


C282Y and H63D Polymorphisms in Hemochromatosis Gene and Risk of Parkinson's Disease: A Meta-Analysis

American Journal of Alzheimer's Disease & Other Dementias[®]
2016, Vol. 31(3) 201-207
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DOI: 10.1177/1533317515602220
aja.sagepub.com


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Abstract

Objective: A meta-analysis was performed to better clarify the association between hemochromatosis (HFE) gene and the risk of Parkinson's disease (PD). **Methods:** Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated from fixed- and random-effect models. Heterogeneity among studies was evaluated using the I^2 and Q test. Egger's test was used to estimate the publication bias. **Results:** We identified 8 articles with 9 independent studies for this meta-analysis. The present meta-analysis showed no significant association of Y allele with the risk of PD in dominant (OR = 0.87, 95% CI = 0.70-1.09), recessive (OR = 1.58, 95% CI = 0.61-4.10), and codominant (OR = 0.88, 95% CI = 0.72-1.09) models for C282Y. There were also no significant associations of D allele with the risk of PD in dominant (OR = 1.04, 95% CI = 0.87-1.24), recessive (OR = 1.23, 95% CI = 0.70-2.18), and codominant (OR = 1.04, 95% CI = 0.89-1.22) genetic models for H63D. No publication bias was detected. **Conclusion:** The meta-analysis indicated that C282Y and H63D polymorphisms in the HFE gene might not be associated with PD.

Keywords

hemochromatosis, gene, Parkinson's disease, meta-analysis

Introduction

Parkinson's disease (PD) is the second most common form of neurodegenerative disease, clinically characterized by resting tremor, muscular rigidity, bradykinesia, and postural instability. Parkinson's disease affects 2% of the population older than 65 years.^{1,2} It is considered a multifactorial disease, in which genetic factors play an important role. Some Mendelian genes linked to inherited forms of PD have been identified, and a number of common genetic variants have been described in many association studies as risk factors for the sporadic form of the disease.³ Several reports showed an involvement of iron-mediated oxidative stress in the pathogenesis of PD.⁴

The gene of hemochromatosis (HFE) encodes the HFE protein whose function is to regulate iron absorption. The role of HFE as an important regulator of cellular iron homeostasis determines its potential involvement in the pathogenesis of PD. Homozygosity or compound heterozygosity for the variants C282Y and H63D of the HFE gene can lead to iron overload and to the disorder known as hereditary HFE.^{4,5} The C282Y mutation is highly penetrant and leads to intracellular sequestration of iron.⁶ The H63D mutation is less penetrant and is a susceptibility factor for HFE.⁷ Its role in iron metabolism makes HFE a potential candidate gene for PD. Studies have been conducted to evaluate the effect of C282Y and H63D genetic polymorphisms in the HFE gene and the risk of PD, however the results

were conflicting. Hence, we perform the current meta-analysis to identify the association of HFE gene with the risk of PD.

Materials and Methods

Literature Search

The available articles published in English (up to January 2015) were identified by extended computer-based searches from the following databases: (1) PubMed and (2) Web of Science. The following key words were used: ("HFE" or "hemochromatosis" or "C282Y" or "H63D") and ("polymorphism" or "mutation" or "genes") and ("Parkinson's disease" or "Parkinson" or "PD"). We also reviewed the references cited in the studies and review articles to identify additional studies not captured by our database searches.

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This article was accepted under the editorship of the former Editor-in-Chief, Carol F. Lippa.

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Table 1. Characteristics of the C282Y Polymorphism in the HFE Gene Genotype Distributions in Studies Included in This Meta-Analysis.

Author	Year	Country	Ethnicity	Number (Case/Control)	Genotype CC/CY/YY		P for HWE in control	P for HWE in case	References
					Case	Control			
Borie et al ¹⁴	2002	Paris	Europe	71/57	66/5/0	52/5/0	.73	.76	14
Buchanan et al ²¹	2002	Australia	Oceania	438/485	391/46/1	405/76/4	.84	.77	21
Dekker et al ¹⁶	2003	Netherlands	Europe	101/2136	89/10/2	1838/290/8	.34	.06	16
Dekker et al ¹⁶	2003	Netherlands	Europe	44/2136	38/6/0	1838/290/8	.34	.63	16
Guerreiro et al ¹⁸	2006	Portugal	Europe	132/115	114/18/0	110/5/0	.81	.40	18
Aamodt et al ¹⁵	2007	Norway	Europe	315/396	263/50/2	330/64/2	.56	.82	15
Halling et al ²⁰	2008	Denmark	Europe	54/110	44/10/0	87/21/2	.58	.45	20
Greco et al ¹⁷	2011	Italy	Europe	181/180	178/3/0	177/3/0	.91	.91	17
Mariani et al ¹⁹	2013	Italy	Europe	73/139	70/3/0	137/2/0	.93	.93	19

Abbreviations: HFE, hemochromatosis; HWE, Hardy-Weinberg equilibrium.

Table 2. Characteristics of the H63D Polymorphism in the HFE Gene Genotype Distributions in Studies Included in This Meta-Analysis.

Author	Year	Country	Ethnicity	Number (Case/Control)	Genotype HH/HD/DD		P for HWE in Control	P for HWE in Case	References
					Case	Control			
Borie et al ¹⁴	2002	Paris	Europe	66/59	42/23/1	39/20/0	.12	.27	14
Dekker et al ¹⁶	2003	Netherlands	Europe	122/2567	89/31/2	1838/661/68	.36	.71	16
Dekker et al ¹⁶	2003	Netherlands	Europe	54/2567	38/16/0	1838/661/68	.36	.20	16
Guerreiro et al ¹⁸	2006	Portugal	Europe	132/115	89/38/5	74/39/2	.22	.71	18
Aamodt et al ¹⁵	2007	Norway	Europe	330/428	263/60/7	330/91/7	.80	.11	15
Halling et al ²⁰	2008	Denmark	Europe	67/125	44/20/3	87/33/5	.41	.71	20
Greco et al ¹⁷	2011	Italy	Europe	181/180	125/49/7	141/36/3	.69	.43	17
Mariani et al ¹⁹	2013	Italy	Europe	77/139	53/24/0	99/38/2	.44	.11	19

Abbreviations: HFE, hemochromatosis; HWE, Hardy-Weinberg equilibrium.

Inclusion Criteria

The inclusion criteria were as follows: (1) case-control or cohort study published as original study to evaluate the association between C282Y and H63D polymorphisms in the HFE gene and risk of PD; (2) numbers for the genotype were reported in case and control groups for case-control studies, exposed and unexposed groups for cohort studies for each genotype, or data provided to calculate them; and (3) participants in each study should come from the same ethnicity and period. The most recent and complete articles were chosen if data from the same population had been published more than once. Two investigators carefully reviewed all identified studies independently to determine whether an individual study was eligible for inclusion in this meta-analysis.

Data Extraction

Two investigators collected the data independently and reached a consensus on all items. The following basic information was extracted from the eligible studies: first author, journal, year of publication, country, ethnicity of studied population, sample size, mean age, and distributions of allele and genotype. When it came to conflicting evaluations, it was resolved by the third reviewer.

Statistical Analysis

Departure from Hardy-Weinberg equilibrium (HWE) for the C282Y and H63D and genotype distribution of HFE gene in cases and controls was tested by χ^2 analysis with exact probability (HWE: $P > .05$). Odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of the association of the C282Y and H63D polymorphisms in HFE gene with the risk of PD. We conducted analysis for 2 polymorphisms considering dominant (YY + CY vs CC) and (DD + HD vs HH), recessive (YY vs CY + CC) and (DD vs HD + HH), and codominant (Y vs C) and (D vs H) models for C282Y and H63D, respectively. The I^2 of Higgins and Thompson⁸ and Q test were used to assess heterogeneity among studies. The DerSimonian and Laird random effect model (REM) was adopted as the pooling method if substantial heterogeneity is present ($I^2 > 50\%$)⁹; otherwise, the fixed-effect model (FEM) was used as the pooling method. Influence analysis¹⁰ was conducted to describe how robust the pooled estimator is to the removal of individual studies. If the main estimate of an individual study's omitted analysis lies outside the 95% CI of the combined analysis, it is suspected of excessive influence. Egger's test¹¹ was used to estimate the publication bias. Besides, both theoretical and empirical evidence suggest that general genetic variants causally associated with common diseases will have small effects (risk ratios mostly < 3.0),^{12,13} considering the fact that

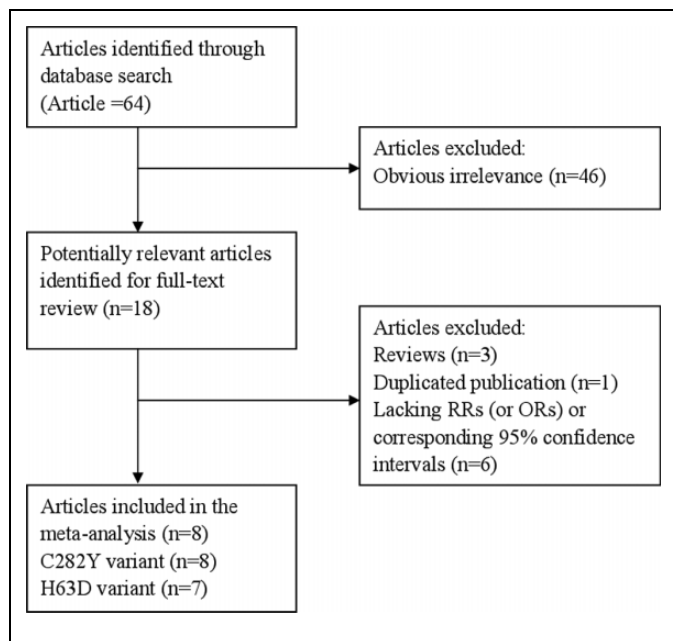


Figure 1. Flowchart of meta-analysis for exclusion/inclusion of studies.

original studies with relatively small participants might be underpowered to detect the effect. Thus, for sensitivity analysis, we further excluded the studies with OR > 3.0 as the criteria to control the impact within each single study on the pooled effect. STATA version 10.0 (Stata Corporation, College Station, Texas) was used to perform statistical analyses. All reported probabilities (*P* values) were 2 sided, with *P* value less than .05 considered statistically significant.

Results

Characteristics of Studies

We identified 8 articles¹⁴⁻²¹ with 9 eligible outcomes for this meta-analysis, including 9 outcomes for the C282Y polymorphism and 8 outcomes for the H63D polymorphism. All included articles were case-control designs. General characteristics and genotype distributions of the above-mentioned polymorphisms are summarized in Tables 1 and 2. Figure 1 presents the flowchart for exclusion/inclusion process.

Quantitative Synthesis

The results of the pooled analysis are summarized in Table 3.

The C282Y Polymorphism

For the C282Y polymorphism, overall, no significant association was found between the Y allele and the risk of PD in dominant (FEM: OR = 0.87, 95% CI = 0.70-1.09), recessive (FEM: OR = 1.58, 95% CI = 0.61-4.10), and codominant (FEM: OR = 0.88, 95% CI = 0.72-1.09) models. Considering

Table 3. Pooled Measures on the Relationship of C282Y and H63D polymorphisms in the HFE Gene With Risk of Parkinson’s Disease.^{a,b,c}

Polymorphism	Inherited Model	All Included Articles				After Excluding Articles With OR > 3.0				
		Pooled OR (95% CI)		Q Value	I ² (%)	Pooled OR (95% CI)		I ² (%)	P for Heterogeneity	Articles Excluded
		FEM	REM			FEM	REM			
All data	Dominant	0.87 (0.70-1.09)	0.95 (0.69-1.30)	12.56	36.3	0.82 (0.65-1.02)	0.82 (0.65-1.02)	0.0	.63	18
	Recessive ^d	1.58 (0.61-4.10)	1.40 (0.43-4.58)	11.56	30.8	0.77 (0.23-2.56)	0.77 (0.23-2.56)	0.0	.56	14,16-19
	Codominant	0.88 (0.72-1.09)	0.95 (0.71-1.29)	12.74	37.2	0.83 (0.67-1.03)	0.83 (0.67-1.03)	0.0	.55	18
H63D	Dominant	1.04 (0.87-1.24)	1.04 (0.87-1.24)	7.00	0.0	-	-	-	-	-
	Recessive	1.23 (0.70-2.18)	1.23 (0.70-2.18)	7.00	0.0	-	-	-	-	-
	Codominant	1.04 (0.89-1.22)	1.04 (0.89-1.22)	7.00	0.0	-	-	-	-	-
Europe	Dominant	1.04 (0.80-1.36)	1.05 (0.79-1.41)	8.64	7.4	0.95 (0.72-1.26)	0.95 (0.72-1.3)	0.0	.93	18
	Recessive ^d	2.37 (0.83-6.82)	2.37 (0.83-6.82)	8.00	0.0	1.19 (0.29-5.00)	1.19 (0.29-5.0)	0.0	.66	16
	Codominant	1.05 (0.82-1.35)	1.05 (0.82-1.36)	8.07	0.9	0.97 (0.75-1.26)	0.97 (0.75-1.3)	0.0	.94	18

Abbreviations: CI, confidence interval; FEM, fixed-effect model; HFE, hemochromatosis; OR, odds ratio; REM, random-effect model.

^aDominant model: YY + CY versus CC for C282Y and DD + HD versus HH for H63D.

^bRecessive model: YY versus CY + CC for C282Y and DD versus HD + HH for H63D.

^cCodominant model: Y versus C for C282Y and for D versus H for H63D.

^dFour articles (Borie et al, Guerreiro et al, Greco et al, and Mariani et al) in C282Y were not sufficient to calculate pooled OR.

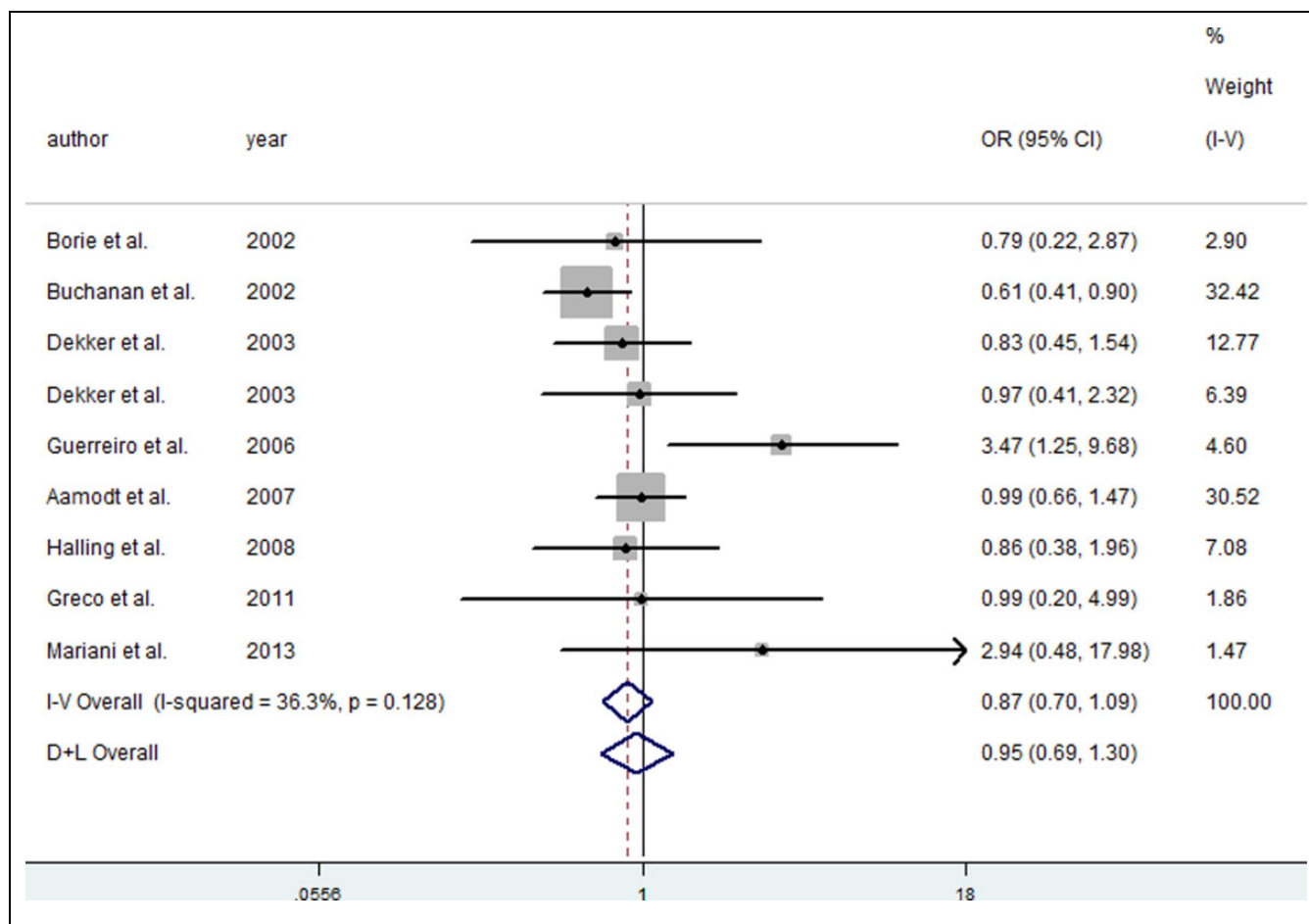


Figure 2. Meta-analysis for the risk of Parkinson's disease (PD) depending on the C282Y polymorphism in the hemochromatosis (HFE) gene. Forest plots of relationship between the C282Y polymorphism in the HFE gene and risk of PD in dominant model. White diamond denotes the pooled odds ratio (OR). Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% confidence intervals (CIs).

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8 of the 9 studies come from Europe, the subgroup analysis for European population was conducted. The Y allele also found no association with risk of PD in dominant (FEM: OR = 1.04, 95% CI = 0.80-1.36), recessive (FEM: OR = 2.37, 95% CI = 0.83-6.82), and codominant (FEM: OR = 1.05, 95% CI = 0.82-1.35) models. All included articles were in HWE for cases and controls. The associations were not altered significantly after excluding articles with OR > 3.0.^{16,18} Figure 2 presents the forest plot of OR for PD in dominant model of the C282Y polymorphism in the HFE gene.

The H63D Polymorphism

For the H63D polymorphism, this meta-analysis showed no significant effect of the D allele on risk of PD in dominant (FEM: OR = 1.04, 95% CI = 0.87-1.24), recessive (REM: OR = 1.23, 95% CI = 0.70-2.18), and codominant (FEM: OR = 1.04, 95% CI = 0.89-1.22) models. The included studies about the H63D polymorphism were all conducted in Europe, so the subgroup analysis about H63D was not further

investigated. All included articles were in HWE for cases and controls, and all included articles were with OR < 3.0. Figure 3 presents the forest plot of OR for PD in codominant model of the H63D polymorphism in the HFE gene.

Sensitivity Analysis After Excluding Articles With OR > 3.0

If the frequency of mutation homozygous was 0 in the case group, then it was not sufficient to calculate pooled OR for recessive model. For this reason, 4 articles^{14,17-19} about C282Y polymorphism were not sufficient to calculate the pooled OR in the recessive model. For the overall risk of PD, after excluding the articles with OR > 3.0,^{16,18} the risk effects of the Y allele showed no significant effect in dominant (FEM: OR = 0.82, 95% CI = 0.65-1.02), recessive (REM: OR = 0.77, 95% CI = 0.23-2.56), and codominant (FEM: OR = 0.83, 95% CI = 0.67-1.03) models. No studies with OR > 3.0 existed in the H63D polymorphism.

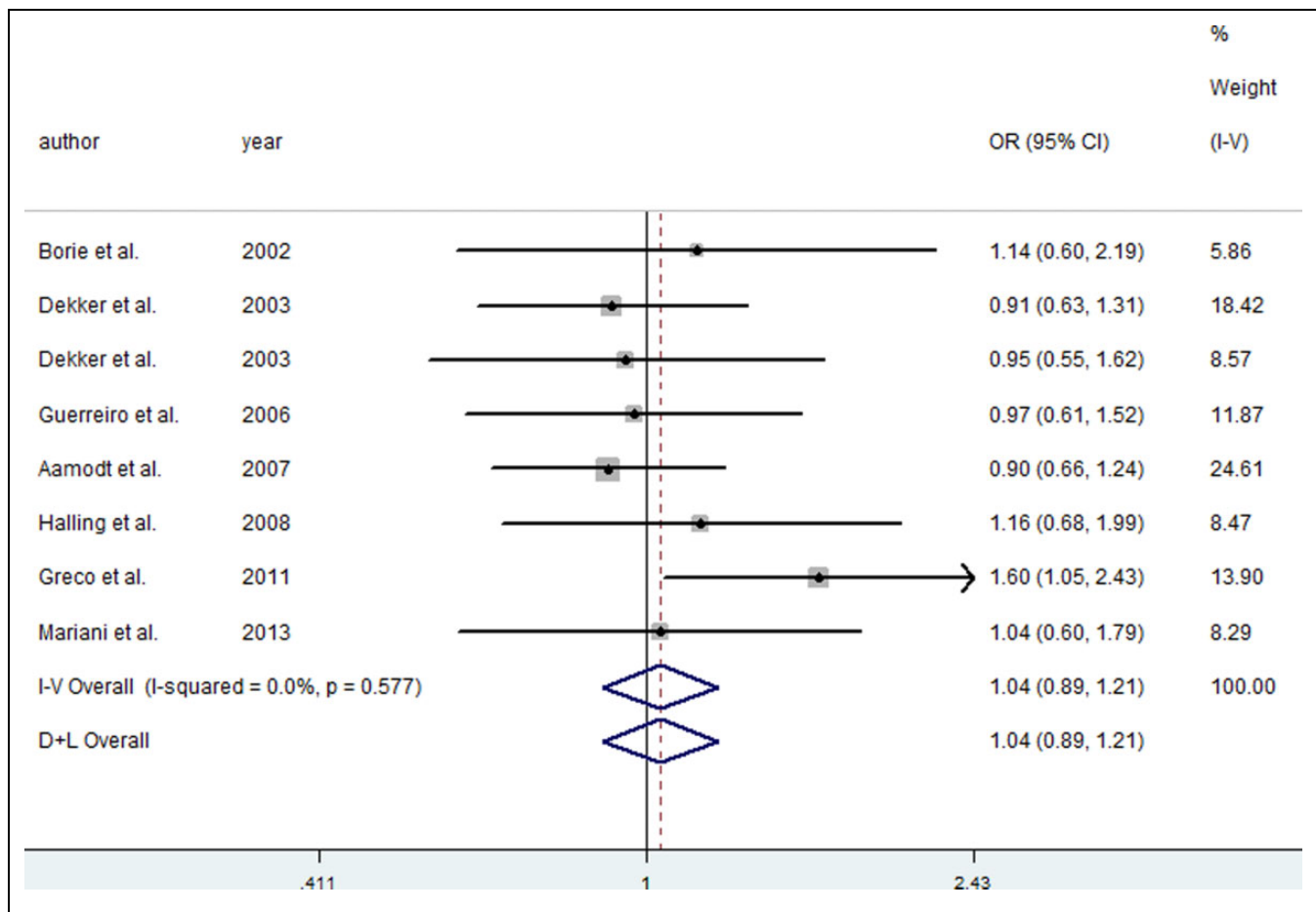


Figure 3. Meta-analysis for the risk of Parkinson's disease (PD) depending on the H63D polymorphism in the hemochromatosis (HFE) gene. Forest plots for relationship between the H63D polymorphism in the HFE gene and risk of PD in codominant model. White diamond denotes the pooled odds ratio (OR). Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% confidence intervals (CIs).

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About Heterogeneity

For the 2 polymorphisms, moderate evidence of heterogeneity ($I^2 < 50\%$) was found in 3 genetic models. For the C282Y polymorphism, only 1 study was conducted in Europe, hence subgroup analyses were performed only on European population and the heterogeneity was effectively decreased or removed after the subgroup analyses.

Influence Analysis

Before and after exclusion of articles with $OR > 3.0$, no individual study was found having excessive influence on the pooled effect in any of the dominant, recessive, and codominant models considering all the polymorphisms.

Publication Bias

Egger's test was used to assess the publication bias. No significant publication bias was detected in any of the above-mentioned inherited models considering the 2 polymorphisms.

Figure 4 presents the result of the publication bias for PD in recessive model of the H63D polymorphism in the HFE gene.

Discussion

Parkinson's disease is a progressive neurodegenerative disease. Many studies had suggested that altered iron homeostasis may be an initial trigger for neuronal cell death in neurodegenerative diseases such as PD.^{22,23} Hemochromatosis gene is an important regulator of cellular iron homeostasis. The C282Y and H63D single-nucleotide polymorphisms within the HFE gene can give rise to phenotypes with altered iron parameters. Recently, studies have been performed to evaluate the correlation between C282Y and H63D polymorphisms in the HFE gene and the risk of PD. However, the results remained controversial. Since an individual study has a relatively small number of participants with low power to detect the effect, a meta-analysis may be the appropriate approach to obtain a more definitive conclusion.

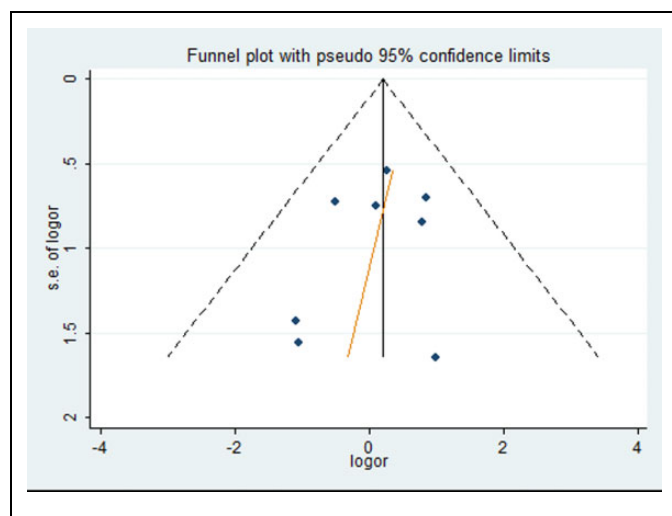


Figure 4. Egger's test of publication bias for Parkinson's disease (PD) in recessive model of the H63D polymorphism in the hemochromatosis (HFE) gene.

In this meta-analysis, we summarize the results of 9 case-control studies published so far on the association between C282Y and H63D polymorphisms in the HFE gene and risk of PD. No significant association of Y allele of C282Y and D allele of H63D was found in all of the genetic models and stratified analysis. The meta-analysis indicated that C282Y and H63D polymorphisms in the HFE gene might not be associated with PD.

For a simple genetic variant with 2 alleles, the classical models of inheritance (dominant, recessive, and codominant model) are typically assumed for complex traits when the inheritance model is unknown.^{24,25} Besides, maximal power is achieved, when the inherited model is unknown, with codominant model alone or all 3 genetic models tested together. Thus, we tested all 3 models simultaneously.²⁶

Moderate heterogeneity was found among all the studies for the C282Y polymorphism in the HFE gene. As the differences exist in different genetic backgrounds populations and only 1 study in Europe, subgroup analysis was performed only including European population. The results did not change significantly, and the heterogeneity was effectively decreased or removed after the subgroup analyses by ethnicity. Moreover, considering general genetic variants associated with common diseases always have small effects, we further excluded the studies with OR > 3.0 to control the impact within each single study on the pooled effect. The results did not change significantly, and the heterogeneity was 0 in all inherited models after excluding articles with OR > 3.0. Besides, in this meta-analysis, for C282Y and H63D polymorphisms, no individual study was found having excessive influence on the pooled effect, and no significant publication bias were found in any of the above-mentioned inherited models, suggesting the associations observed should be stable.

This current meta-analysis, to the best of our knowledge, is the first study to integrate the association between C282Y and

H63D polymorphisms in the HFE gene and risk of PD, and we interpreted our findings with full caution. Nonetheless, there are some limitations that should be addressed in this meta-analysis. For example, lack of original information for included studies made it impracticable to stratify by other variables, such as smoking status, drinking status, family history, or other relevant diseases, which may affect PD.

Conclusion

In conclusion, our meta-analysis suggested that C282Y and H63D polymorphisms in the HFE gene might not be associated with PD. With regard to PD with multifactorial etiology, our study also warrants for well-designed, large-scale studies with consideration of gene-gene and gene-environment interactions to further evaluate this possible association.

Authors' Note

Chunhong Duan and Meiyun Wang equally share the first authorship.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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