HD–Zip genes in land plants are negatively regulated through a conserved microRNA-mediated mechanism that has operated at least since the last common ancestor of bryophytes and seed plants, estimated to have existed more than 400 million years ago. The age of this mechanism is comparable to that of microRNA-mediated regulation of the *let–7* gene in metazoans[12].

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Medical genetics

# A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication[1–3]. Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen *HLA–B*1502*, and Stevens–Johnson syndrome induced by carbamazepine, a drug commonly prescribed for the treatment of seizures. It should be possible to exploit this association in a highly reliable test to predict severe adverse reaction, as well as for investigation of the pathogenesis of Stevens–Johnson syndrome.

We studied 44 patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS), including five with overlapping toxic epidermal necrolysis, in whom the clinical morphology fulfilled Roujeau's diagnostic criteria[1] (see supplementary information). Patients suffered from widespread skin rashes with blisters, skin detachment and mucosa involvement. Controls included 101 patients who had been on carbamazepine for at least three months without adverse reaction ('CBZ-tolerant') and 93 normal individuals. All participants were Han Chinese residing in Taiwan. The study was approved by the institutional review board and informed consent was obtained in all cases.

Genetic factors influencing drug metabolism and the immune response, including *HLA* genotype, might be involved in drug hypersensitivity[4–6]. We therefore genotyped 157 cytochrome-P450 single-nucleotide polymorphisms using high-throughput MALDI–TOF mass spectrometry; we also genotyped all *HLA–B, –C, –A* and *–DRB1* alleles by sequence-specific oligonucleotide reverse lineblot and sequence-based typing[7].

We found that, compared with controls, there was no significant association between any of the cytochrome-P450 single-nucleotide polymorphisms and occurrence of CBZ–SJS. However, the alleles *B*1502, Cw*0801, A*1101* and *DRB1*1202* within the *HLA* region occurred at increased frequency in CBZ–SJS patients relative to the controls (Table 1). In particular, *HLA–B*1502* was present in 100% (44/44) of CBZ–SJS patients but in only 3% (3/101) of CBZ-tolerant patients and in 8.6% (8/93) of the general population.

When the CBZ-tolerant group is used as the control, the presence of *B*1502* has a 93.6% positive-prediction value for CBZ–SJS, whereas its absence has a negative-prediction value of 100%. In a test for CBZ–SJS, the *HLA–B*1502* allele should therefore have 100% sensitivity and 97% specificity.

After discovering six patients who were homozygous for the *HLA–B*1502* allele, we analysed the allele distribution in combined loci and discovered conserved alleles coupled at closely linked loci. This ancestral haplotype was defined as *B*1502, Cw*0801, A*1101, DRB1*1202*. It was present in 66% of the CBZ–SJS patients and in only 3% of the normal subjects, but was absent in CBZ-tolerant patients (Table 1).

The incidence of Stevens–Johnson syndrome in Han Chinese is higher than in Caucasians (8 cases per million person-years in Han Chinese compared with 2–3 cases in Caucasians). Carbamazepine is the drug most commonly associated with the syndrome in Asians (accounting for 25–33% of cases)[8,9], whereas only 5–6% of Caucasian CBZ–SJS cases are caused by it[2,3]. We were unable to include Caucasian CBZ–SJS patients in our study; however, the presence of the *HLA–B*1502* allele in 8% of Han Chinese but only 1–2% of Caucasians[10] may explain the lower incidence of CBZ–SJS in Caucasians. Our findings could affect 1.2 billion Chinese worldwide; we do not yet know how they apply to other populations.

To our knowledge, the striking association of the allele *HLA–B*1502* with carbamazepine-induced Stevens–Johnson syndrome is the strongest so far described between an *HLA* marker and a disease; it even exceeds the classic example of *B27* and ankylosing spondylitis[11]. It remains to be seen whether genes in the vicinity of the *HLA–B* locus, if not *B*1502* itself, participate in the pathogenesis of CBZ–SJS.

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 information.

*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); $P_c = 1.38 \times 10^{-21}$.

To our knowledge, the striking association of the allele *HLA–B*1502* with carbamazepine-induced Stevens–Johnson syndrome is the strongest so far described between an *HLA* marker and a disease; it even exceeds the classic example of *B27* and ankylosing spondylitis[11]. It remains to be seen whether genes in the vicinity of the *HLA–B* locus, if not *B*1502* itself, participate in the pathogenesis of CBZ–SJS.

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**Tumour suppression: Disruption of *HAUSP* gene stabilizes p53**
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