

ORIGINAL ARTICLE

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

Mark McCormack, B.A., Ana Alfirevic, M.D., Ph.D., Stephane Bourgeois, Ph.D., John J. Farrell, M.S., Dalia Kasperavičiūtė, Ph.D., Mary Carrington, Ph.D., Graeme J. Sills, Ph.D., Tony Marson, M.B., Ch.B., M.D., Xiaoming Jia, M.Eng., Paul I.W. de Bakker, Ph.D., Krishna Chinthapalli M.B., B.S., Mariam Molokhia, M.B., Ch.B., Ph.D., Michael R. Johnson, D.Phil., Gerard D. O'Connor, M.R.C.P.I., Elijah Chaila, M.R.C.P.I., Saud Alhusaini, M.B., Kevin V. Shianna, Ph.D., Rodney A. Radtke, M.D., Erin L. Heinzen, Ph.D., Nicole Walley, B.S., Massimo Pandolfo, M.D., Ph.D., Werner Pichler, M.D., B. Kevin Park, Ph.D., Chantal Depondt, M.D., Ph.D., Sanjay M. Sisodiya, M.D., Ph.D., David B. Goldstein, Ph.D., Panos Deloukas, Ph.D., Norman Delanty, B.M., Gianpiero L. Cavalleri, Ph.D., and Munir Pirmohamed, Ph.D., F.R.C.P.

ABSTRACT

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.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Alfirevic at the Wolfson Centre for Personalised Medicine, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Block A: Waterhouse Bldgs., 1-5 Brownlow St., Liverpool L69 3GL, United Kingdom, or at ana.alfirevic@liv.ac.uk.

Mr. McCormack, Dr. Alfirevic, Dr. Cavalleri, and Dr. Pirmohamed contributed equally to this article.

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CARBAMAZEPINE IS ONE OF THE MOST commonly prescribed drugs for the treatment of epilepsy, as well as trigeminal neuralgia and bipolar disorder. A minority of treated persons have hypersensitivity reactions that vary in prevalence and severity,¹ with some forms associated with substantial morbidity and mortality. The mildest form, maculopapular exanthema, occurs in 5 to 10% of treated persons of European ancestry and resolves spontaneously after drug discontinuation. More severe reactions, such as the hypersensitivity syndrome, are associated with mortality of up to 10%² and include symptoms such as rash, fever, eosinophilia, hepatitis, and nephritis. The most severe reactions, such as the Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. The rate of death increases with the degree of epidermal detachment. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. According to the labeling of carbamazepine, as mandated by the Food and Drug Administration (FDA), the estimated incidence of SJS–TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug.

Genomewide approaches are increasingly used to identify genetic predisposing factors for drug-induced hypersensitivity reactions and drug-induced liver injury.³ For example, the HLA-B*1502 allele has been identified as a clinically important predictor of SJS–TEN in Asians of Han Chinese descent who are candidates for treatment with carbamazepine.⁴ This finding led the FDA to require a warning label for carbamazepine to indicate the need for genotyping for HLA-B*1502 before the drug is prescribed. This change seems warranted, given the prospective study described in this issue of the *Journal*,⁵ which shows that withholding carbamazepine from subjects of Han Chinese ancestry who carry the HLA-B*1502 allele substantially decreased the rate of the development of SJS–TEN. The value of HLA-B*1502 in predicting the risk of SJS–TEN has been shown in other Asian populations, including those of Thailand, Malaysia, and India.^{4,6–8} This effect is specific for SJS–TEN, as compared with the full spectrum of carbamazepine-related hypersensitivity reactions, which led to the suggestion that different phenotypes of carbamazepine-induced hypersensitivity may have distinct

genetic predictors. Furthermore, HLA-B*1502 is rare (with a prevalence of less than 2%) in populations of European descent, in which carbamazepine-induced SJS–TEN occurs at a lower incidence than in Asian populations.^{9–12} Using a candidate-gene approach, previous studies have shown weak or moderate signals of association between maculopapular exanthema or the DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome and single-nucleotide polymorphisms (SNPs) in the major histocompatibility complex (MHC) region,^{13–15} and these associations have not been consistently replicated.^{13,14}

We present data from two independent studies that suggest the relevance of an HLA variant to the clinical spectrum of carbamazepine-related hypersensitivity reactions, including maculopapular exanthema, the hypersensitivity syndrome, and SJS–TEN.

METHODS

CASE SUBJECTS

Recruitment

We recruited case subjects at centers collaborating with the University of Liverpool and Walton Centre for Neurology (both hereinafter referred to as “the Liverpool collaborators”) or at centers affiliated with the EPIGEN consortium (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). All case subjects and control subjects were of European ancestry as determined by either self-report or genetic-marker analysis.¹³ Many of these subjects have been described previously in the context of hypersensitivity reactions.^{9,13,16}

Hypersensitivity Syndrome

The group with the hypersensitivity syndrome consisted of 26 subjects: 23 who were recruited through the Liverpool collaborators and 3 who were recruited through the EPIGEN consortium. The hypersensitivity syndrome was defined as the presence of rash or liver involvement within 3 months after the initiation of carbamazepine treatment, accompanied by a minimum of two of the following manifestations: a prolonged recovery phase, despite withdrawal of the drug; fever; involvement of other internal organs (liver, kidney, lung, central nervous system, heart, muscle, thy-

roid, or lymphoid system); or the presence of hematologic abnormalities, such as eosinophilia and atypical lymphocytosis.¹⁷ We considered the DRESS syndrome to be the same as the hypersensitivity syndrome.

Acute Generalized Exanthematous Pustulosis

We recruited one subject with acute generalized exanthematous pustulosis (AGEP), who had a typical pustular reaction with high fever,¹⁸ from a collaborating clinic in Switzerland. We then analyzed the data from this subject together with data from the subjects with the hypersensitivity syndrome.

Maculopapular Exanthema

The group with maculopapular exanthema consisted of 106 subjects: 57 who were recruited through the Liverpool collaborators and 49 who were recruited through the EPIGEN consortium. Maculopapular exanthema was defined as rash without systemic symptoms that required the discontinuation of carbamazepine within 3 months after the initiation of drug therapy.

SJS–TEN

The SJS–TEN group consisted of 12 subjects: 8 who were recruited through the Liverpool collaborators and 4 who were recruited through the EPIGEN consortium. The diagnostic criteria suggested by the RegiSCAR Project (a research network for severe cutaneous adverse drug reactions)^{11,19} were used for this group (see the Supplementary Appendix).

CONTROL SUBJECTS

Population Controls

Genotype data from the Wellcome Trust Case Control Consortium (WTCCC) (www.wtccc.org.uk) were used as a population control group. The Liverpool collaborators used data from a genome-wide association study of samples from 2691 subjects in the U.K. National Blood Services Collection. EPIGEN used samples from a homogeneous subgroup of 1296 subjects in the 1958 British Birth Cohort that were selected by principal component analysis. We did not screen either set of population controls for carbamazepine-related adverse drug reactions. (For details about our access to these data, see the Supplementary Appendix.)

Clinical Controls

The clinical control group consisted of 257 subjects with epilepsy who had been taking carbamazepine for at least 3 months with no clinical or biochemical signs of hypersensitivity. Of these subjects, 44 were recruited by the Liverpool collaborators and 213 were recruited from clinics affiliated with EPIGEN.

GENOMEWIDE GENOTYPING

Genomewide analysis of samples that were initially available from the 22 Liverpool subjects with carbamazepine-induced hypersensitivity syndrome was performed with the use of the Illumina Infinium 1.2M chip at the Wellcome Trust Sanger Institute. Samples from 43 case subjects and 200 control subjects from the EPIGEN consortium were genotyped with the use of the Illumina 610K Quad platform at the Duke University Center for Human Genome Variation. (Details regarding quality controls and principal-components analysis are provided in the Supplementary Appendix.)

IMPUTATION OF HLA ALLELES

We based the imputation of classic HLA alleles in samples from the 22 Liverpool subjects with the hypersensitivity syndrome and control subjects from the U.K. National Blood Service on a dense reference panel of SNP data and four-digit HLA types in 2767 unrelated subjects of European descent, according to a method described recently.²⁰ We imputed classic HLA alleles in the samples from the EPIGEN consortium, using MACH 1.0 on the Web site of the Center for Statistical Genetics (www.sph.umich.edu/csg/abecasis/MACH).²¹ The 1458 subjects in the HLA-typed 1958 British Birth Cohort constituted the reference population. (See the Supplementary Appendix for further details.) We used different approaches to impute the HLA alleles in the Liverpool and EPIGEN subjects, because the two studies were originally independent.

HLA-A HIGH-RESOLUTION GENOTYPING

To confirm the accuracy of imputation, high-resolution, sequence-based HLA-A typing of samples from 22 subjects with the hypersensitivity syndrome and from a subgroup of 44 clinical control subjects (i.e., subjects who did not have adverse reactions to carbamazepine) was per-

formed by Histogenetics. We determined the HLA-A alleles in samples from 49 subjects with maculopapular exanthema and a subgroup of 213 clinical control subjects from the EPIGEN consortium, using sequence-specific polymerase-chain-reaction assay primers (details available on request). Direct genotyping showed 100% concordance with the imputed alleles.

HLA-A*3101 PROXY SNP GENOTYPING

Genotyping of the rs1061235 SNP in samples from all Liverpool subjects (including case subjects with maculopapular exanthema, the hypersensitivity syndrome, or SJS-TEN and clinical control subjects) was performed by KBioscience. This allele has previously been shown to be in complete linkage disequilibrium ($r^2=1$) with the HLA-A*3101 allele in populations of European descent.²²

STATISTICAL ANALYSIS

Statistical analyses were performed with the use of PLINK (version 1.05),²³ RevMan (version 5) (<http://ims.cochrane.org/revman>), and Haploview²⁴ software packages. For the genomewide association studies, both the Liverpool collaborators and the EPIGEN consortium used logistic regression with an additive model of inheritance. They adjusted for population stratification by including significant principal components as covariates in the logistic-regression model and used a P value of less than 5.0×10^{-8} to indicate genomewide significance. Pooled analysis of the different groups of subjects was performed to estimate odds ratios and confidence intervals from summary data with the use of a random-effects model. Between-study heterogeneity was tested by calculating I^2 and Tau.² The z-score directionality or estimated risk was checked for consistency with observed data.

RESULTS

ASSOCIATION WITH THE HYPERSENSITIVITY SYNDROME

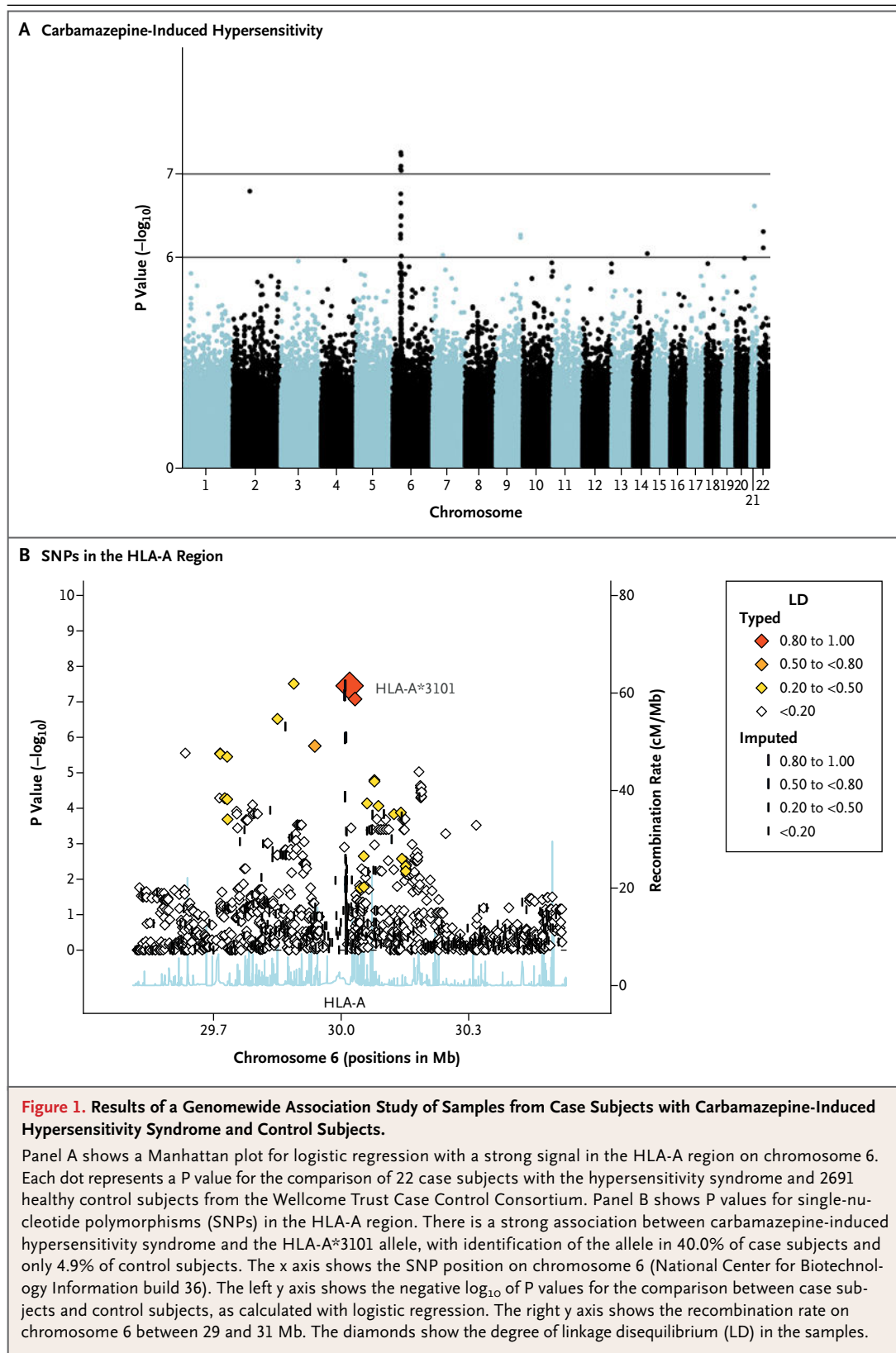
We first conducted an association analysis involving 1.2M SNPs in samples from the 22 Liverpool subjects with carbamazepine-induced hypersensitivity syndrome and from 2691 healthy controls from the U.K. National Blood Services Collection. (The full set of results can be obtained from the European Genotype Archive, access num-

ber EGAS000000000037.) We identified a strong signal in the MHC region on chromosome 6, with several SNPs around HLA-A reaching genomewide significance ($P=3.5 \times 10^{-8}$) (Fig. 1A and 1B). This variant was seen in 40.0% of case subjects but in only 4.9% of control subjects. The top hit (rs1061235) had previously been shown to be a proxy for the HLA-A*3101 allele in persons of European descent.²² Therefore, we focused on this locus as a predictor of response through high-resolution, sequence-based HLA-A typing, which confirmed the absolute correlation ($r^2=1$) between rs1061235 and HLA-A*3101 that had been observed previously.²² No other classic HLA-A alleles reached nominal significance (Table 1 in the Supplementary Appendix).

During the course of this study, samples from 4 additional subjects with the hypersensitivity syndrome and from 1 additional subject with AGEP became available from the Liverpool and EPIGEN centers. Of these 5 subjects, 2 (including the single subject with AGEP) tested positive for HLA-A*3101. A comparison of all 27 subjects with the 257 control subjects without adverse drug reactions produced an odds ratio of 12.41 (95% confidence interval [CI], 1.27 to 121.03; $P=0.03$) (Fig. 2).

ASSOCIATION WITH MACULOPAPULAR EXANTHEMA

EPIGEN investigators performed a genomewide association study of samples from 43 subjects with maculopapular exanthema and 1296 healthy control subjects from the 1958 British Birth Cohort. (The full set of results can be obtained from dbGAP, access number EGAS000000000036.) HLA-A*3101 was the most strongly associated allele ($P=1.11 \times 10^{-6}$) and was observed in 27% of case subjects and 4% of control subjects, although the effect was not significant genomewide (Fig. 3 in the Supplementary Appendix). However, we had access to another 63 case subjects with maculopapular exanthema and 257 control subjects without adverse drug reactions. Our combined analysis of all 106 subjects with maculopapular exanthema and the 257 clinical control subjects showed a significant allelic association with HLA-A*3101 ($P=8.0 \times 10^{-7}$), generating an odds ratio of 8.33 (95% CI, 3.59 to 19.36) (Fig. 2). Although the analyses of samples from subjects with maculopapular exanthema and those with the hypersensitivity syndrome were carried out in the Nether-



lands and Liverpool, respectively, the effect size of HLA-A*3101 on risk was consistent across the EPIGEN and U.K. groups.

ASSOCIATION WITH SJS–TEN

On the basis of our hypothesis that the HLA-A*3101 allele is associated with carbamazepine-induced SJS–TEN, we genotyped HLA-A*3101 in a group of 12 subjects with SJS–TEN who were recruited from both the Liverpool and EPIGEN-affiliated centers. Of these 12 subjects, 5 (42%) carried the allele, as compared with 10 (4%) of the 257 clinical control subjects (odds ratio, 25.93; 95% CI, 4.93 to 116.18; $P=8.0\times10^{-5}$) (Fig. 2).

A pooled analysis of all 145 subjects with carbamazepine-induced hypersensitivity and 257 control subjects without adverse drug reactions showed a strong association between hypersensitivity and the HLA-A*3101 allele (odds ratio, 9.12; 95% CI, 4.03 to 20.65; $P=1.0\times10^{-7}$). On the basis of this pooled collection, we calculated that the presence of HLA-A*3101 had a sensitivity of 26% and a specificity of 96% as a predictor of carbamazepine-associated hypersensitivity. Given that carbamazepine hypersensitivity has a prevalence of 5% (1:20), application of the test criteria from our pooled analysis would increase the post-test probability to 26% (approximately 1:4) on the basis of the positive likelihood ratio of 6.74 (95% CI, 3.51 to 13.00). Since the negative likelihood ratio was 0.77 (95% CI, 0.67 to 0.84), a negative HLA-A*3101 test would reduce the probability of hypersensitivity from 5.0% to 3.8% (1:26 ratio).

DISCUSSION

We found that a variation in the presence of the HLA-A*3101 allele is an important predictor of the full spectrum of carbamazepine-induced hypersensitivity reactions in persons of European descent. Such reactions range from the relatively mild but nevertheless troublesome maculopapular exanthema to more severe reactions, such as the hypersensitivity syndrome and SJS–TEN. Although the presence of the HLA-A*3101 allele is neither necessary nor sufficient for the development of hypersensitivity to carbamazepine, it is associated with a significantly increased risk.

Our data add to growing evidence of the role of different HLA alleles in predisposing patients

to immune-mediated adverse reactions, such as drug-induced hypersensitivity^{4,25–27} and liver injury.^{3,28} The most prominent example thus far is the strong predictive value of the HLA-B*5701 allele for hypersensitivity to the drug abacavir, used for the treatment of human immunodeficiency virus infection.^{25,26,29} FDA guidelines now recommend HLA-B*5701 testing in advance of abacavir prescription. Testing results in a reduction in the incidence of abacavir hypersensitivity^{27,30} and is cost-effective.^{29,31}

Our study now provides strong evidence suggesting that HLA-A*3101 is a predictor of carbamazepine hypersensitivity in Europeans. First, despite the small number of subjects who were included in the analysis, this signal had genome-wide significance. Second, the signal was observed across independent groups of case subjects with different phenotypes of carbamazepine hypersensitivity, with the use of independent sets of control subjects. Third, HLA-A*3101 has previously been shown to be associated with multiple carbamazepine-hypersensitivity phenotypes, including SJS–TEN in Japanese subjects^{15,32} and with carbamazepine-induced maculopapular exanthema in subjects of Han Chinese ancestry.¹⁴ The one subject in our study who had AGEP, a reaction characterized by sterile pustules, neutrophilic inflammation, and high levels of interleukin-8 in skin,³³ also was found to carry the HLA-A*3101 allele. The prevalence of this allele is 2 to 5% in Northern European populations, 2% in Han Chinese populations, and 9% in Japanese populations.^{32,34,35} The finding that HLA-A*3101 is associated with carbamazepine-induced hypersensitivity in populations of different ancestries parallels the finding of HLA-B*5701-associated abacavir hypersensitivity.^{30,36}

HLA-B*1502, a predictor of carbamazepine hypersensitivity reactions in Asian populations, seems to be phenotype-specific in that it predicts the development of SJS–TEN but not the development of the hypersensitivity syndrome or maculopapular exanthema.¹⁴ This finding has led to the suggestion that the pathogenesis of carbamazepine-induced SJS–TEN is distinct from that of the hypersensitivity syndrome. This hypothesis is based on the fact that class I alleles are usually associated with specific CD8+ cytotoxic T-cell reactions, which is consistent with the known pathologic features of SJS–TEN.³⁷ How-

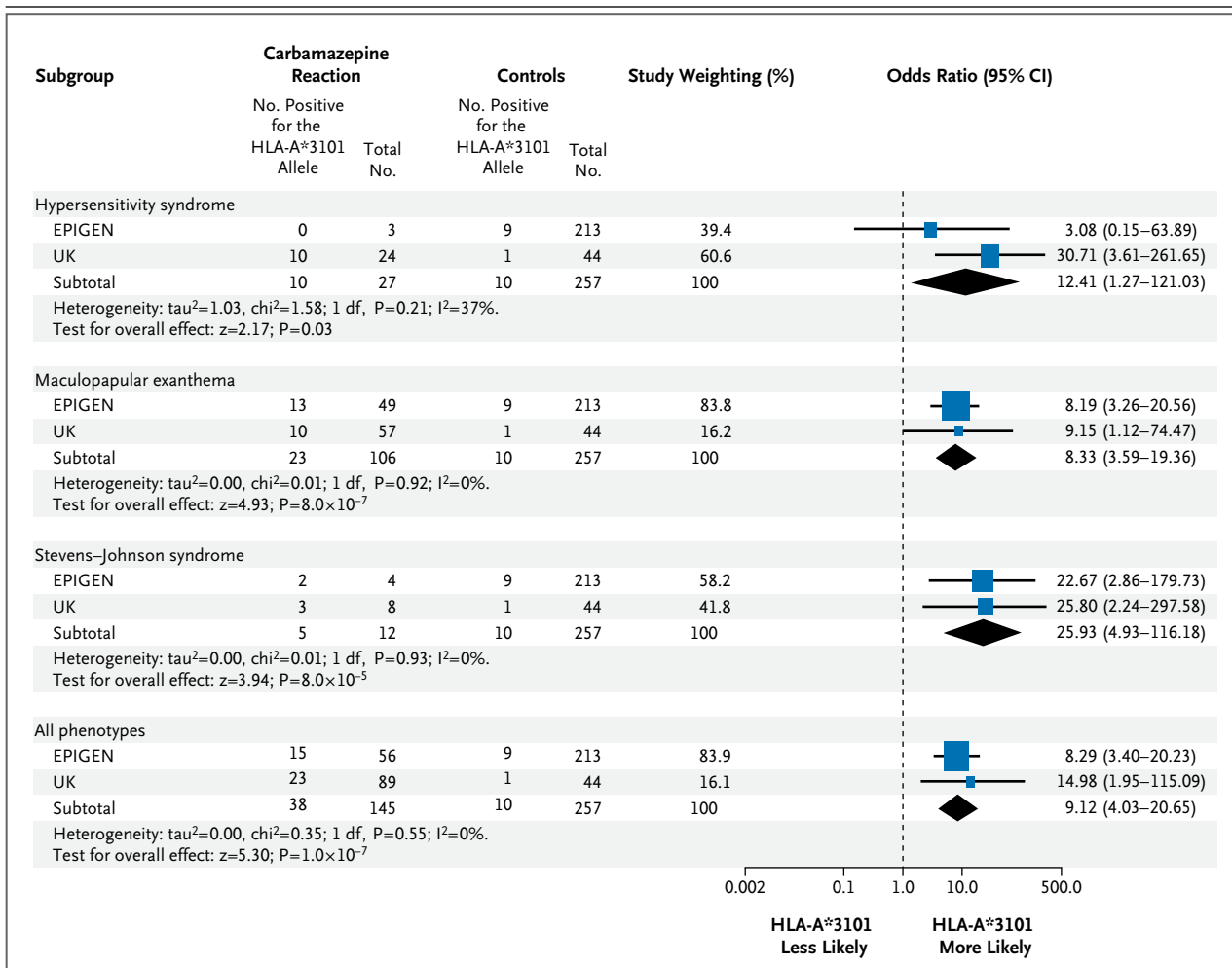


Figure 2. Distribution of the HLA-A*3101 Allele across the Spectrum of Clinical Phenotypes of Case Subjects with Carbamazepine-Induced Hypersensitivity and Control Subjects without Adverse Reactions to Carbamazepine.

Subjects were recruited at centers collaborating with the University of Liverpool and Walton Centre for Neurology (UK) or centers affiliated with the EPIGEN consortium. The sample obtained from one patient with acute generalized exanthematous pustulosis (AGEP) was analyzed with the samples for the group of case subjects with the hypersensitivity syndrome. Since there were no observations of the HLA-A*3101 allele in the three case subjects with the hypersensitivity syndrome in the EPIGEN cohort, 0.5 was added to each value in a two-by-two contingency table to estimate an odds ratio. One patient with the Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS–TEN) was of mixed European and Thai ancestry. Study weighting (indicated by different sizes of squares) refers to the proportion of subjects who were recruited from each study cohort. Diamonds indicate pooled odds ratios. The horizontal lines indicate 95% confidence intervals. The abbreviation df denotes degrees of freedom, and I^2 is the percentage of total variation that is due to heterogeneity rather than chance.

ever, our data suggest that the class I allele HLA-A*3101 may be important for an increased range of phenotypes, including maculopapular exanthema and the hypersensitivity syndrome, at least in European populations. Persons with carbamazepine-induced hypersensitivity syndrome have been shown to have several types of drug-specific T cells in peripheral blood, including CD4+, CD8+, and CD4–CD8+ cells.³⁸ Although there is

no obvious relationship between HLA-A*3101 and HLA-B*1502, reports have indicated a possible overlap in peptide-binding specificity.³⁹ Given the degree of linkage disequilibrium across the extended MHC region, we cannot be certain that either HLA-B*1502 or HLA-A*3101 is causal.

We used samples from healthy volunteers in the WTCCC as control subjects for both genomewide association studies. Given that the

hypersensitivity syndrome occurs in 1 in 5000 to 1 in 10,000 persons, it is unlikely that more than one or two population control subjects would be at risk for hypersensitivity with exposure to carbamazepine. The larger WTCCC collections therefore afforded increased power over that provided by comparison of case subjects with the clinical control subjects. Nevertheless, in analyses involving the 257 clinical control subjects, the association with HLA-A*3101 remained strong for both the hypersensitivity syndrome (odds ratio, 12.41; 95% CI, 1.27 to 121.03) and SJS (odds ratio, 25.93; 95% CI, 4.93 to 116.18), although the effect size was smaller with maculopapular exanthema (odds ratio, 8.33; 95% CI, 3.59 to 19.36).

Additional studies in populations of European descent and other ancestry are required to further characterize this association. The International Serious Adverse Event Consortium is coordinating a global effort to recruit subjects with drug-induced severe adverse events (www.saeconsortium.org). Efforts such as this will facilitate the analysis of larger groups of subjects, which may well uncover other genetic variants associated with a smaller effect size or population-specific variants. Additional work is also required to determine whether the effect of the HLA-A*3101 allele is specific to carbamazepine or whether it also applies to other drugs. A prospective study that is based on the results we present here would facilitate the routine clinical use of HLA-A*3101 testing in carbamazepine treatment. In this issue of the *Journal*, a report describes how prospective HLA-B*1502 typing can prevent carbamazepine-induced SJS-TEN in Han Chinese populations.⁵

We propose that HLA-A*3101 is clinically relevant as a marker to predict hypersensitivity reactions. On the assumption that the prevalence of carbamazepine-induced hypersensitivity is 5.0%, the presence of the HLA-A*3101 allele increases the risk of hypersensitivity to 26.0%, whereas its absence reduces the risk to 3.8%. Among Japanese patients, the estimated reduction is from 2.9% to 1.1%. The sensitivity and specificity values estimated here for Europeans (26% and 96%) and by others for Japanese populations (61% and 88%)³² vary. Among a number of possible reasons for these differences are differences in study size, in the frequency of HLA-A*3101 (and potential interacting variation), and in the

effect size of the allele across the two populations. Nonetheless, these numbers are similar to those underlying the test criteria calculated for the presence of the HLA-B*5701 allele and abacavir hypersensitivity (sensitivity, 45.5%; specificity, 97.6%; and a risk reduction from 7.8% to 2.7%).

On the basis of our data, we have calculated that 83 patients would need to be screened to prevent one case of carbamazepine hypersensitivity; the number in the Japanese population is 56. However, it is important to note that this calculation is based on a conservative estimate of the prevalence of carbamazepine hypersensitivity (5%). The prevalence of carbamazepine-induced hypersensitivity that was determined in the context of the Standard and New Antiepileptic Drugs (SANAD) trial (Current Controlled Trials number, ISRCTN38354748) (also involving subjects of European descent) was 10%.⁴⁰ On the basis of this prevalence, the number of persons who would need to be screened to prevent one instance of carbamazepine-induced hypersensitivity is 39. We therefore suggest that consideration be given to adding the association with HLA-A*3101 to the drug label for carbamazepine.

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APPENDIX

The authors' affiliations are as follows: Molecular and Cellular Therapeutics, the Royal College of Surgeons in Ireland (M. McCormack, S.A., N.D., G.L.C.), and the Division of Neurology, Beaumont Hospital (G.D.O., E.C., N.D.) — both in Dublin; the Department of Molecular and Clinical Pharmacology, University of Liverpool (A.A., G.J.S., T.M., B.K.P., M. Pirmohamed), and Walton Centre for Neurology (T.M.) — both in Liverpool; Wellcome Trust Sanger Institute, Hinxton (S.B., P.D.); and the National Society for Epilepsy, Chalfont-St-Peter, Buckinghamshire (K.C., S.M.S.) — all in the United Kingdom; the Department of Medicine, Boston University (J.F.F.), Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University (M.C.), Harvard-MIT Division of Health Sciences and Technology (X.J.), and the Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School (P.I.W.B.) — all in Boston; the Department of Clinical and Experimental Epilepsy, University College London, Institute of Neurology, Queen Square (D.K., K.C., S.M.S.), the Department of Primary Care and Public Health Sciences, Division of Health and Social Care Research, King's College (M. Molokhia), and the Centre for Neuroscience, Department of Medicine, Imperial College London (M.R.J.) — all in London; the Cancer and Inflammation Program, Laboratory of Experimental Immunology, SAIC-Frederick, National Cancer Institute at Frederick, Frederick, MD (M.C.); the Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA (P.I.W.B.); Julius Center for Health Sciences and Primary Care and the Department of Medical Genetics, Division of Biomedical Genetics, University Medical Center, Utrecht, the Netherlands (P.I.W.B.); the Center for Human Genome Variation (K.V.S., E.L.H., N.W., D.B.G.) and the Department of Medicine (Neurology) (R.A.R.), Duke University Medical School, Durham, NC; the Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels (M. Pandolfo, C.D.); and the Department of Rheumatology, Clinical Immunology, and Allergology, University of Bern, Bern, Switzerland (W.P.).

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