

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Munir Pirmohamed

NHS Chair of Pharmacogenetics

David Weatherall Chair of Medicine

Department of Molecular and Clinical Pharmacology

Institute of Translational Medicine

University of Liverpool



UNIVERSITY OF
LIVERPOOL

THE WOLFSON
CENTRE FOR
PERSONALISED
MEDICINE

MRC

Centre for
Drug Safety Science

MRC Centre for Drug Safety Science: Mission

To use the critical mass and knowledge in drug safety science that we have now accrued within the Centre:

- *to undertake **leading edge science**, and **train** the next generation of drug safety scientists*
- *to understand the fundamental **mechanisms** of **clinically important**, and **currently relevant**, adverse drug reactions*
- *to develop strategies to **improve the benefit-risk ratio** of current and new medicines, for the benefit of patients, industry and regulators.*



iSAEC's Mission



“The iSAEC will identify DNA variants useful in understanding the risk of drug induced serious adverse events.”

Serious cutaneous adverse reactions

Drug-Induced Liver Injury

QT prolongation-torsades de pointes

Osteonecrosis of the Jaw

Drug-induced renal injury

Antipsychotic-induced weight gain



UNIVERSITY OF
LIVERPOOL

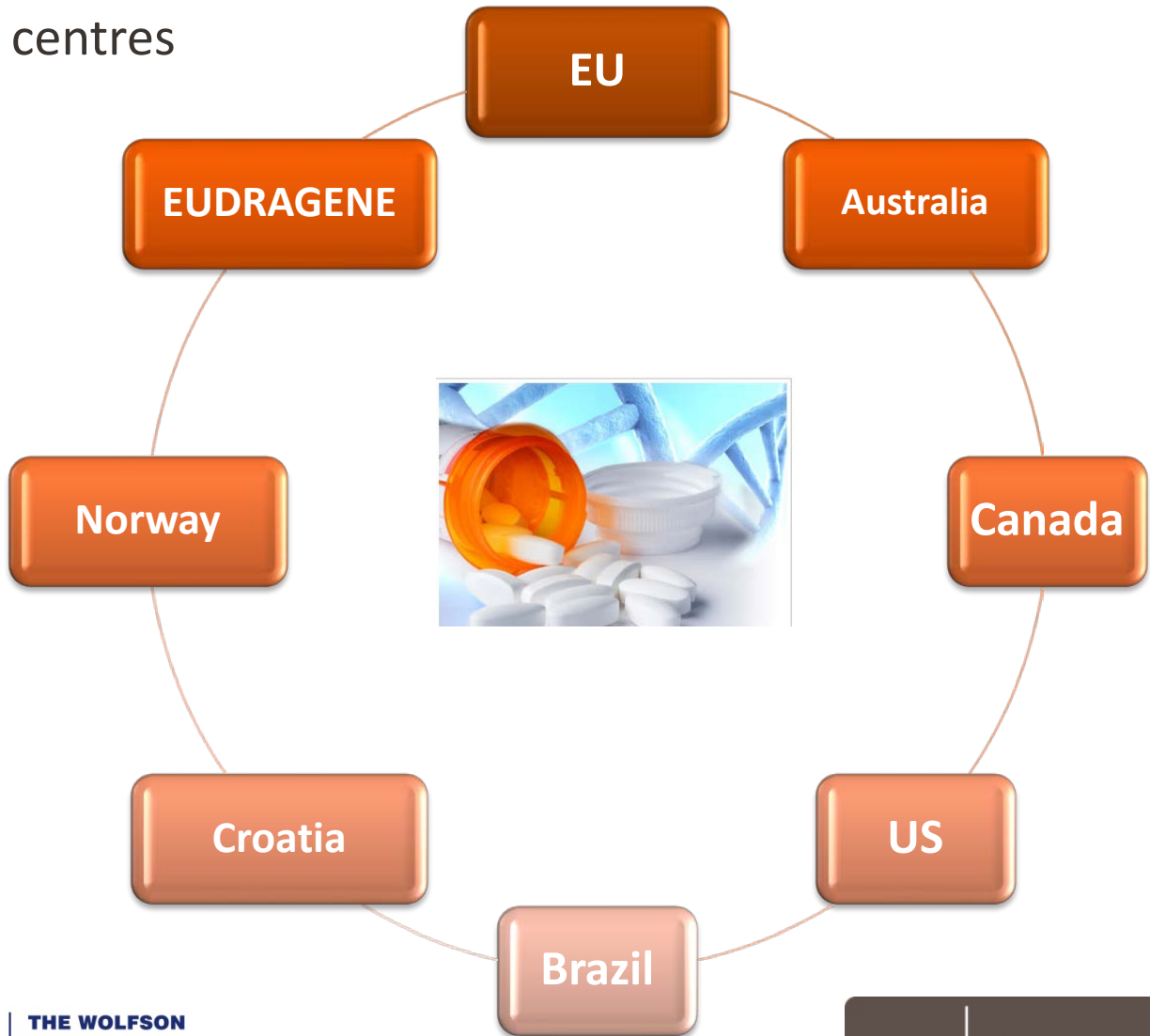
THE WOLFSON
CENTRE FOR
PERSONALISED
MEDICINE

MRC

Centre for
Drug Safety Science

InTernational Consortium on Drug Hypersensitivity (ITCH)

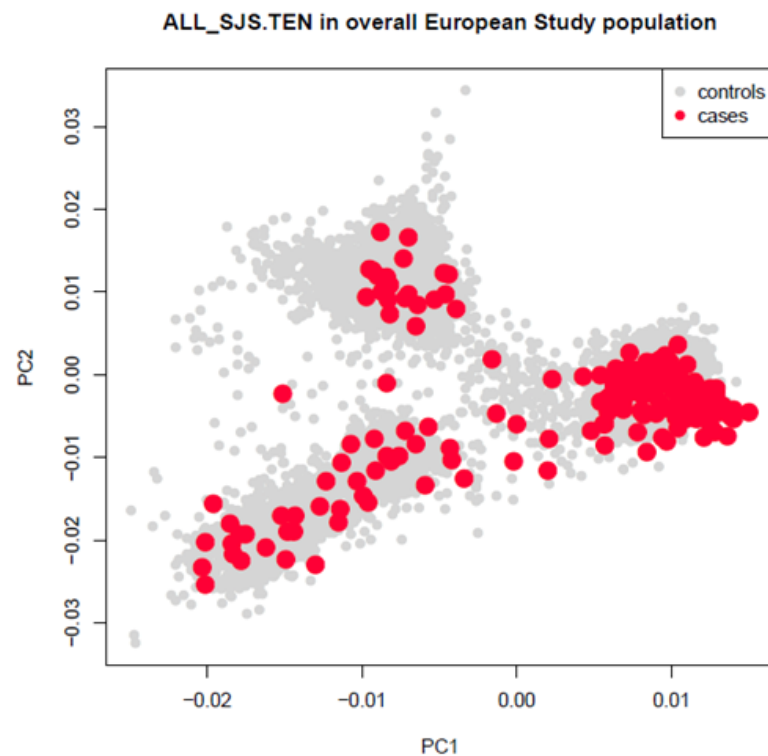
- 12 international centres
- 50 UK centres
- 1500 patients



Sponsored by the International Serious Adverse Event Consortium (iSAEC)

SJS/TEN Patients

DRUGS	SJS/TEN
ALLOPURINOL	10
AMOXICILLIN	16
AMOXICILLIN/CLAVULANIC ACID	5
AMPICILLIN	2
BACAMPICILLIN	1
CARBAMAZEPINE	33
LAMOTRIGINE	18
OTHERS	100
PHENYTOIN	11
SULFASALAZINE	6
TRIMETHOPRIM/SULFAMETHOXAZOLE	26
Total	227

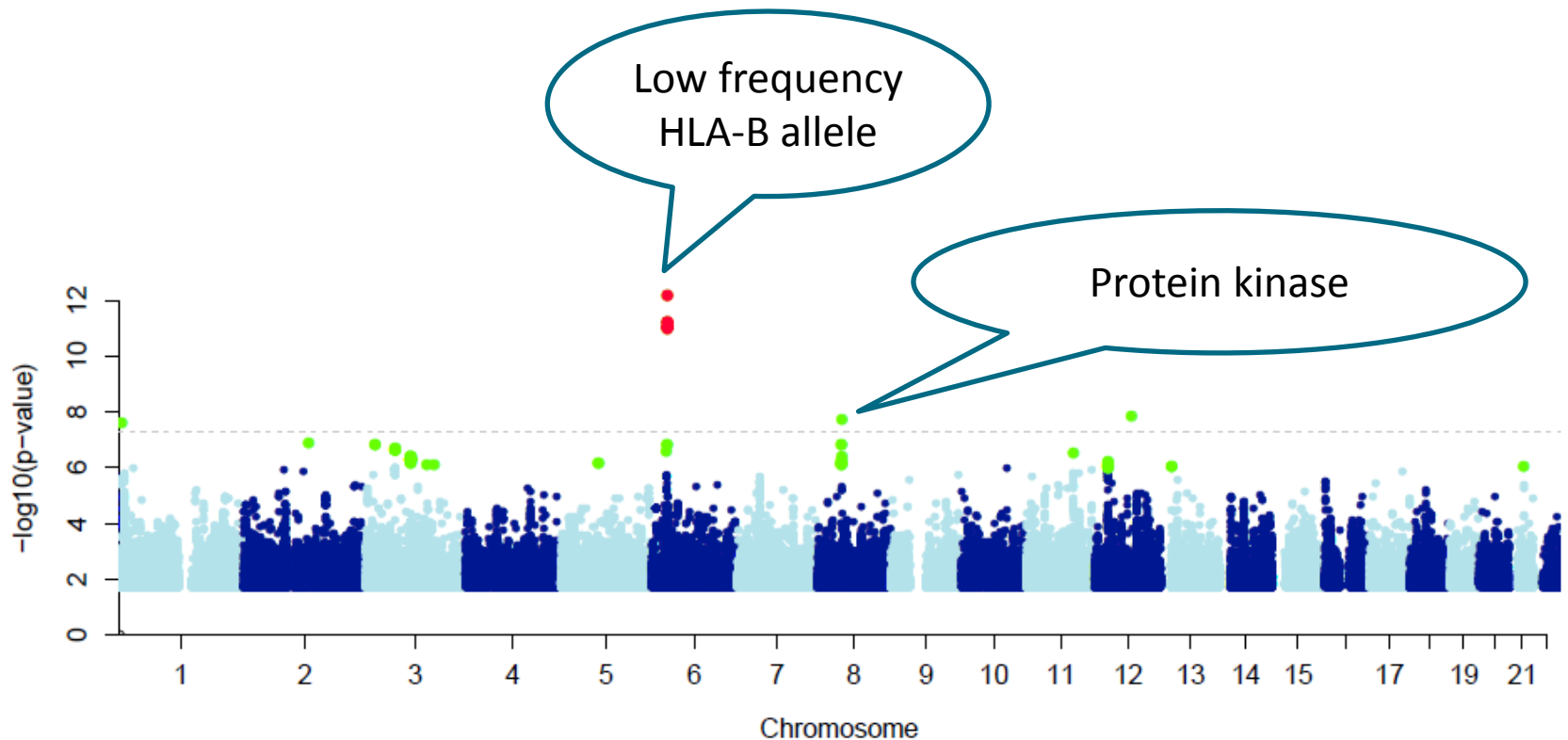


177 Caucasians Cases



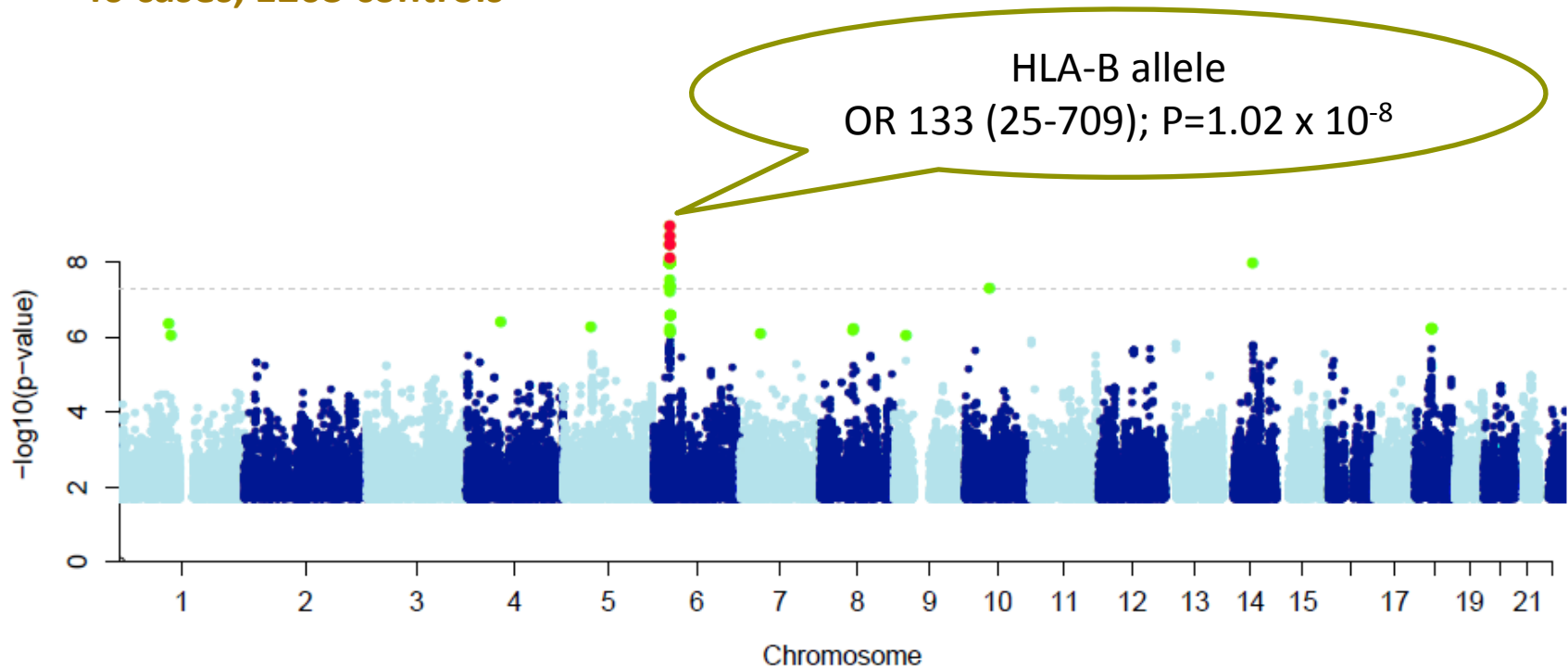
All Caucasian SJS/TEN cases

177 cases, 9237 controls



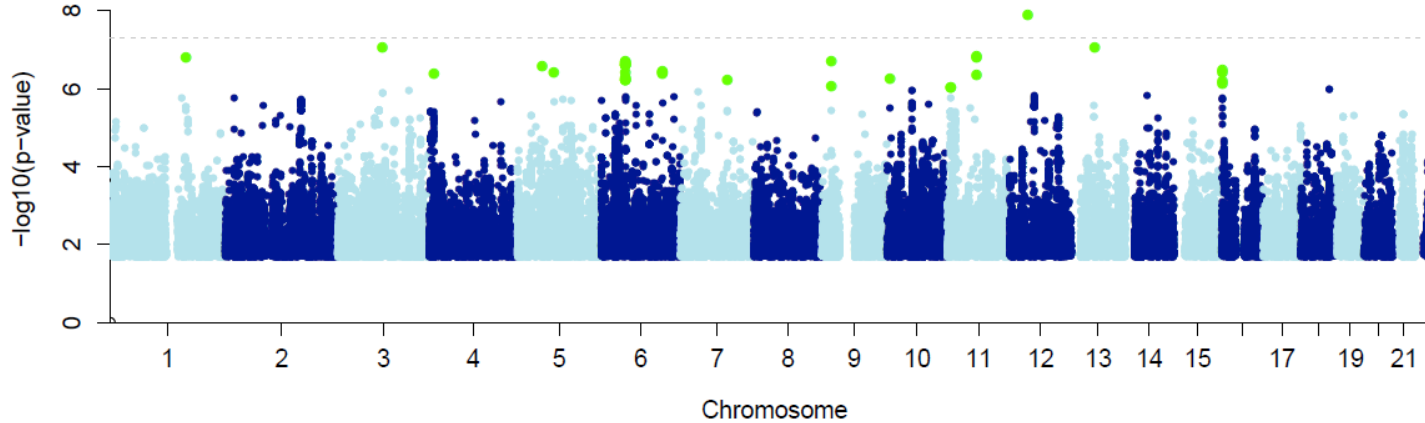
ITALIAN SJS/TEN cases:

40 cases, 1203 controls

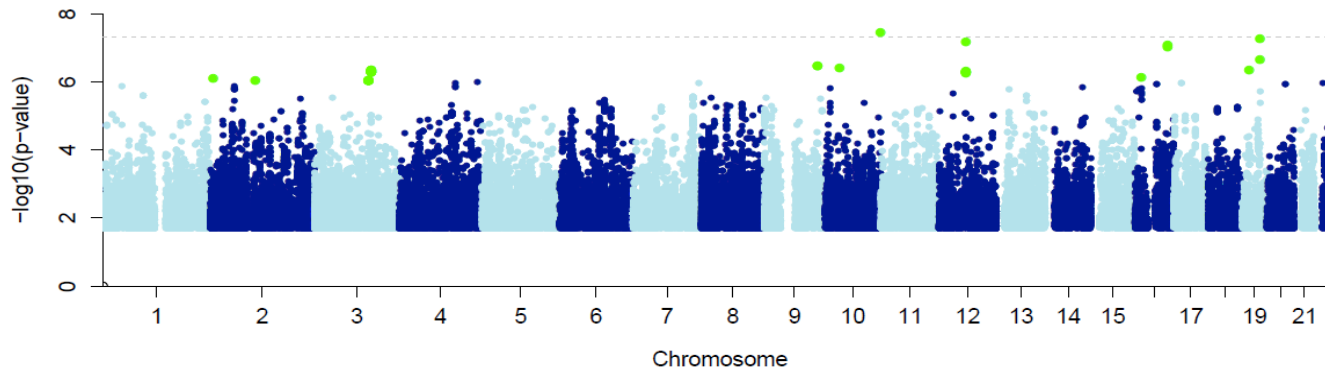


SJS/TEN: No Other Population Specific Signals

North Europeans: 116 cases, 5315 controls

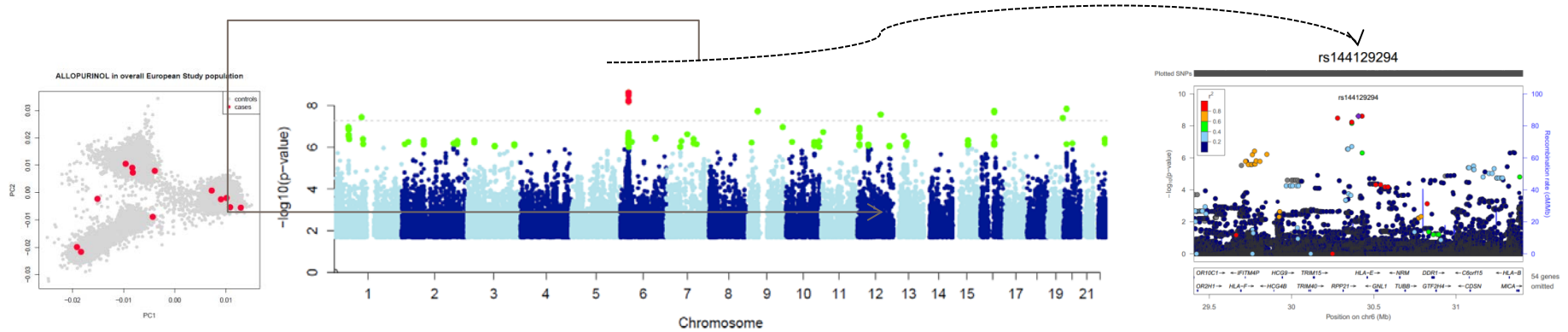


Spanish population: 21 cases, 2622 controls



SJS Allopurinol analysis:

9 Caucasian SJS cases



SNP	CHR	BP	ODDS	Pvalue	L95	U95	FreqCases	FreqContr	Freq1kg
rs144129294	6	30406608	568	2.46E-09	70.66	4565	0.1111	0.000379	0.001
rs150364710	6	30428647	568	2.46E-09	70.66	4565	0.1111	0.000379	0.001
rs116203030	6	30279907	488.7	3.28E-09	62.86	3800	0.1111	0.000379	0.002
rs151052569	6	30365915	672	5.86E-09	75.05	6017	0.1111	0.000379	0.001

SNP	ODDS	UCI	LCI	Pvalue	FreqCases	FreqContr
HLA-B*58:01	45.15	188.2	10.83	1.68E-07	0.2222	0.008567
HLA-A*74:01	1139	20700	62.63	1.98E-06	0.05556	0.000163
HLA-A*33:03	68.66	400.5	11.77	2.60E-06	0.1111	0.00244
HLA-C*03:02	48.3	265.7	8.779	8.31E-06	0.1111	0.002169



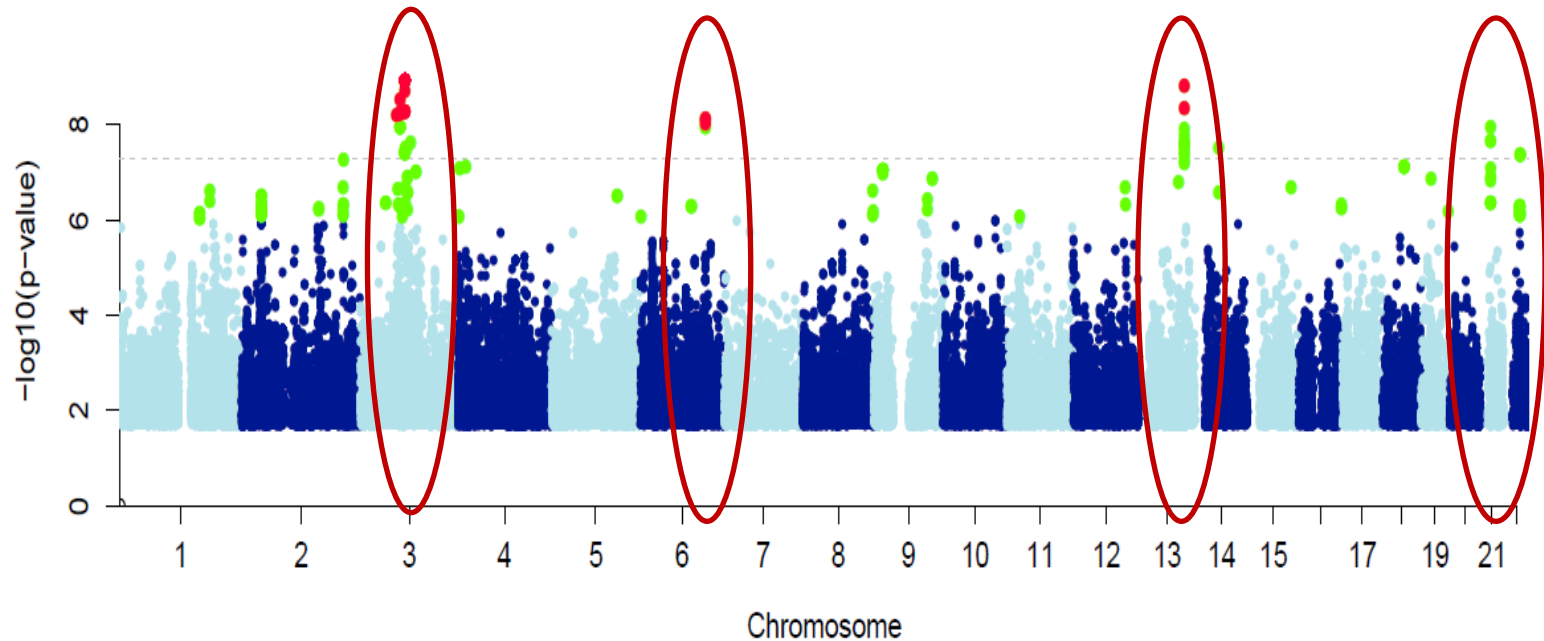
TRIMETHOPRIM/SULFAMETHOXAZOLE

17 north European SJS cases 5315 controls

Common Genome wide significant hits on chr13 and chr6

Uncommon genome wide significant hits on chr3

Borderline genome wide significant hits on chr22 and chr21



Nevirapine Hypersensitivity in Malawi

- NVP treated Malawian HIV patients included:
 - ▶ 182 NVP-tolerant controls
 - ▶ 151 Hypersensitive patients
 - 56 Rash
 - 23 DRESS
 - 51 SJS/TEN
 - 21 DILI



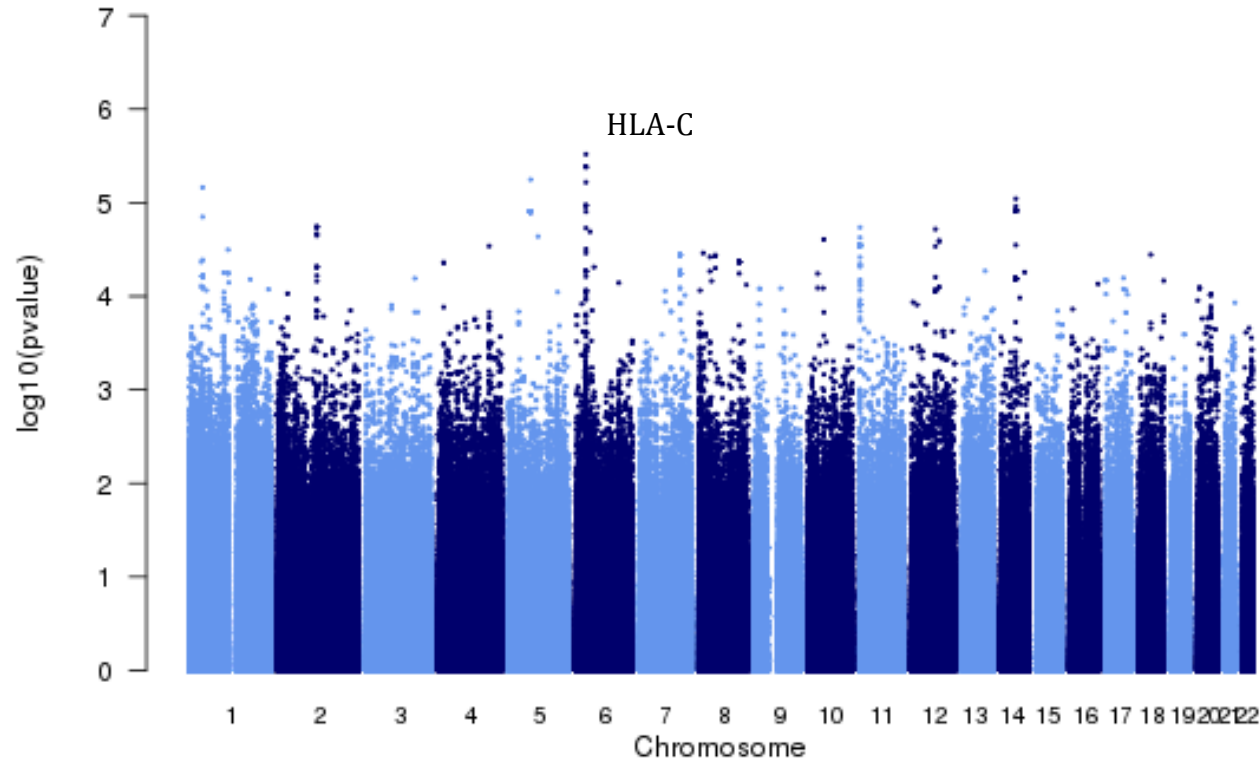
- GWAS and proteomic studies

HMGB1 – total and isoforms that stratify according to both mechanism of release (acetylation status) and function (redox status)



Nevirapine-Induced SJS/TEN

51 SJS/TEN and 182 Tolerant controls
Logistic Regression with CD4+ cell count as covariate
Imputed using 1K genomes phase I data



NVP-Induced SJS/TEN: Replication

Replication Cohort

11 SJS/ TEN and 59 Tolerant controls (Malawian and Ugandan)

Additional Cases

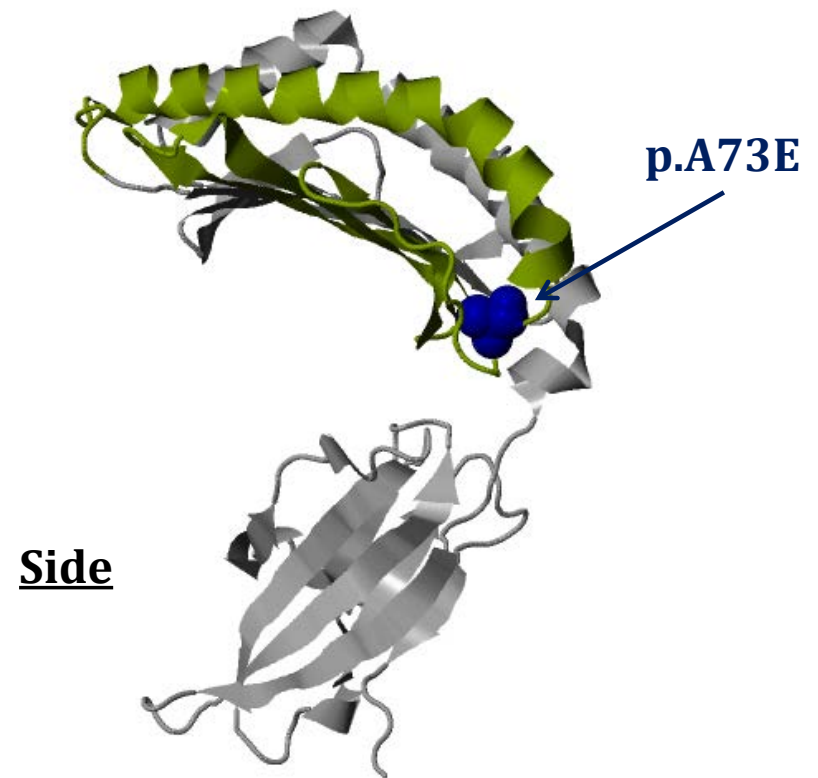
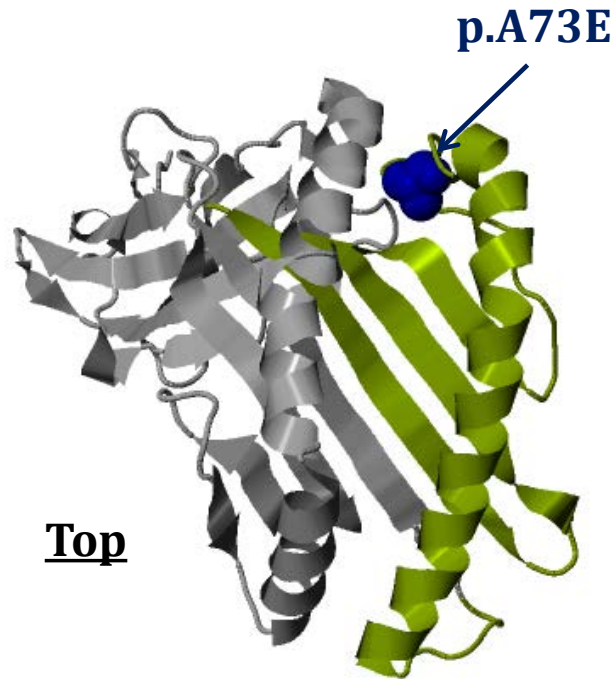
27 SJS/ TEN (Mozambique)*

Initial top hit:rs5010528 (HLA-C)

<u>Cohort</u>		<u>n</u>	<u>MAF</u>	<u>Logistic Regression</u>		<u>Meta-analysis</u>	
				<u>p</u>	<u>OR (95%CI)</u>	<u>p</u>	<u>OR (95%CI)</u>
Discovery	Case	51	0.36	1.48x10 ⁻⁶	4.64 (2.48-8.66)		
	Control	182	0.14				
Replication	Case	11	0.36	0.008	5.63 (1.56-20.35)	4.31x10 ⁻⁸	4.81 (2.74-8.44)
	Control	59	0.12				
Replication	Case	38	0.38	9.6x10 ⁻⁵	6.40 (2.66-15.43)	2.69x10 ⁻¹⁰	5.17 (3.10-8.59)
+additional	Control	59	0.12				

HLA-C 3D Protein Structure

- Amino Acid 73 is within the $\alpha 1$ subunit (yellow) of the peptide recognition site.



Nevirapine forms protein adducts in patients

MRC

Centre for
Drug Safety Science

Chemical
Research in
Toxicology

Article

pubs.acs.org/crt

Detection of Drug Bioactivation in Vivo: Mechanism of Nevirapine–Albumin Conjugate Formation in Patients

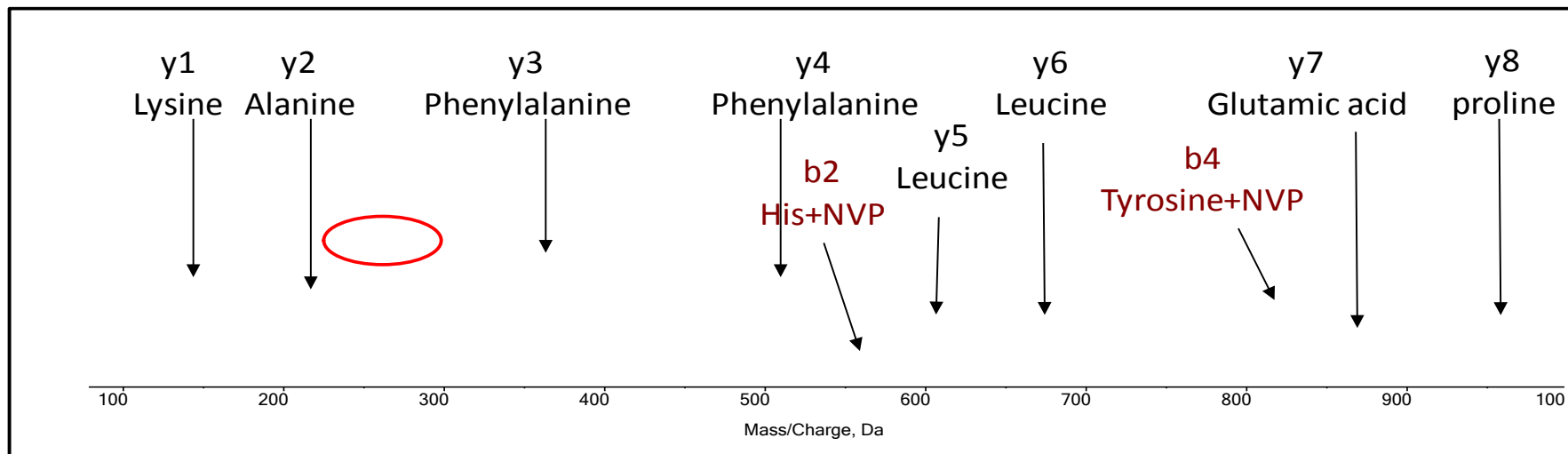
Xiaoli Meng, Alice Howarth, Caroline J. Earnshaw, Rosalind E. Jenkins, Neil S. French, David J. Back, Dean J. Naisbitt, and B. Kevin Park*

MRC Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, U.K.

Nevirapine His146



RH(NVP)PYFYAPPELLFFAK



Summary

- iSAEC as private-public partnership has worked well, and has managed to recruit well phenotyped patients
- Genome-wide approaches are now beginning to bear fruit with several hits identified
- Global collaboration is important to further some of these findings
- Genomic studies will identify predisposing loci, but other studies also important to identify diagnostic and prognostic biomarkers

Acknowledgements

1. iSAEC – Paola Nicoletti, Yufeng Shen, Arthur Holden and many others
2. iSAEC collaborators – contributed cases and adjudication (Shear, Friedmann)
3. Malawi team – Carr, Chaponda, Khoo, Laloo and others

