and elevated blood level of cyclosporin and increase or prolong both its therapeutic and adverse effects. Assessing and managing such drug interactions are significant problems for clinical practice and drug development. In this study, we focused on adverse drug interactions

and created drug-drug interaction networks to characterize and investigate the drug interactions. To create the drug-drug interaction networks, we extracted drug interaction data from Japanese drug package inserts, which contain known information about potential risk of drug interactions. The Japanese drug package inserts are stored in the JAPIC (Japan Pharmaceutical Information Center) database [12]. We have integrated the JAPIC and KEGG databases [3] and provide it as the GenomeNet pharmaceutical products database [13]. Additionally we defined interaction factors and merged drugs into pharmacological/chemical subgroups to characterize the drug interactions. In the resulting drug-drug interaction networks, drugs that are associated with the same interaction factors are closely interconnected, and mechanisms of the drug interactions were identified by the interaction factors (CYP enzyme family or monoamine receptors, for example). Some other drug interactions without interaction factors were characterized by using information from pharmacological/chemical subgroups.

2. Method

2.1. *Datasets*

The GenomeNet pharmaceutical products database provides Japanese drug package insert data linked to the KEGG DRUG database. Each entry contains information on the brand/generic name, physicochemical/pharmacokinetic properties, drug interactions, etc. The drug interaction section lists the drugs or the classes of drugs that cause adverse interactions with the product, and these interactions are classified according to risks, contraindications or cautions for coadministration. Additionally, some drugs contain additional sections which include information on enzymes metabolizing the products like cytochrome P450 family. Most entries are assigned KEGG DRUG IDs (D numbers), which correspond to the active ingredient of the products. The KEGG DRUG database is a chemical structure-based database in which each entry includes information on chemical structure, efficacy, drug target, pathway, ATC code, etc.

2.2. *Drug interaction network*

We used the data from the GenomeNet pharmaceutical products database as of March 26, 2008. 13973 pharmaceutical product entries were stored in the database, of which 7562 entries contained drug interaction information. We extracted drug names from the drug interaction section of each entry and listed JAPIC IDs that correspond to the drug names to create drug interaction data between JAPIC IDs. Next, JAPIC IDs were merged with respect to the D numbers that the JAPIC IDs are assigned because we considered that products assigned the same medicinal properties have the same potential risk of drug interactions. Consequently, we obtained drug interaction data between D numbers and used the data to create drug interaction networks.

To characterize the drug interactions, we defined drug targets and drug-metabolizing enzymes as interaction factors for each D number and searched drug interactions associated with the same interaction factors. Information on the interaction factors was collected from the package insert data and the KEGG DRUG database. Drug target genes data stored in the KEGG DRUG database were merged with respect to each functional type of protein according to KEGG BRITE, which is a collection of hierarchical classifications [3].

2.3. *Pharmacological/chemical subgroups*

We used the Anatomical Therapeutic Chemical classification system (ATC classification system), developed by the WHO Collaborating Centre for Drug Statistics Methodology [14], to group D numbers. The ATC classification system divides drugs at 5 different levels according to the sites of action and their therapeutic and chemical characteristics. Each level is assigned a code which consists of 1 letter or 2 digits corresponding to pharmacological/chemical subgroups of the level. The drugs assigned the same ATC codes indicate that they are assigned the same pharmacological/chemical subgroups. Thus, D numbers were grouped into chemical substance subgroups in terms of the pharmacological/chemical categories based on the ATC classification system.

3. Results

The numbers of extracted interactions between JAPIC IDs are 29,663 and 1,196,494 in contraindications and cautions for coadministration respectively, and we merged JAPIC IDs into D numbers. As a result, 1,513 and 36,040 interactions between D numbers were obtained respectively (Table 1).

Table 1. Number of drug interactions and entries involved in the interactions.

	Contraindications		Cautions	
	Interaction	Entry	Interaction	Entry
JAPIC ID	29,663	3,043	1,196,494	9,432
D number	1,513	517	36,040	1,431

3.1. *Interaction factors*

We created network graphs from the resulting data on the drug interaction and interaction factors. Figure 1 shows the obtained network of contraindications for coadministration. In the network, nodes represent the D numbers that correspond to the drugs, and edges represent interactions. Node sizes are proportional to the numbers of edges they have. Bold edges indicate the interactions between the drugs associated with the same interaction factors and are colored according to the interaction factors.

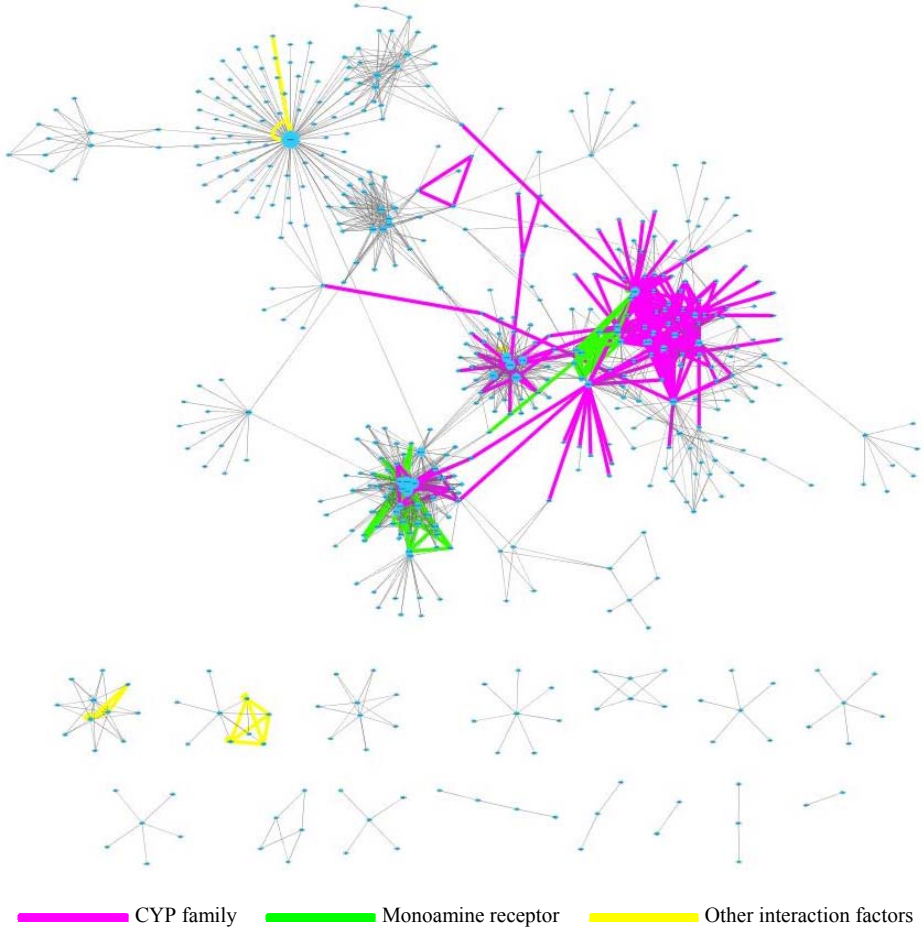

Fig. 1. Drug interaction network of contraindications for coadministration. Interaction factors were merged into the CYP enzyme family, monoamine receptor, and others. Bold edges were colored according to these interaction factor groups.

Obtained interaction factors were 12 and 38 in contraindications and cautions for coadministration, respectively. Table 2 shows the top 5 interaction factors that both drugs in the interaction are associated with. CYP families and monoamine (adrenaline, serotonin, dopamine, histamine, etc.) receptors are the most frequently observed interaction factors which are associated with both drugs in the interactions. The interactions between the drugs associated with the same interaction factors are closely interconnected.

Table 2. Number of interactions and drugs with interaction factor.

Contraindications			Cautions		
Interaction factor	# of interaction	# of drugs	Interaction factor	# of interaction	# of drugs
CYP3A	181	77	CYP3A	1,916	147
Adrenaline receptor	33	17	Adrenaline receptor	200	52
Serotonin receptor	28	8	CYP2C	200	50
CYP2D	17	14	Dopamine receptor	182	42
CYP1A	16	16	CYP1A	113	31

Information on action mechanisms of these interactions are provided in the package inserts. For instance, drug interactions from CYP families are caused by inhibition/induction of the enzymes and result in a decrease/increase in the effects of drugs. In the case of drug interactions with monoamine receptors, both drugs affect the same receptors, which results in the additive effect of the receptors.

Next, we investigated other interactions without interaction factors by using information from pharmacological/chemical subgroups. In the network of contraindications for coadministration, 398 D numbers were assigned ATC codes and merged into 331 pharmacological/chemical subgroups. 1042 D numbers were merged into 941 subgroups in the network of cautions for coadministration. To explore an association between interaction mechanisms and pharmacological/chemical subgroups, we searched hub nodes and common pharmacological/chemical categories of their neighboring nodes.

Figure 2 shows an example of D00951 (Medroxyprogesterone acetate) and its neighboring nodes with pharmacological/chemical subgroup information in the network of contraindications for coadministration. D00951 interacts with 97 different drugs, of which 43 are included in the most common category "Corticosteroids, plain" which corresponds to third level ATC code "D07A". These interactions between D00951 and "Corticosteroids, plain" subgroup increase the risk of side effect of both drugs such as cardiovascular disease [4, 5, 6].

4. Discussion

We created drug interaction networks from Japanese drug package insert information to explore adverse drug interactions. In the resulting networks, many drugs are associated with the same interaction factors and closely connected with each other. Therefore there are many drugs that mostly interact only with drugs associated with the same interaction factors. For example, D02211 (Dihydroergotamine mesilate) interacts with 37 different drugs, of which 30 are associated with CYP3A, and D00560 (Pimozide) interacts with 23 different drugs, of which 21 drugs are associated with CYP3A. Dihydroergotamine mesilate and pimozide are reported to be metabolized by CYP3A [7,8], and coadministrations of the two drugs with CYP3A inhibitors or drugs metabolized by CYP3A cause serious side effects such as QT prolongation or ventricular arrhythmia. These interaction factors enabled us to characterize drug interactions and identify mechanisms of these interactions because their interaction mechanisms or clinical symptoms depend on the interaction factors. Obtained drug interaction networks include many nodes and edges. Particularly, in the network of cautions for coadministration, it is difficult to explore drug interactions from the network graph. For efficient analysis,

elimination of drugs and interactions associated with the same interaction factors may be effective to reduce nodes and edges in the drug networks.

Next, we used ATC classification system to investigate interactions between drugs assigned no information of interaction factors or assigned different interaction factors respectively. We applied the information of pharmacological/chemical subgroups to neighboring nodes of each node and searched their common pharmacological/chemical categories that correspond to third level or forth level of ATC code. In some interactions between drugs and their neighboring nodes, common pharmacological/chemical categories were found in the neighboring nodes, and there are characteristic interaction mechanisms or clinical symptoms related to the pharmacological/chemical categories. We illustrated Figure 2 as an example of the association between interaction mechanisms and pharmacological/chemical subgroups, and Figure 3A shows another example of the associations. D00386 (Triamterene) interacts 8 different drugs, of which 6 drugs are classified "Acetic acid derivatives" subgroup, and these interactions cause acute renal failure [9, 10]. Figure 3B illustrates the case of D00089 (Oxytocin), and these interactions result in the enhancement effect of both drugs and lead to serious events [11]. The results indicate this method using pharmacological/chemical subgroups is effective to investigate drug interactions without information of interaction factors. However, some drug interactions remain uncharacterized. For further research, there is a need for more exhaustive data including drug interactions, targets and other new pharmacological/chemical properties to determine the uncharacterized drug interactions.

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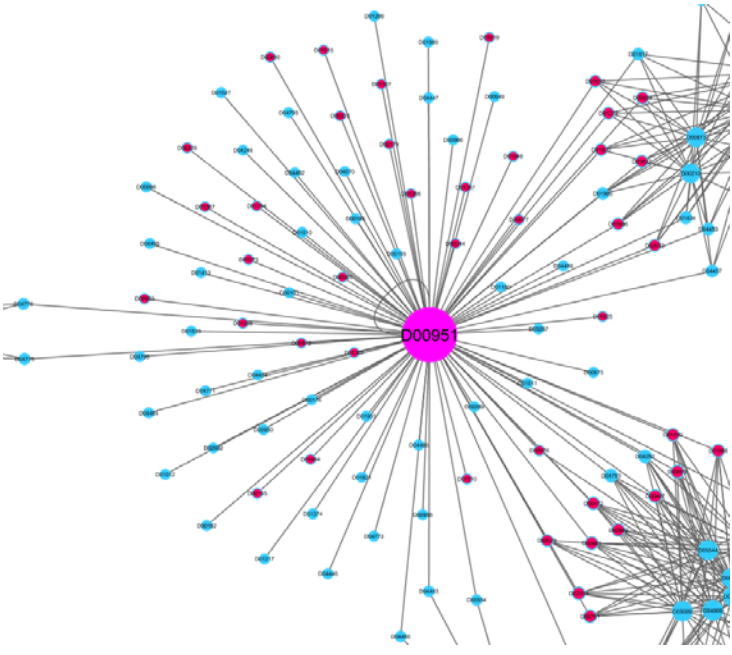

Fig. 2. D00951 and its neighboring nodes in the network of contraindications for coadministration. Red nodes represent nodes that included in the "Corticosteroids, plain" subgroup ("D07A").

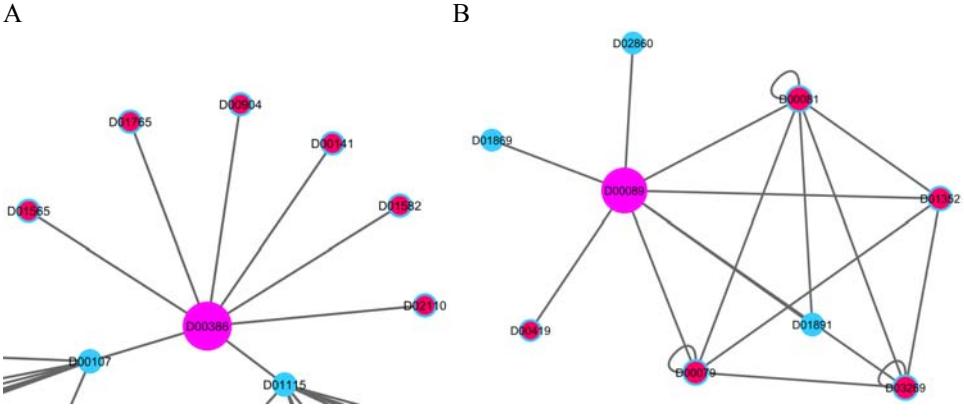

Fig. 3. Associations between interaction mechanisms and pharmacological/chemical subgroups in the network of contraindications for coadministration. Red nodes represent nodes that included in the same pharmacological/chemical subgroups. (A) D00386 (Triamterene) interacts with 6 drugs classified in "Acetic acid derivatives" subgroup. (B) D00089 (Oxytocin) interacts with 5 drugs classified in "Prostaglandins" subgroup.

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