

Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

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Neurology® 2018;90:e332-e341. doi:10.1212/WNL.0000000000004853

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Page 155

Abstract

Objective

To characterize, among European and Han Chinese populations, the genetic predictors of maculopapular exanthema (MPE), a cutaneous adverse drug reaction common to antiepileptic drugs.

Methods

We conducted a case-control genome-wide association study of autosomal genotypes, including Class I and II human leukocyte antigen (HLA) alleles, in 323 cases and 1,321 drug-tolerant controls from epilepsy cohorts of northern European and Han Chinese descent. Results from each cohort were meta-analyzed.

Results

We report an association between a rare variant in the complement factor H-related 4 (*CFHR4*) gene and phenytoin-induced MPE in Europeans ($p = 4.5 \times 10^{-11}$; odds ratio [95% confidence interval] 7 [3.2–16]). This variant is in complete linkage disequilibrium with a missense variant (N1050Y) in the complement factor H (*CFH*) gene. In addition, our results reinforce the association between *HLA-A*31:01* and carbamazepine hypersensitivity. We did not identify significant genetic associations with MPE among Han Chinese patients.

Conclusions

The identification of genetic predictors of MPE in *CFHR4* and *CFH*, members of the complement factor H-related protein family, suggest a new link between regulation of the complement system alternative pathway and phenytoin-induced hypersensitivity in European-ancestral patients.

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The Article Processing Charge was funded by the European Commission OpenAIRE2020 project.

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Glossary

ADR = adverse drug reaction; **AED** = antiepileptic drug; **cADR** = cutaneous adverse drug reaction; **CFH** = complement factor H; **CFHR4** = complement factor H-related 4 gene; **CI** = confidence interval; **CPNDS** = Canadian Pharmacogenomics Network for Drug Safety; **GWAS** = genome-wide association study; **HLA** = human leukocyte antigen; **ILAE-CGC** = International League Against Epilepsy Complex Genetics Consortium; **MPE** = maculopapular exanthema; **OR** = odds ratio; **SJS/TEN** = Stevens-Johnson syndrome and toxic epidermal necrolysis; **SNP** = single nucleotide polymorphism.

Idiosyncratic cutaneous adverse drug reactions (cADRs) can have a genetic predisposition. The *HLA-B*15:02* allele is a predictor of carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) in individuals of Han Chinese and Southeast Asian descent, while a recent meta-analysis suggests that the allele is also a significant risk factor for oxcarbazepine-, phenytoin-, and lamotrigine-induced SJS/TEN.^{1,2} However, the association with *HLA-B*15:02* does not extend to the milder but more common maculopapular exanthema (MPE) phenotype, and the allele is specific to individuals of Asian descent, limiting clinical utility across populations.^{3,4} *HLA-A*31:01* has been confirmed as a transethnic risk factor for carbamazepine-induced cADRs, with the allele observed across populations of European, Japanese, and Korean descent.⁵⁻⁸ Recently, *HLA-A*24:02* has been shown to associate with SJS in Han Chinese patients, irrespective of causal drug studied.⁹ Genetic variation beyond the major histocompatibility locus has also been associated with cADRs. The *CYP2C9*3* allele correlates with phenytoin hypersensitivity in Han Chinese from Taiwan,¹⁰ with a similar effect reported in a Thai population.¹¹ However, a genome-wide association study (GWAS) of lamotrigine and phenytoin-induced cADRs in Europeans did not detect significant predictors.¹² A summary of the associated genetic risk variants for cADRs in various populations is provided in table e-1 (links.lww.com/WNL/A56).

The EpiPGX Consortium was established to identify genetic markers of epilepsy treatment response. The International League Against Epilepsy Complex Genetics Consortium (ILAE-CGC) facilitates the discovery of genetic variants influencing epilepsy predisposition.¹³ The EPIGEN consortium is a worldwide epilepsy genetics research framework and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is an active surveillance network focused on identifying genomic markers of severe adverse drug reactions (ADRs) in children and adults.¹⁴ Collaboration among these consortia has provided detailed phenotypes and genotypes for over 15,000 epilepsy cases, for the investigation of antiepileptic drug (AED)-induced MPE.

Availing of the joint resources of EpiPGX, ILAE-CGC, EPIGEN, and CPNDS, this study aimed to characterize, among European and Han Chinese populations, the genetic predictors of MPE, a cutaneous ADR common to particular AEDs. Specifically, we set out to test the following hypotheses: (1) whether population-specific genetic variants predict

MPE; (2) whether transethnic genetic variants predict MPE; (3) whether population-specific genetic variants predict AED-specific MPE; and (4) whether transethnic genetic variants predict AED-specific MPE.

Methods

Standard protocol approvals, registrations, and patient consents

All study participants provided written, informed consent for genetic analysis. Local institutional review boards approved study protocols at each contributing site.

Study design

We conducted a retrospective case-control study in individuals of European and Han Chinese ethnicity. Participants were exposed to carbamazepine, lamotrigine, phenytoin, or oxcarbazepine. Our analyses were structured to test genetic variants for association with MPE within and across both of the broad ancestral groups, through logistic regression of genotype dosage and subsequent meta-analysis of regression coefficients. We tested for association with (1) aromatic AED-induced MPE vs controls tolerant to at least 3 aromatic AEDs, (2) carbamazepine-induced MPE vs carbamazepine-tolerant controls, (3) lamotrigine-induced MPE vs lamotrigine-tolerant controls, and (4) phenytoin-induced MPE vs phenytoin-tolerant controls. Due to small sample size, oxcarbazepine-related MPE was not analyzed as an individual case cohort.

Cohorts and phenotype definition

Epilepsy cohorts from the ILAE-CGC, EpiPGX, and EPIGEN Consortia were included in the discovery GWAS meta-analysis (table 1). A European-descent replication cohort was assembled from sites in Brazil, Canada (via CPNDS), Liverpool, and other sites across the United Kingdom. Cases were defined as having MPE attributed to carbamazepine, lamotrigine, phenytoin, or oxcarbazepine as determined by their clinician, occurring within 3 months of initiation and resolving upon dose reduction or AED withdrawal. Control patients trialed carbamazepine, lamotrigine, phenytoin, or oxcarbazepine for at least 3 months without reporting a cADR. Epilepsy-specific patient demographics are presented in table e-2 (links.lww.com/WNL/A56).

Genotyping and imputation

Genotyping of a subset of EpiPGX samples was performed at deCODE Genetics (Reykjavik, Iceland) using Illumina (San

Table 1 Breakdown of antiepileptic drug (AED)-induced maculopapular exanthema (MPE) cases and AED-tolerant controls in discovery dataset

Ethnicity	All aromatic AEDs		CBZ		LTG		PHT	
	MPE ^a	Control ^b	MPE	Control	MPE	Control	MPE	Control
European	259	979	95	869	118	812	52	472
Han Chinese ^c	116	342	85	197	16	32	22	58
Subtotal	375	1,321	180	1,066	134	844	74	530

Abbreviations: CBZ = carbamazepine; ILAE = International League Against Epilepsy; LTG = lamotrigine; PHT = phenytoin.

^a Individual participant counts only, despite 16 patients being cross-reactive to more than 1 AED.

^b A total of 1,321 controls were tolerant to all 3 of CBZ, LTG, and PHT.

^c Fifty-two carbamazepine-induced MPE cases from Guangzhou were available for analysis of human leukocyte antigen serotype data only.

Diego, CA) OmniExpress-12 v1.1 and OmniExpress-24 v1.1 single nucleotide polymorphism (SNP) arrays. The remainder of samples were genotyped locally using various Illumina beadchip SNP arrays, details of which are published elsewhere.¹³ Genotyping and imputation quality control is described in appendix e-1 (links.lww.com/WNL/A57).

Study power

We estimated that the study had 80% power to detect a genetic predictor of relative risk (approximated to odds ratio) ≥ 3 with an allele frequency $\geq 2\%$ and an α level of 1.25×10^{-8} . Power for AED-specific and population-specific analyses are detailed in appendix e-1 (links.lww.com/WNL/A57).

Statistical analyses

Association analyses were conducted within the European and Asian subgroups using an additive logistic regression model. To account for genotype uncertainty, SNPTEST was used to apply a missing data likelihood score model that included sex, clinical site, and 5 principal components as covariates to control for bias and population stratification.¹⁵ Fixed effects meta-analyses were conducted across the European and Asian subgroups using the software package METAL, applying genomic control correction within cohorts.¹⁶ The threshold for statistical significance was set at 1.25×10^{-8} , reflecting an empirical Bonferroni correction for 4 tests, of the standard 5×10^{-8} genome-wide significance threshold. Conditional association analysis was performed on loci containing significant markers to establish whether other genetic variants in the region (1 Mb upstream and downstream) were independently associated with MPE. The conditional threshold for significance was set at 5×10^{-6} , based on a genome-wide estimation of 10,000 imputed variants per 2 MB region.¹³ We applied the Stouffer z trend test to the combined results from the discovery and replication cohorts.

Confirmatory genotyping

Where an association signal satisfied the threshold for significance, additional genotyping and resequencing were performed in a subset of patients and results were compared with imputation dosage files. The variant rs78239784 was

confirmed by Sanger sequencing in 100 patients from the original discovery cohort. For the purpose of replication, we genotyped the rs78239784 variant in an independent cohort of 13 phenytoin-induced MPE cases and 88 phenytoin-tolerant controls.

Results

Cohort description

In total, 375 MPE cases and 1,321 controls satisfied our criteria for inclusion in the discovery analyses (see Methods and table 1). There were 16 patients with cross-reactivity to 2 or more aromatic AEDs, 8 of whom were hypersensitive to carbamazepine and lamotrigine. Genome-wide array data for 323 cases and 1,321 controls were available for analysis. Broad European or Han Chinese ancestry was assigned to each participant according to principal components analysis (figure e-1, links.lww.com/WNL/A55).

Genome-wide association analysis of broad aromatic AED-induced MPE

After quality control (see appendix e-1, figure e-2, links.lww.com/WNL/A55, for details), 3,693,290 variants remained for analysis in the European dataset and 4,402,554 variants in the Han Chinese dataset. We only considered autosomal SNPs in our analyses. To test hypothesis (1), that population-specific genetic markers predispose to MPE, a logistic regression analysis of all MPE cases was performed separately in the European and Han Chinese ancestral subgroups. We did not observe any genome-wide significant markers for MPE due to any aromatic AED in either Europeans or Han Chinese. The study was powered to detect an effect of relative risk >3.5 in the European cohort and >5 in the Han Chinese.

To test hypothesis (2), that transethnic genetic markers predispose to MPE, a fixed-effects meta-analysis of the association results for European and Han Chinese ancestral subgroups was performed. We did not observe any genome-wide significant markers for MPE shared among European or Han Chinese subgroups (figure 1A). This analysis was powered to detect an effect size >3 .

Genome-wide association analysis of specific aromatic AED-induced MPE

To test hypothesis (3), that genetic variants for MPE are AED-specific and population-specific, logistic regression analyses of AED-specific MPE was performed separately in the European and Han Chinese ancestral groups (figures e-3 and e-4, links.lww.com/WNL/A55). Within the European subgroup, *HLA-A*31:01* was significantly associated with carbamazepine-induced MPE in Europeans ($p = 1.47 \times 10^{-10}$, odds ratio [OR] [95% confidence interval (CI)] 5.5 [3.0–10]). Conditioning on *HLA-A*31:01* did not reveal additional variants within the human leukocyte antigen (HLA) region that were independently contributing to carbamazepine-induced MPE. No genome-wide significant signals for lamotrigine-induced MPE were observed in Europeans. This analysis was powered to detect an effect size >6 .

For phenytoin-induced MPE, we identified a significant association with rs78239784, an intronic variant of the complement factor H-related 4 gene (*CFHR4*). The risk allele, G, had a minor allele frequency of 12% in our European phenytoin-induced MPE cases compared to 1.5% in European phenytoin-tolerant controls ($p = 2.94 \times 10^{-10}$, OR [95% CI] 8.8 [4.0–19]; figure 2). Conditioning on rs78239784 did not reveal additional variants in this locus that were independently contributing to phenytoin-induced MPE. Using 1000 Genomes Phase III European population data, rs78239784 was found to be in complete linkage disequilibrium with rs35274867 ($r^2 = 1$ and $D' = 1$), a missense variant coding for an asparagine to tyrosine substitution at amino acid 1,050 of the complement factor H (*CFH*) gene. The missense variant was not present in our association results, as it was filtered during quality control because the imputation score was <0.95 . The imputation accuracy of the top variant rs78239784 was confirmed in our cohort via Sanger sequencing and TaqMan approaches. Of 100 samples tested, a 100% concordance rate was found between imputed and resequenced genotypes. Within the Han Chinese subgroup, no significant associations were found between autosomal SNPs or *HLA* alleles and AED-specific MPE. Summary results for known risk loci in our dataset were scrutinized and are presented in table 2. None of these loci was even nominally significant ($p > 0.05$) in the Han Chinese subgroup.

In order to test hypothesis (4), that transethnic genetic markers predispose to AED-specific MPE, we meta-analyzed p values from association results for carbamazepine, lamotrigine, and phenytoin individually, across European and Han Chinese ancestral subgroups. There were no shared genome-wide significant markers among our meta-analyses of AED-specific MPE (figure 1, B–D).

Replication of *CFHR4* signal

To replicate the association with phenytoin-induced MPE in an independent cohort, the variant rs78239784 was genotyped in self-reported European-descent cases and controls

recruited through centers in Liverpool (United Kingdom), Sao Paulo (Brazil), and across Canada (CPNDS). Two heterozygous carriers were identified among 13 phenytoin-induced MPE cases while only a single carrier was observed among 88 phenytoin-tolerant controls yielding a 2-tailed Fisher exact p value of 0.044. Pooling all cases and controls together, we report an overall p value of 4.5×10^{-11} (with a combined OR [95% CI] 7 [3.2–16]) for the association between rs78239784 and phenytoin-induced MPE in Europeans (table 3).

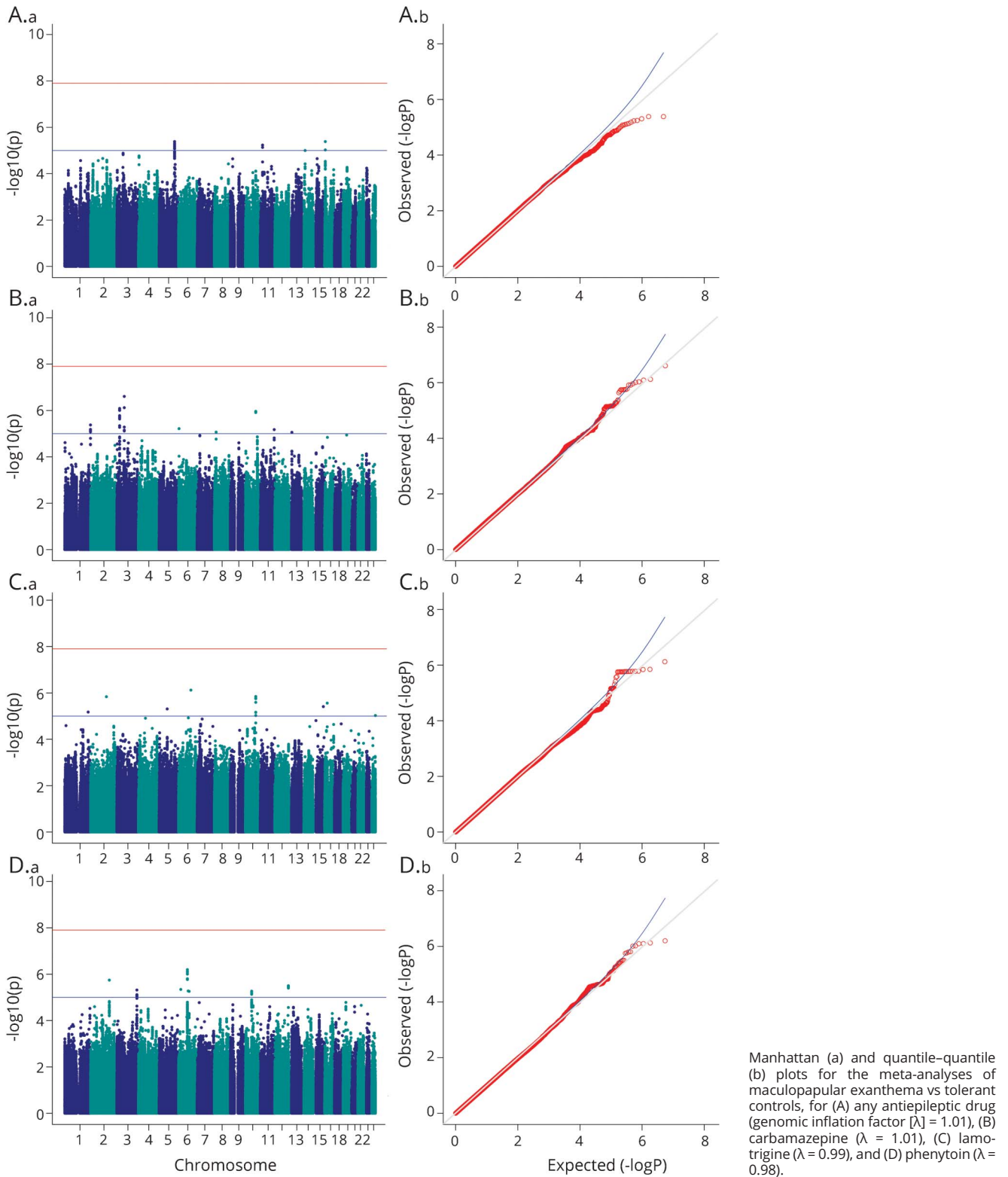
Discussion

We detected a strong association between variants in the complement factor H regulatory pathway and phenytoin-induced MPE in a European-descent patient population. The presence of the associated genotype increases risk for MPE 6-fold. Our results indicate that risk variants for MPE tend to be drug-specific and population-specific.

These results point to the regulators of complement activation gene cluster as a genetic locus contributing to the onset of hypersensitivity to phenytoin. The most significant variant in our European subgroup analysis, rs78239784 (c.59-2448T>G), tags the missense variant rs35274867 (p. N1050Y) in *CFH*, suggesting aberrant complement activation as a potential causal mechanism in a subset of phenytoin-sensitive individuals. According to data from the Exome Aggregation Consortium, *CFH* N1050Y has an allele frequency of approximately 2% in Europeans, 3% in African subpopulations, less than 1% in South Asians, and is almost invariant in East Asians.¹⁷ Given the absence of this allele in East Asian populations, the lack of an association between the *CFH* locus and MPE in our Han Chinese cohort is unsurprising. We propose that population-specific, independent rare variants of large effect may explain a proportion of MPE cases, a similar paradigm to the rare variant model demonstrated in Crohn disease and ulcerative colitis.¹⁸ *CFH* N1050Y has previously been associated with type 2 diabetes-associated end-stage kidney disease in an African American cohort.¹⁹ Defects in *CFH*-related proteins are also associated with overactivation of the complement immune system and can lead to atypical hemolytic-uremic syndrome, C3 glomerulopathy, basal laminar drusen, immunoglobulin A nephropathies, and systemic lupus erythematosus.²⁰ Further, genetic variants in *CFHR4* and *CFH* are associated with risk for age-related macular degeneration.²¹ We did not detect these symptoms among N1050Y carriers. While it is unclear whether phenytoin directly interacts with circulating *CFH*-related proteins, it does not specifically increase serum complement levels.²² Our findings offer an expanded insight into the role of the complement alternative pathway in hypersensitivity to AEDs.

Phenytoin is still used as a first-line treatment for epilepsy in many settings and is listed on the WHO list of essential

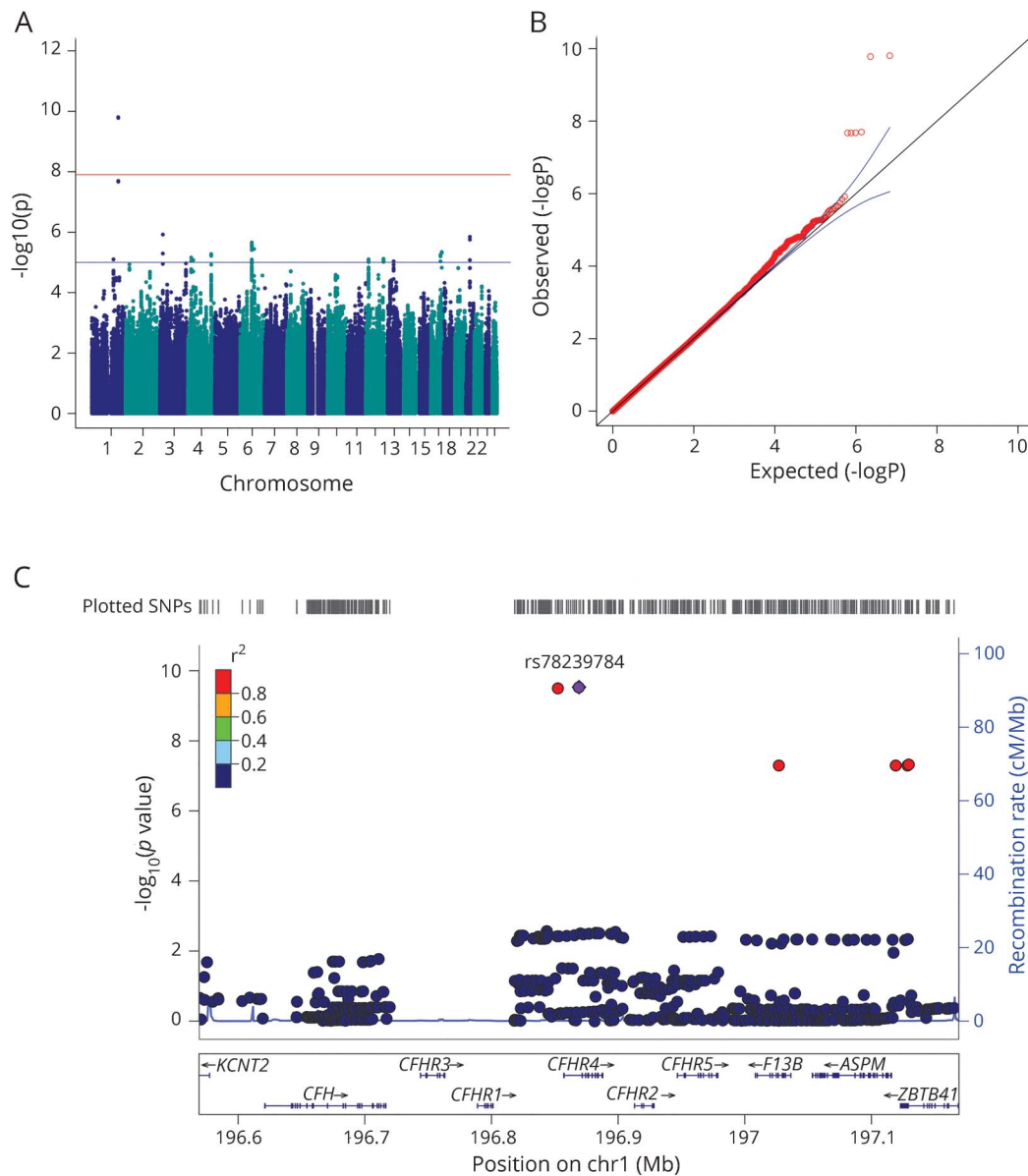
Figure 1 Meta-analysis results across European and Han Chinese cohorts



medicines.²³ Epidemiologic data on prescriptions of AEDs for epilepsy in the United Kingdom show that, in 2008, phenytoin accounted for 18% of all treated person-years in epilepsy and was most frequently used in the elderly.²⁴ Therefore,

a clinically useful prognostic test for phenytoin-induced cutaneous ADRs in European-ancestral individuals would be welcome. The sensitivity of the *CFHR4* variant as a prognostic marker is 16% and the specificity is 97%, which corresponds to

Figure 2 Intronic *CFHR4* variants are associated with phenytoin-induced maculopapular exanthema (MPE) in Europeans



(A) Manhattan and (B) quantile–quantile plot of phenytoin-induced MPE in the European subgroup ($\lambda = 1.01$). The LocusZoom plot (C) highlights the most significant single nucleotide polymorphism (SNP), rs78239784 (purple dot), is an intronic variant in *CFHR4*.

a positive likelihood ratio of 5.93 (95% CI 2.8–12.6) and a negative likelihood ratio of 0.86 (95% CI 0.8–0.9). Assuming the pretest probability of the ADR is 5%, a positive test for this marker increases the probability of MPE to phenytoin sixfold to 30%, while a negative test reduces the probability marginally to 4.3%. There are an estimated 6 million people with epilepsy in Europe, which means approximately 90,000 people are at-risk carriers of this mutation.²⁵ We estimate that 208 (95% CI 103–431) patients of European ancestry would need to be screened to prevent one case, based on a previously reported formula,²⁶ which corresponds to an absolute risk reduction of 0.005 (95% CI 0.002–0.009). As a comparison, it is estimated that 442 Han

Chinese patients would be needed to be screened for *HLA-B*15:02* in order to prevent a single carbamazepine-induced SJS/TEN case. We would suggest that the clinical utility and cost-effectiveness of implementing preemptive screening be evaluated through a prospective study.

We did not replicate the association between *CYP2C9*3* (rs1057910) and MPE in our cohort, irrespective of ethnicity or AED. This is not surprising given that the original association with phenytoin in Han Chinese was largely driven by SJS/TEN cases, which were excluded from this analysis. We did, however, detect a nonsignificant enrichment of *CYP2C9*3* ($p = 0.08$) among the European phenytoin-

Table 2 Association test results for risk alleles for maculopapular exanthema (MPE) across ethnicities

Drug	Marker	European			Han Chinese				
		MPE Homozygosity/heterozygosity/reference (MAF)	Control Homozygosity/heterozygosity/reference (MAF)	OR (95% CI)	p Value	MPE Homozygosity/heterozygosity/reference (MAF)	Control Homozygosity/heterozygosity/reference (MAF)	OR (95% CI)	p Value
CBZ	HLA-B*15:02	0/0/95 (0)	0/0/869 (0)	—	—	0/2/21 (0.04)	3/22/162 (0.07)	0.6 (0.1–2.8)	0.53
CBZ	HLA-A*31:01	0/16/79 (0.08)	0/27/841 (0.02)	5.5 (3.0–10)	1.47×10^{-10}	0/1/22 (0.02)	0/10/156 (0.03)	0.8 (0.1–6.8)	0.81
LTG	HLA-A*24:02	2/14/102 (0.08)	8/122/681 (0.09)	0.9 (0.5–1.5)	0.71	0/4/12 (0.12)	1/7/20 (0.16)	0.7 (0.1–3.5)	0.62
PHT	CYP2C9*3	0/10/42 (0.1)	0/51/421 (0.05)	1.8 (0.9–3.8)	0.08	0/1/21 (0.02)	0/2/56 (0.02)	0.9 (0.1–12)	0.92
PHT	rs78239784	2/8/42 (0.12)	0/14/458 (0.02)	8.8 (4.0–19)	2.94×10^{-10}	0/0/22 (0)	0/0/58 (0)	—	—

Abbreviations: CBZ = carbamazepine; CI = confidence interval; LTG = lamotrigine; MAF = mean allele frequency; OR = odds ratio; PHT = phenytoin. Representative risk alleles from previous genome-wide association study findings and this report for antiepileptic drug-induced skin rash studies (CBZ, LTG, and PHT) were assessed for association in our study. *p* Values from logistic regression model with sex and 5 principal components as covariates.

induced MPE cases, but the effect size we observe (OR 1.8) is smaller than previously reported for phenytoin-induced MPE in Han Chinese (OR 5.5).¹⁰ Notably, 2 *CYP2C9*3* carriers among the phenytoin-induced MPE cases were also heterozygous for the *CFHR4* variant while only 3 of 560 controls were jointly heterozygous. The frequency of *CYP2C9*3* differs between controls from European and Han Chinese subgroups in our study, which is in accordance with background population frequency reported in the Exome Aggregation Consortium (European: 7%, East Asian: 3%). While our results do not support a significant effect of *CYP2C9*3* in MPE, larger cohorts including severe cADR cases may resolve the extent of the association across populations.

*HLA-A*31:01* was the most strongly associated marker with carbamazepine-induced MPE in Europeans in this study. Forty-three of the 95 cases studied here were also included in the discovery publication,⁸ but the effect of the allele remains significant when we restrict to new cases only ($p = 4 \times 10^{-7}$), thus providing an additional independent replication of the initial finding. We confirm that *HLA-B*15:02* is not associated with carbamazepine-induced MPE in Han Chinese, and no novel signals emerged for carbamazepine-induced MPE in either population. No significant predictors of lamotrigine-induced MPE were observed in either population tested. *HLA-A*24:02* was not significantly associated with lamotrigine-induced MPE in either of the European or Han Chinese ancestral subgroups; rather this allele was observed to be more frequent among our lamotrigine-tolerant controls.

Our meta-analyses did not reveal any significant transethnic genetic markers for MPE due to any AED. There were considerably more European-descent patients in this analysis than any other ethnicity, and we recognize this as a limitation of the study. Analysis of non-European cohorts is warranted. A second limitation of our study was the low number of Han Chinese lamotrigine-related MPE cases, relative to European-descent cases. Therefore we cannot conclusively rule out genetic predictors of modest effect size for MPE to lamotrigine in Han Chinese or other non-European descent populations. We recognize that our replication cohort for phenytoin is small and comprises self-reported ancestral Europeans. Since we did not have full genotype array data for these individuals, we relied on Fisher exact test for calculating significance rather than logistic regression with correction for principal components. Additional studies of larger sample size are required to further characterize the association, improve the estimation of the risk effect size, and determine the prognostic ability and economics of screening for this marker. Finally, as this study was not powered to investigate MPE attributed to oxcarbazepine due to low sample size, further investigation is warranted.

We have identified a genetic predictor for a common adverse reaction to phenytoin in European-descent patients, adding a new pharmacogenetic marker for potential use in the treatment of epilepsy. This finding adds to the list of genetic

Table 3 rs78239784 associates with phenytoin-induced maculopapular exanthema in Europeans

rs78239784	Discovery GWAS	Replication	Combined	Control
N	52	13	63	560
Frequency (G)	0.12	0.08	0.11	0.01
p Value	2.9 × 10 ^{-10a}	0.044 ^b	4.5 × 10 ⁻¹¹	—
OR (95% CI)	8.8 (4.0–19)	15 (1.3–17)	7.0 (3.2–16)	—

Abbreviations: CI = confidence interval; GWAS = genome-wide association study; OR = odds ratio.

Discovery, replication, and combined association test results of rs78239784 with phenytoin-induced cutaneous adverse drug reactions in Europeans.

^a p Value from logistic regression model with sex and 5 principal components as covariates.

^b p Value from Fisher exact test.

predictors of hypersensitivity to anticonvulsant therapy and opens up a new avenue for understanding the biology underlying cutaneous adverse reactions. This finding can advance genetic testing in the clinic as it expands the array of genetic tests available to aid clinicians in reducing overall rates of discontinuation due to adverse events and improving patient safety.

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M.M.C., H.G., L.B., S.C., P.K., and G.L.C. contributed to the conception and design of the study and the acquisition, analysis, and interpretation of data. M.M.C. and H.G. performed all statistical analysis. A.I., S.M.S., R.S., S.W., F.B., S.R., K.H., C.L., A.G.M., P.A., M.J.B., B.F., M.R.J., N.S., G.E.B.W., C.J.D., B.C.C., D.S., J.E.Z., M.K., M.P., A.A., C.D., G.J.S., B.P. C.K., P.S., F.Z., A.C., W.S.K., J.W.S., H.L., K.M.K., S.W., M.K.,

L.J.G., R.K., N.D., C.Y., F.C., I.L.-C., T.J.O., W.-p.L., L.J.G., and K.S. contributed to the acquisition, analysis, and interpretation of data. All authors contributed to the critical revision of the final version of the manuscript for important intellectual content.

Acknowledgment

The authors thank the following coinvestigators: the members of the EpiPGX Consortium, the members of the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Consortium, the members of the International League Against Epilepsy Consortium on Complex Epilepsies (ILAE-CGC), and the members of the EPIGEN Consortium (a full list of coinvestigators is found in the e-Appendix); Ana Fulgenico-Maisch, Simona Donatello, Clare O’Kennedy, Lisa Slattery, Paula Corr, and Joanna Fay for clinical assessment of patients, technical assistance with DNA extraction, and sample management; and the patients for their participation in the study.

Study funding

This study was not industry-sponsored. The work was supported by a grant from the European Commission (7th Framework Programme Grant 279062, EpiPGX). M.M.C. and G.L.C. are supported by Science Foundation Ireland, grant 13/CDA/2223, and an RCSI seed funding grant GA 14-1899. This project was supported by the General Research Funds (HKU7623/08M and HKU7747/07M to S.C., CUHK4466/06M to P.K.) and Health and Medical Research Fund (HMRF 01120086 to P.K.) from Hong Kong. Some results presented in this article were prepared using the HPC facilities of the University of Luxembourg. This work was partly undertaken at UCLH/UCL, which received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme (J.W.S., S.M.S.). The work was also supported by the Epilepsy Society, UK (J.W.S., S.M.S.), by the foundation “no epilep,” the German Chapter of the ILAE (DGfE) (both to H.L.). F.C. and I.L.-C. are supported by Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil, through grant 2013/07559-3. J.E.Z. and M.P. thank the NHS Chair of Pharmacogenetics programme and MRC Centre for Drug Safety Science for support in Liverpool. B.C.C. and C.J.D.R. are supported by the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Network (FRN-117588), the Canada Foundation for Innovation and the Canadian Dermatology Foundation. G.E.B.W. is supported by a CIHR Fellowship. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. M.M.C., H.G., and G.L.C. had full access to all the data in the study and the corresponding authors had final responsibility for the decision to submit for publication.

Disclosure

M. McCormack and H. Gui report no disclosures relevant to the manuscript. A. Ingason is an employee of deCODE Genetics/Amgen. D. Speed, G. Wright, E. Zhang, R. Secolin, C. Yasuda, M. Kwok, S. Wolking, F. Becker, and S. Rau report

no disclosures relevant to the manuscript. A. Avbersek is employed by UCB Pharma SPRL, Belgium, as Associate Director. K. Heggeli, C. Leu, C. Depondt, and G. Sills report no disclosures relevant to the manuscript. A. Marson was awarded grants from GSK, Eisai, and UCB Pharma, which funded the National Audit of Seizure Management in Hospitals. P. Auce, M. Brodie, B. Francis, M. Johnson, B. Koeleman, P. Striano, A. Coppola, F. Zara, and W. Kunz report no disclosures relevant to the manuscript. J. Sander has served on scientific advisory boards for UCB Pharma and Eisai; has served on speaker’s bureaus for UCB Pharma, Eisai, Teva, and Lundbeck; has received research support from UCB Pharma, GSK, Eisai, The Marvin Weil Epilepsy Research Fund, and NL Nationaal Epilepsie Fonds; and his current position is endowed by the UK Epilepsy Society. H. Lerche has received speaker or consultancy fees or travel support from Bial, Desitin, Eisai, GlaxoSmithKline, Pfizer, UCB Pharma, or Valeant. K. Klein reports personal fees from UCB Pharma, Novartis Pharma AG, and Eisai, outside of the submitted work. AC was awarded a grant from EISAI and personal fees for speaking from Eisai, outside of the submitted work. S. Weckhuysen and M. Krenn report no disclosures relevant to the manuscript. L. Gudmundsson is an employee of deCODE Genetics/Amgen. K. Stefánsson is an employee of deCODE Genetics/Amgen. R. Krause, N. Shear, C. Ross, and N. Delanty report no disclosures relevant to the manuscript. M. Pirmohamed reports grants from MRC and grants from UK Department of Health during the conduct of the study. B. Carleton, through the Pharmaceutical Outcomes Programme (POPi), has received financial support for its pharmacogenomics research from the Canada Foundation for Innovation (CFI), Canadian Institutes of Health Research, Genome Canada, Genome British Columbia, and the Provincial Health Services Authority. Prof. Carleton has also received support by the University of British Columbia, Child & Family Research Institute, Vancouver, and Pfizer. Prof. Carleton has a patent and applications pending for biomarkers of anthracycline-induced cardiotoxicity and cisplatin-induced ototoxicity but no relevant financial disclosures relevant to this study. F. Cendes reports speaking fees from UCB Pharma, outside of the current work. I. Cendes-Lopes and W. Liao report no disclosures relevant to the manuscript. T. O’Brien reports grants from The Royal Melbourne Foundation during the conduct of the study. S. Sisodiya and S. Cherny report no disclosures relevant to the manuscript. P. Kwan has received speaker or consultancy fees and/or research grants from Eisai, GlaxoSmithKline, Johnson & Johnson, Pfizer, and UCB Pharma. L. Baum and G. Cavalleri report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received February 27, 2017. Accepted in final form October 2, 2017.

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Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

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Cite as: *Neurology*® 2018;90:e332-e341. doi:10.1212/WNL.0000000000004853

Study question

Are there genetic predictors of maculopapular exanthema (MPE), a cutaneous adverse drug reaction common to antiepileptic drugs (AEDs), in European and Han Chinese populations?

Summary answer

An association was found between a rare variant in the *CFHR4* gene and phenytoin-induced MPE in cohorts of European descent.

What is known and what this article adds

Several genetic predictors of hypersensitivity to anticonvulsant therapy exist. The study identified a new pharmacogenetics marker for potential use in the treatment of epilepsy.

Participants and setting

The study was a case-control genome-wide association study (GWAS) of autosomal genotypes, including Class I and II human leukocyte antigen (HLA) alleles, in 323 cases and 1,321 drug-tolerant controls from epilepsy cohorts of northern European and Han Chinese descent. The analyses tested genetic variants for association with MPE within and across both of the broad ancestral groups. Associations were tested as follows: (1) aromatic AED-induced MPE vs controls tolerant to at least 3 aromatic AEDs, (2) carbamazepine-induced MPE vs carbamazepine-tolerant controls, (3) lamotrigine-induced MPE vs lamotrigine-tolerant controls, and (4) phenytoin-induced MPE vs phenytoin-tolerant controls.

Design, size, and duration

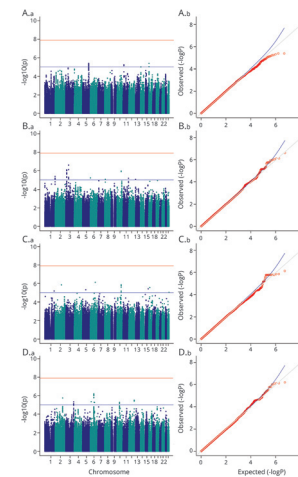
The study is a retrospective case-control study in individuals of European and Han Chinese ethnicity, in which participants were exposed to carbamazepine, lamotrigine, phenytoin, or oxcarbazepine.

Primary outcomes

There is a strong association between variants in the *CFHR4* and *CFH* genes and phenytoin-induced MPE in a European-descent patient population.

Main results and the role of chance

An association was noted between a rare variant in the *CFHR4* gene and phenytoin-induced MPE in Europeans ($p = 4.5 \times 10^{-11}$; odds ratio [95% confidence interval] = 7 [32–16]). This variant is in complete linkage



disequilibrium with a missense variant (N1050Y) in the *CFH* gene. Also, an association between *HLA-A*31:01* and carbamazepine hypersensitivity was reinforced.

Bias, confounding, and other reasons for caution

The study analyzed considerably more European-descent patients and a relatively low number of Han Chinese lamotrigine-related MPE cases. Overall, the small sample sizes limit conclusions in non-European descent populations.

Generalizability to other populations

The small size and predominantly European origin of the study sample and low numbers of Han Chinese participants may limit generalizability to other ethnic groups.

Study funding/potential competing interests

The study was funded by a group of foundation, government, and university grants. Go to [Neurology.org/N](https://doi.org/10.1212/WNL.0000000000004853) for full disclosures.

A draft of the short-form article was written by E. Feric, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

Mark McCormack, Hongsheng Gui, Andrés Ingason, et al.

Neurology 2018;90:e332-e341 Published Online before print December 29, 2017

DOI 10.1212/WNL.0000000000004853

This information is current as of December 29, 2017

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Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women

"Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women" investigated whether greater cardiovascular fitness in midlife is associated with a decreased risk of dementia in women. The authors found that women with high fitness had a lower adjusted hazard ratio for all-cause dementia and delayed age at onset of dementia compared with women with medium fitness. Commenting on the article, Kivimäki et al. believe that the results are overoptimistic. They explain that because of the small number of dementia cases, the results reported are unlikely to be robust. They support their argument by analyzing an alternative scenario with just 2 additional dementia cases in the high-fitness group, which would decrease the population attributable fraction to less than 60%. Hörder et al. agree that the results may be overoptimistic, but they justify the low number of dementia cases in the highest-fitness group as a consequence of the strong effect of high midlife fitness on dementia risk. They add that high fitness could be regarded as a sum of a number of beneficial factors related to dementia risk (e.g., genetics, exercise, diet, nonsmoking, and blood pressure).

Chafic Karam, MD, and Steven Galetta, MD
Neurology® 2018;91:762. doi:10.1212/WNL.0000000000006349

Reader response: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women

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Neurology® 2018;91:762–763. doi:10.1212/WNL.0000000000006348

Hörder et al.¹ advanced the hypothesis that midlife cardiovascular fitness protects against old-age dementia. However, the limitations of the data were not fully discussed. The estimated benefit of greater fitness in terms of dementia prevention is overoptimistic. Using data from tables 3 and 4 in the article,¹ we calculated a population attributable fraction (PAF) of 78.3%, suggesting that 8 of 10 dementia cases would be avoided if all women had high cardiovascular fitness (table). This is more than 2 times greater than the collective PAF for all known modifiable risk factors in the most recent synopsis,² which is itself an upper-bound estimate.³

Because of the small number of dementia cases, the results reported by Hörder et al. are unlikely to be robust. There were only 2 dementia cases in the high-fitness group; 2 additional cases would lead to a PAF of <60%, whereas 2 fewer cases would lead to the conclusion that women with high fitness do not develop dementia at all. The finding by Hörder et al.¹ is also unlikely to be an "underestimate," as suggested by the accompanying editorial.⁴ Results based on 2 cases could be entirely due to chance.

Author disclosures are available upon request (journal@neurology.org).

Table Population attributable fraction for cardiovascular fitness and dementia in the study by Hörder et al. and an alternative scenario with just 2 additional dementia cases

	Total, N (%)	N (cases)	Dementia proportion	Relative risk	PAF (%)
Cardiovascular fitness					
High	40 (20.9)	2	0.050	1.00	
Medium	92 (48.2)	23	0.250	5.00	41.8
Low	59 (30.9)	19	0.322	6.44	36.5
Total	191 (100)	44			78.3
An alternative scenario with 2 additional dementia cases in the high-fitness group					
High	40 (20.9)	4	0.100	1.00	
Medium	92 (48.2)	23	0.250	2.50	30.0
Low	59 (30.9)	19	0.322	3.22	28.5
Total	191 (100)	46			58.5

Abbreviation: PAF = population attributable fraction.

1. Hörder H, Johansson L, Guo X, et al. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. *Neurology* 2018;90:e1298–e1305.
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Author response: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women

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Neurology® 2018;91:763. doi:10.1212/WNL.0000000000006350

We are grateful for the comments by Kivimäki et al. on our article.¹ We agree that the effect of dementia prevention in our study is probably overoptimistic. However, the results still suggest that there is a strong effect of midlife cardiovascular fitness on dementia risk in old age. Kivimäki et al. conclude that results based on 2 individuals with dementia are entirely based on chance. However, 44 individuals developed dementia during the 44-year follow-up period. Two of those were in the highest quintile of fitness. The low number of dementia cases in the highest-fitness group is thus the consequence of the strong effect of high midlife fitness on dementia risk. However, as Kivimäki et al. point out, this makes the exact estimation of the benefit of fitness less robust, but it still suggests a strong effect. Kivimäki et al. report that with 2 more cases, the population attributable fraction would decrease from 78% to approximately 60%. We would argue that this is also a strong effect. In addition, high fitness could be regarded as a sum of a number of beneficial factors related to dementia risk (e.g., genetics, exercise, diet, nonsmoking, and blood pressure).

1. Hörder H, Johansson L, Guo X, et al. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. *Neurology* 2018;90:e1298–e1305.

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Editors' note: Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?

In the editorial “Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?,” Drs. Lee and Dziedzic qualified neuroimaging in stroke as the equivalent of precision medicine, personalizing care based on advanced imaging measures. They cited multiple clinical trials demonstrating that endovascular thrombectomy early after acute ischemic stroke (AIS) onset is highly effective for reducing long-term disability. They added that the use of rapid and robust neuroimaging methods that helped select appropriate patients based on clot location or core/penumbra signatures was critical to the success of these trials. The rest of the editorial addressed the work by Bustamante et al., which studied a potential blood biomarker that may help guide therapeutic decision making in the setting of AIS. Commenting on the article, Dr. Munakomi expresses the need to better identify those patients who would benefit from thrombolysis and thrombectomy through stroke awareness via community education and upgrading facilities for teletherapy management. In response, Dr. Lee points to the need for research to enhance diagnostic tests that would help guide the most appropriate and effective treatments in AIS.

Chafic Karam, MD, and Steven Galetta, MD
Neurology® 2018;91:764. doi:10.1212/WNL.0000000000006351

Reader response: Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?

Sunil Munakomi (Biratnagar, Nepal)
Neurology® 2018;91:764. doi:10.1212/WNL.0000000000006352

I read with great interest the editorial by Lee and Dziedzic.¹ The advances in imaging armamentarium have enabled us to enroll more patients with ischemic stroke for improved therapy through thrombolysis or thrombectomy. However, only a small subset of these cohort groups is currently benefitting. There is a need to maximize enrollment of such target groups through stroke awareness via community education² and upgrading facilities for teletherapy management.³ These approaches would ensure that ideal candidates receive at least the IV thrombolysis treatment within the vital time window and are then followed up for mechanical thrombectomy.

1. Lee JM, Dziedzic T. Personalizing acute therapies for ischemic stroke thrombolysis or thrombectomy? *Neurology* 2018;90:535–536.
2. Stern EB, Berman M, Thomas JJ, Klassen AC. Community education for stroke awareness: an efficacy study. *Stroke* 1999;30:720–723.
3. Zhai YK, Zhu WJ, Hou HL, Sun DX, Zhao J. Efficacy of telemedicine for thrombolytic therapy in acute ischemic stroke: a meta-analysis. *J Telemed Telecare* 2015;21:123–130.

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Author response: Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?

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Neurology® 2018;91:765. doi:10.1212/WNL.0000000000006353

I appreciate Dr. Munakomi's comments, on our editorial,¹ about the importance of public education to increase treatment opportunities for patients with acute ischemic stroke. At the same time, research to enhance diagnostic tests is needed and might help guide the most appropriate and effective treatments. The work by Bustamante et al.² brings us one step closer to a potential blood biomarker that may, one day, help guide therapeutic decision making in the setting of acute ischemic stroke.

1. Lee JM, Dziedzic T. Personalizing acute therapies for ischemic stroke thrombolysis or thrombectomy? *Neurology* 2018;90:535–536.
2. Bustamante A, Ning M, García-Berrocó T, et al. Usefulness of ADAMTS13 to predict response to recanalization therapies in acute ischemic stroke. *Neurology* 2018;90:e995–e1004.

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CORRECTION

Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

Neurology® 2018;91:765. doi:10.1212/WNL.0000000000006483

In the article “Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients” by McCormack et al.,¹ the European Union's Horizon 2020 Research and Innovation Programme was inadvertently omitted from the Study Funding acknowledgment. This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement no. 751761. The authors regret the omission.

Reference

1. McCormack M, Hongsheng G, Ingason A, et al. Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients. *Neurology* 2018;90:e332–e341.