Establishment and application of risk prediction test for dapsone hypersensitivity syndrome----preliminary report

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Outline

- Background
- Methods
- Our findings
- Application
- Acknowledgement
Dapsone (DDS)

- Antibiotic
  - Leprosy
  - Malaria
  - Actinomycetoma
    - *Pneumocystis jirovecii* pneumonia in individuals with HIV infection
  - Autoimmune Bullous diseases
    - Subcorneal pustular dermatosis
    - Erythema elevatum diutinum
Dapsone hypersensitivity syndrome (DHS)

- DHS was noted in 1949 and termed in 1951
- The prevalence of DHS is estimated to be 1.4%
- The mortality rate is about 11-13%
- About 0.5-3.6 of individuals treated with DDS suffer DHS

References:
DHS is a severe idiosyncratic drug reaction

Clinical manifestations: the clinical triad of fever, rash, and systemic involvement (most commonly the liver and the hematological system)

It usually appears four to six weeks after the initiation of therapy
No tests to predict the risk of DHS
Genetic factors have been proven to play an important role in drug-induced hypersensitivity reactions. HLA-B*15:02 allele was identified as an important risk predictor of carbamazepine (CMZ)-induced SJS and TEN in South-East Asia population. The clinical testing of HLA-B*15:02 successfully led to an evident decrease in the incidence of CMZ-induced SJS–TEN in Taiwan population. HLA-A*31:01 allele was found to be associated with CMZ-induced hypersensitivity reactions in European population.

Methods

Subjects

77 DHS cases: all were surviving leprosy patients of Chinese descent

All the DHS cases received DDS as a part of MDT and were diagnosed based on the criteria proposed by Richardus and Smith

39 for the discovery analysis; 38 for the replication analysis

Subjects

2,064 surviving leprosy patients

All the controls also treated with DDS for at least 6 months, but whose DHS status could not be determined due to insufficient medical information

955 individuals in the discovery analysis; 1,109 individuals in the replication analysis
Methods

Subjects were used to estimate the allele frequency of risk predictor in Chinese population:
- including 951 subjects from Guangdong, 523 subjects from Shandong, and 470 subjects from Yunnan provinces.
Methods

SNP genotyping and association analysis

- **Discovery stage:** 39 DHS cases vs 955 controls

- Quality control
- A total of 430,276 SNPs in 39 DHS cases and 833 controls were used in the association analysis

- Illumina Human660W-Quad Beadchips

- All association analyses were performed via logistic regression with an additive model of inheritance using PLINK.
SNP genotyping and association analysis

Replication stage

- 24 non-MHC SNPs
- 31 DHS cases vs 1089 controls
- MHC loci
- HLA-imputation
- 31 DHS cases vs 1089 controls
- Sequencing of HLA-B and C
  - 39 DHS cases vs 78 controls
  - 38 DHS cases vs 206 controls

Imputation of classical HLA alleles and amino acid (AA) variants was performed using Beagle and the reference panel from the CHB and JPT HapMap dataset.

Sequenom MassARRAY

Roche 454 GS-FLX platform
Our findings

Panel A shows a quantile-quantile plot with $\lambda_{GC}=1.012$.

Panel B shows a Manhattan plot. Strongest signal was observed on chromosome 6 located between $HLA-B$ and $MICA$ loci.

Results of genomewide association analysis.
Regional association plots of HLA region

- An allele located in HLA-B is as the most significantly associated allele within the MHC region.

These results indicate that an allele located in HLA-B is the primary risk variant for DHS within the MHC region.
Our findings

- Receiver-operating curve for an additive prediction model of DHS using identified allele as predictor.
- AUC, area under the curve. Overall sensitivity is 85.53%, whereas specificity is 85.69%.

Subjects have 33.6 times higher risk if carrying one copy of the identified allele
100.7 times higher if carrying two copies than the ones not carrying any copy for developing DHS

The clinical testing of the identified could theoretically reduce the risk of DHS by 7 fold (from 1.4% to 0.2%) by excluding the positive subjects from DDS treatment.
Application of risk prediction test

Subjects

In 2012, 12 newly diagnosed leprosy cases from Shandong Province for a retrospective analysis

In 2013, 8 newly diagnosed leprosy cases from Shandong Province for a prospective analysis;

4 newly diagnosed autoimmune bullous diseases for a prospective analysis
Methods

PCR-SSP and Direct sequencing
Only two cases in 17 cases who suffered DHS were found to carry the risk allele, which indicated a complete consistency between clinical manifestation and genotyping results with sensitivity of 100% and specificity of 100%.

Only one individual was found to carry the risk allele and DDS was removed from his treatment. In those individuals treated by DDS, no new DHS is reported in the follow up of 3 months.
We have identified a strong risk factor for DHS in the Chinese population, shedding light on the pathogenesis of DHS.

Our findings will facilitate the development of genetic tests to identify individuals at risk for this potentially life-threatening condition. This will help us to obtain the full benefits of DDS therapy more safely and effectively.
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