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Predicting unintended effects of drugs based on off-target tissue effects

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ABSTRACT

Unintended effects of drugs can be caused by various mechanisms. Conventional analysis of unintended effects has focused on the target proteins of drugs. However, an interaction with off-target tissues of a drug might be one of the unintended effect-related mechanisms. We propose two processes to predict a drug's unintended effects by off-target tissue effects: 1) identification of a drug's off-target tissue and; 2) tissue protein – symptom relation identification (tissue protein – symptom matrix). Using this method, we predicted that 1,177 (10.7%) side-effects were related to off-target tissue effects in 11,041 known side-effects. Off-target tissues and unintended effects of successful repositioning drugs were also predicted. The effectiveness of relations of the proposed tissue protein – symptom matrix were evaluated by using the literature mining method. We predicted unintended effects of drugs as well as those effect-related off-target tissues. By using our prediction, we are able to reduce drug side-effects on off-target tissues and provide a chance to identify new indications of drugs of interest.

1. Introduction

Unintended effects of drugs are related to drug side-effects or repositioning. Therefore, the mechanisms of drugs' unintended effects were intensively studied. In this paper [1], the mechanism of unintended effects were categorized into four kinds: 1) interactions between drugs and main target proteins in primary (target) tissues, 2) interactions between drug and target proteins in different (off-target) tissues, 3) interactions between drugs and off-target proteins in primary or different tissues, and 4) complex interactions between drug main or off-target proteins within tissues. To investigate the second item, which is the off-target tissue effect, has been difficult due to a lack of information between human tissues and proteins. However, in the Human Protein Atlas (HPA) project [2], the researchers released their research results about relations between tissues and proteins on the web. We utilized HPA DB to investigate the second mechanism of drugs' unintended effects.

In the case of humans, approximately 20,000 proteins were produced. However, those all proteins are not uniformly expressed in all of the tissues of our body. In the Human Protein Atlas (HPA) project, they investigated which proteins are synthesized in each tissue/organ of the human body for 90% of proteins that are currently known. Of course, overlapped proteins in human tissues existed. Because of this, after drug administration, we expect to see the medication having an effect on proteins in multiple tissues. In this case, a drug can have unintended effects on off-target tissues.

Our interest is in the effect of the drug on the target proteins located in other tissues than the originally targeted tissues. As an example of this phenomenon, in the case of Fexofenadine (DB00950), which is an anti-histamine drug class, the target protein of the drug is the Histamine receptor H1. This drug has been usually prescribed to allergic rhinitis with hypersecretion of nasal discharge. Tissues expressing this protein are known to include nasopharynx, adrenal gland, bronchus, colon, kidney, lung, parathyroid gland, stomach, testis, smooth muscle, cerebellum, cerebral cortex, hippocampus, and so on [2]. This medicine affects nasopharynx tissue according to the drug's original intended design [3]. The most well-known side-effect of this drug is sleepiness, and cerebral tissues, such as the cerebellum, cerebral cortex, and hippocampus, are known to be involved in sleepiness [4]. In summary, the initial generation of antihistamines was prescribed for treating

Abbreviations: T-SM, Tissue protein – symptom matrix.

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allergic rhinitis, while this drug's side-effect was drowsiness. The next generation of antihistamines could reduce drowsiness as a side-effect by interrupting drug delivery to brain tissues, and this concept is related to the off-target tissue effect.

In this study, we predicted the unintended effects of the drug by examining the off-target tissue effects. Thus, we built a matrix that includes symptoms and target proteins and confirms the phenomenon on currently marketed drugs. We built the matrix by using the target protein involved with tissue information and symptoms from drugs' indications. We can suggest novel drug-induced effects by non-target tissue through the tissue protein – symptom matrix. This paper firstly introduce our prediction methods. Next, we explain the tissue protein – symptom matrix (T-SM). Finally, we show our prediction results and discuss our results sequentially.

2. Methods

2.1. Prediction method

Our proposed prediction method largely consists of two parts. The first part is to identify the off-target tissue of the drug of interest. We utilized the ATC code and target proteins of the drugs to identify the off-target tissue. Firstly, we obtain all tissue information including proteins of interest. The first code of ATC was related to the target tissue of the drug. We defined the off-target tissues as a set of all other tissues, which produce the target proteins, except for the target tissues. Tissue protein information related with the drug are built by combining the off-target tissue and target protein. Tissue protein is defined as the protein produced in particular tissues. This tissue protein information is utilized to find integrations in the tissue protein – symptom matrix.

The second part is to find relations in the tissue protein – symptom matrix. Our T-SM has relations between tissue proteins and symptoms. We can predict the unintended effects of a drug of interest by the off-target tissue effect from confirming the tissue protein on T-SM.

The input data of our prediction method are target proteins of a drug of interest and the first level of the ATC code of the drug. The output data of the prediction method are tissue proteins, symptoms, and T-SM scores. The output symptoms are interpreted as the off-target tissue effects of the drug of interest.

Fig. 1 shows an example of our prediction. There is drug Dr_1, and the first level of the ATC code of Dr_1 is ATC_1. The target protein of Dr_1 is P_1. This target protein exists in $Tissue_1$ and $Tissue_2$ according to the HPA database. The target tissue of Dr_1 is $Tissue_1$ included in the biological system indicated by the ATC code information. Dr_1 can affect $Tissue_2$ through the target protein P_1 enriched in $Tissue_2$. Thus, the off-target tissue effects are $Symptom_1$ and $Symptom_2$. Our prediction is that $Symptom_1$ and $Symptom_2$ were related with $Tissue_2$ by Dr_1's off-target tissue effect.

2.2. Tissue protein – symptom matrix (T-SM)

Our prediction is to assess unintended effects by off-target tissue. If we know the off-target tissue of the drug and the related symptom of the off-target tissue, we can predict the unintended effect of drug that occurs due to off-target tissue effects.

The proposed matrix was built from various information of marketed drugs. This matrix contains relations between tissue proteins and symptoms. The tissue protein means that the proteins existed in tissue. The tissue protein is different from tissue-specific protein. The tissue-specific protein is a protein that only exists in specific tissue. In conclusion, this relation of T-SM represents a symptom caused by a target protein on tissue with tissue protein (Fig. 2).

Tissue protein – symptom matrix was calculated in four steps. The first step is tissue protein-ATC matrix (TP_zATC_k) calculation. One of the data aggregated to develop the protein-tissue matrix P_mT_n is the relation information of the spatial distribution of proteins across the human tissues obtained from Human Protein Atlas (HPA) [2]. The other matrix (T_nATC_k) contains the relations between the first level of ATC codes and associated tissues manually curated from the physiological literature [5]. The tissue protein index z and the elements of the matrix TP_zATC_k were calculated by the formula in the bracket and the arithmetic multiplication of the elements of the matrix P_mT_n and T_nATC_k, respectively, as follows:

$$TP_zATC_k = P_mT_n \times T_nATC_k \,(z = (n-1)m_{\max} + m). \quad (1)$$

The second step was to derive the tissue protein with an ATC

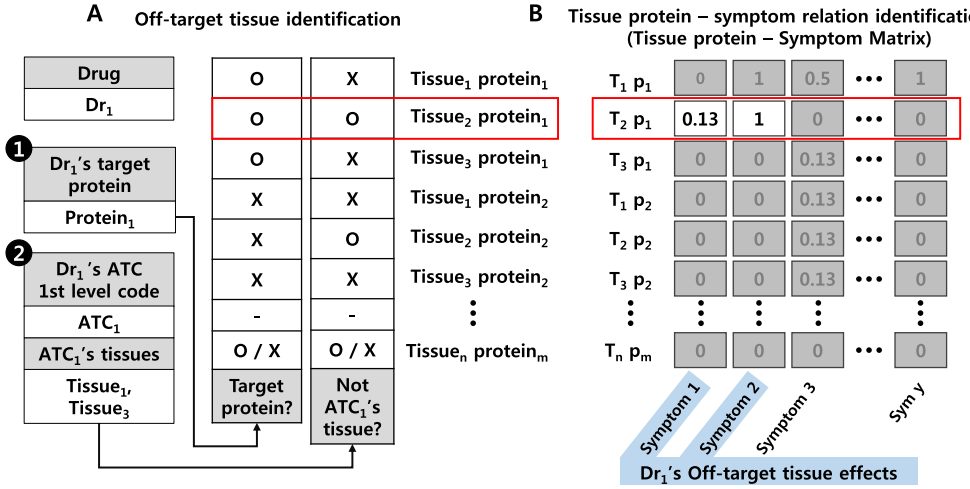

Fig. 1. Prediction method for unintended effects by off-target tissue effects. Our prediction method consists of the following two processes. a) Off-target tissue identification: off-target tissues are defined as tissues producing the target protein P_1 of the drug Dr_1 as well as tissues excluded from the biological system indicated by the first level of the ATC code of the drug Dr_1 and b) Tissue protein – symptom relation identification using the tissue protein – symptom matrix (T-SM): off-target tissue protein (highlighted with red boxes) links between the given drug Dr_1 and symptoms ($Symptom_1$ and $Symptom_2$) were suggested as the off-target tissue effects of the Dr_1 (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

code-drug matrix ($TP_wA_qDr_x$). The TP_zATC_k matrix was developed from the result of the first step and ATC_kDr_x was made from the first level of the ATC codes of the drugs, which were obtained from DrugBank [6]. The arithmetic to derive the tissue protein with ATC code index q and the elements of the $TP_wA_qDr_x$ matrix are shows as follows:

$$TPwA_qDr_y = TP_zATC_k \times ATC_kDr_x (q = (k-1)z_{\max} + z). \quad (2)$$

The third step was the process of making the target tissue protein with an ATC code-drug matrix ($TarTP_wA_qDr_x$). Information on the target proteins of drugs, which was collected from DrugBank, was utilized. The target index t and the elements of the $TarTP_wA_qDr_x$ matrix are determined by

$$TarTPwA_qSym_y = TPwA_qDr_x \times Tar_tDr_x.$$
$$\left(t = q - \left[\frac{q}{m_{\max}}\right] \times m_{\max}\right) \cdot \begin{cases} t = m_{\max}, & if \ \ t = 0 \\ t = t, & if \ \ t \neq 0 \end{cases}. \quad (3)$$

The fourth step as the final is to calculate the target tissue protein with ATC code-symptom matrix (T-SM). The indication information of the drugs from PharmGKB [7] was utilized. T-SM contains the score weighting of the confidence of the relations between target tissue proteins and symptoms by the number of target proteins of the drug potentially treating the symptom. The elements of the T-SM are determined by

$$TarTPwA_qSym_y = \frac{\sum_{x=1}^{x_{\max}} \frac{1}{CT_x} \times TarTPwA_qDr_x \times Dr_xSym_y}{n}$$
$$\begin{cases} CT_x = \sum_{t=1}^{t_{\max}} Tar_tDr_x \\ \begin{cases} n = 1, & if \ \ \frac{1}{CT_x} \times TarTPwA_qDr_x \times Dr_xSym_y > 0 \\ n = 0, & if \ \ \frac{1}{CT_x} \times TarTPwA_qDr_x \times Dr_xSym_y = 0 \end{cases} \end{cases} \quad (4)$$

Where CT_x is the total number of target proteins of the drug Dr_x.

The relations of T-SM were scored by CT_x in final step. For instance, if a drug was exclusively engaged to one target protein, the highest score was assigned to T-SM. In conclusion, the score range is assigned from 0 to 1.

3. Results and discussions

3.1. Tissue protein – symptom matrix (T-SM)

The tissue protein-symptom matrix had 5,338 relations. Those tissue proteins were combined from 83 tissues and 242 drug target proteins. Symptoms, as the other dimension, totaled 58, including headache, apnea, diarrhea, and seizures. Drug information had key roles in identifying the relations of the matrix. As explained in section 2.2, drug information was included into three of the total five relations to create a relation of T-SM. The drug information was collected from 210 marketed drugs.

We show an example of the relation of our matrix. In the matrix, one relation was made between heart beta-1 adrenergic receptor (tissue protein) and angina pectoris (symptom). To create this relation, we should check the relation between beta-1 adrenergic receptor (ADRB1) and brain tissue on the HPA database. And esmolol has an indication for treating angina pectoris as a symptom. The target protein of this drug is ADRB1. The target tissue that was obtained from the ATC code of this drug is the heart. Eventually, heart ADRB1 – angina pectoris relation means that ADRB1 in the heart may affect angina pectoris.

When the relations were established, we assigned a lower score if a drug had many proteins. This score represented the relevance between target proteins and drug-related symptoms. Thus, in the case of a drug that has 1 target protein, the relation has a score of 1.0. However, in the case of a drug that has 3 target proteins, the score of the relation is 0.33. Therefore, the matrix's score represented multiple proteins of one drug. The correctness of the matrix can slightly be improved by changing the scoring function.

3.2. Side-effect prediction (comparison with SIDER database)

We predicted unintended effects by off-target tissue effects of drugs of interest by using the Tissue protein – Symptom Matrix (T-SM). We investigated known drug side-effects. In this investigation, we confirmed that there were many cases related to off-target tissue effects in known side-effects. We obtained drug side-effect information from SIDER [8]. We extracted predictable drugs on T-SM from all drugs in SIDER. The extracted predictable drugs mean that the target proteins of the drugs existed in T-SM. As a result, we analyzed 449 drugs from SIDER (Supplementary data 4). As explained in a previous section, our prediction method needs target protein information and ATC code on the first level of drugs of interest, which were obtained from DrugBank. According to our prediction results, there is a 10.7% (N = 1,177) rate of side-effects as unintended effects by the off-target tissue effect among analyzed known side-effects (N = 11,041). For instance, we briefly investigated top-scored three drugs as follows.

Nicotine is a nicotinic acetylcholine receptor (nAChR) agonist. The nAChR is located in the central nervous system (CNS) and peripheral nervous systems (PNS). According to [9], nicotine in various compounds in cigarette smoke is a frequent cause of coughing by humans and animals in experiments. Pulmonary

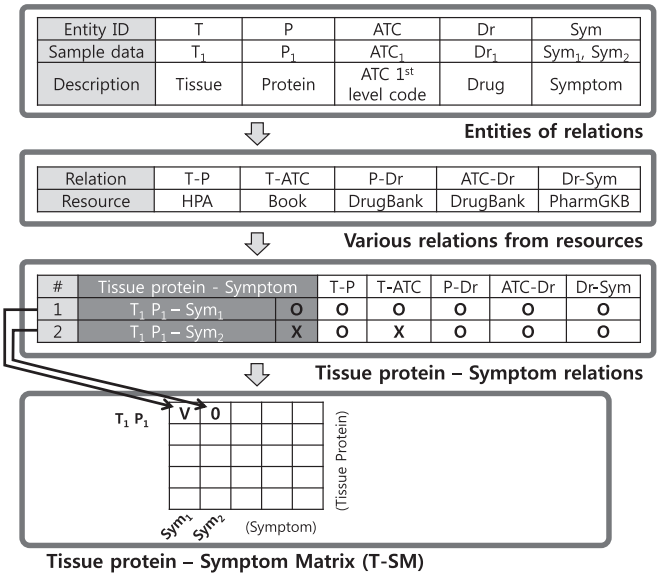

Fig. 2. Schematic of the tissue protein – symptom matrix (T-SM) construction. The relations between each pair of five entities are collected from various databases as illustrated. The five types of relations between each pair of five entities are integral to assign V into the corresponding entry in T-SM (see detailed scoring method in Equation (4)). The score of tissue protein – symptom relation is assigned as 0 by only one missing relation from five types of the relation (Supplementary1).

irritant receptors as cough receptor were produced in the lung and airway. Thus, nicotine could be bonded to these cough receptors. The bindings eventually cause a cough by transmitted signaling in a cough center on the medulla through the branches of the vagus nerves [10]. In conclusion, coughs caused by nicotine could be an off-target tissue effect.

Galantamine is a ligand that acts as a nicotinic acetylcholine receptor (nAChR) binder. This compound is indicated to treat memory impairment through Alzheimer's disease, which affects the CNS. The researchers report that the side-effect of galantamine is respiratory myoclonus [11]. In their study, galantamine causes muscular hyper contractibility and muscle cramps. In this process, galantamine is the cause of respiratory myoclonus. We expect cramping of airway muscles caused coughing from galantamine. The binding of the drug to nAChR in CNS causes an original therapeutic effect, whereas binding to nAChR in the respiratory system causes off-target tissue effects.

3.3. Drug repositioning (comparison with successful drug repositioning)

We checked for the existence of off-target tissue effects related to drug repositioning on successful drug repositioning. We obtained a list of 89 successfully repositioned drugs from a study done by Liu and coworkers [12]. In examining Liu's study, we investigated 11 drugs of 89 that were filtered by analyzing off-target tissues and filtering drugs in DrugBank. Analyzing those drugs' off-target tissues confirmed difference between tissues related with the original drug indications and tissues related with drug repositioning indications.

The first drug is sildenafil, which is one of the most famous drug repositioning cases. The originally designed indication of this drug is hypertension. After drug repositioning, this drug was prescribed for erectile dysfunction. In the result of an analysis by using our proposed T-SM, this drug was related with apnea as symptom. Several tissues that are related with this symptom are brain tissues including the cerebral cortex, lateral ventricle, and hippocampus and respiratory system-related tissue including the bronchus and nasopharynx. Other research groups showed that sildenafil aggravates apnea [13], [14]. One study [14] reported that the mechanism of aggravation is to affect the autonomic nervous system by sildenafil. Therefore, we confirmed that apnea could be affected by sildenafil.

The second drug is mifepristone, which was generally prescribed for terminating pregnancy as original indication. We predicted edema as an unintended effect with several tissues such as skin and lung on T-SM. The drug's repositioning in Liu's list and the treatment of this drug is Cushing syndrome [15]. Interestingly, edema, which is related to the drug on T-SM, is the main symptom of Cushing syndrome [16]. We confirmed that our prediction result corresponds with previous research.

The third drug is sibutramine. The original indication of this drug is obesity, and the repositioning indication of this drug is depression. In our T-SM, brain tissue including soft tissue in peripheral nerves, cerebral cortex, and cerebellum was related to psychophysiological disorders. The target protein of this drug is SLC6A3, which is related to emotion such as depression since SLC6A3 plays the role of a dopamine transporter [17], [18].

3.4. Tissue protein – symptom matrix (T-SM) assessment by literature mining

We evaluated the tissue protein – symptom relations of T-SM by confirming the relations through literature mining. A tissue protein – symptom relation on T-SM contains two pieces of linkage information. One of the linkages is tissue-symptom relation, and the other is protein – symptom relation. We confirmed a conventional co-occurrence of two entities from each relation in one sentence in the abstracts of published papers [19]. We utilized 107,307,095 sentences from abstracts in PubMed published from 1950 to 2013. We performed this analysis by using Hadoop, which is a distributed processing system-based framework, to count the co-occurrences of keywords of interest in approx. 100 million sentences.

Firstly, we compared our results to random sets to assess probable relations in T-SM. We generated 10 random sets to secure statistical significance and utilized average values from the random sets.

The count of significant tissue-symptom relations in T-SM is 1.66 times larger than the averaged count of the relations of 10 random sets. In the case of protein-symptom relation, our result was 3.6 times larger than the random sets. Fig.3a) shows the number of significant relations ($p < 0.05$), which is calculated by a hypergeometric test [20].

Fig. 3b) shows a comparison of the average values of the Jaccard index from all relations of our result and 10 random sets. The value of the Jaccard index means the co-occurrence possibility of two entities in one sentence [21]. So, we counted the occurrences of each single entity in our relation from 100 million sentences and the co-occurrence of two entities in sentences. If a relation has a higher index than others, then the relation is a biologically meaningful one.

We performed difference analysis between the relations of a random set and the relations of our matrix. On tissue-symptom relations, the index of our result was 1.69 times higher than that of the random set. On protein-symptom relations, our result was 2.04 times higher than for a random set. From the result of this analysis, we confirmed that our result had meaningful relations.

Next, we compared the number of significant relations and the average of the Jaccard index between high- and low-scored groups to assess our score. The first analysis was a comparison of the count of significant relations. We counted the significant relations with a p-value that was less than 0.05. Fig. 3c, d) shows the count of significant relations in the high-scored 3–30% group and low-scored 3–30% group. The high-scored groups were a minimum of 2 times and a maximum of 10 times larger than the low-scored groups on all tissue-symptom relations and protein-symptom relations.

In the second analysis, we assessed our score effectiveness by comparing the Jaccard index after classifying our relation's top group and bottom group. Fig. 3e, f) shows the result of the Jaccard index comparison between top group, which was classified by a T-SM score 1, and the bottom group, which had the same number of relations as the top group. In the case of tissue-symptom relations, the number of relations in the top group, which had a T-SM score 1, was 126. The number of relations in the bottom group was the same as that of the top group. The Jaccard index of the top group was 5.081×10^{-4}. This index was approximately 4 times higher than that of the bottom group. In the case of protein-symptom relations, the number of relations in top group was 30. The bottom group also had 30 relations. As a result, the top group's Jaccard index was 22 times larger than that of bottom group. In conclusion, we confirmed T-SM score effectiveness.

4. Conclusion

In this study, we proposed a prediction method for unintended effects of the drug by off-target tissue effect. In most cases, a drug's target proteins were not produced in only one tissue; thus, target proteins could be located in multiple tissues. It means that the drug

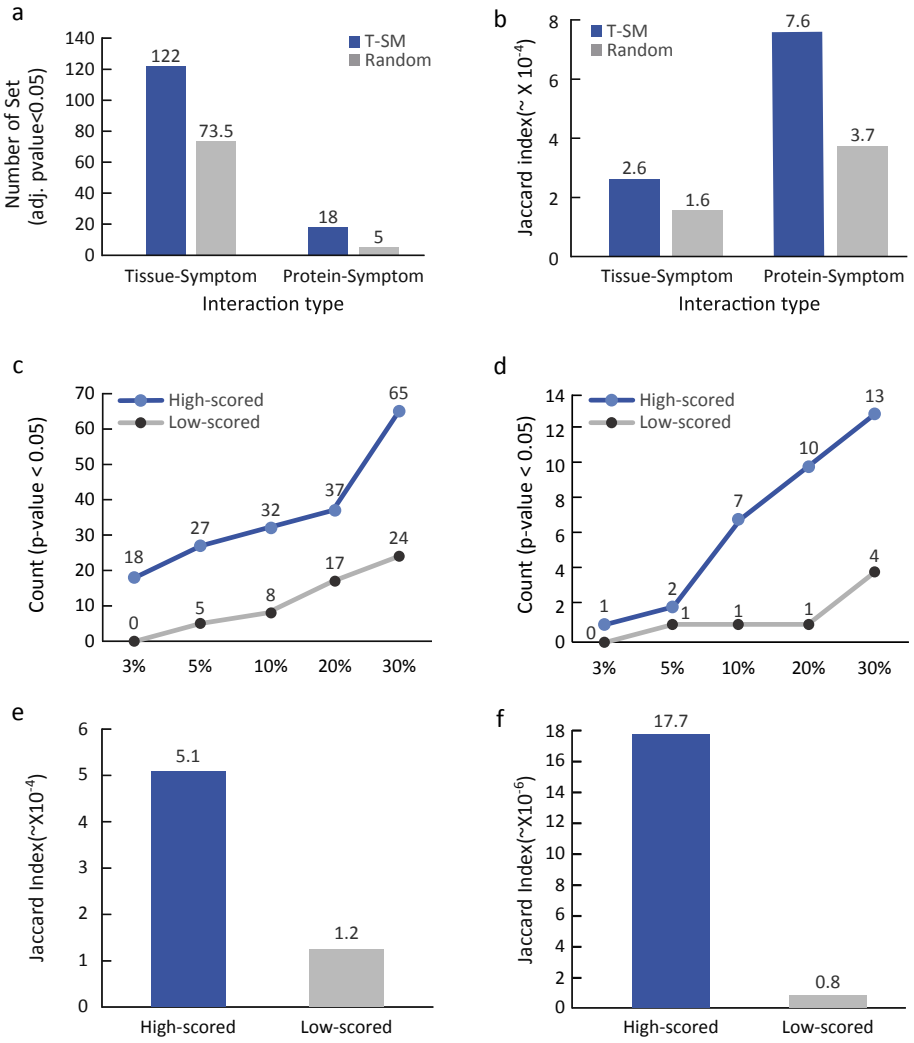

Fig. 3. Graphs of Tissue protein – Symptom Matrix (T-SM) assessment by literature mining. a) The literature-based count comparison of significant ($p < 0.05$) co-occurrence cases of tissue-symptom/protein-symptom pairs between from tissue protein-symptom matrix (T-SM) and from random generation b) The literature-based Jaccard index comparison of tissue-symptom/protein-symptom pairs between form T-SM and from random generation c) The literature-based count comparison of significant ($p < 0.05$) co-occurrence cases of tissue-symptom relations from T-SM between with the high score and with the low score d) The literature-based count comparison of significant ($p < 0.05$) co-occurrence cases of protein-symptom relations from T-SM between with the high-score and with the low-score e) The literature-based Jaccard index comparison of tissue-symptom pairs from T-SM between with the high-score and with the low-score f) The literature-based Jaccard index comparison of protein-symptom pairs from T-SM between with the high-score and with the low-score.

can affect multiple tissues. The off-target tissue effect occurs when a drug affects multiple tissues that are not the drug's target tissues, and these are called off-target tissues. Therefore, our strategy for predicting these kinds of unintended effects was to find off-target tissues of drugs of interest and to identify relations between target proteins in off-target tissues and symptoms.

We used ATC code's first level to find off-target tissues of a drug of interest. This information represents the drug of interest's target system. Thus, all tissues in other systems except the target system can be candidates of the off-target tissue of the drug of interest. Those candidates are filtered out by protein information in the tissue. All proteins are not located in all tissues. Therefore, if we filter out filtered candidates by using target proteins of the drug of interest, we can obtain off-target tissue that can be affected by the drug of interest. Tissue protein information can be produced from off-target tissue and the drug's target protein. In this process, we produce tissue proteins of the drug of interest.

In this research, we have established a Tissue protein – Symptom Matrix (T-SM) having relations between tissue proteins and symptoms. This matrix was calculated from drug - target protein, drug - target system, drug – indication (symptom), tissue - protein, and tissue - system. These relations of the matrix were statistically evaluated by 100 million sentences from abstracts of previous studies. By using T-SM, we analyzed side-effects from SIDER [8] and successful drug repositioning from Liu's study [12]. In this study, we predicted unintended effects by off-target tissue effects. In drug development, if off-target tissue effects are predicted, this prediction can reduce side-effects. This prediction also provides a chance to identify new indications of a drug of interest.

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Conflict of interest

All authors declare that they have no conflict of interest to the publication of this article, and approved the manuscript and this submission.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.11.095.

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