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Master's Dissertation

DEVELOPMENT OF VERIFICATION METHOD FOR THE EFFECTIVENESS AND SAFETY OF OFF-LABEL DRUG USE

생명정보학 기법을 이용한 기존 약물의 새로운 적응증 탐색 연구

February 2015

Young Mee Lee

Lab. of Computational Biology and Bioinformatics
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ABSTRACT

Development of Verification Method for the Effectiveness and Safety of Off-label Drug Use

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Development of a new medication is not an easy task being not only financially costly but also very time consuming without any guarantee of success. Information about medications that has been developed and used until now is well accumulated due to technological advances, especially IT technology. This information has allowed more thorough inspection of safety of existing medications. Also, in case of any safety problem, certain medication could be withdrawn from the market. A newly magnified side effect can give a different perspective so that a change in indication leads to the use of new medication. Mechanism of action and target are not clearly known for all medications, but research on unknown medications is ongoing and those new information are being recorded as big data. In addition, gene information of organisms is continuously being added to the data base and offered to the public research for the health and prolonged life of humanity. Usage of thalidomide had once been stopped due to a risky side effect, however, the mechanism of action that caused certain side effect has been verified and it is now being used to treat multiple myeloma with a new indication. This was possible because there has been sufficient research on drug target and disease associated genes. This research will use bioinformatics

to examine the effectiveness of pre-existing medications that are used for off-label indications. Under the current circumstance where reference is rare and clinical trials are not possible, this research will study the validity of off-label uses of many drugs to determine whether there are any safety issues based on the accumulated information. On the other hand, this research will give theoretical propriety to well-known off-label uses that pharmaceutical companies avoid due to lack of economic profit. Also, this research will suggest that the process of finding a new indication of a new substance can be developed from pre-existing medication using bioinformatics.

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Keywords : Off-label use, Drug repositioning, New indication development, Gene information, Drug information

Student ID: 2011-22113

I dedicate this paper to my family and my professor.

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LIST OF ABBREVIATIONS

AHFS:	American Hospital Formulary Service
ASCO:	The American Society of Clinical Oncology
BLAST:	Basic Local Alignment Search Tool
DDBJ:	The DNA DataBank of Japan
EMA:	European Medicines Agency
EMBL:	The European Molecular Biology Laboratory
FASTA:	DNA and protein sequence alignment software package
FDA:	Food and Drug Administration
GVHD:	Graft Versus Host Disease
HER2:	Human epidermal growth factor receptor 2
HIRA:	The Health Insurance Review & Assessment Service
HIV:	Human Immunodeficiency Virus
MFDS:	Ministry of Food and Drug Safety
MHLW :	Ministry of Health, Labour and Welfare
NCBI:	National Center for Biotechnology Information
NCCN:	The National Comprehensive Cancer Network
PharmGKB:	The Pharmacogenomics Knowledgebase
REM :	Rapid Eye Movement
SMAP:	SMAP software package is designed for the comparison and the similarity search of protein three-dimensional motifs independent on the sequence order
STRING:	The Search Tool for the Retrieval of Interacting Genes/Proteins

CHAPTER I. INTRODUCTION

1.1 The Background of Study

Development of a new medication is not an easy job being not only financially costly but also very time consuming without any guarantee for clinical effectiveness or safety, if it is ever used. Therefore, recently there has been a repositioning of old medication for the new purpose of cure or paradoxical treatment, which was originally designed to cure a certain disease yet by using the revealed side effects it is now used differently. It has been more favorably used than the original treatment purpose. There could be a lot of different approaches which make this development possible and the method of bio information which uses accumulated information of medications could be a more efficient way to reposition existing medications. These studies have been done and still are under process in different aspects. The repositioning of existing medications can be considered as a stage of developing medication processes, and for pharmaceutical companies it is the most important process to find the medication which has a high possibility of being used clinically.

Thalidomide, developed in Europe and once widely used to prevent morning sickness for pregnant women, was removed after being confirmed as a drug which causes fetus malformation. However, it is now used as an essential cure for the complication of Hansen's disease and Multiple Myeloma, though it has limited uses for safety reasons. This medication was launched by Grunenthal, a German pharmaceutical company, in 1957 and was removed

from the market due to the problem of causing malformation at birth in 1961. In 1964, once Thalidomide was proven to be effective on pain relief for Hansen's disease, Celgene got permission for it as a cure of ENL (Erythema Nodosum Leprosum), a Hansen's disease complication, and re-launched it after clinical experimentation for anti-inflammation cure. After this, the study of mechanism of causing malformation by Thalidomide was conducted a lot. As a result, it became known that Thalidomide restrains the formation of the new blood vessel in the early stage of pregnancy when baby's limbs are being formed. Based on this, the attempt of study of using Thalidomide as an anticancer drug which restrains the new blood vessel for growing cancer cells was tried, 2006 Celgene launched it as the cure of Multiple Myeloma (Lee Hyun-gyu, 2011). Thalidomide is exclusively permitted as the safe and effective alternative medicine only for patients who have Hansen's disease, and no other medications could have effect of remedial value. The conversion of Thalidomide as an anti-cancer drug is the result of changing the target focused on the side effect, and it became an undependable remedy for non-curable disease. Propecia was originally developed as a remedy for Prostatomegaly under the name of Proscar. However focusing on the fact that it boosts hair growth as a side effect, with changing the indication for the use of a medication it changes the target of medication and proper dosage and then they got the permission to launch becoming really popular. Even now there are many medications being used for uses other than the original purpose of a medication. The reason is that along the process of the use of the original indication for the use of a medication, unintentional clinical results were witnessed and the result of different uses other than the original use from the permission has accumulated, under the tacit agreement it was to be used as trial if there was no specific remedy and got a good result. After the long time

uses of these medications for other usages, some of the medications have become considered to have got permitted for other uses. However the over-use of those medications beyond the permission should be go through clinical experiments or if that is not possible, at least getting the adequacy of usage is the essential process.

Off-label use of the medications beyond the permission means medications are differently used beyond the contents reported to the authorities and stated in the permission in the matter of the indication for the use of a medicine, dosage, dosing methods and dosing subjects. In the book of "The use of medical supplies off-label use and basis-centered decision-making" (Shin Joo-young et al., 2009), it defines that permitted medical supplies are only prescribed and used as it is stated under the permission from the authorities in the matter of the indication for the use of a medicine, dosage and dosing methods and on the other hand, non-permitted medical supplies mean they didn't get the permission from the authorities and the medications were modified and compounded in different forms. Off-label use meant they got the permission from the authorities, yet they are used differently from one of any of the stated usages in the matter of the indications for the use of a medicine, dosage and dosing methods. Let's take look at the Ministry of Food and Drug Safety on terminology. In 2013, the Ministry of Food and Drug Safety, Drug Review Management Department, TF team made an initial presentation on 'the legal, practical perspectives of the use of off-label' at the 'Korean Society for Clinical Pharmacology and Therapeutics' and 'Korean Pharmaceutical Manufactures Medical Society' spring symposium which is held at Seoul University Hospital. It contains the fact that there has been an actual request for the granting of usage of medical supplies beyond permission because the requested clinical experiments for usage of off-label

are limited due to the characters of diseases, the narrow indication for the use of a medicine and the lack of the number of cases. In 2008, to ensure the proper medical treatment when it has the medical base, the Ministry of Health made the improved methods of medical supplies permission and usage, and then legislated 'The standard and protocol for the granting of beyond usage of permission or reported contents without insurance cover'. In 2010, MFDS (Ministry of Food and Drug Safety) made the basis to evaluate the safety and effectiveness. However with a lot of practical reasons, the use of off-label has not yet been settled, therefore MFDS introduced the protocol for the use of off-label use through this presentation. Off-label use is being used by the name of 'Over-used beyond permission Medications' and it indicates the medications are prescribed beyond the granted usages (effect & efficacy, usage & dosage) or permitted medications under the pharmaceutical law are used differently in medical field. They try to change the term into 'the off-label use'. There are two purposes. One is for clinical reasons of researchers and the other is for the use differently other than permission. For the clinical reasons of the researchers, it gets the permission from the Ministry of Food and Drug Safety because it is to make the basis of use of medications beyond the permission, while the use is different from that for which permission is granted by the Health Insurance Review & Assessment Service based on the legislated basis (Medical News, Kim Chang-won, 2013).

Depending on which organizations use the terms, the terms related to off-label use are of mix-used in Korea. Precisely speaking, the use of medical supplies, usage, dosing methods and dosing subjects are only permitted as it was reported and other than this, everything else becomes off-label use. It is the same meaning of the expression of 'off-label use' in English spoken countries. Off-label use is widely used in specific age groups such as children,

the old, pregnant women, terminally-ill patients and terminal cancer patients who don't have any other options. Table 1.1 shows the catalog of the off-label use medications which requested the permission for the use from the Ministry of Food and Drug Safety. Although an anticancer drug is frequently used as an off-label medication, it is excluded from this chart because it is regularly judged for the effectiveness and the safety not like others due to this disease's critical character. According to the research, 80% of children patients, 50% of cancer patients and 81%of AIDS patients are prescribed at least more than one off-label use medication. It also says about one-fifth of all the medications are used as off-label use, and when it comes to psychiatric medications the use of off-label goes up to 31% (Radley et al., 2006). Sorted by diseases, in the use of medications for heart related diseases and anti-seizure the off-label use medications are more commonly used, yet 73% of use does not have any scientific basis or weak basis. In another research, it is said that the 62% of pediatric prescription is off-label use (Bazzano et al., 2009).

There are many cases that are backed up by documents for the medications which are frequently used as off-label use medications. However, all the documents are the compilation of cases or the reviews of high-profile clinical experts'. Very rarely, the result of a large scale clinical experiment could be used as a basis, but it is just a temporary status of the off-label use as a part of the process of getting permission. To get the permission to launch the medications, it has to get through different stages of complicated and strict processes and then it can be launched after getting the permission for the effects and the side-effects which are proved and stated. However, checking the cases of the side-effects through the post marketing surveillance system, it can be concluded that the information of effectiveness and safety is limited for the permission before it is launched (Chae et al., 2013). Therefore the Post

Marketing Surveillance System (by FDA) becomes an essential request to discover the new indications for the use of a medicine and safety issues. Another perspective, it is the temporary situation that the use off-label medications are clinically used first, and then the authorities which need more general and objective proofs ask for improvement and limit the use.

The reasons for prescribing off-label use medication are that the indications for the use of a medicine, usage, dosing methods and dosing patients. It is ethically difficult to have clinical experiments with children or the old and therefore the clinical experiment of medication on these age groups is not required. Those medications which are used in the market can result in the over-dose depending on ages because of the lack of the information of the child, or the modification of the medication can result in the high rate of off-label use for the child. In the case of rare incurable diseases, it is difficult for pharmaceutical companies to do clinical experiments even though it is possible, it is not profitable for the companies, comparing; expenses for the experiments and the permission to market; therefore they do not attempt to do it. When there are no alternative medications for rare incurable diseases, the authorities of regulation should urge the pharmaceutical companies or research institutions to make the basis. In this situation, if there is a systematical, more objective, proper and usable method for the off-label use, it will be worth trying.

Table 1.1 Off Label used drug claimed for appropriateness and safety for specific diseases in Korea

generic name	indication	off-label use
Naltrexone	Opioid dependence, alcohol dependence	Internet addiction, Pathological Gambling
Deferiprone	Iron chelator indicated for treatment of transfusional iron overload caused by thalassemia syndromes	Iron overload caused by blood transfusion
Leflunomide	Rheumatoid Arthritis, .Psoriatic arthritis	BK virus nephrosis after renal transplantation
Rituximab	Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Rheumatoid Arthritis, Wegener Granulomatosis, Microscopic Polyangiitis	Refractory steroid-dependent nephrotic syndrome in children, Focal Glomerulosclerosis Replases after Renal Transplantation
Methotrexate	Neoplasms, Meningeal Leukemia, Osteosarcoma, Rheumatoid Arthritis, Psoriasis	Chronic non-infectional ocular inflammatory disease
Misoprostol	NSAID-induced gastric ulcer, prophylaxis	Postpartum hemorrhage, cervical ripening procedure-Hysteroscopy, miscarriage
Mycophenolate mofetil	Organ transplant rejection prophylaxis	Lupus
Valacyclovir	Viral infection	Facial paralysis (Bell's palsy)
Verteporfin	Age-related macular degeneration	Central serous chorioretinopathy
Bortezomib	Multiple myeloma	Pre medication for transplant to sensitized patients, acute rejection after renal transplant
Sirolimus	Renal transplant rejection, High immunologic risk; Prophylaxis	PTLD(Post-transplant lymphoproliferative disorder) of pediatric patients after renal transplant

Abxicimab	Myocardial ischemia; Prophylaxis - Percutaneous coronary intervention; Adjunct	1.Cerebrovascular disease, re-occlusion after brain clots dissolved 2. Acute cerebrovascular thrombosis after nerve intercession operation
Erythropoietin	Anemia due to chronic renal failure, zidovudine therapy in HIV-infected patients, and chemotherapy	Pure red blood cell anemia after transplant of homogeneous hematopoietic stem cell
Etanercept	Rheumatoid arthritis, psoriatic arthritis	Refractory acute GVHD(Graft versus Host Disease)
Octreotide	Acromegaly, Carcinoid syndrome, Metastatic; symptomatic treatment	Necrotizing pancreatitis, acute; Adjunct, neonate chylothorax, Metastatic neuroendocrine tumor
Imatinib	Acute lymphoid leukemia, Chronic myeloid leukemia, Gastrointestinal stromal tumor	Fibrous-sclerous chronic GVHD
EGF	Diabetic foot ulcers	Radiation-induced stomatitis
Indigocarmin	Renal function test	Diagnosis & management of tubal factor infertility
Quetiapine	Schizophrenia, bipolar disorder	delirium
Clonazepam	Seizure, panic disorder	Parkinsonism, REM sleep disorder, tremor
Tacrolimus	Severe atopic dermatitis (second-line), organ transplant rejection; Prophylaxis	Vitiligo, Psoriasis, scleroderma, facial lupus
Progesteron	Abnormal uterine bleeding unrelated to menstrual cycle, Endometrial hyperplasia; Prophylaxis	Premature birth of newborn, Short cervix; Prophylaxis

This table is a summary of drugs which were claimed for off-label use to MFDS through HIRA

1.2 The Study of Effectiveness and Safety of the Off-Label Use of Medications

Awareness of the effectiveness and safety of off-label use of medications was started in 2009 in Korea. It was started in July, 2010. There was a questionnaire and request for understanding the current situation of the off-label use medication and safety evaluation, MFDS (the Ministry of Food and Drug Safety) took over the request document from the Health Insurance Review & Assessment Service, and started evaluating the safety and effectiveness. Before then under the pharmaceutical law, hospitals or medical institutes applied for the approval of use of the medication for the off-label use, and then the Health Insurance Review & Assessment Service replied back with the possibility of the use. The committee consisted of medical experts, who examined the submitted documents along with added research documents, and then decided on the adequacy of the off-label use. Based on the result of the adequacy of the off-label use, which was decided by each area's experts' judgment and experience the HIRA (the Health Insurance Review & Assessment Service) informed the adequacy of the medication and the entitlement of insurance to the medical institutes. This process had more to do with the medical insurance policy because its priority focused on the discretion of the entitlement of insurance for the medications which were used differently as off-label use; in other words, when some of the off-label medication was applied; if there was positive effect of treatment and whether it would be entitled for medical insurance.

After the assessment task of the off-label use medications was transferred to the MFDS, not only the adequacy/effectiveness but also the

safety become very important sectors. According to the MFDS's definition[1], 'off-label use medications' means due to the disease's characters which are owned by different patients and the limitation of clinical experiments, the medications are used in the field based on research and clinical experiences beyond the limit of the permission for the medications. The purpose of the assessment is to pursue the proficiency of the assessment and management of the task by setting the standards - the objective of the assessment, assessment standard and the lists of actions for the result - for the safety and the adequacy of the medications which are used beyond the limit of the permission. The objectives of the assessment: 1) the items are requested to be examined by HIRA based on the standard and process of approval for the use of the medications beyond the limit of permission or report not covered by insurance, 2) the items are requested by the Korean Medical Association, the Korean Pharmaceutical Association or related organizations concerning the safety and the adequacy, 3) the items are considered as items to be assessed concerning the safety and the adequacy by the chief of MFDS and the chief of MFDS will assess the items first which cause some safety issues related to the medications for children or pregnant women. The references for the assessment: 1) the references which are submitted by the requester (or the organization) related to the safety and adequacy, 2) the references which were submitted to MFDS for the application of the permission(report): (these include the results of clinical trials which were conducted under the approval from MFDS, the results of re-examination for the new medications, the references related to the information of the safety and so on), 3) the permitted items in the US, the UK, Japan, France, Germany, Italy, Canada and

[1] www.mfds.go.kr/jsp/common/download.jsp?fileinfo.../1/

Switzerland (Codex[2] or the items which can be checked on its website), 4) AHFS, Martindale, Micromedex and etc. the information of the use of the medical supplies, 5) the thesis which are published in PubMed, academic magazines, the texts which are approved by the related academic associations and used by the medical or pharmaceutical universities, 6) the guidance of medical examination and treatment which is accredited by the medical association, 7) the references (letters) of the actions related to the safety which are issued by the MFDS, FDA, Europe EMA, Japan MHLW and other medical authorities, 8) the advisory opinions of the central pharmaceutical review committee or related academic association's advisory opinion, 9) the references of detailed outlays are provided by the HIRA. The standards of the approval for the references of the clinical research are divided into 4 sections depending on the research categories: [category 1] the systematic review on the subject of the randomly sampled control groups (systematic review, Meta analysis), [category 2] the review on the randomly sampled controlled groups or the systematic review on the subject of category 3, [category 3] the review on the semi-randomly sampled control groups, case control study, cohort study, observational and analytic study, [category 4] cross-sectional study, before/after study, case report, case series, non-analytic study. The MFDS requests the clinical experiment as research to a research institute to prove the safety or the effectiveness of the off-label use medications, or advises to add the indication for the use of a medicine of the off-label use which is found through the clinical experiment. However there is often difficulty in the

[2] Codex including the current year and within 3 years[the US one-PDR, Japan codex, the UK one-ABPI DATA SHEET COMPENDIUM, Germany-ROTE LISTE, France-VIDAL, Italy-L'iniformatore Farma-ceutico, Switzerland-Arzneimittel Kompendium der Schweiz, Canada-Compendium of Pharmaceuti-cal and Specialties]

clinical experiment, so no progress is made.

In other countries' cases of off-label use medications, in the US, prescribing medications beyond the limit of the permission is allowed yet the entitlement of medical insurance is considered as individually and the safety and the effectiveness comes with the doctors' responsibility. There should be a lot of difficulties to enable to use the medication for patients because the permission is not made. The pharmaceutical companies cannot market or promote the medications as off-label use except the original purpose of the use. The pharmaceutical companies should get the permission for the off-label use of medication with the clinical experiments after accumulating proven cases of the safety and the effectiveness. However realistically because of the lack of profit, it is common that pharmaceutical companies avoid this process. The American FDA submits a request for clinical experimentation to the company; for the medication that causes safety concerns, raising doubts of its effectiveness. The FDA actively requests clinical experiments for the off-label use medications for the case of rare incurable diseases with no treatments.

If we look at the medications which are in the process of proving the effectiveness of the off-label use medications or already proven clinical experiments[3], there are 69 cases are in the process or related to Rituximab-GVHD(Graft-Versus-Host Disease), there are nine clinical experiments related to Imatinib-GVHD, and there are five research projects undergoing related to Tacrolimus-Vitiligo. Six clinical cases which used Rituximab as a treatment have got the results, four clinical experiments related to Imatinib-GVHD are done and three clinical cases have gotten the result. Two clinical experiments related to Tarcrolimus-Vitiligo have been made. The information

[3] www.clinicaltrials.gov

of clinical experiments brought from Clinicaltrials.gov is collected in March, 2014. Here are frequently used off-label use medications examples; Rituximab, Imatinib, Leflunomide, Tarcrolimus, Bortezomib, Erythropoietin, Verteporfin, Infliximab, Abciximab, Sirolimus, Etanercept, Deferiprone, Misoprostol, Quetiapine, Clonazepam, Mycophenolate, Methotrexate, Octreotide, Progesterone, EGF and so on. The FDA made the guideline for the use of off-label medications and requests the clinical experiments to the pharmaceutical companies or research institutes and if it is possible to do clinical experiments the FDA supports them. In England, only the cases proved by the prescribers with the evidence or experience for the better effectiveness and the safety are allowed to prescribe the off-label use medications[4]. In Australia, in the guidance of the use of the off-label medications, it makes clear that only it is allowed to be used when there is the consent with the patient and the high level of scientific ground[5].

[4] GMC|Good practice in prescribing medicines-guidance for doctors. Gmc-uk.org 2007-02-16

[5] www.ciap.health.nsw.gov.au

1.3 The Necessity of Study Using Bioinformatics

It is essential to have the clinical experimental results on the safety and the effectiveness of the off-label use medications. However it is difficult to have proper clinical experiments due to the lack of the case numbers because most of the cases are either rare diseases or incurable ones. Even though for the small size of clinical experiments, it is hard to find the participants and also there could be the ethical issue raised related to children patients' clinical experiments. Because of all the practical problems, there are many cases which cannot satisfy the requirement of the clinical experiments for the permission system therefore the assessment of adequacy of the off-label use medications make a judgment relying on the research references which provide the basis. If those references satisfy the standards listed above, it does not seem to have any big problems. However because actually the ground of these references is weak, there needs to be a reasonable alternative.

One possible alternative is the repositioning of medications. The repositioning of medications is the method that newly discovers the indications for the use of a medicine by finding out and adding the targets which are not intended but discovered. Apart from the expectations, newly discovered targets reveal as side-effects or effect on the accompanied diseases. For instance, the diabetic treatment, Metformin is used for Polycystic Ovary Syndrome which is frequently shown in the patients who have Metabolic Syndrome as the off-label use[6] (Nathan and Sullivan, 2014) and also used to prevent the weight gains caused by intake of psychotropic medicines or as the off-label use to treat (Generali and Cada, 2013). In the systematic review and

[6] http://www.medscape.com/

the Meta-analysis which is to discover the effectiveness of the off-label use as a treatment for the atypical psychotropic medications for adults, because the atypical psychotropic medications are often used as the off-label use for dementia patients' anxiety, agitation and obsession, the effectiveness of each medication is compared. Among atypical psychotropic medications, Quetiapine is effective on the general anxiety disorder and Risperidone and is effective on obsession (Maher et al., 2011). Apart from the systematic review and the Meta-analysis, the theological method to prove the adequacy of effectiveness of the off-label use is needed.

This paper looks into the methods and the results of studies that try new methods to find indications of drugs using bioinformatics. In the research which uses the Bioinformatics methods to find the new target of the specific existing permitted medications, Xie et. al. (2011) analyzed computer data using SMAP(software and web service for binding pocket similarity search and polypharmacology) software through the systematic review of the X-ray of the "Nelfinavir binding pocket" of the "HIV protease-1 co-crystallized with Nelfinavir" and study of the data bank deposition. The most influential "Nelfinavir off-target" is sorted as ABL, ARK, AKT2, CDK2, EGFR, EPHB4, FAK, FGFR, IGF-1R and PDK1 and with consideration of chemical, structural and energy elements, ARK, ATK2, CDK2, EGFR, FAK, IGF-1R and PDK1 is considered as the most influential "Nelfinavir off-target".

Kinnings et al. (2009) repositioned Parkinson's treatment, Comtan (Substance name: Entacapone) using the chemical system biology for Multiple Drug Resistance Tuberculosis. Kinnings, et al. developed the approaching method of the Chemical System Biology in order to confirm the off-target of the main medications for wide proteome, and in this research, they showed the value of this approaching method by discovering the fact that

Comtan, currently used as Parkinson's treatment, can be used for tuberculosis which has shown resistance to other treatments. This Entacapone, is expected to be combined with Enzyme InhA, and directly block the substrate from combining. The minimal inhibitory concentration of Entacapone for the Tuberculosis bacillus is 260.0 ㎛, which is lower than the concentration that shows cytotoxicity for human beings. If the protocol suggested in this research be generally applied, the development of the new treatment can be accelerated with the guaranteed safety. The research which found the medication's target using the topological character which was analyzed by computer after consolidating the functional genomic data among tuberculosis bacillus, and generating the functional interactive network offered the opportunity of enlarging the potential medication's target range and the opportunity to move to the best target-based strategy (Gaston et al., 2011).

Bleakley and Yamanishi (2009) find it an amazing challenge to predict the accurate, correct and new drug-target interaction under the circumstance that there is not much to be discovered in drug-target interaction. Therefore in their attempted research, they predict the target protein of given medication using "bipartite local model" and then predict the medication for the determined protein as the target. For the "drug-target interaction" estimated with this method, two independent predictions are possible, and combining those two predictions, the prediction of final interaction is individually made. With well delivering this suggestion, four classes of the "drug-target interaction network"; Enzymes, Ion Channels, GPCRs (G protein coupled receptors), and Nuclear receptors are predicted.

Shigemizu et al. (2012) thinks that already permitted medications could be used for the use not intended because with the possibility of processing the huge amount of data, the fast and reliable systematic verification is possible.

In the research, the realigned candidate medications which are effective on Breast cancer, Myelogenous Vitiligo and Prostate cancer are confirmed. The method used and applied here is to find the inverse correlation between the ‘gene expression level’ which is the most unstable cancer tissue and the ‘gene expression level’ which is the most unstable derived by the bioactive compounds. With this method, using various ‘gene signature’ they discovered the bioactive compounds which control given diseases. This is different from the old method which only used the small sized, fixed signature. Candidate medications for breast cancer, myelogenou-vitiligo and prostate cancer, 32% out of the number of 79, 13% out of 94, 17% out of 88 are FDA approved or were suggested in research. It means that this method can be effective in the process of finding and developing new treatments and there is a possibility of implication for the use of individual custom made medications.

The individual custom made treatment for cancer patients is getting more important. The research for cancer done over centuries shows that the molecular biological discovery about carcinogenesis and according to this, even the same type of tumor is started by different mutated oncology and can react differently to the same treatment (Kim and Han, 2013). Take breast cancer as an example of the development of the same and general treatment to individual custom made treatment. Dinh et al. (2007) says that the standard of choice for the supplemental treatments after the surgery of breast cancer shifted from the recurrence risk to the treatment target and reaction. Before the early stage of breast cancer patient’s choice of supplemental systematic treatment focused on patients, the advantage of supplemental treatment by prognosis related to the cancer, and recurrence risk evaluation (Chin et al., 2006). In other words, as far as the choice of supplemental treatment goes, from 1990 to 2005, the anatomical cancer stage such as the size of the cancer,

whether it got spread to the lymph was considered as an important element to choose the method of chemotherapy and it is closely related to the recurrence risk. However after 2005, the treatment reaction element like the hormone receptor expression takes an important role in the decision of the supplemental treatment. The future treatment is the concept of choice, so the treatments are expected to be decided based on the molecule information; the molecule subtype of tumor, the result of risk evaluation of Oncotype Dx and the prediction result of medication's reaction and so on.

The first discovered treatment's target in breast cancer is the estrogen receptor. Tamoxifen is the selective regulator of the receptor; it interrupts the chronicle channel which controls the cell division and growth by competitively refraining the Estradiol combining with the receptor (Jordan and Dowse, 1976). In the 1970s, the Tamoxifen was used non-selectively, and it brought about 30% of prognosis improvement (Buzdar and Hortobagy, 1998). However depending on the revelation of estrogen receptor, when it was used on the selected patients, the advantage of Tamoxifen improved up to 80%. From the early 1990s, as the immunohistochemical staining for estrogen receptor was conducted as the required examination, it became the beginning of the custom-made treatment (Ravdin et al., 1992; Smith et al., 1987).

HER2 (Human epidermal growth factor receptor 2) is the receptor which takes an important role in cell growth, division and survival as the transmembrane glycoprotein of 185 kd. The amplification and over-expression of HER2 is found in 25~30% of breast cancer patients and it is related to the aggressive reveal of tumor, and the bad prognosis (Slamon et al., 1987). In the 1980s after the humanized monoclonal antibody; Trastuzumab which combines with the other domain of HER1 receptor cells being developed, as the result of clinical treatment of five supplementary treatments

released, the innovative development was made in breast cancer treatment. They are HERA, NASBP-B31, and NCCTG/N9831. BCIRG 006 and finHER trial, and all of them showed the reduction of reoccurrence rate by 39%-50% and the reduction of death by 30%(Piccart-Gebhart et al., 2005; Romond et al., 2005; Tan-Chiu et al., 2005; Slamon et al., 2011; Joensuu et al., 2006; Wang et al., 2013). This achievement in the early stage of breast cancer is the biggest one after introducing the Tamoxifen for hormone receptor positive patients, and this success is the result of selective treatment for chosen patients who have the over-expression and amplification of HER2. After this, Lapatinib, Pertuzumab, T-DM1(Trastuzumab) which target HER2 show significant effectiveness of anticancer, enlarging the selection of treatments for the HER2 positive cancer patients and make the dramatic improvement of survival rate. In the future, the development of biomarkers which are related to the activation of P13K channel; the element which is related to the resistance toward Trastuzumab PTEN disappearance and PIK3CA mutation will play a key role. Through proactive large scale researches, the effectiveness will be proved (Wang et al., 2013).

Since Perou et al. (2000) introduced molecular portrait in breast cancer, the importance of molecular subtype is being emphasized more (Paik et al., 2006), now these luminal A, B, basal-like molecule biological subtype is very important in the plan of supplemented systematic treatment. Rather whether hormone receptor expression, HER2 and Ki-67 than the size of tumor or the spread to lymph become more important and through the use of multi-gene assay Oncotype DX or Mammaprint with more accurate indications, the supplemented systematic treatment can be chosen after the surgery. Oncotype DX introduced in 2006 is the representative custom-made treatment which is used effectively to distinguish the patients group who are hormone receptor

positive but spread on lymph negative and yet can get the additional advantage of chemotherapy on Tamoxifen treatment (Perou et al., 2000). Oncotype DX is the indication suggested by The American Society of Clinical Oncology (ASCO) 2007, since 2008, The National Comprehensive Cancer Network (NCCN) advised to reflect the result of 21 gene RT-PCR assay (Oncology DX) based on Category 2B on the decision of supplemented treatment for breast cancer patients in its guide line.

As resistant bacteria appears against the treatment for the disease and the multiple drug resistance of the resistance bacteria widely spread all over the world, there is a need for the methodology which can verify the reason fast and effectively and the inspection method based on the target from information of massive compound has used a lot. However without the knowledge of the structure of target this method is impossible. On the contrary, the entire organism inspection is used more frequently recently because it is possible without knowing the target, but time and expense are the elements of limitation. The elements of limitation can be avoided by prioritizing the order of molecules for the inspection program using a computerized approach. In the research of the predictive model for anti-tuberculosis molecule, four managed classifiers were conducted in bioassay inspection of three opened tuberculosis bacteria inhibitor using the physical-chemical characters of compound. Predictive model was confirmed through various statistical means. In conclusion, in this research, the target-agnostic predictive model for anti-tuberculosis treatment is made by applying the machine learning approach for analyzing high capacity biological inspection data about anti-tuberculosis activities (Periwal et al., 2011). Periwal et al. (2011) made the predictive model using the machine learning approach in 2011, in the 2012 research they made “in-silico predictive model” in the non-balanced massive data of anti-

tuberculosis using four supervised classifiers(Naïve Bayer, Random Forest, J48 and SMO). It offers 3~4 more strengthened ones rather than randomly selected ones.

The side-effects shown when medications on the market are used inform the profile of human-beings' phenotype. This phenotype information sometimes offers additional indication for the use of a medicine for treatment of disease. Yang and Agarwal (2011) drew the interrelation between 3175 side-effects and diseases. This is the result from combining between the interrelation of side effect-medication in medication information and interrelation of medication-disease in PharmGKB (the Pharmacogenomics Knowledgebase). This interrelation, for instance, offered the medication realignment theory of "the medication that causes hypoglycemia as a side-effect could be the potential candidate cure for diabetes". With the character of side-effect, the Naïve Bayes model enables prediction indicators for the use of a medicine as a cure for 145 diseases was made. 92% of this model is over AUC 0.8 and with extension of this method when it was applied to predict new indications for the use of a medicine of clinical compound, 36% of suggested model was AUC 0.7. In this research, it is suggested that medication realignment should be rationalized based on clinical phenotype analysis as well as for the safety evaluation of the harmful effect focusing on the side-effects witnessed on clinical trials.

The research which predicts the combination of medications by combining the date of molecule information and pharmaceutical data has been done (Zhao et al., 2011). The treatment of combination of medications is a good strategy to reduce the side-effects during the treatment of multiple diseases and enhance the effectiveness. However screening the completely new combination of medications thoroughly is not realistic. Therefore using

the new computer approach to predict the combination of medications by combining molecule and medication data, the method of research is organized and expressed by character of the medication's target or the indications of the use of medicine, and if a few of characters are integrated, new characteristic forms are found in the combination of already permitted medications. With this characteristic pattern, not only it is possible to suggest the combination of new medications but also action mechanism of the combination of medications can be explained. 69% of top rank in the predicted combination of medications is proved by researches and the rest of the combination of medications is suggested that it has the possibility of new combination of medications.

There was research which attempted the huge scale docking of small molecule medication corresponding to medication target protein in computer approach research which seeks the new target out of existing medications (Li et al., 2011). As the result of attempting, the relation map of medication-target interrelation interval was obtained and the new interrelation was found. The method used here focused on removing the false positive interrelation prediction by setting up the standard using the matched score with the already known interrelation docking and the specialty. The database accumulated in this way contains 252 of human target protein and 4621 of already permitted or experimental small molecule target out of Drug Bank. By crossing over docking and screening by the strict score, the top medication-target interrelation was selected. The proven fact through is that Nilotinib is a strong MAPK14 inhibitor and it suggests that this medication can be used for infectious diseases.

In the published research, the predicted interrelations of top 31 conducted in this research are shown to be proven experimentally, so this

study method is considered to expect to use this approach. Newly discovered interrelation enables us to realign the applied medication as the off-target related disease treatment, to reveal the mechanism of drug action and to understand the side-effects. Polypharmacy means medicating many medications all at the same time and it is the treatment which combines functionally non-related medications; this is to prevent the drug resistance which could be caused when the medication is selectively effective on only one ligand and polypharmacology is being used with the expectation of more than one effect with one medication using the fact that one medication has more than one target and many mechanism of drug actions. The researches which believe that focusing on polypharmacology will open the future of treatment development are being actively conducted.

Recently in spite of the amazing scientific development and investing a lot on a R&D, newly developed medications often disappear from the pharmaceutical market after being launched because of the side-effects or the safety issues. Drug molecules cause polypharmacology to often interact with other targets and when the interrelation with unintended target expresses, it appears as side-effect. Polypharmacology became one of the prominent challenges in drug development (Reddy and Zhang, 2013). This challenge is seen as the opportunity to find a reasonably developed way for effective and safe treatments. Although polypharmacology is important in medication development and discovering, it is difficult to completely review all of the targets in the applied range with experimental ways. The most possible way is to use omics (proteomics, cheminformatics) technologies (Schmid and Blank, 2010; Joyce and Palsson, 2006). The purpose of using the method of polypharmacology is to find not-known off-target in existing medications (Oprea and Mestres, 2012; Oprea et al., 2011; Achenbach et al., 2011). This

approach needs to integrate computer plan, chemical compound, inside laboratory biological pharmaceutical experiment and clinical experimental from different regulation systems (Yamanishi et al., 2008; Dar et al., 2012). With the basics of chemical similarity, in the new study which predicts new indications for the use of a medicine and unknown side-effects (Keiser et al., 2009) identify new target with ligand and compared 3665 medications which respond to hundreds of targets and were permitted by the FDA and the medication under experiment. The chemical similarity between medications and ligand enables to predict thousands of unexpected connections. Overall 23 new targets were confirmed and five of them seem very pursuable. Understanding, knowledge and prediction of off-target can be a reasonable approach to understand side-effects (Echiborn, 2011). In this study which provides information of 25,000 medications including the ones now off the market because of side-effects or under experiment, the network is made from publicly available information which was collected and edited; about 21,500 of interrelation between medications and 104,000 protein; interrelation protein and protein based on this network, realignment of medications could be started. The network, named "PROMISCUOUS" is publicly available.

The methods to reposition medications used in bioinformatics take other off-target from publicly opened databases along with the medications known to have permission and getting indications for the use of a medicine and use the off-target as main target to figure out if the medications which have indications for the use of a medicine can be used for other use. The general method is to find out the genes which are related to diseases using the genetic information and search the medication which targets the genetic protein. Without any start initiation of disease or medication, aimlessly finding new indications for the use of a medicine toward every medication or

all the diseases can be progressed. Because of the time limit, the size of scale is needed. Therefore in many cases of the study for repositioning of medications, it starts with the medications for diseases which draw social attention or issues limitedly.

GenBank which provides genetic information publicly is a genome sequence database provided by the NCBI (National Centre for Biotechnology Information), NCIBI is the subsidiary organization of NIH and at the same time it is part of The International Nucleotide Sequence Database Collaboration. This united DB is consists of the information of the DNA DataBank of Japan (DDBJ), the European Molecular Biology Laboratory (EMBL) and GenBank at NCBI. The information of these three organizations is updated on daily basis. The information of the sequences of over 100,000 creatures has been gathered for over 30 years and this information is used to provide the DB with the basics for researching, comparing and predicting sequence and structure of DNA or protein of creatures by biologists. The NDBI BLAST program is usually used to search gene information, and includes sequences of other than type strain compare to commercially paid DB yet it is less refined and limited for providing related sequence (Wikipedia). In the research by Park et. al, they analyzed making connections with other opened DB like GenBank, EzTaxon and BIBI and the results showed that analyses performed using GenBank combined with EzTaxon were more discriminative (Park et. al., 2012).

Genotator is an open access in http://genotator.hms.harvard.edu for academic study and it provides the interrelation of relation between genes and diseases. It organized the number of genes in order depending on how relevant the interrelation; by combining data from other areas or taking gene sequence. It is operated based on UNIX and back end, written in perl and

TKperl, it uses sequence analyzing program. The sequence analyzing program is divided into three areas; gene finder (Genie, GRAIL, GeneFinder, xpound, GeneMark), database homology searches (BLASTN, BLASTX), sequence feature predictors (start/stop codons, open reading frames, promoters, splice sites, tRNA genes). Front end is written in perl and TKperl and uses Gregg Helt's bioTKperl widgets. It was developed by SUN (Sun Microsystems, Inc) and installed by SGI (Silicon Graphics International) and DEC (Digital Equipment Corporation) alphas. Because Genotator is not only a commentary method but also easy to use, free and provides the source, it can be manipulated depending on researchers' needs (Harris, 1997). The website, Genotator.hms.harvard.edu was operated by the Harvard Medical School Wall lab. Then its ownership changed over to Stanford Medical School and https://wall-lab.standford.edu/ was in management, but today 2014, September when it will re-open or operate is unknown. Figure 1.1 makes it easy to understand of algorithm of Genotator (Wall et al., 2010). Scoring formula which makes it quantified about the interrelation between gene and disease in Genotator below.

$$Y=X1-X2+\varphi X3+1/\gamma X4+1/\kappa X5$$

Where, Y is Genotator score (GS), X1 is the score of gene-disease association in genetic association database (GAD), X2 is the score of none gene-disease association, X3 is gene prospector's score of gene-disease association (GPS), X4 is DB score from all 11 database which shows genetic information, and X5 is the number of references to provide genetic information. The constant, φ, γ, κ are used to give weights to GPS, DB, REF and overall it is best performed when 100,10,5 are used. In the research of Wall et al, Y was shown as GS, X1 as GAD Y, and X2 as GAD N, X4 as DB

and X5 as REF. Thus,

$$GS=GAD_{Y} - GAD_{N}+\varphi(GPS)+1/\gamma(DB)+1/\kappa(REF),$$

Where,

GAD_{Y} = Total number of "Yes" labeled associations for the gene and disease in the Genetic Association Database

GAD_{N} = Total number of "No" labeled associations for the gene and disease in the Genetic Association Database

GPS = Gene Prospector'Ss score of gene-disease association

DB = Number of total databases (out of 11) that the gene appeared in

REF = Number of total references for the given gene

According to Genotator algorithm, the characters are collected from databases such as GAD, Gene prospector (HuGE navigator) and NCBI and depending on the contribution, relation score is calculated following the scoring algorithm.

The DB provided in Genetator are 11: GeneCards, Genetic Association database, HuGE Navigator, Human Gene Mutation Database, Online mendelian Inheritance in Man, Your Favorite Gene, UniProt, PharmGKB, Entrez Gene, WikiGenes and GenAtlas. The special information from the DB is list of genes, relation with diseases, p-value (from genome wide association studies), Gene Prospector Score, List of Pubmed References, official full name, symbol synonyms, chromosome Number, location on chromosome, gene ID and Ensemle ID. Wall et al. (2010) who are responsible and operate Genotator site confirm that after examining the accuracy of information provided by Genetator about Autism Spectrum Disorder (ASD), Parkinsons's Disease and Alzheimer Disease which are well-known about interrelation

between gene and disease, individually 75%, 60%, 75% match the list of gene and high ranking order in other references and DB. The programming word used is JAVA and Python and can be downloaded as the information of gene in the format of FASTA. In Genetator, the specific information about disease can be learned with interrelation score, so when it comes to treatment, the effectiveness of mediations can be proved more than before.

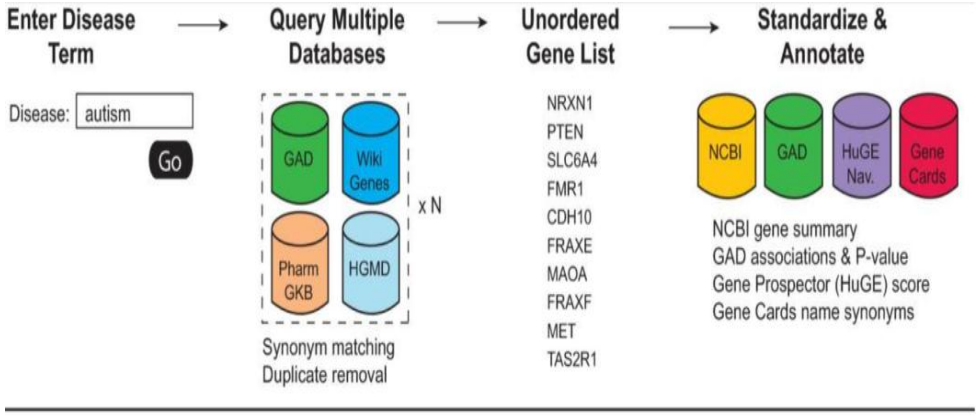
Some DB use the methods from the researches that sample the information needed, find out off-target and suggest realignment of medication. In the case of analyzing the protein of creature with computer and confirming the medication target with topological character in network, the united functional interrelation network is provided by STRINGS (the Search Tool for the Retrieval of Interacting Genes/Proteins) DB. To find out the target with the similarity of ligand, the target is compared using BLAST algorism and Baysian classifiers with the predicted score by SEA (similarity ensemble approach). Confirm medication-target predicted in MDDR (MDL Drug Data Report) and WOMBAT (the World of Molecular Bioactivity) DB, and new medication repositioning which is not in DB can be suggested. The information of genes which can be downloaded in XML format is analyzed using LingPipe-package or text-index is made using Lucene package provided Apache Software Foundation. In the software, Cytoscape, which visualize network, general formats like XGMML or SBML are used. When certain medication is given, the method to predict the target protein is SLMs (bipartite local models). This method predicts the given medications first and predicts the medications targeting the given protein: after individually predicts and then make a network and confirm the medication-target in the network. Another method which compares the accuracy for predicting target is KRM (kernel regression-based Method) and NN (baseline method of a nearest

neighbor) algorism. With BLMs, a few medications can be chosen to practice experimentally.

Generally bioinformatics methodology compares sequence or structure similarity using information of genes analyzed from DB. The next step for this method, the attempt of realigning existing medications for the new use is based on DB and uses the software is organized up to the purpose. http://bioinformatics.charite.de/promiscuous/ an open-access and free website makes network based on structural similarity of medications and enables to use network-based approach as the starting point of medication realignment. Using this website enables to make interrelation network with medication, target and pathway. Genotator mentioned above is meta-database and because it provides the whole lists of diseases-genes interrelation, gene mediated medications realignment can be tried-out. This is a two-step method, first get the genes related to two diseases from Genotator, find the shared (common) gene and then make protein-protein interaction network. As the next step, get the information of medications as treatments for two diseases from DrugBank. With this information, make drug-similarity network. If the target shared between medications, structural similarity, has similar side-effects or having the interrelation with same medications, those medications have a lot in common can be considered as treatments for different diseases. When the study of medications realignment is started, with the clients who had clinical experiment, look for the treatments for the diseases which have no cure and with pharmaceutical companies for developing new products, try to realign the medications first which have accumulated information and side-effects.

One type of medication realignments is off-target use of drugs and the method of confirming the safety and effectiveness with general bioinformatical way is not different from the way of medication realignments.

The difference is that it starts from the medications which have been used for a while. The way of confirming the adequacy of off-target use of drugs and the way of medication realignments are the same, yet off-target use of drugs have been somewhat proved for the side-effects and effectiveness in references or clinical trials. There are many studies which try to find the new indications for the use of a medicine with certain characters from existing medications are under progress and the methodology of these studies is studied and provided. In this study, using Genotator which provides overall information of genes organized from DB, the information of genes for the rare incurable diseases which do not have cure will be described. By revealing off-targets other than permitted off-targets for off-target use of drugs used with some basics, the effect revelation should be explained and additional side-effects can be understood.



Final Ranked Autism Output

Gene Symbol	Genotator Score	Ensembl ID	Gene ID	Gene Name	Synonyms	Chr.	Location	# Refs.	# DBs	HuGE Score	GAD Associations Yes/No
SLC6A4	136.7	ENSG108576	6532	Solute Carrier...	5-HTT|5-HTTLPR|...	17	17q11.1-q12	26	6	1.335	2/4
NRXN1	27.2	ENSG179915	9378	Neurexin 1...	-	2	2p16.3	5	8	0.262	0/0
FMR1	22.6	ENSG102081	2332	Fragile X...	FMRP|FRAXA|...	X	Xq27.3	6	3	0.204	1/0
PTEN	19.6	ENSG171862	5728	Phosphatase...	MHAM|PTEN1|...	10	10q23.3	4	7	0.188	0/0

Figure 1.1 Genotator algorithm. This figure describes how Genotator works. When user enters a disease term, gene information is gathered from 11 database and overlapping terms are deleted and organized. Then, standardization and calculation of association score are carried out based on the information collected from GAD, Gene, Gene Prospector (from HuGE Navigator), and NCBI. (Wall et al. BMC Medical Genomics 2010 3:50 doi:10.1186/1755-8794-3-50)

1.4 The Purpose of Study

The objective of this study is to provide evidence for the safety and effectiveness of agents that are currently being used for off-label indications. The method of finding new targets other than the targets known in existing medications is prevailed in bioinformatics and there have been results in many medications. The genes which are related to target protein of medications-diseases are being known and as the differences in reaction to treatments depending on difference of individual genes draw attention, many studies about custom-made treatment are prevailed. Currently using the medications differently from the permitted contents is taken place a lot in cancer treatment. For instance, as the examination of genes of patients who have lung cancer or colon cancer is expected to EGFR mutation, ALK merge genes and KRAS mutation, it is used when there is no effect on specific cancer treatment. If the mutation is confirmed in the experiment of genes, the effectiveness of treatment can be improved by using other anti-cancer treatments. Breast cancer is one of the cancers which have a well-known genetic factor, 5~10% of patients are familial breast cancer patients. It is well known that the mutation of BRCA1, BRCA2 and p53 can cause breast cancer[7]. When the treatment method is decided for breast cancer patients, based on the medical basics from references as the basic treatment, the molecular and biological characters of breast cancer should be considered (Oh, 2012). The most important thing is to confirm the revelation of hormone receptor and over-revelation of human epidermal growth factor receptor 2 (HER2) protein, depending on this, supplementary chemotherapy and metastatic cancer

[7] http://www.kbcs.or.kr/ Korean Society of Breast Cancer

chemotherapy are decided. Especially about 20% of breast cancer patients over-reveal HER2 protein, and those who over-reveal HER2 protein are reported to have bad prognosis compare to others who don't have (Slamon et al., 1987), the possibility of target treatment was suggested for this, in 1998 as humanized monoclonal antibody Trastuzumab which target extracellular domain of HER2 protein was developed, the improved result of treatment was reported in metastatic breast cancer when HER 2 is revealed compared to the previous treatment with chemotherapy only(Slamon et al., 2001). This development of target treatment became a turning point in breast cancer, and is one of the most important parts in treatment.

As the researches that the target protein of many medications used as off-target use of drugs is connected to not only the gene related to one disease but also related to other diseases have been done, existing medications can be used as new treatments within a short time. The most appropriate way is to sample the information needed from big data using computer approach in order to use the massive information of genes and medication accumulated for the development of the new indications for the use of a medicine. In this study, I try to show the logical possibility of using the same medications for different diseases by making network of genes sampled from Genotator and DrugBank and genes shared in this network as mediator.

There are cases were not permitted in this way yet used but now as a result of clinical experiment, the new indications for the use of a medicine are added. The biological product, Rituximab is one of examples. Early Rituximab was limited to Non-Hodgkin's Lymphoma: NHL as permitted indications for the use of a medicine in 1997 and in 2006, Rheumatoid Arthritis: RA and in 2010, Chronic Lymphocytic Vitiligo: CLL are added. In case of a rare incurable disease, Wegener's Granulomatosis (WG,

Granulomatosis with polyangiitis; GPA) among 85% of patients, as Antineutrophil Cytoplasmic Antibodies; ANCA is proved as an autoimmune disease with positive reaction, is has been used as off-target use and in 2011 April based on the clinical experiment it got additional indications for the use of a medicine (Falk et al., 2011). Anti-neutrophil cell cytoplasm anti-body and ANCA are the anti-bodies highly related to ANCA-associated vasculitis; GPA, Microscopic polyangiitis; MPA and Churg-Strauss syndrome. 70% in MPA and 50% in Churg-Strauss syndrome, it shows relation[8]. In these rare incurable diseases, if the mechanism of outbreak can be studied and revealed from the point of view of the molecular biological, the development or discovering of treatment will be accelerated. There are cases of the use except the original use is applied for the experimental purpose or when treatments are not working.

In French national institute of health and medical research, as the result of applying Rituximab to the patients who have Pemphigus, 59% out of treated patients could live without symptoms for 6 years (Colliou et al., 2013). However Roche, the pharmaceutical company, has no plan to apply for the approval as a treatment for Pemphigus. This company also doesn't encourage the use of Rituximab as off-label use for Pemphigus although they acknowledge that it has been prescribed[9]. Although Roche does not consider adding indications for the use of a medicine because of its lack of actual profit; Pemphigus is a rare autoimmune disease happening 7 in 1,000,000,

[8] http://www.uptodate.com/contents/pathogenesis-of-granulomatosis-with-polyangiitis-wegeners-and-related-vasculitides?source=search_result&search=wegener+granulomatosis&selectedTitle=6%7E150

[9] http://www.newsmp.com/news/articleView.html?idxno=104003

because in the field only treatment is steroid and immune restrainer as supplement and it has high rate of re-occurrence with severe side-effects, there should be substitute medications. Since there are references showing that Rituximab is effective on Pemphigus as off-label use (Cianchini et al., 2007; Ahmed et al., 2006) and target protein is shared as common, there is a theological reason of use as off-target use of drugs(Feldman and Ahmed, 2011; Muller et al., 2010). When there are no treatments at all or treatments which cause severe side-effects, there should be replaceable treatments. Therefore there needs to be support and encouragement from government for clinical experiments and researches for the pharmaceutical companies which pursue economical profit.

Medication realignment using bioinformatics compares the degree of instability in disease-associated genes to medication destabilized genes. In this study, it will be shown that based on the medications which registered and used for off-label use at MFDS and their use, after pairing up original applied diseases and off-label use of drugs, find the common genes, analyze the level of relation of genes with STRING, find medications' target, structure, medication interrelation and side-effects and then make network about similarity of medication and if there are more than two common parts in this network, there would be the same indications for the use of medicine between medications. The hope for this study is that it would be used as one of references to prove that some currently used off-label use are safe and effective.

CHAPTER II. MATERIALS AND METHODS

2.1 Protein-Protein Interaction Network Based Research using STRING

There are many ways to systematic repositioning of medications. The candidate medication can be round in the similarity of diseases or it can be started with hypothetical assumption that similar medications would be effective on the same diseases. For instance, the medications which show the same side-effects would commonly effect on one disease. However these researches have not been proved right yet. The purpose of this study is to find the repositioning of off-label use have been used and new indications for the use of a medicine using the method of repositioning of medications. Two diseases which show the similarity in pre-outbreak are chosen, and get the information of related genes for each disease from Genotator. The list of genes which is needed first out of the information of genes in FASTA format is, organized separately. The shared genes between the diseases which have too many lists of related genes and the diseases which don't have genes well-known are chosen up to the relation score 1.00 to compare only the similar relation level. The interrelation of protein between the shared genes is from STRING DB. STRING shows both directly related interrelation and functional indirectly related interrelation and refer to four DB; Genomic Context, High-throughput Experiments, Co-expressions and Previous Knowledge. STRING has the information of 5,214,234 proteins and 1,133

species of creature. The common genes in paired diseases can be drawn as interrelation network between protein-protein by adopting “Search by name” in STRING. In the past, the data reference obtained by adopting the information of genes was saved on http://string-db.org; after signing on, go to my data and then the applied date and interrelation between protein-protein networks. In the united network, the bold line means strong relation when it is shown with confidence view and the lines of different colors show the type of references which prove the relation. This is the form of summary for 6 of protein-protein interrelation network which are analyzed the interrelation with finding the common genes in 6 paired diseases (Figure 3.1~3.6). Then get the information about medications used as treatments for the diseases as a pair from DrugBank, the drug database. In the first stage, if the target of medication is related to protein-protein interrelation network, that medication can be the candidate of realignment medications which will have new indications for the use of a medicine. However there are targets which are not known yet, in the second stage, based on the similarities of the treatment drugs prescribed for the diseases, the possibility of medication realignment will be examined.

As the first step, the genes which related to the diseases from an open-access information meta-database and Genotator[10] are taken. The information of genes can be downloaded in FASTA format at Genotator. A few types of diseases are classified by comparing the off-label use drugs and the permitted indications for the use of that medication. Genotator calculates the score depending on the possibility of relation of genes related to the individual disease. Because there are many diseases which have no related genes

[10] genotator.hms.harvard.edu

discovered, while there are too many genes related to some diseases, to make it more effective and look in details, the genes which were calculated the scoring up to 1 by Genotator are chosen to make protein-protein interaction network. The genes of diseases which are under registration progress at MFDS to use existing medications as off-label use drugs because there is no treatment or non-acceptance are collected first. Then the common genes the pair of the medication between as the permitted indications for the use of medicine and the off-label use for the disease are looked for. The process of finding genes related to diseases, paring the diseases seems to have possibility of relation and finding the common genes is shown as Figure 2.1 and Figure 2.2.

Hypertension-Wegener, Panic disorder-Alzheimer, Albinism-Melanoma, Hypertension-ARDS(Acute Respiratory Distress Syndrome), Schizophrenia-Panic disorder, and Tourette syndrome-Schizophrenia are paired with under the supposition that they have many common genes related to diseases. The analyzing relation between shared genes in common is done by STRING[11]. The information of target protein about treatment for the diseases listed above is from DrugBank[12]. The first stage is that once the target protein of medication which cures either of disease out of paired diseases is confirmed at protein-protein interrelation network, the medication can be used for the other disease out of paired diseases.

The second stage is to suppose (reason) based on the similarity between candidate medications which will be repositioned. Because not all the target protein of medications is discovered, this process is necessary. The

[11] string-db.org

[12] www.drugbank.ca

target protein of medication, side-effects, the structure of medication and the information of medication interrelation are from DrugBank. DrugBank provides the information of 1558 of medications. 155 of biotech medications and 4200 of medication targets (Version 4.0). The treatments for 6 pair of diseases can be searched with the name of disease on Medscape.com and make the list of the medications for treatment or can be searched with the name of medication as off-label use and confirm off-label indication. Since this process should be done manually, the medications should be limited as a proper size of scale.

2.2 Drug-similarity Network based Research using Cytoscape

The information of the medications as treatment for 6 paired diseases is from DrugBank. This process should be done manually so heterogeneous information is united into consensus terminologies as possible and the descriptive letters are translated into simple terms. For instance, the side-effect expressed as sleep disorder, insomnia, sleep disturbance or trouble with sleeping is united as sleep disorder and the one expressed as tightness in the chest, chest pain, chest pain or discomfort or chest tightness is united as chest pain. The information is about the target of medication, medication interrelation, the substructure of medication and the side-effects of medication, and the drug-similarity network is made using the information collected for the treatments prescribed for the disease. Figure 2.3 shows the list of medication targets are from DrugBank and organized. The node that can be seen in medication-similarity network is the cases that there are shared proteins between the medications, the similarity of medication structure, same side-effects or shared interrelation medications. If less than two nodes are not overlapped, it will be excluded from the candidate medications of repositioning medications. The reason is that the various structures of individual medication are limited to basic structure, and because there seem to have too many medications which have the same structure, only when they have something in common other than the basic structure it seems possible to realign medications. Especially having the shared related genes in paired diseases as the target, the medication has similar side-effects is the proof of being effected on the target. Medication-similarity network is visualized as a

drawing using Cytoscape[13]. The process of making the drug-similarity network is shown in Figure 2.4 from a to f in order.

Among the medications used for Hypertension-Wegener Granulomatosis paired diseases, Rituximab was the permitted treatment for anticancer and arthritis, it has been used as off-label for Wegener Granulomatosis and it got permitted in 2011. Bring in the DrugBank structure of the peptide for Rituximab and another couple of drugs, and put it in Figure 3.7~ 3.11 to show the correlation of structure and function. The target of Rituximab is MS4A1 and the drugs causing an interaction mediated by the target are Ibritumomab, Obinutuzumab, Tositumomab. The targets of Rituximab are 12 (MS4A1, FCGR3B, C1R, C1QA, C1QB, C1QC, FCGR3A, C1S, FCGR1A, FCGR2A, FCGR2B, FCGR2C) and Ibritumomab has the same target. The two drugs are not the same in structure. MS4A1 is the only target of Obinutuzumab and has relatively less side effects than the other three drugs. The targets of Tositumomab are 11(MS4A1, FCGR3B, C1R, C1QA, C1QB, C1QC, FCGR3A, FCGR1A, FCGR2A, FCGR2B, FCGR2C), comparing to Rituximab, only CIS is excluded. So the difference of side effects compared, Hypotension, Vasodilatation, Hypothyroidism, Peripheral edema, Myalgia, Arthralgia, Pharyngitis, Dyspnea, Rhinitis, Pneumonia, etc. appear in only Tositumomab and the type or frequency of other side effects are much less expressed. In 4 drugs of MS4A1 target, bleeding gums, blood in the urine or stools are caused by Rituximab, Ibritumomab, Obinutuzumab and nausea and vomiting, back pain are caused by all 4 of them. Rituximab, Obinutuzumab and Tositumomab have a common interaction with other anti-cancer is Trastuzumab.

[13] http://www.cytoscape.org

The targets of Trastuzmab are 13 (ERBB2, EGFR, C1R, C1QA, C1QB, C1QC, C1S, FCGR1A, FCGR2A, FCGR2B, FCGR2C, FCGR3B, FCGR3A), except for ERBB2 and EGFR, 9 targets are the same with the targets of Rituximab, Ibritumomab, Tositumomab and C1S is consistent with the target as the target of Rituximab and Ibritumomab. Drugs that target the shared gene, TNF on HTN-WG is seven; Etanercept, Adalimumab, Infliximab, Golimumab, Certolizumab, Pomalidomide, Amrinone and the drug which is licensed in rheumatoid arthritis and psoriasis are Etanercept, and it is used as off-label use for vasculitis, granulomatosis and even for alzheimer disease. All the targets of Etanercept are 14 besides TNF; TNFRSF1B, FCGR1A, FCGR3A, FCGR2A, FCGR2B, FCGR2C, LTA, FCGR3B, C1S, C1R, C1QA, C1QB, C1QC. Etanercept's side effects are chills, cough, fever, sneezing, sore throat, congestion in the chest, depression, fast heartbeat, frequent or painful urination, itching, pain, redness, or swelling on the skin, joint or muscle stiffness, tightness, or rigidity, shortness of breath, stomach discomfort or pain, and so on. Drugs that cause interactions are tofacitinib, trastuzumab and rilonacept. Other 3 drugs that target the TNF are infliximab, golimumab, certolizumab known as having only a single target. The drugs which have interactions with infliximab are Golimumab, rilonacept, tofacitinib, and trastuzumab. Side effects are abdominal or stomach pain, chest pain, chills, cough, dizziness, fainting, fever, flushing of the face, headache, hives, itching, muscle pain, nasal congestion, nausea, runny nose, sneezing, sore throat, tightness in the chest, troubled breathing, unusual tiredness or weakness, vomiting and so on.

The drugs which cause an interaction with Golimumab are abatacept, anakinra, belimumab, canakinumab, certolizumab, infliximab, natalizumab, pimecrolimus, rilonacept, tacrolimus, tocilizumab and tofacitinib and as

possible side effects are body aches or pain, chills, cough, difficulty with breathing, ear congestion, fever, headache, loss of voice, muscle aches, sneezing, sore throat, stuffy or runny nose, unusual tiredness or weakness, and the like. Certolizumab has an interaction with abatacept, anakinra, golimumab, natalizumab, rituximab and tofacitinib and the side effects are bladder pain, bloody or cloudy urine, body aches or pain, chills, cough or hoarseness, difficult, burning, or painful urination, difficulty with breathing, ear congestion, fever, frequent urge to urinate, headache, loss of voice, lower back or side pain, nasal congestion, runny nose, sneezing, sore throat, unusual tiredness or weakness and so on. In addition to TNF, there are 11 more targets of Adalimumab; FCGR3B, C1R, C1QA, C1QB, C1QC, FCGR3A, C1S, FCGR1A, FCGR2A, FCGR2B and FCGR2C and the drugs that have an interaction with are canakinumab, rilonacept, tofacitinib and trastuzumab. As side effects, abdominal or stomach fullness, body aches or pain, cough or hoarseness, ear congestion, gas with abdominal or stomach pain, lightheadedness, loss of voice, lower back or side pain, muscle aches and pains, nasal congestion, pain or tenderness around the eyes or cheekbones, rapid and sometimes shallow breathing, shivering, sunken eyes, thirst, trouble sleeping, warmth on the skin and wrinkled skin can be shown.

Pomalidomide has 3 targets, the protein cereblon, TNF and PTGS2 and can have an drug interaction with ketoconazole, rifampicin and the side effects appear to be in the abdominal or stomach pain, black, tarry stools, bladder pain, bleeding gums, bloating or swelling of the face, arms, hands, lower legs, or feet, blood in the urine or stools, bloody nose, body aches or pain, burning, numbness, tingling, or painful sensations, chest pain, chills, cloudy urine, confusion, constipation, cough, decreased or increased urination, depression, difficult, burning, or painful urination, difficulty with breathing,

dizziness, dry mouth, ear congestion, fast or irregular heartbeat, fever, frequent urge to urinate, headache, incoherent speech, increased thirst, loss of appetite, loss of voice, lower back or side pain, metallic taste, muscle pain or cramps, muscle weakness, nasal congestion, nausea or vomiting, numbness or tingling in the hands, feet, or lips, pain, pale skin, pinpoint red spots on the skin, rapid weight gain, runny nose, shakiness in the legs, arms, hands, or feet, sneezing, sore throat, tightness in the chest, trembling or shaking of the hands or feet, troubled breathing with exertion, ulcers, sores , or white spots in the mouth, unsteadiness or awkwardness, unusual bleeding or bruising, unusual weight gain or loss, weakness in the arms, hands, legs, or feet, and the like.

Amrinone has the bipyridines and oligopyridines structure and its targets are PDE3A, DE4B, TNF and PDE3. The side effects are thrombocytopenia, nausea, diarrhea, hepatotoxicity and arrhythmias. It will be determined the effectiveness and safety of off-label use for Wegener's granulomatosis by obtaining the drug-similarity network of the drugs that target TNF and the ones targeting MS4A1 known on paired disease, Hypertension-Wegener Granulomatosis. Rituximab in Wegener granulomatosis has already been granted a permit an also be used for etanercept or infliximab as off-label.

In Panic disorder- Alzheimer disease pair, there are 24 shared genes and drugs that target the HTR2A worth considering realignment medications are donepezil, paroxetine and desipramine, so the drugs-similarity network of these medications is made. Some the drugs used for panic disorder or Alzheimer targeting CHRNA7 CHRNB2 is Gabapentine and Gabapentine and Memantine are 2 drugs that target GRIN2B. Paroxetine, Donepezil and Desipramine are the drugs that targets the HTR2A and the drugs that target HTR2C are Imipramine, Trazodone, Desipramine and clomipramine. The

drugs that target MAOA are Tranylcypromine and Sertraline and the drugs that target SLC6A4 are 12 (Fluvoxamine, citalopram, venlafaxine, imipramine, fluoxetine, trazodone, paroxetine, sertraline, desipramine, escitalopram, clomipramine). It appears the drugs that target the HTR2A have possibility of other uses, donepezil and paroxetine from the drugs, donepezil, paroxetine and desipramine that used for panic disorder and alzheimer have common in piperidine structure and the drugs that cause an interaction with all three in common are isocarboxazid, moclobemide, phenelzine, tolterodine, tranylcypromine, trazodone, trimipramine, triprolidine and zuclopenthiol and the drugs which have an interaction with only donepezil and paroxetine are 4; mesoridazine, pimozide, risperidone and thioridazine. The drugs that have an interaction only with paroxetine and desipramine are 11; desvenlafaxine, galantamine, phenylpropanolamine, rasagiline, sibutramine, tamoxifen, tamsulosin, terbinafine, tramadol, venlafaxine and zolmitriptan. The drugs that have an interaction with donepesial and despramine are 5; cimetidine, quinidine, thiothixene, trospium and ziprasidone. Vomiting, loss of appetite, muscle cramps, muscle and blurred vision as side effects of this is expressed in common.

The common genes in Hypertension-Acute Respiratory Distress Syndrome (ARDS) disease pair are 22 but there is no special treatment of ARDS. The treatment for blood pressure -pril targeting the common gene, ACE of paired diseases can be considered to be as realignment medications and there is a necessary to examine Drotrecogin alfa which targets CLACA along with glutathione which targets GSTM1 or GSTP1. However because ARDS is a serious medical condition that threatens the life, the treatment for this is different from the purpose of the drugs which examined the effectiveness and safety for off-label use in this study, so there will be

suggestion of realignment medication by making drugs-similarity network.

The shared genes in Schizophrenia-Panic Disorder disease pair are 86 and the drugs that target CHRM1 in shared genes used for Schisoperenia or panic disorder are 12(chlorpromazine, loxapine, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone, paroxetine, citalopram, escitalopram, imipramine and desipramine) and the possibility of realignment will be approached through the drug similarity network. Drugs having a common target, HTR2C are all of 9 except paroxetine, citalopram and escitalopram the drugs that target SLC6A4 are 6; loxapine, paroxetine, citalopram, escitalopram, imipramine, desipramine. The side effects can be shown in common are convulsions, fast heartbeat or irregular pulse, sore throat, dizziness or fainting, blurred vision, Agitation, Abdominal or stomach pain, muscle spasms or jerking of all extremities, yellow eyes or skin and the drugs show loss of appetite are paroxetine, citalopram and desipramnine, the drugs show weight loss are paroxetine, citalopram and imipramine. The drugs have dibenzazepines structurally are lozapine, clozapine and quetiapine and the drugs with dibenzazepines structure are imipramine and desipramine.

By collecting the information of the medications for Schizophrenia and ones for Tourette syndrome from DrugBank, drugs-similarity network is made using the information about structure, targets, interaction, side-effects of commonly shared 5 medications (Fluphenazine, Haloperidol, Olanzapine, Risperidone, Ziprasidone). Although Haloperidol is the only permitted medication for Tourette syndrome and Schizophrenia, the safety-effectiveness of other 4 drugs as off-label will be confirmed. Tourette syndrome and Schizophrenia are suitable to prove the adequacy of using as off-label use because they have 25 shared genes which is easy to compare relatively and there are 5 drugs; one is permitted and others are used as off-label. One of

drugs which are used for Tourette syndrome and Schizophrenia, Haloperidol has phenyl-piperidine-butyrophenone structure and the targets are 5; D(2) dopamine receptor, D(1A) dopamine receptor, Glutamate receptor inotropic, NMDA 2B, 5-hydroxytryptamine receptor 2A, D(3) dopamine receptor. The shared targets between drug targets and the shared targets in paired diseases are 3; DRD2, DRD3, 5-hydroxytryptamine receptor 2A (HTR2A) and there are 10 including that are being tested or withdrawn and 5 of them are being allowed to use as drugs. The drugs that have an interaction with haloperidol are 3; trihexyphenidyl, tridihexethyl, procyclidine. The side effects of haloperidol is QT prolongation (CV), EPS, TD, NMS, including blood-related or more.

The fluphenazine has phenothiazine structure with 3 targets, DRD2, DR1A, calmodulin and shares two common targets, DRD2 and DR1A with haloperidol, and has a common target, DRD2 with the paired disease, Schizophrenia-Tourette. 19 out of 21 structure similar drugs are permitted to be used, and DRD2-mediated interactions between medication are 8; haldol, olanzapine, risperidone, ziprasidone and structure similar drugs; trifluoperazine, trifluopromazine, prochlorperazine, promethazine, chlorpromazine, thioridazine, thioproperazine and methotrimeprazine. Stuructuer smilar drugs causing calmodulin-mediated interaction are 2 of them; promethazine and trifluoperazine. The drug interaction DR1A-mediated is haldol, olanzapine, risperidone and ziprasidone and 7 from structure similarity drugs are chlorpromazine, methotrimeprazine, promazine, propiomazine, thioridazine, trioproperazine and trifluopromazine. The fluphenazine's side effects are Tardive Diskinesia (TD), Extrapyramidal Symptom (EPS), Neuroleptic Malignant Syndrome (NMS), blood pressure above (Hypertension: HTN), decreased libido in men, increase sex drive in

women, edema, weight changes, milk secretion and so on.

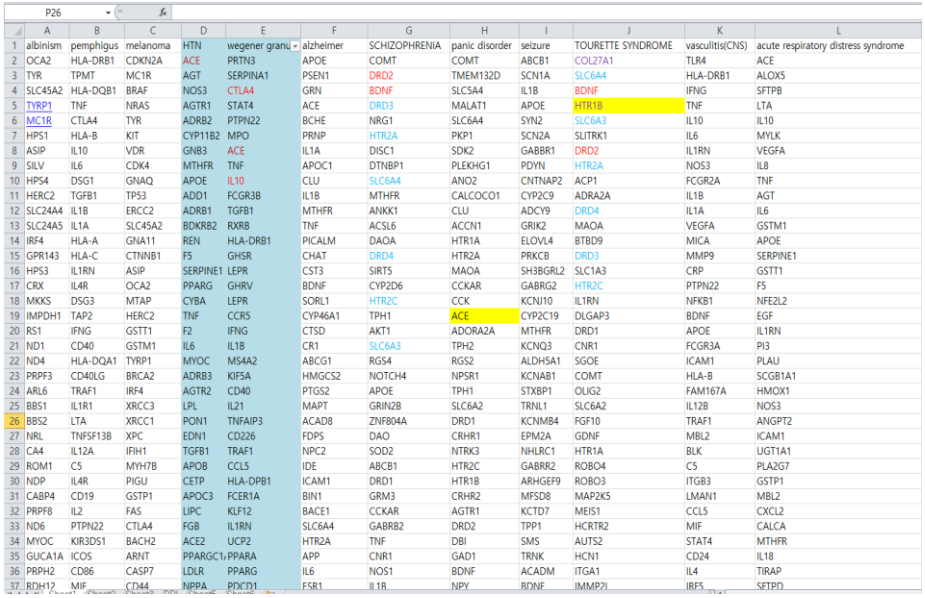
The structure of Olanzapine is benzodiazepine and has one structure similar drug, clozapine with 34 targets and 10 of interaction drugs but there is nothing in common with target-mediator or structure similarity drugs. The common targets with the paired diseases, Tourette syndrome –Schizophrenia are 7; DRD2, DRD3, DRD4, HTR1A, HTR2C, HTR3A, DRD1. The side effects of Olanzapine are reduced attention, swelling, dizziness, blurred vision, weight gain, tremor, gastrointestinal discomfort and so on. The structure of Risperidone is benzisoxazole and its structure similar drug is the one, pliperidone with 14 targets. The common shared targets with the paired disease, Tourette syndrome –Schizophrenia are 7; HTR2A, DRD2, DRD3, DRD4, HTR2C, HTR1A, DRD1. The interaction drug is ziprasidone. The side effects of ziprasidone are NMS, CV/cerebrovascular adverse reaction (stroke), TD, metabolic changes (hyperglycemia), hyperprolactinemia, orthostatic hypotension, leukopenia, somnolence, seizure, priapism and so on. Ziprasidone is benzisoxazole derivative and does not have structure similar drugs and have 25 targets. Drugs that cause interactions between drugs due to the target parameter are mainly olanzapine and risperidone, and have an interaction with fluphenazine via DRD2. The common targets with the paired disease, Schizophrenia-Tourette syndrome are 5; DRD3, DRD4, HTR1A, HTR2C, HTR3A. The side effects of ziprasidone are QT prolongation, NMS, TD, metabolic changes (CV/cerebrovascular risk, hyperglycemia, dislipidemia, weight gain), orthostatic hypotension, leukopenia, seizure, dysphagia, hyperprolactinemia, priapism, temperature control abnormality and so on.

The next is by gathering the information of the drugs which have been used for melanoma and albinism is to make drugs -similarity network. The

common genes of albinism-melanoma are relatively small as 10, since there is no permitted treatment for albinism, in real it seems like Methoxsalen is used as off-label. It is worth studying to see whether Methoxsalen permitted for vitiligo and proriasis is effective and safe when used for albinism. The drug, methozsalen, commonly used for albinism-melanoma has a structure of a benzopyran of series furanocoumarin. The target of the drug is DNA and the drugs cause interactions are 7; ethotoin, fosphenytoin, mephenytoin, phenytoin, tacrine, thiothixene, tizanidine. Drug interactions mediated drug target, DNA relating to cross-linking/alkylation activity have 21 drugs (Pipobroman, Chlorambucil, Mitomycin, Streptozocin, Gemcitabine, Cisplatin, Oxaliplatin, Cyclophosphamide, Furazolidone, Dacarbazine, Temozolomide, Carboplatin, Cytarabine, Busulfan, Melphalan, Flucytosine, Procarbazine, Lomustine, Hydroxychloroquine, Trioxsalen, Thiotepa). The side effects of methoxsalen can be shown as hypotension, cardiovascular symptoms, arrhythmia, rash, allergy, pyrexia, nausea and dysgeusia. Methoxsalen has a permit for indications on vitiligo and psoriasis but using on albinism and melanoma is off-label use. Among 7 and 21 drugs, if they have the same side effects, similar structure and have an interaction mediated by target, these drugs realignment could be considered for the effectiveness on albinism and melanoma.

In 21 drugs which cause drug interaction related to DNA cross-linking/alkylation, trioxsalen has the same substructure with methoxsalen and side effects like blistering peeling of skin, reddened sore skin, swelling feet or lower legs, itching, nausea are shown similarly, because of skin cancer relevance the production was stopped in 2002. As part depigmenting product, Monobenzone, is permitted in the external application on vitiligo and the target is TYR (tyrosinase). The drugs which target TYR are NADH, azelaic

acid and mimosine. Treatments for melanoma are temozolomide, ipilimumab, peginterferon alfa-2b, aldesleukin, dacarbazine, and the drugs permitted for melanoma are 2 of ipilimumab, dacarbazine and others are used as off-label. The side effects of dacarbazine are Redness, pain, or swelling at place of injection, Black, tarry stools, blood in urine or stools, cough or hoarseness, accompanied by fever or chills, lower back or side pain, accompanied by fever or chills, painful or difficult urination, accompanied by fever or chills, pinpoint red spots on skin, unusual bleeding or bruising and the side effects of aldesleukin are agitation, confusion, diarrhea, dizziness, drowsiness, fever or chills, mental depression, nausea and vomiting, shortness of breath, sores in the mouth and on lips, tingling of the hands or feet, unusual decrease in urination, unusual tiredness or weakness, weight gain of 5 to 10 pounds or more. The side effects of Temosolimide can be shown amnesia, black, tarry stools, blood in the urine or stools, convulsions, cough or hoarseness, fever or chills, lower back or side pain, muscle weakness or paralysis on one or both sides of the body, painful or difficult urination, pinpoint red spots on the skin, swelling of the feet or lower legs and unusual bleeding or bruising. The side effects of Ipilimumab are bloody, black, or tarry stools, diarrhea, fever, heartburn, indigestion, itching skin, nausea, rash, severe stomach pain, cramping, or burning, unusual tiredness or weakness, vomiting, vomiting of material that looks like coffee grounds, severe and continuing watery or bloody diarrhea. The target drug of Temozolomide is DNA, Ipilimumab's CTLA4, Peginterferon alfa-2b's IFNAR1, IFNAR2, Aldesleukin's IL2RB, IL2RA, IL2RG and Dacarbazine's DNA, POLA2 and PGD.

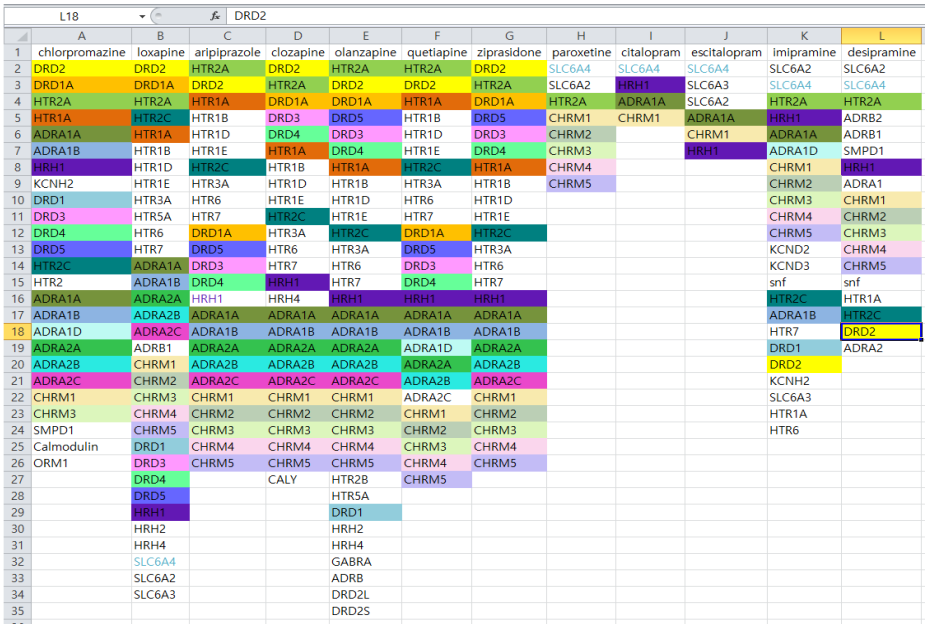


	A	B	C	D	E	F	G	H	I	J	K	L
1	albinism	pemphigus	melanoma	HTN	wegener granu	alzheimer	SCHIZOPHRENIA	panic disorder	seizure	TOURETTE SYNDROME	vasculitis(CNS)	acute respiratory distress syndrome
2	OCA2	HLA-DRB1	CDKN2A	ACE	PRTN3	APOE	COMT	COMT	ABCB1	COL27A1	TLR4	ACE
3	TYR	TPMT	MC1R	AGT	SERPINA1	PSEN1	DRD2	TMEM132D	SCN1A	SLC6A4	HLA-DRB1	ALOX5
4	SLC45A2	HLA-DQB1	BRAF	NOS3	CTLA4	GRN	BDNF	SLC5A4	IL1B	BDNF	IFNG	SFTPB
5	TYRP1	TNF	NRAS	AGTR1	STAT4	ACE	DRD3	MALAT1	APOE	HTR1B	TNF	LTA
6	MC1R	CTLA4	TYR	ADRB2	PTPN22	BCHE	NRG1	SLC6A4	SYN2	SLC6A3	IL10	IL10
7	HPS1	HLA-B	KIT	CYP11B2	MPO	PRNP	HTR2A	PKP1	SCN2A	SLITRK1	IL6	MYLK
8	ASIP	IL10	VDR	GNB3	ACE	IL1A	DISC1	SDK2	GABBR1	DRD2	IL1RN	VEGFA
9	SILV	IL6	CDK4	MTHFR	TNF	APOC1	DTNBP1	PLEKHG1	PDYN	HTR2A	NOS3	IL8
10	HPS4	DSG1	GNAQ	APOE	IL10	CLU	SLC6A4	ANO2	CNTNAP2	ACP1	FCGR2A	TNF
11	HERC2	TGFB1	TP53	ADD1	FCGR3B	IL1B	MTHFR	CALCOCO1	CYP2C9	ADRA2A	IL1B	AGT
12	SLC24A4	IL1B	ERCC2	ADRB1	TGFB1	MTHFR	ANKK1	CLU	ADCY9	DRD4	IL1A	IL6
13	SLC24A5	IL1A	SLC45A2	BDKRB2	RXRB	TNF	ACSL6	ACCN1	GRIK2	MAOA	VEGFA	GSTM1
14	IRF4	HLA-A	GNA11	REN	HLA-DRB1	PICALM	DAOA	HTR1A	ELOVL4	BTBD9	MICA	APOE
15	GPR143	HLA-C	CTNNB1	F5	GHSR	CHAT	DRD4	HTR2A	PRKCB	DRD3	MMP9	SERPINE1
16	HPS3	IL1RN	ASIP	SERPINE1	LEPR	CST3	SIRT5	MAOA	SH3BGRL2	SLC1A3	CRP	GSTT1
17	CRX	IL4R	OCA2	PPARG	GHRV	BDNF	CYP2D6	CCKAR	GABRG2	HTR2C	PTPN22	F5
18	MKKS	DSG3	MTAP	CYBA	LEPR	SORL1	HTR2C	CCK	KCNJ10	IL1RN	NFKB1	NFE2L2
19	IMPDH1	TAP2	HERC2	TNF	CCR5	CYP46A1	TPH1	ACE	CYP2C19	DLGAP3	BDNF	EGF
20	RS1	IFNG	GSTT1	F2	IFNG	CTSD	AKT1	ADORA2A	MTHFR	DRD1	APOE	IL1RN
21	ND1	CD40	GSTM1	IL6	IL1B	CR1	SLC6A3	TPH2	KCNQ3	CNR1	FCGR3A	PI3
22	ND4	HLA-DQA1	TYRP1	MYOC	MS4A2	ABCG1	RGS4	RGS2	ALDH5A1	SGOE	ICAM1	PLAU
23	PRPF3	CD40LG	BRCA2	ADRB3	KIF5A	HMGCS2	NOTCH4	NPSR1	KCNAB1	COMT	HLA-B	SCGB1A1
24	ARL6	TRAF1	IRF4	AGTR2	CD40	PTGS2	APOE	TPH1	STXBP1	OLIG2	FAM167A	HMOX1
25	BBS1	IL1R1	XRCC3	LPL	IL21	MAPT	GRIN2B	SLC6A2	TRNL1	SLC6A2	IL12B	NOS3
26	BBS2	LTA	XRCC1	PON1	TNFAIP3	ACAD8	ZNF804A	DRD1	KCNMB4	FGF10	TRAF1	ANGPT2
27	NRL	TNFSF13B	XPC	EDN1	CD226	FDPS	DAO	CRHR1	EPM2A	GDNF	MBL2	ICAM1
28	CA4	IL12A	IFIH1	TGFB1	TRAF1	NPC2	SOD2	NTRK3	NHLRC1	HTR1A	BLK	UGT1A1
29	ROM1	C5	MYH7B	APOB	CCL5	IDE	ABCB1	HTR2C	GABRR2	ROBO4	C5	PLA2G7
30	NDP	IL4R	PIGU	CETP	HLA-DPB1	ICAM1	DRD1	HTR1B	ARHGEF9	ROBO3	ITGB3	GSTP1
31	CABP4	CD19	GSTP1	APOC3	FCER1A	BIN1	GRM3	CRHR2	MFSD8	MAP2K5	LMAN1	MBL2
32	PRPF8	IL2	FAS	LIPC	KLF12	BACE1	CCKAR	AGTR1	KCTD7	MEIS1	CCL5	CXCL2
33	ND6	PTPN22	CTLA4	FGB	IL1RN	SLC6A4	GABRB2	DRD2	TPP1	HCRTR2	MIF	CALCA
34	MYOC	KIR3DS1	BACH2	ACE2	UCP2	HTR2A	TNF	DBI	SMS	AUTS2	STAT4	MTHFR
35	GUCA1A	ICOS	ARNT	PPARGC1/	PPARA	APP	CNR1	GAD1	TRNK	HCN1	CD24	IL18
36	PRPH2	CD86	CASP7	LDLR	PPARG	IL6	NOS1	BDNF	ACADM	ITGA1	IL4	TIRAP
37	RDH12	MIF	CD44	NPPA	PDCD1	ESR1	IL1B	NPY	BDNF	IMMP2L	IRF5	SFTPD

Figure 2.1 Getting gene list associated with diseases from Genotator Genes of association score down to 1 for each disease were brought from Genotator and organized in Excel

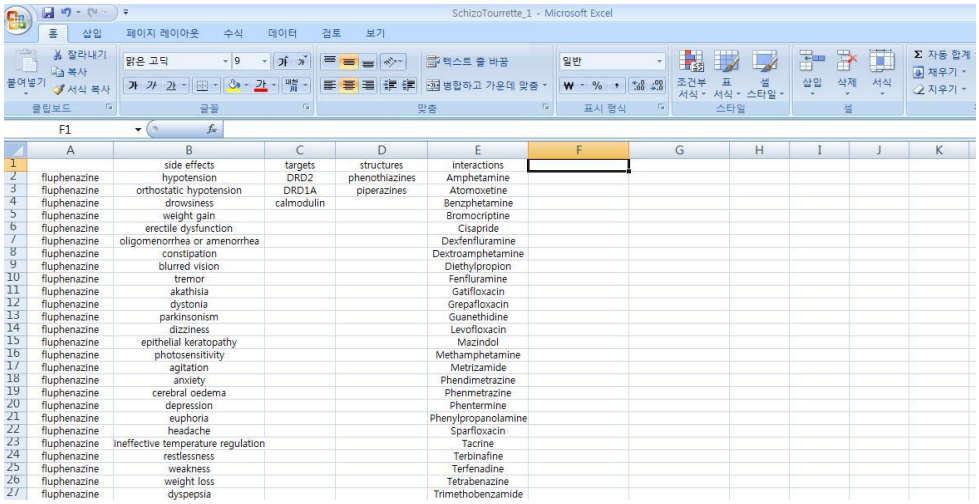
	A	B	C	D	E	F	G	H
1	htn/wg	panic/alz	albi/mela	htn/ards		schi/panic		tourette/schi
2	SERPINA1	ABCB1	ASIP	ACE	ABCB 1	GAD1	MAOB	BDNF
3	CTLA4	ACE	HERC2	AGT	ACE	GAD2	NCAM1	CNR 1
4	ACE	ACHE	IRF4	APOE	APOE	GDNF	NEUROG1	CNTNAP 2
5	TNF	AGTR1	MC1R	CALCA	ASTN 2	GNB3	NOS1	COMT
6	IL10	ALDH2	OCA2	F5	BDNF	GRIA1	NPY	DBH
7	TGFB1	APOE	SLC24A4	GSTM1	CCK	GRIA2	NRG1	DRD 1
8	HLA-DRB1	AR	SLC24A5	GSTP1	CCKAR	GRIA3	NRG2	DRD 2
9	LEPR	BDNF	SLC45A2	GSTT1	CHRM 1	GRIA4	NRG3	DRD3
10	GHRL	CHAT	TYR	HMOX1	CHRM 2	GRIK3	NRXN1	DRD4
11	LEP	CHRNA7	TYRP 1	ICAM1	CHRNA 7	GRIK4	NSF	GDNF
12	CCR5	CHRNB2		IL10	CHRNB 2	GRIN2A	NTF3	HLA-DRB1
13	IL1B	CLU		IL18	CNR 1	GRIN2B	NTRK 3	HTR1A
14	MS4A2	COMT		IL1RN	CNTF	GRM3	PDE4B	HTR2A
15	CD40	DRD3		IL6	CNTNAP2	GRM4	PDYN	HTR2C
16	CCL5	GRIA1		LTA	COMT	GRM5	PPP1R1B	HTR3A
17	HLA-DPB1	GRIN2B		MTHFR	DAOA	HTR1A	RELN	IL10
18	IL1RN	HTR2A		NOS3	DBH	HTR2A	RGS2	IL10RA
19	UCP2	HTR2C		PLA2G7	DISC1	HTR2C	S100B	IL1B
20	PPARA	IL10		SCGB1A1	DLG1	HTR3A	SLC 1A1	IL1 RN
21	PPARG	MAOA		SERPINE1	DRD1	HTR3B	SLC 1A2	MAOA
22	NOD2	NOS3		TNF	DRD2	HTR4	SLC 1A3	OLIG2
23	HLA-DQB1	NTF3		VEGFA	DRD3	HTR5A	SLC 6A3	SLC 1A3
24	C5	RELN			GABBR1	HTR6	SLC 6A4	SLC 6A3
25	SERPINE1	SLC6A4			GABRA5	HTR7	SLC 6A9	SLC 6A4
26	SERPINA3				GABRB2	IL10	SNAP25	TNF
27	CIITA				GABRG2	L1CAM	SNAP29	
28	F5				GABRG3	LEP	TPH1	
29	F2				GABRR1	LEPR	TPH 2	

Figure 2.2 Shared genes in pairs of diseases. The figure shows a table of shared genes between each pair of diseases



	A	B	C	D	E	F	G	H	I	J	K	L
1	chlorpromazine	loxapine	aripiprazole	clozapine	olanzapine	quetiapine	ziprasidone	paroxetine	citalopram	escitalopram	imipramine	desipramine
2	DRD2	DRD2	HTR2A	DRD2	HTR2A	HTR2A	DRD2	SLC6A4	SLC6A4	SLC6A4	SLC6A2	SLC6A2
3	DRD1A	DRD1A	DRD2	HTR2A	DRD2	DRD2	HTR2A	SLC6A2	HRH1	SLC6A3	SLC6A4	SLC6A4
4	HTR2A	HTR2A	HTR1A	DRD1A	DRD1A	HTR1A	DRD1A	HTR2A	ADRA1A	SLC6A2	HTR2A	HTR2A
5	HTR1A	HTR2C	HTR1B	DRD3	DRD5	HTR1B	DRD5	CHRM1	CHRM1	ADRA1A	HRH1	ADRB2
6	ADRA1A	HTR1A	HTR1D	DRD4	DRD3	HTR1D	DRD3	CHRM2		CHRM1	ADRA1A	ADRB1
7	ADRA1B	HTR1B	HTR1E	HTR1A	DRD4	HTR1E	DRD4	CHRM3		HRH1	ADRA1D	SMPD1
8	HRH1	HTR1D	HTR2C	HTR1B	HTR1A	HTR2C	HTR1A	CHRM4			CHRM1	HRH1
9	KCNH2	HTR1E	HTR3A	HTR1D	HTR1B	HTR3A	HTR1B	CHRM5			CHRM2	ADRA1
10	DRD1	HTR3A	HTR6	HTR1E	HTR1D	HTR6	HTR1D				CHRM3	CHRM1
11	DRD3	HTR5A	HTR7	HTR2C	HTR1E	HTR7	HTR1E				CHRM4	CHRM2
12	DRD4	HTR6	DRD1A	HTR3A	HTR2C	DRD1A	HTR2C				CHRM5	CHRM3
13	DRD5	HTR7	DRD5	HTR6	HTR3A	DRD5	HTR3A				KCND2	CHRM4
14	HTR2C	ADRA1A	DRD3	HTR7	HTR6	DRD3	HTR6				KCND3	CHRM5
15	HTR2	ADRA1B	DRD4	HRH1	HTR7	DRD4	HTR7				snf	snf
16	ADRA1A	ADRA2A	HRH1	HRH4	HRH1	HRH1	HRH1				HTR2C	HTR1A
17	ADRA1B	ADRA2B	ADRA1A	ADRA1A	ADRA1A	ADRA1A	ADRA1A				ADRA1B	HTR2C
18	ADRA1D	ADRA2C	ADRA1B	ADRA1B	ADRA1B	ADRA1B	ADRA1B				HTR7	DRD2
19	ADRA2A	ADRB1	ADRA2A	ADRA2A	ADRA2A	ADRA1D	ADRA2A				DRD1	ADRA2
20	ADRA2B	CHRM1	ADRA2B	ADRA2B	ADRA2B	ADRA2A	ADRA2B				DRD2	
21	ADRA2C	CHRM2	ADRA2C	ADRA2C	ADRA2C	ADRA2B	ADRA2C				KCNH2	
22	CHRM1	CHRM3	CHRM1	CHRM1	CHRM1	ADRA2C	CHRM1				SLC6A3	
23	CHRM3	CHRM4	CHRM2	CHRM2	CHRM2	CHRM1	CHRM2				HTR1A	
24	SMPD1	CHRM5	CHRM3	CHRM3	CHRM3	CHRM2	CHRM3				HTR6	
25	Calmodulin	DRD1	CHRM4	CHRM4	CHRM4	CHRM3	CHRM4					
26	ORM1	DRD3	CHRM5	CHRM5	CHRM5	CHRM4	CHRM5					
27		DRD4		CALY	HTR2B	CHRM5						
28		DRD5			HTR5A							
29		HRH1			DRD1							
30		HRH2			HRH2							
31		HRH4			HRH4							
32		SLC6A4			GABRA							
33		SLC6A2			ADRB							
34		SLC6A3			DRD2L							
35					DRD2S							

Figure 2.3 Process of gathering drug target from DrugBank. The figure above shows a table of drug target information used for Schizophrenia and Panic disorder.



	A	B	C	D	E	F	G	H	I	J	K
1		side effects	targets	structures	interactions						
2	fluphenazine	hypotension	DRD2	phenothiazines	Amphetamine						
3	fluphenazine	orthostatic hypotension	DRD1A	piperazines	Atomoxetine						
4	fluphenazine	drowsiness	calmodulin		Benzphetamine						
5	fluphenazine	weight gain			Bromocriptine						
6	fluphenazine	erectile dysfunction			Cisapride						
7	fluphenazine	oligomenorrhea or amenorrhea			Dexfenfluramine						
8	fluphenazine	constipation			Dextroamphetamine						
9	fluphenazine	blurred vision			Diethylpropion						
10	fluphenazine	tremor			Fenfluramine						
11	fluphenazine	akathisia			Gatifloxacin						
12	fluphenazine	dystonia			Grepafloxacin						
13	fluphenazine	parkinsonism			Guanethidine						
14	fluphenazine	dizziness			Levofloxacin						
15	fluphenazine	epithelial keratopathy			Mazindol						
16	fluphenazine	photosensitivity			Methamphetamine						
17	fluphenazine	agitation			Metrizamide						
18	fluphenazine	anxiety			Phendimetrazine						
19	fluphenazine	cerebral oedema			Phenmetrazine						
20	fluphenazine	depression			Phentermine						
21	fluphenazine	euphoria			Phenylpropanolamine						
22	fluphenazine	headache			Sparfloxacin						
23	fluphenazine	ineffective temperature regulation			Tacrine						
24	fluphenazine	restlessness			Terbinafine						
25	fluphenazine	weakness			Terfenadine						
26	fluphenazine	weight loss			Tetrabenazine						
27	fluphenazine	dyspepsia			Trimethobenzamide						

Figure 2.4 a) Excel Data of Drug information from DrugBank

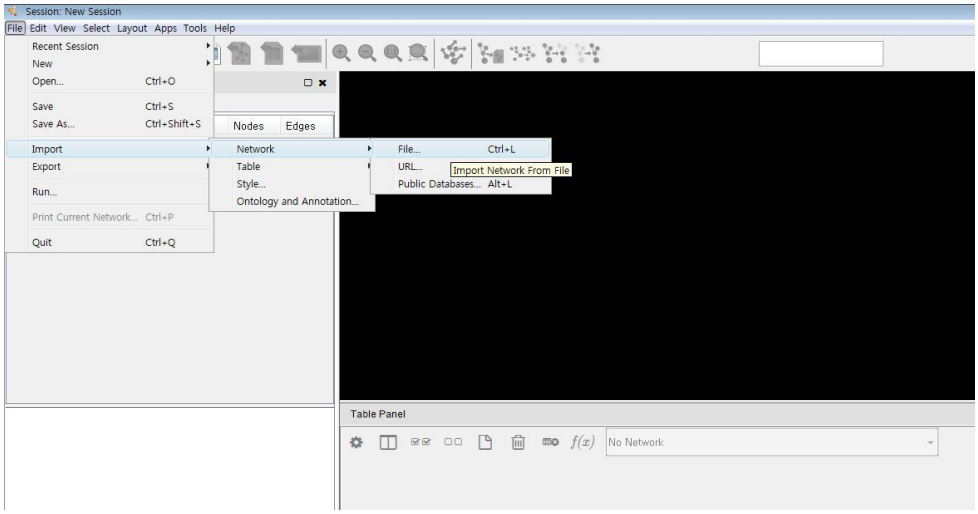


Figure 2.4 b) Open the excel data of drug information at Cytoscape

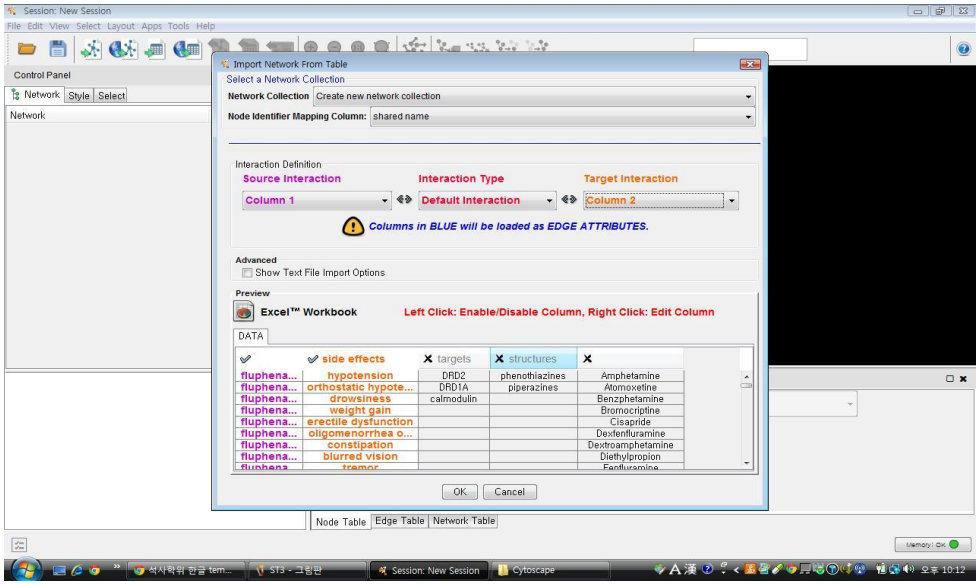


Figure 2.4 c) Build a drug-similarity network regarding side effects, targets, structures and interactions from the excel data of drug information

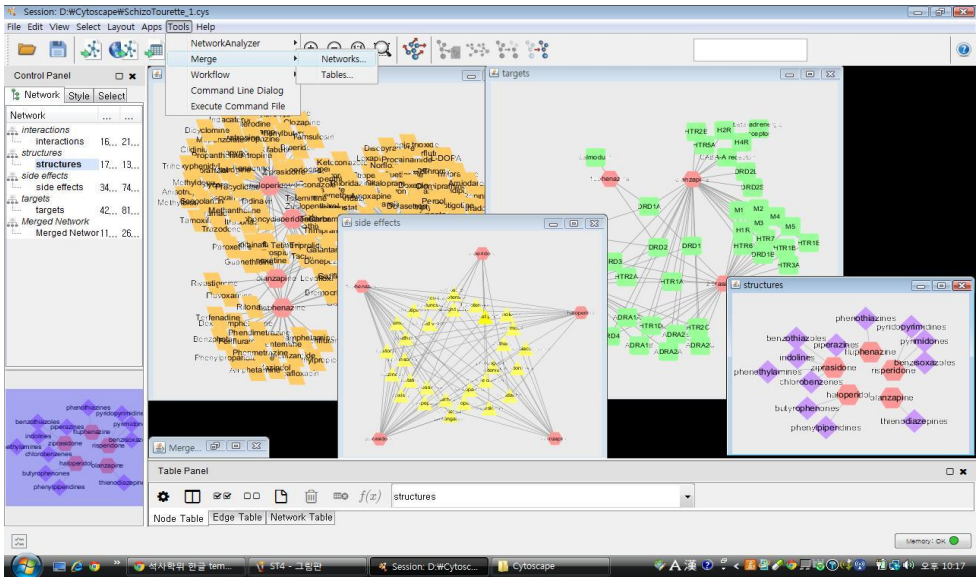


Figure 2.4 d) Created Drug-Similarity network for individual drug information(e.g. side effects)

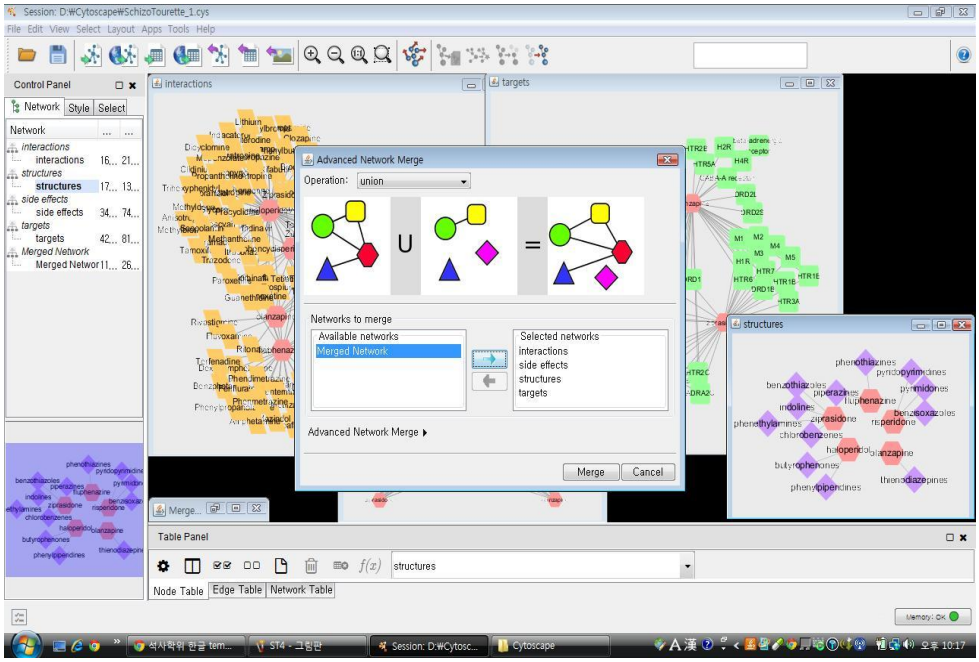


Figure 2.4 e) Build a Drug-Similarity network merging each drug information network

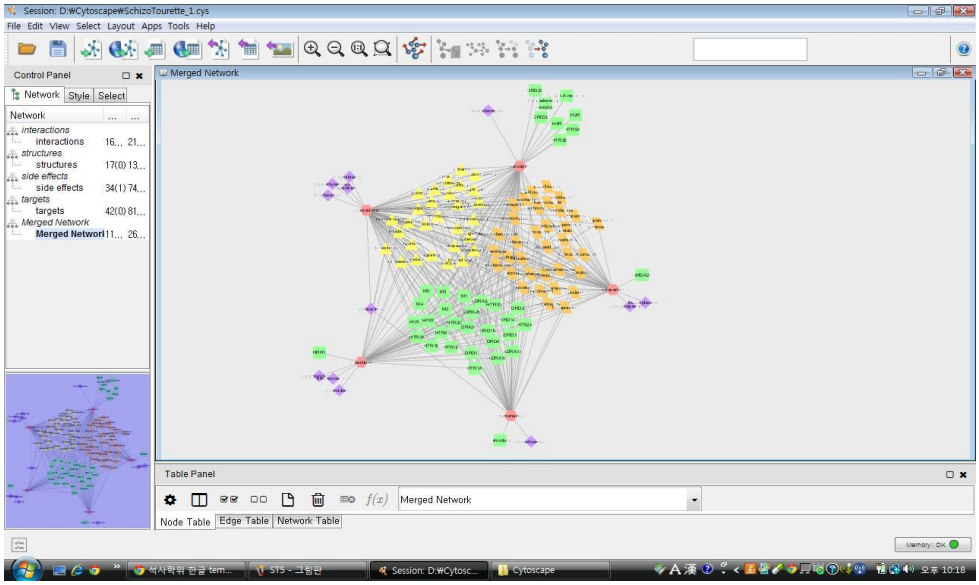


Figure 2.4 f) Merged Drug-Similarity Network

Figure 2.4 Process of the drug-similarity network using Cytoscape. Figure 2.4 (a) through (f) shows how drug information gathered from DrugBank are organized and how drug-similarity networks are drawn using Cytoscape

CHAPTER III. RESULTS

The information of genes related to the disease is found in an open access gene information databases like Genotator and common genes are found by pairing two diseases likely to be associated with each other. The drugs targeting common genes have the possibility to use for both sides of the diseases. In this study, the drugs which target common genes of 5 diseases pairs except the paired disease blood pressure- acute respiratory distress syndrome are examined and there are many cases that those are being used already for the other disease. Using the two stage examining method, after getting the information about the drug that target common genes in between diseases from DrugBank, making drugs-similarity network and the by examining the common parts between drugs, a lot of things are in common other than target like side effects or interaction drugs. Through the drugs-similarity network, it is able to determine the safety depending on the extent and the severity of the side effects and through the structure, common target drug interaction, the effectiveness can be validated. As the result of this study, I suggest the two stage examining method as protocol using protein-protein interaction network for realignment medications and using drugs-similarity network for realignment medications. The result of the study for each of 5 paired diseases experimented according to the protocol is described below.

Panic disorder has the biggest number of disease-related genes, 345 only when it is seen the related score up to 1 on Genotator and Hypertension has 324 related genes. The next is Schizophrenia which has 289 disease-

related genes. The common genes which are found in these pairs are 29 of Hypertension- Wegener's granulomatosis, 24 of Panic disorder-Alzheimer, 10 of Albinism- Melanoma, 22 of Hypertension-Acute respiratory distress syndrome, 86 of Schizophrenia-Panic disorder and 25 of Tourette syndrome-Schizophrenia. The common genes shared in 6 paired diseases are pre-organized on Table 3.1 and the Figure 3.12 the interaction between common genes-protein on Tourette syndrome- Schizophrenia is captured with confidence view. The Figure 3.13 is the collected information of drugs' side effects from rxlist.com or drugs.com through DrugBank. In one paired diseases, Schizophrenia-Panic disorder has the biggest number of common genes; 86 of common genes are found when it uses calculated score 1 as the minimum standard. It enables to predict that there is a high possibility of finding some medications can be used as off-label use in this paired diseases.

3.1 The Result of the paired diseases, Schizophrenia-Tourette syndrome

Common related genes in Schizophrenia-Tourette syndrome chosen from Genotator are 25; BDNF, CNR1, CNTNAP2, COMT, DBH, DRD1, DRD2, DRD3, DRD4, GDNF, HLA-DRB1, HTR1A, HTR2A, HTR2C, HTR3A, IL10, IL10RA, IL1B, IL1RN, MAOA, OLIG2, SLC1A3, SLC6A3, SLC6A4, TNF (Table 3.1) and Figure 3.6 shows the interaction network of common genes in this paired diseases. Common drugs used for this paired diseases are Fluphenazine, Haloperidol, Olanzapine, Risperidone, Ziprasidone and the drug-similarity network is shown in Figure 3.14(b). Haloperidol is the only permitted for both Schizophrenia and Tourette syndrome, and the rest of 4 have a permit for Schizophrenia's indication yet is used for Tourette-syndrome as off-label use. Because all four drugs Schizophrenia-Tourette syndrome common, many of side effects are shared in common, the off-label use seems reasonable. Table 3.2 shows briefly the each drug's target, structure, interaction drugs and side-effects.

The drugs used in these two diseases have each target in common causing drug interaction, the drugs which cause interaction mediated by DRD1A and DRD2 are all 5 of them, and especially DRD2 is the shared common gene in this paired diseases. Dopamine receptor D2 related medications are matched together and then by checking out if there is anything in common, the fact that side effects related to target are matched is confirmed. Drugs that cause weight gain, which can be led by metabolic abnormalities, are 4; fluphenazine, olanzapine, risperidone, ziprasidone and the mediator genes seem to be related to this phenomenon are DRD2 and DRD1A.

This relevance is confirmed in other references. When “DRD2 and weight gain” are searched on Pubmed 1,144 references are about the function of genes, 20 of them are related to weight gain and 8 out of them are about the relation between DRD2 and weight gain caused by the side effects by using psychiatry medication(Llerena et al., 2013; Houston et al., 2012; Lett et al., 2012; Muleer et al., 2012; Lencz et al., 2010; Hong et al., 2010; Lencz and Malhortra, 2009; Malhortra, 2004). The gene related to Priapism caused by side effect is known as the α-1 adrenergic receptor (ADRA1A), Priapism is represented as the result of block effect of receptor when the drugs which have high affinity with this receptor are used. Olanzapine, Risperidone and Ziprasidone have ADRA1A as a drug target and all three are reported to have Priapism as side effect (Andersohn et al., 2010; Carruthers, 1994; Shahani, 2012; Sinkeviciute, 2012).

Among the drugs which are used in common for Schizophrenia-Tourette Syndrome disease pair, the gene which is in common only in Haloperidol, Olanzapine, Risperidone and Ziprasidone is HTR2A and the suspicious side effects which related to this gene are TD, parkinsonism and movement disorder. There are many references associated with HTR2A about motor disturbance caused by the use of antipsychotic medication (Wilffert et al., 2009; Segman et al., 2001). Haloperidol is the highpotency drug which show extrapyramidal syndrome, low blood pressure and anticholin side effect on the patient who get more than 1%. The medication has less side effects yet has almost same effects is chosen in Psychiatric medications. In Schizophrenia’s known pathogenesis, Dopamine theory is the most influential and it is seen as dopaminergic bulimia status. Haloperidol’s pathogenesis is blocking D1, D2 receptor from the brain. Haloperidol’s targets are DRD2, DRD1A, NMDA2B, HTR2A, DRD3 and when they are used for

Schizophrenia, DRD2, DRD3, HTR2A, DRD1 seem to get influenced. Though the pathogenesis of Tourette syndrome is not well known, if Haloperidol is applied for Tourette syndrome, the same genes DRD2, DRD3, HTR2A, and DRD1 seem to get influenced. Motor disturbance, TD and Parkinsonism by the effect of blocking DRD2 are expected.

The targets of Fluphenazine are DRD2, DRD1A and Calmodulin and the clear effect of calmodulin was not found other than known dopamine receptor blocking effect. The drug targets of Olanzapine and Tourette syndrome related genes in common are 9; DRD2, HTR2A, DRD4, DRD3, HTR2C, DRD1, HTR1A, HTR3A 와 HTR2B. The targets which only related to Tourette syndrome are 2; HTR3A and HTR2B. There is a study which shows that the HTR3A function is related to fear disorder (Kondo et al., 2013) and this seems to be based on the study that HTR3A gene has the control function over fear or terror. There are the study that HTR2B is associated with the impulsive behavior (Bevilacqua and Goldman, 2013) and the study that examined how the mutation of HTR2B effect on the patients who have Tourette syndrome (Guo et al., 2012). Also there is study showing the relation between HTR2B and estrogen receptor-α (Kopparapu et al., 2013) and the study reports that it functions as homeostatic regulator of lactation (Collier et al., 2012). When olanzapine is used in Tourette syndrome, other than dopamine receptor blocking effect by acting as antagonistic with targeting HTR3A and HTR2B, as it is possible to control impulsive or fear, the improvement of Tic expressed in Tourette syndrome seems to be more helpful. The significant side effect of Olanzapine is weight gain and known to be related to HTR2C (Wallace et al., 2011). When Olanzapine or other drugs which target other HTR2C such as risperidone or ziprasidone are over used for Tourette syndrome, weight gain is expected as a side effect.

Among 14 drug targets of risperidone, the genes related to Tourette syndrome are 7; DRD2, HTR2A, DRD4, DRD3, HTR2C, DRD1, ADRA2A and the genes related to Schizophrenia are the same in 6; DRD2, DRD3, HTR2A, DRD4, HTR2C, DRD1 yet ADRA2A is the replacement gene of HTR1A. Among the targets of risperidone, the ones only related to Tourette is ADRA2A, which has one of adrenergic genes due to individual genetic polymorphism it is known to be related to obesity, diabetes, cardiovascular reactivity and ADHD. Out of 25 target genes of Ziprasidone, the genes have in common with Schizophrenia are 10; DRD2, DRD3, HTR2A, HTR6, DRD4, HTR2C, HTR3A, DRD1, HTR7, HTR1A and the genes related to Tourette syndrome are 7; HTR1B, DRD2, DRD4, DRD3, HTR2C, HTR1A, HTR3A and the drug target of Ziprasidone which relates to only Tourette syndrome is HTR1B only one. The side effects of Ziprasidone are drowsiness, headache, nausea, EPS, orthostatic hypotension, priapism and hyperprolactinemia. The side effects related to the function of HTR1B can be sexual symptom like anorgasmia, erectile dysfunction and priapism (Jóźków et al., 2013) and substance use disorder (Cao et al., 2013). The drugs which target the common genes, DRD2 and DRD1in 5 of common treatments for Schizophrenia-Tourette syndrome are 94 and 11 each on DrugBank. The drugs targeting DRD2, which have both the similarity of drug structure(phenothiazine) and side effects (EPS, pseudoparkinsonism, TD, drowsiness, lethargy, restlessness, excitement, bizarre dreams, gynecomastia, increased libido, weight gain and so on) are 17; acetophenazine, carphenazine, chlorpromazine, fluphenazine, mesoridazine, methotrimeprazine, perphenazine, pipotiazine, prochlorperazine, promazine, promethazine, propiomazine, triethylperazine, thioproperazine, thioridazine, trifluoperazine and triflupromazine. By using D2 Dopamine Receptor Antagonist, the drugs which having the same target with ziprasidone

and cause interaction are 49, and among them the drug has the same pyridopyrimidine structure with risperidone is Paliperidone and common side effects are headache, extrapyramidal syndrome, somnolence, dizziness, parkinsonism, insomnia, agitation and anxiety. The drugs which have the same structure of Phenothiazine with Fluphenazine are 17 and the side effects are drowsiness, hypotension, extrapyramidal syndrome, sedation and gynecomastia. The drug which has the same structure of phenylpiperidine with Haloperidol and is permitted as second alternative for Tourette syndrome; which has vocal and motor tics, is pimozide. The common side effects are tachycardia, postural hypotension and extrapyramidal syndrome.

The drugs listed here, other than having permitted indication because they have DRD2 as common target, have structural similarity and side effects revelation occur equally, they can be considered high possible medication for realignment as treatment for diseases related to this gene. The permitted drug, haloperidol is for Tourette syndrome while pimozide is permitted to the patients with motor and phonic tic symptoms which is incurable, the target of this drug are 4; DRD2, DRD3, KCNH2, calmodulin. The common target of Haloperidol and Pimozide are DRD2, DRD3 and other 3 drugs, olanzapine, risperidone, ziprasidone target DRD2 and DRD3 as well. The drug which shares the same target which only Pimozide has is Fluphenazine, those two medications target Calmodulin and can show the same side effects such as EPS, drowsiness, restlessness and have similar structure of Benzene derivatives. Pimozide and fluphenazine can be used for both of diseases by targeting the genes shared in this paired disease and it can be seen that it has a common side effect in the target, only the two drugs that share. If not the temporal constraints, other drugs which act as an inhibitor for Calmodulin will be reviewed to realign. The drugs which act as inhibitors for Calmodulin are

cinchocaine, fluphenazine, trifluoperazine, loperamide, perphenazine, phenoxybenzamine, promethazine, pimozide, nifedipine and aprindine. Depending on the degree of affinity of the drug target, revealed expression level or frequency of side effects is a bit different from each other, but it seems to be predicted. Other than Haloperidol which has the permitted indications for Tourette syndrome, 4 other drugs(fluphenazine, olanzapine, risperidone, ziprasidone) used as off-label are shown to have more than two things in common on drugs-similarity network. As can be seen from the individual medical information(through DrugBank, rxlist.com or drugs.com), according to the degree of binding of the target, the expected effectiveness of medication, the severity or frequency of side effects can be known. In this study, these 4 medications used as off-label are individually used for each different Tic symptom and clinically effective to improve different symptoms, to avoid side effects according to the different profile of side effects, the fact that the drugs can be used selectively is proven theologically.

With this method, the existing medications examined and checked if they can be used for other indications. First, because there is no alternative medication, the genes information of disease which use permitted medications for other diseases as off-label gets from public site, the gene database information, Genotator, and get the genes information of other diseases which share the same genes with the target of drugs used as off-label and then find out the shared genes between two diseases. STRING's the protein-protein interaction network enables to see easily. Figure 3.1~3.6 show the interaction between shared genes from each paired disease in 6 paired diseases. As it is seen, the bold line means the level of closeness between genes. Second, the target protein the drugs which are used for two diseases is selected from DrugBank and organized by database, with the common things between drugs

for example, matching the target of treatment, sameness of the infrastructure, a common thing of side effects or the drug causes interactions, drugs-similarity network can be made. Figure 3.14 (b) is drug-similarity network for the treatment of Schizophrenia-Tourette syndrome. Based on this network, phenothiazine structure is in common and the side effects commonly expressed in this structure, weight gain, priapism, tardive dyskinesia, parkinsonism, movement disorder, extrapyramidal syndrome, hypotension are revealed according to the degree and the 17 drugs which target DRD2 can be seen the candidate of medication for Tourette syndrome other than Schizophrenia. Since Fluphennazine is used as off-label, through the stage of clinical experiment, after confirming the safety and effectiveness, it can be used as permitted one. The effectiveness for Tourette syndrome can be checked in details compare to other drugs.

3.2 The Result of the paired diseases, Schizophrenia-Panic Disorder

The shared genes in the paired diseases Schizophrenia-Panic disorder are 86; (ABCB1, ACE, APOE, ASTN2, BDNF, CCK, CCKAR, CHRM1, CHRM2, CHRNA7, CHRNB2, CNR1, CNTF, CNTNAP2, COMT, DAOA, DBH, DISC1, DLG1, DRD1, DRD2, DRD3, GABBR1, GABRA5, GABRB2, GABRG2, GABRG3, GABRR1, GAD1, GAD2, GDNF, GNB3, GRIA1, GRIA2, GRIA3, GRIA4, GRIK3, GRIK4, GRIN2A, GRIN2B, GRM3, GRM4, GRM5, HTR1A, HTR2A, HTR2C, HTR3A, HTR3B, HTR4, HTR5A, HTR6, HTR7, IL10, L1CAM, LEP, LEPR, MAOB, NCAM1, NEUROG1, NOS1, NPY, NRG1, NRG2, NRG3, NRXN1, NSF, NTF3, NTRK3, PDE4B, PDYN, PPP1R1B, RELN, RGS2, S100B, SLC1A1, SLC1A2, SLC1A3, SLC6A3, SLC6A4, SLC6A9, SNAP25, SNAP29, TPH1, TPH2) and is organized in Table 3.1. Among the 12 drugs which used for either Schizophrenia or Panic-disorder, except CHRM1which is the target of all the drugs, the drugs which shared DRD2, HTR2A, ADRA1A, HRH1, HTR2C are 9; chlorpromazine, loxapine, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone, imipramine, desipramine and the drugs which shared SLC6A4 are 6; loxapine, paroxetine, citalopram, escitalopram, imipramine, desipramine. Among these 6 medications, Paroxetine is the only permitted drug for panic disorder and among other shared drugs targeting SLC6A4, Citalopram is the only permitted one for depression, yet it is used for dementia-associated agitation and smoking cessation, ethanol abuse, obsessive-compulsive disorder (OCD), and diabetic neuropathy as off-label. Escitalopram is permitted for depression and anxiety, yet is used for dementia-associated agitation as off-label, and Imipramine and desipramine are also

permitted only for depression yet are used for peripheral neuropathic pain, panic disorder as off-label. The side effects of these drugs including Extrapyramidal syndrome are stomach pain, blurred vision, cough or hoarseness, loss of appetite, loss of bladder control, difficult urination. Because the side effects can have different degree of revelation depending on individual, if the degree appeared to be severe and consistent while monitoring, try to find the best suited ones by changing with other drugs which have side effect profile. The gene which has high relation with Panic disorder is SLC6A4, rather than non-specific drugs because of too many shared genes, Loxapine permitted for Schizophrenia targeting SLC6A4 primarily can be considered realignment for panic disorder. The drugs which cause interaction have a lot in common as it was shown in drug-similarity network (Figure 3.14 (a))and have these side effects, irregular heartbeats, loss of appetite, dizziness, trouble swallowing, priapism, drooling, colored stools, blurred vision, can be expressed in common. In paired disease, the permitted loxapine for Schizophrenia has SLC6A4 as drug target, and because there are a lot of interactions and side effects in common, it can be the candidate medication for realignment as treatment for panic disorder.

3.3 The Result of the paired diseases, Hypertension-Wegener Granulomatosis

The shared related genes in the paired diseases Hypertension-Wegner granulomatosis are 29; SERPINA1, CTLA4, ACE, TNF, IL10, TGFB1, HLA-DRB1, LEPR, GHRL, LEP, CCR5, IL1B, MS4A2, CD40, CCL5, HLA-DPB1, IL1RN, UCP2, PPARA, PPARG, NOD2, HLA-DQB1, C5, SERPINE1, SERPINA3, CIITA, F5, F2 and the per-mitted medication for Wegner granulomatosis is Rituximab, its representative target is MS4A1 and the drugs which have interactions using this target as mediator are ibritumomab, obinutuzumab and tositumomab. The drug which causes interaction in common is Trastuzumab. The drugs which target the gene, TNF related to Wegner Granulomatosis are 7; etanercept, infliximab, adalimumab, golimumab, certolizumab-pegol, pomalidomide and amrinone, and Etanercept and infliximab are used for vasculitis, Wegener Granulomatosis as off-label. The structure of drugs except Obinutuzumab is provided on DrugBank, and shown on Figure 3.7~3.11. As it is shown in drug-similarity network of this paired diseases (Figure 3.14 (c)), the side effects- abdominal pain, back pain, black, tarry stools, blurred vision-can be expressed in common and in the drugs which have TNF as shared target, etanercept, infliximab and adalimumab have drug interaction with tofacitinib and trastuzumab. Based on these, ibritumomab, obinutuzumab, tositumomab, etanercept, infliximab and adalimumab can be considered as the candidate medications for repositioning for Wegener Granulomatosis.

3.4 The Result of the paired diseases, Panic Disorder-Alzheimer Disease

The paired diseases, Panic disorder-Alzheimer disease have 24 of shared genes- ABCB1, ACE, ACHE, AGTR1, ALDH2, APOE, AR, BDNF, CHAT, CHRNA7, CHRNB2, CLU, COMT, DRD3, GRIA1, GRIN2B, HTR2A, HTR2C, IL10, MAOA, NOS3, NTF3, RELN, SLC6A4- and in the drugs permitted for one disease, donepezil, paroxetine and desipramine have HTR2A as a shared target and the drugs which cause interaction are isocarboxazid, moclobemide, phenelzine, tolterodine, tranylcypromine, trazodone, trimipramine, triprolidine and zuclopenthixol. The information of medications which are used for the paired diseases, Panic Disorder-Alzheimer Disease is shown briefly in Table 3.3. The drugs which have the same structure of piperidines are donepezil and paroxetine. The drug-similarity network of the paired diseases is shown on Figure 3.14 (d) and the shared side effects are photosensitivity, difficult urination, blurred vision, loss of bladder control, galactorrhea and loss of appetite. Although Paroxetine is the drug permitted for depression and panic disorder, it is used for impulse control disorders and appetite disorders, dementia, anxiety-related symptoms and vasomotor symptoms of menopause as off-label. The fact that Paroxetine is used for agitation related to dementia as off-label can be confirmed on DrugBank and other DB of drugs information. Paroxetine was used for improving vasomotor symptoms of menopause as off-label now it is permitted to sell with indication. The drug named Brisdelle, which has indication for depression is paroxetine, was permitted to sell in November, 2013 by changing the target for vasomotor symptoms of menopause (hot flashes). However, the amount 7.5mg/day for symptoms of menopause is equivalent of

1/3~1/7 of the amount (20-50mg/day) for depression. The side effects are when the amount for depression taken, asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders are revealed in more than 5 % of rate, and when 7.5mg of the amount for menopause is used, headache, fatigue, malaise, lethargy, nausea and vomiting can be revealed in more than 2% of rate. Thus, depending on the amount of intake, the kinds of side effects are more revealed and the degree of revelation is severer. Therefore intake of only the amount of necessary with the right way for the purpose is effective and is the best way to reduce side effects. As can be seen in individual cases, after the cumulative post-marketing experience with the drug, there are side effects are become known. When the effects unknown about medications and the problems from different dosage and capacity are experienced in the field, with the form of case report starts being reported and at the end, through clinical experiences, it gets the permit which is different from existing use. In the middle of the process, this is the study that reviewing process systematically if it is theologically reasonable to use off-label experimentally.

From this point of view, paroxetine is being used for agitation by dementia as off-label is effective. The reason is that as antagonist works on Sodium-dependent serotonin transporter (SLC6A4), the effect can be caused. On the other hand, from the safety side, as antagonist works on muscarinic acetylcholine receptor (CHRM1), anticholine effects (constipation, dry mouth) can be revealed. When it is changed the amount used for anxiety, 20~50mg/day into 10mg/day for the old, expected side effects can be headache, fatigue, weakness, nausea and vomiting. About safety, the frequency and variety of side effects are expected less than when it is used as the existing indication. Desipramine is permitted for the depression and used

alternatively for neuralgia, refractory anxiety, or hyperactivity disorder (ADHD) as off-label. As this drug works as inhibitor for SLC6A4 and CHRM1, is seems to be effective on improving anxiety related to dementia. From the aspect of safety, when the amount for the old, 25~100mg/day (maximum 150mg/day) is used, fatigue, lethargy, sedation and anticholine effect (constipation, dry mouth, blurred vision) can be revealed.

3.5 The Result of the paired diseases, Albinism-Melanoma

Shared gene are ten as ASIP, HERC2, IRF4, MC1R, OCA2, SLC24A4, SLC24A5, SLC45A2, TYR, TYRP1 in Albinism-Melanoma paired disease and the protein interaction network is showed on Table 3.3. There are two drugs, methoxsalen and monobenzone, for vitiligo. There are 2 drugs called as Azelaic acid, Monobenzone targeting TYR in the shared gene of the paired diseases. The Azelaic acid is a permitted drug for acne vulgaris as a part external drug and the monobenzone is permitted for vitiligo. Burning, tingling, itching, redness or swelling of treated skin might appear as side effects of 2 drugs. The things in common of the target and side effects can be seen using drug-similarity network and both can be considered realigning for albinism and melanoma treatment. The drugs used for Melonama are 5; temozolomide, dacarbazine, aldesleukin, ipilimumb, and vemurafenib, just ipilimumab and dacarbazine are permitted for melanoma and 3 others are being used as off-label drugs. The drug similarity network is shown in Figure 3.14 (e). If the effectiveness of drugs used as off-label is examined, only temozolomide has the same target DNA with dacarbazine permitted for melanoma, the structure is similar to imidazole and trastuzumab is shared as the interaction drug. In the safety aspect, amnesia, blood urine, convulsions, cough or hoarseness, fever or chills, back pain, muscle weakness and painful urination can appear in temozolomide and in dacarbazine, colored stools, blood in urine, cough or hoarseness, fever or chills, back pain, painful urination appear as almost similar side effects. It is considered to be safe if it is examined from drug-similarity network, because Temozolomide can be realigned for the treatment for melanoma and side effects for what have already used as off-label use are

within range of prediction.

In the 5 paired diseases listed above, the drugs used as off-label use are re-viewed with the genes-medicated, which are provided on Genotator, the drug which targets shared gene in a paired diseases is not only a treatment for permitted side of diseases but also it is effective to the other side disease as well. It means that realignment of drugs can be done with this way. In addition, after collecting the information of structures, targets, side effects, and interactive drugs on DrugBank and then create the similar networks with Cytoscape, there are a lot of cases that are overlapped more than twice in the similarities of the drugs in paired diseases. The relation of side effects revelations by targets can be confirmed and possibility for treatments for different diseases can be checked by having shared targets. Based on this, not only for checking the effectiveness and safety for the permitted existing drugs but also for searching new indication, bioinformatics is suggested as new protocol and once the protocol was applied as trial, off-target use was included considerably. The protocol is considered verified. The studies so far were basic and non-complete ones; mainly about the drugs used as off-label use, checking targets and examining side effects. However, if the studies continued to be done, bioinfomatical reviewing would reduce economical efforts and time in the development of new medications.

Analyzing the information of genes between from Genotator and from STRING, using the information of drugs from DrugBank and Cytoscape, creating drug-similarity network is done from March, 2014 to September, 2014.

Table 3.1 Shared genes in pairs of diseases

pairs of disease	shared genes
Hypertension/Wegener Granulomatosis	SERPINA1 CTLA4 ACE TNF IL10 TGFB1 HLA-DRB1 LEPR GHRL LEP CCR5 IL1B MS4A2 CD40 CCL5 HLA-DPB1 IL1RN UCP2 PPARA PPARG NOD2 HLA-DQB1 C5 SERPINE1 SERPINA3 CIITA F5 F2
Panic disorder/Alzheimer	ABCB1 ACE ACHE AGTR1 ALDH2 APOE AR BDNF CHAT CHRNA7 CHRNB2 CLU COMT DRD3 GRIA1 GRIN2B HTR2A HTR2C IL10 MAOA NOS3 NTF3 RELN SLC6A4
Albinism/Melanoma	ASIP HERC2 IRF4 MC1R OCA2 SLC24A4 SLC24A5 SLC45A2 TYR TYRP1
Hypertension/Acute Respiratory Distress Syndrome	ACE AGT APOE CALCA F5 GSTM1 GSTP1 GSTT1 HMOX1 ICAM1 IL10 IL18 IL1RN IL6 LTA MTHFR NOS3 PLA2G7 SCGB1A1 SERPINE1 TNF VEGFA
Schizophrenia/Panic disorder	ABCB1 ACE APOE ASTN2 BDNF CCK CCKAR CHRM1 CHRM2 CHRNA7 CHRNB2 CNR1 CNTF CNTNAP2 COMT DAOA DBH DISC1 DLG1 DRD1 DRD2 DRD3 GABBR1 GABRA5 GABRB2 GABRG2 GABRG3 GABRR1 GAD1 GAD2 GDNF GNB3 GRIA1 GRIA2 GRIA3 GRIA4 GRIK3 GRIK4 GRIN2A GRIN2B GRM3 GRM4 GRM5 HTR1A HTR2A HTR2C HTR3A HTR3B HTR4 HTR5A HTR6 HTR7 IL10 L1CAM LEP LEPR MAOB NCAM1 NEUROG1 NOS1 NPY NRG1 NRG2 NRG3 NRXN1 NSF NTF3 NTRK3 PDE4B PDYN PPP1R1B RELN RGS2 S100B SLC1A1 SLC1A2 SLC1A3 SLC6A3 SLC6A4 SLC6A9 SNAP25 SNAP29 TPH1 TPH2
Tourette syndrome /Schizophrenia	BDNF CNR1 CNTNAP2 COMT DBH DRD1 DRD2 DRD3 DRD4 GDNF HLA-DRB1 HTR1A HTR2A HTR2C HTR3A IL10 IL10RA IL1B IL1RN MAOA OLIG2 SLC1A3 SLC6A3 SLC6A4 TNF

As a first step in finding therapeutic drug, diseases that share genes with targets of off label used drugs were paired. Then for each drug, genes of association score down to 1 were brought from Genotator and genes that are common were organized in table.

Table 3.2 Schizophrenia-Tourette Syndrome Drug Information

	fluphenazine	haloperidol	olanzapine	risperidone	ziprasidone
target	DRD2 DRD1A calmodulin	DRD2 DRD1A NMDA2B HTR2A DRD3	HTR2A, DRD2, DRD1A, DRD1B, DRD3, DRD4, HTR1A, HTR1B, HTR1D, HTR1E, HTR2C, HTR3A, HTR6, HTR7, H1R, ADRA1A, ADRA1B, ADRA2A, ADRA2B, ADRA2C, M1,M2, M3, M4, M5, HTR2B, HTR5A, DRD1, H2R, H4R, GABRA, ADRB, DRD2L, DRD2S	HTR2A, DRD2, DRD3, DRD4, ADRA1A, ADRA1B, HTR1D, HRH1, ADRA2A, ADRA2B, ADRA2C, HTR2C, HTR1A, DRD1	DRD2, HTR2A, DRD1A, DRD1B, DRD3, DRD4, HTR1A, HTR1B, HTR1D, HTR1E, HTR2C, HTR3A, HTR6, HTR7, H1R, ADRA1A, ADRA1B, ADRA2A, ADRA2B, ADRA2C, M1, M2, M3, M4, M5
interaction	Amphetamine Atomoxetine Benzphetamine Bromocriptine Cisapride Dexfenfluramine	Anisotropine Methylbromide Artemether Atomoxetine Atropine Benzatropine Biperiden Carbamazepine Clidinium Clozapine	Donepezil Fluvoxamine Galantamine Ritonavir Rivastigmine Tacrine Tetrabenazine Trimethobenz amide Triprolidine Trospium	Artemether Carbamazepine Donepezil Fluoxetine Galantamine Indinavir Itraconazole Lumefantrine Paliperidone Paroxetine Tacrine Tacrolimus	Abarelix Amantadine Amiodarone Amitriptyline Amoxapine Apomorphine Arsenic trioxide Artemether Asenapine Azithromycin
substructure	Phenothiazines Piperazines	Phenylpiperi dines Butyrophen ones	Thienodiazepines	Pyridopyrim idines Benzisoxazoles	Benzothiazoles

side effect	hypotension, somnolence, weight gain, erectile dysfunction, amenorrhea, anticholinergic effects (dry mouth, constipation, nasal congestion, blurred vision, diminished sweating), extra-pyramidal side effects(tremor, akathisia, muscle rigidity, dystonia, Parkinsonism)	extra-pyramidal side effects, hypotension, anticholinergic side effects, somnolence, prolonged QT interval, increased respiratory rate, anaemia, visual disturbance, headache	weight gain, somnolence, hyperprolactinemia, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, extra-pyramidal symptoms (EPS), orthostatic hypotension, dyspepsia, erectile dysfunction, hyperprolactinaemia, asthenia, decreased libido, QTc interval prolongation, photosensitivity reaction, alopecia, amenorrhea	extra-pyramidal side effects, sexual side effects, galactorrhea, infertility, gynecomastia, reduced bone mineral density, increased prolactin secretion, weight gain, hypotension, sedation	somnolence, headache, hypersalivation, respiratory disorders, nausea, vomiting, drymouth, constipation, dyspepsia, dizziness, extra-pyramidal symptoms, rash, tachycardia, orthostatic hypotension, diarrhea, anorexia, myalgia

Five drugs that are off-label used for Tourette Syndrome that are originally approved for Schizophrenia were analyzed by target, interaction, structure, and side effects based on the data from DrugBank. Data for interaction and side effects are only in part.

Table 3.3 Panic Disorder-Alzheimer Drug Information

drug	donepezil	paroxetine	desipramine
substructure	benzylpiperidines	phenylpiperidines	dibenzazepines
target	ACHE	SLC6A4, SLC6A2, HTR2A, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5	SLC6A2, SLC6A4, HTR2AADRB2, ADRB1, SMPD1, HRH1, ADRA1(ADRA1A, ADRA1B, ADRA1D), CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, SNF, HTR1A, HTR2C, DRD2, ADRA2(A,B,C)
side effect	diarrhea loss of appetite muscle cramps nausea trouble in sleeping unusual tiredness vomiting abnormal dreams constipation dizziness drowsiness frequent urination headache joint pain mental depression pain unusual bleeding weight loss	agitation chest congestion chest pain chills cold sweats confusion difficulty with breathing dizziness irregular heartbeat muscle pain skin rash decrease in body movements enlarged pupils convulsions difficulty with speaking dry mouth	abdominal pain anxiety black, tarry stools blurred vision enlarged pupils tingling feelings chest pain confusion convulsions cough or hoarseness dark urine dizziness dry mouth irregular heartbeat or pulse inability to move inability to speak irritability light-colored stools loss of appetite loss of bladder control muscle spasms nausea
interaction	Acepromazine Aceprometazine Alimemazine Alverine Amantadine Amitriptyline Amoxapine Atropine Azatadine Benzatropine Biperiden	Acenocoumarol Almotriptan Amphetamine Anisindione Asenapine Atomoxetine Benzphetamine Carvedilol Desvenlafaxine Dexfenfluramin	Altretamine Artemether Atazanavir Avanafil Butabarbital Butalbital Carbamazepine Cimetidine Cisapride Clonidine

Drug information of those used for Panic disorder-Alzheimer were gathered from DrugBank and analyzed.

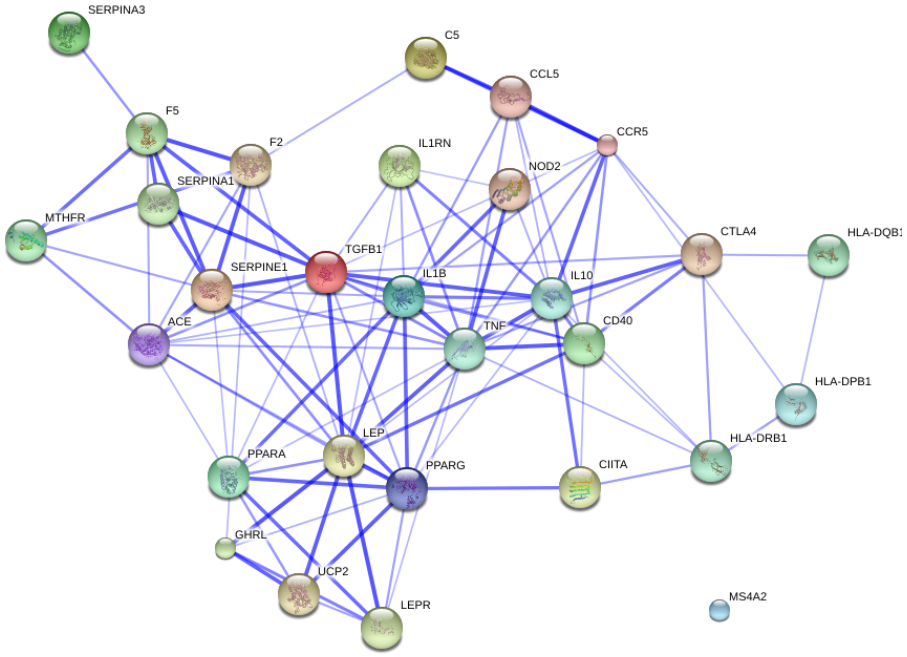


Figure 3.1 Protein-protein interaction network of the disease related genes shared by Hypertension and Wegener Granulomatosis. Of the genes that are related to Hypertension and Wegener Granulomatosis, common genes of association score down to 1 were brought from Genotator. Then, a network of association between the shared genes in this pair of diseases were drawn using STRING. The figure above is an interaction network of the 29 common genes in confidence view in which the bold lines present strong interaction.

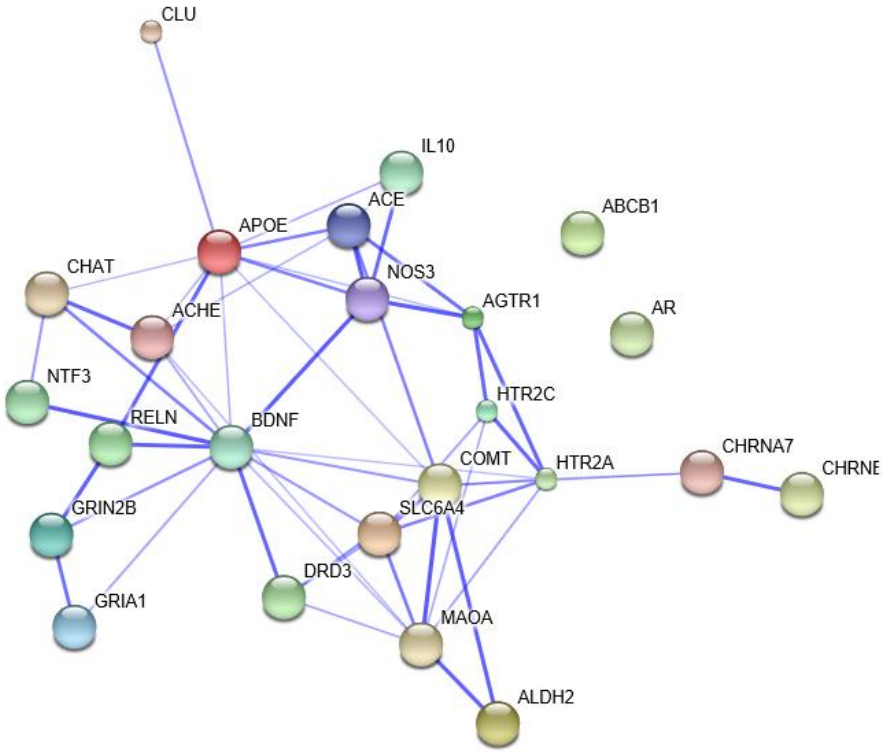


Figure 3.2 Protein-protein interaction network of the disease related genes shared by Panic disorder and Alzheimer disease. The figure above shows correlation between the 24 disease related genes that are common in Panic disorder and Alzheimer disease.

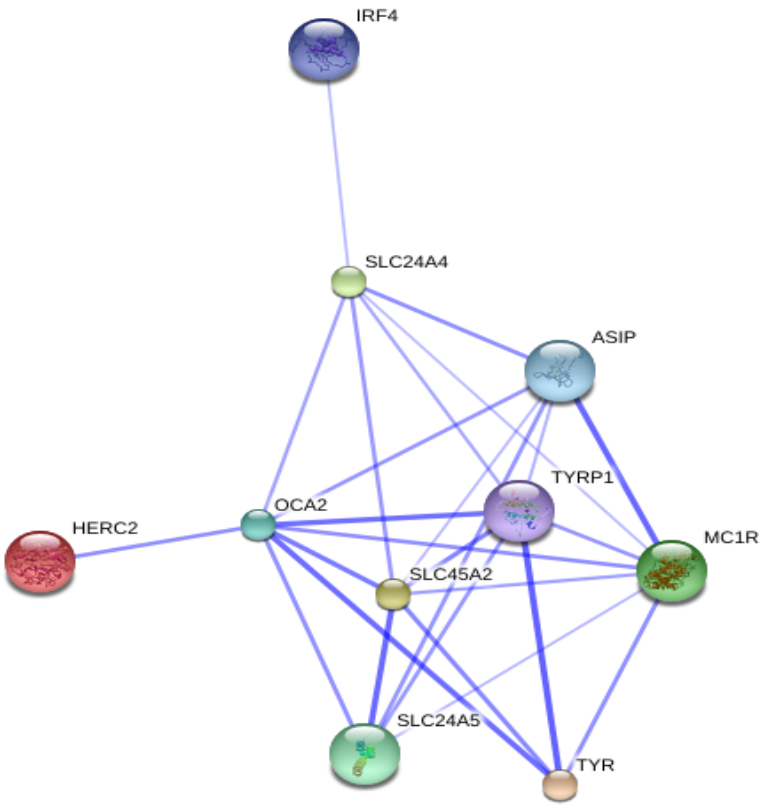


Figure 3.3 Protein-protein interaction network of the disease related genes shared by Albinism and Melanoma. The figure above shows correlation between the 10 disease related genes that are common in Albinism and Melanoma.

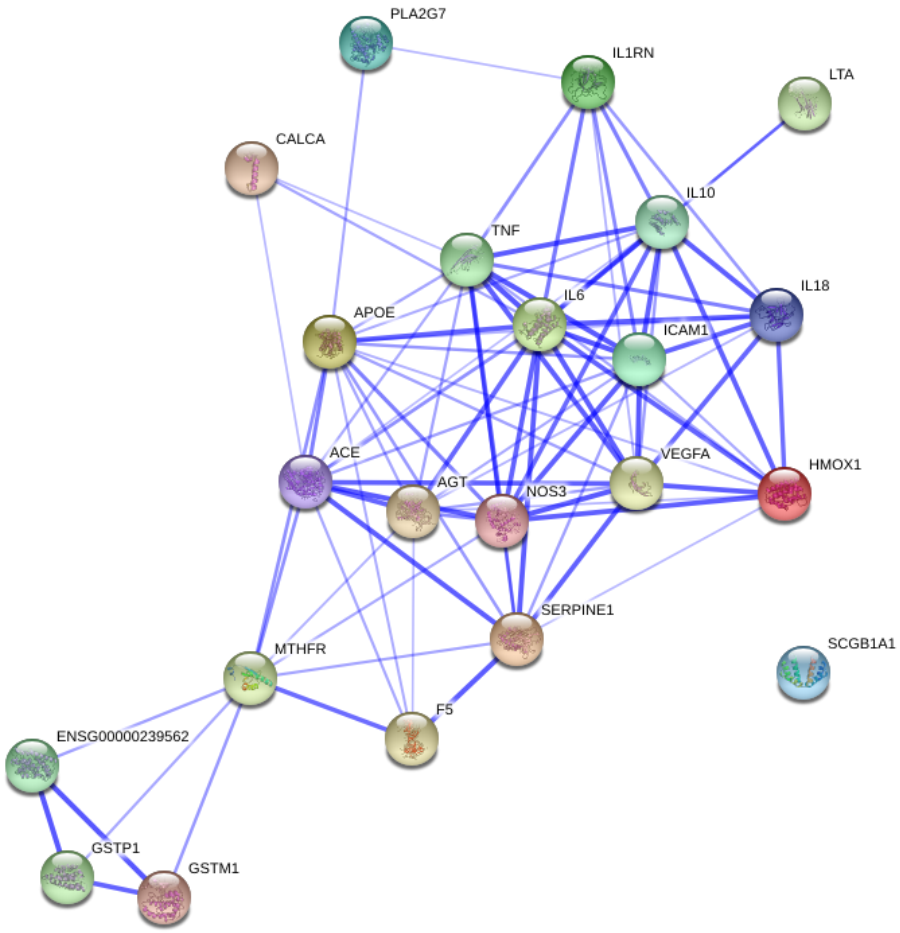


Figure 3.4 Protein-protein interaction network of the disease related genes shared by Hypertension and Acute Respiratory Distress Syndrome. The figure above shows correlation between the 22 disease related genes that are common in Hypertension and Acute Respiratory Distress Syndrome.

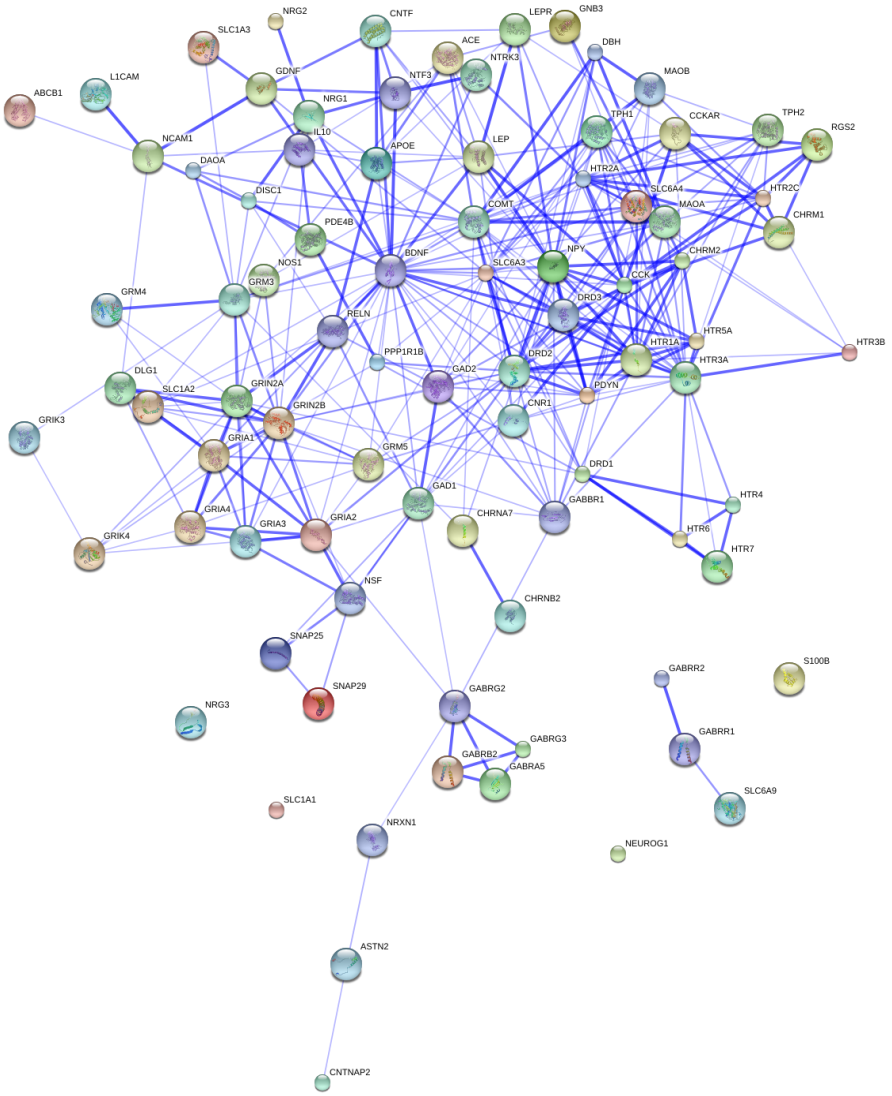


Figure 3.5 Protein-protein interaction network of the disease related genes shared by Schizophrenia and Panic disorder. The figure above shows correlation between the 86 disease related genes of association score down to 1 from Genotator that are common in Schizophrenia and Panic disorder.

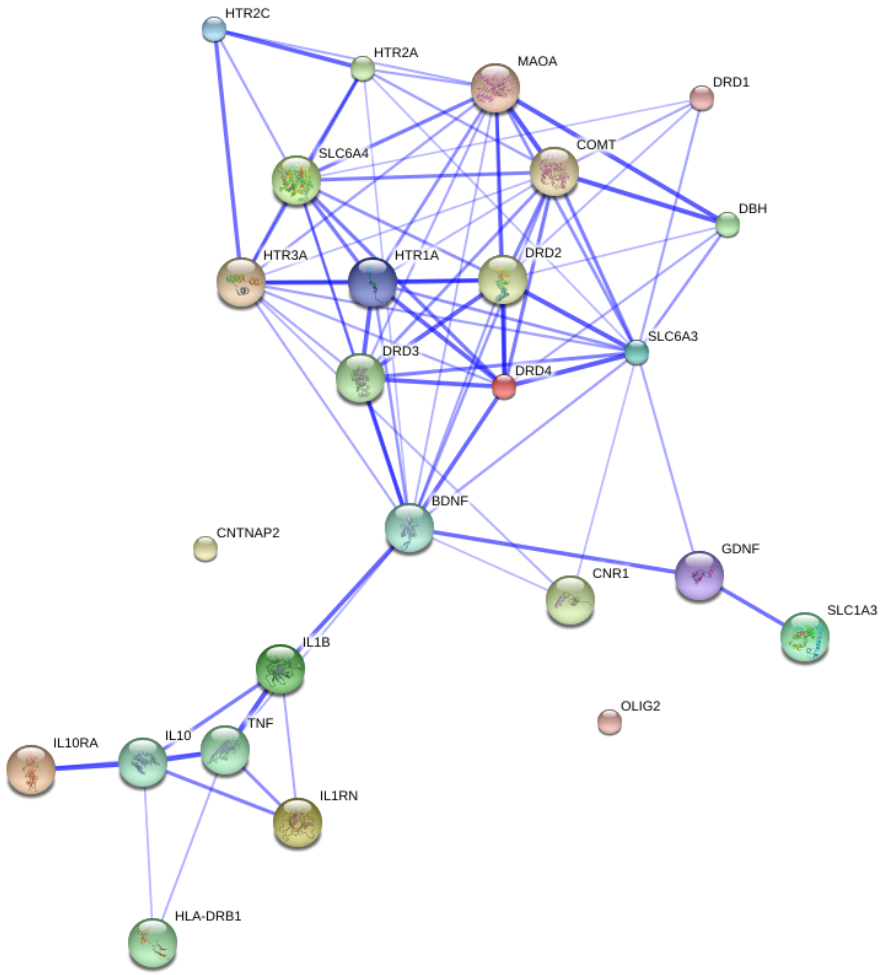


Figure 3.6 Protein-protein interaction network of the disease related genes shared by Tourette syndrome and Schizophrenia. The figure above shows correlation between the 25 disease related genes that are common in Tourette syndrome and Schizophrenia.

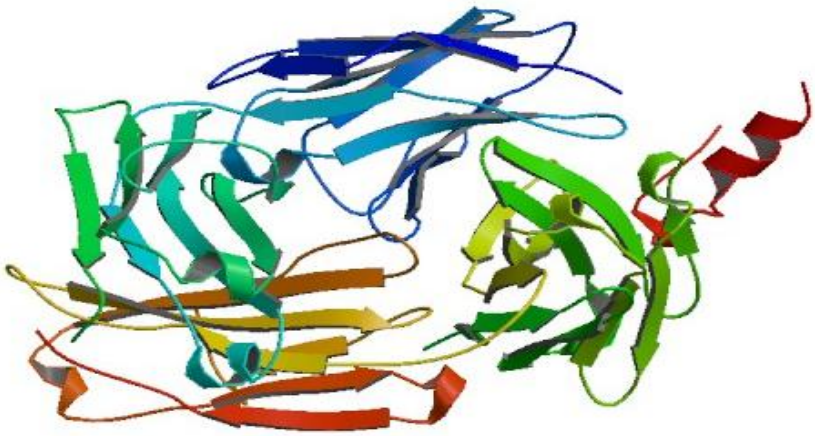


Figure 3.7 Protein Structure of Rituximab from DrugBank (Du et al., 2007)

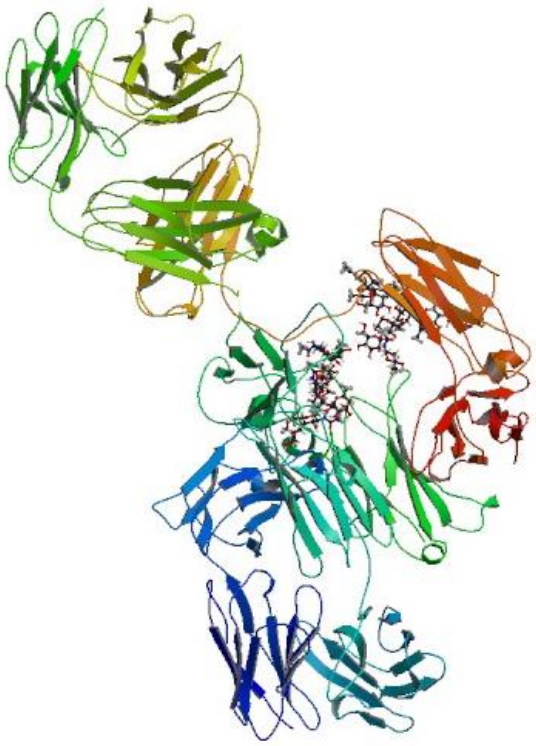


Figure 3.8 Protein Structure of ibritumomab from DrugBank (Harris et al., 1997)

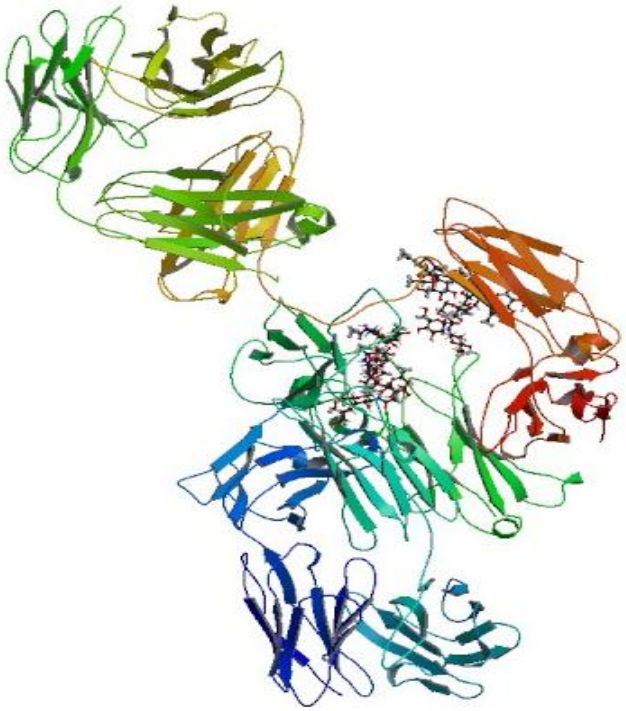


Figure 3.9 Protein Structure of tositumomab from DrugBank (Harris et al., 1997)

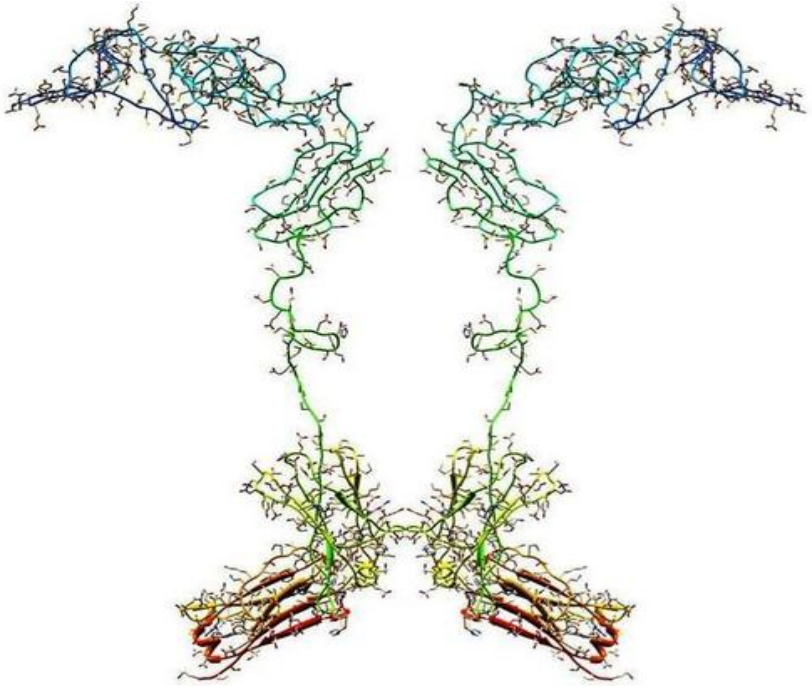


Figure 3.10 Protein Structure of etanercept from DrugBank (Matsumiya et al., 2011)

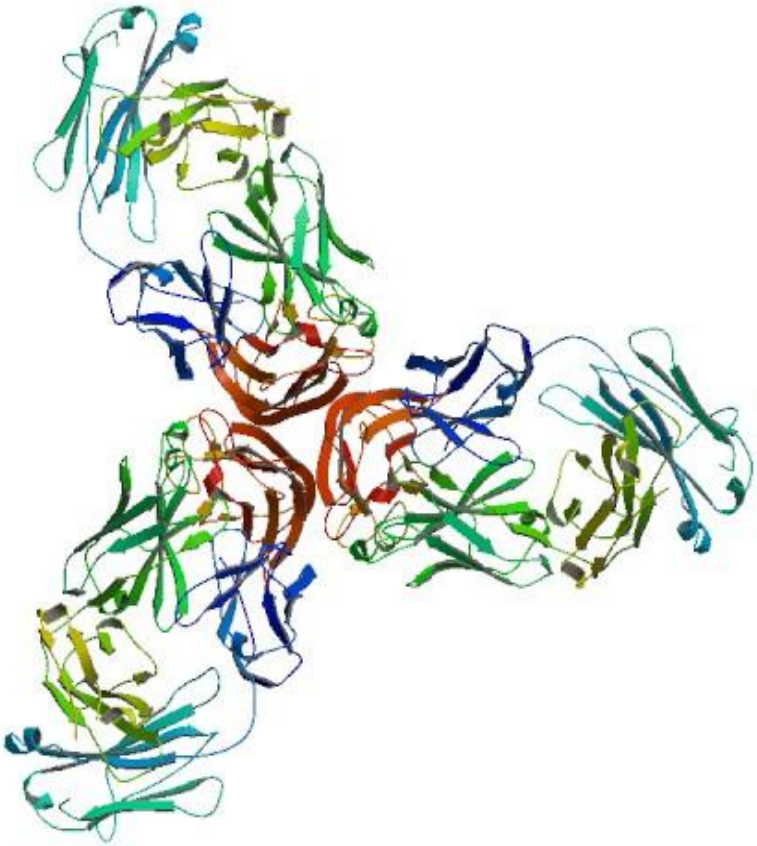


Figure 3.11 Protein Structure of infliximab from DrugBank (Liang et al., 2013)

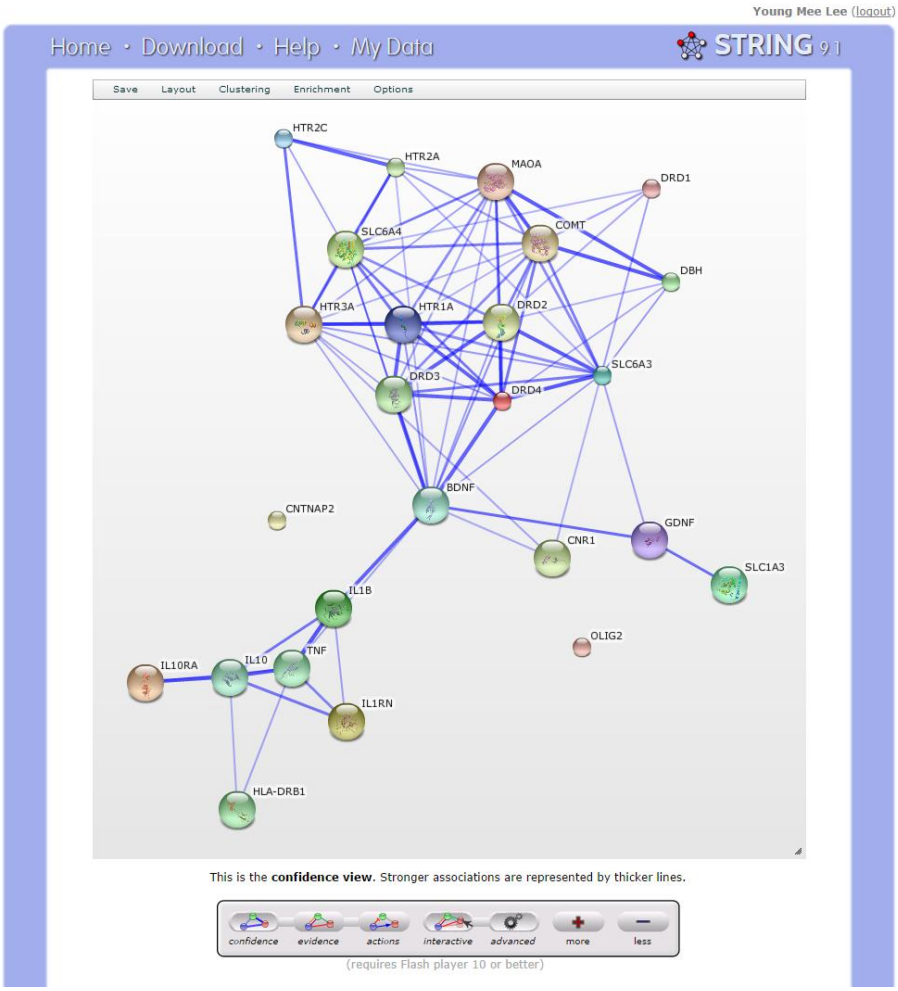


Figure 3.12 Protein-protein interaction network depicted as confidence view. The figure above shows the interaction network between the 25 disease related genes that are common in Tourette syndrome and Schizophrenia obtained from Genotator.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	chlorpromazine	loxapine	aripiprazole	clozapine	olanzapine	quetiapine	ziprasidone	paroxetine	citalopram	escitalopram	imipramine	desipramine			
2	twitching or uncontrollable movements of your eyes, lips, tongue, face, arms, or legs	Difficulty with sp	Difficulty with spe	Blurred visio	Bloating or swe	Chills	Cough	Agitation	Agitation	Coma	Abdominal or stom	Abdominal or stomach pain			
3	tremor, drooling, trou	lip smacking or p	drooling	confusion	blurred vision	cold sweats	difficulty with speakin	chest congestion	blurred vision	confusion	agitation	anxiety			
4	feeling restless, jitter	loss of balance c	loss of balance co	dizziness, fai	change in visio	confusion	drooling	chest pain	confusion	convulsions	blurred vision	black, tarry stools			
5	feeling like you mig	mask-like face	muscle trembling,	fainting	change in walk	dizziness, faint	fear or nervousness	chills	fever	decreased urine o	burning, crawling, it	blurred or double vision			
6	seizure (black-out or	puffing of the ch	restlessness	fast, poundir	clumsiness or u	sleepiness or u	fever	cold sweats	increase in the freque	dizziness	chest pain or discor	burning, crawling, itching, numbness, prickling, "pins a			
7	nausea upper stoma	rapid or fine, wor	shuffling walk	fever	difficulty with sp	(Less common)	inability to sit still	confusion	lack of emotion	fast or irregular h	clay-colored stools	chest pain or discomfort			
8	pale skin, easy bruis	restlessness or de	stiffness of the lin	shakiness in	difficulty with s	Black, tarry sto	loss of balance contro	difficulty with brea	loss of memory	headache	cold sweats	confusion about identity, place, and time			
9	high fever, stiff musc	shuffling walk	twisting movemer	sleepiness or	drooling	blurred vision	muscle trembling, jerk	dizziness, faintness,	menstrual changes	increased thirst	confusion about ide	convulsions			
10	unusual thoughts or	slowed movemer	uncontrolled mov	sweating	impaired vision	changes in pat	need to keep moving	fast, pounding, or i	skin rash or itching	muscle pain or cr	continuing ringing i	cough or hoarseness			
11	decreased night visic	stiffness of the ar	dizziness	trembling or	inability to sit s	chest pain	restlessness	muscle pain or wea	trouble breathing	nausea or vomitir	cough or hoarsenes	dark urine			
12	urinating less than u	trembling and sh	headache	unusual tirec	loss of balance	cough	shuffling walk	skin rash	Rare	shortness of breat	dark urine	dizziness, faintness, or l	lightheadedness when getting		
13	joint pain or swellinc	uncontrolled che	inability to move	Less commor	mask-like face	drooling	sneezing	Rare	Behavior change simil	swelling of the fa	decrease in the freq	dry mouth			
14	slow heart rate, weak	uncontrolled mo	Convulsions	Anxiety	muscle tremblir	fever, muscle a	sore throat	Absence of or decr	bleeding gums	unusual tiredness	difficulty in passing	fainting			
15	dizziness, drowsiness	(Less common)	fast heartbeat	black, tarry s	need to keep m	inability to mo	stiffness of the limbs	bigger, dilated, or	breast tenderness or	enlargement or uni	dizziness, faintness,	fast, irregular, pounding, or racing heartbeat or pulse			
16	breast swelling or di	Constipation (sev	high fever	chest pain	rapid weight ga	inability to sit s	twisting movements o	convulsions (seizur	chills		double vision	inability to move the arms, legs, or facial muscles			
17	changes in menstrua	difficult urination	high or low bloo	chills	restlessness	increased blink	uncontrolled moveme	difficulty with spea	convulsions (seizures)		dry mouth	inability to speak			
18	weight gain, swellinc	inability to move	increased sweatin	convulsions	shuffling walk	lip smacking or	Less common	dry mouth	diarrhea		false beliefs that can	irritability			
19	dry mouth or stuffy r	muscle spasms, e	lip smacking or p	cough or ho	slowed moveme	loss of balance	Blurred vision	fever	difficulty with concentrating		fast, pounding, or ir	light-colored stools			
20	constipation	skin rash	loss of bladder cc	decrease in t	slurred speech	mask-like face	body aches or pain	inability to move th	dizziness or fainting		feeling, seeing, or h	lighthead			
21	impotence, trouble h	twisting moveme	muscle spasm or j	decrease in u	stiffness of the	need to keep r	chest pain	incomplete, sudder	drowsiness		feeling that others a	loss of appetite			
22		(Rare)	puffing of the ch	difficult or la	tic-like (jerky) m	painful or difficu	congestion	increased sensitivit	increased hunger		feeling that others c	loss of bladder control			
23		Convulsions (seiz	rapid or worm-lik	difficulty in p	tingling of the h	puffing of the	dizziness	poor coordination	increased thirst		fever with or withou	muscle spasms or jerking of all extremities			
24		difficult or fast bi	severe muscle stif	discouragem	trembling or sh	rapid or worm-	fast, pounding, or irre	red or purple patch	irregular heartbeat		flushed, dry skin	nausea			
25		fast heartbeat or	sudden loss of co	dry mouth	twisting moverr	restlessness	headache	restlessness	lack of energy		general feeling of ti	nightmares			
26		fever (high)	tiredness	feeling sad	uncontrolled m	shakiness in th	hoarseness	shivering	lethargy		hearing loss	pain or discomfort in the arms, jaw, back, or neck			
27		high or low bloo	uncontrolled che	fever with or	unusual weight	shuffling walk	nervousness	sweating	nosebleed		hostility	painful or difficult urination			
28		increased blinkin	uncontrolled mo	frequent stro	(Less common)	slowed moveme	pounding in the ears	talking, feeling, an	overactive reflexes		hyperventilation	pinpoint red or purple spots on the skin			
29		increased sweatir	unusually pale sk	general feeli	Bladder pain	slurred speech	runny nose	trembling or shaki	painful urination		inability to move th	pounding in the ears			
30		loss of bladder cc	(Incidence not kn	headache	bloody or clou	sores, ulcers, or	slow or fast heartbeat	Incidence not know	poor coordination		irritability	rash			
31		muscle stiffness (	Hives or welts	hyperventilat	bruising	sticking out of	swelling of the tongue	Back, leg, or stoma	purple or red spots on the skin		itching or rash	restlessness			
32		sore throat and fl	Itching skin	irritability	burning, crawlir	stiffness of the	tender, swollen gland	blindness	rapid weight gain		lack of coordinatior	seeing, hearing, or feeling things that are not there			
33		uncontrolled twit	Itching, puffines	lack of appe	chest pain	sweating	trouble with swallowi	blistering, peeling,	red or irritated eyes		lethargy	shakiness and unsteady walk			

Figure 3.13 Collecting the side effects of drugs through DrugBank and unifying terms of the side effect. Editing side effects data of drugs from DrugBank that were duplicated or worded differently. It was necessary to unify the terms in order to analyze drug similarity.

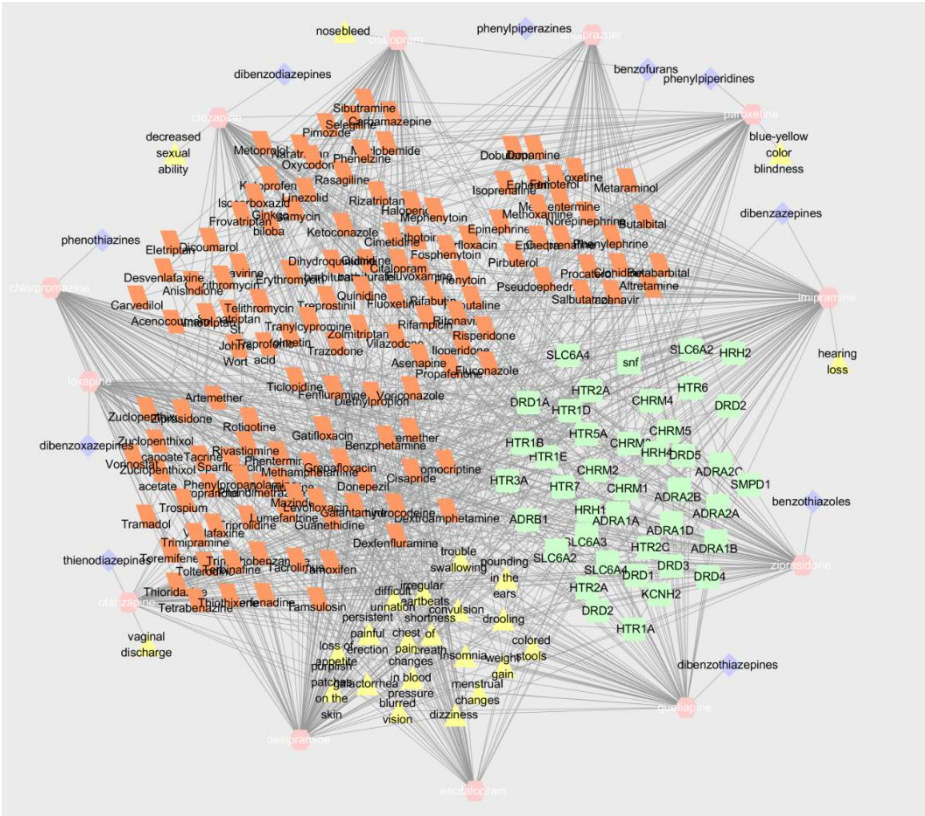


Figure 3.14 Drug-similarity network (a) twelve drugs for both Schizophrenia and Panic Disorder

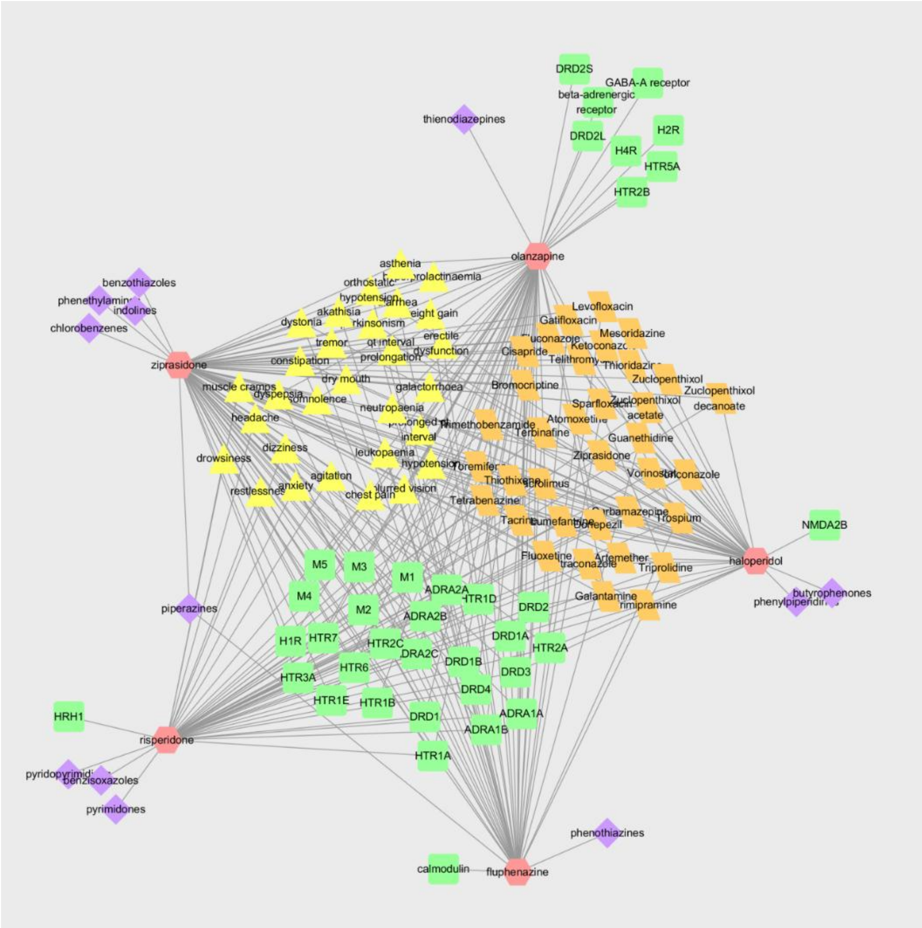


Figure 3.14 Drug-similarity network (b) drugs for Schizophrenia and Tourette Syndrome

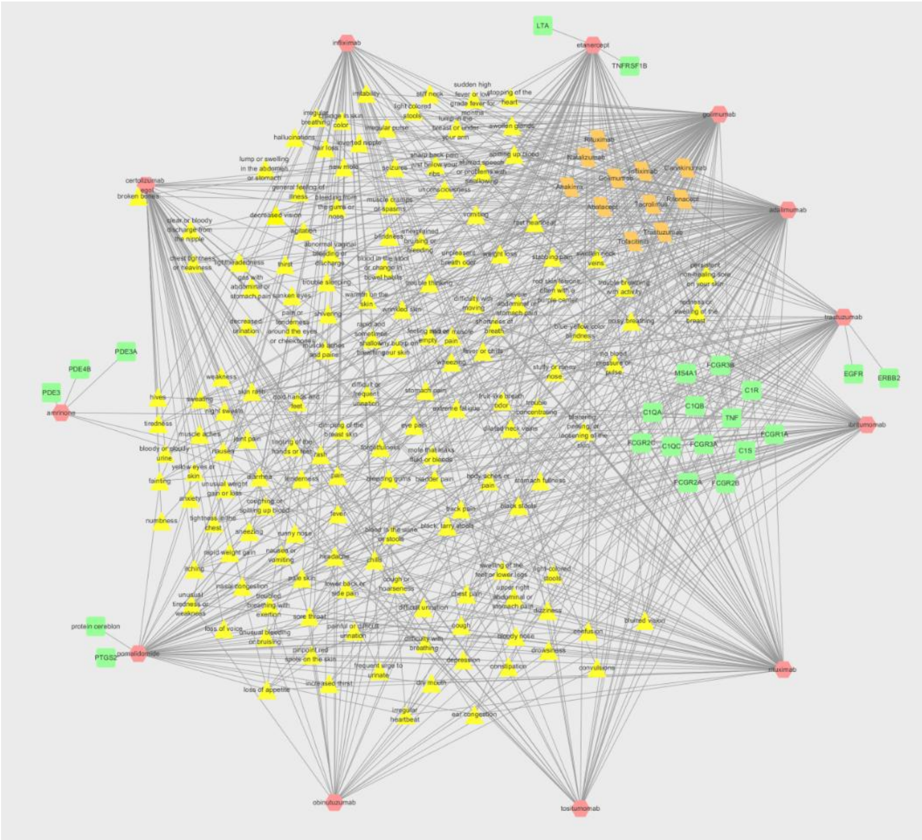


Figure 3.14 Drug-similarity network (c) drugs for Hypertension-Wegener Granulomatosis

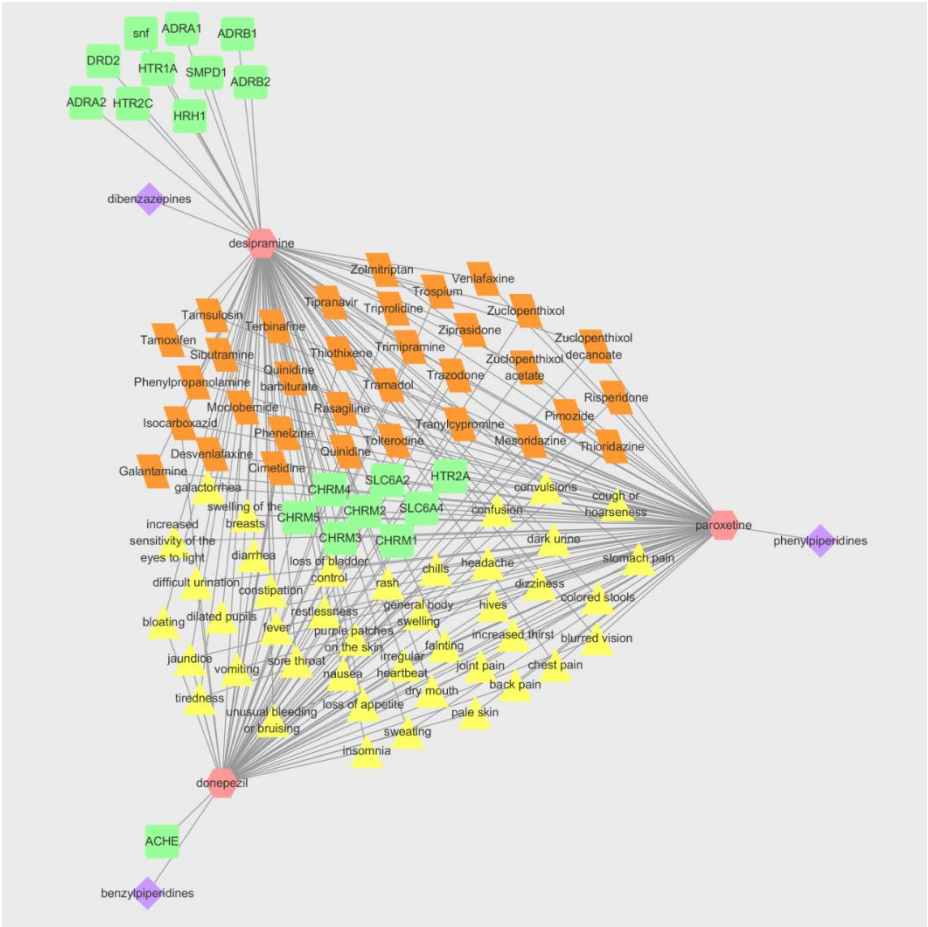


Figure 3.14 Drug-similarity network (d) drugs for Panic Disorder and Alzheimer Disease

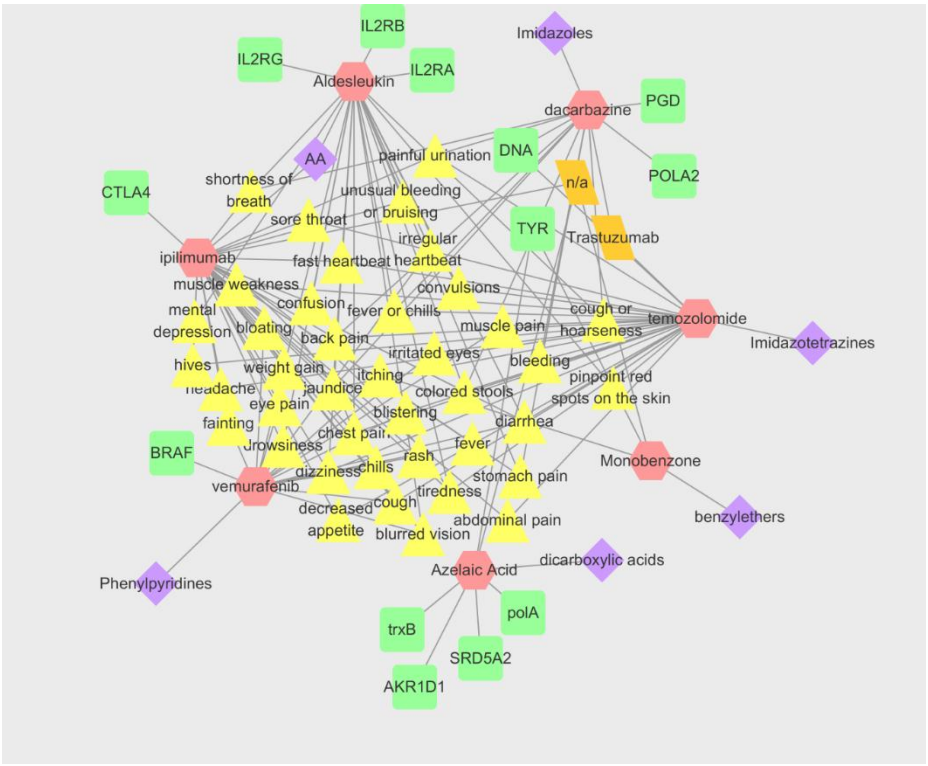


Figure 3.14 Drug-similarity network (e) drugs for Albinism and Melanoma.
A hexagon represents a drug prescribed for a specific disease. A rectangle, parallelogram, triangle and diamond indicate a drug target, a drug that interact with the drug of interest, substructure and side effect, respectively**.**

CHAPTER IV. DISCUSSION

Some genes related to diseases of off-label use of drugs are well known, while other areas are still in an elementary level. Though drugs are used as off-label use, some diseases that do not have any information about the genes related to pathogenesis couldn't help but be excluded. That is why small and trial 6 of paired diseases were made.

Although the safety and effectiveness of some medications for rare incurable diseases can be checked with this study method, there is not much genetic information related to rare incurable diseases at this point. This is the regretful point and the actual reason to limit the scale of study as small. To use Bioinformatics properly, when the genetic information related to diseases should be found first, saved as data and accumulated continuously, it will be useful to find and develop medications quickly. Openness is another necessary element for the studies using bioinformatics methods. Accumulated genetic information and drugs information should be provided in various database forms to be used for free of charge for the public interest.

CHAPTER V.
CONCLUSION AND SUMMARY

5.1 Conclusion

In this study, the information of genes about diseases aimed to be treated with off-label use is brought from Genotator, which is still limited. It is very difficult to get any information about incurable diseases such as Vitiligo, psoriasis, GVHD, Bell's palsy, delirium, Impulse control disorder, uveitis, lupus, multiple myositis, and scleroderma. The reason is that it might be uncertain for pathogenesis of diseases so far. In fact, the information of diseases for psychiatry and autoimmune disease is rarely known. There is the information about drugs permitted and off-target use of drugs as well in DrugBank. However, it just informs the use experimentally. Sometimes, although there are lots of grounds references and theological basic for off-label use, due to economic reasons, without additional permission for indication of drugs, some drugs are used continuously as off-label use. However, many drugs are still used with only the result of clinical experiences with unclosed action mechanism. In the cases when pathogenesis of diseases, related genes, the target of treatment drugs and action mechanism are well known, even the use of off-label use can be proved to be effective and safety prediction can be achieved more accurately. As defined by Wikipedia, DrugBank is the online open access database which provides bio information and the chemical information (sequence, structure, and pathway, chemical,

pharmacological and pharmaceutical information) of medications. Although it is extensive, it plays of basic role as provider of the information of existing drugs helps to discover and realign medications for rare incurable diseases or new diseases. The experts' part is to select and process the database provided and re-analyze that. In bioinformatics approach methods which develop new indications of drugs, using the analysis of the binding site structure, find off-label use or by using the inverse interrelation between unstable genes led by medications and genes unstable related to the diseases, find treatments; chemical systems biological approach; predicting indication with side effects named, Naïve Bayes. However, these methods usually just suggested a couple of new indications. It does not seem to be any studies that the work to try and confirm many medications for various diseases unlike what this study shows. Trying repositioning medications with bioinformatics methods, in many angles, by the larger number of pharmaceutical experts is considered very positive from the public health aspect and saving the cost.

As there are two stages studied in this research, in the first stage, protein-protein interaction network was created by finding common genes between paired diseases. If there are drugs which target the protein of shared genes, it becomes candidate medication for repositioning. In the second stage, drug-similarity network was created for the drugs which target genes from the network created in the first stage. This network is the information of the drugs which target shared genes found in the first stage; about structure other than targets, interacting drugs and side effects. The drug-similarity network is to confirm the safety and effectiveness for realignment of medications. Rare diseases that should use off-label use or the genes related to incurable diseases, that existing drugs are hardly effective are from Genotator and in off-label drugs for these diseases, permitted diseases are paired and shared genes are

discovered. 6 paired diseases are made and the number of shared genes in each paired disease; Wegener Granulomatosis-Hypertension is 29, Panic disorder-Alzheimer is 24, Pigment deficiency-Melanoma is 10, Hypertension-Acute Respiratory Distress Syndrome is 22, Schizophrenia-Panic Disorder is 86 and Tourette syndrome-Schizophrenia is 25 are determined. Relation analyzing for shared genes is done with STRING and protein-protein interaction network is gained. In these paired diseases, the drugs which target shared genes used as treatment are used for both diseases in many cases. In the second stage, the drugs used for those 6 paired diseases are whether permitted or off-label use without concerning, take the information of drugs and target genes from DrugBank and make drug-similarity network. The information collected this way is target of the drug, structure, the drug causing interaction (in particular the interaction target-mediated) and side effects. Drug-similarity network is visualized in drawing using Cytoscape to make shared elements are well seen.

In 6 paired diseases, HTN-ARDS is excluded because acute respiratory distress syndrome is emergent and the information of drugs used as off-label use is too wide. In 5 paired diseases, the drugs which used as off-label use for each disease are examined with genes which are provided from Genotator as mediation, the drug which targets the shared gene in paired diseases is not only the treatment for the one permitted disease but also effective to the other one, therefore this way repositioning medication can be done. On DrugBank, about the drugs used as treatment for paired diseases, collect the information of the structure, target, side effects and medication interaction of drugs and create similarity network using Cytoscape; In many cases, the similarity of drugs used in one paired diseases are overlapped more than two. The revelation of side effects by target is confirmed and by sharing of target the

possibility of treating other diseases is confirmed. Based on this, not only for checking the effectiveness and safety for the permitted existing drugs but also for searching new indication, bioinformatics is suggested as new protocol and once the protocol was applied as trial, off-label use was included considerably. The protocol is considered verified. The studies so far were basic and non-complete ones; mainly about the drugs used as off-label use, checking targets and examining side effects. However, if the studies continued to be done, bioinfomatical reviewing would reduce economical efforts and time in the development of new medications.

The recent example of the drug that used to be off-label use and now permitted indication is Rituximab, this one had only indications for use of lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, in April, 2011, and it got permitted for Wegener-Granulomatosis and microscopic bundles vasculitis. Rituximab has 12 drug targets and it was effective clinically for Wegener Granulomatosis and microscopic bundles vasculitis using MS4A1 as the main target. The other drugs that use MS4A1 as target; ibritumomab, obinutuzumab, tositumomab, are made drug-similarity network to see if they are effective on Wegener-Granulomatosis and microscopic bundles vasculitis. The result is that obinutuzumab doesn't have any information about interaction, ibritumomab and tositumomab have the same drug, trastuzumab which causes interaction with Rituximab and non-special side effects such pain, chills, fever, cough and dizziness in common. Since the drug target of Ibritumomab and tositumomab is MS4A1, the drug causes interaction is the same and the profile of side effects is similar, it can be repositioned for Wegener-Granulomatosis and microscopic bundles vasculitis like rituximab. The other drugs used as off-label use for Wegener-Granulomatosis are etanercept, infliximab and adalimumab and their target is TNF and also the

related gene to Wegener-Granulomatosis is TNF and the interaction drugs caused by effect that blocks this target are overlapped as adalimumab and infliximab and the drugs affect on each drug's effectiveness are in common as Rilonacept and Trastuzumab. The side effects are commonly revealed as chills, cough, abdominal pain and fever. Because of the things are in common, these 3 drugs are effective to Wegener-Granulomatosis and do not seem to have any safety problems. In the paired diseases, Schizophrenia-Tourette syndrome, although four drugs fluphenazine, olanzapine, risperidone and ziprasidon which share the target and have common side effects are permitted only for Schizophrenia, when they are applied to Tourette syndrome as off-label use, it is proved to be safe and effective through drug-similarity network. The final confirmation of the safety and effectiveness for newly repositioned medications will be completed by accumulated references and clinical experiment.

5.2 Summary

This study is to show that using known drugs for different purpose is proper and safe with the bioinformatic methods. In bioinformatics, the study is processed with the terminology; repositioning of medication or change of use of medications and discovery new indicants of existing medications. The side effects discovered in the information of drug use could lead to the change of drug use or by finding drugs targeting the protein in the information of genes and realign them. The method used in this study starts with the drugs used as off-label use and how it is used as off-label use; in other words, it started from bringing the information of genes about indicated diseases from an open access database Genotator. The drug which enables to pair diseases was off-label use. Off-label use drugs have permitted indications of certain diseases. The permitted diseases and diseases not permitted are paired, and the first stage is to look for the shared gene in each gene related to diseases. With these shared genes, protein-protein interaction network was created by genetic relation analysis program, called STRING. The proposal of this study is that medication in paired diseases used for one disease as treatment can be used for the other disease by shared gene-mediated and as the result, the fact that the drugs that target the shared gene have already used on both sides is confirmed. On the second stage, in the 6 of paired diseases, the list of permitted drugs and the off-label use is made and then takes the information of each drug from DrugBank. The information is about targets, side effects, interaction drugs and structures of drugs. The drug-similarity network is made with the information of 4 drugs using Cytoscape. In the network, the drugs that target the shared gene in paired diseases can be repositioned for the indications of other diseases not only for the permitted ones and when side

effects, structure or the drug causes interaction are in common, the safety and effectiveness can be confirmed. Through the bioinformatic methods, finding new indication from the existing medications, in pharmaceutical companies' position, it is faster way to develop the new medications using less time and money and the possibility of success is fairly high. In the point of view of public health, under the situation that there is no treatment for rare incurable diseases, the off label drugs being used clinically can be used with confirmation of safety and the verification of effectiveness and through proper treatment, reducing the treatment cost will bring economic benefit.

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ABSTRACT (Korean)

Development of Verification Method for the Effectiveness and Safety of Off-label Drug Use

생명정보학 기법을 이용한 기존 약물의
새로운 적응증 탐색 연구

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바이오인포매틱스 전공

새로운 약물의 개발은 경제적으로 상당한 비용을 지불해야 하고 시간적으로도 오랜 기간을 성공에 대한 보장 없이 투자해야 하는 쉽지 않은 작업이다. 이제까지 개발되어 사용되고 있는 약물들에 대한 정보는 과학기술의 발달, 특히 IT 기술의 발전으로 방대한 양이 축적되어 있다. 이렇게 쌓인 정보는 사용 중인 약물의 안전성과 관련하여 보다 철저히 약물을 점검할 수 있게 하였고, 만약 안전성에서 문제가 확인되면 해당 약물을 시장에서 퇴출시키기도 하지만 새롭게 부각된 부작용을 보는 시각을 전혀 달리하여 적응증을 바꾸어 새로운 약물로 사용할 수 있게도 한다. 모든 약물의 작용기전과 타깃 단백질이 명백히 밝혀져 있지는 않지만 과거에는 몰랐던 약물의 정보들이 지금도 계속 연구되고 있고 이 연구들을 통해 찾아진 정보들은 빅 데이터로 저장 되고 있다. 또한 생물에 대한 유전자 정보도 밝혀지는 대로 계속 데이터베이스에 축적되면서 인류의 건강과 생명연장을 위한 공적인 연구에 자유롭게 제공되고 있다. 탈리도마이드는 과거에 사용 되었다가 위험성이 밝혀지면서 사용중지 되었

지만 이제 부작용을 일으켰던 약물기전이 확인되면서 적응증을 새롭게 바꾸어 다발성 골수종 치료제로 사용되고 있다. 이런 일이 가능하게 된 것은 약물의 타깃과 질병 유발 관련 단백질에 대한 연구가 충분히 이루어졌기 때문이다. 본 연구에서는 생명정보학적인 방법을 이용해, 기존 약물들이 근거문헌이나 임상 시험 등이 별로 없는 상황에서 치료대안이 없는 소아질환이나 희귀 난치성 질환 등에 허가초과용도로 사용 되고 있는 현실에 비추어 그 사용의 유효성이 있는지 보고, 지금까지 축적된 정보들을 바탕으로 안전성에는 문제가 없는지 그 타당성을 살펴보고자 한다. 한편으로는 제약사들이 경제적 이득이 없어 하려고 하지는 않지만 상당히 알려진 허가초과사용에 이론적인 당위성을 부여해주고, 약물개발의 가장 첫 단계인 새로운 물질의 새로운 적응증을 찾는 과정을 생명정보학적인 방법을 사용해서 기존의 약물에서 찾아낼 수도 있다는 방향을 제시하고자 한다.

주요어: 허가초과사용, 약물재배치, 새로운 적응증 발견, 유전자정보, 약물정보

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