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Japan Pharmacogenomics Data Science Consortium Database and Its Application for Drug Safety Analyses

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Abstract Severe adverse drug reactions (ADRs) are significantly influenced by the genetic background of an individual, and pharmacogenomics (PGx) is strongly expected to reveal the cause of severe ADRs. Genome-wide association studies (GWASs) for severe ADRs have been conducted worldwide, and a genomic database of representative samples of the ethnic population can be used as controls for GWAS for severe ADRs. Six Japanese pharmaceutical companies, Astellas, Daiichi Sankyo, Mitsubishi Tanabe, Otsuka, Taisho, and Takeda, therefore established the Japan Pharmacogenomics Data Science Consortium (JPDSC) and built a Japanese genomic database in 2009. This database promotes the application of PGx in drug development by each member company and PGx researches for expanding Japanese drug safety information at the genomic level.

Keyword Pharmacogenomics · GWAS · Drug safety

Introduction

Pharmacogenomics (PGx) is the leading research field in personalized medicine and has recently obtained good results for drug safety.

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With regard to drug safety, severe adverse drug reactions (ADRs) are one of the major problems in clinical settings. Severe ADRs, such as Stevens-Johnson syndrome, toxic epidermal necrolysis (SJS/TEN), and drug-induced liver injury (DILI) are quite rare and unpredictable in patients, often leading to the withdrawal of drugs already launched in the market.

Early exploratory PGx studies conducted using the candidate gene approach clearly showed that genetic factors significantly associated with severe ADRs. Furthermore, PGx has gradually been recognized by pharmaceutical companies as an important tool for ascertaining the causal genetic factors for drug responsiveness.

In the 1990s and at the end of the human genome project, Japanese academic researchers started developing SNP markers over an entire genome and immediately launched the Millennium Project for exploring disease-associated genes. In 2003, RIKEN published the first successful result of a GWAS of disease-SNP marker association [1].

Thereafter, many GWASs have been conducted worldwide [2], and DNA typing device (DNA microarray) that significantly reduced genotyping costs has been developed. Many pharmaceutical companies realized that GWAS was a technically and costly practical PGx tool for drug development. Japanese pharmaceutical companies also began using PGx and GWAS for drug development. For Japanese PGx research, a qualified Japanese control database was needed, and therefore, six Japanese pharmaceutical companies, Astellas, Daiichi Sankyo, Mitsubishi Tanabe, Otsuka, Taisho, and Takeda, established the Japan Pharmacogenomics Data Science Consortium (JPDSC) for building a Japanese genome database in 2009.

Candidate Gene Approach to GWAS Approach

Before GWAS was used in a practical setting, the candidate gene approach based on biological hypothesis

was the major methodology used for PGx. During the early PGx studies, for example, GlaxoSmithKline (GSK) clarified that some ADR-associated genomic markers identified by the candidate gene approach can be detected by linkage disequilibrium analysis (basic methodology of GWAS) or GWAS approach.

In the case of Tranilast, GSK explored genomic markers of candidate genes associated with high blood bilirubin levels and found a significant association with *UGT1A1*, the causal gene of Gilbert syndrome. GSK also showed that the same gene can be detected by linkage disequilibrium analysis using a number of SNP markers located around *UGT1A1* [3]. In the case of Abacavir, GSK discovered *HLA-B*5701*, by a candidate gene approach, as the gene significantly associated with hypersensitivity. Furthermore, GSK also identified the same gene by GWAS using 500,000 markers with statistical significance [4].

Many genomic markers associated with drug response detected by GWAS have been reported (e.g., simvastatin, carbamazepine, or interferon alpha) [5]. Such markers can be expected to have clinical utility owing to their higher odds ratio, which can be attributed to drugs being xenobiotics, i.e., historically new foreign molecules to the human body, for this reason, only a relatively few genes are thought to be involved in the drug response. Therefore, the GWAS approach became a real option for pharmaceutical companies to explore ADR-associated genomic markers.

Application of a Genomic Database to the Study of ADRs in a Pharmaceutical Company

For ADR research, genomic databases are useful tools that also offer advantages in drug development from a business perspective. During a clinical trial, if several cases of ADRs are observed, ADR GWAS can be immediately carried out with controls from the genomic database and can be completed before the end of the clinical trial, without collecting matched control samples. Thus, important safety information indicating the genetic cause for ADRs becomes immediately available. This information can aid in early decision making for drug development programs. The above approach is fast, has low costs, and is appropriate for businesses. Furthermore, the genomic database can be built by according to population census data, removing relatives, and observing many aspects of the genomic data (e.g., the replication of allele frequency relative to that in other sample populations).

Establishment of JPDSC

In the trend of PGx research progress worldwide, Japanese pharmaceutical companies raised awareness on the PGx issues in the Japanese population, especially drug safety information at the genomic level. They realized the necessity of genomic databases of the Japanese population for the reason described previously. Therefore, six Japanese pharmaceutical companies, Astellas, Daiichi Sankyo, Mitsubishi Tanabe, Otsuka, Taisho, and Takeda established the JPDSC and built the JPDSC database, which contains genotype data of 2994 Japanese healthy individuals, matching the Japanese population census data (Table 1). During collection, the relatives were removed from the database population. The manner of collection is thought to make this database representative of the Japanese population, except the population in Okinawa. This is because excess samples were collected from this region due to the fact that the number of Okinawa samples along with the Japanese population census is too small from a statistical point of view. The population was clinically examined, and finally the DNA samples, genotyping results, and clinical test results were anonymized. The genotypes were obtained using the Illumina HumanOmni2.5-8 v1 DNA Analysis Kit and HLA typing kit.

The JPDSC database is intensively characterized and illustrated in publications on sample and SNP quality checks, population structure, and replication of the research results for interesting SNPs [6•].

Severe ADR Research of JPDSC

The JPDSC database was originally intended to be utilized for drug development programs of each of the member companies. However, for public benefit, JPDSC continues to have research collaboration with the National Institute of Health Science (NIHS) for exploring genomic markers for ADRs, especially those associated with SJS/TEN, DILI, and rhabdomyolysis.

In the first successful case of allopurinol, GWAS was conducted for exploring the genomic biomarker associated with allopurinol-induced SJS/TEN, where 14 Japanese cases were examined along with 991 ethnic-matched controls. The SNPs, rs2734583 in *BAT1*, rs3094011 in *HCP5*, and GA005234 in *MICC* were strongly associated ($P = 2.44 \times 10^{-8}$, odds ratio = 66.8, 95 % confidence interval 19.8–225.0), and they were in absolute linkage disequilibrium with *HLA-B*5801*, which has a strong association with allopurinol-induced SJS/TEN [7••].

In the cases of SJS/TEN of three antiepileptic drugs, zonisamide, phenobarbital, and phenytoin, HLA class I and HLA-DRB1 loci were genotyped. Based on the results, the carrier frequencies of *HLA-A*02:07* in patients with zonisamide-induced SJS/TEN and in the representative Japanese population were 41.7 and 6.81 %,

Table 1 The numbers and proportion of the subjects of JPDSC database and the data of Japanese population census by Japanese Ministry of Internal Affairs and Communication

Region	Collected samples	Frequency	
		JPDSC (male/female)	Japan (male/female)
Hokkaido	120	4.0 (48.7 %/51.3 %)	4.3 (47.2 %/52.8 %)
Tohoku	200	7.3 (52.3 %/47.7 %)	7.3 (47.9 %/52.1 %)
Kanto	1197	39.5 (41.2 %/58.8 %)	33.3 (50.0 %/50.0 %)
Hokuriku	115	4.0 (50.4 %/49.6 %)	4.3 (48.3 %/51.7 %)
Tokai	310	10.3 (52.3 %/47.7 %)	12.7 (49.5 %/50.5 %)
Kinki	430	11.2 (48.2 %/51.8 %)	17.8 (48.2 %/51.8 %)
Chugoku	160	6.1 (54.6 %/45.4 %)	5.9 (47.9 %/52.1 %)
Shikoku	85	3.7 (44.6 %/55.4 %)	3.1 (47.3 %/52.7 %)
Kyushu	280	10.0 (49.7 %/50.3 %)	10.3 (47.0 %/53.0 %)
Okinawa	109	3.9 (50.9 %/49.1 %)	1.1 (49.0 %/51.0 %)
Total	3006	100 %	100 %

respectively. Carrier frequencies of *HLA-B*51:01* in patients with phenobarbital- and phenytoin-induced SJS/TEN and in the population were 75.0, 55.6, and 15.2 %, respectively. These results showed that *HLA-A*02:07* and *HLA-B*51:01* are significantly associated in a dominant manner with SJS/TEN induced by zonisamide and phenobarbital [8••].

Furthermore, with regard to phenytoin, the GWAS of severe cutaneous adverse reactions in a case-controlled manner and further direct sequencing covering a statistically significant locus were conducted. The statistically significant association between *CYP2C9*3* and phenytoin-induced severe cutaneous adverse reactions were successfully discovered in Taiwan population (in GWAS discovery, 60 cases and 412 controls; in replication analysis, 30 cases and 130 phenytoin-tolerant controls) (Table 2). Similar results were observed in the population from Japan (nine cases and 2,869 controls) and Malaysia (six cases and 374 controls) [9••]. This is a thought-provoking research result for the pharmaceutical industry. This indicates that reduced activity of CYP2C9, i.e., high blood concentration of phenytoin may be one of the significant causes for severe cutaneous adverse reactions. This also indicates that if a coadministered drug with phenytoin has CYP2C9 inhibiting activity, it may be a possible cause of severe cutaneous adverse reactions in a manner similar to CYP2C9*3. From the point of view of drug development for the chemical entity with CYP2C9 inhibiting activity, if it is coadministered with phenytoin, it must be avoided during the preclinical status. Estimation of the clinical effect of this avoidance in clinical settings is difficult; however, the directional property of this avoidance seems to be logical and probably correct.

Table 2 rs1057910 (*CYP2C9*3*), the most significant SNP associated with phenytoin-related sever cutaneous adverse reactions in the GWAS and direct sequencing discovery and in the replication analysis

SNP	Position on chromosome 10 (bp)[a]	Near by gene (location)[a]	Minor allele	MAF		*P* value[d]	OR (95 % CI)
				Cases	Controls		
rs1057910 (*CYP2C9*3*)	10q23.33 (96741053)	*CYP2C9* (exon 7)	C	GWAS discovery[b]			
				0.21	0.024	1.5×10^{-12}	11 (5.7–20)
				Replication analysis[c]			
				0. 18	0.012	1.0×10^{-6}	19.2 (5.2–71)

[a] The genomic coordinates are Human Genome Build 37.5. Gene ID is NCBI Entrez gene 1559

[b] 60 cases of severe cutaneous adverse reactions vs 412 controls from general population

[c] 30 cases of severe cutaneous adverse reactions vs 130 phenytoin-tolerant controls

[d] *P* values were calculated by Fisher exact for the risk allele

Future Perspective of JPDSC

Each JPDSC member company applies the database to its own drug development, while JPDSC promotes collaboration of genomics studies with academic researchers for maximizing the chances of increasing public benefits of the JPDSC database.

Current NIHS and JPDSC collaboration intends to explore SNP markers in absolute linkage disequilibrium with HLA alleles associated with ADRs. Such markers will be more available in a clinical practice because of lower genotyping cost compared to direct HLA genotyping. Recently, NIHS and JPDSC showed that three SNPs, rs1150738, rs3869066, and rs259945 are in absolute linkage disequilibrium with *HLA-A*31:01* in Japanese carbamazepine-induced SJS/TEN patients [10••]. Furthermore, if a pharmaceutical company encounters unforeseen severe ADRs, for example, more frequent SJS/TEN that occurs in overseas markets, such research results will encourage the company to try to explore alternative markers for HLA markers in order to develop companion diagnostics for predicting and avoiding severe ADRs and to opt to leave a beneficial drug at the clinical site for patients who need it.

JPDSC continues to update the database. Recently, using the imputation method, it increased the amount of genotyping information in the JPDSC database for bridging the Affymetrix genotyping data, which makes it available to virtually explore genomic markers using genotype data obtained from Affymetrix genotyping devices. Application of next generation sequencing to the JPDSC database is considered in the future plan.

Conclusion

With regard to severe ADRs, many burdens have been pointed out, such as the clinical burden (death from severe ADRs), healthcare burden (cost of hospitalization), sponsor's burden (withdrawal from the market), patient's burden (loss of chance of medication), and social burden (lawsuit against the sponsor). PGx is expected to significantly relieve such burdens. The JPDSC database contains representative genotype data of typical Japanese population samples and is an ideal database for use as the control for Japanese ADR research. JPDSC will aid in the promotion of severe ADR research for obtaining Japanese genomic information for drug safety.

Compliance with Ethical Standards

Conflict of Interest Koji Suematsu declares that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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