ases are magnified by larger sample sizes and the increased number of genetic markers examined in genomewide studies. These problems need to be carefully addressed for whole genome mapping experiments to provide meaningful information for the elucidation of the genetic etiology of common diseases.

William Y.S. Wang, MMBS, PhD
wwang@usyd.edu.au
University of Sydney
Sydney, Australia

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In Reply: We note that all writers indicated broad agreement with our conclusion of the need for robust validation of genetic risk factors to provide convincing evidence that a true genetic risk factor has been identified. We agree with the comments of Dr Feero and colleagues that unbiased studies of whole genome association are likely to lead to important discoveries. Recent findings have illustrated the power of this approach and underscore the frequent need for large sample sizes and replication cohorts to achieve meaningful and convincing results.[1-5] Of interest is that the variants identified in these studies show consistent replication of the identical alleles in diverse cohorts.

Dr Bochud and colleagues point out pitfalls in case-control studies. Our study's aim was to investigate whether previously reported genetic risk factors could be replicated in a large cohort of patients similar to those encountered in clinical practice. Our null results provide little support that any of these would be clinically useful. Exploring gene-gene and gene-environment interactions for unvalidated SNPs was not our aim and would seem likely to merely produce more false-positive results. Heterogeneity of the underlying disease risk factors can reduce power to detect a true effect, but unrecognized population stratification between cases and controls would not be expected to produce uniformly negative results. The fact that our results conform closely to the null indicates little difference in genetic backgrounds of our cases and controls.

Drs McCarthy and Topol are mistaken in their assertion that our data corroborate prior findings of the impact of the GG genotype in thrombospondin 2. Prior studies found an excess of this genotype in controls,[6,7] whereas our results found the opposite. This is explicitly not replication, and we disagree with their suggestion that such opposite results could be considered validation. Moreover, because most SNPs tested were hypothesized to be functionally significant, not merely markers of a disease haplotype, it is highly unlikely that their effects would vary in sign in different cohorts. Their suggestion that variation in haplotype structures might explain some of our results is at variance with substantial data showing the strong concordance of haplotype maps among cohorts of similar genetic backgrounds.[8]

Dr Wang cites important challenges in the design of whole genome association studies. We concur and point to the sizes of recent successful studies as guides to what is needed to provide convincing evidence that a true genetic risk factor has been found.[1-5]

Thomas M. Morgan, MD
morgan_t@kids.wustl.edu
Washington University School of Medicine
St Louis, Missouri

Harlan M. Krumholz, MD, MS
Richard P. Lifton, MD, PhD
Yale University School of Medicine
New Haven, Connecticut

John A. Spertus, MD, MPH
Mid America Heart Institute
Kansas City, Missouri

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Adverse Effects of Incretin Therapy for Type 2 Diabetes

To the Editor: In their meta-analysis studying the efficacy and safety of incretin therapy in persons with type 2 diabetes, Dr Amori and colleagues[1] found that patients treated with dipeptidyl peptidase 4 (DPP4) inhibitors had an increased risk of nasopharyngitis (6.4% for DPP4 inhibitors vs 6.1% for comparator; risk ratio, 1.2; 95% confidence in-

terval, 1.0-1.4). This adverse effect is consistent with our finding that DPP4 enzymatic activity in nasal tissue biopsies taken from patients with chronic rhinosinusitis was inversely correlated with the density of inflammatory cells in the nasal mucosa, and the DPP4 activity increased when chronic sinusitis was treated.[2]

Dipeptidyl peptidase 4 inactivates the proinflammatory peptide substance P that is released by sensory nerve fibers of the nasal mucosa during neurogenic inflammation. In pigs, the administration of recombinant DPP4 considerably attenuated the proinflammatory effect of histamine and capsaicin that causes the release of substance P, as well as the effect of substance P itself.[2] Therefore, DPP4 should be considered as a modulator of the proinflammatory action of substance P.

The review by Amori et al also found a higher incidence of headaches in patients treated with gliptins but did not note whether these patients were the same as those who developed nasopharyngitis. Headache is a major symptom in chronic sinusitis in association with mucosal congestion and decreased sinus drainage. Furthermore, substance P is hypothesized to have a key role in certain forms of headache.[3] These data suggest that DPP4 may play a significant role in the development of inflammatory processes in the upper airway mucosa. Consequently, it would be important to evaluate potential disadvantages of DPP4 inhibitor use in patients with diabetes who have chronic sinusitis and headache.

Eric Grouzmann, PharmD, PhD
eric.grouzmann@chuv.ch
Division de Pharmacologie et Toxicologie Cliniques
Michel Monod, PhD
Service de Dermatologie
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland
Basil N. Landis, MD
Jean-Silvain Lacroix, MD, PhD
Rhinology-Olfactology Unit
Department of Otolaryngology
University Hospital of Geneva
Geneva, Switzerland

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In Reply: The findings previously reported by Dr Grouzmann and colleagues regarding DPP4 activity in nasal tissues and the effect of DPP4 on substance P in patients with chronic rhinosinusitis provide a potential explanation and support for our clinical findings of increased risk of nasopharyngitis and headache in patients with type 2 diabetes treated with DPP4 inhibitors. In our review, we included only publicly available data from the published literature, which did not specify whether there was overlap among patients reporting nasopharyngitis and headache. Therefore, we cannot determine whether, in patients treated with DPP4 inhibitors, headache is a component of nasopharyngitis or if it constitutes a distinct clinical entity. We agree that it would be reasonable for clinicians to be cautious when using DPP4 inhibitors in patients with chronic rhinosinusitis or headache.

Anastassios G. Pittas, MD, MSc
apittas@tufts-nemc.org
Renee E. Amori, MD
Division of Endocrinology, Diabetes and Metabolism
Joseph Lau, MD
Institute for Clinical Research and Health Policy Studies
Tufts–New England Medical Center
Boston, Massachusetts

Financial Disclosures: None reported.

RESEARCH LETTER

Thoracic and Lumbar Vertebroplasties Performed in US Medicare Enrollees, 2001-2005

To the Editor: Percutaneous vertebroplasty involves the vertebral injection of polymethylmethacrylate cement. Although some indication that this procedure is safe and effective for treating osteoporotic compression fractures exists,[1] the US Medicare program promulgated no national coverage policies for this procedure after reviewing the available nonrandomized evidence.[2] Nevertheless, local Medicare contractors in multiple jurisdictions have covered vertebroplasty for various indications since as least 2001. We examined vertebroplasty-use patterns in Medicare patients for 2001-2005.

Methods. Using vertebroplasty-related Current Procedural Terminology, 4th Edition (CPT-4), codes 22520 (primary thoracic vertebroplasty) and 22521 (primary lumbar vertebroplasty), we performed cross-sectional analyses of aggregate 2001-2005 fee-for-service data from the Medicare all-age Part B Extract Summary System,[3] which excludes denied claims and claims for Medicare managed care enrollees. Annual primary vertebroplasty rates (which exclude additional vertebral levels also treated) were therefore expressed per 100 000 Part B fee-for-service enrollees.

Part B Extract Summary System data are cross-stratified by the billing physician's reported specialty and by the listed place of service. We grouped physician specialties into 5 categories: diagnostic or interventional radiology, orthopedic surgery, neurosurgery, anesthesiology or pain management, and other (including neurologists, physiatrists, internists, emergency department physicians, physi-