Royal Liverpool & Broadgreen University Hospitals NHS Trust

LIVERPOOL HEALTH PARTNERS

Immunopharmacogenomics and Adverse Drug Reactions

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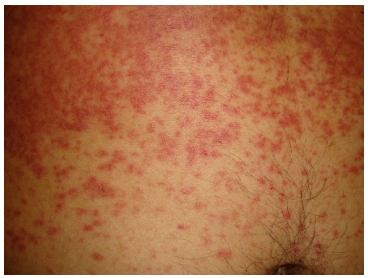
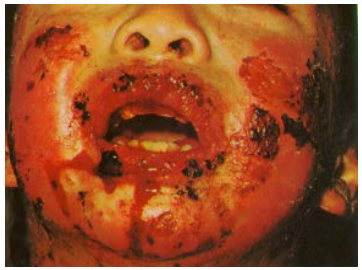
Adverse Drug Reactions: Classification

- **ON TARGET REACTIONS**
  - Predictable from the known primary or secondary pharmacology of the drug
  - Clear dose-dependence relationship within the individual



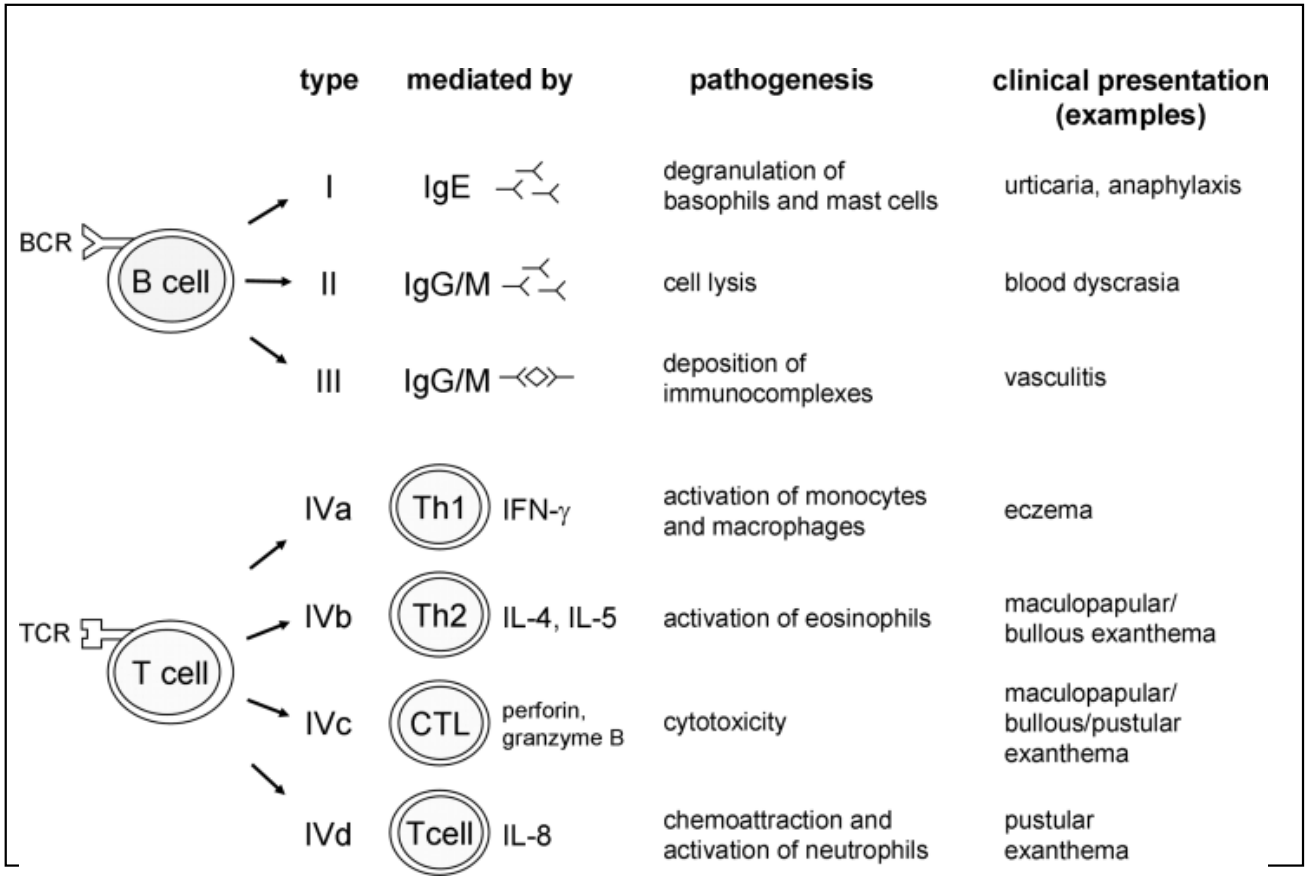


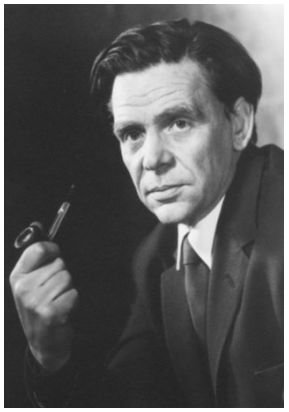
- **OFF TARGET REACTIONS**
  - Not predictable from a knowledge of the basic pharmacology of the drug and can exhibit marked inter-individual susceptibility
  - Complex dose-dependence

Hypersensitivity

an inappropriate immune response leading to tissue damage from an otherwise non-toxic agent

Immune-Mediated Adverse Drug Reactions





Philip Gell

Robin Coombs

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Cellular Pathophysiology of Drug Hypersensitivity Reactions in Skin: Characterization of T-Cell Clones

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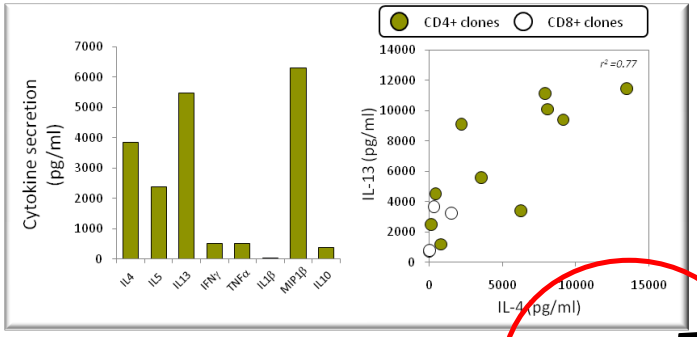
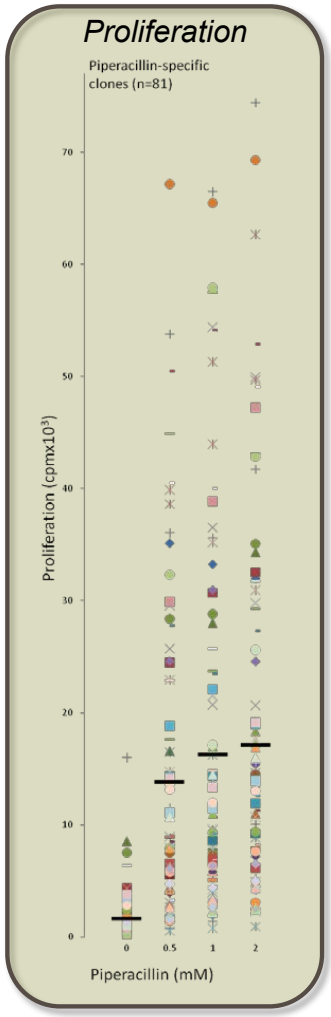


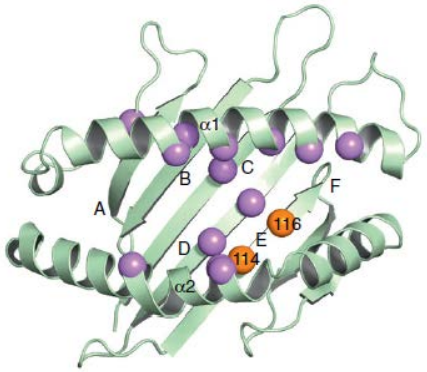


Uetrecht & Naisbitt Pharmacol Rev, 65:779-808, 2013
Pichler, Naisbitt & Park JACI, 127:74-81, 2011

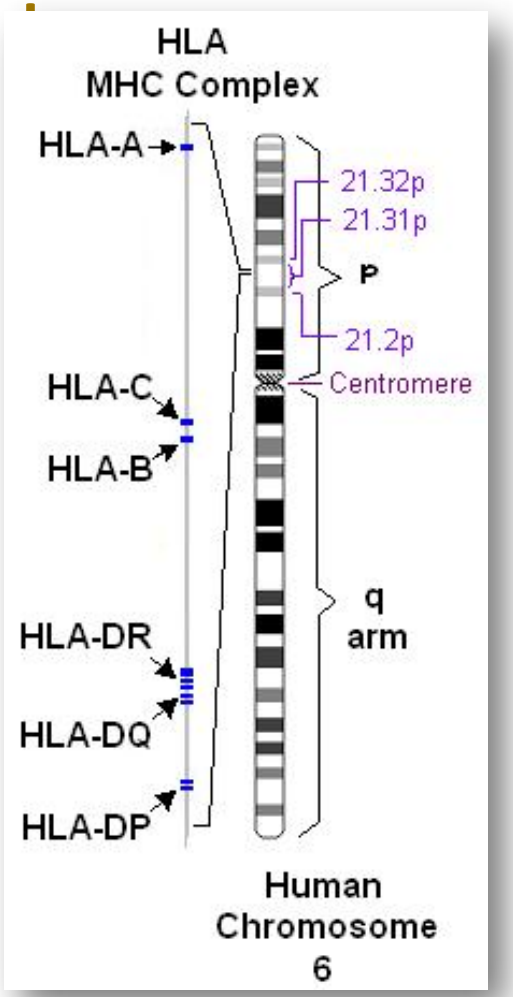
Tissue damage in skin

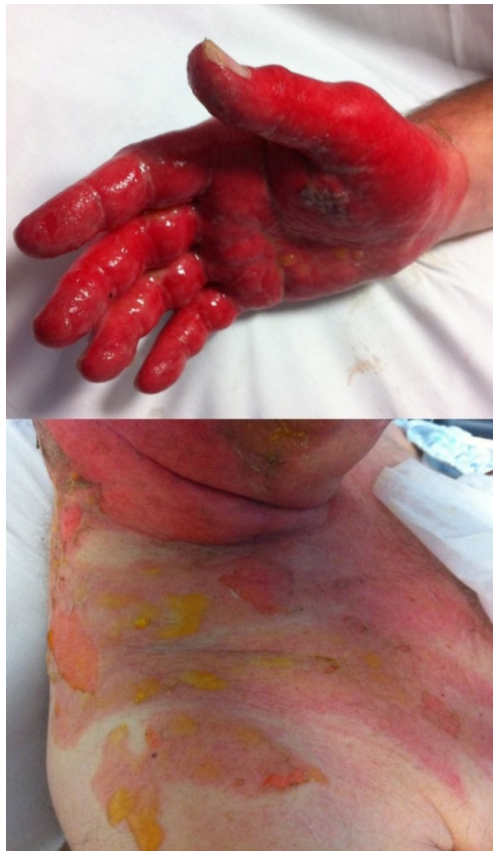
Serious Adverse Drug Reactions an
Human Leucocyte Antigens (HLA)

- On short arm of chromosome 6
- Involved in the pathogenesis of immune-mediated adverse drug reactions



Abacavir hypersensitivity
*HLA-B*57:01*
Decrease incidence from 7% to <1%





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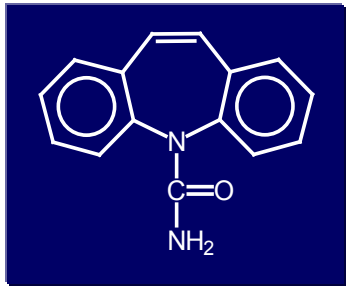
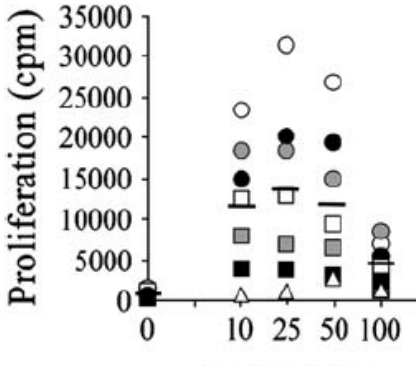
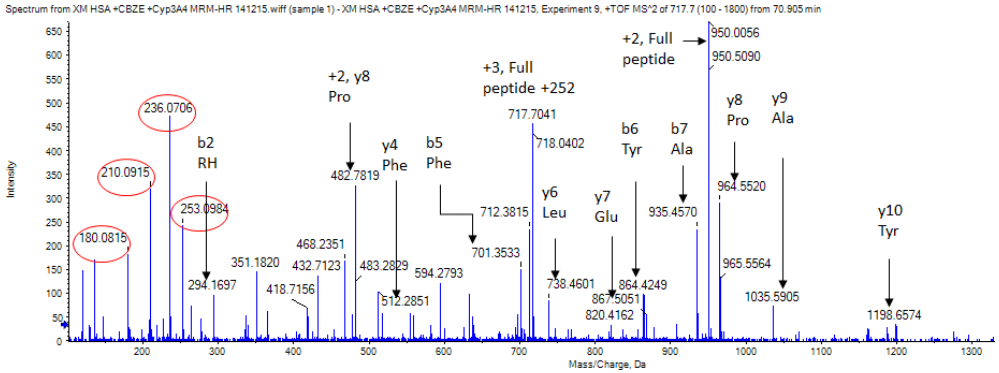
Carbamazepine Hypersensitivity

- More complicated than abacavir hypersensitivity
- Different phenotypes
  - Skin (mild → blistering)
  - Liver
  - Systemic (DRESS)
- Complex metabolism with over 30 metabolites
  - Bioactivation to toxic metabolites via different pathways
  - *In vitro* studies parent compound leads to immune reactions via several mechanisms







145RH([O]CBZ)PYFYAPELLFFAK159

Carbamazepine-modified HSA at His146

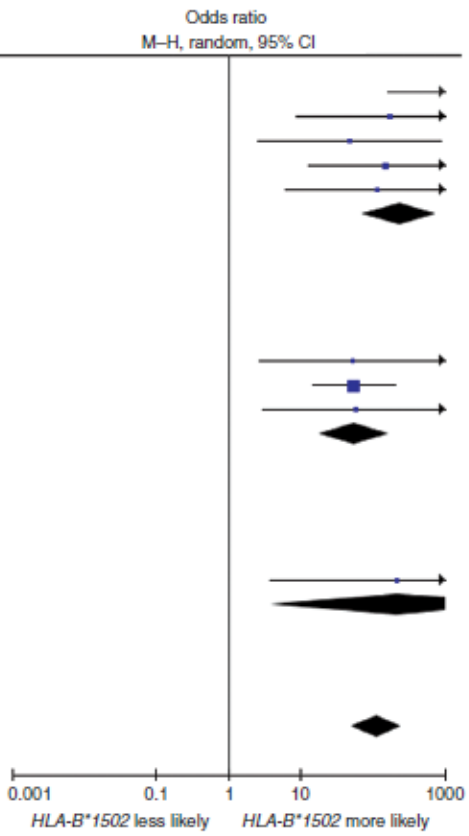
HLA Genotype and Carbamazepine-Induced Cutaneous Adverse Drug Reactions: A Systematic Review

CPT, 2012

VL Yip[1], AG Marson[2], AL Jorgensen[3], M Pirmohamed[1] and A Alfirevic[1]

HLA-B*1502

Study or subgroup	*HLA-B*1502* positive Events	Total	*HLA-B*1502* Negative Events	Total	Weight	Odds ratio M–H, random, 95% CI	Year
1.1.1 Han Chinese							
Hung 2006	59	65	1	139	13.8%	1357.00 [159.84, 11520.40]	2006
Wu 2010	8	12	0	46	7.0%	175.67 [8.64, 3570.35]	2010
Liao 2010	6	22	0	60	7.4%	47.67 [2.55, 890.45]	2010
Zhang 2011	16	18	1	20	10.2%	152.00 [12.59, 1834.92]	2010
Wang 2011	9	20	0	69	7.4%	114.83 [6.25, 2110.92]	2011
Subtotal (95% CI)		137		334	45.7%	236.24 [71.72, 778.11]	
Total events	98		2				
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 4.11$, df = 4 ($P = 0.39$); $I^2 = 3\%$							
Test for overall effect: $Z = 8.99$ ($P < 0.00001$)							
1.1.2 Thai							
Locharernkul 2008	6	14	0	34	7.1%	52.76 [2.70, 1031.31]	2008
Tassaneeyakul 2010	37	42	5	42	36.2%	54.76 [14.62, 205.13]	2010
Kulkantrakorn 2012	6	13	0	33	7.1%	58.07 [2.94, 1147.12]	2011
Subtotal (95% CI)		69		109	50.4%	54.92 [17.94, 168.14]	
Total events	49		5				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, df = 2 ($P = 1.00$); $I^2 = 0\%$							
Test for overall effect: $Z = 7.02$ ($P < 0.00001$)							
1.1.3 Malaysian							
Then 2011	6	6	0	8	3.8%	221.00 [3.85, 12694.65]	2011
Subtotal (95% CI)		6		8	3.8%	221.00 [3.85, 12694.65]	
Total events	6		0				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 2.61$ ($P = 0.009$)							
Total (95% CI)		212		451	100.0%	113.39 [51.24,250.97]	
Total events	153		7				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.43$, df = 8 ($P = 0.49$); $I^2 = 0\%$							
Test for overall effect: $Z = 11.67$ ($P < 0.00001$)							
Test for subgroup differences: $\chi^2 = 3.17$, df = 2 ($P = 0.20$); $I^2 = 36.9\%$							



The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | Keyword, Ti

ORIGINAL ARTICLE

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

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro,

N Engl J Med 2011;364:1126-33.

- To prospectively identify subjects at risk for SJS
- 4877 CBZ naive subjects from 23 hospitals
- 372 (7.7%) were HLA-B*1502 were positive – NOT given CBZ
- No patients developed SJS (compared with historical controls)

- Recommended for testing in US, European and SE Asian drug labels prior to drug prescription
- In patients of SE Asian origin
- Has reduced incidence of SJS/TEN where testing has been undertaken

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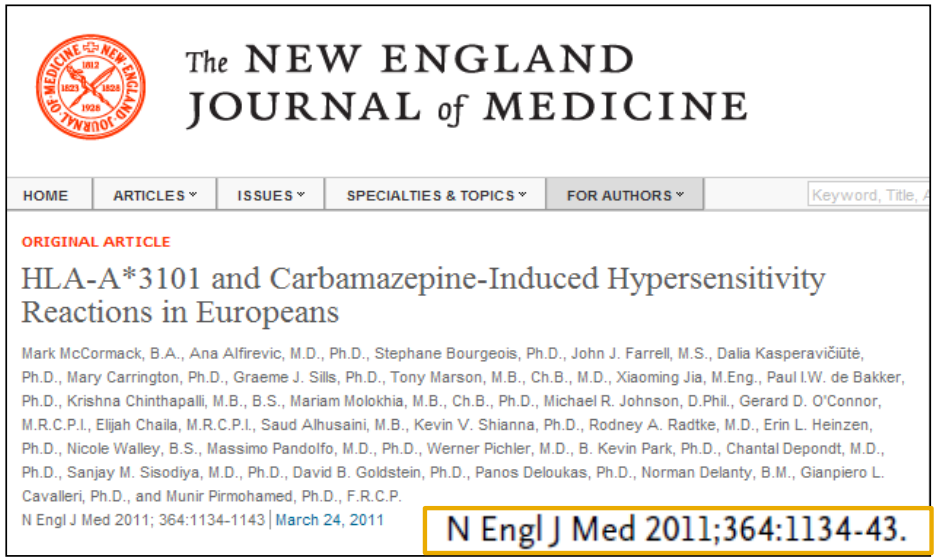

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HOME | ARTICLES | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | Keyword, Title,

ORIGINAL ARTICLE

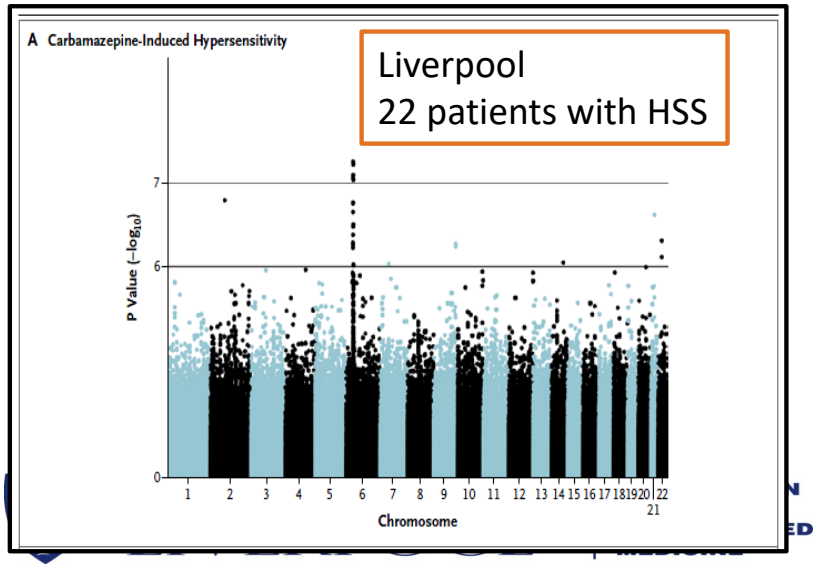
HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

Mark McCormack, B.A., Ana Alfirevic, M.D., Ph.D., Stephane Bourgeois, Ph.D., John J. Farrell, M.S., Dalia Kasperavičiūtė, Ph.D., Mary Carrington, Ph.D., Graeme J. Sills, Ph.D., Tony Marson, M.B., Ch.B., M.D., Xiaoming Jia, M.Eng., Paul I.W. de Bakker, Ph.D., Krishna Chinthapalli, M.B., B.S., Mariam Molokhia, M.B., Ch.B., Ph.D., Michael R. Johnson, D.Phil., Gerard D. O'Connor, M.R.C.P.I., Elijah Chaila, M.R.C.P.I., Saud Alhusaini, M.B., Kevin V. Shianna, Ph.D., Rodney A. Radtke, M.D., Erin L. Heinzen, Ph.D., Nicole Walley, B.S., Massimo Pandolfo, M.D., Ph.D., Werner Pichler, M.D., B. Kevin Park, Ph.D., Chantal Depondt, M.D., Ph.D., Sanjay M. Sisodiya, M.D., Ph.D., David B. Goldstein, Ph.D., Panos Deloukas, Ph.D., Norman Delanty, B.M., Gianpiero L. Cavalleri, Ph.D., and Munir Pirmohamed, Ph.D., F.R.C.P.

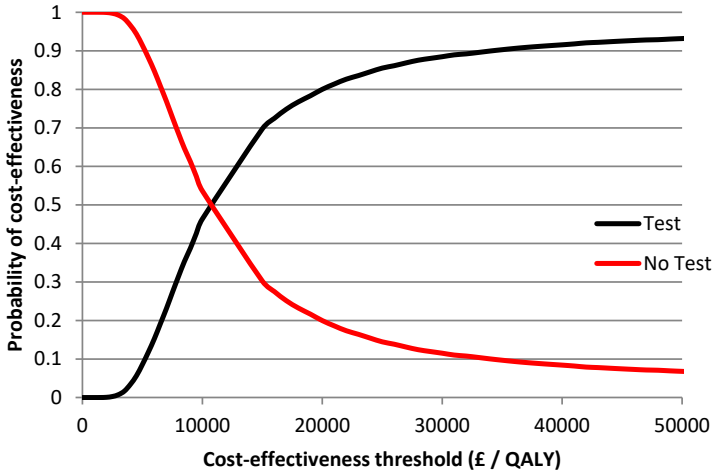
N Engl J Med 2011; 364:1134-1143 | March 24, 2011

N Engl J Med 2011;364:1134-43.

- Replicated in Japanese, Chinese, South Korean, Canadian and EU populations
- NNT = 47
- Cost-effective



Liverpool
22 patients with HSS



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JAMA Neurology | Original Investigation

Association of HLA-A*31:01 Screening With the Incidence of Carbamazepine-Induced Cutaneous Adverse Reactions in a Japanese Population

Taisei Mushiroda, PhD; Yukitoshi Takahashi, MD, PhD; Teiichi Onuma, MD, PhD; Yoshiaki Yamamoto, PhD; Tetsumasa Kamei, MD; Tohru Hoshida, MD; Katsuya Takeuchi, MD, PhD; Kotaro Otsuka, MD, PhD; Mitsutoshi Okazaki, MD, PhD; Masako Watanabe, MD, PhD; Kosuke Kanemoto, MD, PhD; Tomohiro Oshima, MD, PhD; Atsushi Watanabe, MD, PhD; Shiro Minami, MD, PhD; Kayoko Saito, MD, PhD; Hisashi Tanii, MD, PhD; Yasushi Shimo, MD, PhD; Minoru Hara, MD; Shinji Saitoh, MD, PhD; Toshihiko Kinoshita, MD, PhD; Masaki Kato, MD, PhD; Naoto Yamada, MD, PhD; Naoki Akamatsu, MD, PhD; Toshihiko Fukuchi, MD; Shigenobu Ishida, MD; Shingo Yasumoto, MD, PhD; Atsushi Takahashi, PhD; Takeshi Ozeki, PhD; Takahisa Furuta, MD, PhD; Yoshiro Saito, PhD; Nobuyuki Izumida, MEcon; Yoko Kano, MD, PhD; Tetsuo Shiohara, MD, PhD; Michiaki Kubo, MD, PhD; for the GENCAT Study Group

JAMA Neurol. doi:10.1001/jamaneurol.2018.0278
Published online April 2, 2018.

- Prospective study in 36 hospitals in 1202 patients
- HLA-A*31:01 patients given other drugs (17.5% positive)
- 23 patients (2%) had cutaneous ADRs (no patients SJS/TEN; 3 DRESS)
- Compared with historical controls, genotyping reduced the incidence of cADRs by 40-60%
- Warranted in clinical practice

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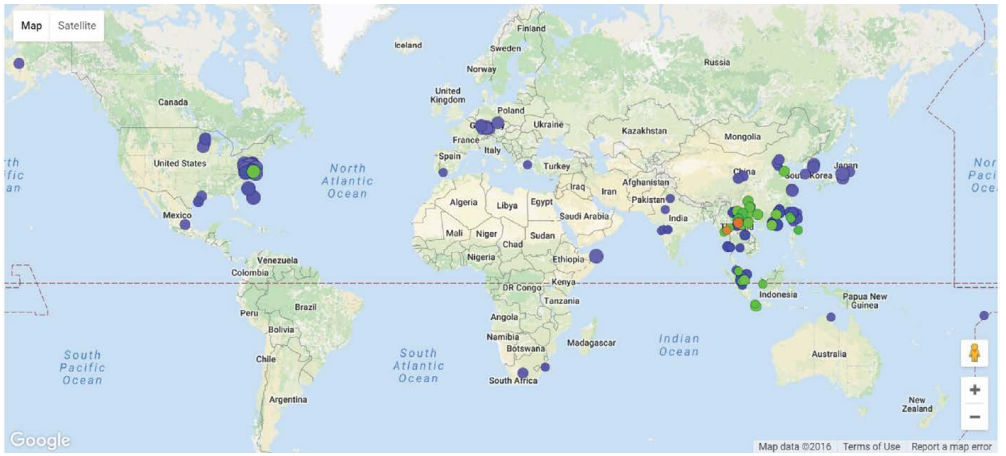
*HLA-A*31:01* and *B*15:02* Allele Frequencies

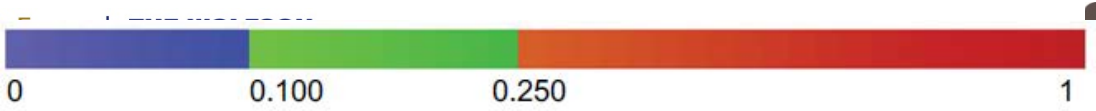
*HLA-A*31:01*

SmPC: Information only

*HLA-B*15:02*

SmPC: Mandatory





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Clinical Pharmacogenetics Implementation Consortium Guideline for *HLA* Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update

Elizabeth J. Phillips[1], Chonlaphat Sukasem[2,3], Michelle Whirl-Carrillo[4], Daniel J. Müller[5,6], Henry M. Dunnenberger[7], Wasun Chantratita[8,9], Barry Goldspiel[10], Yuan-Tsong Chen[11,12], Bruce C. Carleton[13], Alfred L. George Jr.[14], Taisei Mushiroda[15], Teri Klein[4], Roseann S. Gammal[16,17] and Munir Pirmohamed[18]

doi:10.1002/cpt.1004

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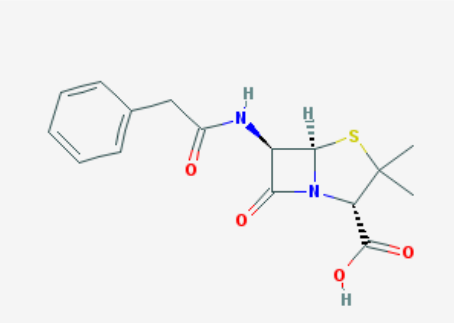
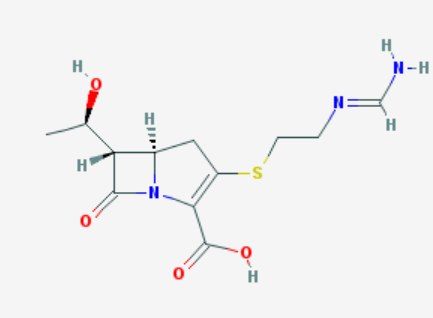
Cross-Reactivity among Beta-Lactams

Curr Allergy Asthma Rep (2016) 16: 24
DOI 10.1007/s11882-016-0594-9

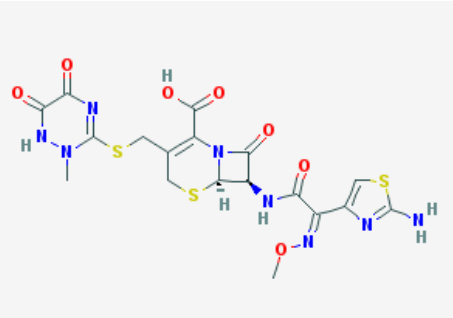
Antonino Romano[1,2] · Francesco Gaeta[1] · Maria Francisca Arribas Poves[3] · Rocco Luigi Valluzzi[1]



Benzylpenicillin

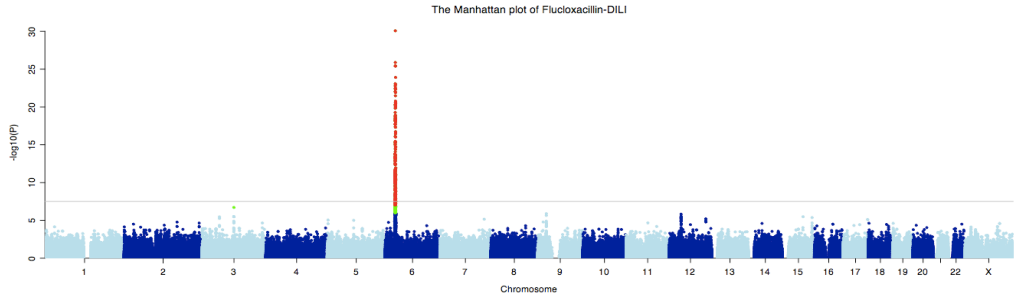


Imipenem



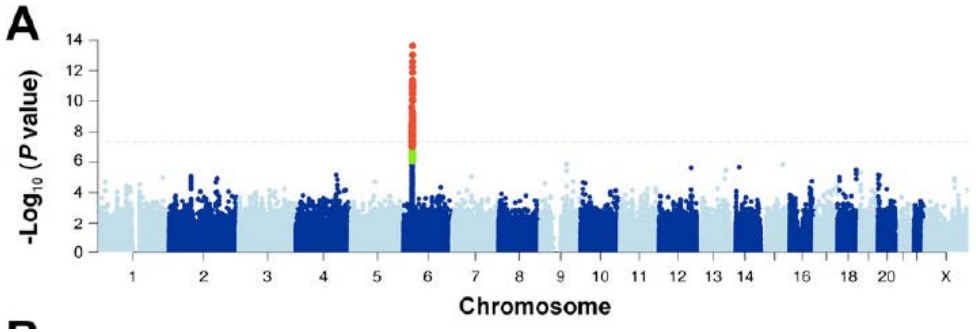
Ceftriaxone

- Cross-reactivity is related to structural similarities among their chain determinants; e.g. between penicillin and cephalosporins (30%)
- Penicillins and carbapenem/aztreonam <1%
- Cross reactivity to recognition of the beta-lactam ring – affecting all beta-lactams – is EXCEPTIONAL



FLUCLOXACILLIN HEPATITIS

*HLA-B*57:01*

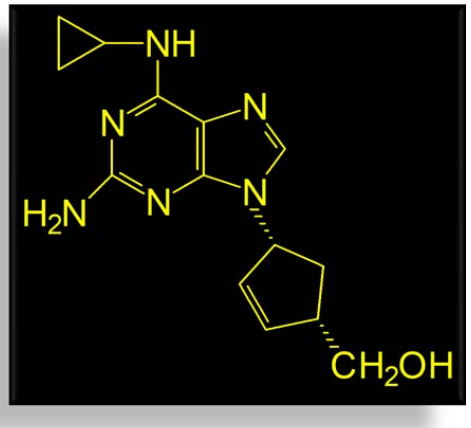


CO-AMOXICLAV HEPATITIS

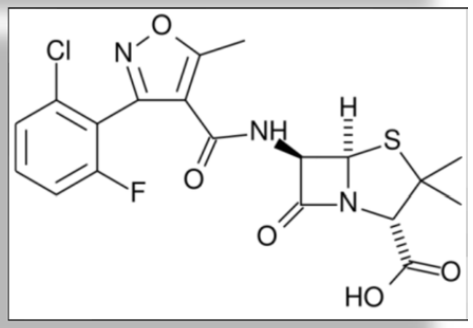
*HLA-DRB1*15:01-DQB1*06:02-HLA-A*02:01*

HLA Allele Associations

HLA-B*57:01



Abacavir

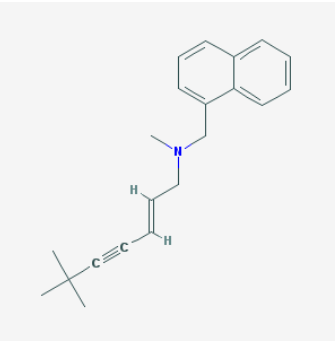


Flucloxacillin

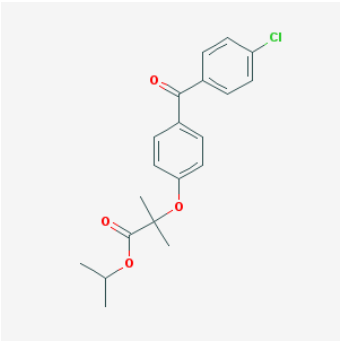
Association of Liver Injury From Specific Drugs, or Groups of Drugs, With Polymorphisms in HLA and Other Genes in a Genome-Wide Association Study

Paola Nicoletti,[1,*] **Guruprasad P. Aithal**,[2,*] Einar S. Bjornsson,[3] Raul J. Andrade,[4] Ashley Sawle,[1] Marco Arrese,[5] Huiman X. Barnhart,[6] Emmanuelle Bondon-Guitton,[7] Paul H. Hayashi,[8] Fernando Bessone,[9] Alfonso Carvajal,[10] Ingolf Cascorbi,[11] Elizabeth T. Cirulli,[6] Naga Chalasani,[12] Anita Conforti,[13] Sally A. Coulthard,[14] Mark J. Daly,[15] Christopher P. Day,[14] John F. Dillon,[16] Robert J. Fontana,[17] Jane I. Grove,[2] Pär Hallberg,[18] Nelia Hernández,[19] Luisa Ibáñez,[20] Gerd A. Kullak-Ublick,[21] Tarja Laitinen,[22] Dominique Larrey,[23] M. Isabel Lucena,[4] Anke H. Maitland-van der Zee,[24] Jennifer H. Martin,[25] Mariam Molokhia,[26] Munir Pirmohamed,[27] Elizabeth E. Powell,[28] Shengying Qin,[29] Jose Serrano,[30] Camilla Stephens,[4] Andrew Stolz,[31] Mia Wadelius,[18] Paul B. Watkins,[32] Aris Floratos,[1] Yufeng Shen,[1] Matthew R. Nelson,[33] Thomas J. Urban,[34,§] and Ann K. Daly[14,§] ; on behalf of International Drug-Induced Liver Injury Consortium, Drug-Induced Liver Injury Network Investigators, and International Serious Adverse Events Consortium

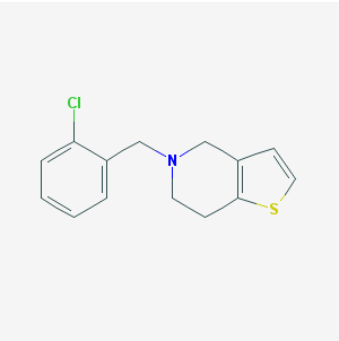
HLA-A*33:01



Terbinafine



Fenofibrate



Ticlopidine

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Development of a stepwise screening approach to assess the intrinsic immunogenicity of drugs

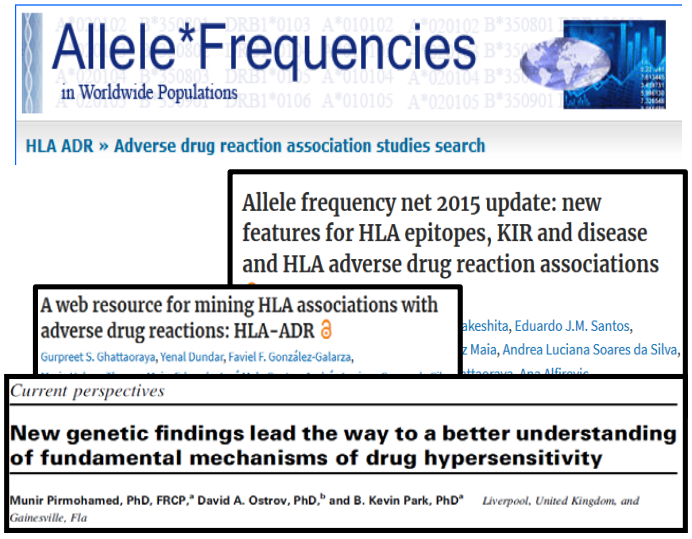
Progress and achievements

- Identification of HLA alleles as predisposing factors
- Generation of a HLA-typed cell bank of 1200 donors
- Development of methods to prime naïve T-cells to drugs
- Demonstration that immune checkpoint inhibitors negatively regulate activation of drug-specific T-cells
- Definition of relationship between HLA allele expression and development of T-cell responses

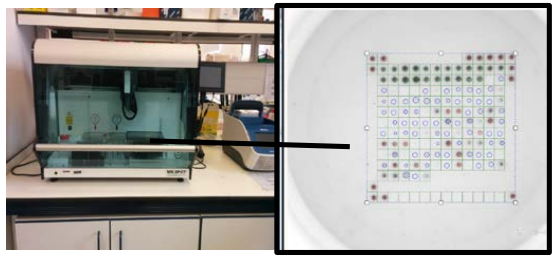
Causal HLA alleles

A*31:01 Carbamazepine	**A*33:03** Ticlopidine	**A*68:01** Lamotrigine	**A*02:06** Cold medicines
C*04:01 Nevirapine			
B*13:01 Dapsone Trichlorethylene	**B*15:02** Carbamazepine Phenytoin	**B*35:05** Nevirapine	**B*44:03** Cold Medicines
B*56:02 Phenytoin	**B*57:01** Abacavir	**B*57:01** Flucloxacillin	**B*58:01** Allopurinol
DRB1*07:01 Ximelagatran Lapatinib Asparaginase	**DRB1*11:01** Statins	**DRB1*13:02** Aspirin	**DRB1*15:01** Lumiracoxib Co-amoxiclav
DQA1*01:02 Lumiracoxib	**DQA1*02:01** Lapatinib		
DQB1*02:01 Ximelagatran Clometacin	**DQB1*05:02** Clozapine	**DQB1*06:02** Co-amoxiclav Lumiracoxib	**DQB1*06:04** Ticlopidine
DQB1*06:09 Aspirin			

Skin injury *Liver injury* *Other*



Clinical decision support system



HISTO SPOT

Development of a stepwise screening approach to assess the intrinsic immunogenicity of drugs

Progress and achievements

- Identification of HLA alleles as predisposing factors
- Generation of a HLA-typed cell bank of 1200 donors
- Development of methods to prime naïve T-cells to drugs
- Demonstration that immune checkpoint inhibitors negatively regulate activation of drug-specific T-cells
- Definition of relationship between HLA allele expression and development of T-cell responses

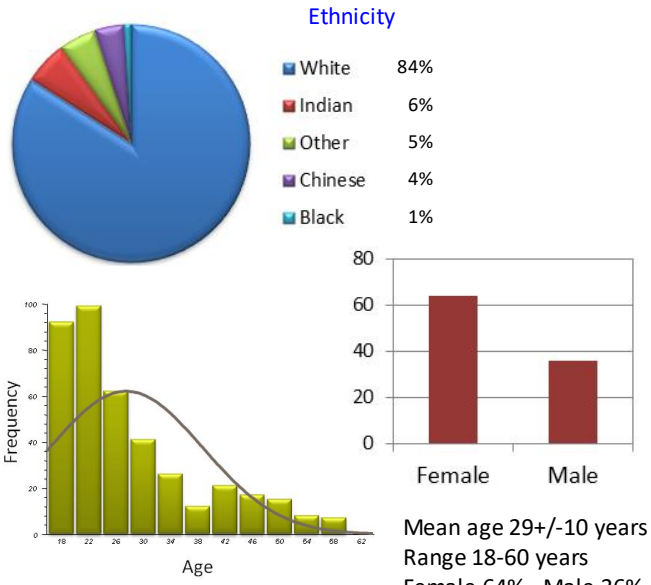
Causal HLA alleles

A*31:01 Carbamazepine	**A*33:03** Ticlopidine	**A*68:01** Lamotrigine	**A*02:06** Cold medicines
C*04:01 Nevirapine			
B*13:01 Dapsone Trichlorethylene	**B*15:02** Carbamazepine Phenytoin	**B*35:05** Nevirapine	**B*44:03** Cold Medicines
B*56:02 Phenytoin	**B*57:01** Abacavir	**B*57:01** Flucloxacillin	**B*58:01** Allopurinol
DRB1*07:01 Ximelagatran Lapatinib Asparaginase	**DRB1*11:01** Statins	**DRB1*13:02** Aspirin	**DRB1*15:01** Lumiracoxib Co-amoxiclav
DQA1*01:02 Lumiracoxib	**DQA1*02:01** Lapatinib		
DQB1*02:01 Ximelagatran Clometacin	**DQB1*05:02** Clozapine	**DQB1*06:02** Co-amoxiclav Lumiracoxib	**DQB1*06:04** Ticlopidine
DQB1*06:09 Aspirin			

Skin injury *Liver injury* *Other*

HLA-typed PBMC bank

- *1200 healthy volunteers recruited*
- *Sequence based HLA typing performed*
- *Cell archive of genotyped lymphocytes stored at -150°C*



Mean age 29+/-10 years
Range 18-60 years
Female 64% , Male 36%

Development of a stepwise screening approach to assess the intrinsic immunogenicity of drugs

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Clinical Syndromes		*Detection of T-cells*				
	HLA association	*Patient T-cells*	*Volunteer T-cells*	*HLA restriction*	*Phenotype*	*Cytotoxicity*
Abacavir hypersensitivity	HLA-B*5701	Yes	Yes	class I	CD8 only	yes
Dapsone Sulfamethoxazole Skin reactions	HLA-B*1301 none	Yes Yes	Yes Yes	? class II	CD4>CD8 CD4>CD8	? yes
Carbamazepine Skin reactions	HLA-B*1502 HLA-A*3101	Yes	Yes	class I	CD8 >CD4	yes
Allopurinol Skin reactions	HLA-B*5801	Yes	Yes	class I	CD8 >CD4	yes
Flucloxacillin DILI	HLA-B*5701	Yes	Yes	class I	CD8 >CD4	yes
Amoxicillin/ clavulanic acid DILI	HLA-A*0201 HLA-DRB1*1501	Yes	Yes	class II	CD4>CD8	yes
Ticlopidine DILI	HLA-DRB1*3303	No	Yes	class I	CD8>CD4	yes
Ximelagatran Lapatinib DILI	HLA-DRB1*0701 HLA-BQA1*0201	Unknown Unknown	No No	? ?	? ?	? ?

Associations of Serious Adverse Drug Reactions with HLA Alleles

Prospective studies have shown that HLA genotyping can reduce the incidence of serious ADRs with

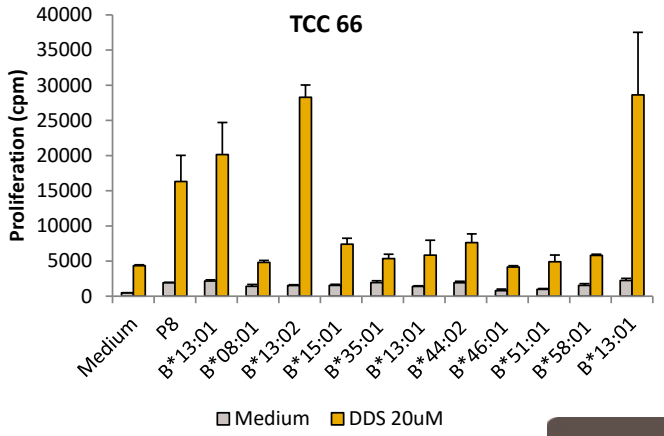
- Abacavir (*HLA-B*57:01*)
- Carbamazepine (*HLA-B*15:02* and *HLA-A*31:01*)
- Allopurinol (*HLA-B*58:01*)
- Dapsone (*HLA-B*13:01*)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

*HLA-B*13:01* and the Dapsone Hypersensitivity Syndrome

F.-R. Zhang, H. Liu, A. Irwanto, X.-A. Fu, Y. Li, G.-Q. Yu, Y.-X. Yu, M.-F. Chen, H.-Q. Low, J.-H. Li, F.-F. Bao, J.-N. Foo, J.-X. Bei, X.-M. Jia, J. Liu, H. Liany, N. Wang, G.-Y. Niu, Z.-Z. Wang, B.-Q. Shi, H.-Q. Tian, H.-X. Liu, S.-S. Ma, Y. Zhou, J.-B. You, Q. Yang, C. Wang, T.-S. Chu, D.-C. Liu, X.-L. Yu, Y.-H. Sun, Y. Ning, Z.-H. Wei, S.-L. Chen, X.-C. Chen, Z.-X. Zhang, Y.-X. Liu, S.L. Pulit, W.-B. Wu, Z.-Y. Zheng, R.-D. Yang, H. Long, Z.-S. Liu, J.-Q. Wang, M. Li, L.-H. Zhang, H. Wang, L.-M. Wang, P. Xiao, J.-L. Li, Z.-M. Huang, J.-X. Huang, Z. Li, J. Liu, L. Xiong, J. Yang, X.-D. Wang, D.-B. Yu, X.-M. Lu, G.-Z. Zhou, L.-B. Yan, J.-P. Shen, G.-C. Zhang, Y.-X. Zeng, P.I.W. de Bakker, S.-M. Chen, and J.-J. Liu



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HLA Associations with Serious Adverse Drug Reactions

A*31:01 Carbamazepine	**A*33:03** Ticlopidine	**A*68:01** Lamotrigine	**A*02:06** Cold medicines	**B*13:01** Dapsone Trichlorethylene	**B*15:02** Carbamazepine Phenytoin
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C*08:(01) Nevirapine	**DRB1*07:01** Ximelagatran Lapatinib Asparaginase	**DRB1*11:01** Statins	**DRB1*13:02** Aspirin	**DRB1*15:01** Lumiracoxib Co-amoxiclav	**DQA1*01:02** Lumiracoxib
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HLA Panel Analytic Validation

- Platform was able to call risk alleles with 100% accuracy at all the loci (n=187 healthy volunteers) using sequence based typing as the standard

Number of Risk Alleles per sample	Number of Samples	% of samples
0	28	15.0
1	39	20.9
2	14	7.5
3	46	24.6
4	34	18.2
5	11	5.9
6	6	3.2
7	8	4.3
8	1	0.5

85% have at least 1 risk allele

Use
- At time needed
- Store data on EHR
- Pre-emptive genotype
- 48 HOUR TURN-AROUND TIME

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Funded by NIHR

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Clinical Decision Support

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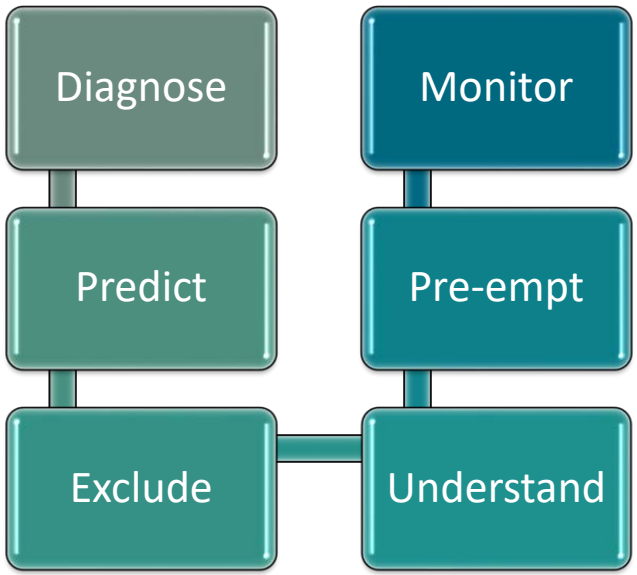
Special Issue: Precision Medicine

Review

Genomics of Adverse Drug Reactions

Ana Alfirevic[1] and Munir Pirmohamed[1,*]

Trends in Pharmacological Sciences, January 2017, Vol. 38, No. 1



Genomic testing can be used for more than prediction

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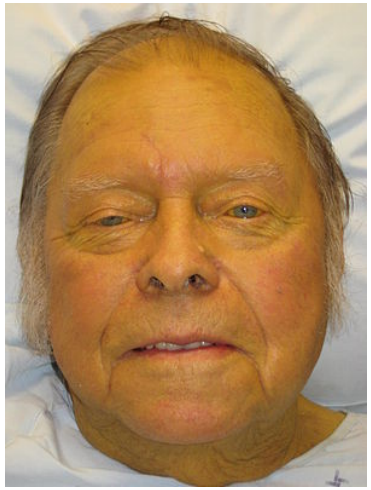
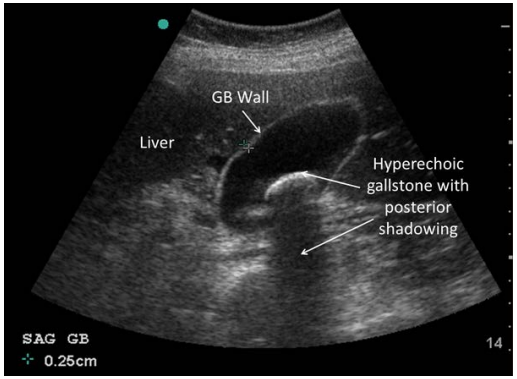
Example of the Use for Diagnosis



- 66 year old man
- Presents with Jaundice
- Patient on flucloxacillin for cellulitis
- Ultrasound – gallstones

- What is the diagnosis?



- HLA-B*57:01 strong association with flucloxacillin hepatitis
- 100% negative predictive value
- Patient was negative for HLA-B*57:01
- Treatment – cholecystectomy
- Not allergic to flucloxacillin – GP informed. Important as patient with history of recurrent cellulitis.

Conclusion

Drug →  → Hypersensitivity Reaction

Variant and Invariant factors
Genetic and Environmental factors

- We do not understand the whole pathway of drug hypersensitivity
- All of us can form drug antigens and can have susceptible HLA alleles, but still not get the hypersensitivity reaction
- Other factors including loss of tolerance may be important
- Important to understand this to develop better diagnostic and predictive tests and improve drug development

Acknowledgements

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- Stephane Bourgeois
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- Paola Nicoletti (ITCH)
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- **MRC, WT, DH, NIHR, EU-FP7**

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