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Association Between Heme Oxygenase-1 Gene Promoter Polymorphisms and Type 2 Diabetes Mellitus: A HuGE Review and Meta-Analysis

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Several studies have recently focused on the association between heme oxygenase-1 (*HMOX1*) gene promoter polymorphisms and susceptibility to type 2 diabetes mellitus; however, results have been conflicting. This systematic Human Genome Epidemiology review and meta-analysis was undertaken to integrate previous findings and summarize the effect size of the association of *HMOX1* gene promoter polymorphisms with susceptibility to type 2 diabetes. The authors retrieved all studies matched to search terms from the PubMed/MEDLINE, EMBASE, and ISI Web of Science databases that had been published through December 31, 2009. The articles were then checked independently by 2 investigators according to the eligibility and exclusion criteria. For all alleles and genotypes, odds ratios were pooled using either fixed-effects or random-effects models. An increased odds ratio for type 2 diabetes was observed in persons with the $(GT)_n$ L (long) allele as compared with those with the $(GT)_n$ S (short) allele (odds ratio = 1.12, 95% confidence interval: 1.02, 1.24; $P = 0.02$). Furthermore, the diabetes odds ratio for persons with the LL genotype, versus those with the SS genotype, was significantly increased (odds ratio = 1.25, 95% confidence interval: 1.04, 1.50; $P = 0.02$). Persons carrying longer $(GT)_n$ repeats in the *HMOX1* gene promoter may have a higher risk of type 2 diabetes.

diabetes mellitus, type 2; epidemiology; genetics; genome, human; heme oxygenase-1; meta-analysis; polymorphism, single nucleotide

Abbreviations: CI, confidence interval; *HMOX1*, heme oxygenase-1; OR, odds ratio; SNP, single nucleotide polymorphism.

***Editor's note**: This article also appears on the Web site of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm).*

GENE AND GENE VARIANTS

The human heme oxygenase-1 (*HMOX1*; also called *HO-1*) gene is localized to human chromosome 22q12 (1). Its encoding product heme oxygenase-1, also known as heat shock protein 32, catalyzes the rate-limiting step of heme to form carbon monoxide, ferrous iron, and biliverdin, which is rapidly converted to bilirubin by biliverdin reductase (2). As the inducible isoform of heme oxygenase, heme oxygenase-1 is highly responsive to its substrate heme and to a broad spectrum of chemical and physical stress agents. Therefore, induction of heme oxygenase-1 has been regarded as a biomarker for cell stress status (3). Among a panel of described polymorphisms in the *HMOX1* gene (4–6), 3 have drawn the most attention: a (GT)n dinucleotide length polymorphism and 2 common single nucleotide polymorphisms (SNPs): G(−1135)A and T(−413)A (4) (see Web Figure 1, which is posted on the *Journal*'s Web site (http://aje.oxfordjournals.org/)). The role of these polymorphisms in the transcriptional activity of the *HMOX1* promoter has been experimentally demonstrated by means of luciferase promoter constructs and transient transfection

into mammalian cell lines (7–9). The (GT)n short length allele (S, <25 repeats) and the A(−413) allele have been linked to significantly increased *HMOX1* promoter activity in comparison with the long length allele (L, ≥25 repeats) and the T(−413) allele, respectively (7–9).

DISEASE

Diabetes mellitus has become a worldwide epidemic. It is estimated that the global number of diabetes cases will reach 366 million by 2030, accounting for 4.4% of the population, creating an increasing health-care burden and economic challenge for virtually all nations (10).

Type 2 diabetes mellitus (hereafter called type 2 diabetes) comprises 90% of diabetes cases around the world, and is a typical disease resulting from gene-environment interactions. Among a number of potential candidate genes, *HMOX1* seems to be a novel one with potent antioxidant, antiinflammatory, and antiproliferative effects (4). Altered *HMOX1* gene expression has been found in circulating monocytes (11), peripheral blood mononuclear cells (6), and muscle samples (12) in patients with type 2 diabetes. Furthermore, the association of *HMOX1* gene $(GT)_n$ microsatellite polymorphisms with type 2 diabetes has also been characterized in the literature (6, 8, 13–16); however, results from these studies have been inconsistent.

To our knowledge, the current meta-analysis is the first to elucidate the potential association between *HMOX1* gene promoter polymorphisms and type 2 diabetes by means of a Human Genome Epidemiology review.

MATERIALS AND METHODS

Identification and eligibility of relevant studies

We searched electronic databases, including PubMed/MEDLINE (US National Library of Medicine), EMBASE (Elsevier B.V., Amsterdam, the Netherlands), and ISI Web of Science (Thomson Reuters, New York, New York), for all studies published through December 31, 2009, that had examined the association between *HMOX1* gene $(GT)_n$ microsatellite polymorphisms and type 2 diabetes. The search strategy was based on combinations of the terms "heme oxygenase-1 *or HMOX1 or HO-1*," "polymorphism," and "type 2 diabetes." Reference lists in retrieved articles were also screened. We included published manuscripts on relevant studies carried out in human subjects in all languages, without any special restriction on the source of cases (newly diagnosed type 2 diabetes, history of type 2 diabetes diagnosis, or type 2 diabetes with complications) and controls (general population, clinic, or hospital). However, manuscripts in the form of reviews or commentaries were excluded.

Data extraction

Data extraction from the included studies was carried out as previously described (17). The following data were extracted from the published article for each study: author name(s), year of publication, ethnicity or geographic location of study subjects, age, sex ratio, use of age and sex matching, disease duration, and consistency of genotype frequencies with Hardy-Weinberg equilibrium. Allele and genotype frequencies were extracted or calculated from published data in the included studies. The bibliographic search and data extraction were conducted independently by 2 authors, and disagreements were resolved by consensus for all data. Laboratory tests for the *HMOX1* gene (GT)n repeat length polymorphism in the included studies are summarized in the Web Appendix.

Statistical analysis

We calculated odds ratios and 95% confidence intervals as the metrics of effect size for each study and overall studies. Two methods were employed to estimate between-study heterogeneity across all eligible comparisons: the χ^2-based Cochran's Q statistic and the I^2 metric, which quantify between-study heterogeneity irrespective of the number of studies (18). Heterogeneity was considered significant at $P < 0.10$ for the Q statistic. For the I^2 metric, the following suggested cutoff points were used: $I^2 = 0\%–<25\%$, no heterogeneity; $I^2 = 25\%–<50\%$, moderate heterogeneity; $I^2 = 50\%–<75\%$, large heterogeneity; and $I^2 = 75\%–100\%$, extreme heterogeneity (17). Data from the studies were combined using a fixed-effects model (Mantel-Haenszel method) when heterogeneity was negligible or a random-effects model (DerSimonian and Laird method) when heterogeneity was significantly present (19). Correspondingly, weights were assigned to studies on the basis of within-study variance for the fixed-effects model or both within-study variance and between-study variance for the random-effects model, which will award relatively more weight to smaller studies than the fixed-effect model (20). Forest plots and funnel plots were used for visualizing the overall effect and evaluating publication bias, respectively. Analyses were conducted using RevMan 5.0 software, developed by the Cochrane Collaboration (21). All P values presented are 2-tailed with a significance level of 0.05.

RESULTS

Six eligible studies matching the search terms and published prior to 2010, comprising 1,965 cases and 3,484 controls, were retrieved from the PubMed/MEDLINE, EMBASE, and ISI Web of Science databases and then reviewed independently by 2 investigators (6, 8, 13–16).

$(GT)_n$ repeat length polymorphism

For the $(GT)_n$ repeat length polymorphism in the *HMOX1* gene promoter, there has not yet been a consensus on the optimum cutpoint, so the harmonization of cutpoints was considered. We excluded 1 study (8) because we observed high inconsistency regarding the cutpoint between this study and the others. In addition, data from this study may have been at least partly covered by and updated in another paper from the same group (16). Thus, only 5 studies in which similar cutpoints had been described were included for further analysis of the association between the *HMOX1* gene $(GT)_n$ microsatellite polymorphism and type 2 diabetes (Table 1

Table 1. Characteristics of Studies Included in a Meta-Analysis of Polymorphisms in the Heme Oxygenase-1 (*HMOX1*) Gene and Susceptibility to Type 2 Diabetes Mellitus

First Author, Year (Reference No.)	Location	Ethnic Origin	Characteristics and Selection of Subjects		No. of Eligible Subjects	
			Cases	Controls	Cases	Controls
Kaneda, 2002 (13)	Japan	Asian	Diabetes cases were identified in accordance with the criteria of the ADA	Controls were selected from patients who underwent selective coronary angiography because of suspected coronary artery disease	205	372
Dick, 2005 (14)	Austria	Caucasian	Diabetes mellitus was defined according to the ADA criteria and was considered to be present in all patients taking antidiabetic medication	Patients with atherosclerosis and without diabetes mellitus	91	145
Arredondo, 2007 (15)	Chile	Hispanic	Type 2 diabetes patients aged >45 years who had experienced 2 years of diabetes evolution, as diagnosed and controlled by the Diabetes Program in the Nutrition Unit of Juan de Dios Hospital (Santiago, Chile)	Unrelated nondiabetic volunteers with no apparent medical or family history of diabetes and without the metabolic syndrome, according to the Adult Treatment Panel III classification	99	90
Chen, 2008 (16)	Taiwan	Asian	Diabetes patients; diagnosis criteria not shown	Nondiabetic participants from northern Taiwan with similar ethnic backgrounds	272	714
Song, 2009 (6)	China	Asian	Type 2 diabetes patients consecutively recruited from persons visiting outpatient clinics, diagnosed in accordance with the World Health Organization's recommended diagnosis criteria	Healthy controls who were frequency-matched to patients by age and sex from an unselected population undergoing routine health check-ups at the same hospital	1,084	1,581

Abbreviation: ADA, American Diabetes Association.

and Table 2). Allelic categories were defined as class S (short) for <25 or <27 $(GT)_n$ repeats and class L (long) for ≥25 or ≥27 $(GT)_n$ repeats in those studies (Web Table 1).

Odds ratios for all alleles and genotypes were pooled using either fixed-effects models or random-effects models, according to the result from the heterogeneity test. An increased odds ratio for type 2 diabetes was observed in persons with the $(GT)_n$ L allele as compared with those with the $(GT)_n$ S allele (odds ratio (OR) = 1.12, 95% confidence interval (CI): 1.02, 1.24; $P = 0.02$) (Figure 1). For genotypes, the odds ratio for type 2 diabetes in persons with the LL or LS allele, as compared with those with the SS allele, showed no significant change (for the LL and LS genotypes vs. the SS genotype, OR = 1.25, 95% CI: 0.93, 1.69; $P = 0.14$). However, the odds ratio for type 2 diabetes in persons with the LL allele, as compared with those with the SS allele, was significantly increased (for the LL genotype vs. the SS genotype, OR = 1.25, 95% CI: 1.04, 1.50; $P = 0.02$). Funnel plot analyses were employed, and no publication bias was found in the included studies (Web Figure 2).

Table 2. Distribution of Genotypes of the (GT)n Repeat Length Polymorphism in Studies of the Heme Oxygenase-1 (*HMOX1*) Gene and Susceptibility to Type 2 Diabetes Mellitus

First Author, Year (Reference No.)	Ethnic Origin	Genotype						Frequency of Class L Allele, %	
		LL		LS		SS			
		No. of Cases	No. of Controls	No. of Cases	No. of Controls	No. of Cases	No. of Controls	Cases	Controls
Kaneda, 2002 (13)	Asian	51	121	123	187	31	64	N/A[a]	N/A
Dick, 2005 (14)	Caucasian	N/A	N/A	N/A	N/A	N/A	N/A	48.9	52.1
Arredondo, 2007 (15)	Hispanic	12	24	85	54	2	12	55.1	56.7
Chen, 2008 (16)	Asian	79	197	133	356	60	161	N/A	N/A
Song, 2009 (6)	Asian	267	346	573	803	244	432	51.1	47.3

Abbreviation: N/A, not available.

[a] Data not available in the published article.

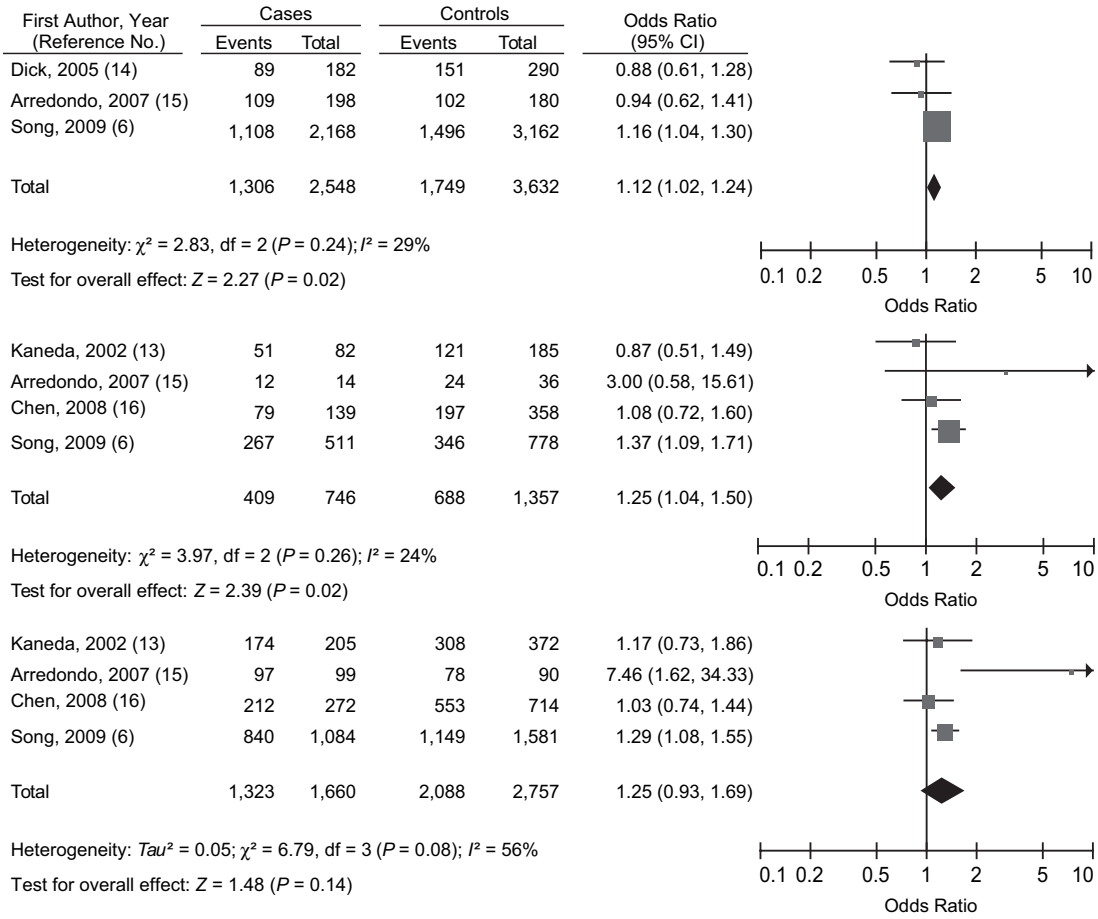

Figure 1. Association between the heme oxygenase-1 (*HMOX1*) (GT)n repeat length polymorphism and type 2 diabetes mellitus in 5 studies published through December 31, 2009 (squares) and in a meta-analysis (diamonds). The sizes of the squares reflect the weighting of individual studies. Upper section: L allele versus S allele, number of events for persons with the L allele, and total for persons with either the L allele or the S allele. Middle section: LL genotype versus SS genotype, number of events for persons with the LL genotype, and total for persons with either the LL genotype or the SS genotype. Lower section: LL genotype and LS genotype versus the SS genotype, number of events for persons with either the LL genotype or the LS genotype, and total for persons with any genotype (LL, LS, or SS). Bars, confidence interval CI.

Other polymorphisms and interactions

Although investigators in all of the included studies had taken the $(GT)_n$ repeat length polymorphism into account, only 1 study had included the T(−413)A SNP simultaneously (6). Unlike the $(GT)_n$ repeat length polymorphism, the T(−413)A SNP did not show any significant differences among subjects with type 2 diabetes, subjects with impaired glucose regulation, and controls for either allelic or genotypic frequencies. Moreover, no significant differences in the expression level of the HMOX1 protein were observed between participants with different genotypes for the T(−413)A SNP. In further combined analyses for haplotypes comprising the (GT)n microsatellite polymorphism and the T(−413)A SNP, the TL haplotype was associated with increased odds of impaired glucose regulation (adjusted OR = 1.82, 95% CI: 1.18, 2.80; $P = 0.007$) and type 2 diabetes (adjusted OR = 1.49, 95% CI: 1.09, 2.03; $P = 0.012$) in comparison with the most frequent haplotype, TS, while no significant associations were found for the other 2 haplotypes, AS and AL. However, associations between other SNPs in the *HMOX1* gene and type 2 diabetes have not yet been demonstrated.

DISCUSSION

The current meta-analysis provided a comprehensive and systematic evaluation of the association between *HMOX1* gene promoter polymorphisms and susceptibility to type 2 diabetes based on a Human Genome Epidemiology review of all research published through December 31, 2009. For the (GT)n microsatellite polymorphism, the odds ratio for type 2 diabetes in persons with the $(GT)_n$ L allele, compared with those with the $(GT)_n$ S allele, was significantly increased. Similar results were found in analysis comparing the odds ratio for type 2 diabetes in persons with the LL and SS genotypes. No significant association was observed in persons with the LL or LS genotype, as compared with those with the SS genotype, in a random-effects model (large

heterogeneity was found between studies). The sample size or precision of the included studies can influence the assigned weight in meta-analysis (20). The overall odds ratio and 95% confidence interval for all included studies was influenced mainly by the study by Song et al. (6), because the sample size of that study was the largest of all of the studies. With regard to SNPs, only T(−413)A was investigated in relation to type 2 diabetes, and the T(−413)A SNP did not show any significant differences among subjects with type 2 diabetes, impaired glucose regulation, and controls for either allelic or genotypic frequencies.

In 1997, the identification of a (GT)n repeat length polymorphism in the human *HMOX1* gene promoter region set off a boom in investigating its application as a genetic marker for human diseases (22). The (GT)n polymorphism in the *HMOX1* gene has been associated with susceptibility to chronic pulmonary emphysema (7), acute respiratory distress syndrome (23), and coronary artery disease with or without type 2 diabetes (8, 13, 16). In those studies, persons with longer (GT)n repeats in the *HMOX1* promoter might have had increased susceptibility to the development of chronic pulmonary emphysema and coronary artery disease, which is in accordance with results from the current meta-analysis focused on type 2 diabetes. However, they might have had reduced risk of acute respiratory distress syndrome. The underlying mechanism remains to be elucidated. A functional study using a luciferase transient transfection assay suggested that constructs with lengths of fewer than 25 repeats showed increased *HMOX1* basal promoter activity (8); this was validated in another study using lymphoblastoid cell lines established from subjects with known GT repeat lengths (24). *HMOX1* mRNA expression and enzyme activity induced by oxidative stress was significantly higher in lymphoblastoid cell lines with SS than in those with the LL (GT)n genotype. Furthermore, lymphoblastoid cell lines with the SS genotype were significantly more resistant to oxidant-induced apoptosis than those with the LL genotype (24). However, it is noteworthy that disparate patterns between HMOX1 protein expression and enzyme activity have been found in peripheral blood mononuclear cells (mononuclear leukocytes) in 2 studies (6, 15) in which persons with type 2 diabetes had a higher proportion carrying the LL genotype in comparison with controls. One of them is the previously published study by Song et al. (6), which showed that the concentration of the HMOX1 protein (mean fluorescence intensity measured by flow cytometry) in those cells, consistently with HMOX1 mRNA expression and enzyme activity in the aforementioned results (24), was significantly lower in subjects with diabetes than in controls (6), while in the other study, Arredondo et al. (15) reported just the opposite result in the form of HMOX1 enzyme activity.

To date, no population testing for *HMOX1* gene polymorphisms, either the (GT)n repeat length polymorphism or SNPs, is in use. The results of this meta-analysis suggest that the *HMOX1* (GT)n L allele may help to identify persons at higher risk of type 2 diabetes; however, we do not suggest that such testing is indicated on a population-wide basis, because only a modest increase in type 2 diabetes risk was observed.

This meta-analysis had several limitations. First, the total number of studies related to the *HMOX1* polymorphism and type 2 diabetes was limited. Second, only 1 study included more than 1,000 cases and 1,000 controls; some of the other studies had relatively small sample sizes, which decreased their statistical power. However, in the meta-analysis, we gave those studies corresponding weights (according to their sample sizes) in order to minimize random bias. Third, although we considered and harmonized the (GT)n repeat length cutpoints, subtle bias from the 2-repeat difference (cutpoint at 25 vs. 27 in different studies) may exist. Fourth, although no publication bias was found on the basis of the funnel plot analyses, the limited number of included studies may have influenced the stability of those analyses. In addition, the results of the current meta-analysis were also challenged by potential errors in the classification of genotypes/phenotypes, as well as the possibility of undiagnosed diabetes among the controls in the included studies.

In conclusion, this systematic review and meta-analysis showed that persons carrying longer $(GT)_n$ repeats in the *HMOX1* gene promoter may have higher risk of type 2 diabetes. However, the T(−413)A SNP did not show any significant differences between subjects with type 2 diabetes and controls for either allelic or genotypic frequencies. Further research on the association between *HMOX1* gene $(GT)_n$ repeats/SNPs and type 2 diabetes in studies with large sample sizes appears warranted.

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