



Carbamazepine Hypersensitivity: Progress Toward Predicting the Unpredictable

HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans.

McCormack M, Alfievic 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. *N Engl J Med.* 2011;364:1134–1143.

BACKGROUND: Carbamazepine causes various forms of hypersensitivity reactions, ranging from maculopapular exanthema to severe blistering reactions. The HLA-B*1502 allele has been shown to be strongly correlated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) in the Han Chinese and other Asian populations but not in European populations. **METHODS:** We performed a genomewide association study of samples obtained from 22 subjects with carbamazepine-induced hypersensitivity syndrome, 43 subjects with carbamazepine-induced maculopapular exanthema, and 3987 control subjects, all of European descent. We tested for an association between disease and HLA alleles through proxy single-nucleotide polymorphisms and imputation, confirming associations by high-resolution sequence-based HLA typing. We replicated the associations in samples from 145 subjects with carbamazepine-induced hypersensitivity reactions. **RESULTS:** The HLA-A*3101 allele, which has a prevalence of 2 to 5% in Northern European populations, was significantly associated with the hypersensitivity syndrome ($P=3.5 \times 10^{-8}$). An independent genomewide association study of samples from subjects with maculopapular exanthema also showed an association with the HLA-A*3101 allele ($P=1.1 \times 10^{-6}$). Follow-up genotyping confirmed the variant as a risk factor for the hypersensitivity syndrome (odds ratio, 12.41; 95% confidence interval [CI], 1.27 to 121.03), maculopapular exanthema (odds ratio, 8.33; 95% CI, 3.59 to 19.36), and SJS-TEN (odds ratio, 25.93; 95% CI, 4.93 to 116.18). **CONCLUSIONS:** The presence of the HLA-A*3101 allele was associated with carbamazepine-induced hypersensitivity reactions among subjects of Northern European ancestry. The presence of the allele increased the risk from 5.0% to 26.0%, whereas its absence reduced the risk from 5.0% to 3.8%. (Funded by the U.K. Department of Health and others.)

Commentary

Cutaneous adverse drug reactions are among some of the most frequent adverse events associated with a number of our commonly used aromatic ring-containing antiepileptic drugs (AEDs), including carbamazepine, phenytoin, oxcarbazepine, and lamotrigine (1–3).

In its mildest form, maculopapular exanthema may occur in perhaps up to 10% of patients receiving carbamazepine. In some patients, however, more severe dermatologic hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms [DRESS] may occur and has been associated with a mortality rate of about 10%. This hypersensitivity syndrome is associated with rash, fever, and organ dysfunction such as nephritis or hepatitis (4), and most commonly presents within the first 2 months of therapy, with flu-like symptoms such as fever and malaise. For patients receiving carbamazepine or phenytoin, the incidence of DRESS is estimated to be 1 in 5,000.

Among the most severe of these reactions are Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Treatment with commonly used AEDs such as carbamazepine, phenytoin, phenobarbital, and lamotrigine is considered to increase the risk of SJS/TEN. For carbamazepine, the risk of developing SJS/TEN in individuals of European descent is about 1 to 6 cases of 10,000 patients exposed (5, 6).

SJS and TEN are considered to be variants of the same process, with the mortality rate for patients developing TEN approaching 30%. Clearly, it would be advantageous to be able to identify patients at possible risk for developing any sort of hypersensitivity reaction to these commonly used medications.

Until relatively recently, dermatologic reactions were considered to be idiosyncratic events, and thus, largely unpredictable. This notion changed however following the demonstration of a relationship between these potentially life-threatening reactions and the human leukocyte antigen (HLA)-B*1502 in various Asian populations (7, 8). Indeed,



avoidance of carbamazepine in patients carrying the HLA-B*1502 allele has recently been shown to substantially reduce the incidence of SJS/TEN in Asian patients (9). The discovery of the involvement of human leukocyte antigen–dependent presentation of a drug for T-cell activation has led to the recognition that a direct, noncovalent binding between a drug and T-cell receptor with an HLA molecule is responsible, leading to T-cell activation and clonal expansion of CD8+ cytotoxic T cells in the skin (10).

Clinically, recognition of the association of this allelic variant represent an important step forward in our ability to predict (and presumably prevent) serious hypersensitivity reactions to carbamazepine. Important questions, however, remained unanswered. For example, would genotype screening for HLA-B*1502 be of value in those patients of other ethnic Asian or European descent? Could these genetic variants be relevant for treatment with other aromatic ring–containing AEDs, such as phenytoin, oxcarbazepine, or lamotrigine?

With respect to generalizability to the broader population, while the HLA-B*1502 allele is quite prevalent in individuals from Southern China (~15%), as well as those from several other Southeast Asian countries (~2–8%), (11) this allele is quite uncommon in Japanese and European Caucasians (<1%). Although the incidence of SJS/TEN is lower in European Caucasians than certain Asian populations, it does clearly still occur.

In the genome-wide association study by McCormack and colleagues, samples were obtained from 26 patients with confirmed carbamazepine hypersensitivity syndrome, 106 patients with carbamazepine associated maculopapular exanthema (rash without systemic involvement), and 12 patients who had developed SJS/TEN. These individuals were then compared with genotype data derived from the Wellcome Trust Case Control Consortium, U.K. National Blood Services Collection, and the 1958 British Birth Cohort. In addition, a clinical control group ($n = 257$) of patients receiving carbamazepine for at least 3 months with no evidence of hypersensitivity were also compared.

For both patients with DRESS and SJS/TEN, a strong signal in the HLA-A region on chromosome 6 was seen with HLA-A*3101 being most strongly associated. This variant, which has a prevalence of up to 5% in Northern Europeans, was observed in 40% of patients with either DRESS or SJS/TEN as compared with only 4 to 5 percent of control subjects. With regard to maculopapular exanthema, HLA-A*3101 was again the most strongly associated allele, being seen in 27% of patients versus 4% of controls.

Although the population of this study was of Caucasian descent, it is interesting to note that HLA-A*3101, which is found in about 9% of Japanese and 2% of Han Chinese, has also been associated with carbamazepine hypersensitivity including SJS/TEN and maculopapular exanthema in these patient populations (12).

Taken together, these data provide compelling evidence that HLA-A*3101 is yet another important predictor of carbamazepine-associated cutaneous hypersensitivity reactions. Confidence in these findings is enhanced when one considers the consistency of the data across several independent groups of case subjects as well as controls. Now, can we use these data

to reliably screen and identify potentially at-risk patients and thereby avoid serious hypersensitivity? Perhaps.

McCormack and colleagues suggest that the presence of this allele increases the risk of a hypersensitivity reaction to 26%, whereas its absence lowers that risk to just under 4%. If one assumes that the prevalence of carbamazepine hypersensitivity is 5% in the European Caucasian population, then about 83 patients would need to be screened to prevent one hypersensitivity reaction. Of course, the number of patients needed to be screened would fall if, in fact, the actual prevalence of hypersensitivity were greater. For example, a carbamazepine hypersensitivity incidence of 10% would reduce the number needed to be screened to 39.

Chen et al. (9) recently reported that prospective screening for the HLA-B*1502 allele and subsequent avoidance of carbamazepine prescription in genetically susceptible Han Chinese patients did in fact reduce the occurrence of SJS/TEN, as compared with historical controls. Interestingly, the absence of the HLA-A*1502 allele did not appear to reduce the incidence of more mild rash and itching in these patients.

Finally, it is reasonable to speculate that given the strong association between either HLA-A*1502 in certain Asian populations or HLA-B*3101 in Northern Europeans and severe carbamazepine hypersensitivity, that we might expect to see similar risk in those patients receiving alternative AEDs such as oxcarbazepine, phenytoin, or lamotrigine. Unfortunately, the supportive evidence is still lacking. With respect to Han Chinese carriers of HLA-B*1502, the data is conflicting. Hung and coworkers (13) suggest an increased risk for oxcarbazepine and phenytoin in these patients. For lamotrigine, however, the presence of this allele (or any other) does not appear to be associated with increased risk of either maculopapular exanthema or SJS/TEN (14–16).

The U.S. FDA now recommends that patients of Asian ancestry be screened for HLA-B*1502 prior to starting treatment with carbamazepine. While helpful, until the study by McCormack et al., clinicians were left with a great deal of uncertainty as to how to apply this information to other patient groups. Will screening for HLA-A*3101 prove to be as beneficial in patients of European (and perhaps Japanese) ancestry as it appears that HLA-B*1502 identification is in Han Chinese? Only additional prospective studies will be able to answer this. For now, however, it seems only reasonable that screening for HLA-A*3101 be strongly considered prior to initiation of carbamazepine in those patients. Clearly, much work remains to be done. Optimistically, one can now realistically envision a time when genomic profiling will lead to safer pharmacological management in patients with epilepsy.

by Barry E. Gidal, PharmD

References

1. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Hume C, Bazil CW, Resor SR, Hirsch LJ. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology*. 2007;68:1701–1709.
2. Zaccra G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia*. 2007;48:1223–1244.
3. Shirzadi M, Alvestad S, Hovdal H, Espeset K, Lydersen S, Brodtkorb E. Comparison of carbamazepine rash in multiple sclerosis and epilepsy.



Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2011.01553.x. © 2011 John Wiley & Sons.

4. Beghi E, Shorvon S. Antiepileptic drugs and the immune system. *Epilepsia*. 2011;52(suppl):40–44.
5. Rzany B, Correia O, Kelly P, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during the first weeks of antiepileptic therapy: A case-control study. *Lancet*. 1999;353:2190–2194.
6. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology*. 2005;64:1134–1138.
7. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia*. 2007;48:1015–1018.
8. Lim KS, Kwan P, Tan CT. Association of HLA-B*1502 allele and carbamazepine-induced severe adverse cutaneous drug reactions among Asians: A review. *Neurol Asia*. 2008;13:15–21.
9. Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D., Jing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D., Sheng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S., Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S., Hung-Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chien-Hsiun Chen, Ph.D., Wen-Hung Chung, M.D., Ph.D., Shuen-lu Hung, Ph.D., Jer-Yuarn Wu, Ph.D., Chi-Feng Chang, Ph.D., Luke Chen, Ph.D., Yuan-Tsong Chen, M.D., Ph.D., and Chen-Yang Shen, Ph.D. for the Taiwan SJS Consortium
10. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med*. 2011;364:1126–1132.
11. Chung W-H, Hung S-I. Genetic markers and danger signals in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Allergol Int*. 2010;59:325–332.
12. Kashiwagi M, Aihara M, Takahashi Y, Yamazaki E, Yamane Y, Song Y, Muramatsu M, Ikezawa Z. Human leukocyte antigen genotypes in carbamazepine-induced severe cutaneous adverse drug response in Japanese patients. *J Dermatol*. 2008;35:683–685.
13. Hung SI, Chung WH, Liu ZS, Chen CH, Hsish MS, Hui RC, Chu CY, Chen YT. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics*. 2010;11:349–356.
14. Kazeem GR, Cox C, Aponte J, Messenheimer J, Brazell C, Nelsen AC, Nelson MR, Foot E. High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients. *Pharmacogenet Genomics*. 2009;19:661–665.
15. An DM, Wu X-T, Hu F-Y, Yan B, Stefan H, Zhou D. Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. *Epilepsy Res* 2010;92:226–230.
16. Shi Y-W, MIN F-L, Liu X-R, Ran Z-X, Gao N-M, Yu M-J, Liao WP. HLA-B alleles and lamotrigine-induced cutaneous adverse drug reactions in Han Chinese population. *Basic and Clinical Pharmacology and Toxicology*. 2011; 109:42–46.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 12/8/2011
2. First Name Barry Last Name Gidal Degree PharmD
3. Are you the Main Assigned Author? Yes No
If no, enter your name as co-author:
4. Manuscript/Article Title:
5. Journal Issue you are submitting for:

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input checked="" type="checkbox"/>				
2. Consulting fee or honorarium	<input type="checkbox"/>	\$0.00	\$10.00	GSK, UCB	
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input checked="" type="checkbox"/>				
2. Consultancy	<input checked="" type="checkbox"/>				
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input checked="" type="checkbox"/>				
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	10K		GSK, UCB	
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input type="checkbox"/>				
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

No other relationships/conditions/circumstances that present a potential conflict of interest.

Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board