The continued need to synthesize the results of genetic associations across multiple studies

To the Editor:

The sequencing of the human genome and the increasing availability of high-throughput genotyping have led to an upsurge in published genetic associations.[1] Identifying true genetic associations among the large volume of false positives has always been a difficult task.[2] The use of systematic reviews, particularly meta-analyses, has been recommended to summarize and assess the cumulative evidence on genetic associations.[3] Even in the era of genome-wide association studies (GWAS), meta-analysis has a role in synthesizing and integrating results of genetic association studies,[4] yet it is not clear if these efforts have kept pace.

Using two applications included in the recently deployed Human Genome Epidemiology (HuGE) Navigator,[5] HuGE Watch and HuGEpedia, we found that meta-analyses increased threefold as a proportion of all published articles on genetic associations from 2001 to 2007 (Table 1); however, meta-analyses still represent only a tiny fraction (3%) of the genetic association literature. Among the 10 most frequently studied diseases (Table 2), genetic associations (e.g., *APOE* and Alzheimer disease) described in 25 or more primary research articles were far more likely to show at least one meta-analysis in the HuGEpedia (range, 47–100%) than those described in 10 to 24 articles (range, 9–69%) or in 5 to 9 articles (range, 0–32%).

The increasing popularity of GWAS reinforces, rather than diminishes, the importance of knowledge synthesis, including meta-analysis.[4] In GWAS, identifying true-positive associations with genetic variants among hundreds of thousands tested is further complicated by the multistage designs used by many GWAS to test for replication of statistically significant results.[6] Meta-analyses may be useful for integrating results across stages to identify true associations and could be used as prior knowledge in Bayesian approaches of selecting variants to carry forward to subsequent stages of analysis.[7] Furthermore, as with candidate gene studies, meta-analyses of GWAS can be used to calculate more precise measures of effect and assess the heterogeneity and generalizability of genetic associations.[4,8]

HuGENet, a global collaboration of researchers dedicated to advancing public health genomics, has collaborated with 11 journals to promote the conduct of systematic reviews, including meta-analysis (HuGE Reviews).[3] Through December 2007, 65 HuGE reviews have been published. Topics are registered with HuGENet and displayed on the HuGE Web site to help prevent duplicate efforts and encourage collaboration between the researchers. Guidance for conducting HuGE Reviews is provided in the HuGENet *HuGE Review Handbook* (http://www.genesens.net/_intranet/doc_nouvelles/HuGE%20Review%20Handbook%20v11.pdf). Authors are also encouraged to use recently published interim guidelines to assess the cumulative evidence for the genetic association of interest.[9] Authors interested in selecting a topic for a HuGE Review can use the HuGE Navigator, as we did, to identify gaps in knowledge synthesis.

Describing and confirming genetic associations is a crucial first step in realizing the potential of genomic medicine. We show that although research on genetic associations is booming, more attention needs to be devoted to efforts to synthesize and interpret research findings. Meta-analyses are most likely to focus on frequently studied genetic associations; however, we did not find meta-analyses in the HuGE Navigator for many associations that have been studied 10 or more times. Assessing the cumulative evidence for associations is important in a field so plagued by nonreplication.[2] We encourage investigators to perform and publish systematic reviews and meta-analyses of genetic associations and for journals to publish this work as part of the ongoing translation of gene discoveries into clinical medicine and public health.

Table 1
Articles reporting genetic associations, including meta-analyses, by year—HuGE Navigator knowledge base

	2001	2002	2003	2004	2005	2006	2007[a]
No. articles examining genetic associations	2148	2776	2961	3645	4334	4808	5846
No. meta-analyses	24	32	61	67	98	142	177
Percent of meta-analyses	1	1	2	2	2	3	3

[a]As of December 12th, 2007.

Table 2
Genetic associations and meta-analyses for the 10 most commonly studied diseases—HuGE Navigator knowledge base[a]

	5–9 Articles			10–24 Articles			25 or More Articles		
	No. genetic associations	No. genetic associations with meta-analyses	Percentage of genetic associations with meta-analyses	No. genetic associations	No. genetic associations with meta-analyses	Percentage of genetic associations with meta-analyses	No. genetic associations	No. genetic associations with meta-analyses	Percentage of genetic associations with meta-analyses
Diabetes mellitus, Type 2	41	8	20	32	13	41	11	9	82
Breast neoplasms	37	5	14	18	7	39	16	12	75
Hypertension	64	0	0	22	2	9	15	7	47
Alzheimer disease	19	6	32	26	15	58	5	5	100
Schizophrenia	33	11	33	16	11	69	10	10	100
Obesity	39	5	13	23	8	35	12	9	75
Myocardial infarction	32	3	9	22	8	36	8	8	100
Diabetes mellitus, Type 1	19	1	5	7	4	57	5	5	100
Lung neoplasms	19	4	21	11	6	55	8	8	100
Coronary disease	29	1	3	22	10	45	16	11	69

[a]As of December 12th, 2007.

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Disclaimer: *The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.*

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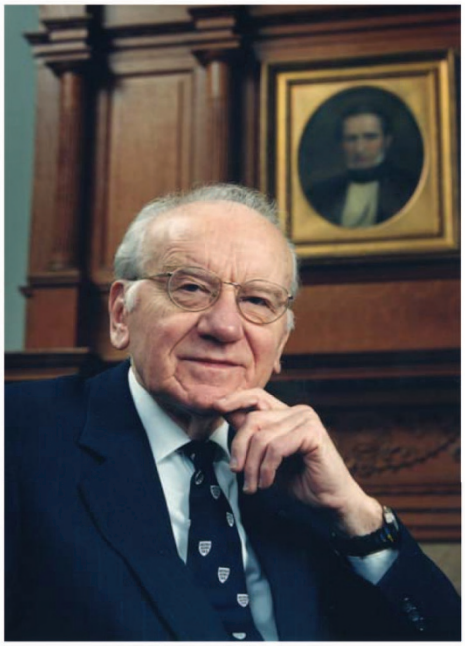

Photo by Keith Weller/Johns Hopkins Medicine

In memory of Victor A. McKusick, 1921-2008, whom we recently featured in our June issue of *Genetics in Medicine*.

A towering figure in genetics and one of the founders of our field. He will be missed.