PGx studies of drug hypersensitivity (SJS/TEN) in Japan

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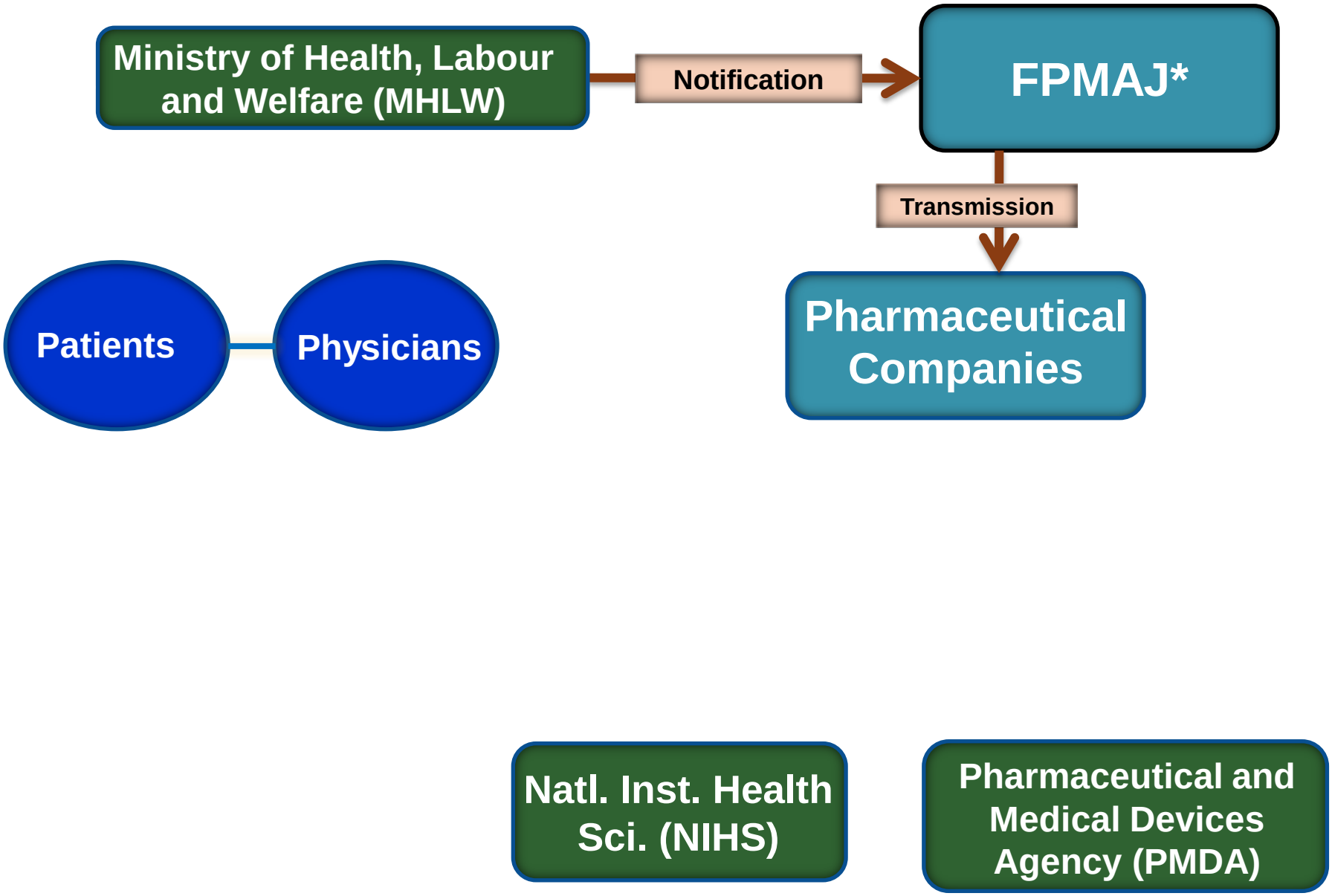
Perspective in this presentation is personal and not as my institute

NIHS network for DNA collection from severe ADR patients



*Federation of Pharmaceutical Manufacturers' Association of Japan

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Sept. 26, 2011 (updated version)

To president of Federation of Pharmaceutical Manufacturers' Association of Japan

Director, Safety division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health Labour and Welfare

Request for cooperation to research on severe adverse drug reactions
(SJS/TEN, rhabdomyolysis, interstitial lung disease)

医薬品の安全対策については、日頃より種々御協力いただいているところですが、当課としても副作用の事後対応から予測・予防型の安全対策への転換を図るため、重篤副作用疾患総合対策事業等の施策を進めているところです。すでに、医薬品による重篤な皮膚障害であるスティーブンス・ジョンソン症候群（SJS）及び中毒性表皮壊死融解症（TEN）、並びに横紋筋融解症に関する研究（発症に関連する因子の解析）が国立医薬品食品衛生研究所医薬安全科学部において実施されています。今般、重篤な皮膚障害、横紋筋融解症に加えて間質性肺疾患も研究の対象とすることとなり、同研究所において本年度より追加実施されることとなりました。これらの研究を効果的かつ適正に実施するためには、医師及び患者等の御協力を得て症例情報を収集することが必要となります。

つきましては、医薬品の服用後に、SJS及びTEN、並びに横紋筋融解症を発症した症例に加え、間質性肺疾患を発症した新規の症例情報（本通知発出後に企業が収集した自発報告）を入手した場合には、薬事法第77条の4の2の規定に基づき必要な副作用報告を行うとともに、国立医薬品食品衛生研究所医薬安全科学部あて連絡することに御協力いただきたく、関係業者への周知方よろしくお願いいたします。

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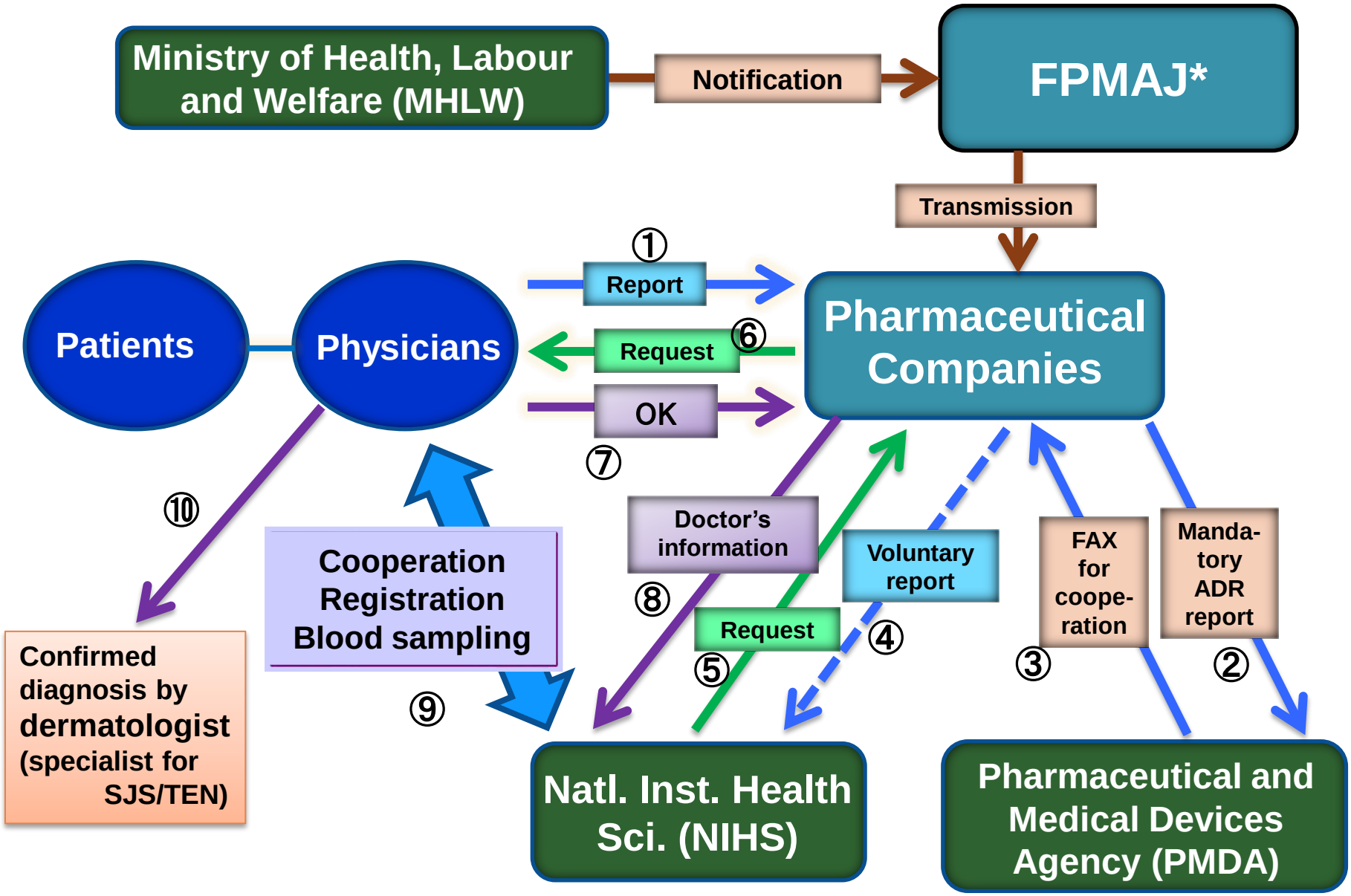
For SJS/TEN E-mail：jscar@nihs.go.jp
For rhabdomyolysis E-mail：jmyo@nihs.go.jp
For Interstitial lung disease E-mail：jlung@nihs.go.jp
電話　０３（３７００）１１４１　内線　５６０
FAX　０３（３７００）９７８８
（できるだけ、E-mail によりご連絡いただくようお願いします。）

NIHS network for DNA collection from severe ADR patients



*Federation of Pharmaceutical Manufacturers' Association of Japan

Overall progress in case collection of our group (2006.6～2013.10)

Activity of NIHS network	Number of cases
Reported from company	1,139 (from more than 90 companies)

Source of registered patients	Number of cases
from NIHS Network system	237 (74%)
from Collaborating institutes	83 (26%)
Total number	320

Confirmed diagnosis	Number of cases
SJS/TEN（definite)	206
SJS/TEN（probable)	35
Other than SJS/TEN	62
Not yet diagnosed	7
Tolerant control	44

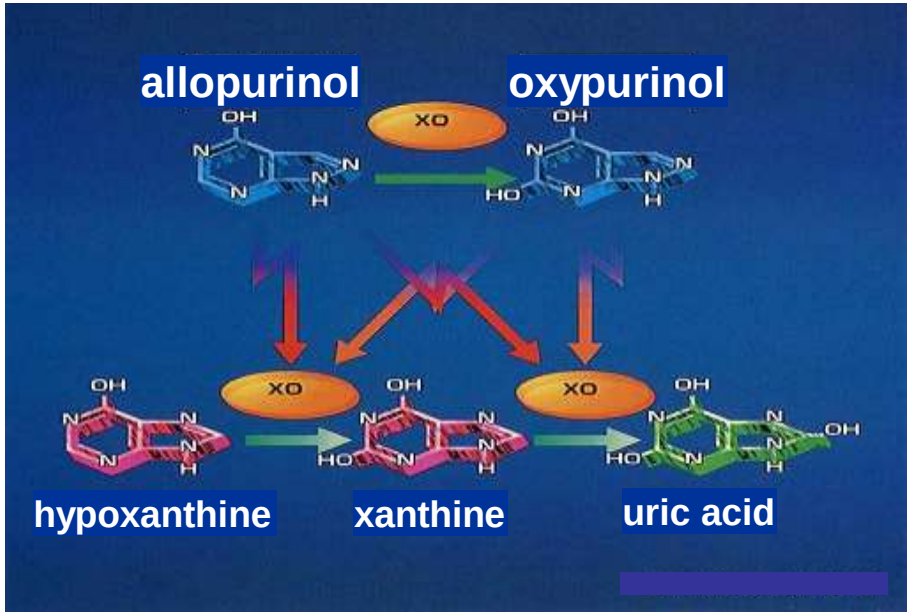
30% of newly onset SJS/TEN patients

HLA-type associated with allopurinol-related SJS/TEN in our JSAR group study

Allopurinol:

Antihyperuricemic drug (Inhibition of uric acid production by competitive inhibition of xanthine oxidase, XO)

From the homepage of GSK



Our results in Japanese

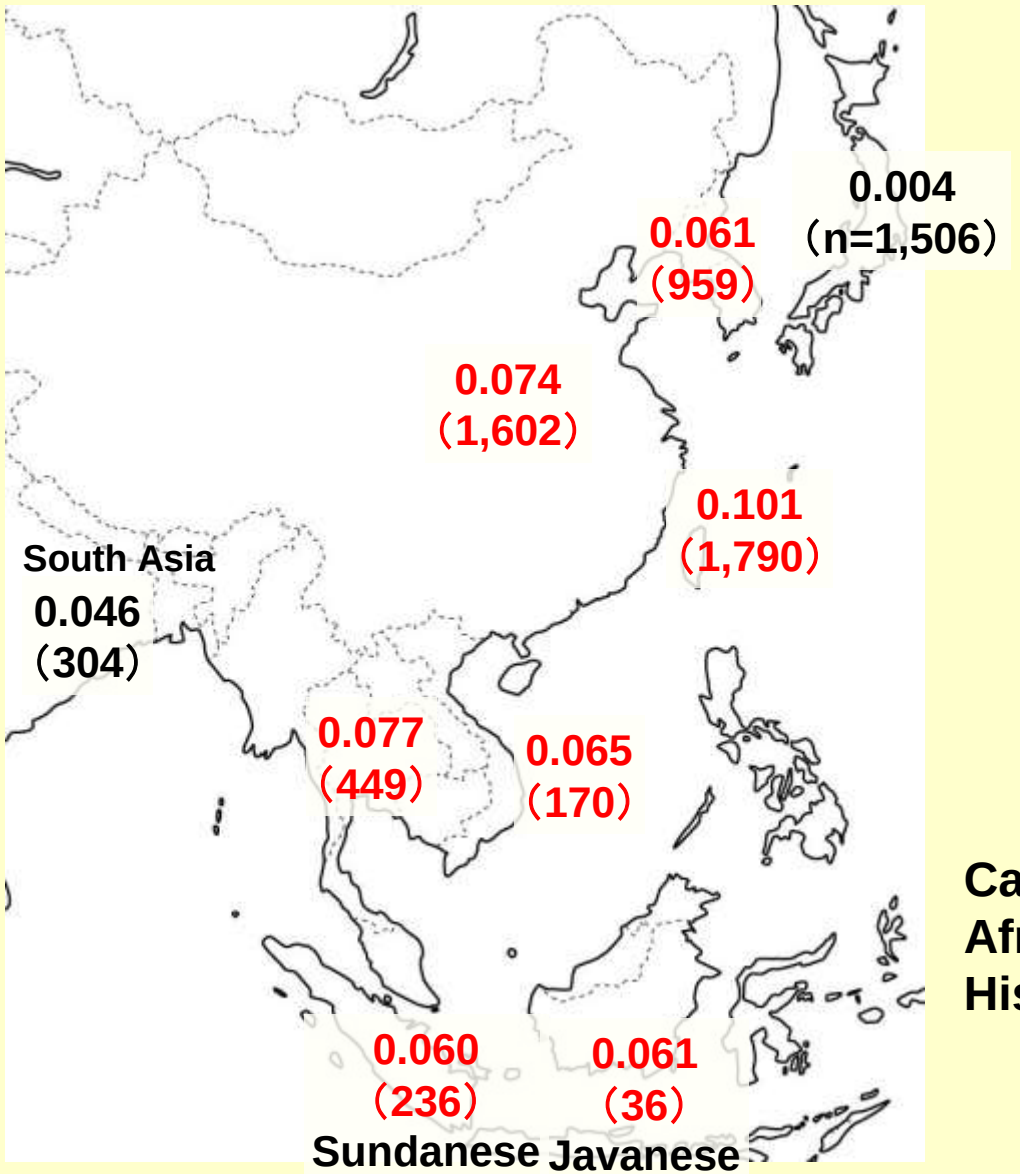
HLA type	Japanese population	SJS/TEN case patients		Odds ratio (95% confident interval)	P-value
	Allele frequency	Carrier frequency (Sensitivity)	Allele frequency		
*B*58:01*	0.6%	10 /18 (55.6%)	27.8%	62.8 (21.2-185.8)	5.4×10^{-12}

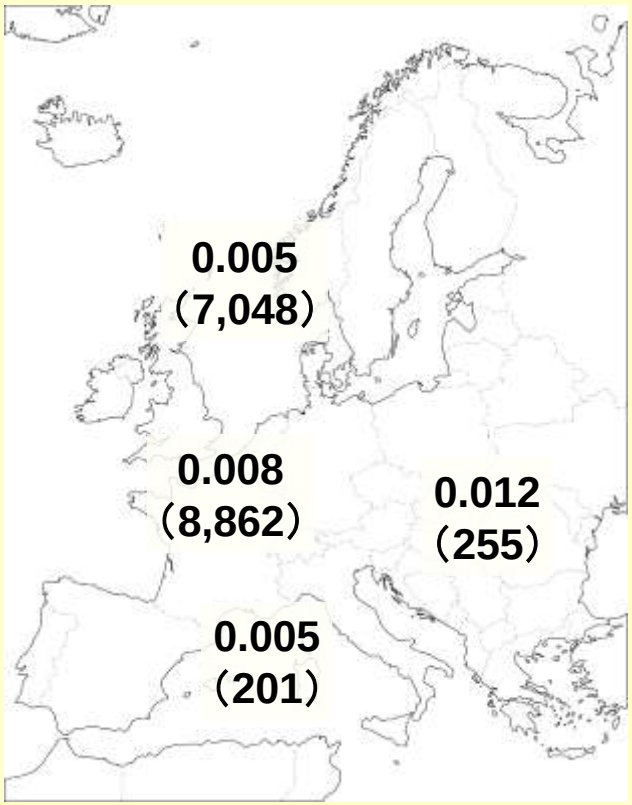
Tohkin et al., *Pharmacogenomics J* , 13: 60-69 (2013)

Other studies with allopurinol-related SCARs in Japanese (other studies)

HLA	SCARs	Carrier frequency (sensitivity)	Reference
*B*58:01*	SJS/TEN/ DIHS	3/3	Dainichi et al., Dermatology 215: 86-88 (2007)
	DIHS	1/3	Kano et al., Acta Derm. Venereol 88: 616-618 (2008)

Population frequencies of *HLA-B*58:01*





Caucasian-Americans: 0.005 (8,426)
African-Americans: 0.034 (2,974)
Hispanic-Americans: 0.015 (1,999)

Kurose et al. Drug Metab Pharmacokinet., 27: 9-54 (2012)

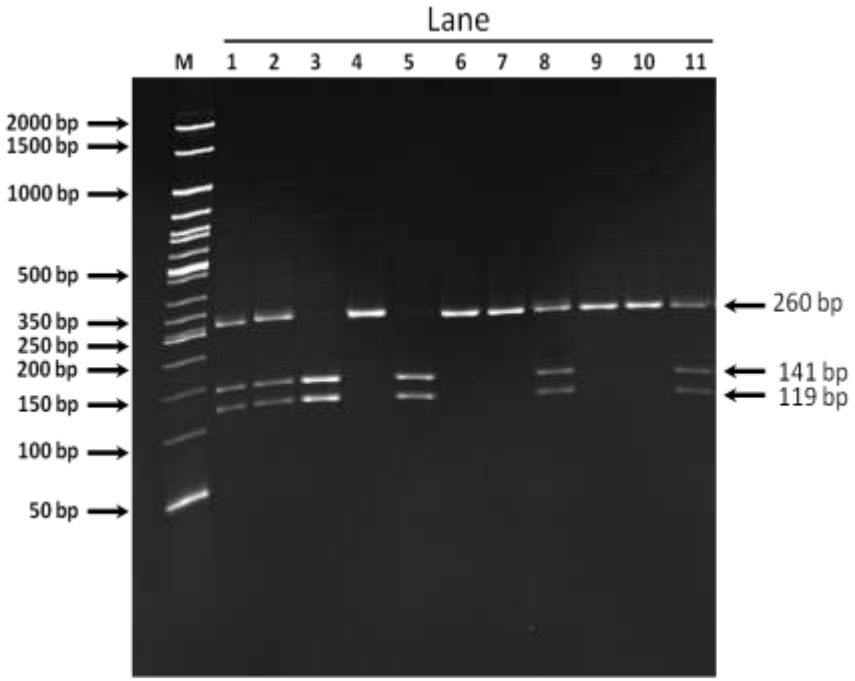
Subject numbers in parenthesis

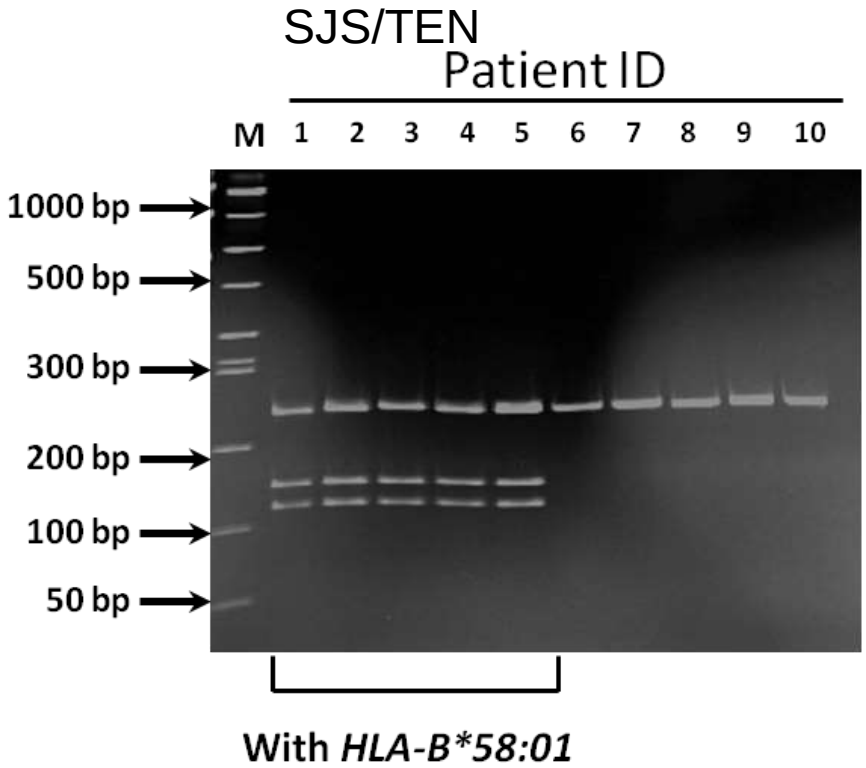
PCR-RFLP for a surrogate marker of *HLA-B*58:01*

rs9263726G>A in the *psoriasis susceptibility 1 candidate 1* (*PSORS1C1*) gene was in absolute linkage disequilibrium (r^2=1, D'=1) with *HLA-B*58:01* in Japanese.

Tohkin et al., Pharmacogenomics J, 13: 60-69 (2013)

Developed an easy and inexpensive PCR-RFLP assay





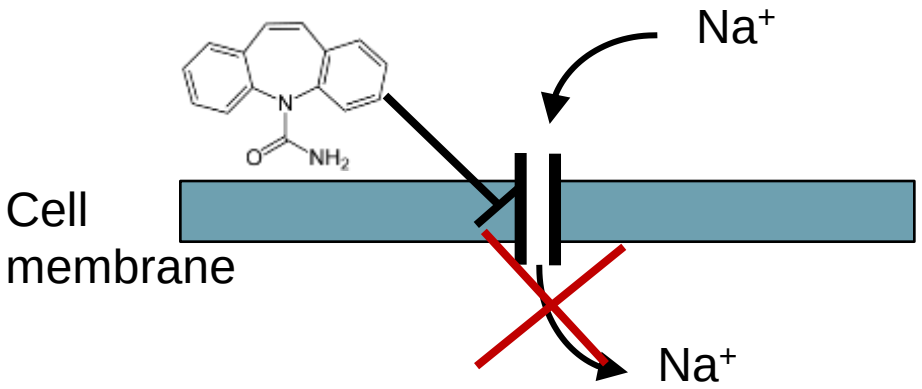
Maekawa et al., Drug Metab. Pharmacokinet. 27: 447-450 (2012)

HLA-types associated with carbamazepine-related SJS/TEN in our JSAR group study

Carbamazepine (CBZ):

Anticonvulsant

It is considered that CBZ inhibits Na^+ channel for neurotransmission.



Inhibition of neural cell excitation

Our results in Japanese

HLA type	Japanese population	SJS/TEN case patients		Odds ratio (95% confident interval)	P-value
	Allele frequency	Carrier frequency (Sensitivity)	Allele frequency		
B*15:02	**rare**	**0/21**	**0**		
B*15:11	**1**	**5/21 (23.8%)**	**11.9**	**12.2 (4.6-32.1)**	**0.0001**
A*31:01	**7**	**9/21 (42.9%)**	**21.4**	**3.2 (1.5-6.7)**	**0.0029**

Sensitivity: 14/21=67% (*HLA-B*15:11* and *HLA-A*31:01* were found in different patients)

Kaniwa et al., Epilepsia,51:2461-2465 (2010)
Kaniwa and Saito, Ther. Adv. Drug Saf., in press.

HLA-types associated with carbamazepine-related SJS/TEN in Japanese (other studies)

HLA	SCARs	Carrier frequency (Sensitivity)	Odds ratio	Reference
*B*15:02*	DIHS	0/10	-	Kano et al., Acta Derm. Venereol 88: 616-618 (2008)
	SCAR	0/22	-	Kashiwagi et al., J Dermatol 35: 683-685 (2008).
	Cutaneous ADRs	0/61	-	Ozeki et al., Hum Mol Genet 20: 1034-1041 (2011)

HLA	SCARs	Carrier frequency (Sensitivity)	Odds ratio	Reference
*A*31:01*	DIHS	21/36	9.5	Ozeki et al., Hum Mol Genet 20: 1034-1041 (2011)
	SJS/TEN	5/6	33.9	
	Other cADRs	19/35	8.0	
	SCAR	11/22	4.33[#]	Kashiwagi et al., J Dermatol 35: 683-685 (2008).
A31	DIHS	8/9	-	Niihara et al., J Dermatol 39: 594-601 (2012)
	Other SCARs	2/6	-	

[#]Calculated based on allele frequency

Population differences in subtype frequencies of serotype HLA-B75 and carbamazepine-related SJS/TEN onset

Population	Population frequency in healthy subjects				
	*HLA-B*15:02*	*HLA-B*15:08*	*HLA-B*15:11*	*HLA-B*15:15*	*HLA-B*15:21*
Japanese	0.001		0.004 – 0.008*		
Korean	0.002-0.022*	0.000	0.000-0.020*	0.000	0.000
Han Chinese	0.019 - 0.124*	0.005 – 0.015	0.000 – 0.017	0.010	0.000 – 0.002
Thai	0.082 – 0.085*		0.010*		0.007 – 0.010*
Indian	0.000 – 0.060*	0.005 – 0.033*			
US-African	0.000 – 0.002	0.000-0.001	0.000	0.000-0.002	0.000
US-Caucasian	0.000	0.000	0.000	0.000-0.006	0.000

http://www.allelefrequencies.net/ (Middleton et al., 2003)

*found in SJS/TEN patients (from scientific reports)

HLA-B75 is associated with carbamzepine-related SJS/TEN

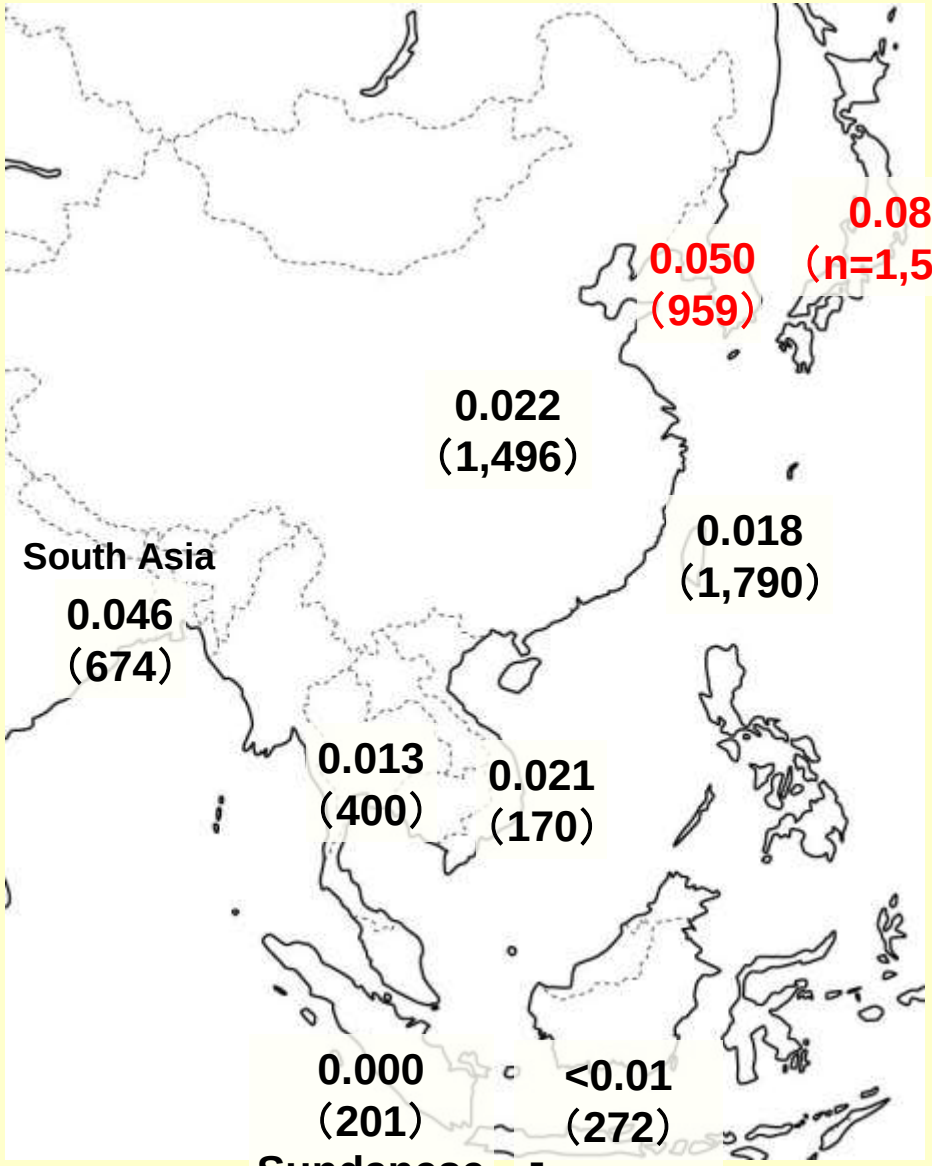
HLA-types associated with carbamazepine-related SJS/TEN in Japanese (other studies)

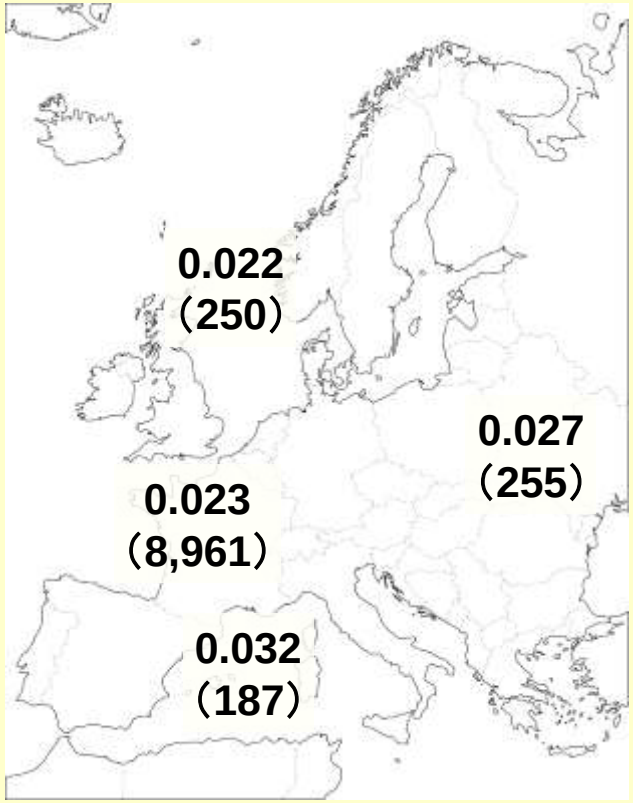
HLA	SCARs	Carrier frequency (Sensitivity)	Odds ratio	Reference
*B*15:02*	DIHS	0/10	-	Kano et al., Acta Derm. Venereol 88: 616-618 (2008)
	SCAR	0/22	-	Kashiwagi et al., J Dermatol 35: 683-685 (2008).
	Cutaneous ADRs	0/61	-	Ozeki et al., Hum Mol Genet 20: 1034-1041 (2011)

HLA	SCARs	Carrier frequency (Sensitivity)	Odds ratio	Reference
*A*31:01*	DIHS	21/36	9.5	Ozeki et al., Hum Mol Genet 20: 1034-1041 (2011)
	SJS/TEN	5/6	33.9	
	Other cADRs	19/35	8.0	
	SCAR	11/22	4.33[#]	Kashiwagi et al., J Dermatol 35: 683-685 (2008).
A31	DIHS	8/9	-	Niihara et al., J Dermatol 39: 594-601 (2012)
	Other SCARs	2/6	-	

[#]Calculated based on allele frequency

Population frequencies of *HLA-A*31:01*





Caucasian Americans: 0.024 (8,427)
African-Americans: 0.010 (2,968)
Hispanic-Americans: 0.048 (1,992)

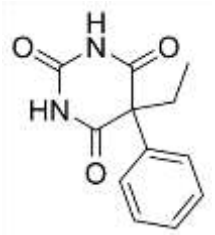
Subject numbers in parenthesis

Kurose et al. Drug Metab Pharmacokinet., 27: 9-54 (2012)

HLA-type associated with phenobarbital-related SJS/TEN in our preliminary study (JSAR group)

Phenobarbital:

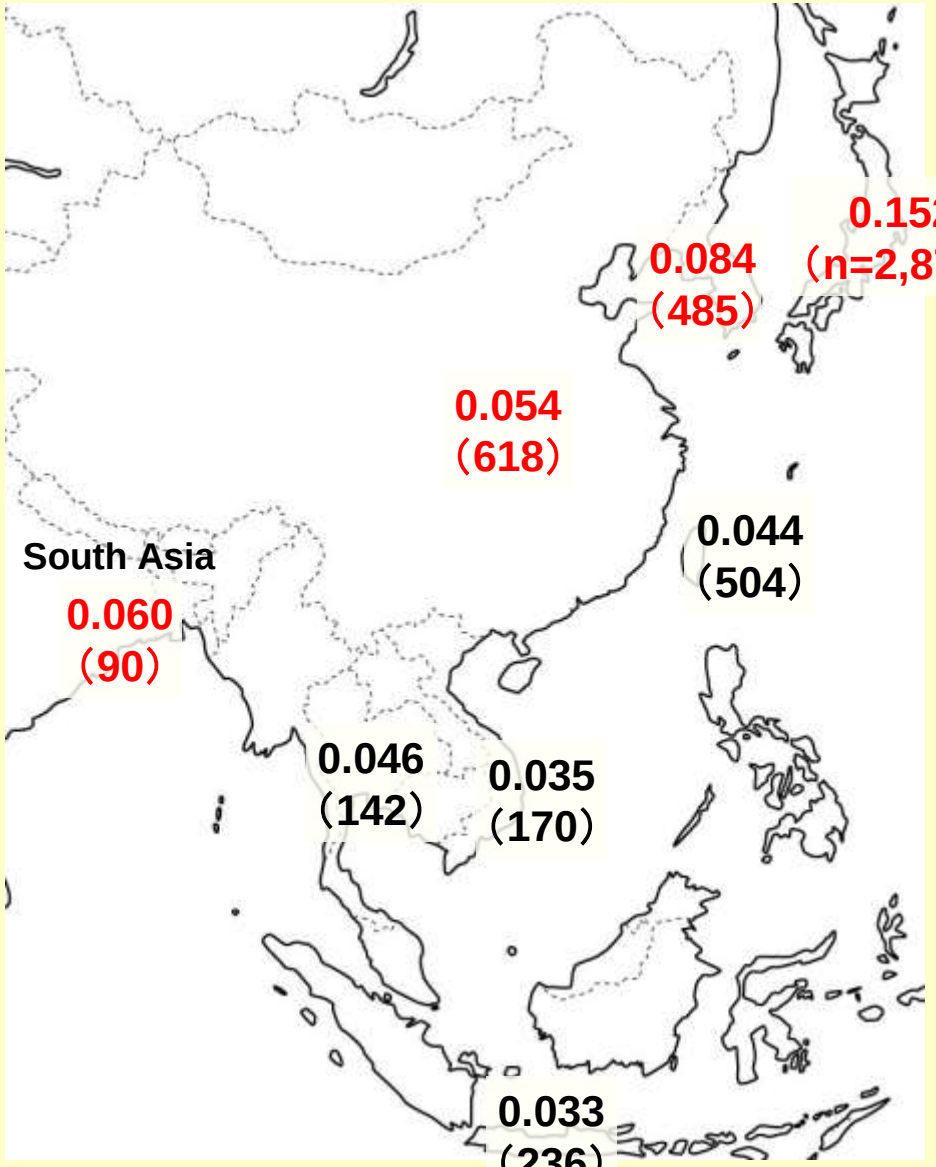
Anticonvulsant（Inhibition of neural cell function through increase in affinity of GABA to $GABA_A$ receptor and Cl^- channel opening）

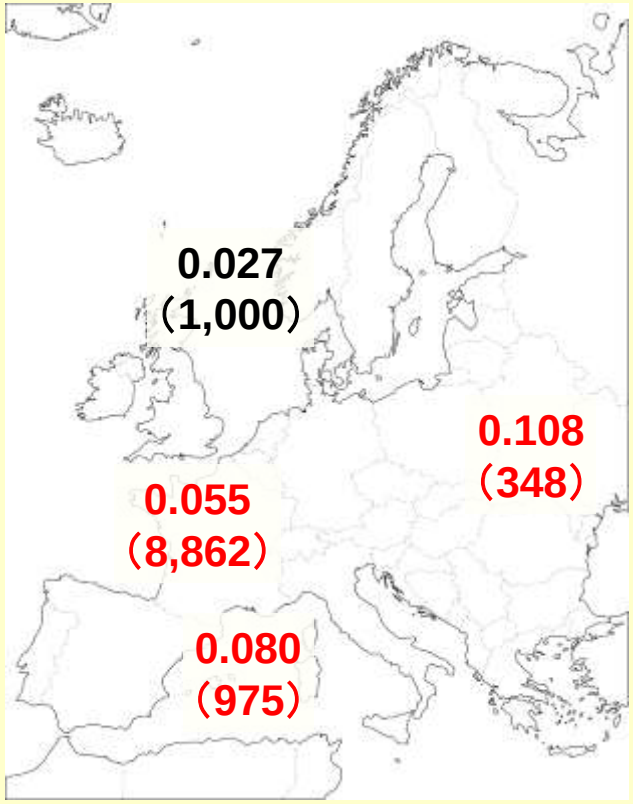


HLA type	Japanese population	SJS/TEN case patients		Odds ratio（95% confident interval）	P-value (Corrected p-value)
	Allele frequency	Carrier frequency (Sensitivity)	Allele frequency		
A*24:20	**47/2878 (1.46%)**	**2/8 (25.0%)**	**12.50%**	**20.08 (3.95-102.07)**	**0.0074 (0.1036)**
B*51:01	**438/2878 (15.2%)**	**6/8 (75.0%)**	**43.75%**	**16.71 (3.66-83.06)**	**0.0003 (0.0042)**
DRB1*04:10	**114/2878 (3.96%)**	**2/8 (25.0%)**	**12.50%**	**8.08 (1.61-40.48)**	**0.0383 (0.5362)**

Kaniwa et al. Pharmacogenomics, in press

Population frequencies *HLA-B*51:01*





Caucasian Americans: 0.039 (1,070)
African-Americans: 0.022 (2,411)
Hispanic-Americans: 0.058 (1,999)

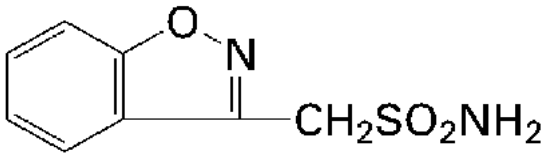
Subject numbers in parenthesis

http://www.allelefrequencies.net/

HLA-type associated with zonisamide-related SJS/TEN in our preliminary study (JSAR group)

Zonisamide:

Anticonvulsant（Inhibition of neurotransmission）
Anti-Parkinson's disease（MAO-B inhibitor; dopamine level increases in co-treatment with levodopa）

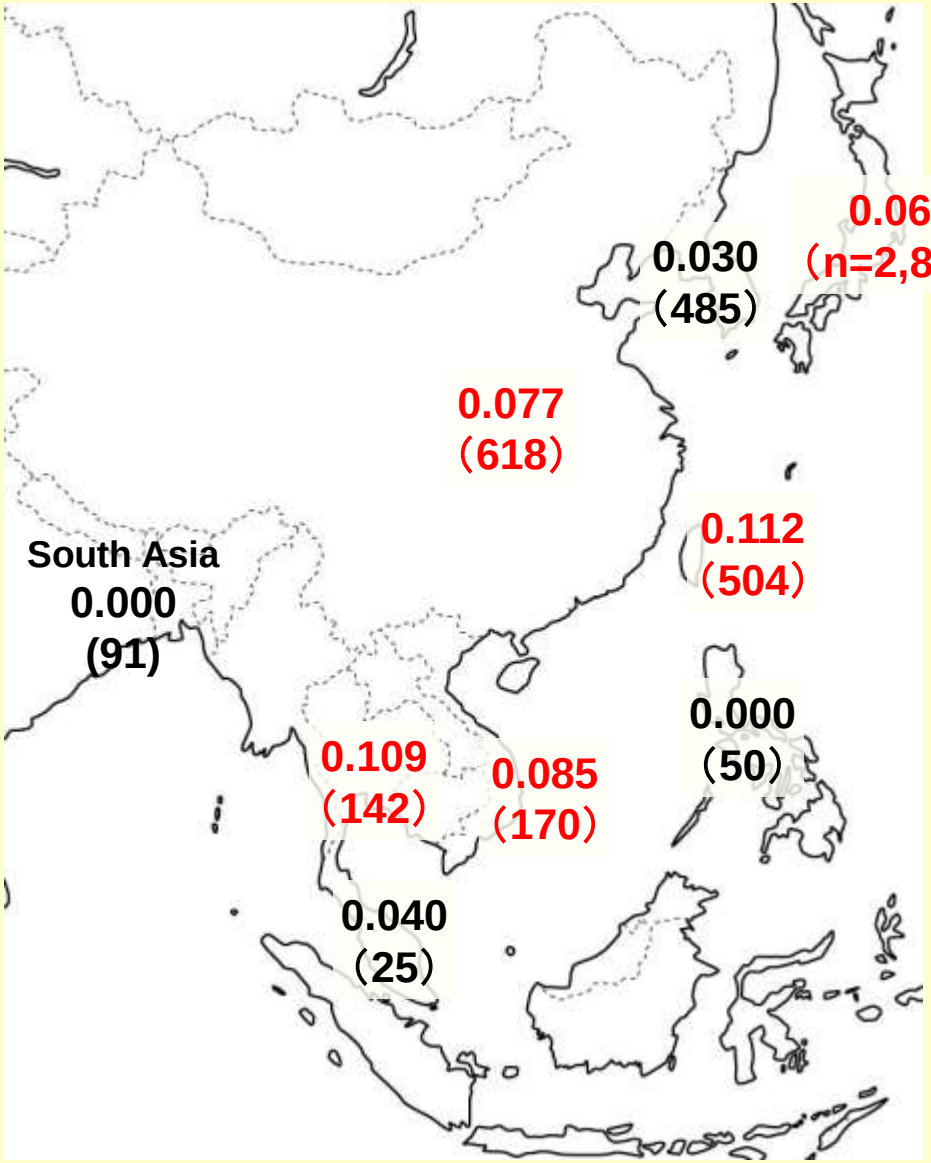


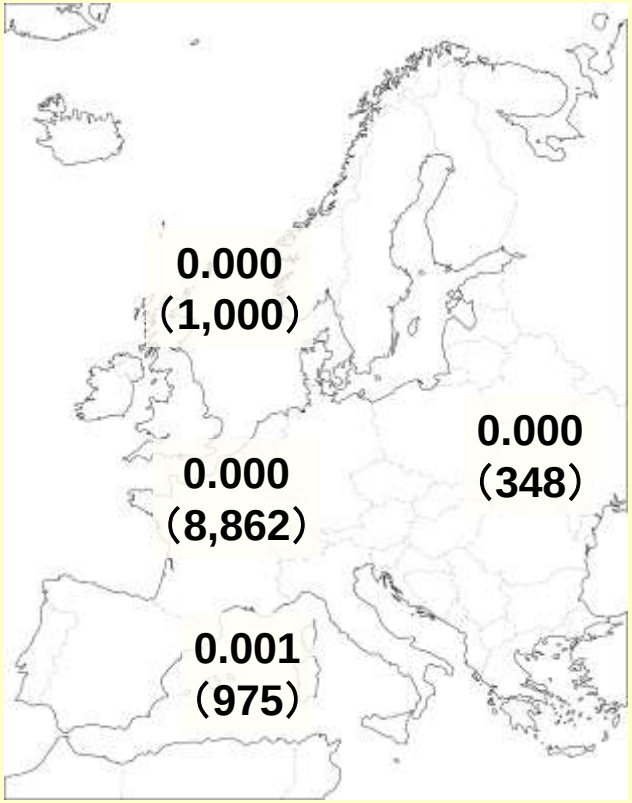
HLA type	Japanese population	SJS/TEN case patients		Odds ratio（95% confident interval）	P-value (Corrected p-value)
	Allele frequency	Carrier frequency (Sensitivity)	Allele frequency		
A*02:07	**196/2878 (6.81%)**	**5/12 (41.7%)**	**20.83**	**9.77 (3.07-31.1)**	**0.0008 (0.0176)**
B*46:01	**276/2878 (9.60%)**	**5/12 (41.7%)**	**20.83**	**6.73 (2.12-21.36)**	**0.0037 (0.0814)**
DRB1*08:03	**457/2878 (15.88%)**	**5/12 (41.7%)**	**20.83**	**3.78 (1.20-11.97)**	**0.0306 (0.6732)**
A*02:07_B*46:01_ C*01:02_ DRB1*08:03#	**120/5756 (2.09%)**	**5/12 (41.7%)**	**20.83**	**12.4 (4.54-33.7)**	**0.015**

#Calculated in allele frequency

Kaniwa et al. Pharmacogenomics, in press

Population frequencies of *HLA-A*02:07*





Caucasian Americans: 0.000 (307)
African-Americans: 0.000 (2,411)
Hispanic-Americans: 0.000 (1,999)

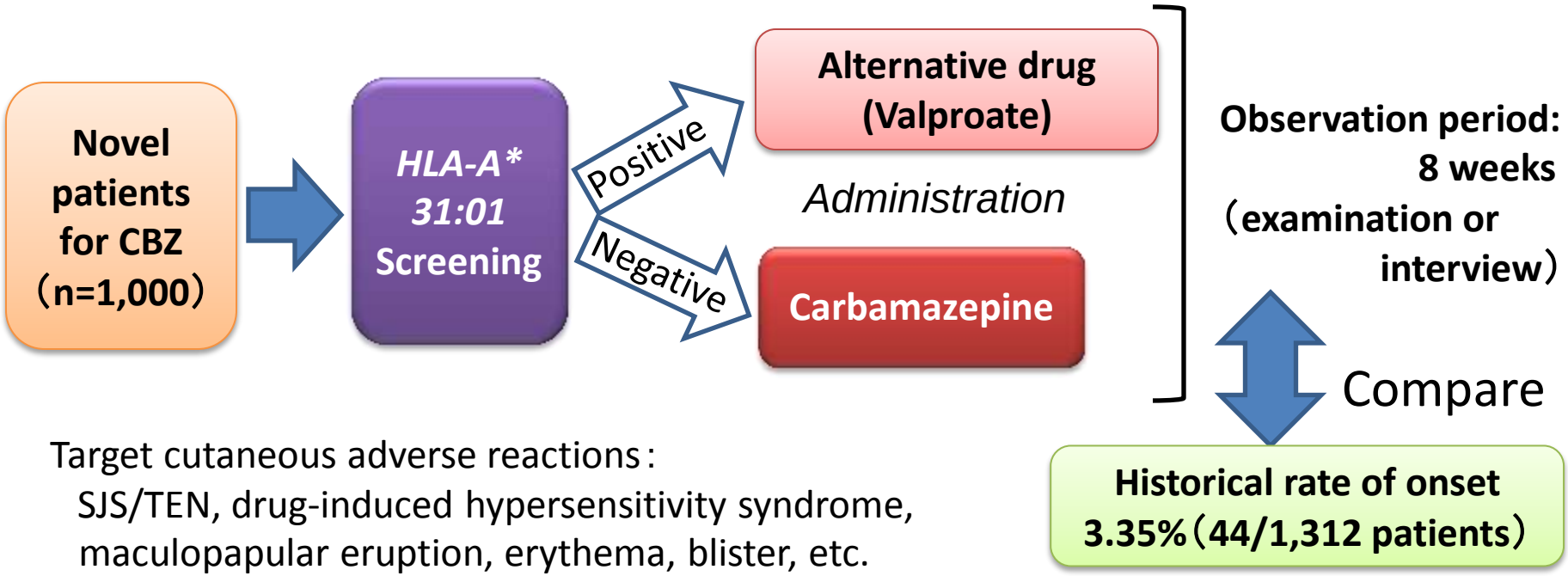
Subject numbers in parenthesis

http://www.allelefrequencies.net/

Prospective clinical study for carbamazepine in Japan

Toward carbamazepine (CBZ) administration based on *HLA-A*31:01* genotype

Riken (PI: Dr. Michiaki Kubo)



Target cutaneous adverse reactions:
SJS/TEN, drug-induced hypersensitivity syndrome, maculopapular eruption, erythema, blister, etc.

Study period: 2011.10～2014.3
Last registration: 2014.1

See http://www.biobankjp.org/pgx/outline/cbz.html

***HLA-A*31:01* test**

(Ozeki et al., Hum Mol Genet 20: 1034-1041 (2011)

Sensitivity: 58.4%
Specificity: 87.1%
Positive predictive value (estimated using population freq.): 12.7%
Negative predictive value (estimated using population freq.): 98.7%

Other pharmacogenomic research on SJS/TEN in Japan

SJS/TEN with ocular complications (by Prof. Kinoshita's group)

Genetic variations	Allele frequency		Odds ratio	P value	Ref.
	SJS/TEN	Healthy volunteer			
*HLA-A*02:06*	0.225 (32/142)	0.084 (19/226)	3.2	0.0001	1
*HLA-A*11:01*	0.028 (4/142)	0.115 (26/226)	0.22	0.003	1
EP3 **(Prostaglandin E receptor 3) rs17131450 C>T**	0.155 (31/200)	0.063 (20/320)	2.78	0.0006	2
IL-4 **rs1801275A>G (Q551R)**	0.046 (7/152)	0.153 (49/320)	0.27	0.0008	3
IL-13 **rs20541G>A (R110Q)**	0.204 (31/152)	0.313 (100/320)	0.56	0.014	3
FASLG **(Fas ligand) rs3830150A>G**	0.243 (37/152)	0.138 (44/320)	2.02	0.004	4
[#]*TLR3* **rs3775296G>T**	0.193 (11/57)	0.050 (8/160)	4.55	0.001	5

[#]Analyzed by recessive mode

1: Ueta M et al., Mol Vis, 14: 550 (2008), 2: Ueta M et al., J Allergy Clin Immunol, 126: 1218 (2010), 3: Ueta M et al., Invest Ophthalmol Vis Sci, 49: 1809 (2008), 4: Ueta M et al., Br J Ophthalmol, 92: 989 (2008), 5. Ueta M et al., Br J Ophthalmol, 91: 962 (2007).

Summary and perspectives for biomarker research on SJS/TEN

Summary

- Japanese MHLW drives forward pharmacogenomic research on SJS/TEN by developing nation-wide case collection system
- Like in other ethnic populations, *HLA-B*58:01* for allopurinol and HLA-B75 and *HLA-A*31:01* for carbamazepine are associated with SJS/TEN
- Preliminary study suggested *HLA-B*51:01* and *HLA-A*02:07* could be associated with phenobarbital- and zonisamide-related SJS/TEN, respectively
- Population frequency of risk allele is probably important for incidence rate of SJS/TEN in a population

Future directions

- More genomic biomarkers should be found for other drugs
  (collaboration with neighboring countries to overcome small sample sizes in one country)
- Generally low positive predictive values by *HLA* test

More scientific efforts is necessary to find other predictive factors

- T cell receptor types **(Ko et al., J. Allergy Clin. Immunol., 128: 1266-1276 (2011))**
- Find rare but strongly associated SNPs using next generation sequencer
- Other types of biomarkers (by proteomics, metabolomics)

Contributors for this presentation

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