

Tailoring drugs to fit a patient's genetic predisposition

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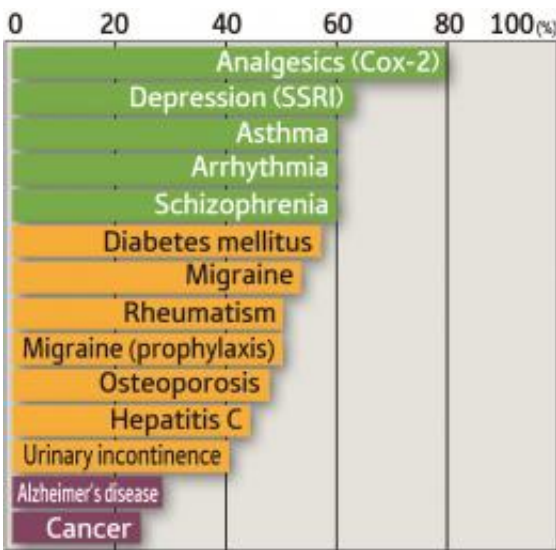


Figure 1: Drug effectiveness on common diseases Not all drugs are equally effective in all patients. Some types of drugs, such as analgesics, are effective on almost all patients, whereas other types, such as anticancer agents, are effective only on 25% of patients. In working towards the realization of personalized medicine, it is important to develop ways of using genetic information to prescribe to patients the most suitable drugs in light of their genetic risk to side effects. Credit: RIKEN

Drugs are not equally effective on all patients. A treatment that is dramatically effective on some patients can be ineffective on others. Drugs can also have serious side effects; in the worst case, a drug used to treat a disease can produce a fatal outcome. By examining genetic

differences among individuals and administering drugs on the basis of such findings, the impact of side effects can be reduced. Taisei Mushiroda, the Laboratory Head of the Research Group for Pharmacogenomics at the RIKEN Center for Genomic Medicine, is making advances in personalized medicine with research into how drugs can be tailored to a patient's genetic information through the analysis of single nucleotide polymorphisms (SNPs).

Preventing fatal side effects using genetic information

Anticancer agents, while effective in only 25% of patients (Fig. 1), have severe side effects that aggravate many patients. In 2001, a study on the efficacy rates of a broad range of drugs was published in the US. According to the paper, the efficacy rate of analgesics was about 80%, whereas rates for cancer or Alzheimer's disease [drug](#) treatments were low at 20–30%. This is because conventional medicine involves uniformly prescribed drugs for different patients, without taking into account their personal dispositions or genetic characteristics.

Side effects from drugs cause severe discomfort to millions of patients worldwide. A survey shows that in the US, about two million patients experience serious side effects annually. "Japan's population is about two-fifths of the US, so approximately 800 thousand Japanese suffer side effects from drugs each year," explains Mushiroda. "The effectiveness and side effects of drugs differ among individuals. If it were possible to predict before administration whether side effects would occur, and prescribe a drug matched to the individual, the number of patients who suffer side effects would decrease."

Pharmacogenomics combines the fields of pharmacology, the study of drug action, with genomics, the study of an organism's genomes.

According to Mushiroda, pharmacology has two goals: “One goal is to develop new drugs; the other is to find how to use existing drugs appropriately. While new drug development is the task for pharmaceutical companies, we are focusing on existing drugs. We aim to make personalized medicine a reality, and thereby improve the quality of life for each patient by using genetic information to prescribe drugs ‘tailored’ to the characteristics of the individual.”

Mushiroda and his team are currently focusing on the side effect known as drug rash. A type of eczema that occurs due to reactions to medication, drug rash is characterized by inflammation of the skin and mucosa, which in more severe cases can lead to fever and inflammation of the internal organs. Drug rash is difficult to treat, with about 10% of patients experiencing fatal complications. Another negative aspect of drug rash resides in the likelihood that symptoms will not ameliorate even when medication is discontinued. After onset, there is no easy way to remedy the condition.

“We are promoting research with a focus on genetic information in order to develop a method for predicting the risk of side effects. Provided that the patient is known to be predisposed to drug rash, it is possible to avoid risk by refraining from using the respective drug or by reducing its dose.”

Identifying the single nucleotide polymorphism (SNP) that plays a key role in drug rash

Japan’s Ministry of Health, Labor and Welfare announced that the gout treatment allopurinol, the antiepileptic drug carbamazepine and the analgesic, anti-inflammatory, antipyretic drug loxoprofen hold the highest incidences of serious drug rash.

“The data we collected showed that the great majority of drug rash cases were caused by carbamazepine. We therefore proceeded to clarify the relationship between carbamazepine and drug rash, using Genome- Wide Association Study (GWAS). We divided our study population into two groups: those who experienced side effects and those who did not. We performed a comprehensive analysis of single nucleotide polymorphisms (SNPs) on the genome to statistically extract SNPs that are significantly associated with drug rash. The gene involved in drug rash was then identified from among those positioned near the SNPs”

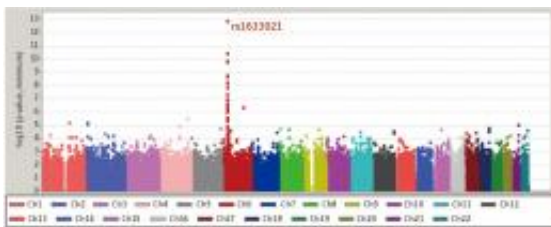


Figure 2: Manhattan plot of GWAS for carbamazepine-induced drug rash This plot identifies which SNPs of the 500,000 found on human chromosomes are associated with carbamazepine-induced drug rash. Each dot corresponds to one SNP, and the SNPs positioned higher on the vertical axis have a more reliable association with this side effect. The plot shows that the chromosome 6 SNPs bear the most reliable association with carbamazepine-induced drug rash. Credit: RIKEN

Strands of DNA carry genetic information in the sequenced arrangement of the four bases A (adenine), T (thymine), G (guanine) and C (cytosine). Consisting of some three billion base pairs, the human genome carries the complete genetic information of a human being. Although there is more than 99% base sequence homology in all people, the remaining 1% of base sequences differ individually. “These

differences are SNPs. It is estimated that more than 10 million SNPs are present in the human genome. They are associated with the appearance and constitution of the individual, and even with how drugs work and what side effects develop.”

Discovery of the drug rash-associated gene

Figure 2 shows a Manhattan plot for the results of a GWAS conducted by Mushiroda. The horizontal axis indicates each SNP’s chromosomal location while the vertical axis indicates the degree of SNP association with drug rash. About 500 thousand SNPs are plotted, and the SNPs positioned higher on the horizontal axis have a more reliable association with drug rash. Mushiroda explains, “This Manhattan plot shows that an SNP named rs1633021, on human chromosome number 6 (Chr6), is prominent at a high position. Extensive analysis located this SNP in the vicinity of the gene called HLA-A.” The HLA-A gene works in the production of the human leukocyte antigen (HLA), a protein involved in immunity, and is known to occur in about 100 different types (base sequence patterns) in Japanese patients. “When we examined all types of the gene one by one, a type named HLA-A*3101 was found to be associated with drug rash in Japanese patients (Fig. 2). The risk of drug rash in persons with this allele is 9.5 times higher than in those without this type.”

According to Mushiroda, it is reasonable to use the limiting phrase “in Japanese patients.”

“This is because the positions and ratios of SNPs vary depending on ancestral origins,” he explains. Even if some SNPs are found to be associated with drug rash in a population other than Japanese, for example in Americans, it is necessary to re-examine which SNP is associated with the side effects in the Japanese population, because the positions and ratios of SNPs differ between the two population groups.

“For example, a paper published in 2004 concluded that type HLA-B*1502 can be used as a biomarker for carbamazepine-induced drug rash in the Han Chinese in Taiwan. The risk of contracting drug rash in persons with HLA-B*1502 is 2,500 times higher than in those without this type.” In the US, with this finding in mind, the drug label of carbamazepine was revised to include the statement that patients with HLA-B*1502 are at increased genetic risk to drug rash and are therefore more predisposed to [side effects](#) of the drug, and were advised to first undergo testing for the presence or absence of HLA-B*1502 before initiating treatment. In this case, patients with HLA-B*1502 refers to patients of Chinese ancestry. This type of gene is rarely found in Japanese patients.

Relationship between drug rash caused by the antiepileptic drug carbamazepine and the HLA-A*3101 gene

Mushiroda and his colleagues conducted a study on Japanese epileptic patients undergoing treatment with carbamazepine. Of the sixty-one patients who experienced drug rash, 37 (about 61%) were found to have the HLA-A*3101 gene. In contrast, of the 376 patients who did not experience drug rash, 329 (about 88%) were found to lack HLA-A*3101.

“Reportedly, about 3% of Japanese patients experience drug rash when taking carbamazepine. About 60% of those have HLA-A*3101. It is therefore recommended that 60% of 3% (about 2%) of Japanese epileptic patients take antiepileptic drugs other than carbamazepine. In this way, the incidence of drug rash can be reduced by 2%,” says Mushiroda. However, as this association was only discovered in 2010, further evidence must be presented before it can be useful in a clinical setting.

Relationship between drug rash caused by HIV antiretroviral drug nevirapine and the HLA-B*3505 type gene

A collaborative study of Thai HIV patients by Mushiroda's team and Thailand's Mahidol University in 2009 identified an SNP that can serve as a biomarker of drug rash caused by the antiretroviral drug, nevirapine. Mushiroda says, "About 20% of patients who received nevirapine experienced drug rash. This is much higher than the aforementioned 3% incidence of carbamazepine-induced drug rash in Japanese patients. Even more problematic is the fact that generic forms of nevirapine are widely used in Thailand with government approval."

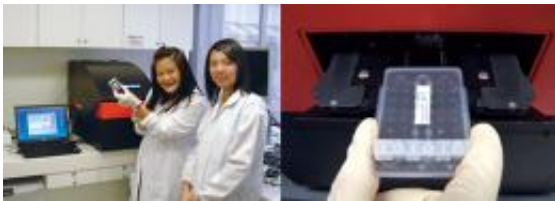


Figure 3: The TPSA-003 genotype analysis system RIKEN and Thailand's Mahidol University are jointly conducting clinical research to demonstrate the feasibility of antiretroviral therapy for HIV infection based on personal genetic information. Developed through collaborative efforts with RIKEN, Toppan Printing Co. Ltd. and RIKEN Genesis Co. Ltd., the TPSA-003 genotype analysis system enables SNP genotyping in one hour. (Photo courtesy of Toppan Printing Co. Ltd.) Credit: RIKEN

Examination of SNPs identified an HLA-B allele named HLA-B*3505 which was found to be associated with nevirapine-induced drug rash. "In this study, of the 143 patients who experienced drug rash, 28 (20%) were found to have HLA-B*3505, whereas of the 181 patients who did

not experience drug rash, 179 (99%) did not have the type,” explains Mushiroda. “The risk of drug rash was thus about 22 times higher in those with HLA-B*3505 than in those without.”

Personalized medicine expected to find clinical applications in 1 or 2 years

The next step after identifying the associated SNP is to determine its applicability in the clinical setting. It is also necessary to verify that SNP diagnosis is effective in both therapeutic and cost-benefit aspects. In ongoing prospective clinical research of nevirapine, it has been estimated that SNP diagnosis would cut annual medical expenditures by about US\$60,000 (about ¥5 million) per hospital. This next phase will be necessary for successful application of the new system to the antiepileptic drug carbamazepine.

Before SNP genotyping can be firmly established in medical practice, however, a quick and accurate method to examine SNPs at the lowest cost is needed. In collaboration with Toppan Printing Co. Ltd. and RIKEN Genesis Co. Ltd., Mushiroda’s team have developed the TPSA-003 genotype analysis system which can help to deliver more economical SNP genotyping (Fig. 3). The system provides results automatically in just one hour, simply by placing a single drop of untreated blood in the dedicated container and inserting the sample in the machine. “This is a groundbreaking machine. The conventional method involves the complex process of separating leukocytes from the blood sample, extracting the DNA from the leukocytes and applying the DNA to the machine to analyze SNPs. Conventionally, DNA extraction alone requires at least half a day even when undertaken by a highly skilled person. With the new system, the same task, including SNP genotyping, is completed in 60 minutes. This means that an accurate diagnosis can be obtained while the patient stays in the waiting room.

Quick diagnosis is a big advantage for the patient as well.”

Thanks to prospective clinical research and development of the fully automated SNP analyzer, SNP genotyping for nevirapine has undergone a major advance toward practical use. Over the next one or two years, the examination is scheduled for use in actual treatment in Thailand. Personalized [medicine](#) has at last entered the stage of practical application. Mushiroda is confident about the future applications for SNP genotyping. “I want to bring SNP genotyping into clinical use in Japan as soon as possible by applying the research design used in our joint research in Thailand. The most important thing is to feed back our research achievements to the [patients](#) themselves.”

Provided by RIKEN

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