European Experience in studying SJS/TEN

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Aims / approach

- Incidence, frequency, demography
  → Case registries, e.g. population-based German Registry (dZh)

- Etiology, exposure times, risk estimation
  → Case-control studies, e.g. SCAR- and EuroSCAR-study
Requirements

- Initiation and organization of a network
- Definition of clinical entities (phenotypes)
- Systematic case ascertainment
- Standardized case validation
- Professional data management and statistical analysis
SJS/TEN
Case ascertainment

- Performed by a trained investigator (health care professional) of each national center with a standardized questionnaire
- Interview directly with the patient, if needed with the treating physician and/or relatives
- Review of the medical record
- Blood sampling, biopsy specimen
- Follow-up investigations
Achievements (1)

Incidence
1-2 cases per one million inhabitants per year

Mortality
≈ 45% in TEN with maculae
≈ 20-25% in SJS, SJS/TEN, TEN together
→ ≈ 70% in TEN-patients >65 years

Mockenhaupt M et al, J Invest Dermatol, 2005
Age distribution in SJS/TEN

Distribution per million in a period of 7 years (2003-2009)

<table>
<thead>
<tr>
<th></th>
<th>SJS</th>
<th>SJS/TEN Overlap</th>
<th>TEN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 years</td>
<td>0.11</td>
<td>0.14</td>
<td>0.10</td>
<td>0.35</td>
</tr>
<tr>
<td>12-18 years</td>
<td>0.23</td>
<td>0.05</td>
<td>0.05</td>
<td>0.32</td>
</tr>
<tr>
<td>19-64 years</td>
<td>0.33</td>
<td>0.22</td>
<td>0.11</td>
<td>0.66</td>
</tr>
<tr>
<td>65-79 years</td>
<td>0.97</td>
<td>0.57</td>
<td>0.22</td>
<td>1.76</td>
</tr>
<tr>
<td>80 and older</td>
<td>1.31</td>
<td>0.89</td>
<td>0.12</td>
<td>2.32</td>
</tr>
<tr>
<td>Total</td>
<td>0.44</td>
<td>0.28</td>
<td>0.12</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Case-control studies

- **SCAR-study** (International case-control study on severe cutaneous adverse reactions with focus on SJS/TEN)

  - France, Italy, Germany, Portugal
  - case inclusion between 1989 and 1995
    
    
    → results on non-drug risk factors reported in Auquier-Dunant A et al, Arch Dermatol, 2002
Case-control studies

- **EuroSCAR-study** (European ongoing case-control surveillance of severe cutaneous adverse reactions with focus on SJS/TEN and AGEP)
  - Austria, France, Germany, Israel, Italy, The Netherlands
  - case inclusion between 1997 and 2001

→ overall results on drug risks published in Mockenhaupt M et al, J Invest Dermatol 2008
EMM
- induced by infections, mainly mycoplasma in children, more often herpes in adults

SJS/TEN
- confluent macules and blisters leading to epidermal detachment
- mainly induced by drugs
Medications associated with a high risk for SJS/TEN

- Nevirapine
- Lamotrigine
- Phenytoin
- Allopurinol
- Cotrimoxazole and other anti-infective sulfonamides
Lamotrigine (n = 14)
Medications associated with a moderate risk for SJS/TEN

- Quinolones
- Cephalosporines
- Macrolides
- Tetracyclines
- NSAIDs of the acetic acid type, e.g. diclofenac
Achievements (2)

Medications NOT associated with a risk for SJS/TEN

- Beta-blockers
- ACE-inhibitors
- Ca-channel-blockers
- Thiazid diuretics
- NSAIDs of the propionic acid type, e.g. ibuprofen
- Furosemid
- Insulin
- Other antidiabetics
Early events in SJS/TEN
Based on 379 cases (EuroSCAR)

Beginning of drug use

14 Days

2 D 1 D 5 D

FIRST SYMPTOMS

DIAGNOSIS

ADMISSION

MAXIMUM DETACHMENT
„ALDEN“ (algorithm for causality assessment in SJS/TEN) can be helpful

Sassolas B et al, Clin Pharmacol Ther, 2010
Algorithm - ALDEN

- Relevant exposure window (4-28 days)
- Recent start of drug intake (w/o prior use)
- Drug notoriety (based on study results)
- Half-life of active substances

→ was specifically created for SJS/TEN and requires a clear diagnosis before application
Protopathic bias in SJS/TEN

NEW DRUG(S)
e.g. analgesics, antipyretics, secretolytics

ADMISSION

DIAGNOSIS

FIRST SYMPTOMS

MAXIMUM DETACHMENT
Causality assessment

• Typical examples for drugs with this problem are paracetamol (acetaminophen), ibuprofen, acetysalicylic acid (ASS) and ambroxol.

• They cannot be blamed to have caused the reaction, when
  - taken and tolerated multiple times before
  - when taken shortly (1-4 days) before the onset of the reaction (objective signs) for treatment of prodromal symptoms.
Causality assessment

Critical thoughts

• 55% of patients with SJS/TEN in the SCAR- and EuroSCAR-studies were exposed to a „highly suspected“ (strongly associated) drug in the relevant time period

• 65% to a „highly suspected“ (strongly associated) and/or „suspected“ (associated) drug

Auquier-Dunant A et al, Arch Dermatol, 2002
Drug causality by application of ALDEN
Based on 979 cases (RegiSCAR) - preliminary results

PROBABLE/VERY PROBABLE: 68%
POSSIBLE: 19%
UNLIKELY: 9.4%
Very unlikely: 3.4%
NO DRUG: 3.4%
Causality assessment

Based on current data

- ≈ 68% of SJS/TEN-cases are drug-induced
- among the ≈ 32% of cases without a patent drug cause
  - up to ≈ 19% MAY BE drug-induced
  - at least 13% and up to 32% ARE NOT drug-induced (idiopathic cases)
- The 13-32% idiopathic cases include 2-5% without any drug intake
Based on current data and experience

- The proportion of idiopathic cases is higher in children (about one third)
- A high proportion of cases attributed to «cold medicines» are more likely idiopathic
- A very low proportion of non drug related cases (< 1%) has an established non-drug cause
  - Acute GVHD
  - Infection: M. pneumoniae, K. pneumoniae
  - Overdose: MTX, colchicin
Aims / approach

• Pathomechanism (genetics, immunology)
  → Case registries, e.g. International RegiSCAR-project

• Outcome (survival, sequelae, treatment)
  → Cohort studies, e.g. International RegiSCAR-project
## Achievements (3) - HLA-study

### EUROPE: mixed population

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA</th>
<th>Patients</th>
<th>European Controls (Literature)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all cases</td>
<td>B*1502</td>
<td>4/12 (33%)</td>
<td>0/8</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Europeans</td>
<td></td>
<td>0/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>B*5801</td>
<td>19/31 (61%)</td>
<td>15/27 (55%)</td>
<td>0.4%</td>
</tr>
<tr>
<td>all cases</td>
<td></td>
<td>15/27 (55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europeans</td>
<td></td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lonjou C et al, Pharmacogenomics J, 2006
Lonjou C et al, Pharmacogenet Genomics, 2008
Genome wide association study (GWAS)

- Principal component analysis (PCA) of the genotype data on RegiSCAR and CNG-European control populations
  
  - was performed using the 495 RegiSCAR-patients that passed the quality control and 5,811 European controls
  
  - 76 outliers were detected (71 patients and 5 controls)
  
  - 424 RegiSCAR-patients are kept

Genin E et al, Orphanet J Rare Dis, 2012
Results of the GWAS
Looking at the signal in the HLA region...

Chromosome 6 with HLA in red

zoom of the HLA region with the sub-region of strongest signal in red
Achievements (4) - cohort-study

SJS/TEN  
\( n = 369 \)

- consent to cohort  
  \( n = 342 \) (93%)
  - In-hospital death: 81
  - Death after discharge: 38
  - Total number of deaths: 119
    (thereof 110 deaths within 1 year after onset)

- no consent to cohort  
  \( n = 27 \) (7%)
  - In-hospital death: 5

Outcome and severity

- Patients at risk:
  - Day 0: 171 SJS, 120 overlap, 51 TEN
  - Day 42: 153 SJS, 85 overlap, 26 TEN
  - Day 365: 99 SJS, 50 overlap, 21 TEN

- Death rates:
  - Day 0: 22% (18%-27%)
  - Day 365: 34% (29%-39%)
### Proportional Hazard model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>Hazard ratio</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period: day 0 – day 365 over one year</td>
<td>Period: day 0 – day 42 left truncated</td>
<td>Period: day 42 – day 365 right truncated</td>
</tr>
<tr>
<td>Classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- SJS (&lt;10% detachment)</td>
<td>1.6 [1.0-2.6]</td>
<td>2.6 [1.4-4.8]</td>
<td>-</td>
</tr>
<tr>
<td>- Overlap (10-30% detach.)</td>
<td>4.6 [2.6-7.9]</td>
<td>7.9 [4.1-14.9]</td>
<td></td>
</tr>
<tr>
<td>- TEN (&gt;30% detachment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (in years)</td>
<td>1.04 [1.03-1.06]</td>
<td>1.04 [1.02-1.05]</td>
<td>1.06 [1.04-1.09]</td>
</tr>
<tr>
<td>Recent cancer</td>
<td>2.5 [1.6-4.1]</td>
<td>-</td>
<td>6.5 [3.3-12.9]</td>
</tr>
<tr>
<td>Severe liver disorders</td>
<td>3.0 [1.8-5.0]</td>
<td>2.5 [1.4-4.4]</td>
<td>6.0 [2.5-14.5]</td>
</tr>
<tr>
<td>Severe kidney disorders</td>
<td>2.1 [1.3-3.4]</td>
<td>2.5 [1.5-4.2]</td>
<td>-</td>
</tr>
</tbody>
</table>

Cohort-study - sequelae

SJS/TEN
n = 369

consent to cohort
n = 342 (93%)
In-hospital death: 81
Death after discharge: 38
Total number of deaths: 119
(thereof 110 deaths within 1 year after onset)

no consent to cohort
n = 27 (7%)
In-hospital death: 5

follow-up data after one year
n = 171
Sequelae of the skin

skin in the acute stage of SJS/TEN

skin at 8+2 weeks follow-up examination
Ocular sequelae after 1 year

Analysis of data from 171 patients

- 119 (70%) reported various eye problems since they were discharged
- In 105 of the patients those symptoms were still present after one year
- 25 of these patients did not suffer from eye problems at 8+/-2 week follow-up
Ocular sequelae after 1 year

- acute eye-involvement in SJS
- neovascularization after severe eye-involvement
Impact of sequelae on daily life

- Skin: 61% some impact, 14% serious impact
- Eyes: 55% some impact, 25% serious impact
- Nails: 33% some impact, 8% serious impact
- Mouth: 35% some impact, 8% serious impact
- Genitalia: 25% some impact, 7% serious impact
- Hair: 21% some impact, 3% serious impact
Summary sequelae

1-year follow-up questionnaire revealed that

• some new and unexpected sequelae were observed such as impaired tooth growth in children, probably due to damage of mucous glands in severe oral involvement

• many symptoms last even last longer than 1 year

→ a follow-up questionnaire sent to patients after 5 years is currently analyzed
Efficacy of treatment in SJS/TEN

- **First Symptoms**
- **Diagnosis**
- **Admission**
- **Maximum Detachment**

- **Steroids**
- **IVIG**

Beginning of drug use

FIRST SYMPTOMS
## Mortality stratified by specific treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality (%)</th>
<th>OR univariate</th>
<th>OR multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive only</td>
<td>22/87 (25%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Steroids only</td>
<td>21/119 (18%)</td>
<td>0.6 (0.3-1.2)</td>
<td>0.4 (0.2-1.1)</td>
</tr>
<tr>
<td>IVIG only</td>
<td>12/35 (34%)</td>
<td>1.5 (0.7-3.6)</td>
<td>1.6 (0.6-4.3)</td>
</tr>
<tr>
<td>IVIG + steroids</td>
<td>7/40 (18%)</td>
<td>0.6 (0.2-1.6)</td>
<td>0.5 (0.1-1.5)</td>
</tr>
</tbody>
</table>

Systematic review

• Analysis was performed in concordance with Cochrane rules

• Results show a beneficial effect for steroids and cyclosporin, but not for IVIG

• Based on these data controlled prospective treatment studies according to standardized protocols may be initiated

Zimmermann S et al, J Allergy Clin Immunol, 2014
Overall achievements

• World-wide largest database on SCAR including
  - clinical data (phenotype)
  - follow-up information (outcome, sequelae)
  - biological samples (blood, tissue)

• „Comprized“ knowledge and large expertise in various fields of SCAR, including clinical issues and treatment, pharmacovigilance, pharmaco-epidemiology and pharmacogenetics

• Besides new findings, old errors could be elucidated and will hopefully be avoided in the future
Thank you very much for your attention !!!

Contact Address / RegiSCAR Coordinator:

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dzh@uniklinik-freiburg.de
Thank you - Vielen Dank - Merci - Gracias for your attention !!!
Back-up for discussion
Clear diagnosis

Important, because of

- different reaction pattern and prognosis
- different exposure windows of drug use before onset of the reaction
- different drugs known to be associated
- comparability of epidemiologic and genetic studies
Case validation

- Performed by an expert committee in separate sessions for different types of SCAR, e.g. SJS/TEN and other blistering conditions (GBFDE, EEMM) with decisions on
  - the final inclusion of a case into the study
  - whether the case is a „definite“, „probable“ or only a „possible“ case of SCAR

→ without information on potential causes
Index-day

• **Definite:** first blister or erosion of skin or mucosa (definite sign); indicated with *

• **Probable:**
  - first involvement of skin or mucosa not explained by other conditions and followed ≤ 7 days by a definite sign
  - if these conditions are preceded by ≤ 1 day by a related symptom (e.g. fever, skin pain, malaise)
Causality assessment

Critical thoughts

• How could the remaining 30 - 35% of SJS/TEN-cases be explained?
  - new drugs, for which a risk is not known?
  - non-drug causes such as infections, autoimmune diseases, other underlying conditions, unknown factors?
  - multiple drug intake with unknown effect on drug metabolism?
MEDICATION HISTORY
Interview no. 9170377

RegiSCAR Study

- Aerius p.o.
- ASS-rat. p.o.
- Aspirin plus C p.o.
- Mg-Mineralien p.o.
- Grippostad C p.o.
- Wick MediNait p.o.
- Cotrim p.o.
- Gelomyrtol p.o.
- Symbicort Inhal.

- rhinitis allergica
- infection
- infection
- infection
- reduced state of health
- feeling sick
- infection
- infection
- infection

- influenza-like illness
- feeling sick
- worse state of health, pruritus
- fever
- spots, skin blisters, erosive lips and oral mucosa
- erosive genital mucosa

- hosp. admission

Index-day: 24/01/06
Causality assessment

- When infections are present, “confounding by indication” is a problem difficult to address
  - e.g. antibiotics or antipyretics taken to treat the infection
- When fever and malaise are already the onset of SJS/TEN, “protopathic bias” may lead to wrong assessment
  - e.g. analgesics, antipyretics or secretolytics taken to treat the prodromal symptoms
Paracetamol – risk in case-control analyses

• in SCAR-study: in France mvRR = 0.6 [0.2-1.3], in Germany, Italy, Portugal mvRR =9.3 [3.9-22]
  - in France 13% exposure among controls, in other countries 3%
• in EuroSCAR: mvRR =1.9 [1.2-2.8]
  - after improved collection of OTC medication
• in SCAR-EuroSCAR: mvRR = 5.0 [2.0–13] in children <15 yrs of age
• in analysis of FDA – SAERs: no increased risk
  Papay J et al, Pharmacoepidem Dr S, 2011
Levi N et al, Pediatrics, 2009; pooled analysis off SCAR-EuroSCAR
Causality assessment

For individual cases is important for

the affected patient

the treating physician
Benefits for patients and treating physicians

• visit of the interviewer („specialist“)
• confirmation of diagnosis
• identification of risk factors and causality assessment for the individual patient
Causality assessment

For individual cases is important for

• institutions of drug safety and pharmacovigilance

• public health perspective

• pathogenetic investigations in reactions with a drug-specific mechanism
• organization of the network
• case ascertainment
• case validation
• study achievements
• future objectives
Coordination

dZh (German Registry), Dept. of Dermatology, Medical Center – University of Freiburg, Germany

Data center

Institute for Medical Biometry and Informatics (IMBI), Medical Center – University of Freiburg, Germany

Blood bank

Centre Investigative Clinique (CIC), Henry Mondor Hospital, Creteil, France
H = Local Hospitals where patients are included
• organization of the network
• case ascertainment
• case validation
• study achievements
• future objectives
AIMS

We want to continue

• high-quality case ascertainment
• professional data management
• standardized case review
• systematic blood sampling

→ as the basis for all further research
AIMS

We want to

• further investigate the pathogenetic mechanisms of SCAR

• start new studies on immunologic pathways and genetic susceptibility

• find the link between the inducing agent, the genetic predisposition and the mediators leading to skin detachment

• establish new collaborations with clinical teams and researchers
AIMS

We want to

• develop guidelines for better diagnostics and treatment of SCAR
• improve patients‘ care after the acute stage of the disease / after discharge
• perform thorough risk evaluation for the purpose of drug safety and pharmacovigilance
• better disseminate findings in SCAR
We need

• basic stable funding to keep the network and ensure case ascertainment

• financial support for specific projects, e.g. specific immunologic investigations, longterm follow-up examinations, e.g. for DRESS…

→ continuous support for continuous efforts
We hope you are convinced that

- the RegiSCAR-study has achieved important results so far incl. a growing international network
- we all have a joint responsibility in improving the benefit-risk ratio of medicines
- rare but severe diseases deserve special attention
- there is still a lot of work to do
We hope that

• more clinicians and researchers are ready to work on SCAR
• regulatory agencies, drug manufacturers, patient associations and others will support the tedious effort of data collection, case validation, blood sampling etc., since there is no high quality research on SCAR without that

→ however, high motivation and frustration tolerance are needed
RegiSCAR

International Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples

SCAR:
- Toxic epidermal necrolysis (TEN)
- Stevens-Johnson syndrome (SJS)
- Acute generalized exanthematous pustulosis (AGEP)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- and recently severe cases of Generalized bullous fixed drug eruption (GBFDE)
International Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples

Aims:

- to build an International Registry of SCAR for continuous surveillance of new drugs
- to organize a centralized collection of biological samples for immunologic and genetic investigations
- to constitute a cohort of ca. 300 patients in order to study the outcome, prognostic factors, sequelae and impact on quality of life
International Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples

**Participating countries**

<table>
<thead>
<tr>
<th>(2003-2005)</th>
<th>since 2006 cases from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>France</td>
</tr>
<tr>
<td>France</td>
<td>Germany</td>
</tr>
<tr>
<td>Germany</td>
<td>Italy</td>
</tr>
<tr>
<td>Israel</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Italy</td>
<td>Taiwan (2007), UK (2008)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>South Africa (2009)</td>
</tr>
<tr>
<td></td>
<td>Spain (2010)</td>
</tr>
</tbody>
</table>
RegiSCAR

International Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples

conflict of interest: nothing to declare

funding sources: grants from
- the European Commission (QLRT-2002-01738)
- GIS-Institut des Maladies Rares and
- INSERM (4CH09G) in France,
- SIDACTION, ANRS,
- DFG (FOR 534) in Germany and
- Else Kröner-Fresenius-Stiftung
Funding by pharmaceutical companies*:

Pfizer, Novartis, Cephalon (TEVA),
GlaxoSmithKline, Boehringer-Ingelheim,
Merck, MSD Sharp&Dohme, Tibotec,
Hoffmann-La-Roche, OM Pharma,
Sanofi-Aventis, Servier, Bayer-Schering,
Grüntenthal, Berlin Chemie/Menarini

* some funding contracts have ended
Summary of HLA-results

Allopurinol-induced SJS/TEN

- 61% (55% of European origin) of our allopurinol-induced cases carried HLA-B*5801 (odds ratio = 130.4; 95% CI [51-331]; p<10-8)

For other drugs

- no single allele was found predominantly, but several alleles (B*51, B*38, B*35, B*58) showed a significant association with SJS/TEN for various drugs
PCA on RegiSCAR and CNG-European control populations

1,228 French controls highlighted
PCA on RegiSCAR and CNG-European control populations

653 German controls highlighted
Association testing

- Comparison of the genotype frequencies of 424 RegiSCAR-patients and 1,881 controls from France and Germany

- Association test accounting for population stratification: trend test corrected for the top 2 principal components of the PCA

Eigenstrat, Price et al., Nature Genetics, 2006
List of the SNPs with $p \leq 10^{-6}$

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Pos</th>
<th>MAF_Cases</th>
<th>MAF_Cont</th>
<th>OR</th>
<th>CI</th>
<th>Annotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2844665</td>
<td>6</td>
<td>31114834</td>
<td>0.28</td>
<td>0.38</td>
<td>0.65</td>
<td>0.55-0.77</td>
<td>C6orf205</td>
</tr>
<tr>
<td>rs3815087</td>
<td>6</td>
<td>31201566</td>
<td>0.31</td>
<td>0.21</td>
<td>1.53</td>
<td>1.29-1.80</td>
<td>PSORS1C1</td>
</tr>
<tr>
<td>rs3130931</td>
<td>6</td>
<td>31242867</td>
<td>0.23</td>
<td>0.31</td>
<td>0.65</td>
<td>0.54-0.83</td>
<td>POU5F1</td>
</tr>
<tr>
<td>rs3130501</td>
<td>6</td>
<td>31244432</td>
<td>0.17</td>
<td>0.26</td>
<td>0.57</td>
<td>0.47-0.71</td>
<td>POU5F1</td>
</tr>
<tr>
<td>rs3094188</td>
<td>6</td>
<td>31250224</td>
<td>0.28</td>
<td>0.37</td>
<td>0.63</td>
<td>0.53-0.77</td>
<td>POU5F1</td>
</tr>
<tr>
<td>rs9469003</td>
<td>6</td>
<td>31515807</td>
<td>0.24</td>
<td>0.15</td>
<td>1.73</td>
<td>1.44-2.08</td>
<td>HCP5</td>
</tr>
</tbody>
</table>

MAF_Cases: Minor Allele Frequency in Cases  
MAF_Cont: Minor Allele Frequency in Controls  
OR: Odds-ratio  
CI: Confidence Interval of the OR  
Annotation: Gene

→ 6 SNPs have $p$-values $\leq 10^{-6}$  
→ all are located in the HLA region on chromosome 6
Impact of the “culprit” drug

- The signal is much stronger in the subset of the 57 allopurinol-induced cases: rs9469003: OR=4.16 [2.83-6.11]

- This might be explained by the HLA-B*5801 association observed in allopurinol-induced cases
  - In Asian samples, this association is complete with all cases carrying this HLA-B*5801 allele.
  - In Europe, HLA-B*5801 is very rare and only found in a fraction of allopurinol-induced cases.