Genome Medicine

RESEARCH HIGHLIGHT

Personalizing carbamazepine therapy

Taisei Mushiroda[1] and Yusuke Nakamura*[1,2]

Abstract

The anticonvulsant carbamazepine has a high incidence of cutaneous adverse drug reactions. A recent prospective clinical trial in Taiwan has indicated that *HLA-B*1502* screening will reduce the incidence of life-threatening adverse reactions to carbamazepine, while a genome-wide association study has identified the *HLA-A*3101* allele as a genetic risk factor for the full spectrum of carbamazepine-induced cutaneous adverse drug reactions in a European population. These studies should aid future decision-making for personalized use of carbamazepine treatment.

Genomic insights into adverse drug reactions

Carbamazepine (CBZ) is a drug frequently used as an anticonvulsant and mood stabilizer in the treatment of epilepsy and bipolar disorder. Cutaneous adverse drug reactions (cADRs) characterized by acute inflammatory reactions in skin and mucous membranes are dose-independent, unpredictable and sometimes life-threatening. Manifestations range from a mild erythematous maculopapular rash to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS), which is also referred to as drug rash with eosinophilia and systemic symptoms (DRESS). Almost all available drugs have been reported to have a risk of causing a cADR, and some drugs, such as CBZ, allopurinol, abacavir and nevirapine, are known to cause a very high incidence of severe cADRs, including SJS and TEN [1].

It has been proposed recently that binding of drugs and/or their metabolites to human leukocyte antigen (HLA) may trigger undesirable immune responses. When the antigen is presented on HLA class II molecules, $CD4^+$ helper T cells are activated. If the antigen is presented on class I molecules, it is likely to activate $CD8^+$ cytotoxic T cells. Although the detailed mechanisms have not been clarified, HLA molecules are considered to be critical in the pathogenesis of severe cADRs. Therefore, genetic association analyses between HLA alleles and cADRs have been performed by many research groups, and several HLA alleles have been identified as major susceptibility factors that predispose an individual to develop cADRs. The first report demonstrating the critical involvement of a specific HLA allele in development of severe cADRs was published in 2002 [2]. This discovery had a big impact and resulted in alterations to the labeling of drugs. The report described a study of 18 Caucasian HIV patients with abacavir-induced hypersensitivity syndrome (HSS), and it revealed that the frequency of *HLA-B*5701* in these patients was significantly higher compared with the abacavir-tolerant control subjects (78% versus 2%; odds ratio, 117). Based on the subsequent large prospective clinical trial in 2008 [3], the US Food and Drug Administration (FDA) updated the label of abacavir to recommend that all patients should be screened for *HLA-B*5701* before initiation of treatment.

New insights into carbamazepine reactions and HLA

Two studies published recently in the *New England Journal of Medicine* should facilitate the development of genetic tests to predict high-risk individuals for potentially life-threatening adverse reactions caused by CBZ [4,5]. Previously, a group in Taiwan reported that the *HLA-B*1502* allele was associated with SJS-TEN induced by CBZ in Han Chinese patients (Table 1) [6,7]. Based on these results, in 2007 the US FDA recommended genotyping all patients with ancestry in populations in which *HLA-B*1502* may be present. The recent prospective clinical trial, published in the *New England Journal of Medicine*, led by the same Taiwanese group, demonstrated that SJS-TEN did not develop in any of the *HLA-B*1502*-negative patients receiving CBZ (n = 4,120), indicating that the *HLA-B*1502* screening should reduce the incidence of life-threatening adverse reactions caused by CBZ [4]. However, allelic frequencies of the HLA loci differ significantly among different ethnic

*Correspondence: yusuke@ims.u-tokyo.ac.jp
[1]Research Group for Pharmacogenomics, RIKEN Center for Genomic Medicine, Yokohama 230-0045, Japan
Full list of author information is available at the end of the article

Table 1. HLA alleles associated with carbamazepine-induced cutaneous adverse drug reactions

Population	Target allele	Type of cADR	Selectivity in cases[a]	Odds ratio	Reference
Han Chinese in Taiwan	*HLA-B*1502*	SJS-TEN	59/60	1,357	[7]
		HSS	0/13	–	[7]
		MPE	1/18	–	[7]
	*HLA-A*3101*	SJS-TEN	1/60	–	[7]
		HSS	2/13	–	[7]
		MPE	6/18	17.5	[7]
Japanese	*HLA-A*3101*	SJS-TEN	5/6	33.9	[9]
		DIHS	21/36	9.5	[9]
		Other	19/35	8.0	[9]
European	*HLA-A*3101*	SJS-TEN	5/12	25.93	[5]
		HSS	10/27	12.41	[5]
		MPE	23/106	8.33	[5]
Thai	*HLA-B*1502*	SJS-TEN	37/42	54.76	[10]
Malaysian	*HLA-B*1502*	SJS-TEN	12/16	16.15	[11]

[a]Number of patients with the target allele/number of patients with type of cADR. cADR, cutaneous adverse drug reaction; DIHS, drug-induced hypersensitivity syndrome; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

groups. For example, the *HLA-B*1502* allele is present at high frequencies in Southeast Asians, such as the Han Chinese in Taiwan (5.9%) and people from Thailand (8.5%), but it is less than 0.1% in Japanese and Caucasian populations [8], although the incidence of CBZ-induced cADRs is also relatively high in these populations. Thus, *HLA-B*1502* is unlikely to be a good genetic predictor for the CBZ-induced cADRs in Japanese and Caucasian populations.

The second study was a multicenter study led by teams from the UK and Ireland, and it used a genome-wide association study (GWAS) approach. The study showed that the *HLA-A*3101* allele was associated with CBZ-induced cADRs, including SJS-TEN [5]. It demonstrated that a SNP showing a significant association had previously been shown to be a proxy for the *HLA-A*3101* allele in subjects of European descent. The subsequent HLA analysis revealed that *HLA-A*3101* was a risk factor for the HSS (odds ratio, 12.41), maculopapular exanthema (MPE; odds ratio, 8.33) and SJS-TEN (odds ratio, 25.93), suggesting that the *HLA-A*3101* allele is an important predictor of the 'full spectrum' of CBZ-induced cADRs (Table 1). The authors concluded that it may be possible to reduce the incidence of CBZ-induced cADRs from 5% to 3.8% by using genetic diagnosis to exclude patients with the *HLA-A*3101* allele from CBZ treatment.

Implications for future research and treatment

Previously, and also using a GWAS, we reported that *HLA-A*3101* allele was a genetic risk factor for the full spectrum of CBZ-induced cADRs, including SJS-TEN and DIHS/DRESS, in a Japanese population (Table 1) [9]. In addition, this allele has been shown to be associated with CBZ-induced MPE in subjects of Han Chinese ancestry (Table 1) [7]. *HLA-A* belongs to the HLA class I heavy chain paralogs that play a central role in the immune system by presenting peptides derived from the endoplasmic reticulum lumen. It is considered that the association of the HLA allele with CBZ-induced cADRs should reflect variations in antigen-binding affinities of HLA-A that might affect the immune response in the pathogenesis of the cADRs. Patients will greatly benefit from *HLA-A*3101* genotyping to predict the risk of CBZ-induced cADRs because there are several alternative drugs to CBZ for treatment of epilepsy; these drugs include valproic acid, gabapentin, levetiracetam, and topiramate, which induce cADRs with lower prevalence compared with CBZ. Although the efficacy of these alternative drugs might be inferior to CBZ for treating epilepsy, the prevention of CBZ-induced cADRs, which are sometimes life-threatening, is more important for patients. Thus, these findings should provide useful information for improving the personalized CBZ treatment of epilepsy.

Interestingly, the Taiwanese study revealed that MPE and HSS did not show a significant association with *HLA-B*1502* (with only one positive subject out of thirty-one patients), while the *HLA-A*3101* allele was observed in only one of sixty patients with SJS-TEN [7], suggesting that the pathogenesis might be different between SJS-TEN and other cADRs, such as MPE. However, the full spectrum of CBZ-induced cADRs, including SJS-TEN, was associated with the *HLA-A*3101* allele in Japanese

and European populations. Both HLA-A and HLA-B belong to major histocompatibility complex class I molecules. Thus, there may be common underlying mechanisms involved in the CBZ-induced cADRs, although *HLA-B*1502* appears to be specifically involved in CBZ-induced SJS-TEN. The discrepancy in the results of association of *HLA-A*3101* with SJS-TEN between Japanese/European and Taiwanese studies might be due to ethnic differences in allele frequencies of *HLA-B*1502*. It has been found that the *HLA-B*1502* allele is extremely rare in Japanese and Caucasians, and this might have a larger effect size on the risk of SJS-TEN than that of *HLA-A*3101*.

Although the impact of the association of *HLA-A*3101* with CBZ-induced cADRs is not as high as that of *HLA-B*1502*, improved labeling of CBZ to recommend the avoidance of CBZ in patients with *HLA-A*3101* should benefit individuals at risk. However, a global network for the collection of data on patients with cADRs is required to show the usefulness of HLA testing for epilepsy treatments. In addition, the clarification of the molecular mechanisms underlying the associations of *HLA-B*1502* and *HLA-A*3101* with the risk of CBZ-induced cADRs would encourage the development of new technology, which may also be useful for the screening of compounds for toxicity earlier in the drug discovery process.

Abbreviations

cADR, cutaneous adverse drug reactions; CBZ, carbamazepine; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; FDA, Food and Drug Administration; GWAS, genome-wide association study; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; SJS, Stevens-Johnson syndrome; SNP, single nucleotide polymorphism; TEN, toxic epidermal necrolysis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Both authors participated in writing the manuscript.

Author details

[1]Research Group for Pharmacogenomics, RIKEN Center for Genomic Medicine, Yokohama 230-0045, Japan. [2]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan

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References

1. Chung WH, Hung SI, Chen YT: **Human leukocyte antigens and drug hypersensitivity.** *Curr Opin Allergy Clin Immunol* 2007, **7:**317-323.
2. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT: **Association between presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir.** *Lancet* 2002, **359:**727-732.
3. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A; PREDICT-1 Study Team: ***HLA-B*5701*** **screening for hypersensitivity to abacavir.** *N Engl J Med* 2008, **358:**568-579.
4. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, Tai CT, Wu SL, Lu CH, Hsu YC, Yu HY, Ro LS, Lu CT, Chu CC, Tsai JJ, Su YH, Lan SH, Sung SF, Lin SY, Chuang HP, Huang LC, Chen YJ, Tsai PJ, Liao HT, Lin YH, Chen CH, Chung WH, Hung SI, Wu JY, Chang CF, *et al*.; Taiwan SJS Consortium: **Carbamazepine-induced toxic effects and *HLA-B*1502*** **screening in Taiwan.** *N Engl J Med* 2011, **364:**1126-1133.
5. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, Sills GJ, Marson T, Jia X, de Bakker PI, Chinthapalli K, Molokhia M, Johnson MR, O'Connor GD, Chaila E, Alhusaini S, Shianna KV, Radtke RA, Heinzen EL, Walley N, Pandolfo M, Pichler W, Park BK, Depondt C, Sisodiya SM, Goldstein DB, Deloukas P, Delanty N, Cavalleri GL, Pirmohamed M: ***HLA-A*3101*** **and carbamazepine-induced hypersensitivity reactions in Europeans.** *N Engl J Med* 2011, **364:**1134-1143.
6. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT: **Medical genetics: a marker for Stevens-Johnson syndrome.** *Nature* 2004, **428:**486.
7. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, Hu SL, Wu MT, Chen GS, Wong TW, Hsiao PF, Chen WH, Shih HY, Fang WH, Wei CY, Lou YH, Huang YL, Lin JJ, Chen YT: **Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions.** *Pharmacogenet Genomics* 2006, **16:**297-306.
8. **The Allele Frequency Net Database** [http://www.allelefrequencies.net/]
9. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, Ikezawa Z, Iijima M, Shiohara T, Hashimoto K, Kamatani N, Nakamura Y: **Genome-wide association study identifies *HLA-A*3101*** **allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population.** *Hum Mol Genet* 2011, **20:**1034-1041.
10. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, Konyoung P, Khunarkornsiri U, Auvichayapat N, Pavakul K, Kulkantrakorn K, Choonhakarn C, Phonhiamhan S, Piyatrakul N, Aungaree T, Pongpakdee S, Yodnopaglaw P: **Association between *HLA-B*1502*** **and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population.** *Epilepsia* 2010, **51:**926-930.
11. Chang CC, Too CL, Murad S, Hussein SH: **Association of *HLA-B*1502*** **allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population.** *Int J Dermatol* 2011, **50:**221-224.

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