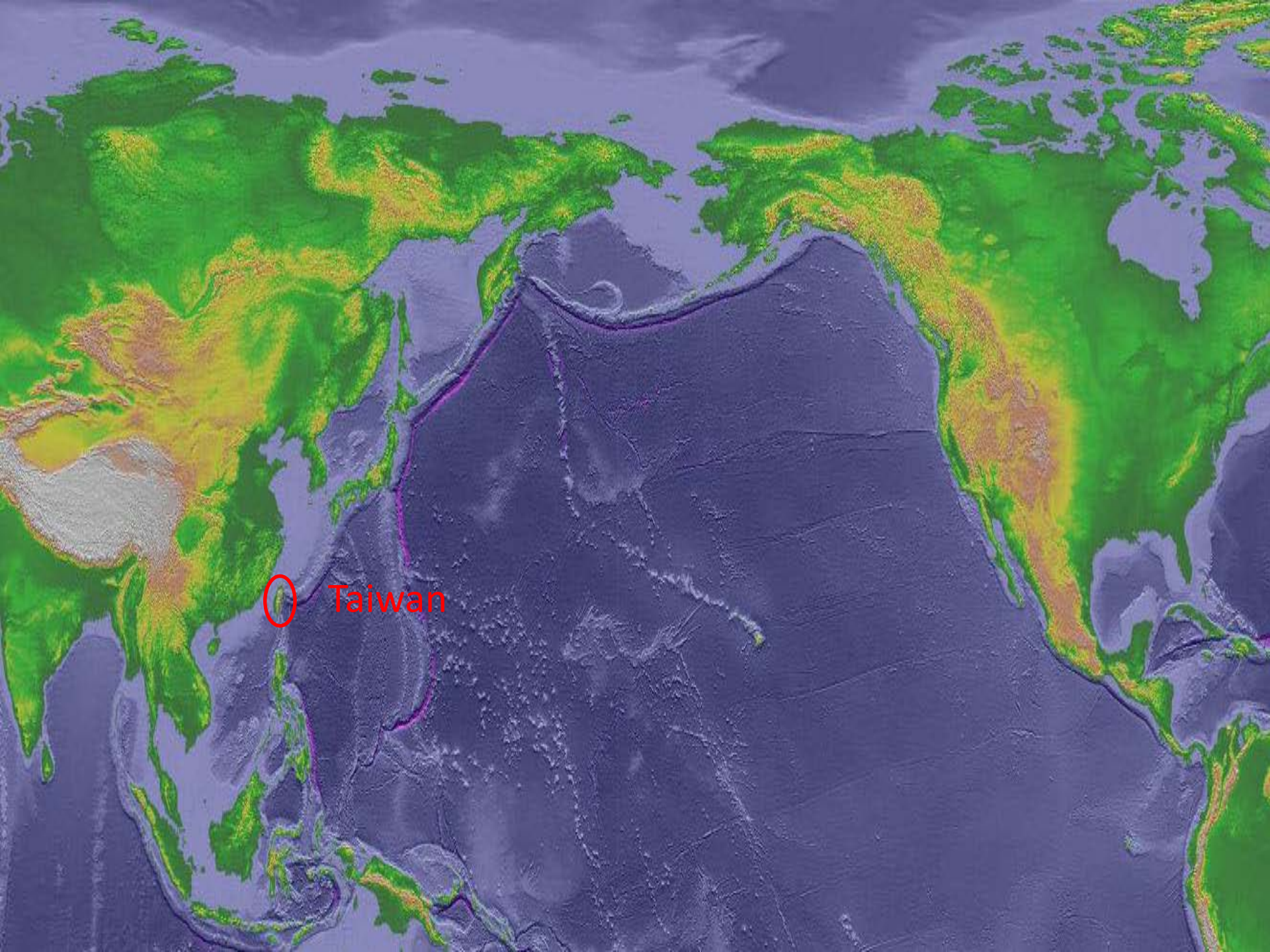
NIH: SJS/TEN workshop (March 3-4, 2015)

SJS/TEN: Taiwan experience

Shuen-Iu Hung, PhD.
Institute of Pharmacology,
National Yang-Ming University,
Taipei, Taiwan
E-mail: sihung@ym.edu.tw


Taiwan

Taiwan

- Population: 23 million, 98% are Han Chinese
- National health insurance covers 99% of the population.
- English-based electronic medical records

  Diagnostic codes: ICD-9-CM

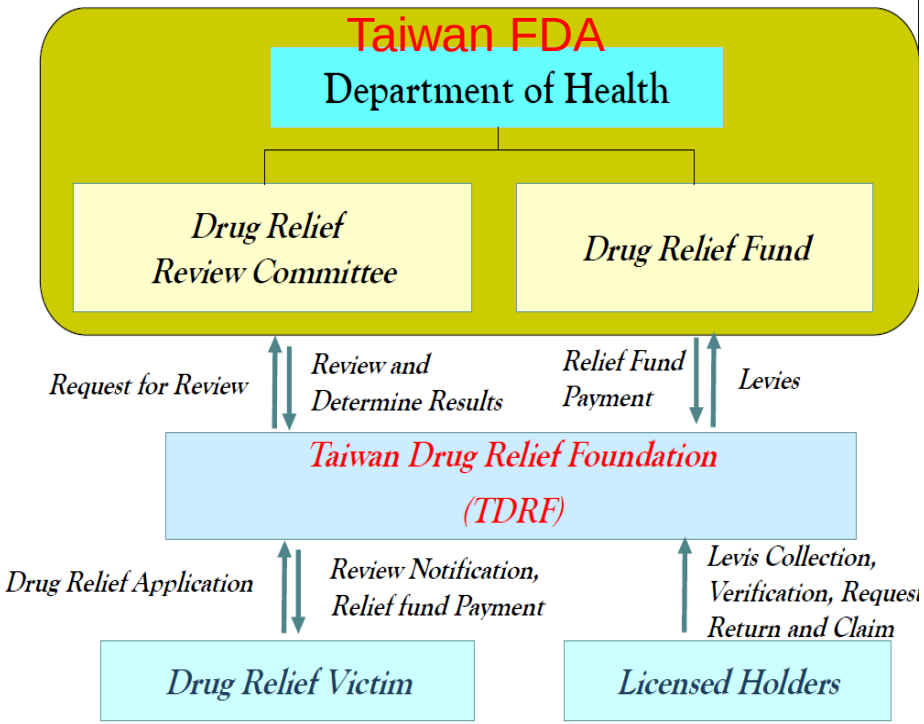
  Joint Commission International (JCI) certification

  College of American Pathologists (CAP) certification
- Taiwan SCAR consortium (>10 medical centers)
- Chang Gung memorial hospital system:

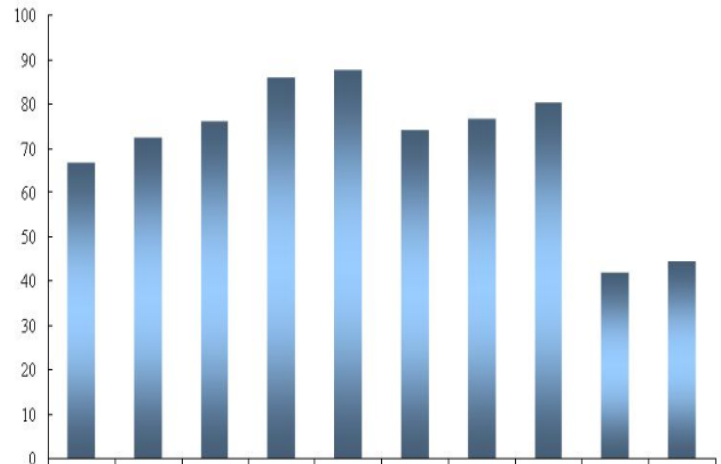
  >10,000 beds, covering 1/10 of health services nationwide

Taiwan Drug Relief Foundation (TDRF)

Relief Fund Operation Infrastructure



Annual Fund Rasied From Pharmaceutical Industry from 2002 to 2010



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
NTD(in millions)	66.78	72.27	76.1	85.92	87.63	74.1	76.53	80.22	41.99	44.59

website: http://www.tdrf.org.tw

Taiwan Drug Relief Foundation

Number of cases been reported to Taiwan ADR relief foundation

(1999 –2015.1)

ADR classification	Sex		No	ADR type	No
	F	M			
Skin and subcutaneous tissue disorders 皮膚及皮下組織疾患	435	440	875 (65%)	Stevens Johnson Syndrome 史蒂文生氏-強生症候群	503
			55%	Toxic Epidermal Necrolysis 毒性表皮壞死溶解症	154
				Drug rash with Eosinophilia and Systemic Symptoms 藥物疹合併嗜伊紅血症及全身症狀	80
				Drug eruption藥物疹	34
				Erythema multiforme多型性紅斑	33
				Other 其他	71
Hepatobiliary disorders 肝膽疾患	49	69	118 (9%)	Acute Hepatitis 急性肝炎	50
				Acute hepatic failure 急性肝衰竭	15
				Fulminant Hepatitis 猛爆性肝炎	15
				Hepatic failure 肝衰竭	9
				Drug-induced hepatitis 藥物性肝炎	8
				Other 其他	21
Immune system disorders 免疫系統疾患	46	72	118 (9%)	Anaphylactic shock 過敏性休克	85
				Drug hypersensitivity 藥物過敏	13
				Hypersensitivity syndrome 過敏症候群	11
				Other 其他	9

Severe cutaneous adverse reaction (SCAR) groups in the world

Drug hypersensitivity meeting (EACCI)

EuroSCAR/RegiSCAR

Japan SCAR/Asian SCAR

SEA-SCAR (Malaysia, Singapore, Philippine, Thailand, Taiwan)

T-SCAR

The drugs associated with fatal ADRs in Taiwan

Ranking	Drugs	Case no
1	Allopurinol	205
2	Phenytoin	132
3	Carbamazepine	113
4	Rifampin/Isoniazid/Pyrazinamide	73/70/68
5	Diclofenac	58
6	Lamotrigine	38
7	Co-trimoxazole	37
8	Mefenamic acid	34
9	Ibuprofen	33
10	Cefazolin	29

TDRF

(1999-2010)

Neurology®
THE MOST WIDELY READ AND HIGHLY CITED PEER-REVIEWED NEUROLOGY JOURNAL
The Official Journal of the American Academy of Neurology

Neurology, 2011

Severe cutaneous adverse reactions to antiepileptic drugs in Asians

Table 1 Causative antiepileptics, demographic data, and major underlying diseases of patients with SCARs

Aromatic AEDs

	Phenotypes, n (%)					
	SJS, 100 (64.9)	SJS-TEN, 5 (3.3)	TEN, 10 (6.5)	SJS/TEN,[a] 115 (74.7)	DRESS, 39 (25.3)	Total, 154 (100)
Culprit drug, n (%)						
CBZ	70 (70.0)	3 (60.0)	5 (50.0)	78 (67.8)	12 (30.8)	90 (58.4)
PHT	14 (14.0)	1 (20.0)	5 (50.0)	20 (17.4)	17 (43.6)	37 (24.0)
LTG	11 (11.0)	1 (20.0)	0 (0.0)	12 (10.4)	6 (15.4)	18 (11.7)
OXC	4 (4.0)	0 (0.0)	0 (0.0)	4 (3.5)	1 (2.5)	5 (3.3)
PB	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.9)	3 (7.7)	4 (2.6)
Age, y, mean ± SD; M/F	47.1 ± 23.6; 42/58	52.6 ± 13.9; 1/4	53.9 ± 17.4; 4/6	47.94 ± 22.74; 47/68	49.0 ± 23.0; 27/12	48.2 ± 22.7; 74/80

nature International weekly journal of science

Nature **428**, 486 (1 April 2004) | doi:10.1038/428486a

Medical genetics: A marker for Stevens–Johnson syndrome

Wen-Hung Chung[1], Shuen-Iu Hung[3], Hong-Shang Hong[1], Mo-Song Hsih[2], Li-Cheng Yang[1], Hsin-Chun Ho[1], Jer-Yuarn Wu[3,4] & Yuan-Tsong Chen[3,5]

Table 1 **Frequency of *HLA* alleles in patients with Stevens–Johnson syndrome**

HLA allele	*CBZ–SJS*	*CBZ-tolerant*	*Normal*
*B*1502*	44 (100%)	3 (3%)*	8 (8.6%)†
*Cw*0801*	41 (93.2%)	17 (16.8%)	13 (14%)
*A*1101*	36 (81.8%)	51 (50.5%)	53 (57%)
*DRB1*1202*	33 (75%)	12 (11.9%)	18 (19.4%)
*B*1502, Cw*0801*	41 (93.2%)	3 (3%)	7 (7.5%)
*B*1502, A*1101*	36 (81.8%)	2 (2%)	6 (6.5%)
*B*1502, DRB1*1202*	33 (75%)	1(1%)	5 (5.4%)
*B*1502, Cw*0801, A*1101, DRB1*1202*	29(66%)	0 (0%)	3 (3.2%)

Frequencies (by number and percentage) of individual or combined loci of the *B*1502* ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; $n = 44$), and in carbamazepine-tolerant ($n = 101$) and normal subjects ($n = 93$). For methods, see supplementary info

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2,504 (95% CI, 126–49,522); corrected *P* value $P_c = 3.13 \times 10^{-27}$.

†Odds ratio (CBZ–SJS/normal): 895 (95% CI, 50–15,869); $P_c = 1.38 \times 10^{-21}$.

($Pc<10^{-20}$, OR: >2500)

Genotype–phenotype association between HLA and carbamazepine-induced hypersensitivity reactions: Strength and clinical correlations

Yi-Hsin Hsiao [a,1], Rosaline Chung-Yee Hui [a,b,1], Tony Wu [b,c], Wan-Chun Chang [d], Mo-Song Hsih [b,c], Chih-Hsun Yang [a,b], Hsin-Chun Ho [a,b], Ya-Ging Chang [a,b], Ming-Jing Chen [a,b], Jing-Yi Lin [a,b], Ding-Ping Chen [e,f], Pi-Yueh Chang [e,f], Tsu-Lan Wu [e,f], Shuen-Iu Hung [d,**], Wen-Hung Chung [a,b,*]

(J Dermatology Science, 2014)

Association between *HLA-B* alleles and carbamazepine-induced hypersensitivity reactions.*

HLA-B allele (serological specificity)	CBZ-tolerant control (*n* = 152)	SJS/TEN (*n* = 112)				DRESS (*n* = 23)			
	Carriers (*n*)	Carriers (*n*)	*P* value	Pc value	OR(95%CI)	Carriers (*n*)	*P* value	Pc value	OR(95%CI)
B*15:01 (B62)	12	1	**0.009**	NS	0.11(0.01–0.8)	1	1.0	NS	53(0.07–4.3)
B*15:02 (B75)	11	99	**1.6×10^{-44}**	**5.8×10^{-43}**	**97.62(42.0–226.8)**	0	0.36	NS	0.26(0.01–4.6)

HLA-B*1502 is associated with CBZ-SJS/TEN, but not DRESS/MPE in Han Chinese.

Pharmacogenetics and Genomics

Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions

Shuen-Iu Hung[a,1], Wen-Hung Chung[b,c,1], Shiou-Hwa Jee[d], Wen-Chieh Chen[e], Yun-Ting Chang[f], Woan-Ruoh Lee[g], Shu-Ling Hu[h], Meng-Tse Wu[i], Gwo-Shing Chen[j], Tak-Wah Wong[k], Pa-Fan Hsiao[l], Wei-Hsuan Chen[a], Han-Yu Shih[a], Wu-Hsiang Fang[a], Chun-Yu Wei[a], Yi-Hui Lou[a], Yau-Li Huang[b], Juei-Jueng Lin[m] and Yuan-Tsong Chen[a,n]

(Pharmacogenetics & Genomics, 2006)

	Number of the Patients (%)	P value	Pc value	Odds Ratio
HLA-B*1502 for CBZ-SJS/TEN	59/60 (97%)	1.6×10^{-41}	1.2×10^{-40}	1357 (193.4-8838.3)
HLA-A*3101 for CBZ-MPE/DRESS	8/31 (38%)	0.0001	0.0021	12.17 (3.6-41.2)

HLA-A*31:01 and carbamazepine-maculopapular eruption/DRESS

*HLA-A*31:01* and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis

E Genin[1,12], D-P Chen[2,3,12], S-I Hung[4,12], P Sekula[5], M Schumacher[5], P-Y Chang[2,3], S-H Tsai[2,3], T-L Wu[2,3], T Bellón[6], R Tamouza[7,8], C Fortier[7,8], A Toubert[7,8], D Charron[7,8], A Hovnanian[8], P Wolkenstein[8], W-H Chung[9], M Mockenhaupt[10] and J-C Roujeau[11]

The Pharmacogenomics Journal 2014

Table 2. Association of *HLA-A*31:01* allele with CBZ-induced SCAR

Subgroup	*Prevalence of the disease*	*HLA allele positive/ number of patients (%)*	*HLA allele positive/number of controls (%)*	*P-value*	*Odds ratio (95% CI)*
Europeans RegiSCAR					
CBZ-DRESS					
Cases *vs* tolerant controls	0.05% (5/10 000)	7/10 (70%)	10/257 (3.9%)[a]	<0.001	57.6 (11.0–341)
Cases *vs* general population		7/10 (70%)	396/8862 (4.5%)[b]	<0.001	49.9 (11.6–244)
CBZ-SJS/TEN					
Cases *vs* tolerant controls	0.005% (1/20 000)	3/20 (15%)	10/257 (3.9%)[a]	NS	—
Cases *vs* general population		3/20 (15%)	396/8862 (4.5%)[b]	NS	—
Chinese					
CBZ-DRESS					
Cases *vs* tolerant controls	0.05% (5/10 000)	5/10 (50%)	3/72 (4.2%)	<0.001	23.0 (4.2–125)
Cases *vs* general population		5/10 (50%)	26/710 (3.7%)[c]	<0.001	26.3 (7.2–96.5)
CBZ-SJS/TEN					
Cases *vs* tolerant controls	0.25% (2.5/1000)	1/53 (1.9%)	3/72 (4.2%)	NS	—
Case *vs* general population		1/53 (1.9%)	26/710 (3.7%)[c]	NS	—

HLA-A*3101 is strongly associated with CBZ-DRESS, but not SJS/TEN.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

NEJM 2011

Prospective screen of HLA-B*1502 in Taiwan

➔ Recruit 4855 subjects

➔ Perform HLA-B*1502 genotyping before prescribing carbamazepine

➔ 367 (7.7%) were HLA-B*1502 carriers. Took the alternative drugs

➔ No SJS/TEN cases were found in this study.

➔ The identification of subjects carrying the HLA-B*1502 allele and the avoidance of CBZ therapy in these subjects was strongly associated with a decrease in the incidence of CBZ-induced SJS–TEN.

Taiwan National health insurance covers the expense of HLA-B*1502 test for CBZ new users. (a routine test before use of CBZ)

Genetic test report

長庚紀念醫院檢驗醫學科檢驗報告單 1 / 1 頁

姓　名：name　　病 歷 號：2752785　　性別 女　　來　源 門診

出生日期 1965/11/06　　年　齡：46　　病床：--　　檢 體 別：血液

採檢時間 2011/06/23 18:00　　採檢時間: 2011/06/23 18:00　　開單醫師/科別：張庭瑜　/ 神經內科

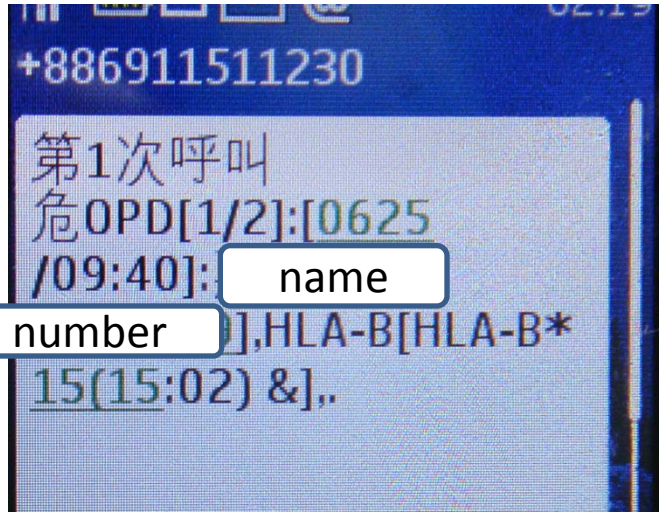
驗證時間 2011/06/29 17:30　　一日尿量:　　P/T: -　　開單日期: 20110623

檢驗組別：分生組　　收件編號：P062300191　　醫檢師/醫師: 王美惠

檢驗項目縮寫	檢驗值	單位	註記	參考值
HLA-B	HLA-B*15(15:02) & HLA-B*40(40:01)			

檢驗結果說明: Data informed ISSO PCR; HLA-B gene on chromosome 6p21.HLA-B*15:02是CBZ引起SJS/TEN的高風險基因(OR=1357)；B*58:01是allopurinol引起過敏的高風險基因(OR=394)；B*57:01是Abacavir引起過敏的高風險基因(OR=960)

Inform the doctor by cell phone texting



HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol

Shuen-Iu Hung[a,b], Wen-Hung Chung[a,b,c,d], Lieh-Bang Liou[e], Chen-Chung Chu[f], Marie Lin[f], Hsien-Ping Huang[a], Yen-Ling Lin[a], Joung-Liang Lan[g], Li-Cheng Yang[c], Hong-Shang Hong[c], Ming-Jing Chen[c], Ping-Chin Lai[h], Mai-Szu Wu[h], Chia-Yu Chu[i], Kuo-Hsien Wang[j], Chien-Hsiun Chen[a], Cathy S. J. Fann[a], Jer-Yuarn Wu[a,k], and Yuan-Tsong Chen[a,l,m]

Table 3. Frequencies of individual or combined loci of HLA-B*5801 extended haplotype in patients with allopurinol-induced SCAR, allopurinol tolerant control, and general population control

PNAS 2005

Genotype	Allopurinol-SCAR (n = 51)	Tolerant control (n = 135)	Odds ratio	Pc value*	General population control (n = 93)	Odds ratio	Pc value*
B*5801	51 (100)	20 (15)	580.3	4.7×10^{-24}	19 (20)	393.5	8.1×10^{-18}
Cw*0302	48 (94)	19 (14)	97.7	1.4×10^{-19}	19 (20)	62.3	2.5×10^{-13}
A*3303	34 (67)	24 (18)	9.3	2.2×10^{-4}	20 (22)	7.3	4.7×10^{-2}
DRB1*0301	33 (65)	17 (13)	12.7	2.8×10^{-6}	14 (15)	10.3	8.5×10^{-4}
B*5801, Cw*0302	48 (94)	19 (14)	97.7	1.4×10^{-19}	19 (20)	62.3	2.6×10^{-13}
B*5801, Cw*0302, A*3303	34 (67)	17 (13)	13.9	5.4×10^{-7}	16 (17)	9.6	1.7×10^{-3}
B*5801, Cw*0302, DRB1*0301	30 (59)	11 (8)	16.1	7.4×10^{-7}	10 (11)	11.9	7.8×10^{-4}
B*5801, Cw*0302, A*3303, DRB1*0301	21 (41)	9 (7)	9.8	0.039	9 (10)	6.5	>0.05

Numbers in parentheses indicate percentage.

*The Pc values were adjusted by using Bonferroni's correction for multiple comparisons to account for the observed alleles.

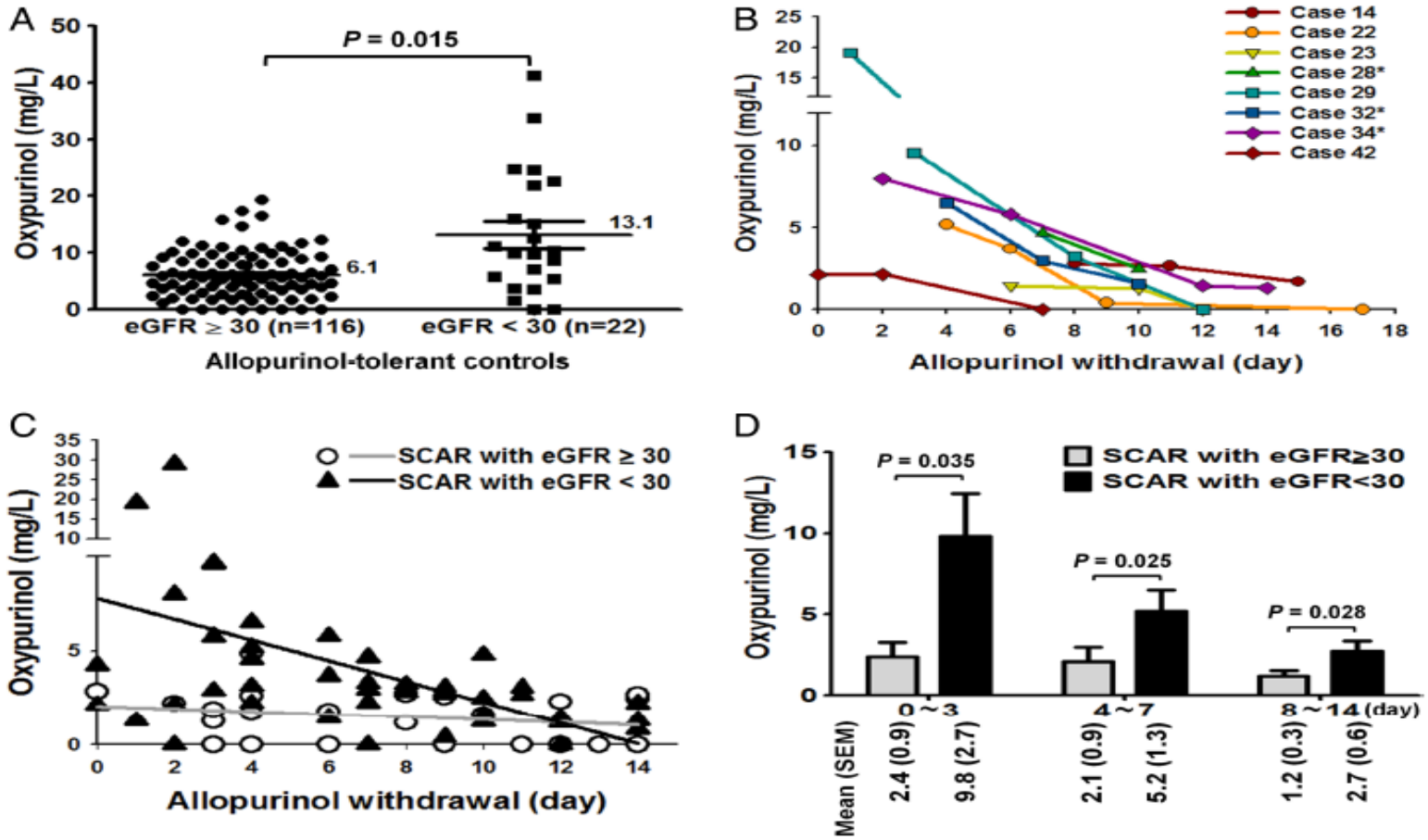
$Pc<10^{-20}$, OR: >500

Sensitivity: 100%, PPV: 3%, NPV: 100%

Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin

Wen-Hung Chung,[1,2,3] Wan-Chun Chang,[4] Sophie L Stocker,[5,6] Chiun-Gung Juo,[7] Garry G Graham,[5,6] Ming-Han H Lee,[5,6] Kenneth M Williams,[5,6] Ya-Chung Tian,[3,8] Kuo-Chang Juan,[3,8] Yeong-Jian Jan Wu,[3,9] Chih-Hsun Yang,[2,3] Chee-Jen Chang,[10,11] Yu-Jr Lin,[10,11] Richard O Day,[5,6] Shuen-Iu Hung[4]

Ann Rheum Dis 2014



HLA-B*5801 routine test for allopurinol new users with high risk(e.g., CKD).

Common risk allele in aromatic antiepileptic-drug induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese

Pharmacogenomics, 2010

Aims: Compared with other categories of drugs, such as antibiotics and NSAIDs, antiepileptic therapies are associated with a high incidence of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). We previously reported that carbamazepine (CBZ)–SJS/TEN is strongly associated with the *HLA-B*1502* in Han Chinese, which has been confirmed in other Southeast Asian countries where the allele is prevalent. Here, we extend the study of HLA susceptibility to three different antiepileptic drugs, phenytoin (PHT), lamotrigine (LTG) and oxcarbazepine (OXC), which have structure similarity to CBZ. **Materials & methods:** We carried out a case–control association study. We enrolled 26 PHT-, six LTG- and three OXC-induced SJS/TEN patients, 113 PHT-tolerant and 67 LTG-tolerant subjects who were on the drug, respectively, for more than 3 months without the adverse reactions, and 93 normal subjects from the general population. The *HLA-A*, *B*, *C* and *DRB1* genotypes were determined. **Results:** We found that *HLA-B*1502* was present in eight out of 26 (30.8%) PHT–SJS/TEN (OR: 5.1; 95% CI: 1.8–15.1; p = 0.0041), two out of six (33%) LTG–SJS (odds ratio [OR]: 5.1; 95% CI: 0.8–33.8; p = 0.1266) and three out of three (100%) OXC–SJS (OR: 80.7; 95% CI: 3.8–1714.4; $p = 8.4 \times 10^{-4}$) patients. In addition, *HLA-B*1301*, *Cw*0801* and *DRB1*1602* also showed an association with PHT–SJS/TEN (p = 0.0128–0.0281; OR: 3.0–4.3). **Conclusion:** Our results indicate that OXC, PHT and LTG, which possess an aromatic ring just as CBZ does, when causing SJS/TEN, share a common risk allele. Aromatic antiepileptic drugs causing SJS/TEN in *HLA-B*1502* carriers may act on a similar pathogenetic mechanism, although other genetic/nongenetic factor(s) may also contribute to the pathomechanism of the disease. We suggest that aromatic antiepileptic drugs, including CBZ, OXC and PHT, should be avoided in the *B*1502* carrier and caution should also be exercised for LTG.

HLA-B*15:02 is weakly associated with phenytoin-SJS/TEN.

(P=0.004, OR=5.1)

JAMA The Journal of the American Medical Association

Genetic Variants Associated With Phenytoin-Related Severe Cutaneous Adverse Reactions

Wen-Hung Chung, MD, PhD; Wan-Chun Chang, MS; Yun-Shien Lee, PhD; Ying-Ying Wu, MS; Chih-Hsun Yang, MD; Hsin-Chun Ho, MD; Ming-Jing Chen, MD; Jing-Yi Lin, MD; Rosaline Chung-Yee Hui, MD, PhD; Ji-Chen Ho, MD; Wei-Ming Wu, MD, PhD; Ting-Jui Chen, MD; Tony Wu, MD, PhD; Yih-Ru Wu, MD, PhD; Mo-Song Hsih, MD; Po-Hsun Tu, MD; Chen-Nen Chang, MD, PhD; Chien-Ning Hsu, PhD; Tsu-Lan Wu, PhD; Siew-Eng Choon, MD; Chao-Kai Hsu, MD, PhD; Der-Yuan Chen, MD, PhD; Chin-San Liu, MD, PhD; Ching-Yuang Lin, MD, PhD; Nahoko Kaniwa, PhD; Yoshiro Saito, PhD; Yukitoshi Takahashi, MD, PhD; Ryosuke Nakamura, PhD; Hiroaki Azukizawa, MD, PhD; Yongyong Shi, PhD; Tzu-Hao Wang, MD, PhD; Shiow-Shuh Chuang, MD, PhD; Shih-Feng Tsai, MD, PhD; Chee-Jen Chang, PhD; Yu-Sun Chang, PhD; Shuen-Iu Hung, PhD; for the Taiwan Severe Cutaneous Adverse Reaction Consortium and the Japan Pharmacogenomics Data Science Consortium

JAMA 2014

Study participants:

(1). Taiwanese (Taiwan SCAR consortium):

90 SCAR cases (48 SJS/TEN, 42 DRESS), 78 MPE cases

130 tolerant controls, 412 subjects from the general population

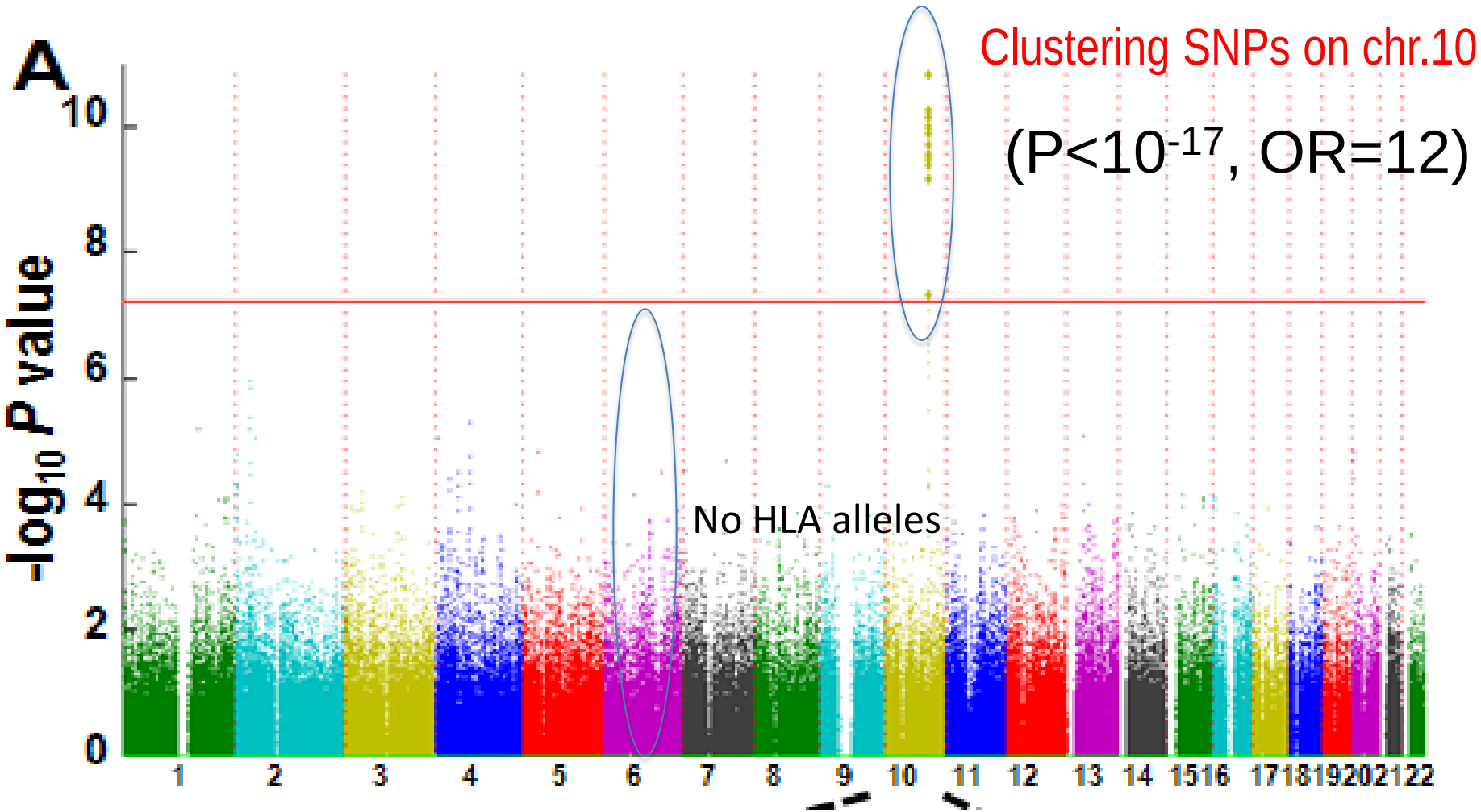
(2). Japanese (Japan Pharmacogenomics Data Science Consortium):

9 SJS/TEN, 2869 population controls

(3). Malaysia:

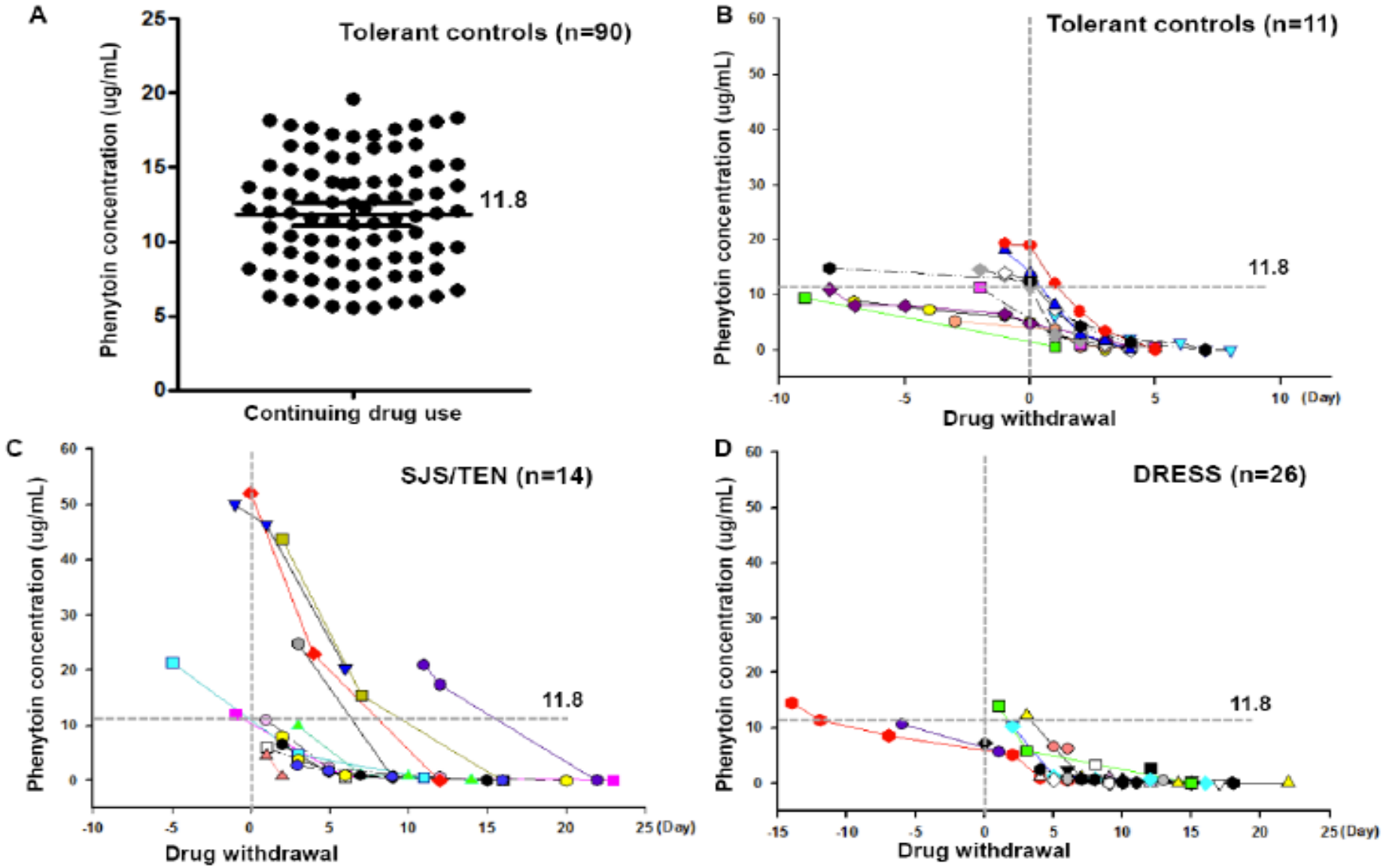
6 SJS/TEN, 374 population controls

Genome-wide association scan (GWAS):
Affymetrix SNP Array 6.0 platform (909,622 SNPs)
cases: 60 phenytoin-induced SCAR (38 SJS/TEN, 22 DRESS)
controls: 412 subjects of general population



JAMA The Journal of the American Medical Association

Delayed clearance of plasma phenytoin in SCAR patients



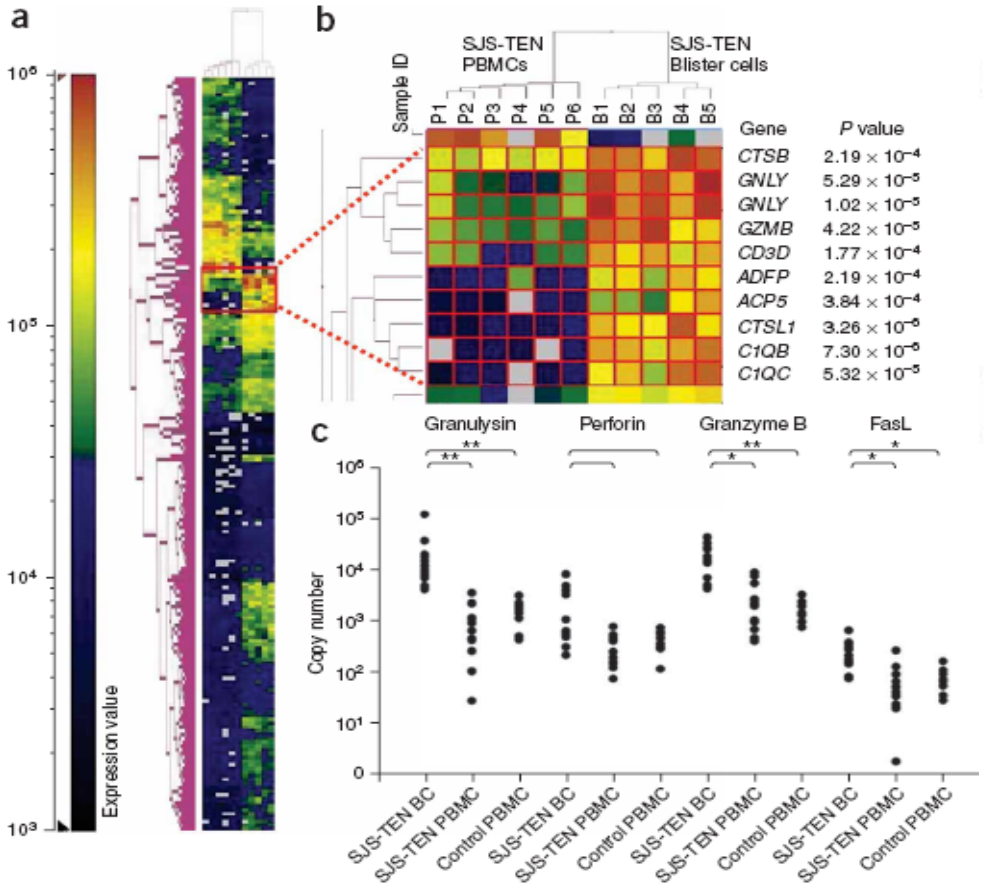
Pathomechanism of SJS/TEN??

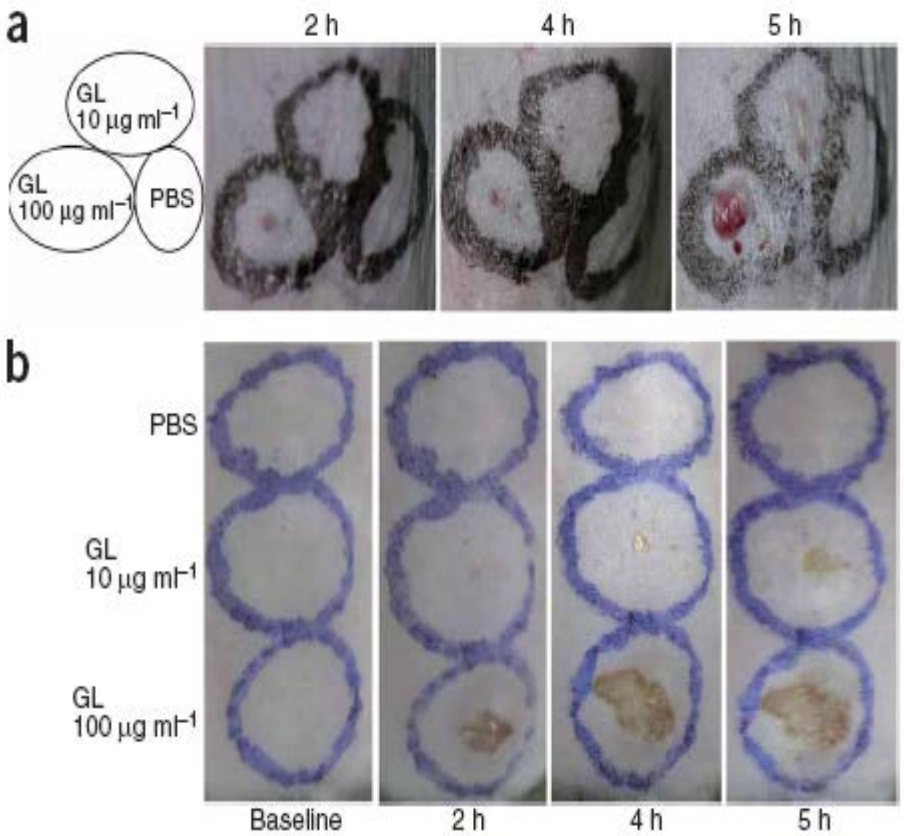
nature medicine

Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis

Nature Medicine 2008

Wen-Hung Chung[1–3,9], Shuen-Iu Hung[2,4,9], Jui-Yung Yang[5], Shih-Chi Su[2], Shien-Ping Huang[2], Chun-Yu Wei[2], See-Wen Chin[4], Chien-Chun Chiou[1], Sung-Chao Chu[6], Hsin-Chun Ho[1], Chih-Hsun Yang[1], Chi-Fang Lu[7], Jer-Yuarn Wu[2], You-Di Liao[2] & Yuan-Tsong Chen[2,8]





Biomarker/disease target:

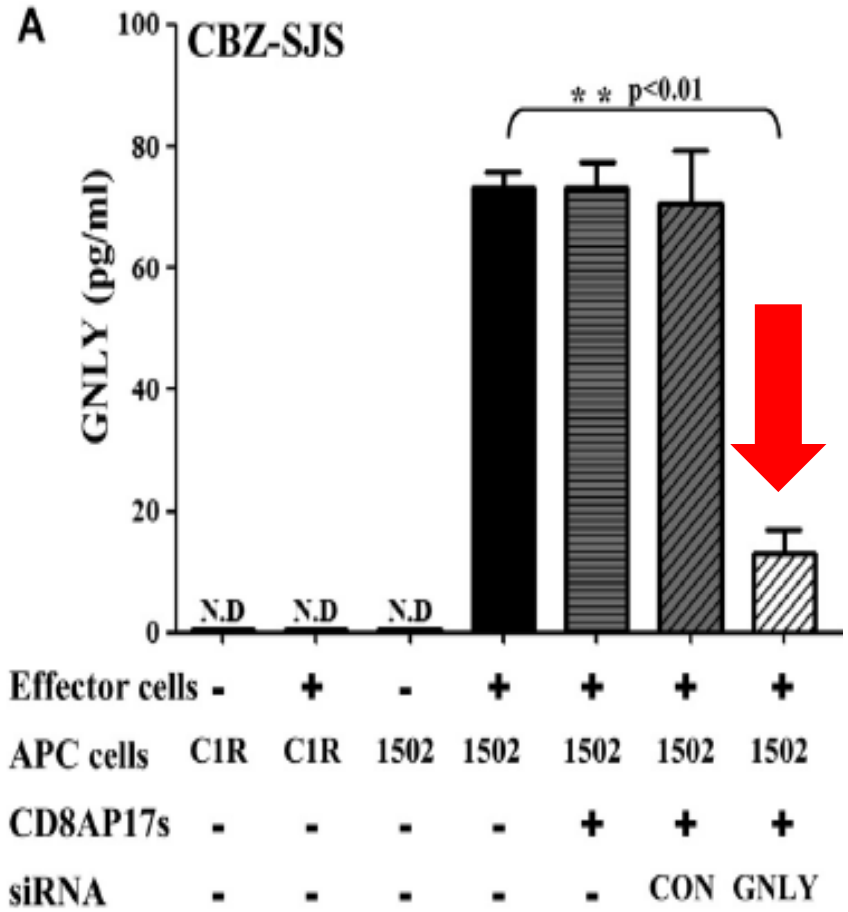
Granulysin is the key mediator of the keratinocytes death in SJS/TEN.

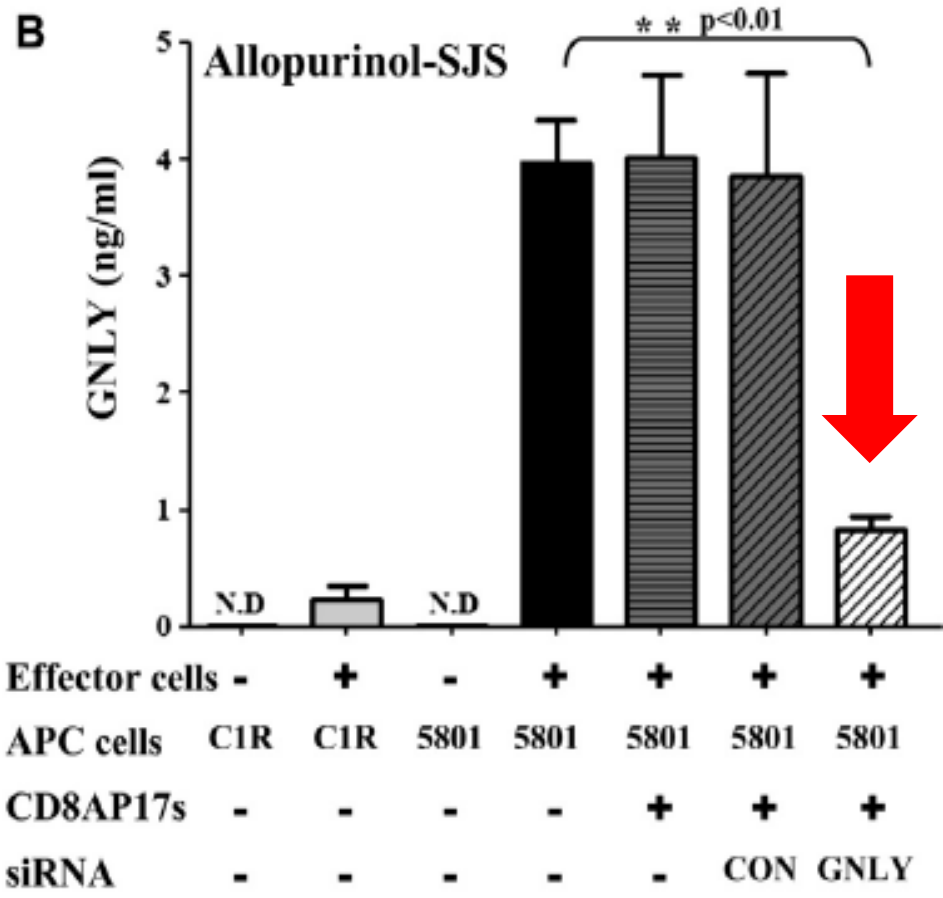
THE JOURNAL OF Allergy AND Clinical Immunology

A new nucleic acid–based agent inhibits cytotoxic T lymphocyte–mediated immune disorders

JACI 2013

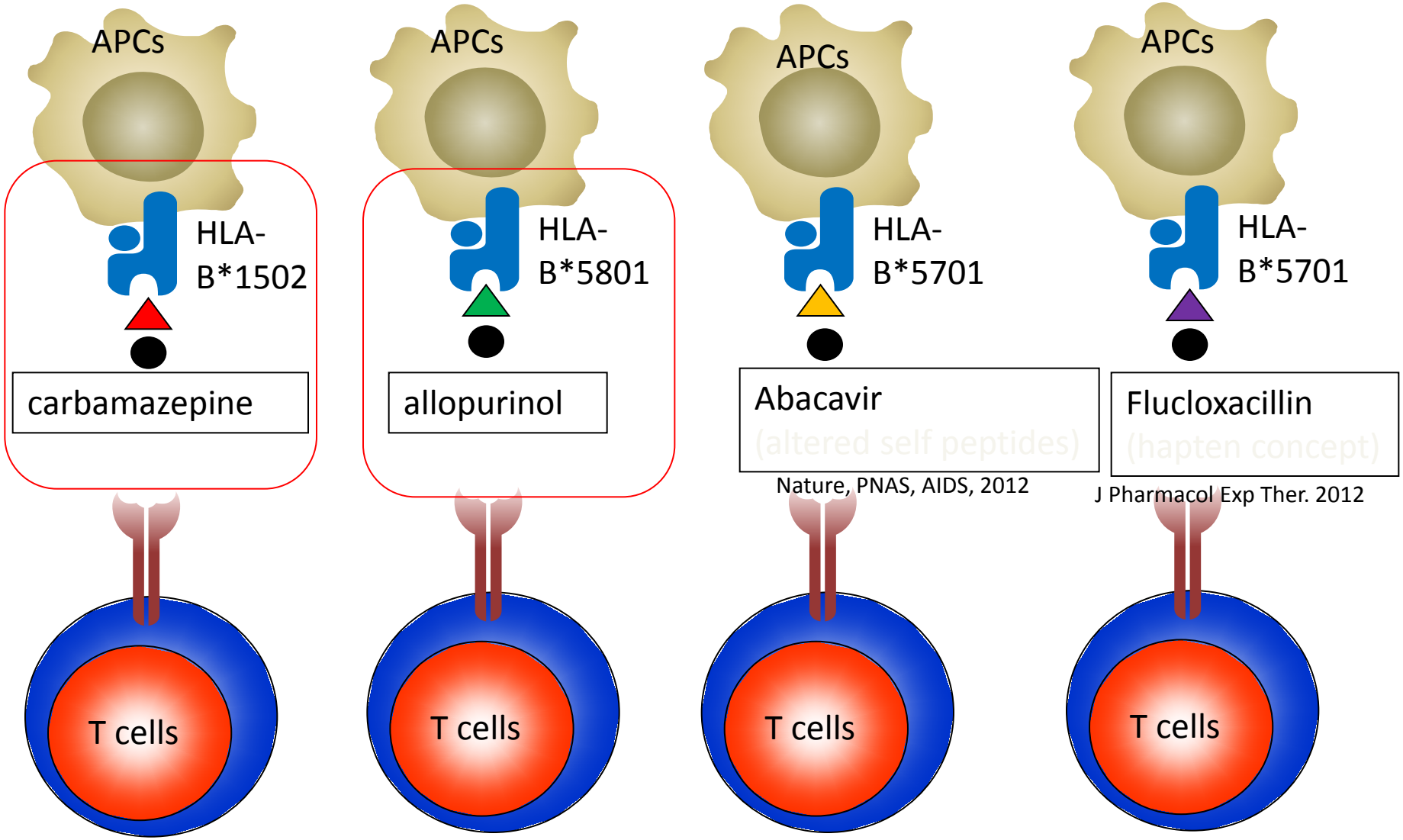
Chuang-Wei Wang, MS,[a,b] Wen-Hung Chung, MD, PhD,[c] Yi-Fang Cheng, PhD,[d] Nien-Wen Ying, MS,[d] Konan Peck, PhD,[d,†] Yuan-Tsong Chen, MD, PhD,[d] and Shuen-lu Hung, PhD[a,b] *Taipei and Taoyuan, Taiwan*





Biomarker/disease target: granulysin as the disease target of SJS/TEN

HLA/drug/peptide/TCR interaction?



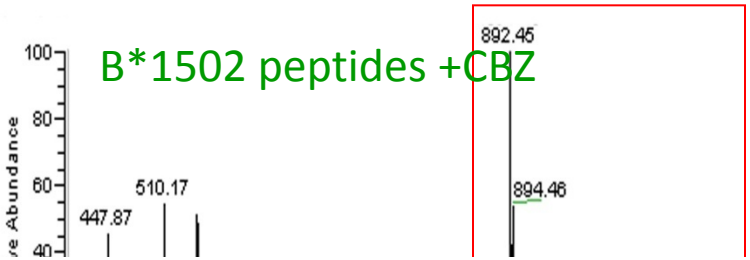
THE JOURNAL OF Allergy AND Clinical Immunology

HLA-B*1502–bound peptides: Implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome

Chih-Wen Ou Yang, MS,[a] Shuen-lu Hung, PhD,[a,b] Chiun-Gung Juo, PhD,[a] Ya-Ping Lin, MS,[a] Wu-Hsiang Fang, MS,[a] I.-Hsuan Lu, MS,[a] Shui-Tein Chen, PhD,[c] and Yuan-Tsong Chen, MD, PhD[a,d] *Taipei, Taiwan, and Durham, NC*

JACI 2007

A

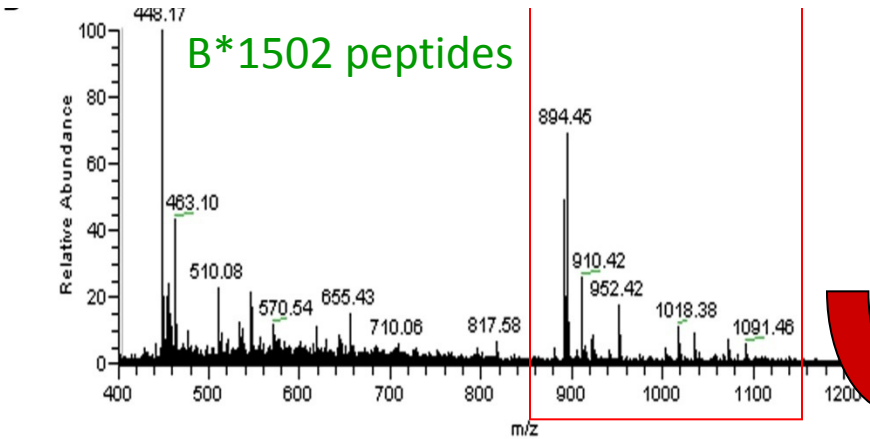


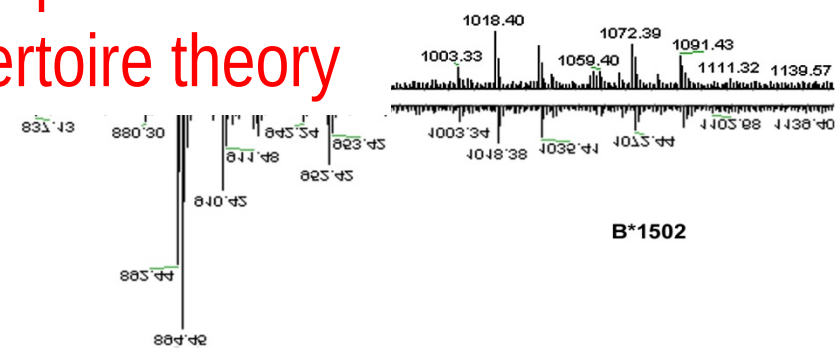
B*1502 peptides + CBZ

C

Not supporting hapten/prohapten concept

Not supporting alternative peptide repertoire theory





B*1502 peptides

Immune interaction:

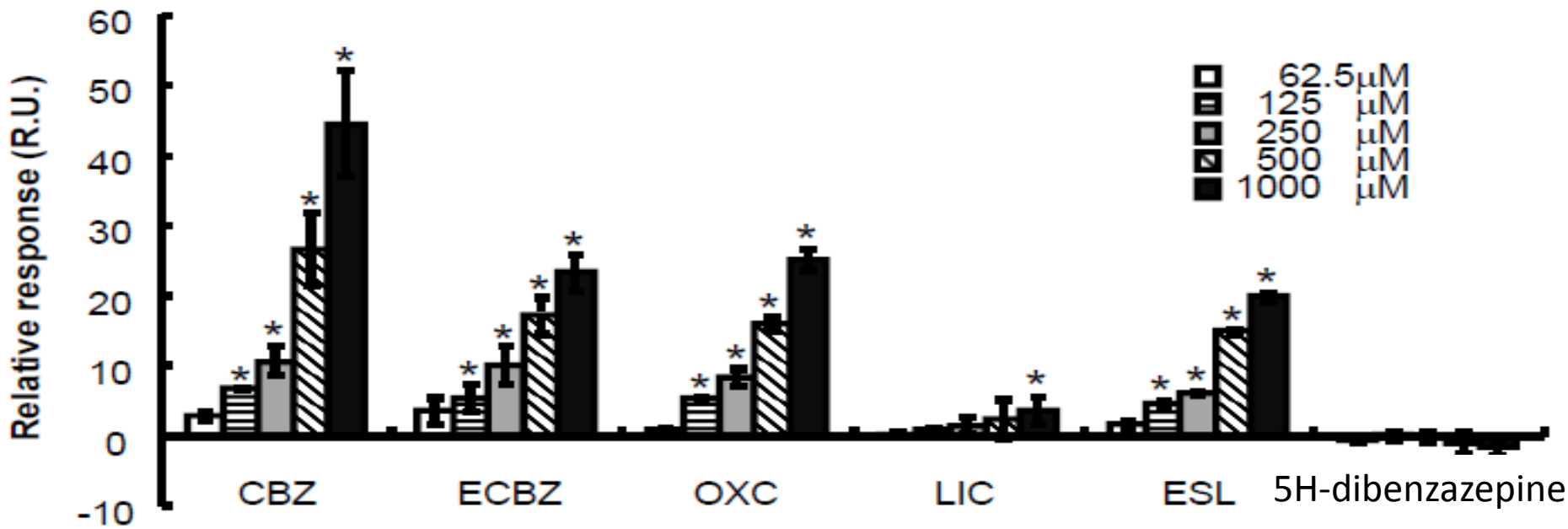
HLA-B*1502-bound peptides: no modification by carbamazepine

THE JOURNAL OF Allergy AND Clinical Immunology

Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome

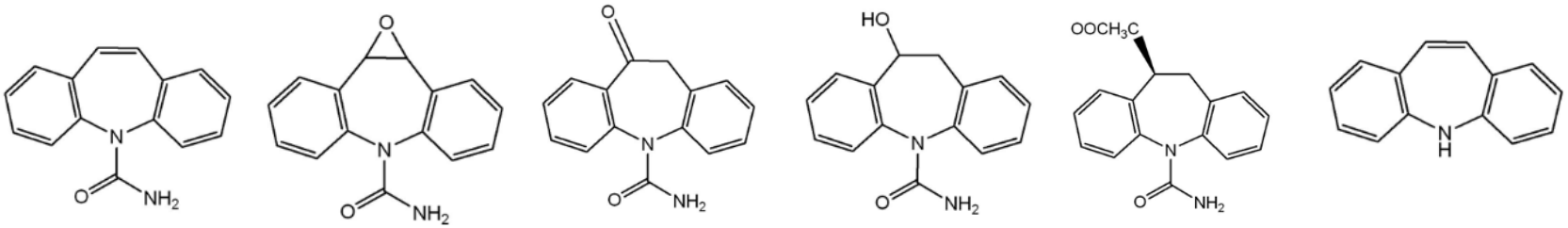
Chun-Yu Wei, MS,[a,b,c] Wen-Hung Chung, MD, PhD,[d] Hsiao-Wen Huang, MS,[b] Yuan-Tsong Chen, MD, PhD,[b*] and Shuen-lu Hung, PhD[b,e] *Taipei, Taiwan*

JACI 2012



5H-dibenzazepine

tri-cyclic ring



Not support “altered self-peptide repertoire” hypothesis.

Not support “hapten concept”.

THE JOURNAL OF Allergy AND Clinical Immunology

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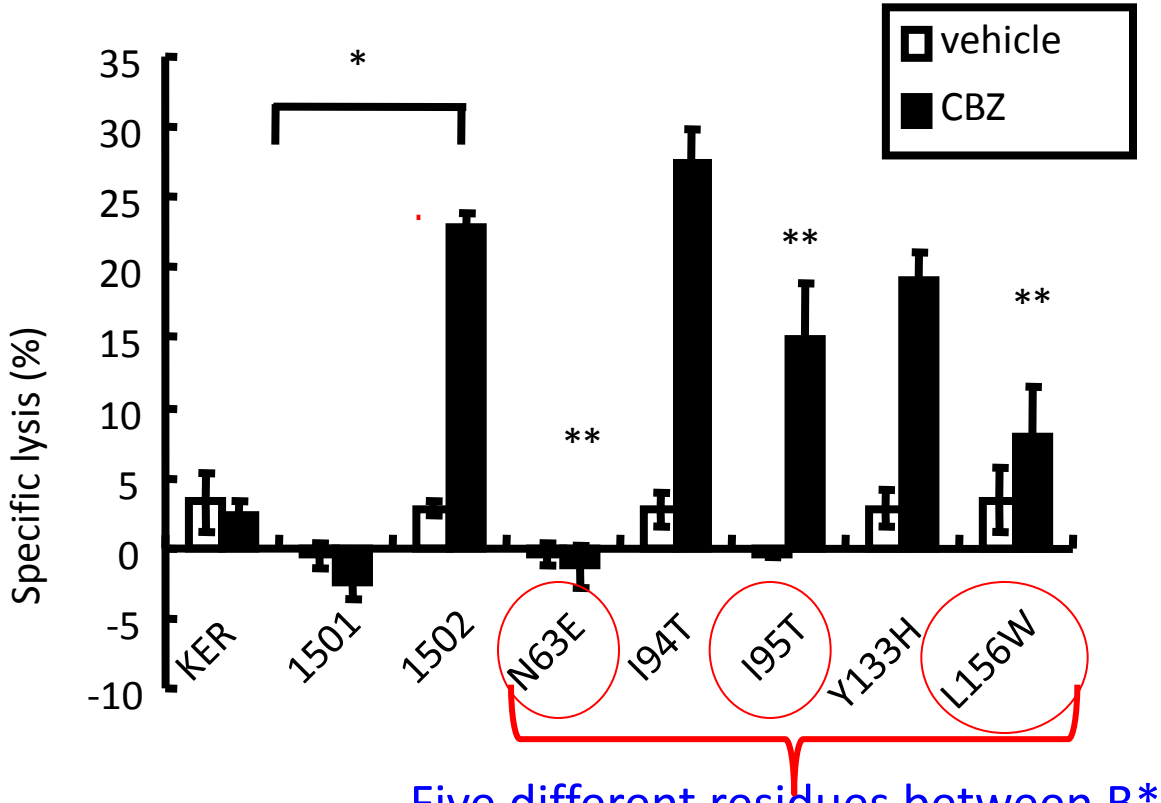
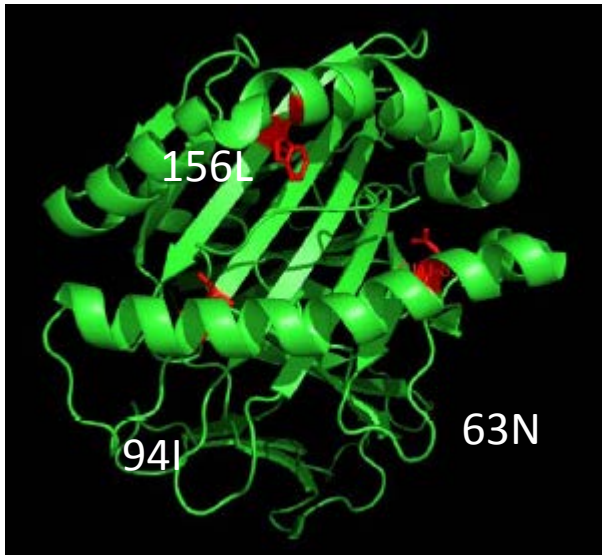
JACI 2012





Five different residues between B*1501 and B*1502

N63 (B pocket), I95, and L156 of HLA-B*1502 are involved in CBZ presentation.

THE JOURNAL OF Allergy AND Clinical Immunology

Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome

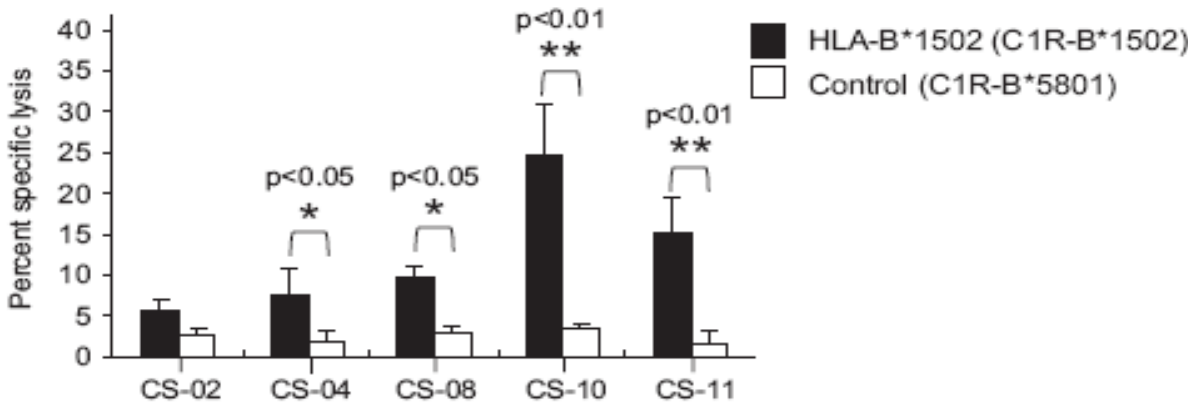
Tai-Ming Ko, MS,[a,b] Wen-Hung Chung, MD, PhD,[c] Chun-Yu Wei, MS,[b] Han-Yu Shih, MS,[a,b] Jung-Kuei Chen, MS,[b] Chia-Hsien Lin, MS,[b] Yuan-Tsong Chen, MD, PhD,[a,b] and Shuen-lu Hung, PhD[b,d,e] *Taipei, Taiwan*

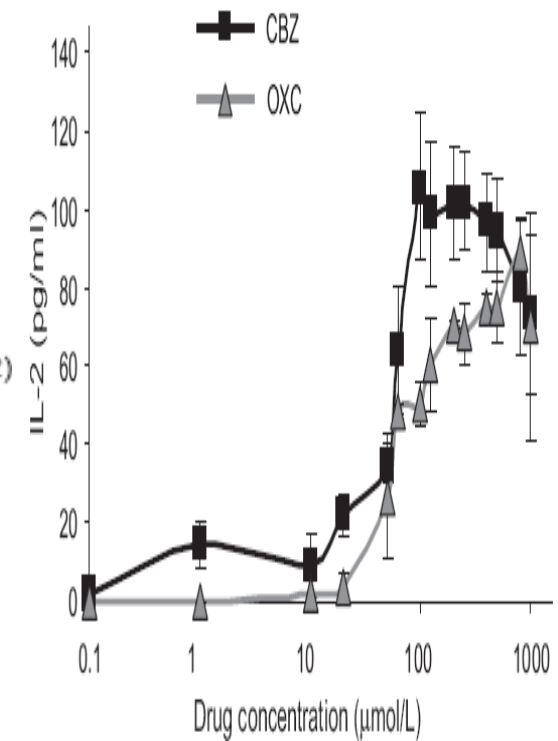
JACI 2011

A

T cell clone	VA subtype (CDR3)	VB subtype (CDR3)
CS-02	VA22(CALSEGTGGFKTIF)	VB15(CATSDWTGGNEQFF)
CS-04,12	VA3(CATSNQAGTALIF)	VB11(CASSGLAGVDNNEQFF)
CS-08	VA22(CALSDRSNTGKLIF)	VB11(CASSGTGNLDEQFF)
CS-10,13	VA22(CAFISGTYKYIF)	VB11(CASSISGSYNEQFF)
CS-11	VA22(CALSEGTGGFKTIF)	VB11(CASSISGSYNEQFF)

B





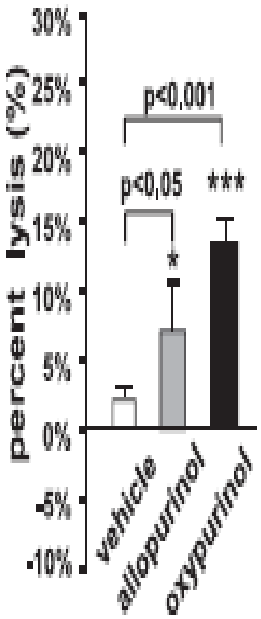
THE JOURNAL OF Allergy AND Clinical Immunology

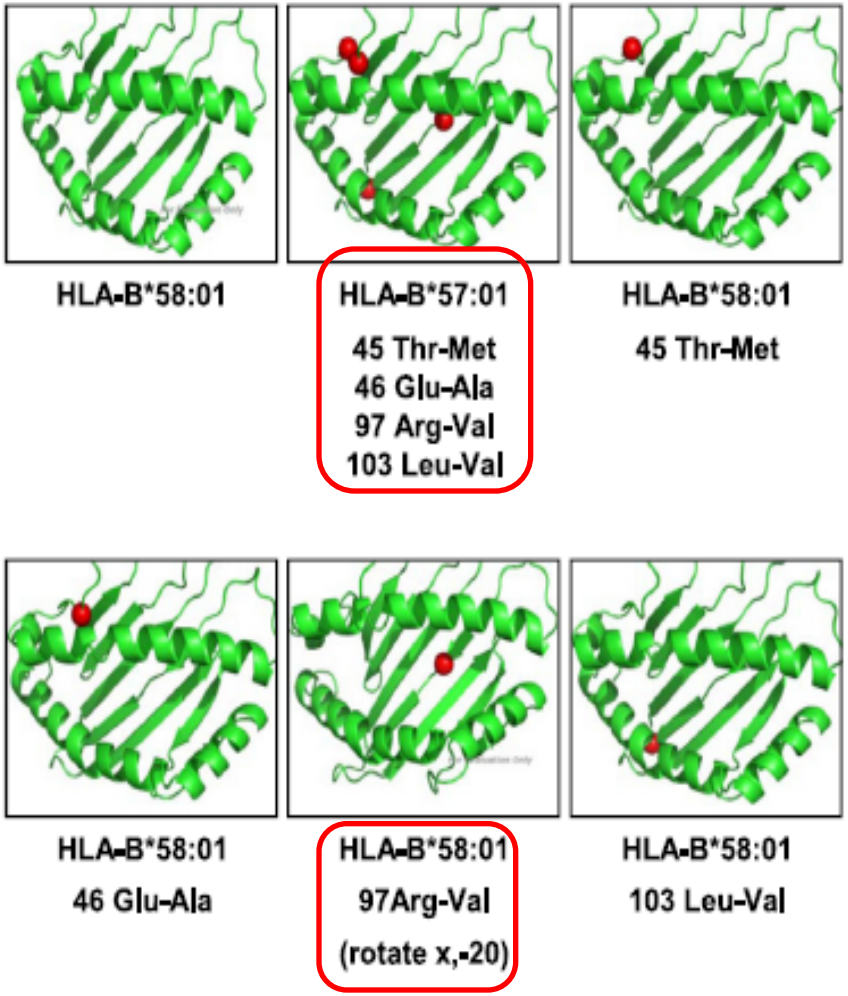
Immunologic basis for allopurinol-induced severe cutaneous adverse reactions: HLA-B*58:01-restricted activation of drug-specific T cells and molecular interaction

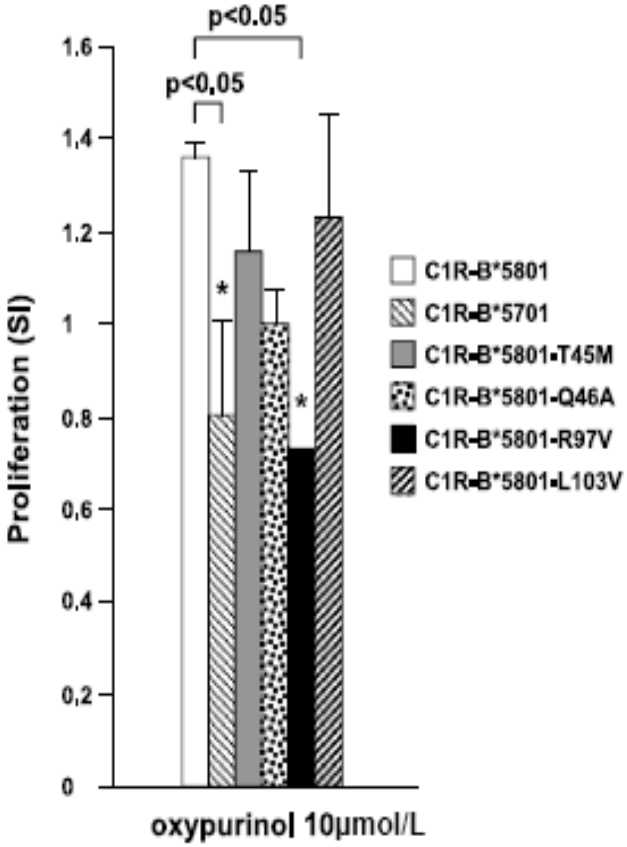
JACI 2014

C Oxypurinol-genera

Allopurinol-SCAR SJS
Patient 6







Factors contribute to SCAR

Genetic factors:
HLA-B*1502,
HLA-B*5801,
CYP2C

Pharmacy: Dose, metabolism, drug-drug interaction?

Drug concentration

Underlying diseases:

Impaired liver/renal function

Immune synapse:
HLA
TCR
Drugs

Immune-environment:
granulysin
Pathogens?
Immune memory?

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